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Importance of Autoimmune Mechanisms of Psoriasis and Role of Pathogenic

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Abstract

Psoriasis could be a chronic, recurrent, immuno-inflammatory unwellness of the skin and joints related to important morbidity and mortality. skin disorder affects or so 2-4% of the Caucasian population worldwide. The precise immuno-inflammatory mechanisms resulting in skin disorder are still to be absolutely outlined. there's rising proof supporting the existence of a relationship between changes in cuneal microbiota and development of skin disorder. underneath sure pathologic conditions related to dysbiosis of the skin microbiome, morbific microbes triggering aberrant immuno-inflammatory responses could spark the onset and relapses of skin disorder. sturdy association of sure human leucocyte antigens (HLAs) at the side of the morbific role of IL-17 suggests the involvement of reaction mechanisms in skin disorder. Multiple clinical trials targeting the IL-17/IL-23 axis in skin disorder are current. Here, we tend to review the rising findings suggesting the reaction nature of psoriasis skin disease of the skin condition and examine new therapeutic approaches for treatment of this chronic immuno-inflammatory disease.

Key words: Autoimmune; Psoriasis; Pathogenic.

INTRUDUCTION

Psoriasis is a chronic, recurrent, immuno-inflammatory disease of the skin and joints which in the most common form is manifested by erythematous, scaly plaques commonly occurring on the elbows, knees, scalp, and trunk [1]. Psoriasis has a complex genetic background. A recent twin study showed that psoriasis represents a multifactorial disorder in which genetic factors account for about 70% of disease susceptibility, whereas environmental factors account for the remaining 30% [2]. These findings indicate that heritability is not the only cause of psoriasis, and other environmental factors such as skin microbiota may also contribute to the susceptibility to this immuno-inflammatory disease.

Histologically, psoriasis is characterized by inflammatory hyperproliferation and thickening of the epidermis, accompanied by altered differentiation of keratinocytes and their accumulation in the upper layers of the epidermis [1]. Increased vascularization of psoriatic plaques follows keratinocyte hyperproliferation that results in a massive influx of innate and adaptive immune cells producing an array of inflammatory mediators which sustain the chronic inflammation [3].

Accumulation of inflammatory CD^{4+} Th1 cells, CD^{8+} cytotoxic T lymphocytes, and Th17 cells are accompanied by increased expression of IL-17A in psoriatic lesions [4-6]. IL-17A, primarily produced by CD^{4+} Th17 cells and δγ T cells, operates at the interface of innate and adaptive immunity by activating keratinocytes to produce IL-17C that along with other keratinocyte-derived mediators serves to sustain the chronic inflammation in psoriatic plaques. Taken together, psoriasis is regarded as an IL-17-mediated inflammatory condition in which IL-17-producing CD^{4+} Th17 T cells, δγ T cells, and keratinocytes play a critical role.

The ability to stimulate acute and chronic inflammation has implicated IL-17 in the pathogenesis of various human systemic and organ-specific autoimmune disorders [7]. In this regard, recent findings that implemented IL-17 in the pathogenesis of psoriasis also suggest an autoimmune nature of this immuno-inflammatory skin disease. The universal involvement of IL-17 in various autoimmune

diseases has identified IL-17 as an ideal target for the development of immunotherapeutic approaches [8-10]. Given the critical role of IL-23 in generating Th17 cells, multiple clinical trials targeting the IL-17/IL-23 axis in the pathogenic mechanisms of psoriasis are underway.

Role of Microflora and Molecular Mimicry in Psoriasis

Although the etiology of psoriasis is not fully elucidated, both hereditary and environmental factors contribute to the onset and periodic exacerbations of the disease. Skin plays a vital protective role as a physical barrier and habitat for resident microflora, a diverse community of microorganisms, generally comprised of harmless and beneficial species. Emerging evidence strongly suggests the existence of an intricate relationship between skin microflora and a complex network of keratinocytes, epithelial cells, and immune cells in the skin. In this regard, it has been long suspected that psoriasis may well be associated with alterations in the composition and representation of the cutaneous bacterial microflora, although classical cultivation-dependent microbiological methods did not permit a detailed identification of the cutaneous bacterial community. Recently, comparative high-throughput pyrosequencing analyses of microbiota in biopsies from psoriatic lesions and normal skin have demonstrated that Firmicutes species were significantly overexpressed, whereas Actinobacteria, the most prevalent and diverse phylum in normal skin, and Propionibacterium species, in particular, were significantly underrepresented in psoriatic lesions. The followed studies have confirmed the decreased presence of Propionibacterium and revealed the decreased abundances of staphylococci in psoriatic lesions compared to healthy skin. Yet, it remains unclear whether the observed change in skin microbiota is the causative factor in the development of psoriasis.

