CAMILA CATALDI DE ALCANTARA

ASSOCIAÇÃO ENTRE AS VARIANTES GENÉTICAS rs2241043, rs2241049 e rs6518661 DO *IL17RA* E A SUSCETIBILIDADE E GRAVIDADE DA PSORÍASE

Londrina
2023

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Tese de doutorado apresentada ao Programa de Patologia Experimental do Departamento de Ciências Patológicas da Universidade Estadual de Londrina, como requisito à obtenção do título de Doutora em Patologia Experimental.

Orientadora: Profª. Drª. Andréa Name Colado Simão

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CAMILA CATALDI DE ALCANTARA

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Londrina, 18 de julho de 2023.

“Foi o melhor dos tempos, foi o pior dos tempos. Foi a idade da sabedoria, foi a idade da tolice. Foi a época da fé, foi a época da incredulidade. Foi a estação da luz, foi a estação das trevas. Foi a primavera da esperança, foi o inverno do desespero. Tínhamos tudo diante de nós, não havia nada antes de nós.”

Charles Dickens (Um Conto de Duas Cidades – 1859)

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ALCANTARA, Camila Cataldi de. **Associação entre as Variantes Genéticas rs2241043, rs2241049 e rs6518661 do *IL17RA* e a Suscetibilidade e Gravidade da Psoríase**. 2023. 126. Tese de Doutorado em Patologia Experimental – Universidade Estadual de Londrina, Londrina, 2023.

RESUMO

INTRODUÇÃO: A psoríase (PsO) é uma doença inflamatória crônica, mediada pelo sistema imunológico e de etiologia desconhecida. A resposta inflamatória normalmente tem início com um fator nocivo aos queratinócitos, estimulando a produção e secreção de citocinas. A indução da diferenciação das células T auxiliadoras dá início à uma produção de citocinas capazes de ativar e recrutar células do sistema imunológico para o local da lesão. Nesse microambiente, a Interleucina (IL) 17 exerce um papel primordial para a fisiopatologia da doença. O caráter multifatorial da PsO e a importância da IL-17 para a sua fisiopatologia evidenciam a necessidade de investigar como o fator genético pode influenciar na suscetibilidade à PsO e na resposta de pacientes aos novos tratamentos desenvolvidos contra essas moléculas. **OBJETIVO:** Revisar a literatura e avaliar a associação entre as variantes genéticas rs2241043, rs2241049 e rs6518661 do gene *IL17RA* e a suscetibilidade e gravidade da PsO. **SUJEITOS E MÉTODOS:** Este é um estudo caso-controle que incluiu 308 participantes de ambos os sexos, com idade entre 18 e 70 anos, sendo 154 pacientes com diagnósticos de PsO e 154 indivíduos saudáveis. O diagnóstico de PsO foi feito por um dermatologista e o Índice de Gravidade e Extensão das Lesões Psoriáticas (PASI) foi usado para determinar a gravidade da doença. Os dados clínicos, epidemiológicos e antropométricos foram obtidos durante consulta clínica através do preenchimento de uma ficha de avaliação previamente estabelecida. As variantes genéticas do gene *IL17RA* foram genotipadas por reação em cadeia da polimerase em tempo real utilizando sondas TaqMan®. Três variantes genéticas localizados na região intrônica do *IL17RA* foram genotipados: T>C rs2241043, A>G rs2241049 e G>A rs6518661. **RESULTADOS:** Os pacientes com PsO eram mais velhos (p<0,001), tinham maior Índice de Massa Corporal (IMC) (p<0,001) e maiores níveis séricos de Proteína C Reativa (p<0,001) e Ferritina (p=0,002) quando comparados aos controles. A presença do alelo G em homozigose par o rs2241049 A>G demonstrou estar associado à proteção contra a PsO nos modelos dominante (OR=0,37, 95% IC 0,18-0,76, p=0,017) e recessivo (OR=0,39, 95% IC 0,20-0,76, p=0,005). A frequência do alelo A foi maior no grupo com PsO e o alelo C, no grupo controle (OR=0,799, 95% IC 0,67-0,95, p=0,0151). O genótipo CC do rs2241043 T>C demonstrou ser um fator de proteção contra o desenvolvimento de PsO grave (OR=0,30, 95% IC 0,10-0,093, p=0,020). Esta associação se manteve independentemente de idade, sexo, etnia e IMC (OR=0,303, 95% IC 0,095-0,965, p=0,043). A presença do alelo A em homozigose para o rs6518661 G>A demonstrou estar associado à proteção contra o desenvolvimento de PsO grave (OR=0,22, 95% IC 0,05-0,99, p=0,020). **CONCLUSÃO:** Este estudo demonstrou que o genótipo GG do *IL17RA* A>G rs2241049 é um fator protetor contra o desenvolvimento de PsO. Além disso, o alelo C em homozigose da variante *IL17RA* T>C rs2241043 e o genótipo AA do *IL17RA* G>A rs6518661 foram associados à proteção contra o desenvolvimento de PsO grave. Mais estudos são necessários para elucidar quais mecanismos genéticos e epigenéticos podem estar envolvidos nas associações, uma vez que esses genes estão localizados em regiões intrônicas.

Palavras-chave: rs2241043. rs2241049. rs6518661. IL-17RA. PASI.

ALCANTARA, Camila Cataldi de. **Evaluation of the Association between rs2241043, rs2241049 and rs6518661 *IL17RA* Genetic Variants and Psoriasis Susceptibility and Severity.** 2023. 126. Doctoral Thesis in Experimental Pathology – State University of Londrina, Londrina, 2023.

ABSTRACT

INTRODUCTION: Psoriasis (PsO) is a chronic inflammatory disease, mediated by the immune system and of unknown etiology. The inflammatory response normally begins with a factor harmful to keratinocytes, stimulating the production and secretion of cytokines. The induction of helper T cell differentiation initiates the production of cytokines capable of activating and recruiting immune system cells to the site of injury. In this microenvironment, Interleukin (IL) 17 plays a key role in the pathophysiology of the disease. The multifactorial nature of PsO and the importance of IL-17 for its pathophysiology highlight the need to investigate how the genetic factor can influence susceptibility to PsO and the response of patients to new treatments developed against these molecules. **OBJECTIVE:** To review the literature and evaluate the association between the rs2241043, rs2241049, and rs6518661 genetic variants of the IL17RA gene and the susceptibility and severity of PsO. **SUBJECTS AND METHODS:** This is a case-control study that included 308 participants of both sexes, aged between 18 and 70 years, 154 patients diagnosed with PsO, and 154 healthy individuals. The diagnosis of PsO was made by a dermatologist and the Psoriatic Area and Severity Index (PASI) was used to determine the severity of the disease. Clinical, epidemiological, and anthropometric data were obtained during a clinical consultation by completing a previously established evaluation form. Genetic variants of the *IL17RA* gene were genotyped by real-time polymerase chain reaction using TaqMan® probes. Three genetic variants located in the intronic region of *IL17RA* were genotyped: T>C rs2241043, A>G rs2241049 and G>A rs6518661. **RESULTS:** Patients with PsO were older ($p<0.001$), had a higher Body Mass Index (BMI) ($p<0.001$), and had higher serum levels of C-Reactive Protein ($p<0.001$) and Ferritin ($p=0.002$) when compared to with control group. The presence of the G allele in homozygosis for rs2241049 A>G has been shown to be associated with protection against PsO in both dominant (OR=0.37, 95% CI 0.18-0.76, $p=0.017$) and recessive (OR =0.39, 95% CI 0.20-0.76, $p=0.005$) models. The frequency of the A allele was higher in the PsO group and the C allele in the control group (OR=0.799, 95% CI 0.67-0.95, $p=0.0151$). The rs2241043 T>C CC genotype was shown to be a protective factor against the development of severe PsO (OR=0.30, 95% CI 0.10-0.093, $p=0.020$). This association was maintained regardless of age, sex, ethnicity, and BMI (OR=0.303, 95% CI 0.095-0.965, $p=0.043$). The presence of the A allele in homozygosis for rs6518661 G>A has been shown to be associated with protection against the development of severe PsO (OR=0.22, 95% CI 0.05-0.99, $p=0.020$). **CONCLUSION:** This study demonstrated that the GG genotype of *IL17RA* A>G rs2241049 is a protective factor against the development of PsO. Furthermore, the homozygous C allele of the *IL17RA* T>C rs2241043 variant and the AA genotype of the *IL17RA* G>A rs6518661 were associated with protection against the development of severe PsO. More studies are needed to elucidate which genetic and epigenetic mechanisms may be involved in the associations since these genes are in intronic regions.

Key words: rs2241043. rs2241049. rs6518661. IL-17RA. PASI.

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LISTA DE ABREVIATURAS E SIGLAS

ADAMTSL5	Proteína Desintegrina e Metaloproteinase com Motivo semelhante à Trombospondina do tipo 5, do inglês - *Disintegrin and metalloproteinase with thrombospondin motifs-like protein 5*
AEHU	Ambulatório de Especialidades do Hospital Universitário
APC	Células Apresentadoras de Antígenos, do inglês - *Antigen Presenting Cells*
CASPAR	Critérios para a Classificação de Artrite Psoriática, do inglês - *Classification Criteria of Psoriatic Arthritis*
CD	Grupamento de Diferenciação, do inglês - *Cluster of Differentiation*
CRP	Proteína C Reativa, do inglês *C-Reactive Protein*
CVD	Doenças Cardiovasculares, do inglês - *Cardiovascular Disease*
DCs	Células Dendríticas, do inglês - *Dendritic Cells*
DM2	Diabetes Mellitus do tipo 2
FOXP3	Do inglês - *Forkhead box 3*
HIV	Vírus da Imunodeficiência humana, do inglês - *Human Immunodeficiency Virus*
IBD	Doenças Inflamtórias Intestinais, do inglês - *Inflammatory Bowel Disease*
IC	Intervalo de Confiança
IFN	Interferon
IFN-α	Interferon alfa
IFN-β	Interferon beta
IMC	Indíce de Massa Corporal
IL	Interleucina
LD	Desequilíbrio de Ligação, do inglês - *Linkage Disequilibrium*
M1	Macrófagos do Tipo 1
mAbs	Anticorpos Monoclonal, do inglês - *Monoclonal Antibodies*
mDC	Células Dendríticas Mielóides, do inglês - *Myeloid Dendritic Cells*
MetS	Síndrome Metabólica, do inglês - *Metabolic Syndrome*
MHC	Complexo Principal de Histocompatibilidade, do inglês - *Major Histocompatibility Complex*
NB-UVB	Faixas Estreiras de UVB, do inglês - *Narrow-band Ultraviolet B*
OR	Razão de Chances, do inglês - *Odds Ratio*
PASI	Índice de Gravidade e Extensão das Lesões Psoriáticas, do inglês - *Psoriasis Area and Severity Index*
PCR	Reação em Cadeia da Polimerase, do inglês - *Polymerase Chain Reaction*
PsA	Artrite Psoriática, do inglês - *Psoriatic Arthritis*
PsO	Psoríase

PSORS1	Suscetibilidade à Psoríase do Tipo 1, do inglês - *Psoriasis Susceptibility 1*
PUVA	Psoraleno e raios Violeta A, do inglês - *Psoralen plus ultraviolet A*
qPCR	PCR em Tempo Real, do inglês - *quantitative PCR*
SBD	Sociedade Brasileira de Dermatologia
SNP	Polimorfismo de Nucleotídeo Único, o inglês - *Single Nucleotide Polymorphism*
SNV	Variação de Nucleotídeo Único, do inglês - *Single Nucleotide Variant*
Tc	Células T citotóxicas, do inglês - *T cytotoxic cell*
TCLE	Termo de Consentimento Livre e Esclarecido
TGF-β	Fator de Crescimento Transformador Beta, do inglês - *Transforming growth factor beta*
Th	Células T auxiliadoras, do inglês - *T helper Cells*
T_M	Célula T de memória
TNF	Fator de Necrose Tumoral, do inglês - *Tumor Necrosis Factor*
TNF-α	Fator de Necrose Tumoral alfa, do inglês - *Tumor Necrosis Factor alpha*
TREG	Célula T reguladora
UEL	Universidade Estadual de Londrina
UV	Ultravioleta

SUMÁRIO

1 INTRODUÇÃO

1.1 ASPECTOS CLÍNICOS E EPIDEMIOLÓGICOS DA PSORÍASE

A psoríase (PsO) é uma doença crônica, imuno-mediada e inflamatória do tecido cutâneo que afeta mais de 60 milhões de pessoas no mundo entre homens e mulheres de todas as idades. Apesar de ser distribuída igualmente entre os sexos, as mulheres costumam apresentar os sintomas cerca de 10 anos antes quando comparadas aos homens (RAHARJA; MAHIL; BARKER, 2021). Os fatores de risco para o desenvolvimento de PsO são inespecíficos e podem envolver diversos aspectos da vida do indivíduo, dessa forma, é considerada uma doença multifatorial (KAMIYA et al., 2019; LEE et al., 2018).

O fator genético representa o principal componente no surgimento da PsO, sendo determinante naqueles cujo histórico familiar é positivo para a doença (GUPTA; DEBBANEH; LIAO, 2014). O gene *HLACω6*, que codifica o Complexo Principal de Histocompatibilidade (MHC – do inglês *Major Histocompatibility Complex*) de Classe I, é o mais estudado dentro os fatores genéticos associados à PsO (OWCZAREK, 2022). Dois antígenos reconhecidos pelo HLA-Cw6 foram associados como possíveis gatilhos no início da resposta imunológica na PsO, sendo eles a catelicidina LL-37 e a proteína desintegrina e metaloproteinase com motivo semelhante à trombospondina do tipo 5 (ADAMTSL5 – do inglês *Disintegrin and metalloproteinase with thrombospondin motifs-like protein 5*), ambos presentes em células da pele como os melanócitos e queratinócitos (FUENTES-DUCULAN et al., 2017).

Infecções bacterianas e virais também são fatores de risco para o surgimento ou agravamento de PsO (TENG et al., 2021). As infecções por bactérias dos gêneros estreptococos e estafilococos são as mais associadas à PsO e, entre as doenças virais, o vírus da imunodeficiência humana (HIV – do inglês *Human Immunodeficiency Virus*) é o principal gatilho para o desenvolvimento ou exacerbação da doença (ZHOU; YAO, 2022).

Além do fator genético e das infecções por patógenos, outros fatores podem ser considerados risco ao desenvolvimento de PsO como, por exemplo, o uso de medicamentos como os betabloqueadores, lítio e antimaláricos. Curiosamente, os medicamentos administrados no tratamento de doenças inflamatórias crônicas e

agudas, como inibidores do Fator de Necrose Tumoral (TNF – do inglês *Tumor Necrosis Factor*) e Interferons (IFN) também estão associados ao desenvolvimento de PsO ou da sua exacerbação (BALAK; HAJDARBEGOVIC, 2017). Por fim, o estilo de vida também é considerado um fator de risco associado à PsO. O consumo de álcool, tabagismo, sedentarismo e obesidade estão entre os principais hábitos que influenciam na deflagração da doença. Ainda como fator ambiental, a alimentação também está associada não só ao início da PsO como no seu agravamento, sendo necessário, algumas vezes, intervir diretamente nesse fator durante o tratamento (BARREA et al., 2016; MUSUMECI et al., 2022).

O diagnóstico primário de PsO é feito por médico dermatologista a partir da avaliação clínica das lesões. Uma biópsia pode ser necessária, caso haja dúvidas sobre o diagnóstico. As lesões psoriáticas estão localizadas, em sua maioria, no couro cabeludo, cotovelos, nádegas e regiões de dobra; no entanto, podem acometer qualquer parte do corpo, inclusive as unhas. A PsO em placa é a principal forma da doença, representando até 90% das manifestações sendo caracterizada por placas avermelhadas, ressecadas e escamosas. Os pacientes com lesões ativas podem queixar-se de coceira, dor e sangramento. Além disso, a constante atividade inflamatória provoca um espessamento do tecido acometido (ARMSTRONG; READ, 2020).

Outros tipos menos comuns de PsO incluem a gutata, eritrodérmica, pustular e palmoplantar. A PsO gutata é caracterizada por pequenas lesões em forma de gota, localizadas no tronco, braços, pernas e couro cabeludo. Ao contrário da PsO em placa, as lesões da gutata são cobertas por uma fina camada escamosa. A PsO pustular generalizada se caracteriza pelo surgimento de lesões purulentas e eritematosas ao longo do corpo e, quando localizadas nos pés e mãos, também recebem o nome de PsO palmoplantar. Por sua vez, a PsO eritrodérmica é a forma mais rara e grave da doença. Caracterizada pelo acometimento de mais de 90% do corpo, os pacientes acometidos podem experimentar dor intensa, desequilíbrio eletrolítico, prurido e hipotermia. Se não tratada da forma correta, essa forma da doença pode levar o paciente a óbito (GRIFFITHS et al., 2021; UPPALA et al., 2021).

O tratamento mais adequado para cada paciente com PsO é escolhido após a avaliação das lesões, da presença ou não de artrite psoriática (PsA – do inglês *Psoriatic Arthirits*) e a associações à outras comorbidades. A avaliação das lesões é feita através de uma ferramenta utilizada para mensurar a gravidade e a extensão da

PsO, chamada de Índice de Gravidade e Extensão das Lesões Psoriáticas (PASI – do inglês *Psoriasis Area and Severity Index*). O PASI atribui pontuação para cada categoria avaliada. Para determinar a gravidade da doença são avaliados a intensidade do eritema, do espessamento da pele e da escamação. Para determinar a extensão, quatro áreas do corpo são analisadas: cabeça e pescoço, membros superiores, tronco e membros inferiores. O cálculo pode ser realizado com uma calculadora de PASI (ANEXO A) e o resultado é utilizado para o manejo clínico do paciente e para avaliar se a terapia escolhida foi eficiente. Um PASI abaixo de 3 é considerado PsO leve, entre 3 e 10 é considerado PsO moderada e acima de 10 é considerada PsO grave (KIM; JEROME; YEUNG, 2017).

Além do PASI, a presença de PsA também é avaliada; no entanto, apenas cerca de 15% dos casos são corretamente identificados. Apesar de ser uma comorbidade que afeta quase 30% dos pacientes diagnosticados com PsO, o fato de uma manifestação reumatológica se apresentar em uma doença dermatológica dificulta o diagnóstico e, dessa forma, se faz necessário que médicos dermatologistas e reumatologistas trabalhem em conjunto. O atraso no diagnóstico pode acarretar comprometimento de ossos e articulações, como erosões e deformidades (KISHIMOTO et al., 2021).

Por ser uma doença inflamatória crônica, os pacientes com PsO estão constantemente submetidos ao risco de desenvolvimento de comorbidades sistêmicas como diabetes mellitus do tipo 2 (DM2), doenças cardiovasculares (CVD – do inglês *Cardiovascular Disease*), síndrome metabólica (MetS – do inglês *Metabolic Syndrome*), doenças inflamatórias intestinais (IBD – do inglês *Inflammatory Bowel Disease*) e obesidade (BU et al., 2022; MASSON; LOBO; MOLINERO, 2020). A presença de comorbidades associadas à PsO diminui a qualidade de vida dos pacientes, afetando seus relacionamentos pessoais e sociais e aumentando o estresse psicológico (ROUSSET; HALIOUA, 2018).

As manifestações clínicas da PsO, bem como suas comorbidades, estão intimamente associadas à reação pró-inflamatória constante. Apesar de ser uma reação localizada no tecido cutâneo, os efeitos se mostram sistêmicos. A compreensão sobre sua fisiopatologia contribui para um manejo terapêutico mais apropriado e que tenha um impacto positivo na qualidade e expectativa de vida desses pacientes (TASHIRO; SAWADA, 2022).

1.2 FISIOPATOLOGIA DA PSORÍASE

A pele é considerada o maior órgão do corpo humano, cuja função principal é ser a primeira linha de defesa física e química contra patógenos externos. Composta por três camadas essenciais, cada uma delas é constituída por células específicas e exercem papéis distintos na manutenção da homeostase tecidual (CHAMBERS; VUKMANOVIC-STEJIC, 2020).

A imunologia da pele saudável é complexa e envolve células, moléculas e microrganismos comensais que realizam o processo de cicatrização das lesões teciduais a fim de recuperarem a barreira cutânea e atuam em sinergia para proteger o hospedeiro contra patógenos. As células residentes estão distribuídas ao longo das camadas de tecido onde cada uma exerce uma função e produz substâncias importantes para a manutenção e recuperação da integridade do órgão (PIIPPONEN; LI; LANDÉN, 2020).

Além das células estromais, células do sistema imune inato e adaptativo também residem no tecido cutâneo, onde realizam a vigilância imunológica contra ameaças externas e participam da reparação de lesões. As células apresentadoras de antígeno (APC – do inglês *Antigen Presenting Cells*), que possuem atividade fagocitária, localizadas na epiderme são chamadas de células de Langerhans. Esses fagócitos estendem seus dendritos ao longo dos queratinócitos à procura de moléculas e células estranhas. Na derme, as células dendríticas (DCs – do inglês *Dendritic Cells*) dermais e os macrófagos são as sentinelas e iniciam a resposta imunológica ao reconhecerem patógenos invasores. As células T, por sua vez, residem no tecido cutâneo em forma de célula T de memória (T_M) e células T reguladoras (T_{REG}). Ambas possuem o papel de regulação do sistema imunológico. A T_M mantém a vigilância do ambiente tecidual e é responsável pela robustez da resposta imunológica. A T_{REG} controla a resposta imunológica e a tolerância contra os microrganismos comensais (NGUYEN; SOULIKA, 2019).

Por conferir uma barreira física, química e imunológica contra ameaças externas, a pele hospeda uma grande variedade de células e microrganismos que são indispensáveis para a manutenção e homeostase do tecido (SWANEY; KALAN, 2021). Em condições normais, há um equilíbrio entre essas estruturas e as substâncias produzidas por elas. No entanto, quando há um desequilíbrio e o processo de doença

se instala, essas mesmas células podem contribuir para a fisiopatologia e serem responsáveis pelas lesões teciduais que se seguem.

Os principais desencadeadores das lesões psoriáticas são traumas e infecções que induzem os queratinócitos a iniciarem uma resposta inflamatória. A partir daí, há uma produção e secreção de grande quantidade de citocinas e quimiocinas, cujo efeito biológico provoca o surgimento das principais comorbidades supracitadas associadas a essa doença (BOEHNCKE, 2018).

