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Review Article

The Interleukin-1 Family: A Key Regulator in the Pathogenesis of Psoriasis

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Abstract

Interleukin-1 (IL-1) family members, as most potent molecules of the innate immune system, are key regulators of multiple inflammatory diseases. The family includes seven ligands with agonist activity (IL-1α and IL-1β, IL-18, IL-33, IL-36α, IL-36β, IL-36γ), three receptor antagonists (IL-1Ra, IL-36Ra, IL-38), and one anti-inflammatory cytokine (IL-37). Most of these cytokines are abundantly expressed in skin under the regulation of IL-17 and act on innate immune cells to influence their survival and function. This review provides an overview of all the members of the IL-1 family and its potential regulatory roles in the pathogenesis of psoriasis.

Keywords: IL-1 family; IL-17; IL-17/IL-1 axis; Psoriasis

Introduction

Interleukin-1(IL-1) family members, as the central mediator of innate immunity and inflammation, play a key role in the biology of multiple inflammatory diseases. So far, 11 members of the IL-1 family have been identified, including seven ligands with agonist activity (IL-1α and IL-1β, IL-18, IL-33, IL-36α, IL-36β, IL-36γ), three receptor antagonists (IL-1Ra, IL-36Ra, IL-38), and one anti-inflammatory cytokine (IL-37) (Table 1). According to the length of their precursor and the propiece for each precursor, the IL-1 family can also be categorized into three subfamilies including IL-1, IL-36 and IL-18. IL-1 family members signal through a group of closely related receptor complexes: IL-1R1 and IL-1RAcP complex as IL-1α/β receptor, ST2 and IL-1RAcPcomplex as IL-33 receptor, IL-18Rα and IL-18Rβ complex as IL-18 receptor, and IL-1Rrp2 and IL-1RAcP complex as IL-36 receptor. The activation of these receptor complexes initiates and/or amplifies innate immune responses. Three other IL-1 receptor family members are IL-1R2, IL18BP and SIGIRR (also known as TIR8), which all act as negative regulators of IL-1 signaling [1,2].

Psoriasis is a common chronic inflammatory skin disease characterized by hyperplasia of epidermal keratinocytes and infiltrating immune cells. It is considered as a mixed Th1 and Th17 cell-mediated immune disease. Increasing evidence from experimental and clinical findings points to the important function of IL-1 family and IL-17 in the pathogenesis of psoriasis [3-8]. Most of IL-1 family members have been reported constitutively expressed by keratinocytes *in vivo* and shown to be highly expressed in the psoriatic skin [9-12]. This increasing expression of IL-1 family members contributes to Th17 cell development, leading to the production of IL-17 [13,14]. Therefore, IL-1 family is considered as an important mediator in the initiation and maintenance of psoriatic plaques. However, not only IL-1 family induces Th17 cells to produce IL-17, IL-17 in turn can act on keratinocytes to produce more IL-1 family cytokines [15,16]. These observations thereby indicate that the IL-17/IL-1 axis plays important roles in the pathogenesis of psoriasis. In this review, we summarize the experimental and clinical findings to consolidate our understanding on the function of IL-1 family members in psoriasis.

IL-1 Family and Psoriasis

IL-1 subfamily

IL-1α and IL-1β: IL-1α (IL-1F1) and IL-1β (IL-1F2) are the first two members of IL-1 family discovered. Despite their identical activities, IL-1α and IL-1β have several differences. Firstly, IL-1β is secreted and circulates systemically, whereas IL-1α is generally

Table 1: Nomenclature and main functions of IL-1 family members in psoriasis.

