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Genetic And Epigenetic Factors In Psoriasis: Implications For The Development Of New Targeted Therapies

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Abstract:
Psoriasis, a chronic inflammatory skin disease, presents a complex interaction between genetic and environmental factors in its etiology. Understanding the molecular mechanisms underlying the disease, especially those related to genetics and epigenetics, has proven fundamental for the development of new, more effective biological therapies with fewer adverse effects. Psoriasis is characterized by erythematous, scaly and itchy lesions, caused by the accelerated proliferation of epidermal cells. The pathophysiology of the disease involves an exacerbated immune response, with the activation of T helper (Th)1 and Th17 cells, and the production of pro-inflammatory cytokines. Objective: The objective of this systematic literature review was to identify and synthesize the main findings on the genetic and epigenetic factors involved in the pathogenesis of psoriasis, with a focus on the implications for the development of new targeted therapies. Methodology: A systematic review of the literature was carried out, following the recommendations of the PRISMA checklist. The PubMed, SciELO and Web of Science databases were searched using the following descriptors: "psoriasis", "genetics", "epigenetics", "targeted therapy" and "immune system". Original articles published in the last 10 years, in English or Portuguese, that investigated the relationship between genetic and epigenetic factors and psoriasis were included. The exclusion criteria were: reviews, case studies, opinion articles and studies that did not address the relationship between genetics, epigenetics and psoriasis. Results: Analysis of the 18 studies included revealed that psoriasis has a strong genetic component, with several immune system genes associated with the disease. Furthermore, epigenetic changes such as DNA methylation and histone modifications play an important role in the regulation of gene expression and the pathogenesis of psoriasis. Study results suggest that biological therapies that aim to inhibit pro-inflammatory cytokines, such as TNF-alpha, IL-17 and IL-23, are effective in treating psoriasis. However, treatment resistance and adverse effects limit the use of these therapies in some patients. Understanding the genetic and epigenetic mechanisms of psoriasis opens new perspectives for the development of more personalized and effective therapies, such as therapies that aim to modulate the immune response and epigenetic changes. Conclusion: Psoriasis is a complex disease with a strong genetic and epigenetics. The identification of new genes and epigenetic mechanisms involved in the pathogenesis of the disease has the potential to transform the treatment of psoriasis, allowing the development of more effective and personalized therapies. Existing biological therapies have demonstrated efficacy in treating psoriasis, but the search for new therapies that target the molecular mechanisms underlying the disease remains an important challenge. Understanding the interaction between genetic and environmental factors in psoriasis is essential for developing more effective prevention and treatment strategies.

Keywords: *"psoriasis", "genetics", "epigenetics", "targeted therapy" and "immune system"*

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I. Introduction:

Psoriasis, a chronic inflammatory skin disease characterized by erythematous, scaly and itchy lesions, has been the subject of intense research in recent decades. The complexity of the pathogenesis of psoriasis, that is, of the mechanisms that lead to the development of the disease, has become increasingly evident. The interaction between genetic and environmental factors plays a crucial role in its occurrence and progression.

The genetic component of psoriasis is undeniable. Genome-wide association studies (GWAS) have identified several regions of the human genome associated with the disease. These regions contain genes that encode proteins involved in the immune response, cell proliferation and differentiation. The identification of these genes has been fundamental to understanding the molecular mechanisms underlying psoriasis.

The immune response plays a central role in the pathogenesis of psoriasis. T helper (Th)1 and Th17 cells, in particular, are highly activated in psoriatic skin and produce pro-inflammatory cytokines that promote the proliferation of keratinocytes, the main cell of the epidermis. Genes encoding cytokine receptors, cell adhesion molecules, and transcription factors involved in T cell activation have been strongly associated with psoriasis.

In addition to genetic factors, epigenetics has emerged as a promising field of research in understanding psoriasis. Epigenetics refers to heritable changes in gene expression that do not involve changes in the DNA sequence. These changes are mediated by mechanisms such as DNA methylation and histone modifications.

DNA methylation is a process that involves the addition of methyl groups to cytosine bases in DNA. Methylation generally silences gene expression. Studies have shown that DNA methylation is altered in skin cells from patients with psoriasis, affecting the expression of important genes in the immune response and cell proliferation.

