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Psoriasis: A mixed autoimmune and autoinflammatory disease

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Abstract

In recent years marked progress has been made in our understanding of the critical biologic and immunologic pathways involved in psoriasis. Genetic studies have demonstrated that susceptibility to psoriasis involves components of both the adaptive and innate immune system and not surprisingly activation of both of these arms of the immune system is found in psoriatic skin. While adaptive immune responses predominate in chronic plaque psoriasis, innate and autoinflammatory responses dominate in pustular forms of psoriasis, with other clinical subtypes extending on a spectrum between plaque and pustular psoriasis. This makes psoriasis a unique disease where both autoimmune and autoinflammatory responses co-exist, with the balance between the two being critical in shaping its clinical presentation.

Graphical abstract

Overview figure. Immunologically psoriasis is characterized by a mixture of both autoimmune and autoinflammatory immune responses. The balance between the two dictate the clinical presentation of psoriasis with chronic plaque psoriasis having prominent adaptive / autoimmune responses while pustular psoriasis is dominated by autoinflammatory immune responses. Available evidence indicates that other clinical subtypes of psoriasis exist on a spectrum between these two clinical phenotypes.

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Keywords

Psoriasis; pustular psoriasis; autoimmunity; autoinflammatory; IL-36

Introduction

Psoriasis is a chronic inflammatory condition of the skin often accompanied by inflammatory arthritis. Psoriasis exists on a fairly broad spectrum in terms of clinical manifestations. On one end, there is chronic plaque psoriasis, characterized by relatively stable and localized erythematous scaly plaques, sharply demarcated from normal skin, while on the opposite end there is generalized pustular psoriasis. Generalized pustular psoriasis is a rare clinical subtype of psoriasis, and typically presents explosively with a widespread involvement characterized by diffuse redness and subcorneal pustules, and frequently accompanied by systemic symptoms and signs. Interestingly, this strikingly different clinical presentation of psoriasis represents activation of different arms of the immune system, with the adaptive immune system being dominant in chronic plaque psoriasis but the innate immune and autoinflammatory responses being dominant in generalized pustular psoriasis.

Autoinflammatory and autoimmune disease are often distinguished clinically and immunologically. Both share the prefix “auto-” which define a pathologic process directed against self. In autoimmunity, this involves activation of the adaptive immune system, such as T or B cells, whereas autoinflammatory reactions are driven by endogenous danger signals, metabolic mediators and/or cytokines. The musculoskeletal system and skin are frequently involved in both autoimmune and autoinflammatory diseases and they can be either monogenic or polygenic in nature. However, for most complex inflammatory diseases, such as psoriasis, these two processes often co-exist and one may feed into and activate the other – therefore inflammatory conditions may represent a variable mixture of both autoimmune and autoinflammatory responses.

In this review, we will discuss the evidence for the autoimmune basis of psoriasis as well as the nature and biology of the autoinflammatory processes that are activated. Notably, clinical

subtypes of psoriasis show striking differences in terms of the balance between these two processes. Thus, chronic plaque psoriasis is characterized by inflammatory processes primarily associated with activation of the adaptive immune system, whereas generalized pustular psoriasis is characterized by activation of innate immune responses.

Genetics, adaptive immune system and evidence for autoimmunity in psoriasis

Of all the psoriasis studies that have been performed, genetic studies published in the last two decades have arguably provided the most robust insights into the critical pathogenic mechanisms in psoriasis. These have demonstrated that psoriasis is a complex genetic disorder involving multiple risk variants involved in various biological processes such as inflammation (cytokine and cytokine receptors), antigen presentation, epidermal biology, cell signaling, and transcriptional regulation (Figure 1). It is worth noting that the great majority of studies done on the genetics of psoriasis have focused on the chronic plaque psoriasis subtype. Interestingly, when the risk genes are viewed through the prism of participation in either adaptive vs. innate immune system the genetic variants predisposing to chronic plaque psoriasis consist of a mixture of genes involved in either one of those two inflammatory axes (Figure 2).

The first psoriasis-associated signal identified[1] is the MHC class I molecule; HLA-Cw*0602, which was confirmed as a risk variant by sequence and haplotype analysis in 2006[2], and remains one of the strongest and most prominent genetic risk factor for psoriasis susceptibility identified to date. Association between HLA-Cw*0602 is particularly strong in patients with an early age at onset[3] and in patients with the guttate subtype[4]. Other genes associated with psoriasis susceptibility and involved in antigen presentation, are the *ERAP1* and *ERAP2* genes[5,6]. *ERAP1* and *ERAP2* encode for aminopeptidases, which are located in the endoplasmic reticulum, and have an important role in trimming of peptides to an optimal length for presentation by MHC class I molecules. Consistent with their role in antigen presentation in psoriasis, *ERAP1* variants have been shown to interact with HLA-Cw*0602, and markedly increasing the risk of psoriasis[5]. So far interaction between *ERAP2* and HLA-Cw*0602 has not yet been demonstrated.

