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Role of 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 path mechanism. 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.

Keywords: Psoriasis; Skin; Inflammation; Cytokines

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INTRODUCTION

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. 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. As such, psoriasis is now generally regarded as a T cell-mediated immune disease with a mixed Th1/Th17 cytokine environment [3–5].

There are five main types of psoriasis: plaque, guttate, inverse, pustular, and erythrodermic. Plaque psoriasis, also known as psoriasis vulgaris, makes up about 90% of cases. It typically presents with red patches with white scales on top. Areas of the body most commonly affected are the back of the forearms, shins, around the navel, and the scalp. Guttate psoriasis has drop-shaped lesions. Pustular psoriasis presents with small non-infectious pus-filled blisters. Inverse psoriasis forms red patches in skin folds. Erythrodermic psoriasis occurs when the rash becomes very widespread, and can develop from any of the other types. Fingernails and toenails are affected in most people at some point in time. This may include pits in the nails or changes in nail color **[**6].

Psoriasis is generally thought to be a genetic disease which is triggered by environmental factors. In twin studies, identical twins are three times more likely to both be affected compared to non-identical twins; this suggests that genetic factors predispose to psoriasis. Symptoms often worsen during winter and with certain medications such as beta blockers or NSAIDs. infections and psychological stress may also play a role. Psoriasis is not contagious.

The underlying mechanism involves the immune system reacting to skin cells. Diagnosis is typically based on the signs and symptoms.

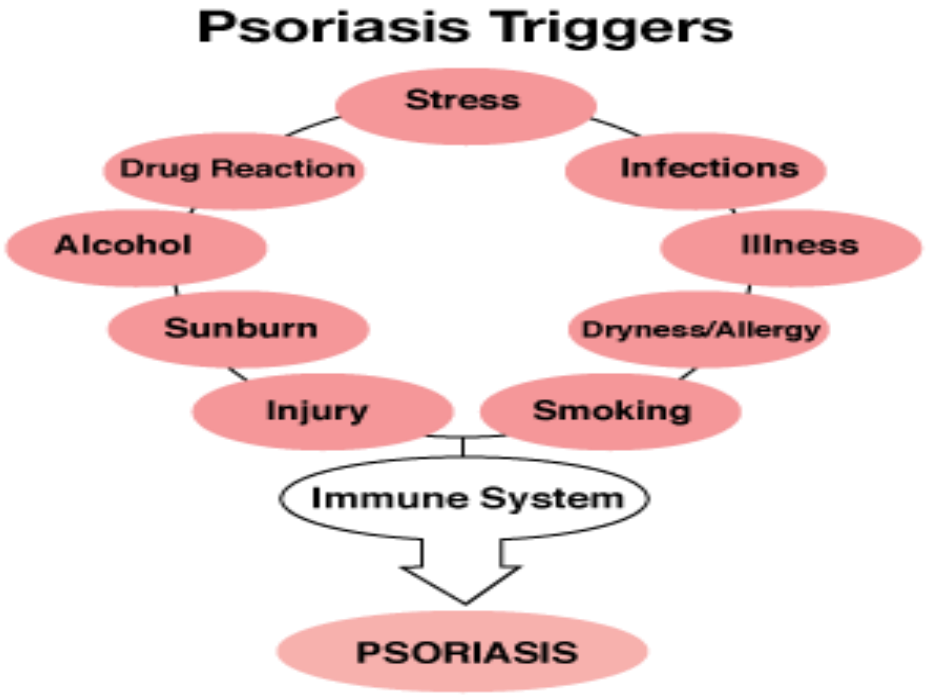

Figure 1: Various Triggers for the stimulation of Immune system causing Psoriasis

There is no cure for psoriasis. However, various treatments can help control the symptoms. These treatments may include steroid creams, vitamin D3 cream, ultraviolet light, and immune system suppressing medications such as methotrexate. About 75% of cases can be managed with creams alone. The disease affects 2–4% of the population. Men and women are affected with equal frequency. The disease may begin at any age.Psoriasis is associated with an increased risk of psoriatic arthritis, lymphomas, cardiovascular disease, Crohn's disease, and depression.Psoriatic arthritis affects up to 30% of individuals with psoriasis [7].