Subfamily	Family member	Receptor(co-receptor)	Expression in lesional skin of psoriasis	Function in psoriasis	Whether induced by IL-17
IL-1 subfamily	IL-1α(IL-1F1)	IL-1R1(IL-1RAcP)	Low	Proinflammatory	Yes
	IL-1β(IL-1F2)	IL-1R1(IL-1RAcP)	High	Proinflammatory	Yes
	IL-1Ra(IL-1F3)	IL-1R1	No change	Antagonist for IL-1α, IL-1β	Unknown
	IL-33(IL-1F11)	ST2(IL-1RAcP)	High	Proinflammatory	Yes
IL-36 subfamily	IL-36α(IL-1F6)	IL-1Rrp2(IL-1RAcP)	High	Proinflammatory	Yes
	IL-36β(IL-1F8)	IL-1Rrp2(IL-1RAcP)	High	Proinflammatory	Yes
	IL-36γ(IL1-F9)	IL-1Rrp2(IL-1RAcP)	High	Proinflammatory	Yes
	IL-36Ra(IL-1F5)	IL-1Rrp2	High	Antagonist for IL-36α, IL-36β, IL-36γ	Unknown
	IL-38(IL-1F10)	IL-1Rrp2 (IL-36R)	High	Antagonist for IL-36α, IL-36β, IL-36γ	Unknown
IL-18 subfamily	IL-18(IL-1F4)	IL-18Rα(IL-18Rβ)	Unknown	Unknown	Unknown
	IL-37(IL-1F7)	IL-18Rα	Unknown	Anti-inflammatory	Unknown

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associated with the plasma membrane of the producing cell and so acts locally. Secondly, IL-1β is mainly produced by monocytes and macrophages, whereas IL-1α is highly expressed by keratinocytes and endothelial cells. Thirdly, the two genes are differentially regulated during development and have different contributions during immune responses. Lastly, the pro-domain of IL-1α but not IL-1β has a nuclear localization sequence [17]. Although IL-1α and IL-1β have these differences, both of them bind to the same receptor complex including IL-1R1 and IL-1RAcP, and signal through myeloid differentiation primary response protein (MyD88). While this signaling can be negatively regulated by IL-1 receptor antagonist, IL-1Ra (IL-1F3), which is the natural antagonist of IL-1α and IL-1β [18].

In skin lesions of psoriasis patients, IL-1β has been shown to be markedly increased, and effective treatment of psoriasis led to a significant decrease in epidermal IL-1β expression, suggesting that IL-1 subfamily plays a role in the pathogenesis of psoriasis [10,12]. Moreover, IL-17 was markedly increased in lesional skin of psoriasis patients, and these patients treated with Secukinumab, a fully human anti-IL-17A monoclonal antibody, had a reduction of 75% or more in the Psoriasis Area-and-Severity Index score (PASI75) [19-21]. However, it was not clear whether IL-17 regulated IL-1 expression in these studies. In 2013, the studies from Albanesi's and Chen's groups showed that IL-17A induced IL-1β expression in macrophages via the activation of MAPKs, NF-κB and AP-1[22], and IL-17, in combination of IL-4, markedly increased IL-1α and IL-1Ra in supernatants and cell lysates of cultured keratinocytes [16], while the studies from Cooper's and Mee's groups showed decreased IL-1α but increased IL-1β expression in lesional skin of psoriasis patients [23,24]. Moreover, when Muhr et al. compared IL-1 subfamily gene expression in keratinocytes from psoriasis patients and healthy individuals in the presence of IL-17, they found that IL-17 induced IL-1β but not IL-1α and IL-1Ra expression in keratinocytes from healthy individuals [15]. Therefore, how IL-17 specifically regulates the expression of IL-1 subfamily members in psoriasis needs further investigation.

To confirm the role of IL-1α, IL-1β and IL-1Ra in the pathogenesis of psoriasis *in vivo*, transgenic mice targeting related genes were generated. Skin lesions with hyper proliferative epidermis and increased antimicrobial transcripts including S100A7, S100A9, DEFB4 were observed in *Il1a* and *Il1rn* transgenic mice, suggesting IL-1α signaling enables to initiate an inflammatory reaction in psoriatic development [25,26]. In addition, the deficiency of IL-1Ra in mice resulted in spontaneous psoriatic-like lesions [27]. In human, children born with a genetic deficiency of Interleukin-1-Receptor Antagonist (IL-1RA) or functional inactive IL-1RA suffer from severe systemic and local inflammation, including pustular skin eruption [28,29]. Moreover, the profile of the transcriptome from psoriatic tissue and IL-1α-treated cultured human keratinocytes revealed a high correlation of the transcriptome profile between IL-1α-treated keratinocytes and psoriatic tissues, suggesting the inflammatory milieu in the epidermal microenvironment in psoriasis is more likely dependent on evolutionarily ancient cytokines such as IL-1α, rather than those of the adaptive immune response [30]. Furthermore, IL-1β, as well as IFN-γ, was able to induce the psoriatic regenerative epidermal phenotype including keratin16, keratin17, and keratinocyte Transglutaminase (TGK), ICAM-1 and HLA-DR in both normal human skin and non-lesional skin from psoriatic patients, and IL-1RA inhibited the effects of IFN-γ on the expression of keratin 17 and TGK in normal skin but not in non-lesional skin of patients with psoriasis, suggesting IL-1RA system may be dysregulated in psoriatic skin [31]. However, whether IL-1β acts directly or indirectly to these target genes remains unclear. Altogether, these findings demonstrate the tremendous impact of IL-1 subfamily members on psoriasis, and suggest that the blockage of IL-1 signaling might have a broader clinical impact on psoriasis.