MHC class I molecules, including HLA-Cw*0602, play an important role in presenting cytoplasmic antigens to CD8⁺ T cells[7]. CD8⁺ T cells are key effector cells in psoriasis, and represent the majority of intra-epidermal T cells in psoriatic plaques. The psoriatic CD8⁺ T cells have characteristics of tissue-resident memory cells (TRM) and are retained in the epidermis after successful therapy[8]. A large proportion of CD8⁺ T cells in psoriatic lesions are oligoclonal[9] suggesting that these cells have expanded as a response to a limited set of antigens. These cells produce pathogenic IL-17, a key driver of psoriasis inflammation[10,11], and neutralization of CD8⁺ T cells[12] or inhibition of T cell trafficking into the epidermis[13] prevents development of psoriasis in a xenograft model. These observations suggest that CD8⁺ T cells may be engaged in pathogenic crosstalk with keratinocytes through HLA-Cw*0602 and that this process is the central driver of inflammatory activity in chronic plaque psoriasis [12] (Figure 3).

Given this large body of evidence for the role of antigen presentation and involvement of autoreactive CD8+ T cells, what is known about the nature of the self-antigen in the pathogenesis of psoriasis? Several studies have attempted to address this and several putative autoantigens in psoriasis have been proposed. One of these is keratin 17, which involvement was proposed on the basis of keratin 17 homology to streptococcal M-proteins[14], but streptococci are one of the best established environmental triggers of psoriasis, particularly guttate psoriasis, which is strongly, if not exclusively, associated with HLA-Cw*0602[4]. In one of the studies, HLA-Cw*0602 positive patients showed an increased IFN- γ response by CD8+ T cells to peptides from keratin 17, while HLA-Cw*0602 negative patients had minimal or no responses[15]. The antimicrobial peptide LL-37 has also been implicated as a potential self-antigen in psoriasis[16], and the ADAMTS-like protein 5 (ADAMTSL5)[17]. It was recently shown that CD8+ T cells respond to peptides derived from the ADAMTSL5 protein in a HLA-Cw*0602 restricted fashion, resulting in release of IL-17A and IFN- γ [17]. All three of these putative autoantigens in psoriasis are strongly induced in psoriatic skin[18,19], with LL-37 and ADAMTSL5 having fairly widespread expression patterns[19], but keratin 17 expression is limited to the psoriatic epidermis[18].

Lipid-specific T cells may also contribute to inflammation in psoriatic epidermis. The lipid species that are presented act more as danger signals than true antigens and are therefore better classified as part of the innate immune responses although responses to these lipid antigens require components of the adaptive immune system. Lipid antigens can be presented on CD1 molecules and recognized by T cells (Figure 3). Frequency of both CD1b[20] and CD1a[21] autoreactive T cells is found to increase in psoriasis patients compared to healthy controls. Several phospholipases, including PLA2G4D and PLA2G2F, are increased in psoriatic skin[21,22], but these enzymes play a role in generation of phospholipid neoantigens. No genetic variants in psoriasis have been associated with lipid processing or presentation.

Neutrophils, IL-36 and autoinflammatory responses in psoriasis

Neutrophils are the most abundant leukocyte in humans and are essential for driving innate immune responses against pathogens[23]. While neutrophils are a minor inflammatory population in chronic plaque psoriasis lesions, the presence and infiltration of neutrophils into the epidermis is one of the hallmark histologic features of psoriasis. Neutrophils are found in low numbers in the epidermis and stratum corneum in chronic plaque lesions as spongiform pustules of Kogoj or Munro's microabscesses respectively, but are the predominant leukocyte population in pustular psoriasis skin lesions, which are characterized by large collections of intra-epidermal and subcorneal neutrophils. Neutrophil chemoattractants such as CXCL1, CXCL2, CXCL8 (IL-8) are highly expressed in plaque psoriasis and about 5-10 times higher still in pustular psoriasis[24].

