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Review Article

Cytokines in psoriasis

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ABSTRACT

Psoriasis is a common inflammatory skin disease with an incompletely understood etiology. The disease is characterized by red, scaly and well-demarcated skin lesions formed by the hyperproliferation of epidermal keratinocytes. This hyperproliferation is driven by cytokines secreted by activated resident immune cells, an infiltrate of T cells, dendritic cells and cells of the innate immune system, as well as the keratinocytes themselves. Psoriasis has a strong hereditary character and has a complex genetic background. Genome-wide association studies have identified polymorphisms within or near a number of genes encoding cytokines, cytokine receptors or elements of their signal transduction pathways, further implicating these cytokines in the psoriasis pathomechanism. A considerable number of inflammatory cytokines have been shown to be elevated in lesional psoriasis skin, and the serum concentrations of a subset of these also correlate with psoriasis disease severity. The combined effects of the cytokines found in psoriasis lesions likely explain most of the clinical features of psoriasis, such as the hyperproliferation of keratinocytes, increased neovascularization and skin inflammation. Thus, understanding which cytokines play a pivotal role in the disease process can suggest potential therapeutic targets. A number of cytokines have been therapeutically targeted with success, revolutionizing treatment of this disease. Here we review a number of key cytokines implicated in the pathogenesis of psoriasis.

1. Psoriasis, an immune-mediated skin disease

Psoriasis is a common immune-mediated inflammatory skin disease affecting all major human populations with the greatest prevalence of 2–3% in those of northern European ancestry [1]. The most common form of the disease is chronic plaque psoriasis (*psoriasis vulgaris*), which manifests as plaques of red, scaly and well-demarcated regions of inflamed skin. These plaques are the result of increased keratinocyte proliferation, where up to an eight-fold increase in epidermal cell turnover has been demonstrated [2], leading to a thickening of the epidermis (acanthosis) and altered keratinocyte differentiation. This marked hastening of the transit of keratinocytes to the upper layers of the epidermis results in perturbation of their normal maturation program, resulting in altered protein expression, loss of a mature granular layer and retention of keratinocyte nuclei (parakeratosis). These changes are accompanied by dermal angiogenesis leading to an increasingly complex underlying vascular system, giving the plaques their deep red coloration (Fig. 1). This increased vascularity allows for a greater influx of inflammatory cells into the skin, further driving the inflammation. T cells and a myriad of cells from the adaptive and innate arms of the immune system are present early in lesions, forming characteristic nests of activated leukocytes in the reticular dermis, with a mixed CD4/CD8+ T cell infiltrate in the papillary dermis and an exclusively CD8+ T cell population in the epidermis (Fig. 1). As such, psoriasis is now generally regarded as a T cell-mediated immune disease with a mixed Th1/Th17 cytokine environment [3–5].

2. Psoriasis, the product of a cytokine storm

A decade ago we [6] and others [7] suggested that the interplay between cytokines expressed in psoriasis skin (Fig. 2) could explain most of the clinical features of psoriasis, such as the hyperproliferation of keratinocytes, increased neovascularization and inflammation, and that by determining which cytokines played a central role in the disease process, interesting therapeutic targets could be

Abbreviations: NHK, normal human keratinocyte; qRT-PCR, quantitative reverse transcription polymerase chain reaction; pDC, plasmacytoid dendritic cells; mDC, myeloid dendritic cell; MO-DC, monocyte-derived dendritic cell; APC, antigen-presenting cell; TLR, Toll-like receptor; GPP, generalized pustular psoriasis; PPP, palmar-plantar pustulosis.

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identified [6]. In the time since, drugs targeting tumor necrosis factor (TNF)-α, interleukin (IL)-12/23, IL-17, IL-22, IL-23, granulocyte monocyte-colony stimulating factor (GM-CSF), as well as inhibitors of the Janus kinases (JAK1/2/3) downstream of a number of cytokine receptors, have reached the clinic or are currently in clinical trials [8]. Recently several technologies have been developed that allow the quantification of multiple cytokines and growth factors in tissues both at the level of protein [9] and mRNA using cDNA microarrays [10] and high-throughput complementary DNA sequencing (RNA-seq) [11] giving an increasingly more sensitive and global view of the psoriasis transcriptome (Fig. 2). Here we present a short survey of key cytokines implicated in the pathogenesis of psoriasis.

3. The IL-1 family in psoriasis: masters of inflammation

IL-1 is viewed as the archetypal pro-inflammatory cytokine, studied for its fever-inducing and inflammatory properties since the 1940s and as such IL-1 was the first cytokine detected in skin [12]. The IL-1 family of cytokines now contains 11 ligands and 9 receptors, many of which are altered in their expression in both non-lesional and lesional psoriasis skin compared with healthy control skin [13]. The canonical IL-1 family members IL-1α and IL-1β are both present in normal healthy epidermis [14,15] and act by recruiting IL-1R1 and the accessory protein IL-1RAcP, a process moderated by the decoy receptor IL-1R2 and the receptor antagonist IL-1Ra. IL-1α and IL-1β are both expressed as immature pro-proteins but have differential requirements for activation. Keratinocytes constitute a major reservoir of IL-1α [16] and although pro-IL-1α is active as a cell membrane-associated cytokine, under conditions of cell stress, particularly stimuli that trigger cytoplasmic NOD-like receptor activation, cytoplasmic pro-IL-1α is rapidly processed by calpain-like proteases and secreted. Depending on the stimulus, this process may be either independent of caspase-1 or require the presence, but not catalytic activity of, caspase-1 [17]. On the other hand, the activity of IL-1β, along with IL-1 family member IL-18, always requires post-translational cleavage of the pro-protein by caspase-1 for activity. Cell stress, infection or local danger signals trigger the assembly of inflammasome complexes [15,18,19], which activate caspase-1, which in turn cleaves pro-IL-1β to its active form. The IL-1 family conspicuously lacks signal sequences for conventional cytokine secretion via the endoplasmic reticulum – Golgi pathways and the mechanism of secretion may vary with cell type and inducing stimulus, with proposed mechanisms involving lysosome exocytosis, multivesicular body formation and exosome release or pyroptosis [20]. Interestingly, pro-IL-1α also contains a nuclear localization motif in its N-terminal domain [21] which permits its translocation to the nucleus and activation of NF-κB and AP-1, a mechanism that may lower the signaling threshold for an inflammatory response by IL-1α-expressing cells.