Over recent years, significant progress has been made in Characterisation of the underlying pathogenic mechanisms in psoriasis, a common cutaneous disease that is associated with major systemic co-morbidity and reduced life expectancy. Basic science discoveries have informed the design of novel therapeutic approaches, many of which are now under evaluation in late-stage clinical trials. Here we describe the complex interplay between immune cell types and cytokine networks that acts within self-perpetuating feedback loops to drive cutaneous inflammation in psoriasis. Genetic studies have been pivotal in the construction of the disease model and more recently have uncovered a distinct aetiology for rare, pustular variants of psoriasis. The translation of mechanistic insights into potential advancements in clinical care will also be described, including several treatments that target the interleukin-23 (IL-23)/T17 immune axis. The therapeutic armamentarium for psoriasis has expanded over the past two decades with the development of several highly selective

therapies that are both efficacious and have a favourable safety profile. Novel insights into psoriasis immune pathogenesis have informed the design of these treatments, and in turn, mechanistic studies within clinical trials are helping to further characterise the role of different cellular players and cytokine axes in the pathogenic disease model. Psoriasis is a phenotypically heterogeneous, immune mediated skin condition that often follows a relapsing and remitting course. It is a common, complex trait that affects approximately 2 % of the general population and is associated with multiple co-morbidities including arthritis, cardiovascular disease, obesity, hypertension, Diabetes mellitus, reduced quality of life and depression [8-11].

The role of cytokines in psoriasis

TNFα

TNFα is produced by several different cells types in the context of cutaneous inflammation, including macrophages, keratinocytes, Th1 cells, T17 cells, Th22 cells and BDCA-1 − inflammatory DCs [12, 13]. Although parts of the literatureare conflicting [14], there is evidence that circulating levels of TNFα (in addition to IFNγ, IL-12) are elevated in psoriasis and correlate with disease severity [15, 16]. TNFα regulates the ability of antigen presenting cells such as DCs to activate T cells [17]. It induces the expression of Creactive protein (part of the acute phase response), several cytokines such as IL-6 (which mediates T cell proliferation and keratinocyte hyperproliferation), and chemokines including CCL20 (recruits myeloid DCs and T17 cells) and IL-8 (for recruitment of neutrophils). Through the upregulation of intercellular adhesion molecule-I (ICAM-1), TNFα promotes the infiltration of inflammatory cells such as T cells and monocytes into the skin. It also facilitates IL-23 production by DCs and enhances the effects of other cytokines relevant to psoriasis pathogenesis such as IL-17. Therefore, TNF antagonists mediate part of their effect via suppression of the IL-23/ Th17 axis [18]. TNFα has a broad range of effects since TNF receptors (TNFR) are expressed on multiple cell types. There are two types of receptors, TNFR1 and TNFR2. Whereas TNFR2 is expressed predominantly on endothelial and haematopoietic cells, TNFR1 is present on nearly all cell types [19].Once activated by engagement with TNFα, TNFR modulate multiple aspects of cell function such as proliferation, survival, activation, differentiation and apoptosis, by activating signalling cascades involving NF-κB, mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase [20, 21]. Although TNFα blockade is very effective therapeutically, which supports its role in disease pathogenesis, the diverse actions of the cytokine have resulted in numerous drug-associated side effects. Therefore,more targeted immunotherapies are now being investigated.

IFNγ

In addition to TNFα, Th1 cells are a key source of IFNγ, which is a type II IFN. It is also secreted byDCs and natural killer (NK) cells. Signal transducer and activator of transcription (STAT) 1 is activated downstream of IFNγ and this regulates many genes that are found to be expressed in psoriatic skin lesions [22]. RNA microarrays have demonstrated that a large number of IFNγ-related genes are differentially regulated in psoriasis [23]. However, it was shown that antagonism of IFNγ using a humanised monoclonal antibody does not significantly improve psoriasis [24]. Further, in a clinical trial of an IL-23-specific monoclonal antibody, there was no effect on IFNG expression in patients with psoriasis despite a complete clinical and histologic response, in contrast to the significant reduction in IL17 messenger RNA levels observed [25]. This suggests that IFNγ is not critical in sustaining chronic psoriasis lesions. It is instead postulated that IFNγ is more relevant in the early stages of disease, through the activation of antigen presenting cells [26]. It promotes the release of IL-1 and IL-23 from DCs, which in turn drives T17 and Th22 cell differentiation and activation. IFNγ also stimulates chemokines (e.g.CXCL10, CXCL11) and adhesion molecule release from keratinocytes, thus facilitating the recruitment of lymphocytes to inflammatory plaques. Although it is known to have an anti-proliferative effect on keratinocytes, this effect is abrogated in psoriatic lesions via the upregulation of suppressor of cytokine signalling (SOCS) 1 in response to high levels of IFNγ [27]. Type I IFN Type I IFNs comprise IFNα and IFNβ, amongst others [28]. Several observations have indicated an important role for these cytokines in psoriasis development, particularly in the early stages. Treatment with type I IFN for conditions such as hepatitis and multiple sclerosis has been shown to exacerbate existing psoriasis vulgaris and induce new lesions [29, 30]. The type I IFN signalling pathway is activated in lesional keratinocytes and patients have abnormal serum levels of IFNs [31, 32]. In further support, an increase in IFNα level in xenograft mouse models precedes the development of psoriaticchanges and anti-IFNα antibodies block classical psoriatic skin changes such as T cell infiltration into plaques [33]. As discussed above, plasmacytoid DCs, which infiltrate psoriatic skin lesions, are a major source of type I IFN [33] and this promotes myeloid DC phenotypic maturation and activation, thus facilitating T cell priming. Type I IFN signalling modulates the production of IFNγ and IL-17 [34, 35] and has been implicated in the differentiation and activation of T cells, in particular Th1 and T17 cells [36]. Thus, it may drive downstream inflammatory circuits, leading to keratinocyte hyperproliferation. In addition to the indirect modulation of T cell responses via regulation of DCs, type I IFN may have direct pro-survival and pro-proliferative effects on Tcells [37]. Finally, type I IFNs are rapidly induced in many different cell types in response