IL-33

IL-33(IL-1F11) is the most recently identified member of the IL-1 family and is a ligand for the orphan receptor ST2 [32]. In contrast to other IL-1 family members, it is not typically expressed by haematopoietic cells but is abundantly expressed in the endothelial cells and keratinocytes. In psoriasis patients, both IL-33 and ST2 significantly increased in lesional and non-lesional skin, compared to those in healthy skin [33-36]. The studies from Balato's and Theoharides's groups showed that IL-33 was strongly associated with endothelial cells in psoriatic skin compared to non-lesional psoriatic skin and healthy controls [33,36]. Moreover, IL-33 was secreted by psoriatic keratinocytes and was present in nucleus as well as cytoplasm in keratinocytes [33]. The expression of IL-33 was partially under the regulation of IL-17A. The study from Meephansan's group showed that IL-17A induced IL-33 expression at mRNA and protein levels in time and dose-dependent manners in Normal Human Epidermal Keratinocytes (NHEKs). This induction was via the activation of EGFR, ERK, p38 and STAT3, as IL-17A-induced IL-33 expression was blocked by the addition of EGFR, ERK, p38 and STAT3 inhibitors [35]. However, an intrinsic mechanism by which IL-17 regulates IL-33 expression in keratinocytes warrants further investigation.

IL-33, as a dual function protein, acts as both a cytokine to activate a number of immune cells with potent pro-inflammatory effects and intracellular nuclear factor to suppress pro-inflammatory gene transcription [37,38]. IL-33 induces mast cell degranulation, maturation and the production of IL-1, IL-6, IL-13, TNF-α, CCL2 and CCL3 in psoriatic lesional skin [39,40]. In 2010, a relationship between IL-33 and peptide Substance P (SP), VEGF in mast cell was well studied. IL-33 augmented the effect of SP on inducing mast cell release of VEGF, leading to increased angiogenesis in psoriasis [36]. Our previous data showed that IL-17 induced REG3A to regulate keratinocyte hyperproliferation in psoriasis [41], and the induction of REG3A by IL-17 was dependent on IL-33(unpublished data). These results thereby demonstrate the important role of IL-33 in psoriasis-like plaque formation and targeting IL-33 may provide a new treatment strategy for psoriasis.

IL-36 subfamily

IL-36 proteins: IL-36 proteins contain IL-36 ligands and IL-36Ra. IL-36 ligands include IL-36α, IL-36β and IL-36γ (formerly IL-1F6, IL-1F8 and IL-1F9) that signal through the IL-1 receptor family members such as IL-1Rrp2 (IL-1RL2) and IL-1RAcP [42-44]. IL-36Ra (IL-1F5) is an antagonist of IL-36 signaling. IL-36Ra binds to IL-1Rrp2, blocks IL-36 ligand binding to the IL-1Rrp2 receptor and the subsequent recruitment of IL-1RAcP [45].

IL-36 is abundantly expressed in skin and a few other tissues. Their expression can be strongly induced in monocytes and keratinocytes

[2]. Accumulating evidence suggests that IL-36 is a crucial cytokine in the pathogenesis of psoriasis [11,42,43,46]. In 2001, Debets et al. first reported that IL-36 proteins were over expressed in psoriatic lesional skin [43]. This observation was further confirmed by other scientists. Johnston's group showed IL-36Ra (IL-1F5), IL-36α (IL-1F6), IL-36β (IL-1F8), IL-36γ (IL-1F9) were significantly higher in psoriatic lesional skin than those in non-lesional skin [11]. Blumberg et al. also found increased expression of IL-1Rrp2, IL-36Ra and IL-36α in human psoriatic skin [42]. Moreover, IL-36 has been shown to be under the regulation of IL-17. Carrier's study reported that IL-36 cytokines were increased in a Th17-dominant psoriasis-like animal model [47]. Muhr's study showed that IL-17 induced IL-1 family members IL-36α and IL-36γ, but not anti-inflammatory members IL-1Ra, IL-36Ra and IL-37 in keratinocytes from psoriatic skin, when compared to those from healthy individuals [15].