Quando ocorre uma lesão no tecido cutâneo o reconhecimento dos autoantígenos associados à PsO, LL-37 e ADAMTSL5, se dá pela molécula de MHC de Classe I e a secreção dessas pelos queratinócitos e melanócitos é responsável por ativar e estimular as DCs a secretarem IFN alfa (IFN-α), ativar as células T auxiliadoras (Th – do inglês *T helper cells*) ou do grupamento de diferenciação (CD – do inglês *Cluster of Differentiation*) 4 positivas ($CD4^+$) e T citotóxica (Tc – do inglês *T cytotoxic cells*) ou $CD8^+$, além de estimular o próprio queratinócito a secretar IFN-α e IFN beta (IFN-β) (ORSMOND et al., 2021). A participação dos queratinócitos na deflagração da PsO levanta um questionamento se a célula em si é a responsável pela fisiopatologia que se segue à sua ativação ou se ela é apenas um coadjuvante na resposta imunológica desregulada presente na doença (NI; LAI, 2020).

A secreção de IFN-α ativa e estimula a maturação das células dendríticas mielóides (mDC – do inglês *Myeloid Dendritic Cells*) ou células de Langerhan. Como APCs, a principal função dessas células é processar e apresentar antígenos às células T *naïve*, induzindo sua diferenciação e expansão clonal em células Th do tipo 1 (Th1), 17 (Th17) e 22 (Th22), principalmente (TIAN; LAI, 2022). A fase de manutenção da PsO, quando a doença se encontra ativa, é mediada pelas células T e suas citocinas. As células Th1 são produtoras e secretoras de citocinas como a Interleucina (IL)-2, TNF - alfa (TNF-α) e IFN-γ. As células Th17 secretam IL-6, IL-17, IL-21 e IL-22. Já a célula Th22 secreta a IL-22. Essa cascata de citocinas é responsável por ativar e recrutar células do sistema imune inato como os neutrófilos e os macrófagos inflamatórios do tipo 1 (M1) para o local da lesão, perpetuando a resposta inflamatória (GRÄN et al., 2020).

A retroalimentação é um mecanismo importante para a continuidade da resposta pró-inflamatória na PsO. As mDC são secretoras de IL-12 e IL-23, importantes para a diferenciação das células Th1 e Th17, respectivamente. Sua importância é tanta que um dos tratamentos envolve um anticorpo anti-IL-12/IL-23, o ustequinumabe. As

citocinas produzidas por Th1 ativam células M1 que, por sua vez, são produtoras de IL-1β. Ao lado da IL-23, a IL-1β induz a produção e secreção de IL-17, IL-21 e IL-22 (SINGH et al., 2021). A resposta Th1, por muitos anos, foi considerada a principal resposta inflamatória presente na PsO. No entanto, alguns estudos recentes revelaram que a participação das células Th17 bem como, sua principal citocina, a IL-17 desempenham uma função tão importante quanto na deflagração e conservação da resposta pró-inflamatória e no desenvolvimento das lesões psoriáticas (CATALDI et al., 2019; PUIG et al., 2022).

No microambiente das lesões, a IL-17 exerce um papel primordial para a fisiopatologia da doença. Essa citocina tem ação direta nos queratinócitos, induzindo sua proliferação anormal e acelerada, uma das causas do rearranjo e espessamento tecidual característicos da PsO (GIRONÉS PETIT et al., 2021). Dentre as seis isoformas da IL-17, a que atua majoritariamente na PsO e nos queratinócitos é a IL-17A, por meio de sua ligação ao seu receptor IL-17RA. A ativação desse complexo gera uma resposta capaz de inundar o tecido com componentes da resposta pró-inflamatória (TOLLENAERE et al., 2021; YAMANAKA; YAMAMOTO; HONDA, 2021). Os anticorpos monoclonais (mAbs – do inglês *Monoclonal Antibodies*) brodalumabe, secuquinumabe, ixekizumabe e bimekizumabe utilizados no tratamento da PsO são dirigidos contra as diversas isoformas da IL-17 e do receptor IL-17RA não só como tratamento da doença em si, mas também para a redução das comorbidades associadas (VIDAL et al., 2021). E por exercer uma função importante na diferenciação e proliferação das células Th17, a IL-23 também é alvo de tratamento com mAb. Além do ustequinumabe, outras opções disponíveis são o guselkumabe, rizankizumabe, tildrakizumabe e mirikizumabe O bloqueio do eixo IL-23/IL-17 vem demonstrando ser uma estratégia farmacológica para o tratamento da PsO, o que ratifica a posição das células Th17 e suas citocinas como atores principais na fisiopatologia desta doença (BUGAUT; ARACTINGI, 2021) (FIGURA 1).

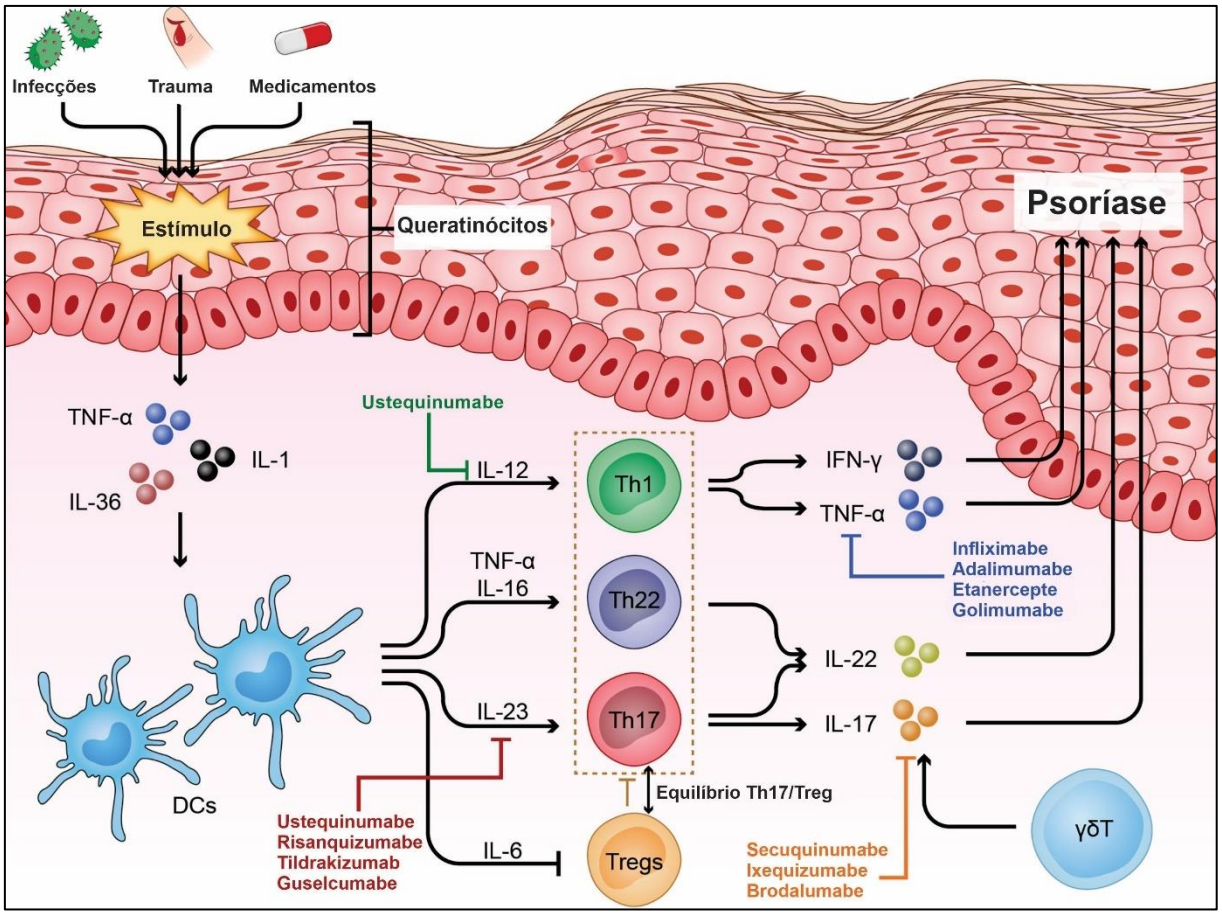


Figura 1 – Fisiopatologia da Psoríase. A psoríase é uma doença inflamatória crônica multifatorial. Estímulos como infecções cutâneas, traumas e uso de medicamentos podem induzir as células dendríticas a produzirem citocinas pró-inflamatórias como a IL-6, IL-12, IL-23 e a TNF-α. Essas citocinas, por sua vez, induzem a diferenciação das células T auxiliadoras em Th1, Th17 e Th22, principais células envolvidas na fisiopatologia da doença. As moléculas produzidas pelos linfócitos T estão envolvidos no desenvolvimento das lesões psoriáticas e, dessa forma, são alvos terapêuticos no tratamento da psoríase. **Legenda:** Células Dendríticas (DCs), Interleucinas (IL), Células T auxiliadora (Th), Fator de Necrose Tumoral alfa (TNF-α), Célula T regulatórias (Treg), Interferon-gama (IFN-γ), Células T gama-delta (γδT). **Fonte:** Adaptado de Hu e colaboradores (2021) (HU et al., 2021).

A estratégia de bloqueio da resposta Th17 através de sua citocina e seu receptor é direcionada por estudos que demonstraram que há um aumento nos níveis séricos de IL-17 (CATALDI et al., 2019; LAO et al., 2023) e aumento na expressão dessa citocina nas lesões psoriáticas (DIVYAPRIYA et al., 2021). E, igualmente importante, os receptores de IL-17 seguem a mesma tendência ao passo que estudos evidenciam o aumento da expressão desses receptores nas lesões causadas pela PsO (JOHANSEN et al., 2009) e sua associação com marcadores pró-inflamatórios da PsO (VAN BAARSEN et al., 2014). Além disso, o bloqueio do receptor de IL-17 está associado à uma evolução no quadro clínico de pacientes com PsO (TOMALIN et al., 2020). O caráter multifatorial da PsO e a importância da IL-17 para a sua fisiopatologia evidenciam a necessidade de se investigar como o fator genético

poderia influenciar na suscetibilidade e gravidade à PsO e na resposta de pacientes aos novos tratamentos desenvolvidos contra essas moléculas.

1.3 VARIANTES EM GENES DE CITOCINAS AVALIADOS NA PSORÍASE

Variação genética é qualquer alteração na sequência do genoma de um determinado indivíduo quando comparado ao genoma de referência. Essa variação pode ou não ter um significado clínico, dependendo do tipo de alteração e onde ocorreu no genótipo. A variação mais comum é a Variação de Nucleotídeo Único (SNV, do inglês *Single Nucleotide Variant*) onde há uma troca de um nucleotídeo por outro em uma determinado sequência de DNA (ZOU et al., 2020).

Outro termo que pode ser encontrado na literatura para essas alterações é o Polimorfismo de Nucleotídeo Único (SNP, do inglês *Single Nucleotide Polymorphism*). Apesar de serem utilizados como sinônimos, os termos não são intercambiáveis, uma vez que o polimorfismo ocorre quando a variante está presente em mais de 1% da população (KIM; MISRA, 2007). Sendo assim, para fins de padronização, o presente texto utiliza o termo SNV para as alterações genéticas estudadas na PsO.

Como dito anteriormente, o gene *HLACω6* é considerado um fator de risco para a PsO e essa associação já conhecida há alguns anos (TIILIKAINEN et al., 1980). Este gene está localizado na região do MHC, mais precisamente dentro do lócus de suscetibilidade à psoríase do tipo 1 (PSORS1 – do inglês *Psoriasis Susceptibility 1*) (NAIR et al., 2006). Um estudo conduzido em 2018, no Reino Unido por Dand e colaboradores, reuniu cerca de 1300 pacientes com PsO. Os pacientes positivos para o alelo *HLA-C*06:02* apresentaram uma boa resposta ao tratamento com ustequinumabe. No entanto, pacientes positivos para o alelo não respondiam bem ao tratamento com o adalimumabe (DAND et al., 2019). Os dados corroboram o fato de, apesar de multifatorial, o fator genético desempenha um papel importante na fisiopatologia da PsO.

Nos últimos anos, estudos sobre variantes genéticas na PsO concentraram-se, principalmente, nos genes codificadores das citocinas pró e anti-inflamatórias envolvidos no surgimento da PsO e suas comorbidades. Em 2013, Johnston e colaboradores recrutaram 49 indivíduos, sendo 25 controles saudáveis e 24 pacientes com PsO e verificaram a presença dos alelos de risco para os genes *IL12A*, *IL12B*, *IL23A* e *IL1B* e quantificaram os níveis séricos das citocinas IL-12, IL-22, IL-23, IL-17

e IFN-γ. Os resultados demonstraram que a presença do alelo de risco para a *IL12B*, definido pela presença do alelo G na variante rs6887695 e do alelo A na variante rs3212227, aumenta os níveis séricos de IL-12 e reduz o de IL-23. O aumento da IL-12 estimula a produção de IFN-γ, polarizando a resposta imunológica para Th1 em comparação à resposta Th17 (JOHNSTON et al., 2013).

No mesmo ano, um total de 575 pacientes Chineses diagnosticados com PsO foram recrutados e genotipados para o SNV rs6887695 da IL-12β. Os pacientes foram divididos em pediátricos ou adultos, dependendo da idade em que houve o diagnóstico da doença e, posteriormente, estratificados em PsO em placa ou outro tipo de PsO. Os resultados demonstraram que a presença do alelo de risco para o SNV rs688795 está associado ao surgimento da PsO em placa, mas não influencia no surgimento precoce da doença (WU et al., 2013). A associação entre a *IL12B* rs6887695 e a PsO também foi encontrada por Eiris e colaboradores, em 2014, demonstrando que as variações genéticas na PsO são importantes no surgimento da doença (EIRÍS et al., 2014).

Outras citocinas pró-inflamatórias como a IL-6 e o TNF-α também são alvos de estudo, dada a natureza da resposta imunológica observada durante o curso da doença (CATALDI et al., 2019). Em uma meta-análise, realizada pelo grupo de pesquisa de Zhu e colaboradores (2013), foram reunidos 26 artigos científicos relacionados aos SNVs *TNFA* -308 A>G (rs1800629), -238 A>G (rs361525), -857T>C (rs1799724), -1031C>T (rs1799964), -863A>C (rs1800630) e -488A>G (rs80267659) e suas associações com o desenvolvimento de PsO em placa e/ou PsA. Os dados demonstraram que a presença de variantes no *TNFA* -238A>G (rs361525) e TNFα -308A>G (rs1800629) está associada com a suscetibilidade à PsO em placa ou PsA. Esse achado levanta o questionamento por parte dos autores se a terapia com o antagonista de TNF-α pode ser eficiente para esses pacientes (ZHU et al., 2013a).

Outra meta-análise, realizada por Zhuang e colaboradores (2013), também reuniu dados da literatura sobre variantes genéticas do *TNFA*. Foram 16 estudos sobre o SNV *TNFA* -308 G>A (rs1800629) e 14 sobre o SNV *TNFA* -238 G>A (rs361525). Apesar dos achados do estudo anterior, essa meta-análise demonstrou que a variante genética do SNV *TNFA* -308 G>A (rs1800629) está associada ao risco reduzido de PsO, onde a presença do alelo A é um efeito protetor, enquanto o SNV *TNFA* -238 G>A (rs361525) está associado ao risco aumentado de PsO, onde a presença do alelo A, nesse SNV, é o fator de risco (ZHUANG et al., 2013). Os dados conflitantes

demonstraram que muito ainda precisa ser estudado para que a etiologia e a fisiopatologia da PsO sejam melhor compreendidas.

Dentro do grupo de citocinas pró-inflamatórias do sistema imune inato, recentemente, o gene *IL36G*, que codifica a citocina IL-36γ, mostrou estar associado à PsO. Moreira e colaboradores (2023) realizaram a genotipagem para o *IL36G* C>T (rs13392494) e A>G (rs7584409) em 154 pacientes brasileiros com PsO comparando-os com indivíduos controles. Os resultados demonstraram que a presença do alelo G para o rs7584409 estava associado à uma proteção de quase 50% ao desenvolvimento de PsO. No entanto, o mesmo alelo mostrou estar associado à PsO moderada e ao desenvolvimento de PsA naqueles pacientes já diagnosticados com PsO. Por sua vez, o rs13392494 não apresentou associação com a suscetibilidade à PsO (MOREIRA et al., 2023).

Outro eixo importante para a fisiopatologia da PsO está baseado na produção de citocinas pró-inflamatórias pelas células Th17. Estudos voltados para os efeitos dessas citocinas são menos numerosos na literatura, se comparados às citocinas Th1 e as citocinas pró-inflamatórias da imunidade inata (LOURES et al., 2019; ZHU et al., 2013b). No entanto, são igualmente importantes, uma vez que, como mencionado anteriormente, a PsO é multifatorial, inclusive na forma como o sistema imunológico atua no percurso na doença (DE ALCANTARA; REICHE; SIMÃO, 2021).

Com o desenvolvimento de novas terapias direcionadas a interromper a resposta mediada por Th17, se faz necessário entender como suas variantes genéticas podem influenciar na fisiopatologia da PsO e no manejo farmacoterapêutico. Os genes *IL17A* e *IL17RA* são, normalmente, os escolhidos para a genotipagem (KUTWIN et al., 2021). O gene *IL17A* está localizado na segunda sub-banda, da segunda banda, da primeira região do braço curto do cromossomo 6 (6p12.2) entre as posições 52186375 e 52190638. O gene *IL17RA* está localizado na primeira sub-banda, da primeira banda, da primeira região do braço longo do cromossomo 22 (22q11.1) entre as posições 17085000 e 17115693 (FIGURA 2), responsável por codificar a proteína de membrana IL-17RA que se liga à IL-17A e IL-17F, gerando uma cascata de resposta inflamatória (GU; WU; LI, 2013).

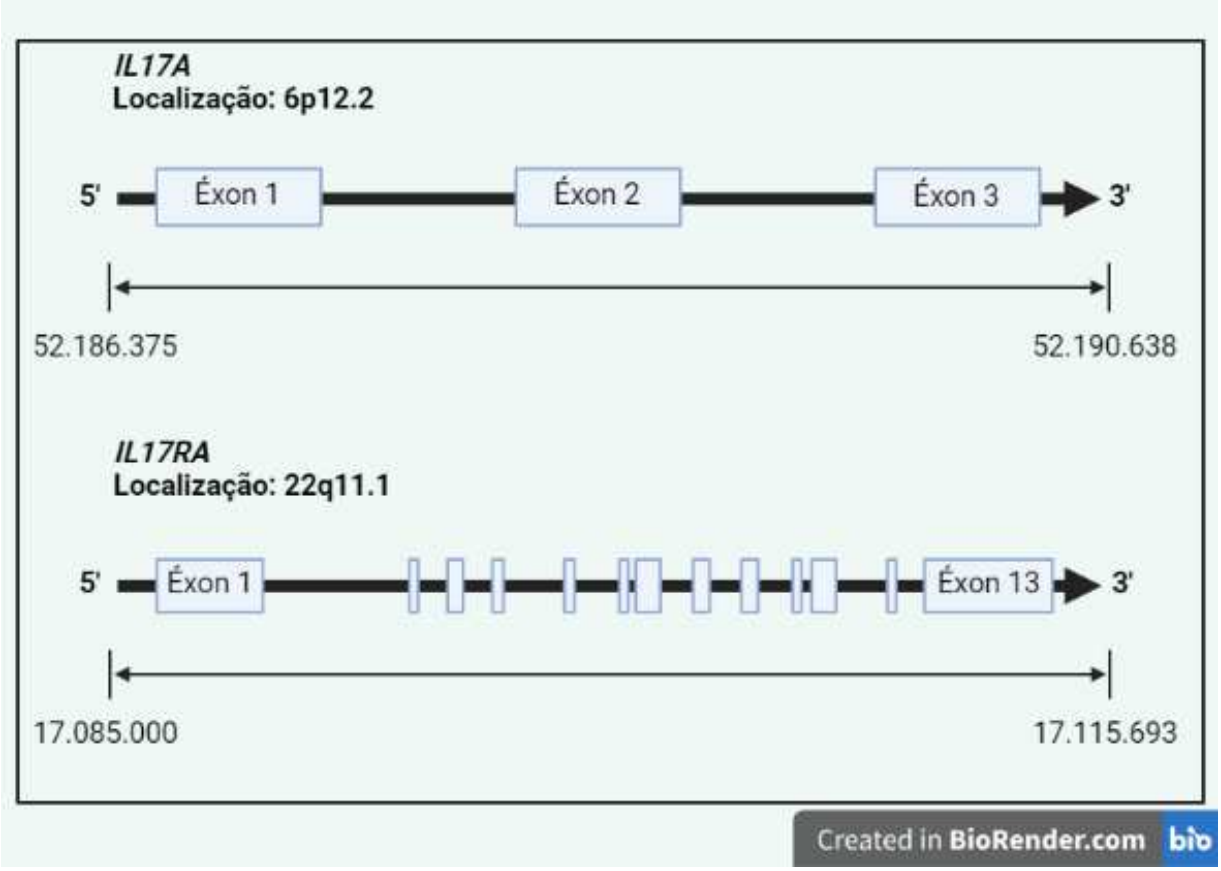


Figura 2 – Estrutura dos genes *IL17A* e *IL17RA*. O gene que codifica a citocina IL-17A está localizado no braço curto do cromossomo 6 e possui 3 regiões codificantes (éxons). O gene que codifica o receptor de IL-17A está localizado no braço longo do cromossomo 22 e possui 13 regiões codificantes. **Fonte:** Adaptado de Aghaei e colaboradores (2020) (AGHAEI et al., 2020).

Em 2012, Catonoso e colaboradores realizaram a genotipagem em uma população Italiana de 118 pacientes com PsO e 254 controles saudáveis para um total de 40 SNVs, entre eles: 22 para o gene *IL23R*, 3 para o gene *IL17A*, 1 para gene *IL23A* e 14 para o gene *IL17RA*. Dos 40 SNVs analisados, apenas um de IL-23R (rs12041432) demonstrou uma associação entre o modelo recessivo, genótipo GG, e a manifestação de sintomas articulares. Os resultados obtidos são opostos a outros estudos sugeridos pelos autores, o que levanta o questionamento sobre a influência de fatores ambientais na suscetibilidade de uma população ao desenvolvimento da PsO (CATANOSO et al., 2013).

Objetivando esclarecer a importância das citocinas Th17, o grupo de Batalla e colaboradores fizeram a genotipagem para os SNVs rs4819554 (G>A) e rs879577 (C>T) do gene *IL17RA* em 242 pacientes com PsO de diversas regiões da Espanha. Todos os pacientes faziam uso de uma terapia anti-TNF, 105 utilizavam o adalimumabe, 91 utilizavam o etanercepte e 42, o infliximabe. Os autores encontraram

uma associação entre o SNV rs4819554 (G>A) e a resposta frente ao tratamento com anti-TNF. Pacientes que não respondiam ao tratamento até a 12ª semana, com genótipo GA, se tornaram responsivos na 24ª semana. Já os pacientes com genótipo AA eram responsivos na 12ª semana e permaneceram na 24ª semana (BATALLA et al., 2018).