Although the cause-effect relationship between dysbiosis of the skin microflora and auto-inflammatory mechanisms of psoriasis has yet to be fully elucidated, recent studies showed that tonsillar infections caused by Streptococcus pyogenes often precede the onset of psoriasis whereas periodic exacerbations are associated with skin colonization by Staphylococcus aureus, Malassezia, or Candida albicans. Different mechanisms have been proposed to describe how infections can trigger and/or exacerbate autoimmune diseases. Molecular mimicry is a mechanism in which a microbial antigen shares structural similarities with self-antigens and is typically characterized by the appearance of autoantibodies and self-reactive T cell clones. The concept of molecular mimicry has thus been proposed as a triggering mechanism of various autoimmune diseases including the onset and periodic exacerbations of psoriasis. In individuals susceptible to psoriasis, tonsillar infections with group-A hemolytic Streptococcus pyogenes may induce the rise of pathogen-specific T cell clones which may also cross-react with keratinocyte-derived autoantigens. Specifically, oligoclonal T cells were identified in the blood and psoriatic lesions which cross-reacted with determinants common to streptococcal M-protein and keratin. It appears that those psoriatic T cell clones selectively accumulated and persisted in the lesions but not in the healthy skin of patients with psoriasis.

Evidence for an Autoimmune Etiology

Autoimmunity is characterized by the breakdown of self-tolerance and abnormal antibody-mediated and/or T cell-mediated immune responses against self-antigens. Our understanding of the pathogenesis of psoriasis has evolved greatly over the years, and the question of autoimmunity is frequently debated. However, identification of genetic risk variants, the discovery of multiple autoantigens, and the role of Th17 cells commonly involved in various autoimmune diseases provide strong support for the concept of autoimmune pathogenic mechanisms of psoriasis.

Genetic variations have been identified for many common autoimmune diseases. Genome-wide association (GWA) studies have discovered numerous single nucleotide polymorphisms (SNPs) that confer susceptibility to various autoimmune diseases [24]. Like other autoimmune diseases, psoriasis has been shown to have a strong genetic component, with a concordance rate in identical twins of 40-70%. Over sixty psoriasis susceptibility loci have been identified among which the MHC Class I molecule HLA-Cw*0602 is the most significant since more than 60% of psoriasis patients are hetero- or homozygous for this allele [25]. Other psoriasis susceptibility loci, to name a few, include ERAP1 encoding for an Endoplasmic Reticulum Aminopeptidase 1 and ERAP2, which are both involved in antigen processing and presentation, IL23R, as well as TNFAIP3 (TNF-alpha induced protein 3), in which polymorphisms have also been implicated in rheumatoid arthritis, type 1 diabetes, celiac disease, and Crohn's disease.

The discovery of autoantigens further supports the autoimmune concept in the pathogenesis of psoriasis. Molecular mimicry has been recognized as a triggering factor of many autoimmune diseases. Molecular mimicry has also been implicated in the pathogenesis of psoriasis. Streptococcal throat infection is a known trigger of acute guttate psoriasis, with an incidence of preceding infection ranging between 56-97%. Homology between the streptococcal M-protein and keratin 17 yields cross-reactive CD^{8+} T cells seen in patients with psoriasis, especially in patients with HLA-Cw*0602. Another autoantigen that has been implicated in psoriasis is cathelicidin/LL-37, an antimicrobial peptide synthesized by keratinocytes and neutrophils in reaction to infection or trauma to the skin. Autoreactive T cells against cathelicidin were found in the peripheral blood of 75% of patients with moderate to severe psoriasis. It was recently found that ADAMTSL5 (ADAMTS-like protein 5) serves as a psoriasis autoantigen which overexpression by melanocytes is observed in HLA-Cw*0602 positive patients. TCRs of CD^{8+} T cells recognize ADAMTSL5 presented by melanocytes in psoriatic lesions and generate IL-17, a signature cytokine in psoriasis.

In addition to T cell-mediated immune responses, circulating autoantibodies against calpastatin, a natural inhibitor of the protease calpain, have been identified in psoriasis patients but not healthy controls. Of importance, anti-calpastatin auto-antibodies were also found in various autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis, systemic sclerosis, Sjögren's Syndrome, and overlap syndrome which further support the concept of psoriasis as an autoimmune disease. In addition, several autoantibodies such as anti-heat shock protein 65 antibodies, anti-stratum corneum antibodies, and anti-squamous cell carcinoma antigen antibodies have been identified in psoriasis, although their clinical significance has yet to be determined.