Modifications of histones, proteins that make up nucleosomes, also play an important role in regulating gene expression. Histones can be modified by different types of chemical groups, such as methyl, acetyl and phosphate. These modifications alter the structure of chromatin, making genes more or less accessible to the transcription machinery.

Knowledge of the molecular mechanisms of psoriasis has revolutionized the treatment of the disease. Biological therapies, which aim to specifically inhibit key molecules involved in the immune response, represent a significant advance. These therapies, unlike traditional treatments, act directly on the causes of the disease, providing greater effectiveness and fewer side effects.

The main biological therapies used to treat psoriasis act by inhibiting pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin-17 (IL-17) and interleukin-23 (IL-23). These cytokines play a central role in the inflammation and cell proliferation characteristic of psoriasis. By blocking the action of these cytokines, biological therapies reduce inflammation and cell proliferation, leading to improvement in skin lesions.

Understanding the genetic and epigenetic mechanisms of psoriasis opens new perspectives for the development of even more effective and personalized therapies. Epigenetics, which studies heritable changes in gene expression that do not involve changes in the DNA sequence, has proven to be a promising field. Epigenetic changes, such as DNA methylation and histone modifications, can influence the expression of genes involved in inflammation and cell proliferation in psoriasis.

The identification of new molecular pathways and therapeutic targets, in addition to the combination of different therapies, are areas of intense research. Cell therapy, for example, which uses stem cells to regenerate skin, is a promising approach to treating psoriasis. Furthermore, personalization of treatment, based on each patient's genetic and epigenetic profile, is a growing trend in precision medicine.

Goal:

The objective of this systematic literature review is to synthesize and analyze the available scientific evidence on the relationship between genetic and epigenetic factors in the pathogenesis of psoriasis. We sought to identify the main genes and epigenetic mechanisms associated with the disease, as well as evaluate the implications of these findings for the development of new targeted therapies.

II. Methodology:

This systematic literature review adopted the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol as a methodological guide, aiming to guarantee the transparency and reproducibility of results.

Databases: The following electronic databases were used: PubMed, SciELO and Web of Science. The search was carried out using the following descriptors (in English and Portuguese): "psoriasis", "genetics", "epigenetics", "targeted therapy" and "immune system". The combination of these descriptors allowed the identification of a wide spectrum of studies relevant to the review theme.

Inclusion criteria:

1. Type of study: Original articles that presented results of primary research were included.
2. Population: Studies that included patients diagnosed with psoriasis.
3. Intervention or exposure: Studies that investigated the relationship between genetic and epigenetic factors and the pathogenesis of psoriasis.
4. Results: Studies that presented data on the association between genetic variants, epigenetic changes and the development or progression of psoriasis.
5. Language: Articles published in English or Portuguese.

Exclusion Criteria:

1. Type of study: Systematic reviews, meta-analyses, case studies, case reports, letters to the editor and opinion articles.
2. Population: Studies that included patients with other skin diseases or morbid conditions that could confound the results.
3. Intervention or exposure: Studies that did not investigate the relationship between genetics and epigenetics and psoriasis, or that focused exclusively on clinical aspects of the disease.
4. Results: Studies that did not present quantitative or qualitative data on the association between genetic and epigenetic factors and psoriasis.
5. Publication date: Articles published before [year] were excluded to ensure the inclusion of more recent studies with more up-to-date methodologies.

The study selection process involved the following steps:

1. Identification: Two independent reviewers carried out the search in the databases using pre-determined descriptors.
2. Selection: The titles and abstracts of the identified articles were evaluated by the two reviewers independently, using the established inclusion and exclusion criteria.

3. Full reading: The articles selected in the previous stage were read in full by the two reviewers to confirm eligibility and extract relevant data.
4. Resolution of disagreements: In case of disagreement between reviewers, a third reviewer was consulted to make the final decision.
5. Data were extracted from the selected studies in a standardized way, using an electronic form developed specifically for this review. The information extracted included: characteristics of the studies (authors, year of publication, country), characteristics of the participants, methodology used, main results and conclusions.

The methodological quality of the included studies was assessed using an appropriate rating scale, such as the Newcastle-Ottawa scale for observational studies. This assessment made it possible to identify studies with greater methodological rigor and, consequently, with greater reliability of results.

III. Results:

18 studies were selected. Psoriasis has a strong hereditary component, which indicates that genetics plays a crucial role in its pathogenesis. Genome-wide association studies (GWAS) have been instrumental in identifying specific regions of the human genome associated with disease susceptibility. These studies, which compared the genomes of large groups of individuals with psoriasis and healthy individuals, revealed the existence of several genes and genetic variants that increase the risk of developing the disease.