De forma geral, o maior entendimento sobre o papel das citocinas na PsO propiciará a descoberta de tratamentos mais eficazes contra a doença, levando em consideração, inclusive o perfil genético dos pacientes. Um estudo realizado em 2017 na Coréia do Sul com 208 pacientes com PsO e 266 controles analisou SNV em 12 genes, entre eles, *IL17A*, *IL17F* e *IL17RA*. Os resultados demonstraram que há uma suscetibilidade ao desenvolvimento de PsO em pacientes em homozigose recessiva, genótipo CC, para o SNV da *IL17F* T>C (rs763780) (KIM et al., 2017). Resultados como esse, apesar de obtidos em uma população com baixa variedade étnica, auxilia no desenvolvimento de tratamentos mais eficazes, à medida que o mecanismo da doença se torna mais evidente.

Como complemento, o mesmo grupo de pesquisa recrutou 116 pacientes com PsO e 97 controles saudáveis. A genotipagem foi realizada para o SNVs rs763780 (T>C) do *IL17F* e confirmada a suscetibilidade a PsO para a presença do alelo C. Além disso, foram quantificadas 14 citocinas associadas à fisiopatologia da doença. Os resultados demonstraram que os pacientes heterozigotos e homozigotos para o alelo C tinham níveis séricos de IL-17F mais elevados em comparação aqueles que eram homozigotos para o alelo T, demonstrando que as citocinas Th17, nessa população são importantes na doença e, possivelmente, no tratamento (CHOI et al., 2019).

Em contraposição a esse estudo, Kaur e colaboradores (2018) encontraram que a presença dos genótipos TC e TT para o SNV rs763780 (T>C) do gene *IL17F* contribui com a patogenicidade da PsO. Além disso, os genótipos GT e TT para o SNV rs10484879 (G>T) do gene *IL17A* também estão associados ao desenvolvimento da doença. É importante ressaltar que esse estudo foi realizado em 166 pacientes com PsO e 150 controles saudáveis da população indiana (KAUR et al., 2018). A população indiana se assemelha, no que diz respeito à variedade, à brasileira em questões de miscigenação cultural e étnica. Resultados obtidos nessas populações dificilmente encontrarão correlação em população mais homogêneas geneticamente, como a população coreana do estudo citado acima.

O mesmo SNV do *IL17F* rs763780 (T>C) e o SNV rs2275913 (G>A) do *IL17A* foram avaliados na população turca, em um estudo caso-controle que reuniu 83 pacientes com PsO, recebendo tratamento com diversos agentes biológicos, e 69 controles saudáveis. Não houve correlação entre nenhum SNV e o desenvolvimento da doença, demonstrando mais um dado contraditório com relação ao SNV rs763780. No entanto, os resultados obtidos encontraram que o SNV rs275913 pode estar associado à duração da doença e maior responsividade à monoterapia convencional (OZKOL et al., 2021).

Diante de diversos dados contraditórios com relação ao papel das variantes genéticas da IL-17 na PsO, Villalpando e colaboradores (2021) realizaram uma meta-análise para avaliar a associação entre as variações gênicas do *IL17A*, *IL17F* e *IL17RA* encontradas em diversos estudos sobre PsO. Foram encontrados 221 estudos ao total, mas apenas 15 foram elegíveis para realizar a meta-análise. Apenas o SNV para o *IL17F* T>C rs763780 obteve um resultado significativo tanto para a predisposição ao desenvolvimento de PsO quanto para a manifestação da artrite psoriática (VILLALPANDO-VARGAS et al., 2021). Essa variante foi a que obteve mais resultados contraditórios no estudo de Populações, o que demonstra que ainda é necessária uma investigação mais aprofundada de sua associação com a fisiopatologia da PsO.

Apesar da PsO ser uma doença predominantemente inflamatória, as citocinas anti-inflamatórias também exercem uma função importante na fisiopatologia dessa doença (CATALDI et al., 2019). Alguns estudos sobre variantes genéticas buscam entender como a atuação dessas moléculas influenciam na manifestação da doença, seja na gravidade, na duração ou no tipo de PsO desenvolvida pelos pacientes.

Em 2012, Lee e colaboradores publicaram uma meta-análise sobre variantes genéticas da citocina anti-inflamatória IL-10 em pacientes psoriáticos. Dos estudos encontrados em base de dados, oito foram selecionados para a meta-análise, totalizando aproximadamente 1000 pacientes com PsO e 1200 controles, dentre eles, europeus, asiáticos e árabes. As variantes genéticas avaliadas foram *IL10* -1082 G>A (rs1800896), -592 C>A (1800872) e -819 C>T (1800871). Os resultados sugeriram que a variação genética no *IL10* -1082 G>A (rs1800896) confere uma maior suscetibilidade à PsO em pacientes asiáticos. No entanto, os autores ressaltam que devido a um número reduzido de estudos elegíveis para a meta-análise, a

interpretação do resultado precisa ser feita com cautela e um maior aprofundamento sobre o papel da IL-10 na PsO deve ser realizado (LEE et al., 2012).

Em concordância com esse resultado, Karam e colaboradores (2014) recrutaram 110 pacientes com PsO em placa e 120 controles saudáveis e dosaram IL-10 e TNF no soro desses indivíduos, bem como a análise das variantes genéticas envolvendo essas moléculas, *IL10* -1082 G>A (rs1800896) e *TNFA* -308A>G (rs1800629), respectivamente. Com relação aos níveis séricos de citocina, como esperado, a IL-10 estava reduzida e o TNF-α aumentado em pacientes com PsO quando comparados ao grupo controle. Com relação à genotipagem do *IL10* -1082 G>A (rs1800896), os pacientes com PsO tinham mais o alelo G e, consequentemente, frequência maior no genótipo GG e GA quando comparados aos controles. No entanto, os níveis de IL-10 eram maiores entre aqueles que tinham o genótipo GG. Dessa forma, os autores levantaram a questão sobre verdadeira influência dessa variante genética na fisiopatologia da PsO. Com relação ao *TNFA* -308A>G (rs1800629), o alelo G e o genótipo GG também foram encontrados com maior frequência em pacientes com PsO quando comparados ao grupo controle e, assim como na IL-10, os níveis séricos de TNF-α eram menores nesse alelo. Os autores baseiam esse resultado contraditório do Desequilíbrio de Ligação (LD – do inglês *Linkage Disequilibrium*) que ocorre nos alelos ao longo do MHC. Os autores sugerem que o número amostral reduzido pode ter afetado o poder estatístico dos resultados encontrados por eles e que mais estudos deverão ser realizados para analisar a influência das variações genéticas e dos níveis séricos de citocinas em pacientes com PsO (KARAM; ZIDAN; KHATER, 2014).

Além da IL-10, outras citocinas anti-inflamatórias como a IL-4 e o Fator de Crescimento Transformador Beta (TGF-β, do inglês - *Transforming growth factor beta*), além do gene regulador da resposta imunológica, *FOXP3* (do inglês – *Forkhead box 3*), também foram alvos de estudo em pacientes com PsO. Em 2017, em um estudo conduzido na Índia por Indhumathi e colaboradores, cerca de 360 pacientes com PsO e 360 controles saudáveis foram recrutados e submetidos a análise de variante genética para *IL4* (rs2243250), *IL10* (rs1800871 e rs1800896) e *FOXP3* (rs3761548), além da dosagem sérica de IL-4 e IL-10. Os resultados demonstraram que os genótipos CT+TT do *IL4* estavam associados à níveis séricos mais elevados de IL-4 quando comparados ao genótipo de maior frequência CC. Além disso, o alelo menos frequente C conferia proteção ao desenvolvimento de PsO. Para a IL-10, a variante genética rs1800871 foi observada como um fator de risco para a PsO na presença do

genótipo CC, em contrapartida, a rs1800896 não obteve resultados significativos para a população estudada. Por sua vez, a variante *FOXP3* (rs3761548) não exibiu uma associação com a PsO (INDHUMATHI et al., 2017).

Em 2018, no Egito, setenta pacientes de PsO e 100 controles saudáveis foram incluídos no estudo de El-hadidi e colaboradores e genotipados para a variante genética no códon 10 do *TGFB1* (T869C). Os resultados demonstraram que a variação genética do *TGFB1* está associada à suscetibilidade a PsO, onde o genótipo menos frequente TT está associado à um risco 3 vezes maior de desenvolver psoríase, no entanto, o genótipo TC não demonstrou essa associação. Ademais, o genótipo TT esteve mais frequente em pacientes com um histórico positivo de PsO na família. Não houve, nesse caso, a dosagem sérica de TGF-β1 para verificar se os resultados da genotipagem refletem nos níveis sanguíneos dessa citocina (ALHADIDI et al., 2018). Complementando esses achados, em 2020, um estudo conduzido por Ahmed e colaboradores na população iraquiana recrutou 100 pacientes com PsO em placa e 50 controles saudáveis para a dosagem sérica de TGF-β1 e a genotipagem do códon 10 (rs1800470) e códon 25 (rs1800471). Os resultados demonstraram que o genótipo CC tanto para o códon 10, quanto para o 25, foi menos frequente no grupo de pacientes com PsO quando comparados aos genótipos TC+CC para o códon 10 e GG+GC para o códon 25 para o mesmo grupo. No entanto, não houve associação entre os genótipos dos pacientes com os níveis de TGF-β1, apesar dessa citocina estar em menores níveis plasmáticos em pacientes com PsO se comparados aos controles (AHMED et al., 2020).

Por ser uma doença multifatorial, os achados com relação às variantes genéticas nem sempre demonstram um envolvimento direto na fisiopatologia da PsO. Além disso, as diferenças étnicas e culturais das populações estudadas refletem nos resultados encontrados nos estudos supracitados e explicam, parcialmente, os conflitos apresentados na expressão dos genes e no surgimento ou não da doença. Muitos estudos ainda precisam ser conduzidos a fim de encontrar um ponto de convergência entre as diversas populações. No entanto, o maior entendimento do desenvolvimento e da manifestação da PsO em determinada população auxilia em um manejo terapêutico mais direcionado e, consequentemente, mais eficiente.

1.4 TRATAMENTO DA PSORÍASE

A PsO não tem cura, dessa forma, como toda doença crônica, necessita de tratamento a longo prazo. Diversas terapias estão disponíveis, desde o tratamento tópico ao sistêmico, e a escolha pelo método mais adequado vai depender da apresentação clínica, do tamanho da área do corpo afetada, da gravidade dos sinais e sintomas e da adaptação do paciente ao tratamento. O objetivo é reduzir o PASI de 75 a 90% melhorando, assim, a qualidade de vida dos pacientes (RAHARJA; MAHIL; BARKER, 2021).

A primeira linha de tratamento para PsO leve a moderada é a terapia tópica. Diversos fármacos são utilizados com o objetivo de reduzir a reação inflamatória local e proteger o tecido cutâneo contra a perda de água, evitando o ressecamento, lesões mais graves e infecções por microrganismos patogênicos. Nesta categoria estão incluídos: antralina ou ditranol, um antraceno disponível em forma de creme, óleo ou pasta. O ditranol é aplicado durante a noite, mas seu uso enfrenta resistência porque tinge, temporariamente, a pele em um tom castanho; os inibidores de calcineurina, como o tacrolimo; os retinóides, como a vitamina A; os análogos da vitamina D, como o calcitriol; o fluorouracil, um quimioterápico antimetabólico que diminui a proliferação epidérmica; e os corticosteroides, considerados padrão ouro até o início do uso do metotrexato, caso seja necessário (RAMANUNNY et al., 2019).

A segunda linha de tratamento inclui a fototerapia e os agentes sistêmicos convencionais. A radiação ultravioleta (UV) inibe a síntese de DNA e reduz a proliferação dos queratinócitos. Normalmente, o tratamento é realizado em associação a um medicamento que aumenta a sensibilidade da pele aos raios UV. Esse procedimento recebe o nome de Psoraleno e raios ultravioleta A (PUVA – do inglês *Psoralen plus ultraviolet A*). A terapia com Faixas Estreitas de UVB (NB-UVB – do inglês *Narrow-band Ultraviolet B*) também é utilizada em pacientes com PsO; no entanto, não é necessário o uso de nenhum medicamento antes do procedimento, o que reduz os efeitos adversos (KEMÉNY; VARGA; NOVAK, 2019). Paralelo a isso, a exposição à luz solar também é recomendada, como uma intervenção não farmacológica. A produção de vitamina D, durante a exposição solar, inibe a secreção de citocinas inflamatórias e induz a produção da IL-10 (KECHICHIAN; EZZEDINE, 2018).

A terapia oral é realizada com os agentes sistêmicos convencionais, como o metotrexato, ciclosporina e acitretina. O metotrexato é um antimetabólito, inibidor da síntese de DNA e considerado o padrão ouro para o tratamento de PsO, mas seu uso

precisa ser monitorado de perto, devido seu potencial nefrotóxico e hepatotóxico. A ciclosporina é um imunossupressor, inibidor da calcineurina e pode ser utilizada; no entanto, seus efeitos adversos e as taxas de recaída após a cessão da terapia, limitam seu uso. A acitretina é um retinóide derivado da vitamina A e devido a suas propriedades fotossensibilizantes também podem estar associados à terapia com PUVA. No entanto, como é teratogênica, seu uso em mulheres é limitado (TOKUYAMA; MABUCHI, 2020).

A última linha de tratamento para a PsO é a terapia com mAbs desenvolvidos através da tecnologia do DNA recombinante. Diversos agentes biológicos estão disponíveis na indústria farmacêutica (DAVE; ALKESWANI, 2021). A escolha de um deles vai depender do histórico anterior de tratamento do paciente e das manifestações clínicas da doença. Os mAbs têm como alvo citocinas e células que participam da fisiopatologia da PsO, são eles: o etanercepte e o adalimumabe, inibidores da TNF-α; o guselkumabe, rizanquinumabe e mirikizumabe são inibidores da IL-23; o tildraquizumabe se liga seletivamente à porção p19 da IL-23 e inibe sua ligação ao receptor; o secuquinumabe e o ixekizumabe são inibidores da IL-17A; o bimekizumabe inibe as citocinas IL-17A e IL-17F; o brodalumabe é um inibidor do receptor de IL-17, dessa forma, inibe a sua ligação com a citocina; e o ustequinumabe, por sua vez, tem como alvo a unidade p40 das citocinas IL-12/IL-23 (RØNHOLT; IVERSEN, 2017).

Portanto, o tratamento da PsO busca reduzir suas manifestações clínicas e aumentar a qualidade de vida do paciente. O conhecimento mais aprofundado da fisiopatologia e de como as variantes genéticas modulam o desenvolvimento e o curso da PsO auxiliam na escolha do medicamento e no desenvolvimento de fármacos cada vez mais específicos e eficazes para o manejo terapêutico dessa doença.

2 JUSTIFICATIVA

A fisiopatologia da PsO está associada à uma reação pró-inflamatória mediada, principalmente, pelas células Th1. No entanto, sabe-se que as células Th17 desempenham um papel importante no surgimento e manutenção da doença. Os estudos disponíveis na literatura sobre a atuação das células Th17 estão majoritariamente focados em suas citocinas e pouco se sabe sobre os receptores dessas substâncias e sua relevância na PsO.

Com o avanço dos métodos de biologia molecular, se faz necessário aprofundar os conhecimentos sobre os componentes genéticos que influenciam na PsO e as informações sobre os receptores de IL-17, quando presentes, se mostram conflitantes. Além de escassos, os estudos sobre esses receptores foram realizados em populações europeias e asiáticas, cuja homogeneidade genética e cultural é distinta da população brasileira. Além disso, não há dados na literatura sobre os estudos de variantes genéticas dos receptores de IL-17 em pacientes com PsO em pacientes brasileiros.

Simultaneamente, nosso grupo de pesquisa tem realizado estudos em variantes genéticas na PsO (MOREIRA et al., 2023), bem como em outras doenças autoimunes, como IBD (GONÇALVES et al., 2021; INOUE et al., 2022) e esclerose múltipla (FLAUZINO et al., 2019). A escolha das variantes genéticas T>C (rs2241043), A>G (rs2241049) e G>A (rs6518661) do gene *IL17RA* foram pautadas nos estudos em andamento e na importância do eixo de resposta Th17 já verificado por resultados prévios (CATALDI et al., 2019) e por revisões bibliográficas conduzidos por nosso grupo de pesquisa (DE ALCANTARA; REICHE; SIMÃO, 2021).

É importante ressaltar que o estudo sobre as variantes genéticas abrem um leque de oportunidades para o desenvolvimento de novos fármacos contra potenciais novos alvos terapêuticos e possibilitam um entendimento maior sobre o manejo farmacoterapêutico mais adequado a cada paciente levando em consideração fatores genéticos individuais.

3 OBJETIVOS

3.1. OBJETIVO GERAL

Realizar uma revisão da literatura de variantes genéticas na PsO e avaliar a associação entre as variantes genéticas T>C (rs2241043), A>G (rs2241049) e G>A (rs6518661) do gene *IL17RA* e a suscetibilidade e gravidade da PsO.

3.2. OBJETIVOS ESPECÍFICOS

- Comparar a frequência das variantes genéticas do gene *IL17RA* em pacientes com PsO e indivíduos controle;
- Avaliar a associação das variantes genéticas do gene *IL17RA* e a suscetibilidade de desenvolver PsO;
- Avaliar a associação das variantes genéticas do gene *IL17RA* e a gravidade da doença em pacientes diagnosticados com PsO.
- Comparar a frequência de haplótipos das variantes genéticas do gene *IL17RA* em pacientes com PsO e indivíduos controle.
- Avaliar a associação dos haplótipos das variantes genéticas do gene *IL17RA* e a susceptibilidade de desenvolvimento de PsO.

4 SUJEITOS E MÉTODOS

4.1. Delineamento do Estudo e Aspectos Éticos

Este é um estudo caso-controle que incluiu 308 participantes de ambos os sexos, com idade entre 18 e 70 anos, sendo 154 pacientes com diagnósticos de PsO (148 com PsO em placa, 1 PsO pustular, 4 PsO palmoplantar e 1 PsO eritrodérmica) atendidos no Ambulatório de Dermatologia do Ambulatório de Especialidades do Hospital Universitário (AEHU) da Universidade Estadual de Londrina (UEL) e 154 indivíduos saudáveis (grupo controle) doadores de sangue no Hemocentro Regional de Londrina. Os critérios de exclusão foram o paciente apresentar doenças tireoidianas, renais, adrenais, hepáticas, gastrointestinais, infecciosas, oncológicas e outras doenças autoimunes.

O diagnóstico de PsO foi realizado por um médico dermatologista de acordo com os critérios elaborados pela Sociedade Brasileira de Dermatologia (SBD) em 2012 (ROMITI; CARVALHO; DUARTE, 2021). O PASI (ANEXO A) foi utilizado para determinar a gravidade da doença (FREDRIKSSON; PETTERSSON, 1978). O diagnóstico de artrite psoriática foi realizado levando em consideração os critérios para a classificação de artrite psoriática (CASPAR – do inglês *Classification Criteria of Psoriatic Arthritis*) (RITCHLIN; COLBERT; GLADMAN, 2017).

A realização dessa pesquisa foi aprovada pelo Comitê de Ética em Pesquisa Envolvendo Seres Humanos da UEL, conforme o número CAAE: 37420820.0.0000.5231, Número do Parecer: 4.304.205 (ANEXO B). A pesquisa seguiu as normas de boas práticas clínicas e foi conduzida de acordo com os princípios expressos na Declaração de Helsinki e suas alterações posteriores. O termo de consentimento livre e esclarecido (TCLE) foi obtido de todos os participantes que se voluntariaram para o estudo (APÊNDICE A).

4.2. Dados Clínicos, Epidemiológicos e Antropométricos

Os dados clínicos, epidemiológicos e antropométricos foram obtidos por médico dermatologista durante consulta clínica. As informações foram registradas em ficha de

avaliação (APÊNDICE B), previamente estabelecida pelos pesquisadores durante o delineamento do projeto.

4.3. Coleta de Sangue e Exames Bioquímicos

A coleta de sangue foi realizada por punção venosa utilizando tubos estéreis da marca BD Vacutainer Ultratouch (Becton, Dickinson and Company, Franklin Lakes, Nova Jersey, EUA) de coleta a vácuo sem e com anticoagulante. As amostras foram encaminhadas ao laboratório para o cadastro, processamento, separação e armazenamento. O plasma, *buffy coat* e sangue total foram aliquotados em microtubos de centrifugação, identificados e armazenados em *freezer* -80°C até a realização dos experimentos.

A resposta inflamatória aguda foi determinada pelos níveis de Proteína C Reativa (CRP – do inglês *C-Reactive Protein*), que foram determinados por ensaio turbidimétrico (C8000, Abbott, Architect Abbott Laboratories, Abbott Park, IL, EUA). A resposta inflamatória crônica foi determinada pelos níveis de ferritina, que foram obtidos por imunoensaio quimioluminescente de micropatículas (CMIA, Architect, Abbott Laboratory, Abbott Park, IL, EUA). Ambas as análises foram realizadas no soro dos pacientes obtido no dia da coleta de material biológico.

4.4. Extração do DNA

A extração do DNA genômico se deu com a utilização do kit de extração manual da BIOPUR MINI SPIN PLUS (Biometrix Diagnóstica Ltda, Curitiba, Paraná, Brasil) de acordo com o manual de instruções fornecido pelo fabricante, com algumas modificações, como o volume de *buffy coat* (200 ul) utilizado e a temperatura do tampão de eluição (70°C) a partir do sangue periférico. A quantificação e a pureza do DNA extraído foram realizadas utilizando o aparelho NanoDrop™ (Thermo Fisher Scientific, Viena, Austria) e concentração do material genético foi padronizada para 1,1 ng/ul em um volume final de 100 ul.

4.5. Análise das Variantes Genéticas do Gene *IL17RA*

As variantes genéticas do gene *IL17RA* foram genotipadas por reação em cadeia da polimerase (PCR – do inglês *Polymerase Chain Reaction*) em tempo real (qPCR – do inglês *quantitative* PCR) utilizando sondas TaqMan® (StepOne, Applied Biosystems by Life Technologies, Carlsbad, CA, USA) contendo *primers* específicos e sondas fluorescentes para determinação dos genótipos. Os níveis de fluorescência dos produtos de PCR foram avaliados pelo termociclador StepOne (Applied Biosystems, Foster City, CA, USA). Três SNVs da *IL17RA* foram genotipados: T>C rs2241043, A>G rs2241049 e G>A rs6518661.

