Interaction between Immunoglobulin E and Interleukin 17 in the pathogenesis of Psoriasis

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Abstract

Psoriasis is a common cutaneous disorder characterized by inflammation and abnormal epidermal proliferation with a prevalence of 2-3% in the general population. Interleukin-17A (IL-17A) is a pro-inflammatory cytokine that have a pivotal role in the pathogenesis of psoriasis through its effects on neutrophil recruitment, host defense and immunoinflammatory pathology. The IL-17A directly promotes the differentiation of IgE-secreting cells and IgE production upon anti-CD40/IL-4 co-stimulation. Several studies have reported high levels of IgE in sera of patients with psoriasis. Therefore, this interaction between IL-17 and IgE could have a role in psoriasis pathogenesis.

Keywords: Psoriasis, Immunoglobulin E, Interleukin 17, pathogenesis.

Introduction

Psoriasis is a common cutaneous disorder characterized by inflammation and abnormal epidermal proliferation with a prevalence of 2-3% in the general population (1). According to the large population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey, the prevalence worldwide has been found to vary both geographically and among different ethnic groups within the same region. Higher prevalence was reported in regions distant from the equator. The prevalence of psoriasis varied from 0.14% in east Asia to 5.32% in central Europe (2).

Psoriasis has several clinical variants (Table 1). Chronic plaque psoriasis (CPP), the most common variant of psoriasis, is usually manifested as well-demarcated erythematous
plaques with silvery scales on elbows, knees, and scalp. However, any skin surface may be affected as well (3).

A family history of psoriasis is common among patients with psoriasis. Approximately 30% of patients have a first-degree relative with psoriasis, and the risk of psoriasis increases with the number of affected relatives a patient has (4).

**Table (1): Different variants of psoriasis**

<table>
<thead>
<tr>
<th>Variant</th>
<th>Characteristic features</th>
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</thead>
<tbody>
<tr>
<td>Chronic plaque Psoriasis (CPP)</td>
<td>The most common type. Well-defined, erythematous, indurated plaques covered with silvery scales on scalp, extensor aspect of extremities and trunk.</td>
</tr>
<tr>
<td>Annular psoriasis</td>
<td>Rapidly evolving or involuting psoriatic plaques may have an annular configuration.</td>
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<tr>
<td>Guttate psoriasis</td>
<td>Affects mainly young adults, often triggered by streptococcal pharyngitis, characterized by small scaly erythematous lesions affecting mainly trunk.</td>
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<tr>
<td>Linear psoriasis</td>
<td>Scaly erythematous lesions arranged in linear configuration.</td>
</tr>
<tr>
<td>Sebopsoraisis</td>
<td>Lesions with features of both psoriasis and seborrheic dermatitis affecting the scalp, eyebrows, ears and napkin area particularly in infants and obese patients.</td>
</tr>
<tr>
<td>Intertriginous (flexural) psoriasis</td>
<td>Well demarcated shiny erythematous non-scaly plaques affecting axillae, groin and inframammary areas.</td>
</tr>
<tr>
<td>Palmoplantar psoriasis</td>
<td>Lesions could be typical psoriatic, eczematous, pustular or mixed.</td>
</tr>
<tr>
<td>Nail psoriasis</td>
<td>Fine pitting is the most common abnormality. Nail discoloration, subungual hyperkeratosis, onycholysis and oil drops are also common features.</td>
</tr>
<tr>
<td>Follicular psoriasis</td>
<td>Follicular psoriatic lesions on the extensor prominences of elbows and knees.</td>
</tr>
<tr>
<td>Pustular psoriasis</td>
<td>Small sterile superficial pustules on an inflammatory base, may arise de novo or on top of chronic plaque psoriasis. Often precipitated by pregnancy or hypocalcaemia.</td>
</tr>
<tr>
<td>Erythrodermic psoriasis</td>
<td>Widespread erythema and scaling with palmoplantar keratoderma. It is a serious condition that may lead to fluid loss, electrolyte disturbances and thermoregulatory abnormalities</td>
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Role of immune cells

Genetic data on HLA associations as well as data on the presence of oligoclonal T cells in psoriatic lesional skin and their reactivity towards cutaneous antigens have underlined the importance of immune cells in psoriasis pathogenesis. Putative autoantigens in psoriasis include keratins, heat shock proteins, the Cathelicidin antimicrobial peptides (CAMP) LL37, and the melanocytic antigen disintegrin-like and metalloprotease domain containing thrombospondin ADAMTS-like protein 5 (ADAMTSL5) (5).

1. Role of skin-resident memory T cells:

Resident memory T cells (TRM) preferentially reside in epithelial barrier tissues including the skin. They can respond rapidly to pathogenic invaders in these sites, so they are crucial for host protection from harmful microorganisms. A recent study revealed the augmentation of TRM cells in lesional skin of patients with psoriasis. Moreover, TRM cells in psoriatic skin express higher levels of both IL17A and IL22 compared to healthy individuals. The majority of TRM cells in the epidermis express CD103 marker. TRM cells residing in the dermis show lower expression of this marker. CD103 expression on TRM influences the balance between effector and regulatory T cell activity (6).