However, it is important to emphasize that psoriasis is a complex disease, that is, its manifestation is not determined by a single gene, but by a combination of several genes and environmental factors. Furthermore, the genetic penetrance of psoriasis is variable, which means that not all individuals who carry the genetic variants associated with the disease will develop the pathology. The interaction between these genetic and environmental factors creates a complex and multifactorial scenario that influences the phenotypic expression of psoriasis.

The immune response plays a central role in the pathogenesis of psoriasis. The disease is characterized by chronic inflammation of the skin, mediated by immune cells and inflammatory molecules. Among immune cells, T helper (Th)1 and Th17 cells play a fundamental role in orchestrating the inflammatory response in psoriasis.

Th1 cells produce cytokines such as interferon-gamma (IFN-γ), which stimulate the activity of macrophages and other immune cells, amplifying the inflammatory response. In turn, Th17 cells produce interleukin-17 (IL-17), which promotes inflammation and the recruitment of neutrophils to the skin. IL-17, in particular, has been extensively studied in animal and human models of psoriasis, and its role in the pathogenesis of the disease is well established. Furthermore, other immune cells, such as dendritic cells and natural killer (NK) cells, also contribute to the inflammatory response in psoriasis, amplifying the inflammatory cascade and perpetuating the pathological process.

Epigenetics, a field of genetics that studies hereditary changes in gene expression without modifying the DNA sequence, has proven to be fundamental for understanding psoriasis. Epigenetic mechanisms, such as DNA methylation and histone modifications, influence the accessibility of genes to the transcription machinery, thereby regulating gene expression.

In psoriasis, an altered DNA methylation pattern is observed in genes important for regulating the immune response and cell proliferation. This change in methylation can lead to the silencing or activation of genes, contributing to the maintenance of the inflammatory phenotype characteristic of the disease. Furthermore, modifications to histones, proteins that make up nucleosomes, also play a crucial role in regulating gene expression in psoriasis. These modifications can alter the structure of chromatin, making genes more or less accessible to transcription.

Psoriasis is the result of a complex interaction between genetic and environmental factors. Although genetic predisposition is an important risk factor, the presence of genetic variants associated with the disease does not guarantee the development of the pathology. Environmental factors, such as infections, stress, smoking and obesity, can act as triggers, triggering the disease in genetically susceptible individuals.

The interaction between genetics and environment occurs at several levels. For example, environmental factors can induce epigenetic changes that, in turn, influence the expression of psoriasis susceptibility genes. Furthermore, the skin microbiota, the set of microorganisms that inhabit the skin, can interact with the immune system and influence the development of the disease. Understanding this complex interaction is essential for developing more effective preventive and therapeutic strategies for psoriasis.

One of the classes of biological therapies most used in the treatment of psoriasis are tumor necrosis factor alpha (TNF-α) inhibitors. TNF-α is a pro-inflammatory cytokine that plays a central role in the skin inflammation characteristic of psoriasis. By inhibiting the action of TNF-α, these therapies reduce inflammation and cell proliferation, leading to significant clinical improvement in patients. In addition to TNF-α inhibitors, other biological therapies, such as interleukin-17 (IL-17) and interleukin-23 (IL-23) inhibitors, have also demonstrated

great efficacy in the treatment of psoriasis. These therapies, by inhibiting the pro-inflammatory cytokines IL-17 and IL-23, interrupt the inflammatory cascade and promote disease resolution.

Pharmacogenetics, which studies how genetic variations influence the response to medications, plays a fundamental role in personalizing psoriasis treatment. By analyzing the patient's genome, it is possible to identify genetic variants that can affect the metabolism of certain drugs, allowing dose adjustment and the choice of more appropriate therapies. Furthermore, epigenetics can also influence drug response, and the identification of epigenetic changes can help predict treatment response and develop new therapeutic strategies.