Once secreted, the two IL-1 isoforms have similar functions, acting in an autocrine and paracrine fashion on keratinocytes and also on local fibroblasts, vascular endothelium and lymphocytes. IL-1 has rapid and profound effects on keratinocytes, inducing a swath of gene transcripts involved with inflammation and antimicrobial responses, a transcriptional signature which closely resembles differences seen in lesional versus non-lesional psoriatic skin [22,23], suggesting that IL-1 could be an important mediator in psoriasis pathogenesis. IL-1 also drives the expression of ICAM and VCAM-1 by dermal endothelial cells, as well as the secretion of platelet aggregating factor, nitric oxide and prostaglandin I_2, leading to the increased recruitment of immune cells to the skin. Interestingly, IL-1α but not IL-1β appears to be critical for the formation of T cell-APC dermal clusters, which provide an extra-lymphoid environment for intimate contact between DCs, T cells and macrophages for the elicitation of immune reposes [24]. APCs are exquisitely sensitive to IL-1, upregulating a host of maturation markers, priming for antigen presentation to T cells. Moreover, IL-1 appears to be a key cytokine in the development of skin Th17 responses in psoriasis, with IL-1 and IL-23 cooperating in the induction of IL-17 production by T cells [25]. The use of synthetic IL-1R antagonists, such as anakinra, are helpful in the treatment of rheumatoid arthritis [26] but have failed to show efficacy for psoriasis [27], possibly because IL-1Ra is already abundant in psoriatic lesions [28]. A number of case reports suggest that IL-1 antagonism may be a useful approach for treating pustular variants of psoriasis [29], however, there is currently a lack of adequately controlled trials to support this.

4. The IL-36 sub-family: specialists in epithelial inflammation

Analogous to IL-1α, -1β, -1Ra, and their receptor IL-1RI, the subfamily of IL-36 cytokines includes three receptor agonists: IL-36α (formerly known as IL-1F6) [30], IL-36β (IL-1F8) [31,32], and IL-36γ (IL-1F9) [32,33], and a receptor antagonist, IL-36Ra (IL-1F5). These cytokines bind their cognate receptor IL-36R (IL-1Rrp2)/IL-1RAcP (shared with IL-1RI) to signal via NF-κB and MAP kinases [32]. In humans, the IL-36 receptor is widely expressed by epithelia [13,34,35] and antigen-presenting cells, but not human T cells or neutrophils [36].

The role of the IL-36 cytokine system in skin inflammation has been extensively demonstrated [13,30,32,33]. All of the IL-36 family members have been shown to be upregulated in human psoriasis lesions [13,30,33] with IL-36γ correlating particularly well with psoriasis disease severity [37]. In addition, the IL-36 family is active in a number of mouse models of skin inflammation [13,30,36,38]. Expression of murine IL-36α induces leukocyte infiltration and skin inflammation [30,36] and blockade of the IL-36 system could ameliorate imiquimod-Toll-like receptor (TLR)-7/8 induced skin inflammation [38], indicating that IL-36 cytokines are critical members of the cytokine milieu that drives skin inflammation in this model. Thus far, all IL-36 ligands appear to be functionally equivalent with respect to their activity on human cells. IL-36 induces the expression of antimicrobial peptides, cytokines and chemokines by keratinocytes [13,36], and drives the activation of APCs [36,39]. These observations are consistent with a role for IL-36 in driving psoriatic skin inflammation by attracting neutrophils, myeloid cells and T cells into developing psoriasis lesions and altering APC function to potentiate the inflammatory cycle. In early experiments, microgram quantities of recombinant IL-36 ligands were required for inducing keratinocyte responses [13,40], however removal of 5, 4 or 19 amino acids N terminal to a A-X-Asp motif of IL-36α, β, or γ, respectively, results in up to a 10,000-fold increase in activity [41]; however, these peptides do not contain a caspase-1 cleavage motif and the enzyme(s) responsible for cleaving the peptides have yet to be identified. Moreover, the IL-36 cytokines do not have a signal peptide to direct their secretion, thus like IL-1α, both their processing and release from the cell are currently unclear.

The potential importance of the IL-36 family in psoriasis is highlighted by the discovery that loss-of-function mutations in the IL-36 receptor antagonist gene *IL36RN* underlie a rare but debilitating form of psoriasis, generalized pustular psoriasis (GPP) [42,43]. Such mutations leave IL-36 agonist activity unchecked, driving a neutrophilic skin inflammation. Although inhibition of the canonical IL-1 system has not proved to be an effective therapeutic approach in psoriasis [27], targeting the IL-36 system holds promise, particularly in the debilitating conditions GPP and the closely-related disease palmar-plantar pustulosis (PPP), particularly where