The Role of IL-17 in the Pathogenesis and Treatment of Psoriasis

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Introduction

Psoriasis is a chronic inflammatory disease characterized by skin lesions and systemic inflammation. It is thought to be due to aberrant activation of the interleukin (IL)-23/T-helper (Th)17 immunologic pathway through a complex interplay between genetics and the environment.[1] Psoriasis is associated not only with physical morbidity, but also significant psychosocial impairment and a negative impact on quality of life.[2]

Our understanding of the pathophysiology of psoriasis has greatly increased over the past few decades, in parallel with the development of new drugs to treat it. Prior to the 1980s, psoriasis was believed to be primarily a keratinocyte disorder, whereas, in the1980s, it was thought to be a disease primarily caused by general T cell activation. By the 1990s, the increasing importance of Th1 cells, IL-12, interferon gamma (IFNγ), and tumor necrosis alpha (TNFα) was noted.[3,4] Beginning around 2005, psoriasis was no longer considered a prototype Th1-mediated kin disease, but rather an IL-23/Th17 driven disease.[5] With greater knowledge of psoriasis' immunopathogenesis, new, rationally designed drugs have been brought to market, which raise the bar in efficacy and carry greater safety profiles than their predecessors.

Structural and Immune Function In Healthy Skin

Considered the body's largest organ, the skin provides a barrier between the harsh external environment and our internal organs. In fact, the skin serves several specific "barrier" functions. First, as a protective function, the stratum corneum maintains normal physiologic function for deeper skin layers. It acts as a sensor to barrier compromise, stimulating repair mechanisms. The skin also serves an antioxidant role, with endogenous molecules like superoxide dismutase that quell reactive oxygen species. In addition, the stratum corneum acts as a permeability barrier to water, maintaining skin hydration and preventing water loss into the environment. When water loss is detected, the skin releases stored precursor lipids from lamellar bodies to repair the mortar between the skin cell bricks, improving the barrier and reducing transepidermal water loss (TEWL) across the stratum corneum.[6]

The skin plays a role in the body's immune system, with both circulating blood cells that migrate into the skin and resident cells playing independent roles.[7] In healthy skin, pro-inflammatory and balancing regulatory processes maintain homeostasis in response to external pathogens and during wound healing. In the case of psoriasis, there is an immune imbalance, with an overabundance of pro-inflammatory mediators and cells and a lack of regulation.

In order to understand the immune defects that lead to psoriasis, one must have a basic knowledge of normal skin immune function, including the characteristics of immune cells themselves and their interactions.

Keratinocytes. While best known as structural cells in the epidermis, keratinocytes are directly influenced by immune cell signals and play an important role themselves in inflammatory processes. Dendritic and T-cell cell derived cytokines stimulate activation and proliferation of keratinocytes. In the case of psoriasis, hyperproliferation with resulting abnormal cellular differentiation explain the clinical appearance of thick, scaly psoriatic plaques. Moreover, keratinocytes themselves produce pro-inflammatory cytokines that promote both antimicrobial peptide production and lead to dendritic cell and T-cell activation.[8,9]

Neutrophils. Neutrophils are the most abundant type of white blood cells in the body. They are considered first-responders to sites of infection or other exposure during the acute phase of inflammation, where they initiate an initial immune attack. In cases of infection, neutrophils attack foreign organisms through degranulation and phagocytosis. Large accumulations of neutrophils clinically manifest as pus in the skin. In addition, neutrophils are involved in the initiation of psoriatic lesions, and they are histologically observed in the stratum corneum of psoriatic plaques as Munro's microabscesses and in the stratum spinosum as spongiform pustules of Kogoj.[10] Neutrophil activity is stimulated by IL-17A, and neutrophils release IL-17A and chemotactic factors themselves, which promote Th17 cell recruitment to skin.[11]

Dendritic cells. Dendritic cells are immune cells that exist throughout the body. They process antigens and present them to other immune cells, hence their designation as antigen-presenting cells. Their interaction with both B-cells and T-cells result in activation with subsequent cytokine production. Once activated, mature dendritic cells migrate in

high numbers to lymphoid tissue. In the case of psoriasis, both plasmacytoid dendritic cells and cluster of differentiation (CD)11c+ dermal dendritic cells have been identified in high levels in psoriatic plaques. Activated dendritic cells produce the pro-inflammatory cytokines IL-12 and IL-23. IL-12 in turn promotes differentiation of Th1 T-cells, while IL-23 is the driving factor behind the survival, proliferation, and activation of Th17 T-cells.[12]