4.6. Análise Estatística

O tamanho amostral de 154 indivíduos em cada grupo foi calculado como descrito em Gail e colaboradores (2019), assumindo um poder estatístico de 90% e intervalo de confiança (IC) de 95% e utilizando o software R (GAIL; HANEUSE, 2019). Dados categóricos foram avaliados pelo método do qui-quadrado (X^2) ou Exato de Fisher, conforme apropriado. Os resultados obtidos foram expressos em número absoluto (n) e porcentagem (%). Os dados contínuos foram analisados pelo teste paramétrico *t-Student* e o resultado expresso em média e mais ou menos o desvio padrão ou pelo teste não-paramétrico de Mann-Whitney e os resultados expressos em mediana e percentis (25-75%), de acordo com a distribuição dos dados obtidos.

A associação e frequência das variantes genéticas da *IL17RA* foram analisadas em modelos alélicos, dominante, codominante, recessivo e overdominante, como descrito por Horita e colaboradores (2015) (HORITA; KANEKO, 2015) utilizando a ferramenta online de análise de SNV, o SNPStats, disponível no endereço eletrônico https://www.snpstats.net/start.htm (SOLÉ et al., 2006). A análise da regressão logística binária foi realizada para avaliar o efeito das SNVs nos grupos estudados e foi avaliada em razão de chances (OR – do inglês *Odds Ratio*) e o IC considerado foi de 95%.

Os testes foram considerados estatisticamente significativos quando $p<0,05$. As análises estatísticas foram realizadas utilizando o SPSS IBM versão 24 para plataforma Windows (SPSS Inc., Chicado, IL, EUA).

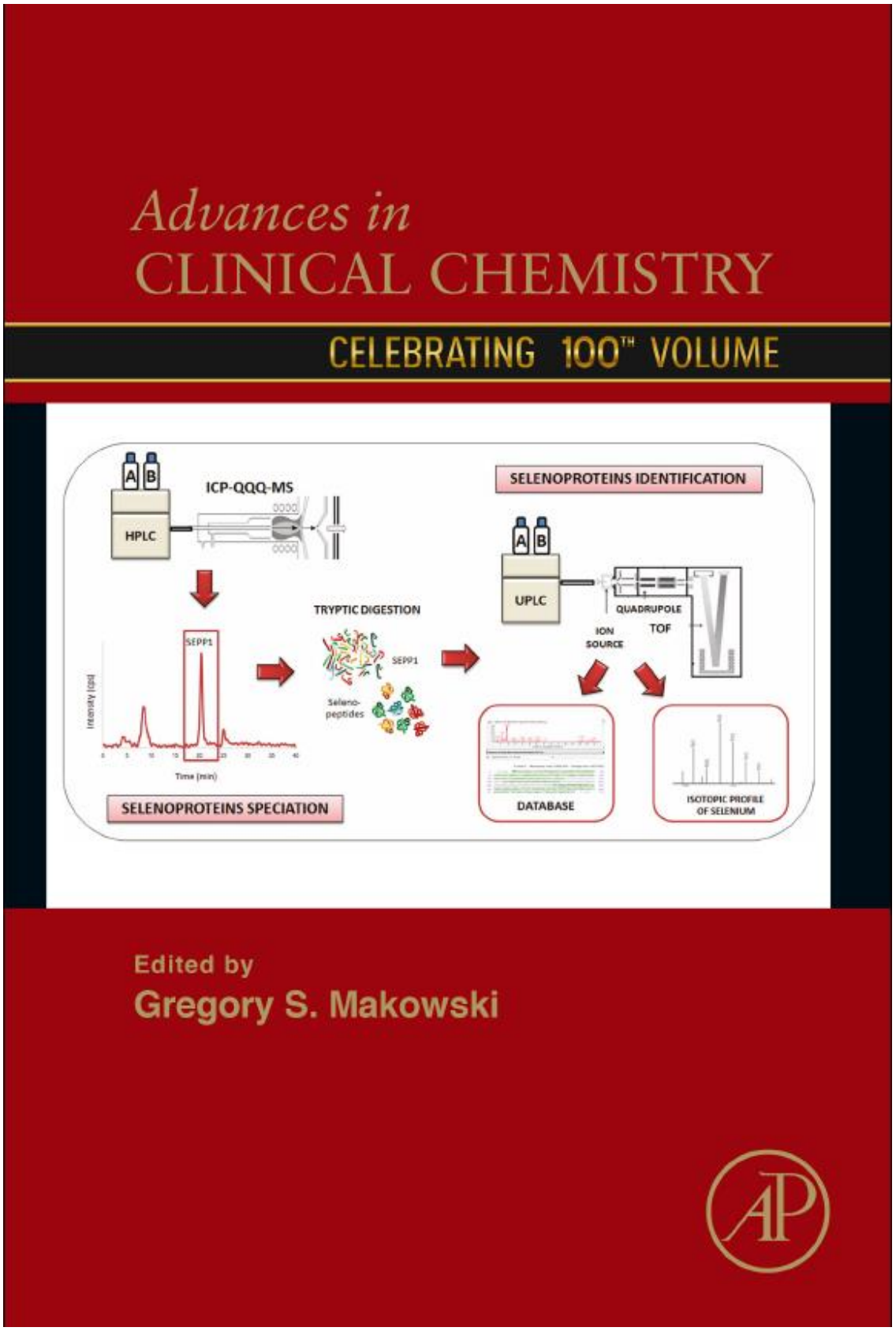
5 RESULTADOS E DISCUSSÕES

Este trabalho deu origem à um capítulo de livro e à um artigo:

5.1. "CYTOKINES IN PSORIASIS" – publicado na revista Advances in Clinical Chemistry.

5.2. "***IL17RA* GENETIC VARIANTS ARE ASSOCIATED WITH SUSCEPTIBILITY AND SEVERITY TO PSORIASIS IN BRAZILIAN PATIENTS."** – submetido à revista Molecular Immunology com fator de impacto 3,6.

5.1 CAPÍTULO DE LIVRO



CHAPTER FIVE

Cytokines in psoriasis

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Contents

Abstract

Psoriasis is chronic, immune-mediated, inflammatory disease with a multifactorial etiology that affects the skin tissue and causes the appearance of dry and scaly lesions of anywhere on the body. The study of the pathophysiology of psoriasis reveals a network of immune cells that, together with their cytokines, initiates a chronic inflammatory response. Previously attributed to T helper (Th)1 cytokines, currently the Th17 cytokine family is the major effector in the pathogenesis of psoriatic disease and strongly influences the inflammatory pattern established during the disease activity. In addition, the vast network of cells that orchestrates the pathophysiology makes psoriasis complex to study. Along with this, variations in genes that code the cytokines make psoriasis more clinically heterogeneous and present a challenge for the development of drugs that can be used in the treatment of the patients with this disease. Therefore, it is important to clarify the mechanisms by which the cytokines are involved in the pathophysiology of psoriasis and how this knowledge is translated to the medical practice.

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1. Introduction

Psoriasis is an immune-mediated disease that commits the skin and provokes a chronic inflammation of the tissue. The immunological cells and their cytokines are responsible for the presence of skin lesions and systemic effects [1]. The cutaneous tissue suffers a major influence on the disease outcome. Nevertheless, nails and joints can also be affected. The main clinical manifestations are red, dry and scaly lesions that may be followed by itching, pain and burning sensation [2].

Psoriasis vulgaris or in plaque is the most frequent form of the disease and affects, approximately, 90% of the diagnosed patients. However, there are other types of psoriasis, such as guttate, inverse, pustular and erythrodermic [3]. Psoriatic arthritis (PsA) is a recurrent comorbidity that can affect about 30% of patients with psoriasis [4]. The clinical features of PsA are bone erosion and cutaneous disease aggravation [5]. Despite the high frequency, about 15% of PsA cases are not properly diagnosed [6].

Dermatologists are responsible for the psoriasis diagnostic and, in most cases, it is based on clinical findings without the need of biopsy. Specialists adopt Psoriasis Area and Severity Index (PASI) as an assistance tool to evaluate the disease severity. The PASI calculation is based on the affected area and lesion characteristics. The higher the PASI, the greater the severity of the disease. By determination, patients with mild to moderate psoriasis have a PASI >12 and those with severe psoriasis have a PASI ≤ 12 [7].

The etiology of psoriasis is unknown, nevertheless, genetic and epigenetic factors can be strongly related to this disease [8,9]. Moreover, the inflammation pattern displayed by the patients demonstrates the important role of the immune system in the outcome of the disease [10]. In the United States, about 0.51% of the population is diagnosed with psoriasis and it affects men and women equally [11,12].

2. Pathophysiology

Psoriasis is a multifactorial disease that can be triggered by external stimuli, such as trauma, infection, burns and medicines [13]. Somehow, those factors activate the keratinocytes in the skin and induce them to produce cytokines, including tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-1β and IL-6. The cytokine function is to activate

and to recruit skin and blood immunological cells. The activation cascade that follows is extensive and involves the innate and adaptive cutaneous immune responses. Therefore, the hallmark of psoriasis is sustained inflammation that lead to uncontrolled keratinocyte proliferation and dysfunctional differentiation [14,15].

The myeloid dendritic cells (mDC) or Langerhans cells are the main cells that are activated during the pathogenesis of psoriasis. After their activation, the mDC target lymph node to promote the differentiation of naïve T helper cells (Th0) in T helper (Th) 1 and Th17 cells. Initially, the Th1 response was considered solely responsible for the chronic inflammation observed in psoriasis. Nevertheless, the involvement of Th17 is well reported in this disease [16]. Although Th22 is less mentioned, it also plays an important role as its cytokine, IL-22, induces keratinocyte hyperplasia and increases rate of cell turnover [17].

In addition to T lymphocyte cells, other blood cells are also activated and recruited to the cutaneous tissue in psoriasis. Neutrophils [18], plasmacytoid dendritic cells (pDC) [19], mast cells [20] and natural killer (NK) cells [21] enter into the tissue guided by keratinocyte cytokines [22,23]. The presence of different cells and their cytokines is responsible for the clinical manifestations of psoriasis and perpetuates the inflammation response in the local of the lesion (Fig. 1).

3. Pro-inflammatory cytokines

3.1 Innate cytokines

IL-1β is a pro-inflammatory cytokine often reported in human skin diseases [24]. Targeting this cytokine is a strategy for the treatment of skin inflammation in some diseases, such as atopic dermatitis, psoriasis and cutaneous lupus erythematosus [25]. Regarding the role of cytokines of the innate immune response in the pathophysiology of psoriasis, the available data are conflicting. The psoriatic skin demonstrates a high expression of IL-1β and a high level of this cytokine in the tissue [26–28]. Nevertheless, the effects of IL-1β seem to be confined to the cutaneous tissue as its serum levels obtained from psoriatic patients do not show a significant difference when compared with healthy individuals [29]. Interestingly, the relationship between IL-1β and the skin can be observed in treatment protocols. The administration of an IL-1β inhibitor by the cutaneous via attenuates the clinical features of some psoriasis subtypes [30]. Despite its local effect, the IL-1β plays an important role in psoriasis outset as a whole. Two genetic variants of *IL1β*, rs16944 and rs2853550, are

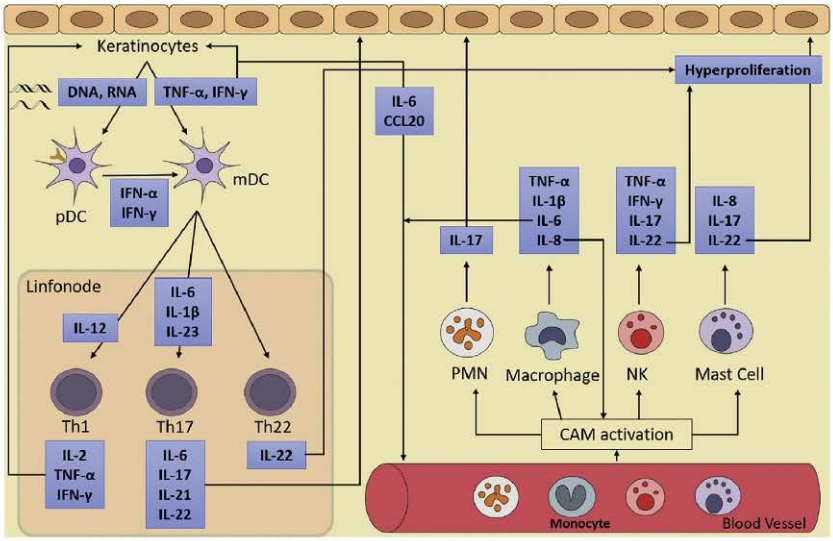

Fig. 1 Inflammatory response of the pathophysiology of psoriasis. Damage to the skin tissue causes the release of intracellular content, such as RNA and DNA, and stimulates keratinocytes to produce pro-inflammatory cytokines, such as TNF-α and IFN-γ. The secretion of these cytokines stimulates keratinocytes to produce IL-6 and CCL20 that activate cell adhesion molecules and attract immune cells from the blood vessel into the tissue. The intracellular content of keratinocytes is recognized by the membrane receptors present in pDC and stimulates them to produce IFN-α and IFN-γ which, together with TNF-α, activate mDC. The activated mDCs are directed to the lymph nodes where they stimulate the differentiation and proliferation of Th1 lymphocytes, in a microenvironment containing IL-12, Th17 lymphocytes, in a microenvironment containing IL-6, IL-1β and IL-22, and Th22. After differentiation, the lymphocytes go to the skin tissue and produce their pro-inflammatory cytokines, such as: IL-2, TNF-α, IFN-γ (Th1); IL-6, IL-17, IL-21 and IL-22 (Th17) e; IL-22 (Th22). The activation of cell adhesion molecules allows the arrival of cells from the innate immune system to the lesion site and the secretion of more cytokines that help propagate the inflammatory response, such as: neutrophils, IL-17 producers; macrophages, which produce IL-1β, IL-6, IL-8 and TNF-α; IL-17, IL-22, IFN-γ and TNF-α e producing NK cells; mast cells, which produce IL-8, IL-17 and IL-22. Legend: Interleukin (IL), Interferon– α / γ (IFN-α/γ), Tumor Necrosis Factor - alpha (TNF-α), T helper cell (Th), Polymorphonuclear Cells (PMN), Natural Killers Cells (NK), Myeloid Dendritic Cells (mDC), Plasmacytoid Dendritic Cells (pDC); Chemokine C—C Ligand 20 (CCL20).

associated with late onset of psoriasis that occurs in patients who are over than 40 years old and it is a mild manifestation of the disease [31].

As an immune-mediated disease, it is expected to find other cytokines beyond IL-1β in the pathophysiology of psoriasis. TNF-α and IL-6 serum levels are often elevated in patients with psoriasis [29,32] and TNF-α has a positive correlation with PASI [32]. The association between the latter

cytokines and psoriasis calls the attention to the management of the patients with cytokine inhibitors that are one of the strategies in psoriasis therapy. The administration of a drug that aims to TNF-α blockage is associated with the PASI improvement and a down-regulation in the expression of Th1 and Th17 related genes. Furthermore, the imbalance between pro-inflammatory and anti-inflammatory response is restored, once the expression of Th2 cytokines is also regulated [33]. Along with that, the therapy with TNF-α inhibitors reduces the formation of platelet-lymphocyte complexes which, indirectly, means a reduction of cardiovascular risk. The formation of such complexes is associated with endothelium dysfunction and further atherosclerosis development [34].

Conversely, the treatment with TNF-α inhibitors can lead to the onset of psoriasis in patients with other inflammatory diseases. The therapy with adalimumab in Behçet's disease gives rise to lesions similar to palmoplantar psoriasis by mechanisms still unknown. In this case, concomitant azathioprine treatment allows psoriasis to be treated without adalimumab withdrawal [35]. The therapy with infliximab in Crohn's disease (CD) paradoxical leads to the development of psoriasis in patients with no family history. The infliximab change sometimes, is necessary, although, the drug is effective in keeping CD patients in remission [36]. In pediatric patients, the long-term exposure to TNF-α inhibitors increases the risk of psoriasis, although there is a limited data about this age range [37]. Undoubtedly, TNF-α is an important cytokine in the pathogenesis of psoriasis. While its blockage is used as a treatment, it can also give rise to the disease by itself. In any case, this cytokine may even predict susceptibility to psoriasis. The *TNFA* −238G > A, −380G > A and −857C > T genetic variants may identify an individual's predisposition to the development of psoriasis [38]. Although the genotyping analysis is not performed in routine laboratory tests, this information can help the diagnosis of the onset of this disease.

IL-6, in turn, does not present consistent data regarding its use as a target for the treatment of patients with psoriasis. Despite IL-6 is involved in the pathophysiology of psoriasis, IL-6 inhibitors do not alter the clinical condition of the patients and, in some cases, worsen the lesions [39]. Interestingly, in cases of pustular psoriasis, IL-6 plays an important role and the therapy with IL-6 inhibitors reduces the leukocyte infiltration and improves the clinical signs of the disease [40].

Another cytokine reported in psoriasis is interferon (IFN)-γ [41]. NK cells are the main IFN-γ-producing cells; nevertheless, it can be also produced by Th1 cells [42]. The data available about IFN-γ behavior in psoriasis pathogenesis are conflicting. Evidence suggests the presence of

elevated IFN-γ serum levels in psoriasis [43,44] and their association with the severity of the disease [45]. Curiously, NK cells have their cytotoxicity diminished in psoriasis vulgaris, as well as their cytokines [46], what might explain, in part, why the levels of the cytokines are always no significant in patients with this disease [47]. Along with that, IFN-γ has dichotomic role according to the producing cells. In guttate psoriasis, IFN-γ produced by $CD4^+$ T cells is important to the pathogenesis of the disease. By contrast, in plaque psoriasis, IFN-γ produced by $CD8^+$ T cells plays a role in the maintenance of psoriasis and leads to chronic inflammation [48]. In any case, IFN-γ proves to be an important inflammatory effector in the pathophysiology of psoriasis [49].

3.2 Th1 cytokines

IL-12 is responsible to promote the differentiation and proliferation of Th1 cells and, therefore, it is considered a pro-inflammatory cytokine [50]. In psoriasis, Th1 and Th17 profiles play an important role in the pathogenesis, hence, it is expected that their cytokines are in high levels in in serum sample of these patients [1]. In matter of fact, a Japanese study demonstrated increased IL-12 in patients with psoriasis [32] and the same result has been found in Brazilian [47] and in Mexican [51] population. The importance of IL-12 in psoriasis is corroborated when this cytokine is blocked by a specific inhibitor. The administration of anti-IL-12 decreases the number of T cells in the skin lesion and reduces the expression of IFN-γ. The shift toward a proinflammatory pattern improves the PASI in high responder patients. In addition, anti-IL-12 affects the production of IL-8 by the keratinocytes. Low IL-8 results in less activation of skin cells and less leukocyte infiltration in cutaneous tissue [52]. The effectiveness of anti-IL-12 can be seen in cases where this therapy replaces the standard therapies. In more severe cases, such as generalized pustular psoriasis, the treatment with anti-IL-12 is an option [53]. These results highlight the importance of IL-12 in the pathophysiology of psoriasis. Interestingly, am experimental study with mice demonstrated a protective role for IL-12 in the formation of psoriatic lesions. The knockout mice for the *IL12β* gene showed a reduction of Th1 cytokines, such as IFN-γ. In contrast, there was an increase in Th17 cytokines, as well as chemokines and the entry of neutrophils into the lesions. The absence of IL-12 worsened the severity of the lesions and, although it was evaluated in mice, the study raised questions about the blocking of IL-12 in humans [54].

Stimulated by IL-12, Th1 cells produce TNF-β, IFN-γ and IL-2 [55]. The same way as the other Th1 cytokines, IL-2 is reported to be increased in patients with psoriasis [56]. IL-2 is especially important in PsA, where it is possible to find high levels of the soluble form of its receptor (sIL-2R) and these levels are related to the severity of cutaneous involvement [57]. In addition, the serum levels of the cytokine by itself can be found in higher values in patients who developed joint comorbidity compared to those who did not, as well as healthy controls [58]. Despite the serum levels of IL-2 seem to be in agreement throughout the studies, the expression of the *IL2* gene offers different results, according to the studied population. The study of the *IL2* −330 G > T variant did not show any significant difference between the frequency of genotypes when comparing patients and healthy controls. Despite this, the less frequent T allele was more frequent among in the patients with severe psoriasis [59]. In turn, the study of the same gene variant in the Turkish population has shown different results. The frequency of the GT genotype was lower in patients with psoriasis compared to controls, while the frequency of the GG genotype was lower and the TT genotype was higher in patients with PsA compared to those who did not develop the comorbidity. The frequency of the TT genotype was higher in patients with mild psoriasis when compared to those with moderate to severe disease, contrary to what was observed in the Indian population [60]. The conflicting results of these studies point to the need for further researches to clarify the importance of IL-2 in the pathogenesis of psoriasis.

3.3 Th17 cytokines

IL-23 is part of the IL-12 family and both share the same p40 subunit. However, IL-23 is responsible for the differentiation and proliferation of Th17 cells; therefore, it is also considered a pro-inflammatory cytokine [50]. Due to its role in the development of Th17 cells, IL-23 is seen as a key cytokine in the pathogenesis of psoriasis. Its importance would go beyond IL-12, which would give to the Th17 cells a more prominent role in the development of diseases, where previously this emphasis was given to Th1 cells [61]. Through IL-23 signaling, Th17 cells produce IL-17 and IL-21. Both cytokines are involved in the recruitment of neutrophils and in the formation of psoriatic lesions [62]. The study of Kulig and colleagues illustrates the importance of IL-23 in this skin disease. By stating that IL-12 has a protective role in psoriasis, the study shows that, in the absence of

IL-12, IL-23 is responsible for the worsening of the lesions. This finding point to the question of the treatment with IL-12 inhibitors and brings to light the treatment that inhibits the two cytokines or IL-23 alone, through its p19 subunit [54]. The association of IL-23 with the Th17 cells makes them a promising therapeutic target. Therefore, with the aim of replacing conventional therapies, there is an enormous development of new anti-IL-23 pharmaceuticals [63,64].

IL-17 is a cytokine produced, although not exclusively, in large quantities by Th17 cells. Its presence is recurrent in the pathophysiology of inflammatory diseases, which includes the psoriasis [65]. The presence of IL-17 in psoriatic lesions has been reported and, interestingly, the largest amount of cytokine came from $CD8^+$ Th17 cells, although $CD4^+$ Th17 cells are present and also produce IL-17. The production of IL-17 stimulates keratinocytes to produce Human β-Defensin 2 (HBD2), an antimicrobial peptide whose levels are increased in inflammatory diseases. IL-17 is functional and interacts with the skin cells [66]. The interaction with keratinocytes is possible by the expression of IL-17 receptor (IL-17R) in these cells. This signaling not only stimulates the production of HBD2, but also the chemoattractant cytokines, such as the CXC ligand 6 (CXCL6), CXC ligand 8 (CXCL8) and CC ligand 20 (CCL20) chemokines, allowing leukocyte infiltration in psoriatic lesions [67]. In addition to keratinocytes, IL-17R is also expressed in fibroblasts and this discovery is important for the development of PsA. Increased IL-17, produced by $CD4^+$ Th17 cells, can also be detected in synovial fluid of patients with psoriasis [68].