One of the key inflammatory mediators that drives neutrophil inflammation in psoriasis appears to be the IL-36 family of cytokines. IL-36 belongs to the IL-1 family of cytokines, which consists of 11 cytokines and 9 cell-surface receptors[25,26]. There are three pro-inflammatory IL-36 cytokines; IL-36 α , IL-36 β and IL-36 γ and one receptor antagonist; IL-36Ra, which has 52% amino-acid similarity with IL-1RA[27]. IL-36Ra inhibits the

activity of the other three IL-36 cytokines at the level of the IL-36 receptor. The members of the IL-36 family are highly expressed in plaque psoriasis[28], and are robust inducers of neutrophil chemokines including CXCL1 and CXCL8 (IL-8)[29]. Notably, the effect of IL-36 is mainly on keratinocytes and myeloid dendritic cells but not T-cells, which lack expression of the IL-36 receptors[29].

Several genetic mutations have been associated with pustular psoriasis. Loss-of-function mutations in the IL-36 receptor antagonist (*IL36RN*) are associated with generalized pustular psoriasis[30,31]. These mutations lead to unopposed activity of the IL-36 cytokines, which in turn increases the expression of neutrophil chemokines including IL-8[31]. This is analogous to the unopposed inflammatory responses seen in deficiency of the IL-1 receptor antagonist (*IL1RN*)[32]. As IL-36 cytokines further induce mRNA expression and secretion of IL-36 cytokines, this leads to vicious self-sustaining cycle of inflammation, and therefore this axis is best classified as being autoinflammatory in nature. *IL36RN* mutations have also been demonstrated in localized pustular forms of psoriasis[33], but, interestingly, *IL36RN* mutations do not appear to increase susceptibility to chronic plaque psoriasis[34]. Other genetic mutations identified to contribute to pustular forms of psoriasis include *APIS3*[35] and *CARD14*[36]. *APIS3* encodes a subunit of AP-1, and through abnormal accumulation of p62 impacts NF- κ B signaling, and increases expression of IL-1 β , IL-36 and neutrophil chemokines including CXCL8[35]. *CARD14* is a scaffold protein that mediates NF- κ B signal transduction in keratinocytes[36]. Psoriasis associated *CARD14* mutations are associated with increased NF- κ B activation[36], and increased mRNA expression for CXCL8 and IL-36 cytokines[37]. Of these three pustular risk genes only the *CARD14* gene is also associated with increased risk of chronic plaque psoriasis[36].

Apart from being attracted into psoriatic plaques, neutrophils also have a role in amplifying the IL-36 autoinflammatory loop in psoriasis. Similar to other IL-1 family members, the IL-36 family of cytokines are secreted via a non-classical pathway involving multivesicular bodies and exosomes[38]. Most of the IL-1 family of cytokines are expressed as inactive precursors and must be processed to become biologically active[39]. Whereas IL-1 β and IL-18 require caspase-1 for processing intracellularly before secretion, IL-36 cytokines are thought to be secreted as full length inactive proteins, with secretion triggered by danger-signals such as ATP[28]. To become fully active the IL-36 cytokine family requires N-terminal processing to fully turn on their pro-inflammatory activity[40-42]. Neutrophils appear to have a key role in amplifying the IL-36 autoinflammatory loop in psoriasis. Thus, neutrophils, upon activation, release extracellular traps that contain several proteases including protease 3, elastase and cathepsin G[42]. The proteases in these neutrophil extracellular traps (NETs) retain their protease activity and differentially process and cleave IL-36 α , IL-36 β and IL-36 γ to their truncated and more biologically active forms[40,42] (Figure 3). Keratinocytes also have a role in this process and it was recently demonstrated that epithelial cell-derived proteases, such as cathepsin S, are also able to activate IL-36[43]. The relevance of epithelial cell-derived proteases in contrast to neutrophil derived proteases in psoriasis is not yet clear. However, a significant fraction of the cleavage induced by neutrophil derived proteases generated inactive forms of IL-36[40], whereas this doesn't appear to be the case with cathepsin S.

The epidermis is capable of regulating this inflammatory cascade beyond just expressing and secreting the IL-36RA. Endogenous keratinocyte derived serine proteases, such as serpins A1 and A3, are increased in both plaque and pustular psoriasis and are capable of inhibiting both neutrophil elastase (serpin A1) and cathepsin G (serpin A3)[24]. However, as these are only modestly elevated in psoriasis and irreversibly inhibit their respective proteases in a 1:1 fashion, it is likely that there are other mechanisms involved by which this inflammatory axis can be turned off.