2. Role of dendritic cells:

Besides T cells, dendritic cells (DCs) can reside in the skin. They are a key population of the immune system, bridging the breaks between innate and adaptive immunity. In psoriasis, certain DC populations like plasmacytoid DCs (pDCs) and dermal myeloid DCs (mDCs) dominate the inflammatory skin, while the number of epidermal Langerhans cells (LCs) seems to stay stable as compared to non-lesional skin. During initial inflammation, an increased number of pDCs is activated, which results in the release of type I interferon (IFN-α) (7).

Complexes formed by self-DNA or self-RNA and the antimicrobial peptide LL37 have been shown to activate pDCs through Toll-like receptor 9 (TLR9) or TLR7/8, respectively. Recently, a novel mechanism of pDC activation has been described. As shown for antimicrobial peptides, the Th17-associated cytokine IL-26 can also form complexes with DNA from dying bacterial or host tissue cells and these complexes also promote IFN-α production by pDCs through TLR9 stimulation (8).
These innate mechanisms seem to be relevant for pDC activation in psoriasis pathogenesis. The activation of pDCs is followed by an increase of CD11c+ mDCs, which express tumor necrosis factor-α (TNF-α), inducible nitric oxide synthase (iNOS), and IL-23. Inflammatory CD11c+ mDCs do not express CD1c in contrast to skin-resident CD1c+ mDCs. Another DC population that can produce IL-23 is the so-called 6-sulfo LacNAc (Lactose Neuraminic acid) (slan)-expressing population (slanDCs). Moreover, CD163+ macrophages can produce IL-23. Taken together, the major function of DCs and macrophages in psoriasis pathogenesis is to provide the signals that promote Th17-mediated inflammation (9).

3. Role of T helper-1 cells:
Activated CD4+ and CD8+ lymphocytes were initially considered to be equally important in the inflammation associated with psoriasis because large numbers of activated CD4+ and CD8+ lymphocytes were identified in the skin and peripheral blood of psoriatic patients. Subsequently, CD4+Th cells were shown to play a more important role than CD8+ lymphocytes, because psoriasis-like skin lesions developed in mice transplanted with activated Th cells from psoriatic patients (10). Moreover, the levels of Th1 cytokines, such as IFN-γ, TNF-α and IL-12, were elevated in psoriatic lesions while no such increases in expression of Th2 cytokines (e.g., IL-4, IL-5 and IL-10) were observed. These findings characterized psoriasis as a Th1-type disease. However, keratinocyte proliferation is not induced by IFN-γ or TNF-α, neither. The pathogenesis of psoriasis could not be fully understood based only on Th1 functions, and it was predicted that other inflammatory cells should participate in psoriasis pathogenesis (11).

4. Role of T helper-17 cells:
The differentiation and activation of Th17 population from naïve T cells depend on cytokines such as IL-6, IL-21, IL-1, TGF-β, and IL-23. The cytokine, IL-23, its receptor; IL23R, and its downstream signaling molecule STAT3 are all linked to the genetic susceptibility for developing psoriasis. The transcription factor STAT3 is also activated by IL-6 and IL-21. Together with the other Th17-characterizing transcription factor; Retinoic acid receptor (RAR)-related orphan receptor gamma (RORγ), STAT3 is responsible for IL-17A and IL-17F expression (12).
Th17 cells produce cytokines including; IL-17F, IL-21, IL-22, TNF, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Some Th17 populations also secrete IL-9 or IL-10, depending on the signals they receive during initial activation (13). Skin-infiltrating Th17 cells seem to be the central cells orchestrating psoriasis pathogenesis. They interact with keratinocytes, endothelial cells and various immune cells including; DCs and neutrophilic granulocytes. The reactivation of memory Th17 cells is presumably responsible for the chronic course of the disease (14).

**Role of interleukin-17 in psoriasis pathogenesis**

The pro-inflammatory cytokine, IL-17 is produced by activated Th-17 cells in response to stimulation through T cell receptor. Th-17 cells secrete not only IL-17A, but also IL-17F, IL-21, IL-22 and IL-23; these cytokines most likely cooperate to induce multiple inflammatory and hematopoietic effects on epithelial, endothelial, and fibroblastic cells (15). The IL-17 is a prototype member of the IL-17 family of cytokines, which contains six structurally related isoforms: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F (16).

Other cells secreting IL-17 cytokines include CD8+ T cells, γδ T cells, natural killer T (NKT) cells, natural killer (NK) cells, monocytes, macrophages, DCs, microglia, neutrophils, eosinophils, astrocytes, and oligodendrocytes. Thus, cells of both innate and adaptive immune systems as well as non-immune cells produce IL-17 (15).