To confirm the pathological role of IL-36 proteins in psoriasis development, IL-36α transgenic mouse was generated by Blumberg's group. The mouse exhibited psoriatic skin phenotype with thickened scaly skin, acanthosis, hyperkeratosis and a mixed inflammatory cell infiltrate in the dermis [42]. Cytokines implicated in the pathogenesis of psoriasis, such as IL-23, IL-17 and TNF-α, were increased in this model, and they were induced in wild-type mouse skin by IL-36α and in turn induced IL-36α production in keratinocytes. The combination of IL-36α transgene with an IL-36Ra deficiency resulted in the exacerbation of the psoriatic phenotype, demonstrating the antagonistic activity of IL-36Ra *in vivo* [42]. Moreover, the psoriatic phenotypes were ameliorated after IL-36α transgenic mice crossed with IL-36Ra transgenic mice. In summary, dysregulated expression of IL-36 agonists and antagonists promotes cutaneous inflammation, leading to psoriatic inflammatory skin disorders.

Increasing evidence further dissects the roles of IL-36 proteins in the pathogenesis of psoriasis. Towne's group reported that IL-36α, IL-36β and IL-36γ activated IL-8 promoter and induced IL-6 secretion through the MAPKs, JNK and ERK1/2 pathway [44]. Microarray analysis was performed by Johnston's group after reconstituted epidermal cultures treated with recombinant IL-36α, IL-36β and IL-36γ. Strikingly, these cytokines not only induced IL-8 expression but also induced the expression of Antimicrobial Peptides (AMPs), Matrix Metalloproteinase's (MMPs) and growth factors. In particular, IL-36β effectively induced HBD-2, HBD-3, MMP19 and MMP9 [11]. IL-36α and IL-36β but not IL-36γ directly induced TNF-α, IL-6, IL-8, hBD2, S100A7, and these effects of IL-36α and IL-36β were synergized with IL-17A and TNF-α [47]. In addition to keratinocytes, IL-36 subfamily has also been reported to target another cell types such as dendritic cells, as IL-36 receptor is expressed in this cell type [48-50]. In Bone Marrow-Derived Dendritic Cells (BMDCs), IL-36 induced the expression of IL-12, IL-1β, IL-6, TNF-α and IL-23. In addition, IL-36β enhanced the expression of CD80, CD86 and MHC class II by BMDCs [50]. Besides BMDCs, IL-36 induced the expression of IFN-γ, IL-4 and IL-17 in CD4+ T cells, suggesting a critical role of IL-36 subfamily members in the stimulation of T helper cell responses [50].

Moreover, a link between IL-36Ra and Generalized Pustular Psoriasis (GPP), a different form of psoriasis, has been identified [51-53]. Marrakchi et al. performed homozygosity mapping and direct sequencing in nine Tunisian multiplex families with autosomal recessive GPP and found that familial GPP was caused by the deficiency of IL-36Ra, that is, all the patients with GPP were found to carry a loss function mutation in *IL-36RN*. This aberrant IL-36Ra structure and function led to deregulated secretion of inflammatory cytokines (IL-1α, IL-6, IL-8, TNF-α) [51]. In 2013, Sugiura et al. reported that the majority of cases of GPP without a history of psoriasis vulgaris were caused by homozygous or compound heterozygous mutations of *IL36RN*, although only a few cases of GPP preceded or accompanied by psoriasis vulgar were found to have *IL36RN* mutations [52]. In 2014, a case of GPP was successful treated by Granulocyte and Monocyte Adsorption apheresis (GMA), suggesting that granulocytes/monocytes play a major role in the immunopathogenesis of GPP caused by deficiency of IL-36Ra [53].