Th17 cells. Th17 cells are a distinct class of helper T-cells separate from Th1 and Th2 cells. These CD4+ effector T-cells mature in response to IL-23 produced by dendritic cells in the skin. Th17 cells are the primary cells responsible for immune defense against extracellular pathogens, e.g., *Candida albicans* and *Staphylococcus aureus*, in the skin and mucous membranes, and they influence both innate and adaptive responses. When activated, Th17 cells have the capability of producing large amounts of pro-inflammatory cytokines, namely IL-17A, as well as IL-17F, IL-22, and TNFα.[13] Other cytokines produced by Th17 cells include IL-21, granulocyte macrophage colony stimulating factor (GM-CSF), and C-C motif chemokine ligand (CCL) 20. Collectively, the cytokines produced by Th17 cells have effects on cell differentiation, recruitment and activation of immune cells, and release of antimicrobial peptides.[14,15]

Both over-activity and under-activity of Th17 T-cell responses are associated with disease in the skin. Hyperactivity is involved in the pathogenesis of psoriasis. Low activity of Th17 cell function is associated with the development of Candida infections of the skin and mucous membranes.[16] Job syndrome (aka, hyperimmunoglobulin E syndrome) is characterized by eczematous skin lesions, recurrent staphylococcal skin infections, and mucocutaneous candidiasis. There are gene defects in signal transducer and activator of transcription (STAT) 3 in this condition, which leads to loss of IL-17A production.[17]

Th1 cells. Th1 cells are subtypes of T-cells that produce cytokines, including IFNγ, IL-2, and TNFα, and which are involved in immune defense against intracellular pathogens (e.g., *M. tuberculosis*). Differentiation of Th1 cells from naïve T-cells is stimulated by IL-12 produced by dendritic cells.[18,19]

Regulatory T cells. Regulatory T cells (T-reg) are a subset of CD4+ T-cells which function to suppress the activation of effector and memory T-cells. In regulating T-cells, T-reg cells maintain peripheral tolerance and prevent self-reactivity. T-reg cells activity is supported by TGF-β and IL-10. It has been demonstrated that the numbers of T-reg cells as well as their suppressive functioning is reduced in psoriasis patients.[18]

Mast cells. Mast cells are blood cells particularly important in allergy and itch. They contain vasoactive mediators, including histamine, leukotrienes, prostaglandins, and kinins. They also play a key role in inflammation and produce pro-inflammatory cytokines, such as TNFα. Messengers, such as IL-23, stimulate mast cells to produce IL-17, which, along with IL-17 produced by Th17 cells and neutrophils, contributes to inflammation seen in psoriasis. Mast cells are abundant in the dermis of psoriatic plaques and are thought to play a role in stress-related psoriasis exacerbations.[20,21]

Macrophages. Macrophages are white blood cells primarily involved in the phagocytosis of foreign and cellular debris. Additionally, they secrete pro-inflammatory cytokines. In particular, macrophages are known to produce TNFα, which activate dendritic cells and T-cells to promote inflammatory processes. Of note, large numbers of macrophages are observed in psoriatic plaques.[22]

Structural and Immunologic Defects in Psoriasis

Psoriatic skin demonstrates many differences from healthy skin on both the macroscopic and microscopic level. While the stratum corneum of healthy skin has a basket-weave appearance histologically, keratinocytes in psoriasis cells are retained and become densely stacked, clinically giving the appearance of white, micaceous scale.[23] Moreover, stratum corneum function is compromised, shown by increases in TEWL levels.[24] Psoriatic keratinocytes are characterized by hyperproliferation, rapid mitoses with abnormal differentiation, and retained nuclei. There is reduction in the size of the granular layer with epidermal acanthosis and elongated dermal papillae and enlargement of dermal vasculature.[25] These histologic changes correlate with the thick, erythematous plaques that are clinically observed.

In additional to structural changes, there are complex immunologic abnormalities seen in psoriatic patients. Th17 T-cells have been identified as the key abnormal cell involved in psoriatic immune dysregulation, and circulating Th17 cell levels have been found to be statistically higher ($P<0.001$) in psoriasis patients compared to non-psoriasis comparator patients.[26] Over-activity of Th17 cells lead to defects in antigen presentation, innate and adaptive immune cell function, and imbalanced cytokine production, which all contribute to the pathologic inflammation observed in psoriasis.[7,14]

Current theories on the pathogenesis of psoriasis suggest that exogenous triggers interact with the patient's immune system leading to dysregulated inflammation in genetically susceptible individuals. There is little data on triggering factors, but generally accepted ones include emotional stress, medications, cigarette smoking, and certain infections.[27,28]