to viral infections. Since genetic studies have indicated the importance of innate antiviral immune responses in psoriasis pathogenesis, this also underlines type I IFN as a critical disease cytokine. Specifically, several genes regulating type I IFN production (e.g. DDX58, IFIH1, RNF114) and signalling (e.g. TYK2) have been associated with disease susceptibility in GWAS.

IL-23

IL-23 is a heterodimer that is composed of an IL-23p19 subunit (encoded by IL23A) and IL-12/IL-23p40 (shared with IL- 12 and encoded by IL12B). It binds to IL-23R, which is associated with Jak2 and Tyk2. Engagement of the receptor triggers a signalling cascade that involves activation of STAT3. IL-23 is released by DCs and macrophages and mediates the terminal differentiation and activation of T17 cells (including induction of IL-17A and IFNγ), activation of keratinocytes and upregulation of TNFα expression in macrophages.

Genetic studies that link single nucleotide polymorphisms in/near IL-23R, IL23A, IL12B, TYK2 and STAT3 with psoriasis susceptibility have highlighted IL-23 as a critical cytokine in disease pathogenesis [38–41]. In support, psoriasis lesions have elevated levels of IL-23 expression [42] and this is reversed after successful treatment with medications such as etanercept [43] and alefacept [44]. Further, anti-IL-12/IL-23 and anti-IL-23 agents are highly effective therapeutic agents [45]. Evidence from mouse models, in which psoriasiform histological changes arise from intradermal injection of IL- 23 or overexpression of IL-12/IL-23p40 in keratinocytes, also indicate the importance of this cytokine [46].

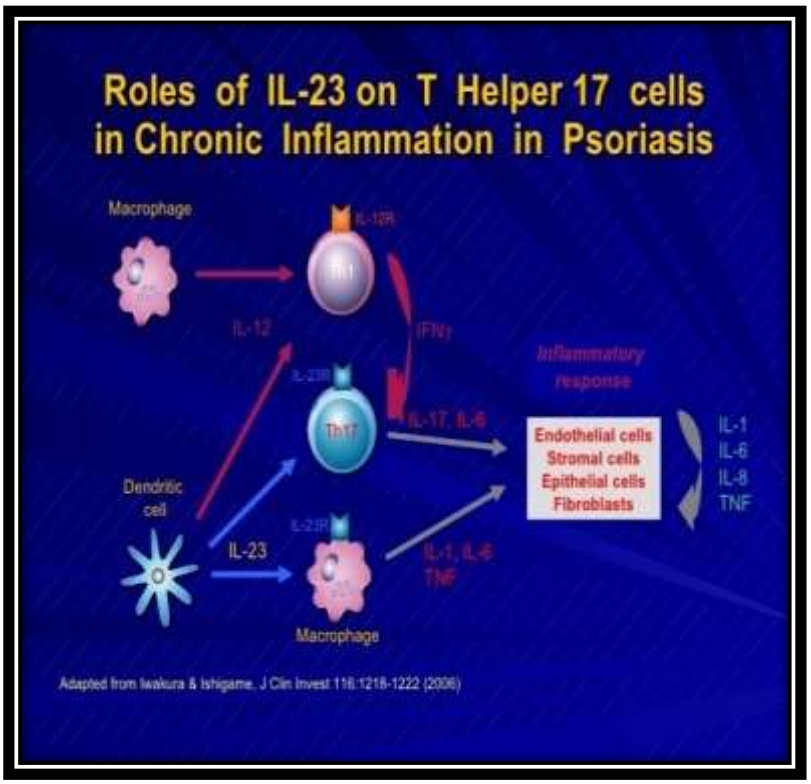

Figure-2: Il-23 stimulates maturation and differentiation of Th 17 Cells which secretes IL-17 , a proinflammatory cytokine