Psoriasis as a spectrum of autoimmune to autoinflammatory processes

Psoriasis, as discussed above, exists on both a clinical and immunological spectrum in a delicate balance between adaptive and innate immune responses. On one end there is chronic plaque psoriasis where adaptive immune responses dominate, and on the opposite end there is generalized pustular psoriasis where the innate immune system and IL-36 autoinflammatory responses drive and dominate the inflammatory responses (Figure 4). Interestingly, while elevated in both plaque and pustular psoriasis, *IL1B* does not appear to have as critical role, and IL-1 antagonists are generally not effective in psoriasis[44], although some reports have suggested efficacy in generalized pustular psoriasis[45,46]. Notably, clinical subtypes of psoriasis, such as erythrodermic and inverse psoriasis and localized pustular forms of psoriasis pustulosis palmoplantaris (PPP) have IL-36 responses in-between those of plaque and pustular psoriasis (Figure 4). Therefore, psoriasis is a unique disease where each of its individual clinical phenotypes represents a different balance between autoimmune and autoinflammatory immune processes. Greater appreciation of these processes, and how they interact and feed into one another, will provide us with greater understanding of the disease processes involved in psoriasis and its clinical subtypes and provide new avenues for treatment.

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Highlights

- Plaque psoriasis exhibits both autoimmune and autoinflammatory immune responses
- The autoinflammatory loop in psoriasis is driven by IL-36 cytokine responses
- Neutrophils and keratinocytes promote autoinflammatory responses in psoriasis
- Psoriasis subtypes have variable balance of autoimmune and autoinflammatory responses

Figure 1.

Identified genetic risk loci in psoriasis since 2006. To date over 60 genetic risk loci have been identified in psoriasis. These involve distinct biological processes such as antigen presentation, cytokines and receptors, epidermal function, cell signaling, and transcriptional regulation.

Figure 2. Risk loci in context of adaptive vs. innate immune system function. This is a simplified view of the biologic function of psoriasis associated genetic risk loci in terms of adaptive (red) vs. innate (blue) immune system role. The risk loci highlighted by a red outline (*IL36RN*, *CARD14* and *APIS3*) have been implicated as risk factors for pustular psoriasis. Other loci (white) are not easily classified in terms of role in adaptive vs. innate immune system responses. The adaptive and innate immune system are closely integrated in psoriasis with activation of one generally leading to the activation of the other. Both systems contribute to all clinical subtypes of psoriasis but to a variable degree depending on the subtype.

Figure 3.

Autoimmune vs. inflammatory responses in psoriasis. A) Antigen presentation plays a key role in psoriasis. Two endoplasmic aminopeptidases involved in processing of peptide antigens; ERAP1 and ERAP2, are established susceptibility genes in psoriasis along with HLA-Cw6 (highlighted in red). These have a role in processing and presenting antigens to CD8+ T cells, which on activation release pro-inflammatory cytokines including IL-17, TNF- α and IFN- γ . Another antigen presenting pathway involved in psoriasis involves presentation of lipid antigens to T and NKT cells through surface CD1 molecules. No susceptibility genes have yet been identified in that pathway. B) keratinocytes are the principal producer of IL-36 cytokines. Their expression is induced by pro-inflammatory cytokines including IL-1, IL-17 and TNF- α . Release of IL-36 cytokines from keratinocytes is triggered by danger signals such as ATP. Secreted IL-36 cytokines are found in full-length form (fIL-36), and have minimal biologic activity. When exposed to neutrophil nets, neutrophil proteases, or keratinocyte derived proteases (cathepsin S), fIL-36 is converted into a shorter, more active form (truncated IL-36; tIL-36). Truncated IL-36 (tIL-36) has approximately 500-fold increase (500 $\times$) in biologic activity. IL-36 cytokines act on the IL-36 receptor and induce expression of more IL-36 thereby promoting a self-sustaining cycle of inflammation that brings in additional leukocytes. Keratinocytes may regulate this

process through secretion of serine-protease inhibitors such as serpin A1 and serpin A3, or the IL-36 receptor antagonist (IL-36RA). The three genetic variants associated with pustular psoriasis (*IL36RN*, *CARD14*, and *APIS3*, highlighted in red) are involved in this process.

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Figure 4.

Autoimmune vs autoinflammatory responses in psoriasis. Plaque psoriasis and generalized pustular psoriasis are located on opposite ends of the balance between autoimmune and autoinflammatory responses. Thus, plaque psoriasis is characterized and enriched in biologic categories such as “adaptive immune response”, “antigen processing and presentation” as well as leukocyte-mediated immunity”. In contrast, generalized pustular psoriasis is characterized by massive neutrophil infiltration and enriched in biological categories including “granulocyte chemotaxis”, “positive regulation of chemotaxis”, and “antimicrobial humoral response”. Expression of the two principal autoinflammatory mediators; *IL1B* and *IL36G* across different clinical subtypes (plaque psoriasis vs erythrodermic vs. inverse, vs. generalized pustular psoriasis (GPP) vs. localized pustular psoriasis (PPP)) (mRNA expression of *IL1B* was only detectable in a subset of patients).