Association between psoriasis and other autoimmune diseases has been the subject of the ongoing investigation. A recent retrospective cohort study has demonstrated that patients with psoriasis are at higher risk of developing at least one other autoimmune disease with rheumatoid arthritis having the strongest association (3.6; 95% CI 3.4-3.9). Another case-control study involving 12,506 psoriasis patients found that 0.29% of the patients had celiac disease compared with 0.11 % in the control group. Psoriasis patients were also found to have higher rates of Crohn's disease and ulcerative colitis. Similarly, an association of psoriasis with Hashimoto's thyroiditis, Sjögren's Syndrome, and dermatomyositis has been recently reported. Taken together, the results of these association studies suggest a common aberrant mechanism(s) linking the development of classical autoimmune diseases and psoriasis, supporting the concept of psoriasis having an autoimmune nature.

The IL-23/TH17 Axis in the Pathogenic Mechanisms of Psoriasis

Since its discovery in the early nineties, IL-17 took the central stage in immuno-inflammatory mechanisms underlying the development of autoimmune diseases. Thus, IL-17 was implemented in pathogenic mechanisms of inflammatory bowel diseases, multiple sclerosis, and rheumatoid arthritis, in which both serum and tissue have elevated concentrations of IL-17 (reviewed in [7]. In a similar manner, our understanding of the pathogenesis of psoriasis has evolved around the pathologic role of IL-17 since Th17 cells were identified in the dermis of psoriatic plaques [4]. It was shown that IL-17 mainly produced by Th17 cells and dg T cells is responsible for downstream activation of an array of transcription factors leading to epidermal hyperplasia, leukocyte recruitment, and amplified skin inflammation [4-6].

The IL-17 family consists of six cytokines, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. Although IL-17B, IL-17C, and IL-17D exhibit pro-inflammatory properties, their exact roles remain elusive. On the other hand, IL-17E, also known as IL-25, promotes Th2 type responses and suppresses Th1 and Th17 cells. IL-17A and IL-17F are the two most closely related members of the IL-17 family which share 50% amino acid sequence homology. IL-17A and IL-17F may also exist as an IL-17A/F heterodimer. Both IL-17A and IL-17F serve to protect and maintain the skin and mucosal barriers in healthy tissues, however, overproduction of these cytokines also plays a central role in the pathogenic mechanisms of psoriasis. The IL-17 receptor (IL-17R) is a heterodimer comprised of five subunits, a.k.a. IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE. Psoriasis-relevant IL-17A, IL-17F, and IL-17A/F bind to a heterodimeric IL-17RA/IL-17RC with IL-17A being selectively recognized by IL-17RA and IL-17F by IL-17RC.

In the skin, IL-17A and IL-17F are mainly produced by Th17 cells and dg T cells. Unequivocally, IL-17-producing CD^{4+} Th17 cells are culprits in the development of

psoriatic plaques, as they have been isolated in the dermis of psoriatic lesions. In addition to the production of IL-17, activated Th17 cells also secrete IL-21 and IL-22. IL-22 is an IL-10 family cytokine that acts through STAT3 and has been shown to increase epidermal thickness through inhibition of keratinocyte differentiation. Treatment with neutralizing anti-IL-22 antibodies prevented the development of psoriasiform disease in mice thereby identifying IL-22 as an important pathogenic factor in psoriasis and potential molecular target for disease therapy. Furthermore, cooperation between IL-17A and IL-22 leads to the recruitment of leukocytes in the skin to further potentiate the inflammation. IL-17A and IL-17F also stimulate keratinocytes to synthesize various chemokines including CXCL2, CXCL3, CXCL5, and CXCL8 (IL-8) which mediate the chemotaxis of neutrophils and macrophages to the lesional skin leading to the formation of Munro micro abscesses, one of the characteristic histologic features of psoriasis.

IL-23 plays an important role in the activation of Th17 cell-mediated immunity [11]. Following some inciting event, whether it is infection or trauma, autoantigens are released in the epidermis and activate myeloid dendritic cells (mDCs). Activated mDCs are the main source of IL-23 in psoriatic plaques. Although TGF-b1, IL-6, and IL-1b are required for Th17 cells differentiation from naïve CD^{4+} cells, IL-23 is the cornerstone cytokine in this process. In the absence of IL-23, the cytokines TGF-b1, IL-6, and IL-1b stimulate differentiation of T regulatory cells capable of potent suppression of inflammation.

