Immunopathogenesis of Psoriasis and Pharmacological Perspectives

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ABSTRACT. Psoriasis is a chronic inflammatory disorder resulting from a combination of genetic and environmental factors, although the precise causal agents have not yet been identified. The immune system has a major role in the development of psoriasis, and the possibility exists that self antigens, antigens from microbial agents, or microbial superantigens initiate a vigorous immune response. Different subsets of T lymphocytes and dendritic cells, mast cells, and granulocytes participate in the pathogenesis; and several cytokines and chemokines have been identified in tissue lesions. Tumor necrosis factor–α, interleukin 17 (IL–17), and IL–23 are key cytokines with important pathogenetic roles in psoriasis. Angiogenesis is a prominent early event in lesional psoriatic skin. Potential targets in the treatment of this disorder include biologic agents aimed at blockade of cytokines, chemokines, and angiogenic factors. (J Rheumatol 2009;36 Suppl 83:9-11; doi:10.3899/jrheum.090210)

Key Indexing Terms:
IMMUNITY PSORIASIS CELLS

Psoriasis results from a combination of genetic and environmental factors. Two to three percent of the population worldwide is affected by psoriasis. Although the etiology of the disease remains unknown, many factors trigger or exacerbate psoriasis, including bacterial pharyngitis, stress, HIV-1, and various medications. The disease is characterized by proliferation of the epidermis, and the immune system has a prominent role in its development[1].

In psoriatic skin lesions there is a mixture of innate immune cells [neutrophils, mast cells, dendritic antigen presenting cells (APC), and natural killer T cells (NKT)], adaptive immune cells (CD4+ and CD8+ T lymphocytes), and inflammatory infiltrate. There are 2 subsets of CD8+ T cells: an epidermal homing subset expressing integrin (CD103) and a subset that remains in the dermis, in transit either to or from the epidermis. The antigen specificity of skin infiltrating T cells has not yet been identified. These cells may recognize self (epidermal or keratinocyte derived) polypeptides, microbial antigens, or superantigens[1,2]. Antigen recognition by T cells requires that mature, professional APC process polypeptides, load them onto major histocompatibility complex class I or II molecules, and ultimately present the processed peptides to the T cells together with a multitude of signals. Conjugation of the T cell and the APC and the formation of the immunologic synapse results in complete activation of T cells and the secretion of cytokines that are found in psoriatic lesions [interferon–γ (IFN–γ), tumor necrosis factor–α (TNF–α)].

The presence of dendritic cell (DC) subsets, whose frequency is normally very low in peripheral blood, together with activated T cells, constitutes a fundamental aspect of the disease process, because *in situ* recruitment of both cell types drives the chronic T cell activation in skin lesions. Thus, identification of this cell network within the psoriatic lesions is a fundamental aspect of how the immune system functions (or dysfunctions) in psoriasis.

Th17 cells are a distinct lineage of proinflammatory T helper cells that are essential for autoimmune diseases. In humans, commitment to the Th17 lineage is dependent on IL–1β and IL–23[3,4]. Th17 cells synthesize IL–17A, IL–17F, IL–22, IL–26, and IFN–γ and express transcription factor retinoid orphan receptor gamma T and CD161. Psoriatic skin lesions contain IL–23-producing DC[5] and IL–17A, which is responsible for tissue neutrophilia. IL–23 consists of a unique p19 subunit coupled to the p40 subunit of IL–12. Interestingly, a fully human monoclonal antibody that binds to p40, neutralizing the effects of both IL–23 and IL–12, is effective in the treatment of psoriasis[6].

Several subsets of T lymphocytes have immunoregulatory functions. For example, a CD4+ T cell subset that constitutively expresses CD25 has been termed the T-regulatory cell (T_{reg}). These cells suppress immune responses and prevent the development of autoimmune diseases[7]. T_{reg} cells can suppress the activities of CD4+ and CD8+

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T cells in a nonantigen-specific manner, both *in vitro* and *in vivo*, through 2 mechanisms: cell contact and suppressive cytokines such as IL–10 and transforming growth factor–β[8]. Mast cells are essential in inducing T_{reg} cell-dependent peripheral tolerance[9]. Deficient T_{reg} cell activity has been associated with a number of autoimmune conditions. Sugiyama, *et al* demonstrated deficient T_{reg} cell activity in the peripheral blood and in skin lesions of patients with psoriasis[10].