The action of IL-17 is not only on epithelial cells, but also affects endothelial cells and immune cells. In the microenvironment where IL-17 is present, it is also possible to observe an increase in pro-inflammatory cytokines, chemokines, as well as endothelial and pro-coagulant activation [69]. IL-17 is also present in the serum of patients with severe PASI. It is possible to detect high levels of IL-17 messenger RNA (mRNA) in tissues of psoriasis subtypes when compared to intact tissue. In addition, patients with pustular psoriasis have the highest levels of IL-17 mRNA when compared to other subtypes, such as guttate and in plaque [70]. In addition to tissue biopsy, it is possible to detect high levels of IL-17 in the serum of patients with psoriasis when compared to healthy individuals [71], and these levels are positively associated with PASI [72]. Because IL-17 plays a significant role in the pathogenesis of psoriasis, therapy with anti-IL-17 monoclonal antibodies is effective in cases of moderate to severe psoriasis [73].

Another cytokine produced by Th17 cells, although not exclusively, is IL-21. Its participation in psoriasis is still the subject of many studies, but it has already been observed in other autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus [74]. In psoriasis, IL-21 is found at high levels in the lesions and the IL-21 receptor (IL-21R) is expressed by keratinocytes. Cytokine signaling in epithelial cells promotes tissue hyperplasia [75], increases effector cell recruitment and regulates IFN-γ production [76]. The discovery that IL-21 induces a greater proliferation of Th17 cells at the expense of regulatory T cells (Treg) highlights the importance to this cytokine [77], and indicates a new target for the development of new therapeutic strategies, such as we have observed in other chronic inflammatory diseases [78,79].

3.4 Other cytokines

IL-8 is a chemokine produced by macrophages and other cell types, such as epithelial cells, airway smooth muscle cells and endothelial cells and its properties has been known for a long time. Its main function is to attract neutrophils through a concentration gradient and this chemoattraction makes IL-8 an important cytokine in inflammatory processes [80] and the presence of neutrophils responding to IL-8 has already been observed in biopsy samples in pustular psoriasis [81]. In addition, the production of IL-8 can be stimulated by extracellular matrix (ECM) proteins, such as cysteine-rich angiogenic inducer 61 (Cry61) without the presence of TNF-α and IL-1β, contributing to the increase in neutrophil recruitment and for the remodeling of injured tissue [82]. Visfatin, one of the prominent adipokines produced by adipose tissue, also influences the production of IL-8 by the keratinocytes. However, alone, it is not able to increase IL-8 levels and TNF-α induction is required [83]. This relationship between visfatin and IL-8 is important, since this adipokine is increased in patients with psoriasis, regardless of the presence of obesity [84]. Although IL-8 is not considered the main cytokine in psoriasis, some treatments aim to reduce its plasma levels, such as Narrow Band Ultraviolet B (NB-UVB) [85] and Yinxieling decoction, a Chinese herbal formula [86]. Both approaches achieved a reduction not only of IL-8 levels but also of PASI of the patients with psoriasis.

Obesity is a very common metabolic disorder observed in patients with psoriasis [87] and can lead to the onset of metabolic syndrome (MetS), type 2 diabetes mellitus and cardiovascular diseases [88]. Adipose tissue produces

cytokines, also called adipokines, with pro and anti-inflammatory effects. Obesity, by itself, is a pro-inflammatory state and, when associated with psoriasis, contributes to a greater severity of the disease [89]. Leptin is an adipokine responsible for hunger control. Obese patients have high levels of leptin and become resistant to it. Leptin increases the expression of adhesion molecules and cytokines in the vascular endothelium, such as TNF-α and IL-6, which also act on the endothelium [90]. A meta-analysis with 26 studies carried out with patients with psoriasis has demonstrated that leptin levels are higher in these patients when compared to healthy controls [91]. The increase in leptin in patients with psoriasis can contribute to the inflammatory response and the appearance of MetS [92]. MetS is associated with greater expression of adhesion molecules and platelet factors in patients with psoriasis, which contributes to the process of atherosclerosis and the increased cardiovascular risk [93].

IL-22 is a cytokine that belongs to the IL-10 family produced by several immune cells, such as Th17, Th22 and NK. In keratinocytes, IL-22 plays a role in the tissue repair and wound healing [94]. In psoriasis, high levels of IL-22 are mainly associated with changes in skin tissue during disease activity [95]. This excess of IL-22 may be related to the deficiency of the IL-22 binding protein, an inhibitor, which prevents the cytokine from binding to its receptor [96]. In addition, greater amounts of IL-22 are found in the skin of pediatric patients with psoriasis when compared to healthy children and adults with psoriasis, which may be an indication of the importance of this cytokine in these patients [97]. Despite their relevant role in the pathophysiology of psoriasis, the IL-22 inhibitors tested in clinical trials have not achieved the desired efficacy. It is still necessary to develop other type of inhibitors for this cytokine [98].

4. Anti-inflammatory cytokines

4.1 Th2 cytokines

Healthy epithelial tissue is a producer and promoter of anti-inflammatory cytokines. Keratinocytes produce IL-10, whose function is to inhibit the Th1 response [99]. Langerhans cells produce IL-4 favoring the polarization toward type 2 macrophages (M2) and the Th2 response [100]. Fibroblasts from healthy individuals are producers of the transforming growth factor (TGF)-β, which, in this context, controls cell proliferation and differentiation and participates in the tissue healing process [101]. In addition,

TGF-β together with IL-2, promotes the differentiation and proliferation of Treg cells [102].

The literature is not assertive regarding the Th2 profile when compared to the Th1 and Th17 profiles in the pathophysiology of psoriasis. In fact, the pathophysiology of psoriasis is mediated by pro-inflammatory profiles. However, it is not possible to determine the behavior of Th2 cytokines in the same way as other profiles. Some authors have reported that there is no difference between Th2 cytokines in patients with psoriasis compared to healthy controls [103,104]. Although the expression of pro-inflammatory cytokines is at high levels in these patients, Th2 cytokines appear to be affected. This finding is interesting, since the cytokine profiles regulate each other, it is expected to find changes in the levels of anti-inflammatory cytokines [104]. Contrary to these results, peripheral blood immunophenotyping in patients with psoriasis has demonstrated that there is a down-regulation of Th2 cells when compared to healthy controls [105].

In turn, cytokines considered as Th2 profile do not always follow this pattern of behavior. IL-4, for example, is considered a hallmark of Th2 cells and can be found at high levels in patients whose PASI is considered mild. Probably, it is an attempt of the immune system to counterbalance the predominant inflammatory response in this disease [47]. The presence of high levels of IL-4 is important to regulate the pro-inflammatory response. The anti-inflammatory effects of IL-4 can be seen in the reduction of levels of IL-1 and IL-6 expression in psoriatic skin. In addition, IL-4 also inhibits the HBD2 protein [106]. Despite this, the effects of IL-4 are directed at the differentiation of Th17 cells, when it inhibits the secretion of IL-23 by dendritic cells. However, the same effect cannot be seen in inhibiting the Th1 response [107].

Due to the IL-4 anti-inflammatory potential, therapy with this cytokine is already mentioned as a therapeutic strategy to induce the Th2 response to inhibit the Th1 response in inflammatory diseases [108]. In patients with psoriasis, the administration of a drug containing IL-4, IL-10 and IL-11 promotes an improvement in PASI and in the quality of life of them [109]. In addition, experiments with injured fibroblasts from psoriatic patients demonstrated a lower production of reactive oxygen species (ROS) when treated with drugs containing IL-4 and IL-10 when compared with control fibroblasts. The reduction in ROS production is one of the important factors in resolving the inflammatory response in these patients [110].

Interestingly, the profile of Th2 cells appears to be more important in diseases such as atopic dermatitis, where these cells are the main source of

inflammation and lesion formation [111]. Patients with atopic dermatitis have a predominance of Th2 cytokines, such as IL-4 and IL-13, and the presence of cells induced by this profile, such as basophils. However, patients with psoriasis have these same cytokines at lower levels than those with atopic dermatitis. This difference between both diseases reflects the pathophysiology of them [112]. While atopic dermatitis is mediated by a Th2 response, similar to hypersensitivity reactions, psoriasis is mediated by Th1 and Th17, typical pattern of inflammatory diseases.

4.2 Treg cytokines

Treg cells that express FOXP3 are important regulators of the immune system and inflammatory response. The production of IL-10 and TGF-β inhibits not only the pro-inflammatory cytokines, but also the cells that produce these cytokines. In addition, Th17 cells and Tregs share the need for TGF-β for their differentiation and proliferation, that is, inhibiting Th17 may favor the increase in Treg cells and vice versa [113]. In psoriasis, the reduced suppressive function and proliferation rate of Treg cells is also under speculation. This behavior can be explained by the activation of STAT3 by pro-inflammatory cytokines, which alters the functions of Treg cells in these patients. The inhibition of STAT3 restores the suppressive and replicative capacity of Treg cells, although it does not elucidate the mechanism by which this relationship occurs [114].

IL-10 is a pleiotropic cytokine that acts on several cell types. Because it has an anti-inflammatory function in psoriasis, it is treated as a Treg cytokine; however, IL-10 can be produced by other T cell subtypes [115]. Therefore, it is also possible to see it linked to Th2 cells in psoriasis. Regardless of the IL-10 producing cells, this cytokine has been postulated for many years as a key cytokine in psoriasis. Asadullah et al. [116] demonstrated that the levels of mRNA and the cytokine itself were more reduced in patients with psoriasis compared to patients with other diseases that also affected the skin tissue. Administration of recombinant IL-10 over a 30-day period reduced the PASI of the patients with psoriasis. In addition, IL-10 was able to reduce Th1 cytokines, such as IFN-γ, and to increase Th2 cytokines, such as IL-4 [116].

In fact, the administration of IL-10 in patients with PsA also has benefits and corroborates the anti-inflammatory function of this cytokine in the context of psoriasis. Therapy with IL-10 not only reduces the production of Th1 cytokines, but also decreases monocytic activity by decreasing TNF-α and

IL-1β cytokines. In addition, with less endothelial activation, due to reduced serum levels of P-selectin, occurs less leukocyte infiltration into synovial tissue. As a result, there is an improvement in the PASI of patients undergoing an IL-10 therapy protocol [117].

Although IL-10 therapy shows promising results, the most used strategy is to inhibit pro-inflammatory activity and, therefore, to increase the anti-inflammatory response. Etanercept is a TNF-α inhibitor used in the treatment of psoriasis. The administration of this drug reduces the production of cytokines such as IL-17 and IL-8. However, the most pertinent observation regarding the effects of etanercept is the reduction of infiltration of Th17 cells in the skin and the concomitant increase in IL-10 [118]. These same results can also be observed in clinical trials with other types of inhibitors. KD025 is a selective inhibitor of the Rho associated coiled-coil protein containing protein kinase 2 (ROCK2) and was used in a phase 2 study in patients with psoriasis. Oral use of this drug for 12 weeks demonstrated that there was a reduction in the number of Th17 cells and their cytokines, IL-17 and IL-23. Along with this result, there was an increase in the number of $FOXP3^{+}$ cells and an increase in IL-10. The PASI of patients was reduced after treatment and the result was correlated with circulating IL-17 levels [119]. The mechanism by which the reduction in the number of Th17 cells and their cytokines increases IL-10 is not well understood. However, it is possible to conclude that both are important in the pathophysiology of psoriasis.

Despite being an important cytokine for Treg, TGF-β shows limited and conflicting results with regard to its performance in psoriasis. In 2002, Flisiak and colleagues did not find significant difference in TGF-β levels among 41 Polish patients with psoriasis and 13 healthy controls; however, TGF-β was associated with increased PASI in patients with psoriasis [120]. In turn, Zaher et al., and also found no significant differences in TGF- β when 10 patients with psoriasis were compared with 22 controls; however, TGF-β was also related to increased PASI [121]. Despite this, in 2003, Doi and colleagues showed a reduction in the levels of TGF-β and its receptors in samples from patients with psoriasis when compared 10 samples of normal tissue and 21 samples of psoriatic lesions using immunohistochemistry. These authors also argued that this reduction in TGF-β contributed to the hyper-proliferation of keratinocytes [122]. This statement is consistent with a study carried out by Di Fusco and collaborators who argue that TGF-β is, in fact, involved in the regulation of keratinocyte proliferation [123].

4.3 Other cytokines

As well as leptin, adiponectin is an adipokine produced by adipocytes. However, its activity is anti-inflammatory and its function is to modulate the inflammatory response through the inhibition of macrophage type 1 (M1) and the secretion of IL-2, IL-6, TNF-α and IFN-γ and, consequently, to increase the expression of IL-10 and a polarization toward to M2 [124]. Obesity and chronic inflammation are two factors that reduce the expression of adiponectin [125]. Obesity is characterized by an inflammatory response mediated by TNF-α and IL-6 [126] and these two cytokines are responsible for inhibiting the production of adiponectin and, thereby, altering their metabolic and immunological functions [127].

The association between adiponectin and psoriasis is already known. The development of comorbidities in psoriasis may be related to the role of adiponectin during the inflammatory response [128]. Patients with PsA and reduced levels of adiponectin have MetS as the most frequent condition [129]. This behavior is expected, since the levels of adiponectin have a negative correlation with the body mass index (BMI), that is, the higher the degree of obesity, the lower the serum levels of adiponectin [130].

The strong association between low serum levels of adiponectin and psoriasis suggests that this adipokine plays an important role in the pathophysiology of the disease [47]. Therapy with an TNF-α inhibitors demonstrates that a reduction in TNF-α levels implies an increase in adiponectin [131]. This relationship can be explained by the fact that adiponectin is inhibited by pro-inflammatory cytokines and, frequently, high levels of TNF-α and reduced adiponectin are found in patients with psoriasis [132]. This inverse relationship, between TNF-α and adiponectin, may even be a predictor of PsA development, helping to differentiate patients with psoriasis [133].

Despite this, adiponectin may not be associated with the severity of psoriasis, but with metabolic variables presented by the patients with this disease. In fact, psoriatic patients who have comorbidities such as type 2 diabetes mellitus, MetS or just overweight have their adiponectin reduced [134]. Studies that suggest an important role of adiponectin in patients with psoriasis, probably highlighted its anti-inflammatory or its metabolic biologic properties

5. Cytokines genetic variants

Previously called genetic polymorphisms, genetic variations are those variations in the DNA sequence that occur in 1% or more in a given

population. The most frequent genetic variation is the single nucleotide variation (SNV), where there is a change of a single nitrogenous base in the DNA sequence, which may or may not alter the expression product of the gene in question [135]. There are about 424 genes containing SNV associated with psoriasis and many of them are related to the immune response [136].

Over 40 susceptibility loci have been found to be associated with psoriasis using genome-wide studies [9]. These genes are involved in T cell signaling, antigen presentation and skin barrier function [137]. Conventional genetic linkage analyses identified 10 chromosomal regions (termed *PSORS1* to *PSORS10*) significantly associated with psoriasis. Of these, *PSORS1*, located within the major histocompatibility complex region on chromosome 6, is believed to confer 35–50% of the heritability of psoriasis (Nestle et al., 2009), with *HLA-Cw6* thought to be the susceptibility allele for early-onset psoriasis within this region [138].

The study of a genetic variant in psoriasis is usually focused on gene regions involved in the inflammatory pathways, mainly the pro and anti-inflammatory cytokines and their receptors, since they are the main ones involved in psoriatic injury. In 2003, Balding and colleagues conducted a study with 147 psoriasis patients and 389 healthy controls, where they analyzed the frequency of 7 SNVs that could be associated with psoriasis and PsA, including *IL1B* +3953C > T (rs1143634), *IL6* –174 G > C (rs1800795), *TNFA* −308G > A (rs1800629), *TNFB* +252A > G (rs909253), *IL-10* –1082A > G (rs1800896), *IL10* − 592C > A (rs1800872), and *ILRA* (intron 2, 86 base pairs, variable-number tandem repeat). Of all the genes evaluated, only the genetic variants of *TNFA* −308G > A and *TNFB* +252A > G were significantly associated with the early age of onset of the disease, presence of joint erosions in PsA and progression to early joint erosion in PsA [139].

In 2007, in a meta-analysis, Li and collaborators gathered studies carried out up to that moment that analyzed genetic variants in the −238G > A (rs361525) and −308G > A (rs1800629) promoter regions in the *TNFA* gene and their associations with the risk of psoriasis. The result demonstrated that there is a risk effect for the –238G > A variant genotype and a protective effect for the –308G > A genotype both for the AA + AG genotypes, when compared to the homozygous GG genotype, the most frequent genotype [140]. In 2012, in a retrospective study, Vasilopoulos and colleagues recruited 80 Greek patients with psoriasis under monotherapy with TNF-α inhibitor for at least 6 months. Of them, 44 patients were treated with etanercept, 22 with infliximab and 14 with adalimumab. The SNVs selected for the genotyping of

these patients were: *TNFA* −238G > A (rs361525), *TNFA* −308G > A (rs1800629) and *TNFA* −857C > T (rs1799724); *TNFRSF1A* 36A > G (rs4149584) and *TNFRSF1B* 676T > G (rs1061622). The results demonstrated that homozygosity of the most frequent allele for *TNFA* −857C > T and *TNFRSF1B* 676T > G are positively associated with the response to treatment with etanercept, but not with the other two inhibitors [141].

In Serbia, a study of 130 plaque psoriasis patients detected and analyzed genetic variants for *TNFA* −308G > A (rs1800629), *IL12B* +1188A > C (rs3212227) and *IFNG* +874T > A (rs2430561). However, there was no significant difference in the frequency of alleles or in the distribution of the genotype between patients and healthy controls [142]. Although *TNFA* −308G > A (rs1800629) is extensively studied in psoriasis, many studies do not obtain significant results for this genetic variant. In 2017, in India, Rajesh and colleagues conducted an assessment of the profile of *TNFA* −308G > A (rs1800629) in 74 patients with plaque psoriasis and, again, found no significant difference between patients and healthy controls that could associate the genetic variant to the risk of developing the disease [143].

Another SNV studied in psoriasis is related to the pro-inflammatory cytokine IL-6. In 2012, Renzo and collaborators, genotyped for the *IL6* −174G > C (rs1800795) variant in the promoter region of 80 patients with psoriasis, men and Caucasian Italians, on a follow-up study of 24 weeks under treatment of infliximab, etanercept and adalimumab. The results showed that obese patients with the G allele of the genetic variant predicted low response to TNF-α inhibitors. Taken together latter results could be considered risk factors for the prognosis and therapy of patients with psoriasis [144].

Data in the literature demonstrate that this same genetic variant *IL6* −174G > C (rs1800795) has been studied a few more times over the years. In Romania, in 2013, 69 patients with psoriasis were genotyped for *IL12B* 3′untranslated region (UTR) +1188A > C (rs3212227), *IL12B* (rs6887695), *IL23R* (rs7530511), *IL23R* A > G (rs11209026) and *IL6* −174G > A (rs1800795) and for the presence of *HLA-Cw6*. The results demonstrated that *HLA-Cw6* negative patients who have variants for the *IL6* and *IL12B* genes related are at reduced risk for psoriasis [145]. For the record, the *HLA-Cw6* allele is strongly associated with psoriasis; however, its role in the development of the disease is not known for sure [146].

In 2016, 406 patients with psoriasis were evaluated in a case-control study with the aim to assess whether the genetic variation of *IL6*

−174G > C (rs1800795) predisposes to psoriasis and whether there is an association of the variation of this gene with topical treatment and therapy with NB-UVB. The results showed that this gene variation may be a marker for susceptibility to psoriasis, but it does not alter responsiveness to treatment [147]. In the same year of 2016, Spanish researchers released a study in which 125 patients with psoriasis were recruited and genotyped for the promoter regions of the *IL1B* –511G > A (rs16944) and *IL6* –174G > C (rs1800795) genes. The results showed that the G allele of *IL1B* variant is associated with more pronounced inflammatory activity and the G allele of *IL6* variant has a strong tendency to associate with peripheral patterns of the disease [148]. Another genetic variant of *IL6*, −572G > C (rs1800796), has also been studied in autoimmune diseases, such as rheumatoid arthritis [149]. However, no data were found for this variant regarding psoriasis.

In addition to the pro-inflammatory cytokines, *IL10* and *FOXP3* gene variations are also studied in psoriasis, since both are markers of Treg cells. Regarding *IL10,* Karam and colleagues genotyped 110 patients with plaque psoriasis for *IL10* −1082A > G (rs1800896) and also for *TNFA* −308G > A (rs1800629). The results showed that there is an increase in the G allele frequency in patients with psoriasis for the *IL10* variant, demonstrating its association with the disease. In addition, *TNFA* was also associated with psoriasis, where the G allele frequency was also increased in patients with the disease. The authors also quantified the cytokines encoded by these genes and IL-10 was significantly reduced in patients compared to control and TNF-α was increased in patients and with a positive correlation with disease severity [150].

In 2017, Galimova and collaborators performed 48 cytokine SNVs of the IL-10 family, whose representatives are IL-10, IL-19, IL-20 and IL-24. Three hundred and seventy seven Russians of European descent were recruited and the combination of two SNVs, *IL10* T > C (rs1554286) and *IL20* T > C (rs1518108), was associated with a reduction in the risk of psoriasis, providing, probably, a protective role for the development of the disease [151]. Another type of genetic variation, *IL10* −592C > A (rs1800872), has been described in autoimmune diseases, such as systemic lupus erythematosus in Iranian patients [152]; however, no report has been found in patients with psoriasis.

The search for *FOXP3* genetic variants in psoriasis also presents limited data in the literature with only four reported studies. In 2008, in China, 524 patients were genotyped for the *FOXP3* variants −3499A > G (rs3761547), −3279C > A (rs3761548), −2383C/T (rs3761549) and G > T(rs4824747).

The study found a potent regulating site, rs3761548, which is correlated with *FOXP3* transcription. Patients with homozygosity for in the AA genotype had greater clinical severity, concomitance with other autoimmune diseases and reduced levels of FoxP3 when compared to homozygosis for CC genotype [153]. Still in China, in the same year, among 524 patients with psoriasis (478 diagnosed before age 40 and 46 diagnosed after age 40), were evaluated for *FOXP3* gene SNVs, including −6054 deletion/ATT (rs5902434), −3279 A > C (rs3761548), −924A > G (rs2232365), IVS9 +459A > G (rs228083) and association of genotype and frequency of alleles were verified in patients and controls. The results showed that in combined genotype analyses, the *FOXP3* −3279 AC + AA genotypes were more obviously associated in males and severe psoriasis patients with PASI score > 20. Meanwhile, the FOXP3 IVS9 + 459 GA + GG genotypes were also associated with severe psoriasis patients. However, the other two SNVs studied did not present any statistically significant results in this population [154].