IL-38

IL-38(IL-F10) is originally identified in silicon. Its gene is located in the IL-1 family cluster on chromosome 2 next to the genes encoding IL-1R1 and IL-36Ra [1,54]. As one of three IL-1 family receptor antagonists, IL-38 shares 43% homology with IL-36Ra [54]. It binds to the IL-36R to inhibit IL-36 signaling as IL-36Ra does [55]. IL-38 polymorphism is associated with psoriatic arthritis, suggesting IL-38 might play a role in the pathogenesis of this inflammatory skin disease [56-58]. However, until now, no study reports that IL-38 is regulated by IL-17A. Conversely, addition of IL-38 in peripheral blood mononuclear cells inhibited the production of IL-22 and IL-17A, suggesting IL-38 may be involved in the regulation of IL-17 expression [55].

IL-18 subfamily: IL-18 and IL-37

IL-18(IL-1F4) and IL-37(IL-1F7) are expressed by macrophages and dendritic cells as well as epithelial cells, such as keratinocytes. Both IL-18 and IL-37 bind to the same receptor IL-18Rα. However, IL-18 acts as a proinflammatory factor, while IL-37 serves as a natural brake of inflammation. There is no direct evidence support that IL-17 induces the expression of IL-18 and IL-37, but it is reported that IL-18 was decreased in cuprizone-treated Act1 knockout mice compared to that in WT mice, indicating the essential role of IL-17-Act1-mediated signaling in the production of IL-18 [59]. More importantly, IL-18 has also been implicated in several autoimmune diseases such as psoriasis. Arican et al reported IL-18 expression was increased in the serum of psoriatic patients and correlated with disease severity [60]. However, so far no report shows that IL-37 is correlated with the pathogenesis of psoriasis.

Conclusions and Perspectives

Psoriasis is a common immune-mediated inflammatory disease. The pathogenesis of psoriasis is a complex integration of genetic, immunological and environmental components [8]. IL-17/IL-1 axis exerts a proinflammatory effect on keratinocytes and immune cells in psoriasis. IL-17 secreted by Th17 cells and γδ T cells induces keratinocyte activation with the release of the proinflammatory cytokines such as IL-1 family members. IL-1, in turn, can act on T cells and induce Th17 cells differentiation from naïve precursors, as well as in the promotion of IL-17- and IL-22- producing T cells. These events sustain and amplify the chronic inflammation in psoriasis (Figure 1). Moreover, cytokines of IL-1 family induce the production of multiple antimicrobial peptides or proteins in keratinocytes, leading to hyperproliferation of skin epidermis. So far, biological

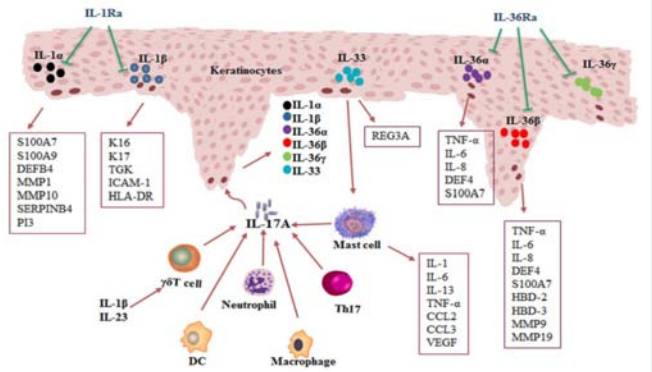

Figure 1: The pathological roles of IL-17-IL-1 axis in psoriasis.

agents that target IL-17 and its receptor have been developed for psoriasis treatment and shown promising effects on phase 3 clinical studies [19-21, 61-63]. However, although there is accumulating evidence supporting the involvement of IL-1 family cytokines in the pathogenesis of psoriasis and anti-IL-1 strategies have had a tremendous impact on the therapy of some auto-inflammatory disorders [18], scarce biological agent specifically targeting IL-1 is developed for the treatment of psoriasis. The expression of IL-1 family members, especially IL-36 subfamily members, is limited to skin, airway and a few other tissues, suggesting that its inhibition may have fewer systemic consequences. Therefore, one can speculate that IL-36 subfamily member might be a promising therapeutic target for the treatment of psoriasis. However, better understanding of the pathophysiology of IL-1 family cytokines in psoriasis is required to this end.

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