NKT are a subset of T cells[11] distinct from NK cells in that they express a T-cell receptor (TCR), but also certain NK receptors such as CD94 and CD161. These cells express a limited TCR repertoire, typically Vα24JαQ and Vβ11 in humans, which limits them to recognizing only a narrow spectrum of antigens. NKT recognize glycolipids (α–galactosylceramide or glycosylphosphatidyl inositol) presented in the context of CD1d on the APC, rather than processed polypeptides. The natural ligands for NKT have not been identified, and the definitive role of these cells in psoriasis remains to be fully elucidated[1]. A primary abnormality in the lesion of psoriasis is the perivascular accumulation of neutrophils and their influx into the epidermis. Neutrophils can contribute to the hyperproliferation of keratinocytes induced by leukocyte elastase[12].

Human mast cells are usually distributed throughout normal connective tissue and produce a wide array of mediators and cell-cell signaling molecules. This variety may account for the cells' unique features in the immune system[13]. Skin mast cell density is increased in psoriasis[14]. Expression of both CD30 and CD30L is upregulated in lesional skin, as is the density of IL–8+ mast cells. Engagement of CD30L on mast cells induces the release of several chemokines [IL–8, monocyte chemoattractant protein–1, and macrophage inflammatory protein 1β (MIP–1β)][14]. Corticotropin-releasing hormone (CRH) coordinates the systemic stress response, with repercussions on the inflammatory response. Psoriasis is exacerbated by stress, and mast cells express CRH receptors and synthesize CRH[15]. CRH also stimulates secretion of vascular endothelial growth factor-A (VEGF-A) from mast cells through the activation of CRH receptors[16]. The expression of VEGF and serum levels of VEGF are related to disease activity[17]. Mast cells express several isoforms of VEGF[1,18,19], and angiogenesis is critical for psoriasis[20]. Angiopoietins are the major ligands of the endothelial receptor Tie–2. Angiopoietin 1 (Ang–1) induces Tie–2 signaling and maintains vessel formation, while Ang–2 destabilizes vessels by blocking Tie–2 signaling as an antagonist of Ang–1 and acts with VEGF to initiate angiogenesis[21]. Ang–1 and Ang–2 and Tie–2 expression is upregulated in perivascular regions in lesional psoriatic skin[22]. Therefore, mast cells, which are closely associated with blood vessels and increase at angiogenic sites, can contribute to various aspects of angiogenesis[19]. Activation of human mast cells leads to the *de novo* synthesis of a wide spectrum of cytokines (e.g., TNF–α, stem cell factor)[13,23] and chemokines (e.g., IL–8, MIP–1α)[24]. Human skin mast cells contain and release TNF–α[25], thus contributing to the local production of TNF–α in psoriasis, and the IL–8 findings might explain the neutrophil infiltration in this disorder. Mast cells in psoriatic skin are strongly positive for IFN–γ[26], thus contributing to Th1 polarization in this disorder. Collect-ively, these findings provide evidence for the important role of mast cells in the pathogenesis of psoriasis.

The psoriatic plaque contains Th1 type cytokines (IFN–γ, IL–2, and TNF–α)[27]. APC infiltrating the skin lesions also contribute to the local cytokines, which include IL–18, IL–23, and TNF–α. IL–18 and IL–23 both induce IFN–γ production by Th1 cells. IL–23 is a dominant cytokine in psoriatic plaques[5,28]. TNF–α is a key proinflammatory cytokine with an important pathogenic role in psoriasis. The central role of TNF–α is confirmed by the therapeutic efficacy of TNF–α-targeting agents (etanercept, infliximab, and adalimumab)[17].

CONCLUSIONS

An intricate network of different cell types interacts to induce chronic inflammation in psoriasis. Advances in understanding the immunopathogenesis of psoriasis have led to improvements in treatment. Targeting the TNF–α/TNF–αR system and IL–12/IL–23 clearly benefits the majority of patients with psoriatic skin lesions. Future challenges include careful monitoring of patients receiving new biologics and investigating the longterm sequelae of chronic inflammatory inhibitors as regards potential risks of infections and neoplasms. In addition, we must carry on working to define the cytokine and chemokine networks operative both upstream and downstream from TNF–α.

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