In 2019, a study aimed to evaluate the role of *FOXP3* −3279C > A (rs3761548) genetic variation in susceptibility to psoriasis in 80 patients and 80 controls. The results demonstrated that this SNV was correlated with a significant susceptibility to psoriasis and that there was an increased frequency of the CC genotype and the C allele in patients when compared to the controls. In addition, the authors found that the CC genotype was a predictor for plaque psoriasis, unlike the AA and AC genotypes. Despite the association of these genotypes with the disease, the study showed no association with any variable of severity or the development of comorbidities [155].

In turn, in Brazil, only three studies on genetic variants of cytokines associated with psoriasis were reported and all of them evaluated the *TNFA* gene. The first, carried out in 2009, Biral and collaborators aimed to analyze the possible association of haplotypes formed by HLA class I markers and *TNFA* microsatellites. The authors included 60 patients aging 18–80 years old recruited from a University Hospital in Campinas, São Paulo. The *HLA-B* and *HLA-C* alleles and the microsatellites *TNFa, TNFb, TNFc, TNFd* and *TNFe* were identified. The results demonstrated that the HLA-B*57, HLA-Cw*06, TNFa2, TNFb5, TNFc2, TNFd4 and TNFe3 haplotype was related to the susceptibility for developing psoriasis before the age of 40 [156]. In 2010, the same research group selected 69 patients who underwent a follow-up study between 1997 and 2007 with the objective to assess whether the *TNFA* promoting region could be a genetic risk factor for psoriasis compared to HLA classes I and II. For this purpose, the *TNFA* −308G > A (rs1800629) and *TNFA* −238G/A (rs361525) promoting regions were evaluated, as well as the HLA-A, -B,

-C, -DR and -DQ alleles. The study suggested that the *HLA-B*57* allele was associated with a more moderate form of the disease. In turn, *HLA-B*37*, *HLA-Cw*06*, *HLA-Cw*12* and *HLA-DRB1*07* alleles were associated with a more severe form of psoriasis. However, there was no statistical difference between patients and controls with respect to the allele, genotype or haplotype of *TNFA* SNVs, indicating that these variants gene cannot be considered a genetic risk factor for psoriasis [157].

In 2015, Cardili and collaborators conducted a case-control study with 125 Brazilian patients, aging 18–75 years old, and 202 healthy controls aging 18 and 59 years old to evaluate the distribution of *HLA-C* and *TNFA* −238G > A (rs361525) and −308G > A (1800629) in relation to the alleles of the promoter region, genotypes and haplotypes. The results indicated a high frequency of the *HLA-C*06* allele and its role as a marker of susceptibility to psoriasis, mainly of early-onset in Brazilian patients. Regarding *TNFA*, the authors found a high frequency of the *TNF* −308 GA genotype in these patients, which was also associated with generalized forms of the disease, suggesting that this genetic variant is associated with the susceptibility and severity of the disease. On the other hand, *TNFA* −308 GG genotype was significantly higher in controls, when compared with the patients. In addition, the combination of the *TNFA* −238A/*HLA-C*06* and *TNFA* −238A/*HLA-C*15* haplotypes confer greater susceptibility or protection, respectively, to psoriasis [158].

Much has been published about genetic variations in psoriasis in different population worldwide; however, the data are still conflicting. In the Brazilian population, a more in-depth study on the various cytokines that make up the microenvironment of psoriatic lesions and how they influence the prognosis and treatment of patients is lacking. In addition, almost all of the aforementioned studies did not evaluate plasma levels of cytokines and genetic variations, concurrently, to better understand how the dynamics of the disease and how the genetic factor modulates the response to drugs. Therefore, it is necessary to assess how the patient's genotype could interfere and/or interact with the pathophysiology of psoriasis and with the cytokines previously identified as being important in the disease [47].

6. Cytokines in treatment

The treatment of psoriasis aims to control symptoms, to reduce PASI and to improve the patient's quality of life. Therefore, the therapy chosen must be in accordance with the diagnosis of the type and severity of psoriasis and the patient's adaptation. Topical treatment is usually used in cases of mild

to moderate psoriasis, and in combination with other therapies in the most severe cases. The medications used are: (1) corticosteroids, such as hydrocortisone, for up to 8 weeks; (2) dithranol, an anthracene derivative, used under medical supervision; (3) vitamin D; (4) the immunosuppressant tacrolimus and tazarotene, an ointment-shaped retinoid. Second-line treatment is used in severe cases or in those which topical treatment has not been effective and comprises two approaches: phototherapy and systemic therapy. Phototherapy with ultraviolet radiation (UV) can be used in cases of psoriasis vulgaris and guttate, combined with 5 or 8-methoxypsoralen, also known as PUVA (Psoralen + UVA), a medication that increases skin sensitivity to UVA rays. Systemic therapy can be performed with three drugs: (1) methotrexate, an inhibitor of folic acid metabolism; (2) cyclosporine, an immunosuppressant that inhibits the synthesis of IL-2 and its receptors and (3) acitretin, a derivative of vitamin A, which reduces skin peeling. Finally, the use of monoclonal antibodies is adopted when psoriatic lesions are in critical areas, such as the face, hands and genitals [159]. Monoclonal antibodies directed to cytokines used during the treatment of psoriasis are summarized (Table 1). The interaction between cytokines and cells in which medications act is shown (Fig. 2).

Despite being used in the treatment of psoriasis, some patients do not show an effective response to TNF-α inhibitors and the mechanism by which this occurs is not yet fully understood. It is believed that the variants in the *TNFA* and the production of antibodies against the inhibitors used in the treatment are among the reasons why these drugs have low effectiveness [169]. And in order to fill this and other gaps left by the treatment of the patients with psoriasis, clinical trials are being conducted for the development of new drugs for the management of the disease. Drugs under study according to the website clinicaltrials.gov are summarized (Table 2) [170].

7. Conclusion

In summary, psoriasis is a disease that affects the skin and can cause lesions to appear anywhere on the body. Affecting men and women equally, its etiology remains unknown and this disease is given a multifactorial character. Although the exact pathogenesis of psoriasis yet to be elucidated, it is thought to be a complex interplay between environmental factors, T cells, dendritic cells, multiple cytokines and genetic variants, which dysregulate innate and adaptive immune responses in the skin. Therefore, there is a vast interaction between cells of the epithelial tissue and immune cells that makes the study of psoriasis a complex challenge.

Table 1 Biologic medications for treatment of psoriasis.

Cytokine	Medication	Mechanism of action	Structure
TNF-α [160–163]	Etanercept	TNF-α inhibitor by competitively binding mimicking TNF-α receptor	Dimeric human fusion protein IgG1 Fc region
	Infliximab	Binding with high affinity and specificity to soluble and transmembrane forms of TNF-α	Chimeric antibody: Human IgG1 Fc region; Variable Murine Region
	Adalimumab	Binding and neutralization of soluble and transmembrane forms of TNF-α	Human IgG1 monoclonal antibody
	Certolizumab	Binding to TNF-α	Fab portion of humanized monoclonal antibody conjugated to polyethylene glycol
IL-12/23 [164]	Ustekinumab	Binding to p40 subunit shared by IL-12 and IL-23	Human IgGκ monoclonal antibody
IL-17 [165–167]	Secukinumab	Binding and neutralization of IL-17A	Human IgG1κ monoclonal antibody
	Ixekizumab	IL-17 pathway	Humanized IgG4 monoclonal antibody
	Brodalumab	Binding to IL-17RA	Human IgG monoclonal antibody
IL-23 [163,168]	Guselkumab	Binding to p19 subunit of IL-23	Human IgG1λ monoclonal antibody
	Risankizumab	Inhibits IL-23 by specifically targeting the p19 subunit	Humanized IgG1 monoclonal antibody
	Tildrakizumab	Selectively blocks IL-23 by binding to its p19 subunit	Humanized IgG1κ

Ig: immunoglobulin; TNF: tumor necrosis factor; IL: Interleukin; IL-17RA: interleukin 17 receptor antagonist; Fc: fragment crystallizable.

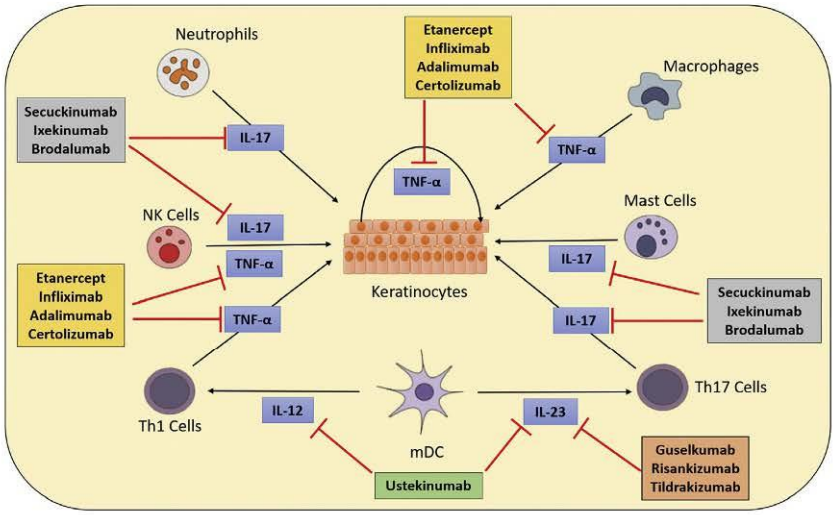

Fig. 2 Targets of biological medications used in the management of psoriasis. The pathophysiology of psoriasis demonstrates a complex interaction between cells and their cytokines. The purpose of the drugs used to treat psoriasis is to inhibit the action of these cytokines, regardless of the producing cell. Etanercept, Infliximab, Adalimumab and Certolizumab are TNF inhibitors. Secukinumab, Ixekizumab and Brodalumab are inhibitors of IL-17. Guselkumab, Risankizumab and Tildrakizumab are inhibitors of IL-23. Ustekinumab is an inhibitor of IL-12 and IL-23. Legend: Interleukin (IL), Tumor Necrosis Factor - alpha (TNF-α), T helper cell (Th), Natural Killers Cells (NK), Myeloid Dendritic Cells (mDC).

Table 2 Anticytokine biologic medications in clinical trials for treatment of psoriasis according to the website ClinicalTrials.gov.

Target	Medication	Status	ClinicalTrials ID	Location
IL-23	Mirikizumab	Phase III	NCT03535194	Multicenter
	Risankizumab	Phase III	NCT03219437	Brazil
			NCT03518047	Russia
			NCT03478787	Multicenter
IL-17	Tildrakizumab	Phase III	NCT01729754	–
	Bimekizumab	Phase III	NCT03536884	Multicenter
			NCT03412747	Multicenter
	BCD-85	Phase III	NCT03598751	Belarus; Russia
	ABY-035	Phase I	NCT02690142	United Kingdom

ID: Identifier; IL: Interleukin.
The suffix "mab" stands for "monoclonal antibody."

Mainly, the pathophysiology of psoriasis is orchestrated by Th1 and Th17 cells and their pro-inflammatory cytokines. The TNF-α and IL-17 cytokines play an important role in the pathophysiology, whereas IL-12 and IL-23 appear as promising cytokines in the development of new drugs. In turn, the anti-inflammatory defense conferred by Th2 and Treg cells, have conflicting results with regard to their regulatory activity. The biological function of these cytokines can be explained, in part, by the genetic variation in the Th2 and Th17 related genes presented in certain populations and the therapeutic failures presented by some patients during treatment with immunobiological may be due to these genetic differences. Concomitant to this, there is the influence that a given cytokine has on the production and secretion of another cytokine. And this communication network can also check the heterogeneity of psoriasis and its subtypes. Thus, it is possible to conclude that the study of the pathophysiology of psoriasis exposes a disease whose interaction between immune and non-immune cells can make patient management a challenge, while opening the way for the development of new therapeutic strategies that meet the demands for drugs more effective.

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5.2 ARTIGO

Highlights

- *IL17RA* variants exert a role in the psoriasis pathophysiology;
- *IL17RA* rs2241043 (T>C) CC genotype is associated with severity of psoriasis;
- *IL17RA* rs2241049 (A>G) G allele is associated with protection to psoriasis;
- *IL17RA* rs651661 (G>A) AA genotype is associated with severity of psoriasis;
- *IL17RA* T/A/A haplotype is associated with an elevated risk of psoriasis;

ABSTRACT

Introduction: Psoriasis (PsO) is a chronic inflammatory disease of the skin tissue mediated by the immune system. In the microenvironment of lesions, Interleukin 17 (IL-17) plays a crucial role in the pathophysiology of the disease. This cytokine directly affects keratinocytes, inducing their abnormal and accelerated proliferation. The multifactorial nature of PsO and the importance of IL-17 for its pathophysiology highlight the need to investigate how genetic factors can influence susceptibility to PsO.

Objective: The aim of this study was to evaluate the association between the genetic variants of the *IL17RA* gene and the susceptibility and severity of PsO.

Material and Methods: This case-control study included 154 patients with diagnoses of PsO and 154 healthy controls. The diagnosis of PsO was performed by a dermatologist, and Psoriatic Activity and Severity Index (PASI) was used to determine the severity of the disease. Three *IL17RA* SNVs were genotyped: T>C rs2241043, A>G rs2241049, and G>A rs6518661.

Results: The presence of the G allele in homozygosis in *IL17RA* A>G rs2241049 was associated with a protective factor against the development of PsO (OR=0.39, 95% CI 0.20-0.76, p=0.005). The *IL17RA* CC genotype (rs2241043) (OR=0.30, 95% CI 0.10-0.093, p=0.020) and AA genotype (rs6518661) (OR=0.22, 95% CI 0.05-0.99, p=0.020) were associated with PASI.

Conclusion: Our study demonstrated that the *IL17RA* A>G rs2241049 GG genotype is a protective factor against the development of PsO. In addition, the homozygous C allele of the *IL17RA* T>C rs2241043 and *IL17RA* G>A rs6518661 variants were associated with protection against the development of severe PsO. More studies are needed to elucidate which genetic and epigenetic mechanisms are involved in the associations since these genes are in intronic regions.

Keywords: Psoriasis; interleukin 17, *IL17RA* genetic variant; PASI; psoriatic arthritis.

Il17RA genetic variants are associated with susceptibility and severity of psoriasis

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1 Introduction

Psoriasis (PsO) is a skin-inflammatory chronic disease characterized by the presence of red and scaly plaques on the elbows, knees, and scalp [1]. The etiology of PsO is multifactorial with the interaction between genetic variants (*HLACω6*), lifestyle (alcohol use, smoking, obesity, sedentary), environmental influence such as medications [beta blockers, lithium, antimalarials, tumor necrosis factor (TNF) inhibitors], as well as infections caused by *Staphylococcus*, *Streptococcus*, and *Human Immunodeficiency Virus* (HIV) [2-5]. Because of its proinflammatory pattern, PsO patients constantly face the possibility of developing systemic comorbidity as type 2 mellitus diabetes, cardiovascular diseases, metabolic syndrome, inflammatory bowel

disease, and obesity [6,7]. Furthermore, PsO itself can provoke the arising of psoriatic arthritis (PsA), a comorbidity of psoriasis that affects the joint of 15% of patients [8].

In the last few years, T helper (Th) 17 lymphocyte inflammatory response in PsO is in evidence as new immunobiological therapies driven against interleukin (IL)-17 are coming to light [9-11]. Those therapies target the disease and the outburst of associated comorbidity [12]. Therefore, extensive studies on this inflammatory response are more demanding, which include the genetic variants that can play an important role in PsO pathophysiology and its pharmacotherapeutic management. Recently, our research group demonstrated the influence of Th17 response axis in pathophysiology [13,14] and the importance of genetic variants in PsO susceptibility [15].

In the case of Th17 cells, both cytokine and its receptor genes, *IL17A* and *IL17RA*, respectively, are selected to be genotyped in PsO patients, since the proteins encoded by these genes are part of the inflammatory signaling cascade [16]. Although there is evidence of the association between *IL17RA* and anti-TNF response in PsO [17], little data about *IL17RA* variants in PsO is available in the literature, and the existing results are conflicting [18]. For this reason and for results obtained by our research group for other autoimmune diseases, the aim of this study is to evaluate the association between *IL17RA* T>C rs2241043, A>G rs2241049, and G>A rs6518661 genetic variants in susceptibility and severity in PsO.

2 Material and Methods

Subjects

This is a case-control study that included 308 participants of both sexes, aged between 18 and 70 years, 154 patients with diagnoses of PsO (148 with plaque PsO, 1 pustular PsO, 4 palmoplantar PsO, and 1 erythrodermic PsO) were selected among the ambulatory of Dermatology of the University Hospital of Londrina, Paraná, Brazil and 154 healthy controls (HC) enrolled from the blood donors at the Regional Blood Center of Londrina. Exclusion criteria were for the patient to present thyroid, renal, adrenal, hepatic, gastrointestinal, infectious, oncological, and other autoimmune diseases.

The diagnosis of PsO was made by a dermatologist according to the criteria established by the Brazilian Society of Dermatology [19]. Psoriasis Activity and

Severity Index (PASI) was used to determine disease severity, where PASI≤10 was considered mild to moderate PsO, and PASI>10 was considered severe PsO [20]. The diagnosis of PsA was determined considering the Classification Criteria of Psoriatic Arthritis (CASPAR) [20]. Clinical, epidemiological, and anthropometric data were obtained by a dermatologist during a clinical examination. The information was recorded in an evaluation form, previously established by the researchers during the project design.

This research was approved by the Ethics Committee for Research Involving Human Beings of the State University of Londrina, Paraná, Brazil (CAAE: 37420820.0.0000.5231). Written informed consent was obtained from all subjects.

Blood Collection and Biochemical Analysis

Blood collection was performed through venipuncture using sterile (BD Vacutainer™ Ultratouch tubes, Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA) for vacuum collection with and without anticoagulant. The samples were sent to the laboratory for registration, processing, separation, and storage. Plasma, buffy coat, and whole blood were aliquoted in centrifuge microtubes, identified, and stored in a -80 °C until the experiments were carried out. C-Reactive Protein (CRP) levels were determined by turbidimetric assay (C8000™, Abbott, Architect Abbott Laboratories, Abbott Park, IL, USA). Ferritin levels were obtained by chemiluminescent microparticle immunoassay (CMIA™, Architect, Abbott Laboratory, Abbott Park, IL, USA). Both analyses were performed on patient serum obtained on the day of collection of biological material.

DNA Extraction and Genetic Variants Genotyping

Genomic DNA extraction was performed using the manual extraction with resin column (BIOPUR™ MINI SPIN PLUS, Biometrix Diagnóstica Ltda, Curitiba, Paraná, Brazil) according to the instruction manual provided by the manufacturer, with some modifications, such as the volume of buffy coat (200 uL) used and the temperature of the elution buffer (70 °C) from the peripheral blood. The extracted DNA was quantified using the NanoDrop™ espectrofotometer (Thermo Fisher™ Scientific, Vienna, Austria), and the concentration of the genetic material was standardized to 1.1 ng/uL. Three *IL17RA* SNVs were genotyped: T>C rs2241043, A>G rs2241049, and G>A rs6518661 by real-time quantitative PCR (qPCR) using TaqMan™ probes containing

specific primers and fluorescent probes. The fluorescence levels of qPCR products were measured using the thermal cycler (StepOne™, Applied Biosystems by Life Technologies, Carlsbad, CA, USA).

Statistical Analysis

The sample size of 154 individuals in each group was calculated assuming a statistical power of 90% and a confidence interval (CI) of 95% using the R software [21]. Categorical data were evaluated using the chi-square (X^2) or Fisher's exact method, as appropriate. The results obtained were expressed in absolute numbers (n) and percentages (%). Continuous data were analyzed using the student's t-test, and the result was expressed as mean and standard deviation (±SD), or by the non-parametric Mann-Whitney test, and results were expressed as the median and percentile range (25-75%) according to the distribution of the data obtained. The association and frequency of *IL17RA* variants were analyzed in allelic, dominant, codominant, recessive, and overdominant genetic models [22] using the online SNV analysis tool, SNPStats, available at https://www.snpstats.net/start.htm [23]. Binary logistic regression analysis was performed to assess the effect of SNVs on the studied groups and was evaluated in terms of odds ratio (OR), and the CI considered was 95%. The tests were considered statistically significant when $p<0.05$. Statistical analyzes were performed using SPSS IBM version 24 for the Windows platform (SPSS Inc., Chicago, IL, USA).

3 Results

Descriptive Statistical

Sociodemographic and clinical data of the PsO patients and HC are shown in **Table 1**. Both groups did not differ in sex ($p = 1.000$), ethnicity ($p = 0.819$), and smoking behavior ($p = 0.359$); however, patients with PsO were older ($p < 0.001$) and had higher body mass index (BMI) ($p < 0.001$) than HC. Moreover, proinflammatory markers, such as CRP ($p < 0.001$) and ferritin ($p = 0.002$) showed higher serum levels than HC.

Approximately 28% (n = 43) of the case group had severe PsO (PASI > 10) and the mean PASI value was 7.059 (±0.455). Plaque PsO was the most diagnosed type

in patients, affecting 148 (96.1%) individuals. Nevertheless, other six (3.9%) patients were diagnosed with different types of PsO, such as pustular PsO (n=1), palmoplantar PsO (n=4), and erythrodermic PsO (n=1). In addition to the determination of PsO type, 23 (14.9%) patients were diagnosed with PsA, as a PsO comorbidity.

The patients were also categorized into two groups according to systemic and topic PsO treatment. The systemic group included 86 (55.8%) patients and the drugs used were methotrexate (n=35), acitretin (n=14), adalimumab (n=13), ustekinumab (n=9), etanercept (n=7), secukinumab (n=5), ciclosporin (n=2), phototherapy (n=2) and prednisone (n=1). The topic group included 62 (41.6%) patients and the drugs were clobetasol (n=20), betamethasone + citric acid (n=12), calcipotriol + betamethasone (n=13), betamethasone and salicylic acid (n=9), betamethasone (n=8), calcipotriol (n=6), fludroxicortida (n=3) and halobetasol (n=1); 17 (11%) patients were included in both medication groups (data not shown).