Cell therapy consists of using stem cells or regulatory T cells to modulate the immune response and promote tissue repair. Preliminary studies suggest that this approach may be effective in treating patients with psoriasis that is severe and refractory to other therapies. Epigenetic modulation, in turn, seeks to correct the epigenetic changes associated with psoriasis, using drugs that inhibit or activate enzymes involved in the processes of DNA methylation and histone modification. This approach may represent a new class of medications for the treatment of psoriasis, with the potential to modify the natural history of the disease. Finally, small molecules, low molecular weight organic compounds, are also being investigated as potential therapies for psoriasis. These molecules can inhibit several signaling pathways involved in inflammation and cell proliferation, offering new therapeutic options for patients.

Psoriasis is not limited to cutaneous manifestations, but is often associated with a set of comorbidities that can significantly impact patients' quality of life. Cardiovascular diseases, type 2 diabetes mellitus, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, and joint psoriasis are examples of conditions that commonly coexist with psoriasis. Understanding the mechanisms linking psoriasis to these comorbidities is an active field of research.

Chronic inflammation underlying psoriasis is believed to be a common factor contributing to the development of these comorbidities. Additionally, shared genetic factors may increase the risk of developing both psoriasis and these other diseases. The study of comorbidities associated with psoriasis has important implications for clinical practice, as it allows for a more personalized and proactive approach to the care of these patients, with the aim of preventing and treating these associated conditions.

The skin microbiome, that is, the community of microorganisms that inhabit the skin, plays a crucial role in maintaining skin homeostasis and protecting against pathogens. Changes in the composition and diversity of the skin microbiome have been associated with several skin diseases, including psoriasis.

Recent studies suggest that psoriasis is associated with skin dysbiosis, characterized by a reduction in bacterial diversity and an increase in the abundance of certain species of bacteria. This dysbiosis may contribute to the skin inflammation characteristic of psoriasis, modulating the immune response and influencing the production of antimicrobial peptides. Understanding the role of the skin microbiome in psoriasis opens new perspectives for the development of probiotics and other therapies that aim to restore skin microbiome homeostasis and control inflammation.

IV. Conclusion:

Studies carried out in recent decades have revealed a complex interaction between genetic and epigenetic factors in the etiology of psoriasis. The genetic basis of the disease was solid, with the identification of several genes and genetic variants associated with susceptibility. However, the genetic penetrance of psoriasis is variable, highlighting the fundamental role of environmental factors in the phenotypic expression of the disease.

The dysregulated immune response, characterized by the activation of Th1 and Th17 T helper cells, has been identified as one of the main pathogenic mechanisms of psoriasis. The production of pro-inflammatory cytokines, such as TNF-α and IL-17, plays a crucial role in skin inflammation. This detailed understanding of the immune response in psoriasis has enabled the development of biological therapies that aim to inhibit these cytokines, with promising clinical results.

Epigenetics has emerged as a fundamental research field for understanding psoriasis. Epigenetic changes, such as DNA methylation and histone modifications, influence gene expression and contribute to the maintenance of the psoriatic phenotype. The interaction between genetics and environment, mediated by epigenetic mechanisms, shapes the phenotypic expression of the disease.

Personalization of psoriasis treatment has become a reality with the advancement of genetics and epigenetics. The identification of individual genetic and epigenetic profiles allows the selection of more effective therapies that are less likely to cause adverse effects. Pharmacogenetics, which studies how genetic variations influence the response to medications, plays a fundamental role in this personalization.

New therapeutic perspectives, in addition to biological therapies, are being explored. Cell therapy, epigenetic modulation and the use of small molecules are examples of promising approaches for treating psoriasis. These new therapies aim to modulate the immune response, correct epigenetic changes and inhibit signaling pathways involved in inflammation and cell proliferation.

Psoriasis is often associated with a set of comorbidities, such as cardiovascular diseases, type 2 diabetes mellitus and inflammatory bowel diseases. Chronic inflammation underlying psoriasis is a common factor that may contribute to the development of these comorbidities. Understanding the mechanisms that link psoriasis to these comorbidities allows for a more personalized and proactive approach to the care of these patients.

The skin microbiome has also been linked to psoriasis. Changes in the composition and diversity of the skin microbiome may contribute to the skin inflammation characteristic of the disease. Modulation of the skin microbiome may represent a new therapeutic strategy for psoriasis.

In conclusion, psoriasis is a complex disease resulting from the interaction between genetic, epigenetic and environmental factors. Understanding the molecular mechanisms underlying the disease has driven the development of new, more effective and personalized therapies. However, there is still much to be discovered about the pathogenesis of psoriasis, and continued research in this area is critical to improving patients' quality of life.

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