IL-17A

IL-17A belongs to the family of pro-inflammatory cytokines that comprises IL-17A-F [47]. It is overexpressed in psoriasis (both skin and blood [48]) and its involvement in the immunopathogenesis of psoriasis has been increasinglyrecognised [49]. Given that IL-17 may promote the development of cardiovascular diseases [50], and the established link between psoriasis and such co-morbid conditions, targeting of IL-17 therapeutically may have benefits beyond the sole attenuation of skin inflammation. However, the biological effects of IL-17A in various tissues are complex. Indeed, it may also help to stabilise atherosclerotic plaques [51], which emphasises the need to enrol patients receiving IL-17 inhibitors in long-term safety registries.Lesional psoriatic Tcells produce large amounts of IL-17A when activated ex vivo; however, Tcells from healthy skin do not produce IL-17A with the same stimuli [52]. Analysis of the psoriasis transcriptome also reveals enrichment for IL-17A genes [53]. More recently, IL-17A blocking agents have been shown to have rapid and high efficacy in clinical trials, as described later, further emphasising the pathogenic role of IL-17A signalling in psoriasis [54–56]. IL-17A is produced by T17 cells, neutrophils, mast cells and NK cells. Keratinocytes are the predominant cells that express IL-17 receptors (IL-17R; likely consisting of two IL- 17RA subunits complexed with one IL-17RC subunit) in psoriasis [57]. The active form of IL-17A consists of either IL-17A homodimers or IL-17A-IL-17F heterodimers; the former having greater biological activity. Engagement of IL-17R induces the activation of NF-κB signalling. GWAS have implicated several genes encoding components of the NF-κB pathway in psoriasis susceptibility including TNFAIP3, TNIP1, NFKBIA, REL and TRAP3IP2 [38–41]. For example, a loss of function coding variant in TRAP3IP2 is associated with psoriasis. TRAP3IP2 encodes ACT1, which is involved in IL-17 signalling, and Act-1-deficient mice demonstrate upregulated T17 cell responses and spontaneous skin inflammation [58]. This underscores the immunological insights that can be gained from genetic data. The downstream expression of a large number of genes in response to IL-17A has been shown in a three-dimensional human epidermis model (419 gene probes upregulated and 216 gene probes downregulated) [59]. Keratinocytes are stimulated by IL-17A to produce AMPs; pro-inflammatory cytokines such as IL-19 (driving epidermal hyperplasia), IL- 1, IL-6, and IL-23; and chemokines such as IL-8. In addition to promoting the mobilisation and activation of neutrophils, IL-8 is also a chemotaxin for T cells and NK cells. Although the role of regulatory T cells in the pathogenesis of psoriasis remains to be fully elucidated, IL-6 is

thought to render effector Tcells refractory to regulatory Tcell-mediated suppression [60]. IL-17A also increases production of the chemokine CCL20 [61, 62] and ICAM-1, which facilitate cutaneous recruitment of DCs and T cells. Taken together, IL-17A is crucial to establishing positive feedback loops such that epidermal hyperplasia and the cutaneous inflammatory response are sustained and amplified. For example, recruited DCs may secrete more IL-23, which promotes further T17 cell activation and hence release of IL-17A. This influences keratinocytes, leading to the recruitment of more DCs and T cells to the inflamed skin. IL-17 has recently been shown to act in synergy with TNFα to induce proinflammatory cytokine production by keratinocytes [63]. Indeed, genes that are synergistically regulated by IL-17 and TNFα were more effectively blocked by anti-IL-17A than TNF antagonists [64], suggesting that IL-17A may have a dominant pathogenic effect.