Association between PsO and SNVs

Table 2 shows the association between *IL17RA* A>G rs2241049 and the susceptibility to PsO. The allele A was more frequent in patients with PsO, while the allele G was more frequent in HC (OR=0.799, 95% CI 0.67-0.95, p = 0.0151). The presence of the G allele in homozygosis was associated with a protective factor against the development of PsO in the codominant (OR=0.37, 95% CI 0.18-0.76, p=0.017) and recessive (OR=0.39, 95% CI 0.20-0.76, p=0.005) genetic models. Both *IL17RA* T>C rs2241043 (**Supplementary Table 1**) and G>A rs6518661 (**Supplementary Table 2**) SNVs did not show an association with PsO.

Binary logistic regression was performed between *IL17RA* A>G rs2241049 and confounding covariates, and the results demonstrate that the presence of the G allele in homozygosis was associated with protection against PsO (OR=0.391, 95% CI 0.199-0.768, p=0.006), independently of sex and ethnicity (regression #1). Nevertheless, age (OR=1.039, 95% CI 1.016-.1.063, p=0.001) in regression #2, BMI (OR=1.133, 95% CI 1.073-1.197, p<0.001) in regression #3 and ferritin levels (OR=1.002, 95% CI 1.000-1.004, p=0.028) might influence even in the presence of GG genotype (**Table 3**)

Association between PASI and SNVs

Table 4 shows the association between *IL17RA* T>C rs2241043 and severe PsO (PASI > 10). There was no significant difference among the T and the C allelic frequencies (OR=0.904, 95% CI 0.79-1.04, p=0.1630) when comparing PASI ≤ 10 and PASI > 10. However, the presence of the CC genotype showed to be a protective factor against severe PsO (OR=0.30, 95% CI 0.10-0.093, p=0.020). On the other hand, in **Table 5**, *IL17RA* G>A rs6518661 demonstrated that the presence of the AA genotype was associated with protection against severe PsO (OR=0.22, 95% CI 0.05-0.99, p=0.020). Nevertheless, this association did not remain significant when the results were adjusted by some confounding variables (**Supplementary Table 3**). Moreover, no association was observed between *IL17RA* A>G rs2241049 and PASI (**Supplementary Table 4**).

Binary logistic regression was performed between *IL17RA* T>C rs2241043 and confounding covariates, and **Table 6** shows this analysis with PASI > 10 as the dependent variable and PASI ≤ 10 as the reference group. The results demonstrated that the presence of the C allele in homozygosis shows a protection against severe PsO (OR=0.303, 95% CI 0.095-0.965, p=0.043), independently of sex, ethnicity, age, and BMI (regression #3).

Haplotypes analysis between HC and PsO

Table 7 shows the estimated frequencies of the haplotypes observed among PsO and HC. The investigation of specific haplotypes within the *IL17RA* gene (T>C rs2241043, A>G rs2241049, and G>A rs6518661) in relation to PsO susceptibility yielded significant findings. Individuals carrying the T/A/A haplotype exhibited twofold increased odds of PsO (OR=2.00, 95% CI: 1.10 - 3.62, p=0.023) and this association remained robust even after adjusting for age, sex, and ethnicity (OR=1.95, 95% CI: 1.06 - 3.60, p=0.033) (**Table 8**). Further adjustment for BMI, showed a slightly attenuated association but not significant (OR=1.81, 95% CI: 0.96 - 3.42, p=0.067), suggesting a potential role of BMI as a modifying factor in this genetic influence (**Supplementary Table 5)**.

4

5 Discussion

The main finding of the present study is that *IL17RA* (rs2241049) genetic variant is associated with the protection of PsO development. Besides, the *IL17RA* rs2241043 CC genotype was associated with 70% of protection to PsO severity. The *IL17RA* rs6518661 AA genotype, by itself, is associated with 78% of protection against severe PsO. Nevertheless, in the presence of confounding variables, such as BMI, this association is lost. This finding is important to corroborate the multifactorial nature of PsO, where, in this case, environmental factors interact with genetic ones. These results show the significant genetic contribution of specific haplotypes within the *IL17RA* gene to PsO susceptibility, with BMI potentially acting as a modulating factor. The Linkage Disequilibrium (LD) suggests that the alleles at these loci are in some degree of LD, meaning they are not randomly distributed. However, the magnitude of the values is relatively low, indicating a relatively weak association

IL-17 receptor A (IL-17RA) is the main receptor of IL-17 cytokine. Its expression is found in various diversity of cell lines. Nevertheless, the receptors expressed in keratinocytes and fibroblasts are the most responsive to IL-17 [12]. In lesioned psoriatic skin, the IL-17R family showed to be overexpressed when compared to non-lesional skin [24], and IL-17RA expressions seem to be associated with higher levels of inflammatory markers as erythrocyte sedimentation rate (ESR) and CRP [25]. In addition to that, the blockage of IL-17RA was demonstrated to improve PsO features [26], which highlights the need to understand the role played by this receptor in disease pathophysiology.

In our study, three *IL17RA* SNVs were genotyped, namely rs2241043, rs2241049, and rs6518661. Few studies are available in the literature that approaches the association between *IL17RA* genetic variants and PsO. A total of 40 SNVs, including three within the *IL17A* gene) in a case-control cohort performed in the Italian population [27]. Among those SNVs there were the same three *IL17RA* genes that our group researched (rs2241043, rs2241049, and rs6518661). Nevertheless, in disagreement with our results, none of the three SNVs demonstrated to be related to PsO susceptibility [27]. The failure of association was also reported by other study in 208 Korean patients with PsO, which showed no association between five *IL17RA*

SNVs, including rs2241049, and PsO [28]. Both studies [27, 28], which included at least one of our chosen SNVs, demonstrated controversial results when compared to our findings. The differences in the described interleukin genetic backgrounds may exist,

These data underscore how the pattern of genetic variation can change across populations and can potentially influencing, together with multi-faceted environmental factors, the disease susceptibilities of these populations. These apparent conflicting results highlight the need to further investigate how *IL17RA* SNVs can influence the development of PsO and its comorbidities. Other factors may explain the lack of association between the *IL17RA* SNVs and PsO in these previous studies, such as environmental factors, the sampling time and sample patients with different clinical subtypes and degree of severity of PSO, as well as different methods used for the genotyping.

The *IL17RA* variant plays a crucial role in the pathogenesis of autoimmune diseases by influencing the immune response and inflammatory processes. A study carried out with 455 patients with ankylosing spondylitis (AS) demonstrated an association between *IL17RA* copy number loss and an increased susceptibility to AS and provided valuable insights into the contribution of *IL17RA* in autoimmune disorders [29]. The elevated expression of IL17-RA in peripheral blood mononuclear cells (PBMCs) of patients with AS compared to HC underscores its significance in the disease process. The observed correlation between reduced *IL17RA* copy number and an increased risk of AS suggests that lower *IL17RA* gene dosage might compromise the immune system's ability to effectively regulate inflammatory responses, possibly contributing to disease susceptibility [29].

The association between the *IL17RA* genetic variants and autoimmune conditions, such as PsO and AS, underscores the critical role of IL-17A signaling in inflammatory diseases. In PsO and AS, the dysregulation of IL-17A-related pathways contributes to disease pathogenesis. The *IL17RA* rs2241049 homozygous GG genotype was associated with protection against PsO development. Similarly, a lower copy number of *IL17RA* is associated with an increased susceptibility to the disease in AS. This indicates that alterations in the IL-17A signaling pathway mediated by *IL17RA* contribute to the development of both PsO and AS.

A systematic review and meta-analysis [30] aimed to consolidate the understanding of the association between genetic variants in IL-17 family genes and human disease susceptibility. Through meta-analysis and comprehensive assessment, the study identified seven significant variants associated with 18 human diseases, with solid evidence supporting the involvement of four variants (*IL17A* rs2275913, *IL17A* rs8193037, *IL17F* rs1889570, *IL17F* rs763780) in conditions such as cancer, spondyloarthritis, asthma, multiple sclerosis, and rheumatoid arthritis. Bioinformatics analysis highlighted the potential functional implications of these variants. The study concluded that IL-17 family gene variants play a substantial role in the susceptibility to several diseases, emphasizing the pivotal contribution of IL-17 regions in genetic predisposition to both cancer and noncancerous disorders [30]. This study highlights how variants in IL-17 family genes are associated with susceptibility to various human diseases, including autoimmune conditions. These findings align with our results in PsO, which reveal specific associations between *IL17RA* genetic variants and disease susceptibility and severity. These insights emphasize the complex interplay between genetic factors and environmental influences in disease development. *IL17RA* variants are suggested to modulate IL-17 signaling pathways, underlining their role in autoimmune pathogenesis, and offering potential implications for personalized treatment approaches.

In the present study, we also analyzed the association between specific haplotypes within the *IL17RA* gene and PsO susceptibility and the revealed a noteworthy association between the T/A/A haplotype and an elevated risk of PsO in our cohort, suggesting a potential genetic predisposition conferred by this haplotype. Furthermore, LD analysis indicated non-random associations between the investigated genetic variations within the *IL17RA* gene. All three SNVs are in an intronic region of the gene and our results demonstrated that intronic SNVs can be associated with PsO. These findings suggest a plausible role of *IL17RA* genetic variations in PsO susceptibility, possibly through their influence on the expression or function of the IL17-RA protein, a key player in immune responses. Nevertheless, further investigation is needed to elucidate how these variants impact *IL17RA* transcription and how it can be related to PsO, its comorbidity, and response to therapies.

The role of non-coding RNAs (ncRNAs), specifically long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) in the context of PsO was reviewed [31]. The

authors call attention to the emerging understanding of how these ncRNAs, which do not code for proteins, play significant roles in regulating gene transcription and post-transcriptional processes, suggesting that these ncRNAs might serve as potential therapeutic targets and contribute to a deeper comprehension of PsO pathogenesis [31]. The correlation between those findings and our results lies in the potential interplay between genetic variations and ncRNA-mediated regulatory mechanisms in the complex landscape of PsO pathogenesis.

Somehow, our three genotyped SNVs were associated with PsO. Nevertheless, the association of *IL17RA* G>A rs6518661 with mild to moderate PsO was not remained when BMI was added to the adjustment, which highlights the interactions between genetic and environmental factors regarding PsO severity [32,33]. A mendelian randomization study investigated the causal relationship between BMI and PsO and supported the idea that high BMI leads to high risk of PsO [34]. This observation aligns with our observation of the interference of the BMI covariate in the genetic factors of PsO severity. Together, these findings could suggest that BMI, as an environmental and lifestyle factor, might interact with genetic variations such as the *IL17RA* G>A rs6518661 SNV to influence the severity of PsO. Higher BMI could potentially modify the effects of genetic predisposition, either exacerbating or attenuating the risk conferred by specific genetic variants.

Some limitations of the present study should be considered, such as the small sample size of the patients with PsO, which can explain statistical trends; the case-control design which does not allow making inferences on causal relationships; the lack of studies regarding the SNVs genotyped by our group limits the comparison of our results to others. On the other hand, as a strength, our findings highlight the importance of elucidating how these SNVs can influence the development of PsO in the Brazilian population. The adjustment for confounding variables makes our statistical analysis robust regarding associations found between SNVs and PsO susceptibility and severity. To our knowledge, this is the first study to genotype these *IL17RA* genetic variants in PsO from Brazilian population.

In conclusion, our study demonstrated that the GG genotype of the rs2241049 *IL17RA* variant may be a protective factor against PsO. In addition, the C allele in homozygosis of the rs2241043 *IL17RA* variant was associated with protection against the development of severe PsO. The AA genotype in *IL17RA* G>A rs6518661 was also

associated with protection against severe PsO. However, BMI as an environmental factor played an important role even if in the presence of this genotype. Further studies are needed to elucidate if those variants interfere in receptor transcription and which genetic and epigenetic mechanisms are involved in those associations.

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7 Tables

Table 1 Sociodemographic and clinical data in healthy controls and patients with psoriasis.

Variables	Control (n=154)	Psoriasis (n=154)	p-value
Sex (F/M)	74/80	74/80	1.000
Ethnicity (C/NC)	123/31	119/32	0.819
Age (Years)	47 (37-53)	54 (28-63)	< 0.001
BMI (kg/m^2)	26.89 (± 4.13)	29.87 (± 5.66)	< 0.001
Smoking (Y/N)	21/132	25/117	0.359
CRP (mg/L)	1.70 (0.29-3.74)	3.50 (0.50-6.80)	< 0.001
Ferritin (ng/L)	167.91 (± 3.39)	223.45 (± 14.92)	0.002
PASI		7.059 (± 0.455)	-
PASI > 10		43 (27.9)	-
Plaque Psoriasis		148 (96.1)	-
Other Types of Psoriasis*		6 (3.9)	-
Psoriatic Arthritis		23 (14.9)	-
Psoriasis Medications			
Systemic		86 (55.8)	-
Topic		62 (41.6)	-
Systemic + Topic		17 (11.0)	-

Mean (± Stardad Deviation); Median (25% percentile - 75% percentile); N (%); BMI = Body Mass Index; CRP = C Reactive Protein; Y = Yes; N = No; C = Caucasian; NC = Non-Caucasian; F = Female; M = Male; PASI: Psoriasis Activity and Severity Index; *Pustular Psoriasis (1), Palmoplantar Psoriasis (4), Erythrodermic Psoriasis (1).

Table 2 Association between control and disease groups and *IL17RA* A>G rs2241049.

Model	Genotype	Controls	Psoriasis	OR (95% CI)	p-value
Allelic	A	154	209	0.799 (0.67-0.95)	0.0151
	G	112	99		
Codominant	AA	50 (37.6%)	70 (45.5%)	Reference	
	AG	54 (40.6%)	69 (44.8%)	0.91 (0.55-1.52)	0.017
	GG	29 (21.8%)	15 (9.7%)	0.37 (0.18-0.76)	
Dominant	AA	50 (37.6%)	70 (45.5%)	Reference	0.180
	AG+GG	83 (62.4%)	84 (54.5%)	0.72 (0.45-1.16)	
Recessive	AA+AG	104 (78,2%)	139 (90.3%)	Reference	0.005
	GG	29 (21.8%)	15 (9.7%)	0.39 (0.20-0.76)	
Overdominant	AA+GG	79 (59.4%)	85 (55.2%)	Reference	0.470
	AG	54 (40.6%)	69 (44.8%)	1.19 (0.74-1.90)	

Data were expressed by absolute number (%). OR: Odds Ratio, CI: Confidence Interval.

Table 3 Binary logistic regression analysis for *IL17RA* A>G rs2241049 with psoriasis as the dependent variable and healthy controls as the reference group.

Regression	Explanatory Variables	Wald	df	p-value	OR	CI 95%
#1	Sex	0.503	1	0.478	1.187	0.739 - 1.907
	Ethnicity	0.002	1	0.967	1.012	0.567 - 1.808
	*IL17RA*_AG	7.425	1	0.006	0.391	0.199 - 0.768
#2	Sex	0.011	1	0.916	0.974	0.592 - 1.600
	Ethnicity	0.006	1	0.940	0.977	0.538 - 1.775
	Age	11.343	1	0.001	1.039	1.016 - 1.063
	*IL17RA*_AG	7.475	1	0.006	0.383	0.193 - 0.762
#3	Sex	0.032	1	0.857	0.953	0.562 - 1.616
	Ethnicity	0.104	1	0.748	1.107	0.597 - 2.052
	Age	9.406	1	0.002	1.038	1.014 - 1.063
	BMI	20.396	1	<0.001	1.133	1.073 - 1.197
	*IL17RA*_AG	6.003	1	0.014	0.402	0.194 - 0.833
#4	Sex	0.669	1	0.413	0.774	0.419 - 1.429
	Ethnicity	0.669	1	0.413	1.326	0.674 - 2.606
	Age	5.115	1	0.024	1.029	1.004 - 1.054
	BMI	12.668	1	<0.001	1.110	1.048 - 1.176
	CRP	2.580	1	0.108	1.051	0.989 - 1.117
	Ferritin	4.814	1	0.028	1.002	1.000 - 1.004
	*IL17RA*_AG	8.317	1	0.004	0.316	0.145 - 0.692

BMI: Body Mass Index; CRP: C-Reactive Protein; CI: Confidence Interval; OR: Odds Ratio*;* *IL17RA*_AG (rs2241049): AA+AG vs GG (recessive model).

Table 4 Association between PASI and *IL17RA* T>C rs2241043.

Model	Genotype	PASI ≤ 10	PASI > 10	OR (95% CI)	p-value
Allelic	T	117	53	0.904 (0.79-1.04)	0.1630
	C	105	33		
Codominant	TT	34 (30.6%)	14 (32.6%)	Reference	
	TC	49 (44.2%)	25 (58.1%)	1.24 (0.56-.2.72)	0.058
	CC	28 (25.2%)	4 (9.3%)	0.35 (0.10-1.17)	
Dominant	TT	34 (30.6%)	14 (32.6%)	Reference	0.820
	TC+CC	77 (69.4%)	29 (67.4%)	0.91 (0.43-1.95)	
Recessive	TT+TC	83 (74.8%)	39 (90.7%)	Reference	0.020
	CC	28 (25.2%)	4 (9.3%)	0.30 (0.10-0.93)	
Overdominant	TT+CC	62 (55.9%)	18 (41.9%)	Reference	0.120
	TC	49 (44.1%)	25 (58.1%)	1.76 (0.86-3.58)	

Data were expressed by absolute number (%). OR: Odds Ratio. CI: Confidence Interval; PASI: Psoriasis Activity and Severity Index; PASI ≤ 10: mild to moderate psoriasis; PASI > 10: severe psoriasis.

Table 5 Association between PASI and *IL17RA* G>A rs6518661.

Model	Genotype	PASI ≤ 10	PASI > 10	OR (95% CI)	p-value
Allelic	G	135	58	0.925 (0.81-1.07)	0.297
	A	87	28		
Codominant	GG	44 (39.6%)	17 (39.5%)	Reference	0.050
	GA	47 (42.4%)	24 (55.8%)	1.32 (0.63-2.78)	
	AA	20 (18.0%)	2 (4.7%)	0.26 (0.05-1.23)	
Dominant	GG	44 (39.6%)	17 (39.5%)	Reference	0.990
	GA+AA	67 (60.4%)	26 (60.5%)	1.00 (0.49-2.06)	
Recessive	GG+GA	91 (82.0%)	41 (95.3%)	Reference	0.020
	AA	20 (18.0%)	2 (4.7%)	0.22 (0.05-0.99)	
Overdominant	GG+AA	64 (57.7%)	19 (44.2%)	Reference	0.130
	GA	47 (42.3%)	24 (55.8%)	1.72 (0.85-3.50)	

Data were expressed by absolute number (%). OR: Odds Ratio. CI: Confidence Interval; PASI: Psoriasis Activity and Severity Index; PASI ≤ 10: mild to moderate psoriasis; PASI > 10: severe psoriasis.

Table 6 Binary logistic regression analysis for *IL17RA* T>C rs2241043 with PASI > 10 as the dependent variable and PASI ≤ 10 as the reference group.

Regression	Explanatory Variables	Wald	df	p-value	OR	CI 95%
#1	Sex	0.023	1	0.879	0.944	0.453 - 1.969
	Ethnicity	0.288	1	0.591	0.779	0.313 - 1.938
	*IL17RA*_TC	4.493	1	0.034	0.296	0.096 - 0.912
#2	Sex	0.002	1	0.962	1.018	0.482 - 2.150
	Ethnicity	0.116	1	0.733	0.852	0.339 - 2.142
	Age	1.898	1	0.168	0.981	0.956 - 1.008
	*IL17RA*_TC	4.502	1	0.034	0.295	0.095 - 0.911
#3	Sex	0.142	1	0.706	1.159	0.539 - 2.492
	Ethnicity	0.059	1	0.808	0.891	0.352 - 2.255
	Age	2.274	1	0.132	0.979	0.952 - 1.006
	BMI	0.399	1	0.528	1.022	0.954 - 1.095
	*IL17RA*_TC	4.082	1	0.043	0.303	0.095 - 0.965

BMI: Body Mass Index; CRP: C-Reactive Protein; CI: Confidence Interval; OR: Odds Ratio; PASI: Psoriasis Activity and Severity Index; PASI ≤ 10: mild to moderate psoriasis; PASI > 10: severe psoriasis; *IL17RA*_TC (rs2241043): TT+TC vs CC (recessive model).

Table 7 Haplotype frequencies estimation between healthy controls and patients with psoriasis.

	IL17RA **T>C rs2241043**	**IL17RA A>G rs2241049**	***IL17RA*** **G>A rs6518661**	**TOTAL (n=288)**	**Healthy Control**	**Psoriasis**	**Cumulative frequency**
1	T	G	G	0.2053	0.2512	0.1633	0.2053
2	T	A	A	0.1995	0.1567	0.2411	0.4047
3	C	G	G	0.1532	0.1549	0.1537	0.5580
4	C	A	G	0.1473	0.1282	0.1665	0.7053
5	C	A	A	0.1471	0.1635	0.1279	0.8523
6	T	A	G	0.1379	0.1290	0.1431	0.9902
7	T	G	A	0.0098	0.0163	0.0044	1
8	C	G	A	0	0	0	1

Table 8 – Haplotype association between healthy controls and patients with psoriasis.

	IL17RA **T>C rs2241043**	***IL17RA*** **A>G rs2241049**	***IL17RA*** **G>A rs6518661**	**Frequency**	**OR (95% CI)**	**P value**
1	T	G	G	0.2072	1.00	---
2	T	A	A	0.1954	1.95 (1.06 - 3.60)	0.033
3	C	G	G	0.1532	1.35 (0.67 - 2.71)	0.41
4	C	A	G	0.1498	1.68 (0.89 - 3.19)	0.11
5	C	A	A	0.1474	1.23 (0.68 - 2.24)	0.49
6	T	A	G	0.1368	1.50 (0.74 - 3.05)	0.26
rare	*	*	*	0.0101	0.65 (0.05 - 7.70)	0.73

Data was adjusted by age, sex, and ethnicity. OR: Odds Ratio; CI: Confidence Interval.

8 Supplementary Tables

Supplementary Table 1 – Association between response group and *IL17RA* T>C rs2241043.

Model	Genotype	Controls	Psoriasis	OR (95% CI)	P value
Allelic	T	146	170	1.10 (0.72-1.39)	0.999
	C	118	138		
Codominant	TT	43 (32.6%)	48 (31.2%)	reference	
	TC	60 (45.4%)	74 (48.0%)	1.10 (0.65-1.88)	0.910
	CC	29 (22.0%)	32 (20.8%)	0.99 (0.52-1.89)	
Dominant	TT	43 (32.6%)	48 (31.2%)	reference	0.800
	TC+CC	89 (67.4%)	106 (68.8%)	1.07 (0.65-1.76)	
Recessive	TT+TC	103 (78.0%)	122 (79.2%)	reference	0.810
	CC	29 (22.0%)	32 (20.8%)	0.93 (0.53-1.64)	
Overdominant	TT+CC	72 (54.5%)	80 (52.0%)	reference	0.660
	TC	60 (45.5%)	74 (48.0%)	1.11 (0.70-1.77)	

Data were expressed by absolute number (%). Bold values represent statistically significant data. OR: Odds Ratio, CI: Confidence Interval.