**IL-17 immune signaling**

The IL-17A induces the expression of intercellular cell adhesion molecule 1 (ICAM-1) for granulocyte recruitment and inflammation in keratinocytes, IL-1 and TNF in macrophages, iNOS and cyclooxygenase-2 (COX-2) in chondrocytes, and COX-2-dependent prostaglandin E2-mediated receptor activator of nuclear factor κB (NF-κB) ligand (RANKL) in osteoblasts (17).

Furthermore, IL-17A promotes stem cell factor (SCF) expression and G-CSF-mediated granulopoiesis. IL-17A is also involved in neutrophil recruitment through binding to CXCL8 (IL-8), CXCL1, CXCL2, and CXCL5 (18).
**IL-17 and psoriasis**

High levels of IL-17 have been detected in sera and lesional skin of patients with psoriasis. The central role of IL-17 in psoriasis was reported which included upregulation of IL-17 and related genes in lesional and non-lesional skin of patients with psoriasis and production of IL-17A by cells associated with psoriasis (19). Increased levels of Th17 cytokines; IL-17 and IL-22 were also reported in the sera of psoriasis patients, as well as increased IL-17 mRNA levels in psoriatic lesions. Moreover, there was increased frequency of IL-17- producing T cells in the dermis of psoriatic lesions (20).

Overproduction of IL-17 leads to increased proliferation and aberrant differentiation of keratinocytes and contributes to skin barrier disruption by down-regulating the expression of molecules involved in keratinocyte differentiation, such as fillagrin (21).

In addition, IL-17 participates in generating and amplifying the inflammatory network by promoting the release of antimicrobial peptides and proinflammatory cytokines/chemokines (22).

The factors induced by IL-17 are targeted toward the activation of a neutrophil/Th17 cell-dependent immune response. These include IL-8, a potent neutrophil chemo-attractant; G-CSF, a survival factor for neutrophils; CCL20 that favors Th17 cell recruitment; and the key Th17 polarizing cytokines IL-1β and IL-6. In addition, IL-17 directly contributes to leukocyte migration and tissue remodeling by promoting the secretion of metalloproteases (15).

IL-17 synergizes with and potentiates the effects of many other inflammatory mediators including IL-10, IL-1 and type-I cytokines (e.g. TNFα). The genes synergistically upregulated by TNFα and IL-17 in keratinocytes were shown to mimic the gene signature observed in psoriatic lesions. Similarly, IL-17, together with TNF and IL-22, were reported to upregulate the expression of the IL-1 like family member IL-36, which in turn was found to augment the function of Th17 cytokines, revealing the existence of a feedback loop between Th17 and IL-36 cytokines (23).

The effects of IL-17 are not limited to keratinocytes and include several other cells, including endothelial cells, fibroblasts, chondrocytes, and synovial cells. IL-17 is clearly
of major importance also in psoriasis-associated comorbidities namely, psoriatic arthritis and cardiovascular disease/atherosclerosis (24).

**Interaction between IgE and IL-17 in the Pathogenesis of Psoriasis**

High levels of serum IgE have been detected in patients with psoriasis. IgE production is usually dominated by Th2 cytokines that are downregulated in psoriasis. Therefore, other mechanisms may be implicated in the over-production of IgE in psoriasis. Psoriasis is an immune-mediated inflammatory skin disorder and there is evidence that high levels of IL-17 play a pivotal role in psoriasis pathogenesis (25).

The IL-17 has been found to exert a pro-allergic action on B cells by triggering IgE production. Th17 cells are increased in allergic subjects and therefore these cells contribute to IgE production by peripheral blood mononuclear cells (PBMCs) (26). Further indication for a pro-allergic, IgE-promoting function of IL-17 comes from the analysis of the IL-17/-/- mice. In particular, ovalbumin-sensitized IL-17/-/- mice have reductions specifically in IgG1 and, most profoundly, IgE levels compared to those in IL-17+/+ mice (27). Moreover, Th17-mediated autoimmune gastritis is accompanied by high serum IgE levels (28).

On the other contrary, enhanced Th17 function, encountered in some inflammatory diseases (e.g. multiple sclerosis, Crohn’s disease) does not lead to enhanced IgE production. Therefore, IL-17 may actually act as a cofactor contributing to the enhanced IgE production in allergic individuals, but it does not clearly act on its own (29).

The mechanisms behind the changes in IgE production in the context of IL-17A hyper or hypoexpression have remained unexplored so far (30). Interestingly, IL-17 promotes B-cell activity and function in germinal centers of BXD2 strain mice, suggesting that B cells might be a substantial target for IL-17. B cells display increased survival, proliferation, and differentiation into plasma cells upon IL-17-mediated stimulation (30). Another mechanism of IgE relation to IL-17 is through the activation of complement C3a. IgE sensitization of Th17 lymphocytes leads to cascade of antigen presentation to CD4+ cells that differentiate later to IL-17 secreting cells with increased production of IL-17 (31).
Conclusion

There could be an interaction between IL-17 and IgE in the pathogenesis of psoriasis. The exact relationship between them is still obscure. Future studies are needed to investigate the possible interaction between IL-17 and IgE in psoriasis pathogenesis.

References