IL-22

IL-22 is a member of the IL-10 family of cytokines and has been found to be upregulated in the skin and sera of patients with psoriasis [65, 66]. Expression is also reduced following anti-psoriatic therapies [67]. The production of IL-22 by Th22 cells and Th17 cells is induced by IL-23 and it mediates multiple effects on keratinocytes , including hyperproliferation, differentiation, migration, and proinflammatory cytokine and AMP production [68, 69]. IL-22 has been shown to act in synergy with IL-17A to induce AMP production by keratinocytes [70]. Blockade of IL-22 in vivo or genetic deletion caused reduced IL-23-induced epidermal hyperplasia [71], and IL-23-mediated epidermal hyperplasia in a murine model of psoriasiformskin inflammation was found to be dependent on IL-22 [72]. These data highlight potential crosstalk between the IL-23/T17 pathway and IL-22/Th22. However, in contrast to the IL-23/T17 pathway, there is a lack of genetic data in support of a role for IL-22 in disease pathogenesis. Further, trials of a human monoclonal antibody targeted against IL-22 (fezakinumab) were discontinued since preliminary analyses showed that the efficacy endpoints could not be achieved [73]. The negative findings from both genetics and clinical studies suggest that IL-22 may not be as critical to the disease process as had initially been anticipated from earlier immunological studies. Pustular psoriasis Pustular psoriasis is a rare, severe subtype of psoriasis that has been shown by genetic studies to have a distinct aetiology from psoriasis vulgaris. In particular, a lack of association of pustular psoriasis with the PSORS1 locus has been demonstrated, in striking contrast to psoriasis vulgaris [74]. It is characterised clinically by the presence of sterile pustules on variably erythematous skin and histologically by diffuse dermal neutrophilic infiltration and micropustules in the epidermis [75, 76]. It encompasses generalized pustular psoriasis, in which patients experience acute flares of widespread cutaneous pustulation associated with systemic upset, and chronic,

localised forms such as palmoplantar psoriasis and acrodermatitis continua of Hallopeau. Recently, IL-1 family cytokines have been shown to have a potential pathogenic role in pustular psoriasis since loss of function, autosomal recessive mutations in IL36RN were described in association with this disease subtype [77–78]. Targeted sequencing studies further revealed that mutations in IL36RN are not associated with psoriasis vulgaris, emphasising distinct pathogenic mechanisms for pustular and plaque forms of psoriasis and the potential for stratification of psoriasis subtypes using genetic biomarkers [79]. IL36RN encodes an antagonist (IL-36Ra) that blocks innate immune IL-1 family cytokines (IL-36α, IL-36β and IL- 36γ) from binding to their receptor (IL-1RL2) [80]. This prevents subsequent activation of the NF-κB pathway. Therefore, IL-36Ra deficiency leads to unopposed IL-1 activity that may result in the significant cutaneous neutrophil recruitment that is observed in pustular psoriasis. IL-36 cytokines also cause upregulation of IL-23 by DCs and keratinocytes [81], IL-6 and IL-8, which helps to sustain cutaneous inflammation. In further support of a role for aberrant IL-1 signalling in pustular psoriasis, the disease is associated with pathogenic mutations in AP1S3, silencing of which has been shown to disrupt the endosomal translocation of Toll-like receptor 3 (TLR3), leading to impaired IFNβ induction [82]. Given that IFNβ downregulates the production of IL-1 [83], it is possible that mutations in AP1S3, which encodes a subunit of adaptor protein complex 1 and is involved in clathrin-mediated vesicular transport of proteins between the trans-Golgi network and endosomes, result in IL-1 over-production. By virtue of the aforementioned pathogenic insights delivered by genetic studies, IL-1 blockade is now emerging as a promisingtherapeutic strategy for this clinical variant.Pustular psoriasis is also associated with missense mutations in CARD14 [84]. CARD14 is highly expressed in the skin and encodes a protein involved in TRAF2-dependentNF-κB activation. It has been previously implicated inpsoriasis vulgaris, which suggests some potential shared disease pathways in distinct subtypes of psoriasis.

CONCLUSION

The exact pathogenesis of plaque psoriasis remains to be fully determined, but it is thought to depend on environmental and genetic factors that stimulate dysregulated innate and adaptive immune responses in the skin. The cytokine interleukin (IL)-17A plays a key role in host defence against extracellular bacteria and fungi. An increasing body of evidence suggests that IL-17A is also important in psoriasis pathogenesis. While IL-17A is a key product of Th17 cells, it is also produced by neutrophils, mast cells and Tc17 cells. The release of these inflammatory mediators leads to the recruitment and differentation of inflammatory cells. Activated dendritic cells then produce IL-23, a critical factor for Th17 development and T-

cells produce IL-17 leading to further keratinocyte activation and hyperplasia. This creates a vicious cycle of inflammation & acanthosis that characterizes psoriasis.

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