Supplementary Table 2 – Association between response group and *IL17RA* G>A rs6518661.

Model	Genotype	Controls	Psoriasis	OR (95% CI)	P value
Allelic	G	175	193	1.17 (0.84-1.65)	0.382
	A	89	115		
Codominant	GG	60 (45.4%)	61 (39.6%)	reference	
	GA	55 (41.7%)	71 (46.1%)	1.27 (0.77-2.10)	0.610
	AA	17 (12.9%)	22 (14.3%)	1.27 (0.62-2.63)	
Dominant	GG	60 (45.5%)	61 (39.6%)	reference	0.320
	GA+AA	72 (54.5%)	93 (60.4%)	1.27 (0.79-2.03)	
Recessive	GG+GA	115 (87.1%)	132 (85.7%)	reference	0.730
	AA	17 (12.9%)	22 (14.3%)	1.13 (0.57-2.23)	
Overdominant	GG+AA	77 (58.3%)	83 (53.9%)	reference	0.450
	GA	55 (41.7%)	71 (46.1%)	1.20 (0.75-1.91)	

Data were expressed by absolute number (%). OR: Odds Ratio, CI: Confidence Interval.

Supplementary Table 3 – Binary logistic regression analysis for *IL17RA* G>A rs6518661 with PASI > 10 as the dependent variable and PASI ≤ 10 as the reference group.

Regression	**Explanatory Variables**	**Wald**	**df**	**p-value**	**OR**	**CI 95%**
#1	Sex	0.061	1	0.805	1.096	0.529 - 2.270
	Ethnicity	0.145	1	0.703	0.838	0.336 - 2.086
	*IL17RA*_GA	3.528	1	0.060	0.236	0.052 - 1.065
#2	Sex	0.215	1	0.643	1.192	0.567 - 2.506
	Ethnicity	0.044	1	0.833	0.905	0.359 - 2.284
	Age	2.695	1	0.101	1.023	0.996 - 1.051
	*IL17RA*_GA	4.076	1	0.044	0.208	0.045 - 0.955
#3	Sex	0.500	1	0.480	1.317	0.614 - 2.823
	Ethnicity	0.014	1	0.905	0.945	0.372 2.398
	Age	2715	1	0.099	1.024	0.996 - 1.053
	BMI	0.044	1	0.834	0.993	0.930 - 1.061
	*IL17RA*_GA	3.531	1	0.060	0.231	0.050 - 1.065

BMI: Body Mass Index; CRP: C-Reactive Protein; CI: Confidence Interval; OR: Odds Ratio; PASI: Psoriasis Activity and Severity Index; PASI ≤ 10: mild to moderate psoriasis; PASI > 10: severe psoriasis; IL17RA_GA (rs6518661): GG+GA vs AA (recessive model).

Supplementary Table 4 – Association between PASI and *IL17RA* A>G rs2241049.

Model	**Genotype**	**PASI ≤ 10**	**PASI > 10**	**OR (95% CI)**	**p-value**
Allelic	A	156	53	1.47 (0.88-2.48)	0.174
	G	66	33		
Codominant	AA	53 (47.8%)	17 (39.5%)	Reference	
	AG	50 (45.0%)	19 (44.2%)	1.18 (0.55-2.53)	0.240
	GG	8 (7.2%)	7 (16.3%)	2.73 (0.86-8.63)	
Dominant	AA	53 (47.8%)	17 (39.5%)	Reference	0.360
	AG+GG	58 (52.2%)	26 (60.5%)	1.40 (0.68-2.86)	
Recessive	AA+AG	103 (92.8%)	36 (83.7%)	Reference	0.100
	GG	8 (7.2%)	7 (16.3%)	2.50 (0.85-7.39)	
Overdominant	AA+GG	61 (55.0%)	24 (55.8%)	Reference	0.920
	AG	50 (45.0%)	19 (44.2%)	0.97 (0.48-1.96)	

Data were expressed by absolute number (%). OR: Odds Ratio. CI: Confidence Interval; PASI: Psoriasis Activity and Severity Index; PASI ≤ 10: mild to moderate psoriasis; PASI > 10: severe psoriasis.

Supplementary Table 5 – Linkage Disequilibrium between rs2241043, rs2241049 and rs6518661 *IL17RA* variations.

D statistic			
	IL17RA T>C rs2241043	*IL17RA* A>G rs2241049	*IL17RA* G>A rs6518661
IL17RA T>C rs2241043	*	-0.0136	-0.0145
IL17RA A>G rs2241049	*	*	-0.1215
IL17RA G>A rs6518661	*	*	*
D' statistic			
	IL17RA T>C rs2241043	*IL17RA* A>G rs2241049	*IL17RA* G>A rs6518661
IL17RA T>C rs2241043	*	0.0825	0.0905
I*L17RA* A>G rs2241049	*	*	0.9265
IL17RA G>A rs6518661	*	*	*
r statistic			
	IL17RA T>C rs2241043	*IL17RA* A>G rs2241049	*IL17RA* G>A rs6518661
IL17RA T>C rs2241043	*	-0.0566	-0.0607
IL17RA A>G rs2241049	*	*	-0.5259
IL17RA G>A rs6518661	*	*	*
p-values			
	IL17RA T>C rs2241043	*IL17RA* A>G rs2241049	*IL17RA* G>A rs6518661
IL17RA T>C rs2241043	*	0.1755	0.1475
IL17RA A>G rs2241049	*	*	0
IL17RA G>A rs6518661	*	*	*

6 CONCLUSÃO

- As variantes genéticas T>C (rs2241043), A>G (rs2241049) e G>A (rs6518661) do gene *IL17RA* estão associadas a suscetibilidade e gravidade da PsO.
- A presença do genótipo GG do A>G rs2241049 está associado à 63% de proteção no modelo codominante e 61% de proteção no modelo recessivo contra o desenvolvimento de PsO.
- A presença do genótipo CC do T>C rs2241043 no modelo recessivo está associado à uma proteção de 70% contra o desenvolvimento de PsO grave, onde o PASI > 10.
- A presença do genótipo AA do G>A rs6518661 no modelo recessivo está associado à uma proteção de 78% contra o desenvolvimento de PsO grave.
- A presença do haplótipo T/A/A do gene *IL17RA* está associado ao risco elevado ao desenvolvimento de PsO.

7 CONSIDERAÇÕES FINAIS

Este estudo demonstrou que as variantes genéticas da *IL17RA* estão associadas à suscetibilidade ao desenvolvimento de PsO. A principal limitação desse estudo se baseia no seu delineamento transversal, que não permite fazer inferência de causalidade. Além disso, o número reduzido de estudos relacionados às variantes genotipadas neste trabalho limita a comparação com outros resultados disponíveis na literatura. No entanto, até esse momento, esse é o primeiro estudo de genotipagem de variantes genéticas intrônicas do gene *IL17RA* na população brasileira e os resultados obtidos levantam o questionamento sobre a verdadeira função das regiões intrônicas. A possibilidade dessas variantes genéticas influenciarem na forma como o gene é transcrito ainda precisa ser investigada e mais estudos são necessários para elucidar quais os mecanismos de genética e epigenética estão envolvidos nas associações entre essas variantes genéticas e o desenvolvimento e gravidade da PsO.

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APÊNDICES

APÊNDICE A – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO (TCLE)

Termo de Consentimento Livre e Esclarecido

"AVALIAÇÃO DAS VARIANTES DE GENES DE CITOCINAS PRÓ E ANTI-INFLAMATÓRIAS NA SUSCETIBILIDADE À PSORÍASE: ASSOCIAÇÃO COM CARACTERÍSTICAS CLÍNICAS, GRAVIDADE DA DOENÇA E RESPOSTA TERAPÊUTICA AO USO DE INIBIDORES DO FATOR DE NECROSE TUMORAL ALFA"

Prezado(a) Senhor(a):

Gostaríamos de convidá-lo (a) para participar da pesquisa **"Avaliação Das Variantes De Genes De Citocinas Pró E Anti-Inflamatórias Na Suscetibilidade À Psoríase: Associação Com Características Clínicas, Gravidade Da Doença E Resposta Terapêutica Ao Uso De Inibidores Do Fator De Necrose Tumoral Alfa"**, a ser realizada no Ambulatório de Dermatologia do Ambulatório de Especialidade do Hospital Universitário (AEHU). O objetivo da pesquisa é estudar os mecanismos imunológicos e genéticos envolvidos na psoríase. Sua participação é muito importante e ela se daria da seguinte forma: realização de uma avaliação clínica pelo médico dermatologista e uma coleta de sangue.

Esclarecemos que sua participação é totalmente voluntária, podendo você: recusar-se a participar, ou mesmo desistir a qualquer momento, sem que isto acarrete qualquer ônus ou prejuízo à sua pessoa. Esclarecemos, também, que suas informações serão utilizadas somente para os fins desta pesquisa e serão tratadas com o mais absoluto sigilo e confidencialidade, de modo a preservar a sua identidade. Todos os dados coletados, clínicos e laboratoriais, serão descartados após a publicação do estudo.

Esclarecemos ainda, que você não pagará e nem será remunerado(a) por sua participação. Garantimos, no entanto, que todas as despesas decorrentes da pesquisa serão ressarcidas, quando devidas e decorrentes especificamente de sua participação.

Os benefícios esperados são contribuir para o melhor entendimento dos mecanismos fisiopatológicos envolvidos no desenvolvimento da doença. Quanto aos riscos, informamos que sua participação não acarretará qualquer risco à sua saúde nem alteração de qualquer um dos seus tratamentos. Serão coletados, ao total, 6 tubos de sangue ou, aproximadamente, 23mL. 3 tubos de EDTA e 3 tubos de SORO. A coleta de sangue pode ocasionar sinais decorrentes da punção venosa e consiste: dor no local da punção venosa ou pequeno hematoma e, muito raramente, vermelhidão ou infecção local. Mesmo sendo mínimos, caso ocorra algum tipo de desconforto o participante será prontamente atendido e

*Termo de Consentimento Livre Esclarecido apresentado conforme normas da Resolução 466/2012 de 12 de dezembro de 2012.

amparado pelos farmacêuticos responsáveis pela coleta de sangue e um dos pesquisadores deste estudo.

Além disso, os pesquisadores terão acesso ao seu prontuário para colher informações como tempo de diagnóstico, tipo de psoríase, gravidade da doença, histórico familiar, tratamentos anteriores e presença de comorbidades. Essas informações são importantes e necessárias para o entendimento da doença. No entanto, nenhuma informação do prontuário do paciente será divulgada ou enviada a terceiros. Nos comprometemos a manter sigilo das suas informações e utiliza-las tão somente para a pesquisa.

Caso você tenha dúvidas ou necessite de maiores esclarecimentos poderá nos contatar **(Andréa Name Colado Simão, Avenida Robert Koch 60, telefone: 3371-2321, 99627-8181, deianame@yahoo.com.br),,** ou procurar o Comitê de Ética em Pesquisa Envolvendo Seres Humanos da Universidade Estadual de Londrina, situado junto ao prédio do LABESC – Laboratório Escola, no Campus Universitário, telefone 3371-5455, e-mail: cep268@uel.br.

Este termo deverá ser preenchido em duas vias de igual teor, sendo uma delas devidamente preenchida, assinada e entregue a você.

Londrina, ___ de _____de 20__.

Pesquisador Responsável

Profa Dra. Andréa Name Colado Simão

RG: 6.226.736-4

Tel: 3371-2321 / 99627-8181

Eu, _____ (**colocar nome por extenso do participante da pesquisa**), tendo sido devidamente esclarecido sobre os procedimentos da pesquisa, concordo em participar voluntariamente da pesquisa descrita acima.

Assinatura (ou impressão dactiloscópica):_____

Data:_____

*Termo de Consentimento Livre Esclarecido apresentado conforme normas da Resolução 466/2012 de 12 de dezembro de 2012.

APÊNDICE B – FICHA DE AVALIAÇÃO

Nome:		**Prontuário:**
Data:	**Telefone:**	
Idade:	**Data de nascimento:**	**Data do diagnóstico:**
Etnia	**( ) Caucasiano**	**( ) Não Caucasiano** **( ) Oriental**
Doença:	**( ) Psoríase em placas** **( ) Psoríase gotada** **( ) Psoríase Eritrodérmica** **( ) Psoríase pustulosa**	**( ) Artrite Psoriásica** **( ) Outras** **Qual:**
Outras Doenças:		
Tabagismo	**( ) Não**	**( ) Sim** **Quantos/dia:**
Diabetes	**( ) Não**	**( ) Sim**
HAS	**( ) Não**	**( ) Sim**
Alcoolismo	**( ) Não**	**( ) Sim**
Depressão	**( ) Não**	**( ) Sim** **Psiquiatra?**
Atividade Física	**( ) Não**	**( ) Sim** **Frequência:**
Peso: Kg	**Altura:** m	**IMC:**
PAS/PAD: x mmHg	**Circunferência abdominal:** cm	**PASI:**
Uso de Medicamentos:		

ANEXOS

ANEXO A – ÍNDICE DE GRAVIDADE E EXTENSÃO DAS LESÕES PSORIÁTICAS (PASI)

PASI (Índice de área e gravidade da psoríase)

Índice de gravidade	Eritema	Descamação	Infiltração
Ausente	0	0	0
Leve	1	1	1
Moderado	2	2	2
Grave	3	3	3
Muito grave	4	4	4

Porcentagem da área corporal acometida	(A) Indicador da extensão
nenhum	0
< 10%	1
10 - 30%	2
30 - 50%	3
50 - 70%	4
70 - 90%	5
90 - 100%	6

	Eritema		Descamação		Infiltração		(A) Área acometida		Total
Cabeça	(	+		+		) x		x (0,1) =	T1
Tronco	(	+		+		) x		x (0,3) =	T2
Extremidades superiores	(	+		+		) x		x (0,2) =	T3
Extremidades Inferiores	(	+		+		) x		x (0,4) =	T4

PASI (T1 + T2 + T3 + T4)

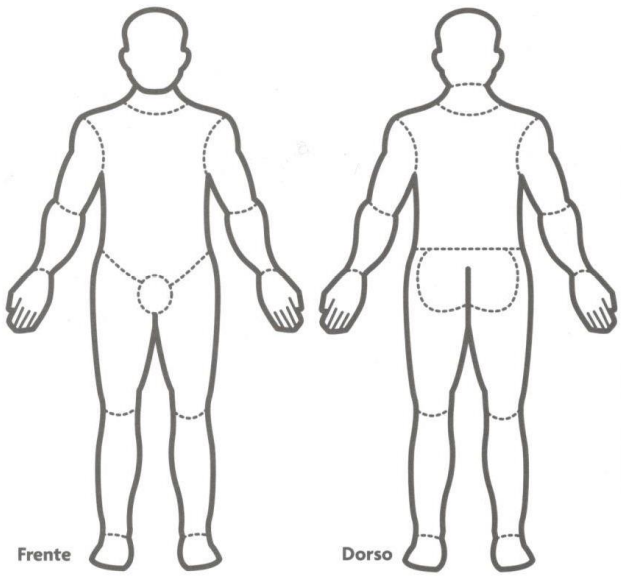
CASPAR 2006 (Critérios classificatórios de Artrite Psoriásica)

Doença articular inflamatória estabelecida e pelo menos três pontos nos seguintes critérios:

- ☐ Psoríase cutânea atual **2 pontos**
- ☐ História de psoríase **1 ponto**
- ☐ História familiar de psoríase **1 ponto**
- ☐ Dactilite **1 ponto**
- ☐ Neoformação óssea justa-articular **1 ponto**
- ☐ Fator reumatoide negativo **1 ponto**
- ☐ Distrofia ungueal **1 ponto**

Escore CASPAR total = _____

Referência: Taylor W, Gladman D, Helliwell P, et al.: Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 54:2665-73, 2006.



ANEXO B – DOCUMENTO DE APROVAÇÃO DO COMITÊ DE ÉTICA DA UEL

UNIVERSIDADE ESTADUAL DE LONDRINA - UEL

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: AVALIAÇÃO DAS VARIANTES DE GENES DE CITOCINAS PRÓ E ANTI-INFLAMATÓRIAS NA SUSCETIBILIDADE À PSORÍASE: ASSOCIAÇÃO COM CARACTERÍSTICAS CLÍNICAS, GRAVIDADE DA DOENÇA E RESPOSTA TERAPÊUTICA AO USO DE INIBIDORES DO FATOR DE NECROSE TUMORAL

Pesquisador: Andréa Name Colado Simão

Área Temática:

Versão: 2

CAAE: 37420820.0.0000.5231

Instituição Proponente: CCS - Departamento de Patologia, Análises Clínicas e Toxicologias

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.304.205

Apresentação do Projeto:

A psoríase é uma doença imunomediada que acomete a pele e apesar de etiologia desconhecida, sabe-se que fatores genéticos, epigenéticos e ambientais podem influenciar no desenvolvimento dessa doença. Poucos estudos sobre variantes genéticas disponíveis na literatura avaliam os níveis plasmáticos das citocinas codificadas pelos genes estudados e como essas variações influenciam na fisiopatologia e manejo terapêutico do paciente. A fim de preencher essa lacuna e aumentar o entendimento sobre como o fator genético pode interferir no fenótipo e na qualidade de vida do paciente, se faz necessário o estudo com variantes genéticas e níveis séricos das principais citocinas envolvidas na psoríase.

Objetivo da Pesquisa:

Avaliar as variantes de genes de citocinas pró e anti-inflamatórias na psoríase, assim como sua associação com características clínicas, gravidade da doença e resposta terapêutica ao uso de inibidores do TNF.

Avaliação dos Riscos e Benefícios:

Riscos:

Não acarretará qualquer risco à sua saúde nem alteração de qualquer um dos seus tratamentos. A coleta de sangue pode ocasionar sinais decorrentes da punção venosa e consiste: dor no local da

Endereço: LABESC - Sala 14
Bairro: Campus Universitário **CEP:** 86.057-970
UF: PR **Município:** LONDRINA
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punção venosa ou pequeno hematoma e, muito raramente, vermelhidão ou infecção local. Mesmo sendo mínimos, caso ocorra algum tipo de desconforto o participante será prontamente atendido e amparado pelos farmacêuticos responsáveis pela coleta de sangue e um dos pesquisadores deste estudo.
Benefícios:
Os resultados contribuirão para o melhor entendimento dos mecanismos fisiopatológicos envolvidos no desenvolvimento da doença.

Comentários e Considerações sobre a Pesquisa:
A pesquisa visa elucidar o papel de variantes genéticas e níveis plasmáticos das citocinas para estabelecer um paralelo em relação ao desenvolvimento da doença e a análise destes mediadores imunológicos.

Considerações sobre os Termos de apresentação obrigatória:
1. Folha de rosto adequadamente apresentada e assinada pela instituição proponente.
2. Carta do Hospital Universitário;
3. Apresentou TCLE em forma de convite e contém os riscos e benefícios claramente descritos;
4. Apresentou cronograma compatível;

Conclusões ou Pendências e Lista de Inadequações:
Conclusões ou Pendências e Lista de Inadequações:
1. Quanto às pendencias respondidas, a pesquisadora inseriu no TCLE bem como no projeto a necessidade de consulta ao prontuário do paciente
2. A pesquisadora esclareceu quanto ao volume de sangue dos pacientes que serão utilizados e acrescentou estas informação no TCLE e no corpo do projeto.
3. Atendendo a recomendação de dar preferencia a assinatura do pesquisador no momento do convite ao paciente, a pesquisadora retirou a assinatura digitalizada e orienta a assinatura presencial.

Considerações Finais a critério do CEP:
Prezado(a) Pesquisador(a),
Este é seu parecer final de aprovação, vinculado ao Comitê de Ética em Pesquisas Envolvendo Seres Humanos da Universidade Estadual de Londrina. É sua responsabilidade apresenta-Lo aos órgãos

e/ou instituições pertinentes.

Ressaltamos, para início da pesquisa, as seguintes atribuições do pesquisador, conforme Resolução CNS 466/2012 e 510/2016:

A responsabilidade do pesquisador é indelegável e indeclinável e compreende os aspectos éticos e legais, cabendo-lhe:

- conduzir o processo de Consentimento e de Assentimento Livre e Esclarecido;
- apresentar dados solicitados pelo sistema CEP/CONEP a qualquer momento;
- desenvolver o projeto conforme delineado, justificando, quando ocorridas, a sua mudança ou interrupção;
- elaborar e apresentar os relatórios parciais e final;
- manter os dados da pesquisa em arquivo, físico ou digital, sob sua guarda e responsabilidade, por um período mínimo de 5 (cinco) anos após o término da pesquisa;
- encaminhar os resultados da pesquisa para publicação, com os devidos créditos aos pesquisadores e pessoal técnico integrante do projeto;
- justificar fundamentadamente, perante o sistema CEP/CONEP, interrupção do projeto ou a não publicação dos resultados.

Coordenação CEP/UEL.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1506761.pdf	24/09/2020 12:16:55		Aceito
Outros	CARTA_RESPOSTA_PSORIASE.pdf	24/09/2020 12:16:35	CAMILA CATALDI DE ALCANTARA	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_PSORIASE_CEP_ALTERADO.pdf	24/09/2020 12:16:21	CAMILA CATALDI DE ALCANTARA	Aceito
Parecer Anterior	PB_PARECER_CONSUBSTANCIADO_CEP_4276625_PSORIASE_LIGIA.pdf	24/09/2020 12:13:13	CAMILA CATALDI DE ALCANTARA	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_PSORIASE.pdf	05/09/2020 15:47:57	CAMILA CATALDI DE ALCANTARA	Aceito
Declaração de	PARACER_PROJETO_PSORIASE_HU.	05/09/2020	CAMILA CATALDI	Aceito

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Instituição e Infraestrutura	PARACER_PROJETO_PSORIASE_HU.pdf	15:46:03	DE ALCANTARA	Aceito
Outros	CONFIDENCIALIDADE_E_SIGILO_PSORIASE_ASSINADO.pdf	05/09/2020 15:44:16	CAMILA CATALDI DE ALCANTARA	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	BANCO_MATERIAL_BIOLOGICO_PSORIASE_ASSINADO.pdf	05/09/2020 15:40:40	CAMILA CATALDI DE ALCANTARA	Aceito
Folha de Rosto	FOLHA_DE_ROSTO_PSORIASE_CEP.pdf	05/09/2020 15:39:08	CAMILA CATALDI DE ALCANTARA	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

LONDRINA, 28 de Setembro de 2020

Assinado por:
Adriana Lourenço Soares Russo
(Coordenador(a))