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The new psoriasis pathway: toward a unified theory of immunopathogenesis

'...research in the pathogenesis of psoriasis has focused on immune deregulation and how these activated Th1 cells and the cytokines they produce form the driving force for induction and maintenance of a psoriatic plaque.'

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Psoriasis is characterized by thick, scaly red plaques that show a predilection for the elbows, knees and scalp but may develop in any area of the skin. Histologically, these lesions have a characteristic thickening of the epidermis with proliferation of epidermal keratinocytes. There are collections of neutrophils in the epidermis. T cells and dendritic cells infiltrate the dermis and there are hyperplasic, dilated blood vessels in the papillary dermis. The endothelial cells are activated and stain for different adhesion molecules, such as ICAM-1, VCAM-1 and E-selectin, to allow for continued inflammatory cell trafficking into the skin.

'...the introduction of activated T cells was sufficient to induce psoriasis in genetically susceptible keratinocytes.'

Thus, multiple cell types must interact to form a psoriatic plaque. Much of the research in the pathogenesis of psoriasis has focused on immune deregulation and how these activated Th1 cells and the cytokines they produce form the driving force for induction and maintenance of a psoriatic plaque. The classic mouse model that first started this line of research was developed by Wrone-Smith and Nickoloff. Symptomless skin from a psoriatic patient was transplanted on an immunodeficient (severe combined immunodeficiency disease) mouse. T cells from the same patient were activated *in vitro* and then injected into the xenografted skin. In time, the graft became histologically identical to skin from a plaque of psoriasis complete with keratinocyte and vascular changes. This change did not occur in skin from patients without psoriasis or when the T cells were not activated *in vitro*. Thus, the introduction of activated T cells was sufficient to induce psoriasis in genetically susceptible keratinocytes [1].

This T-cell activation in psoriasis has focused on a 'type 1' response. The classic mediator of this type 1 response is the cytokine IFN-γ. This classic response focuses on an undefined trigger on the antigen-presenting cells in the dermis (CD11c dendritic cells), which eventually stimulates T cells [1,2]. The early inducers of this response are IL-12 and -23, which stimulate the T cell toward Th1 differentiation. These activated Th1 cells can produce various inflammatory mediators, including IFN-γ, TNF-α, and IL-17. Numerous downstream molecules are then triggered by this cytokine influx that contribute to the psoriatic plaque. The type 1 cytokines promote keratinocyte hyperplasia, dilation of vascular channels and upregulation of adhesion molecules (e.g., cutaneous lymphocyte-associated antigen and VCAM) to allow for additional inflammatory cells, and provide an inflammatory milieu of chemokines to potentiate this chronic response [3].

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Activated T lymphocytes were also the focus of the newer psoriasis treatments. At first glance, these medications also appear to be targeting the type 1 response. TNF-α is a classic cytokine produced by Th1 cells, and anti-TNF medications are quite effective in controlling psoriasis [3]. IL-12 is thought to initiate cytokines in inflammatory reactions to push the differentiation of T cells toward the type 1 phenotype. The anti-IL-12/23 (which share an identical p40 subunit) antibodies are currently in Phase III trials for psoriasis and also seem to be quite effective in controlling psoriasis [4].

However, the IL-23 cytokine has played a major role in breaking the classic Th1/Th2 hypotheses. This interleukin also drives a newly discovered population of T cells, the Th17 cells. This novel T cell produces inflammatory mediators, including IL-17, IL-22, IL-6 and TNF-α. The old model of a linear Th1 cytokine-driven inflammatory pathway, with IL-12 activation of Th1 cells and IFN-γ stimulating the initial changes in a psoriasis plaque, needs to be expanded. With over 100 different gene products upregulated in a psoriatic plaque [5] (and only a limited number of those can be explained by IFN-γ stimulation alone [6]), it is more likely that this is a complicated, cross-activated system that is stimulated and regulated on many different levels. It is also likely that the keratinocyte is no longer merely a secondary target from inflammation but may play a primary role in the initiation and maintenance of the psoriatic plaque with the activated T cells. A closer examination of each of these cells and new interleukins will help to shed light on this newer system and how it relates to psoriasis.