Of importance, IL-23 has crucial roles in the pathogenesis of autoimmunity as it induces local tissue inflammation which is mainly mediated by IL-23-dependent production of IL-17 by Th17 cells [11]. The transcription factor STAT3 is a key facilitator in the IL-23 signaling pathway, and upon activation, it induces transcription of inflammatory cytokines including IL-17A, IL-17F, IL-22, and IFN-g by Th17 cells. Emerging evidence unequivocally suggests that the IL-23/IL-17 axis represents the central immuno-inflammatory pathway in the pathogenesis of psoriasis and provides the rationale for the development of new anti-IL-17 and anti-IL-23 immuno-therapeutic approaches for the treatment of patients with moderate-to-severe psoriasis plaques.

Targeting the IL-23/IL-17 Axis

To date, the antibodies that specifically neutralize IL-23 or IL-17 have shown remarkable effectiveness for the treatment of psoriasis in clinical trials. As of December 2018, a search of the ClinicalTrials.gov database has revealed 25 either recruiting, active, or completed clinical trials using anti-IL-17 or anti-IL-17 receptor monoclonal antibodies for the treatment of moderate-to-severe psoriasis. In early 2016, the US Food and Drug Administration (FDA) has approved the first anti-IL-17 monoclonal antibody for the treatment of active psoriatic arthritis. Following in the footsteps of Novartis, Eli Lilly has received the US FDA approval for anti-IL-17 monoclonal antibody for treatment of moderate-to-severe psoriasis. In February 2017, the anti-IL-17 receptor antagonist has received the US FDA approval to treat moderate-to-severe plaque psoriasis in people who have not improved with other treatments.

Similarly, our search of the ClinicalTrials.gov database has revealed 11 clinical trials using anti-IL-23 monoclonal antibodies. In October 2017, the U.S. Food and Drug Administration (FDA) has approved an expanded indication for an anti-p40 subunit of IL-12/IL-23 monoclonal antibody for the treatment of adolescents (12 years of age or older) with moderate to severe plaque psoriasis.

CASE REPORT

A 24-year-old female, with a history of CCDLE, 4 years of evolution, no personal or family acne history, treated with corticosteroids and hydroxychloroquine 200mg/day during the last three months with little clinical improvement. At the time of consultation, she had an indurated, well-defined, erythematous plate, with a 6 x 7 cm diameter and whitish adherent scales. Regarding nasolabial folds, it also presented areas with hyperkeratosis, scars, atrophy, and comedones grouped by sectors. On the nose bridge, we observed 3 discoid plates (2 cm in diameter) with irregular edges like the previously described lesion.

Complementary examinations were requested: Hemogram, blood glucose, uremia, creatinemia, complete urine, CPK, liver function tests, Complementemia, cholesterol, and triglycerides, resulting in normal parameters. Dosage of B subunit of human chorionic gonadotropin (hCG) was also performed to rule out pregnancy and immunological profile for lupus. Both studies were negative. The liver function tests, lipid profile, and the dosage of B subunit of hCG were repeated on the second and fourth months of treatment.

A biopsy of the lesion was performed, which revealed thinned epidermis with hyperparakeratosis, comedogenic expansion in one of the margins, and chronic periadnexal and perivascular inflammatory infiltrate.

With the histopathological findings, laboratory and clinical characteristics, the diagnosis of CCDLE with the acneiform presentation was confirmed. Treatment with Isotretinoin 0.75 mg/kg/day for 5 months, contraception, and sunscreen were indicated. In the clinical control, the patient had a noticeable improvement, which was demonstrated by the reduction of erythema, infiltration, number of comedones, and the disappearance of the scales.

CONCLUSION

Psoriasis has long been viewed as a chronic immune-mediated disease of the skin and little joints that are most typically manifested by the formation of demarcated erythroderma plaques. though the etiology of skin condition has been elusive, rising proof powerfully implicates molecular mimicry as a triggering issue of skin condition in genetically inclined people. Autoreactive T cells and current autoantibodies were additionally found in psoriatic patients. Taken along, these findings support the thought that skin condition is Associate in Nursing autoimmune disorder. moreover, accumulated proof without ambiguity shows that IL-17 and IL-23 cytokines are key players within the pathological process of skin condition. during this regard, an improved understanding of the immunology of skin condition has light-emitting diode to the event of latest therapeutic modalities that by selection target IL-17 and IL-23. Biological agents, like neutralizing anti-IL-17 and anti-IL-23 organism antibodies, are developed and tested in multiple clinical trials showing their effectiveness within the treatment of moderate to severe plaque skin conditions. Despite the effectiveness of those biological agents Associate in Nursing-IL17 and IL-23 antibodies could probably cause general immunological disorder related to an accrued risk of infections and malignancies. Therefore, future clinical studies are required to determine the security record of those biological agents by showing that the advantages of anti-IL-17 and anti-IL-23 therapies overweight any potential adverse effects of those medicine within the treatment of moderate to severe plaque skin conditions.

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