A single external factor is not enough to cause psoriasis. After an initial trigger, the inflammatory response must be propagated by continued immune dysregulation in the affected patient. It is currently thought that immature plasmacytoid dendritic cells in the skin are activated to produce IFN-alpha. Myeloid dendritic cells then become activated and begin to produce pro-inflammatory cytokines, including IL-23.[29,30] High levels of IL-23 in turn promote maturation of naïve T-cells into Th17 type cells.[31] These Th17 cells then produce IL-17A, the key cytokine involved in the development of psoriasis. Other pro-inflammatory cytokines, such as IL-17F, IL-22, and TNFα are also released by the Th17 cells. Elevated IL-17 levels promote keratinocyte hyperproliferation and stimulate them to produce pro-

inflammatory cytokines. At the same time, neutrophils and macrophages are recruited into psoriatic plaques, producing IL-17A and TNFα, respectively.[32,33] Collectively, there is an unchecked shift in the immune response with high levels of pro-inflammatory cytokines and recruitment of activated blood cells. With lower than normal levels of T regulatory cells, the Th17 cell pathway is not suppressed as it is in individuals with healthy skin, resulting in an immune imbalance and inflammatory state.[19]

IL-17 Cytokine Family

The IL-17 family is a key pathogenic messenger in the development of psoriasis. IL-17A and IL-17F cytokines are produced primarily by Th17 T-cells in response to inflammatory triggers, namely the presence of IL-23 from activated dendritic cells. Binding of IL-17 to its receptor stimulates several activities on both structural skin cells as well as circulating and resident skin immune cells. In the case of psoriasis, keratinocyte hyperproliferation, maturation of myeloid dendritic cells, and recruitment and activation of neutrophils and macrophages are all IL-17 dependent activities.[14,34] Collectively, these activities initiate and propagate the inflammation and architectural changes in the skin that manifest clinically as psoriatic lesions.

The IL-17 cytokine family is made up of six distinct subtypes, designated IL-17A through IL-17F, found throughout the body in different tissue types. They bind five different types of receptor subunits, IL-17RA to IL-17RE. IL-17A and IL-17F are the two main ligands active in psoriasis. Both IL-17A and IL-17F are produced by primarily Th17 cells, mast cells, neutrophils, CD8+ T-cells, and natural killer cells.[15,35] They have 50 percent homology and actually bind the same receptors, IL-17RA and IL-17RC.[5] However, IL-17A has stronger activity in binding the receptor and producing a downstream signal. IL-17C is found primarily in the kidney, colon, and lung, although it is also produced by activated keratinocytes. IL-17E is found in the lung, gastrointestinal tract, and from circulating blood cells including eosinophils, basophils, mast cells, and natural killer cells.[15,35]

Psoriasis is a Systemic Disease

While psoriasis patients suffer from skin lesions, skin plaques are really only one manifestation of systemic inflammation. Diagnosing (and treating) psoriasis has larger implications for patients' overall health. Support for the notion of psoriasis as a systemic disease comes from FDG-positron emission tomography (PET)/CT scans, demonstrating inflammation throughout the body in psoriasis patients, which is not observed in controls.[36,37] Psoriasis is known to carry several co-morbidities, which should be considered a continuum of the same inflammatory processes rather than distinct conditions. Psoriasis patients suffer from metabolic syndrome, with hypertriglyceridemia, obesity, and diabetes, hypertension, and low high-density lipoprotein. Cardiovascular disease and systemic vascular inflammation with hypertension are frequently observed in psoriatics as well. Finally, psoriatic arthritis occurs in up to 30 percent of psoriasis patients and is important to treat in order to prevent joint destruction.[38]

In addition to the physical changes seen in psoriasis, patients frequently suffer from psychosocial impairments and quality-of-life (QoL) issues.[39] Depression is common. While depression may be the result of the skin's appearance or come from skin discomfort, new data suggests that there may be a direct link between Th17 cell hyperactivity and increased IL-17 levels to depression itself. This association, however, is currently unclear and more research is needed to establish a causal relationship.[40] In addition to depression, psoriasis patients commonly suffer from anxiety, self-esteem issues and self-consciousness, sexual dysfunction, frustration and anger, and sleep disturbances.[41] IL-17A inhibition has been associated not only with clinical clearance of psoriatic skin lesions, but also with early improvements in QoL measures.[42] Research is needed to evaluate whether any differences exist in improvement of depression and QoL exist between treatments with anti-IL-17 therapies compared to other modalities.

Conclusion

Psoriasis is a chronic, systemic inflammatory disease with manifestations both in the skin and throughout the body. It is caused by a complex, dysregulated interaction between immune and non-immune cells with resulting abnormal inflammation. The Th17 helper T-cell is thought to be the central player in the pathogenesis of psoriasis, with the pro-inflammatory cytokine IL-17A as a key effector messenger. Greater understanding of the immunology of the disease has brought with it the development of newer medications, including those that use IL-17 as its therapeutic target.

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