'IFN-α is a classic cytokine produced by Th1 cells, and anti-TNF medications are quite effective in controlling psoriasis.'

Th17 cells

This population of T cells is a different class of T cells that seems to be active in very specific and limited disease states, namely autoimmune diseases and, occasionally, in specific microbial infections. IL-6, which activates nuclear signal transducer and activator of transcription (STAT)-3 transcription [7] and TGF-β (both made by active dendritic cells in the dermis) are needed for the establishment of this T-cell lineage [8]. TGF-β upregulates the IL-23 receptor (IL-23R) on this T cell [9], and IL-23 is needed for the establishment and long-term survival of this cell in tissues [10]. This cell is present in active psoriatic plaques [11] and two of the major cytokines that this T cell produces, IL-17 and IL-22, are also recently discovered players in psoriasis.

IL-17

The interleukin that the memory Th17 cells were named after is also linked to autoimmune disease. It has been shown to induce changes that we would normally find in an active psoriatic plaque: it stimulates neutrophil recruitment [12], angiogenesis [13] and multiple matrix metaloproteinases [14]. It has additive and synergistic effects with IL-1 (a classic type 1 cytokine), as well as TNF-α [15].

IL-23

As discussed, this interleukin is made by activated dendritic cells [11], as well as macrophages and keratinocytes. It is the main inducer of the T17 cells [16] and also activates nuclear STAT-3 transcription. Since it shares the common p40 subunit with IL-12, it was initially thought to be a similar molecule. However, IL-12 is a potent inducer of IFN-γ and the classic Th1 response and does not seem to induce T17 cells. The addition of IL-23 can show an increase in IL-17 and IL-22 but not IFN-γ [17]. IL-23 is overexpressed in psoriatic skin (unlike IL-12), and addition of this interleukin in the epidermis induces a marked acanthosis and mixed infiltrate. Although IL-12 can cause similar changes, the acanthosis is not as marked [18]. IL-23 expression is significantly higher in psoriatic lesional skin compared with nonlesional and normal controls [19].

Interestingly, an *IL-23R* gene mutation on T cells has been associated with psoriasis [20] and other autoimmune processes, such as inflammatory bowel disease [21].

IL-22

A key cytokine in the acanthosis and inflammation induced by IL-23 is IL-22. IL-22 is made by Th17 cells, as well as natural killer and mast cells. It does not affect T-helper differentiation and its receptor is not found on any activated or resting immune cells. It is found in the pancreas, the GI tract and epidermal keratinocytes to regulate tissue protection and promote wound healing [22]. Inflammation through IFN-γ increases the sensitivity of keratinocytes to this interleukin and upregulates the IL-22R. Synergistically with IL-17, it induces defensins, matrix metalloproteinases and other molecules, including S100A7 [23], which enhances keratinocyte mobility [24], proliferation and the inflammatory response seen specifically in a psoriatic plaque. S100A7 seems to be important in the early evolution of a psoriasis plaque and is a key chemotactic molecule for neutrophils and CD4 lymphocytes [25]. It is almost undetectable in normal skin but highly expressed in psoriatic keratinocytes [26].

There are several recent articles that demonstrate how IL-22 appears to be the primary interleukin responsible for the epidermal hyperplasia induced by IL-23. It inhibits normal keratinocyte differentiation, and changes the keratin expression pattern to that of hyperplastic keratinocytes with keratin 6 [22]. Interfering with IL-22 will decrease epidermal acanthosis [17].

IL-22 appears to activate only a few inflammatory molecules, unlike IFN-γ, which activates many downstream pathways. This molecule has very specific key inflammatory properties, and the genes activated in the keratinocyte by this interleukin play an important role in psoriasis. Elevated IL-22 in the blood also correlates with severity of the psoriatic skin disease. IL-22 is also found to be increased in the psoriatic plaque [27]. In the colon, it appears to have cross-talk with some of the typical inflammatory mediators for psoriasis, namely TNF-α. IL-22 increases mRNA expression of TNF-α, and TNF-α upregulates the IL-22R [28]. In a mouse model of psoriasis, TNF-α was shown to induce cross-talk between IL-23-activated T cells

(which make IL-22) and keratinocytes [18]. It is one of a few links between activated keratinocytes and activated T cells and this link seems to be through STAT-3 activation.

STAT-3

Both IL-23 and IL-22 induce STAT-3 nuclear transcription in transgenic mouse models of psoriasis. STAT-3 is fairly specific for psoriasis and is found in its active form in the nuclei of keratinocytes in psoriatic plaques but not in other hyperproliferative epidermal disorders, such as lichen planus. Activating STAT-3 in the keratinocytes of mouse epidermis produces a clinical and histological picture close to human psoriasis. In fact, activated STAT-3 is even found in the basal layer of uninvolved psoriatic skin and may be important in the predisposition of psoriatic skin to make psoriatic plaques. In lesional skin, STAT-3 is localized to the nucleus in both basilar and suprabasilar keratinocytes. Activated T cells are essential to this activation of STAT-3 [29].

'...genes, including *VEGF*, *TGF-α* and cyclin D-1, are regulated by STAT-3 and contribute to psoriasiform lesions in mouse models.'

Studies of STAT-3-deficient mice have shown that STAT-3 is essential for keratinocyte migration and wound healing. ICAM, which is essential for T-cell recruitment into the skin, also appears to be upregulated by STAT-3 [29,30]. Various other genes, including *VEGF*, *TGF-α* and cyclin D-1, are regulated by STAT-3 and contribute to psoriasiform lesions in mouse models [29]. Interestingly, anti-TNF treatment decreased STAT-3 levels in keratinocytes of psoriatic skin within 48 h, even before any change was physically seen in the psoriatic plaque.

STAT-3 also plays a role in T cells, particularly Th17 cells. When stimulated, STAT-3 binds directly to an *IL-17* promoter [31]. TNF-α alone cannot induce STAT-3, but both IFN-γ and TNF-α can induce this nuclear transcription factor. IL-23 and IL-6 also both stimulate STAT-3 [7].

Putting all of this information together, we can no longer think of psoriasis as only a linear Th1 response. It is a complicated network of intertwining pathways from multiple inflammatory mediators. Older research and drug therapies have focused on this Th1 response. For example, TNF is certainly a major player in the Th1 immune response and anti-TNF treatments have worked well in psoriasis. However, TNF also plays a role in the Th17 response. It upregulates the IL-22R, it is made by Th17 cells and synergistically enhances IL-17 effects in the skin and, together with IFN-γ, stimulates STAT-3 nuclear transcription factors in the T cell.

In addition to T-cell activation, it is likely that the keratinocyte itself plays a key role in the initiation and maintenance of a psoriatic plaque. No longer can we view the keratinocyte as an innocent bystander susceptible to the inflammation produced by activated T cells. Although the initial signal for the change in the activated keratinocyte is still unclear, STAT-3 activation provides an important link between keratinocytes and immune cells.

Newer therapies in the pipeline, including an anti-IL12/23 fully humanized antibody, have also shown promise in treating psoriasis. Clearly, this medication can focus on IL-12 as a classic Th1 cytokine but it probably also combats psoriasis via the IL-23 pathway. This antibody is then able to target two separate but important inflammatory pathways in psoriasis, the Th1 and Th17 responses. In the future, it is likely that for autoimmune diseases, such as psoriasis, we will be able to focus on pathways that are very specific to that disease. For example, focusing on the Th17 cells or STAT-3 activation in keratinocytes will probably have fewer downstream effects than classic Th1 cytokines, such as IFN-γ. This is an exciting time for immunologists and physicians who treat autoimmune disease and these emerging pathways will lead to newer, safer and more effective strategies for combating these complicated autoimmune diseases.

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