Pathogenesis and treatment of psoriasis: exploiting pathophysiological pathways for precision medicine

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ABSTRACT

Psoriasis is a common, chronic inflammatory skin disease associated with multi-system manifestations including arthritis and obesity. Our knowledge of the aetiology of the condition, including the key genomic, immune and environmental factors, has led to the development of targeted, precision therapies that alleviate patient morbidity. This article reviews the key pathophysiological pathways and therapeutic targets and highlights future areas of interest in psoriasis research.

Introduction

Psoriasis is a complex multifactorial condition related to a combination of genetic, environmental and immunological factors that affects 1.3-2.2% of the world population (1). It represents a clinically heterogeneous disease, with clearly defined clinical subtypes including chronic plaque (or psoriasis vulgaris), guttate psoriasis, and generalised or localised (pustular) psoriasis. The chronic plaque form is most common (85–90%) (2, 3) and the clinical manifestations include well-demarcated, symmetrical erythematous plaques with adherent silvery scale. Common affected sites include the scalp, elbows, knees and pre-sacral area of the back. Nail involvement is common and psoriatic arthritis is recognised in approximately 30% of people with psoriasis.

Genomic basis of psoriasis

Genetics

The genetic basis of psoriasis is supported by the increased incidence of the disease observed in first and second-degree relatives of psoriasis patients (4) and a 2–3 fold increased risk in monozygotic twins compared to dizygotic twins.

Studies of the human leukocyte antigens (HLA) have identified a variant, HLA-Cw6, which is strongly linked with psoriasis, particularly the early onset form (5).

Genome wide linkage analyses have identified multiple chromosomal loci statistically linked to psoriasis susceptibility (PSORS1-12) (6). The most important of these loci is PSORS1 (7), with an odds ratio of approximately 4.7 (8). PSORS1 is located within the major histocompatibility complex (MHC) on chromosome 6p21 – a region containing genes such as HLA-C (linked to the HLA-Cw6 allele), coiled-coil alpha-helical rod protein 1 (CCHCR1) and corneodesmosin (CDSN). Single nucleotide polymorphism (SNP) characterisation across the PSORS1 locus combined with family based association studies have identified two SNP markers that define a 10kb region proximal to HLA-C that serves as a major psoriasis risk haplotype (9).

Due to the extensive linkage disequilibrium within PSORS1 identification of a causative allele has been difficult but HLACw6 is a major candidate, with further possible associated risk alleles across the MHC (10). The functional mechanism by which disease associated alleles confer susceptibility to psoriasis is unknown. However, expression of HLA-Cw6 on antigen-presenting cells enables a potential regulatory role of the innate and adaptive immune system, which may contribute to the immune dysregulation in psoriasis (11). Sequence variants in the HLA-C promoter region can abolish the response to key cytokines interferon (IFN) gamma and tumour necrosis factor (TNF)-alpha (12).

Genome wide association studies (GWAS) have identified approximately 50 genetic loci associated with psoriasis risk (8, 13-16). The gene variants of interest can broadly be categorised into skin specific and immune (both innate and adaptive) specific genes (17). The immune genes highlight fundamental

immunological processes and pathways that appear crucial for disease susceptibility, namely antigen presentation, nuclear factor kappa B (NF-κB) signalling (important in sustaining chronic inflammation), the IL-23/IL-17 axis, innate immune signalling and the type I IFN pathway. Interestingly, SNP's in these loci are associated with other autoimmune diseases including inflammatory bowel disease and ankylosing spondylitis (13).

An example of an important immunogenetic association is gene variants in the IL-23 receptor (IL-23R) - a crucial psoriasis cytokine receptor - that appear to confer protection to developing psoriasis (18). SNP's in the genes responsible for subunits of the IL-23 cytokine and IL-23 receptor genes (19-21) have been associated with modifications in disease risk and are differentially expressed according to disease severity (22).

Transcriptomics

Meta-analysis of gene expression studies has defined a core psoriasis transcriptome (23). Microarray analysis of differentially expressed genes in psoriasis has reinforced the view that the development and potentiation of psoriasis is dependent on key cytokines and related pathways including IL-23/IL-17, TNF and type 1 IFN regulated genes.

Transcriptomic analysis allows classification of patients into different molecular subgroups (disease endotypes); for example, those that have enrichment of pathways related to transforming growth factor β and ErbB (24). Recognition of these pathways may also guide stratified therapy as normalisation of upregulated cytokines and chemokines crucial in the IL-17 pathway is seen after IL-17 targeted therapy for psoriasis (25, 26).

Our group (27) performed transcriptional profiling of skin using a xenotransplantation (XT) mouse model of psoriasis. Differential gene expression was analysed between normal skin on the XT model after injection with recombinant IL-22 (creating a psoriasis like phenotype), normal skin, psoriatic skin and psoriatic skin treated with an anti-IL-22 antibody. IL-22 is a cytokine that is highly expressed in psoriasis and induces keratinocyte proliferation and stimulates anti-microbial peptides (28). Transcriptional profiling identified PIM1, a gene encoding a serine-threonine kinase, which was regulated by IL-22 and upregulated in psoriatic skin vasculature. The increased vascularisation and epidermal thickening seen in psoriasis could be partially reduced in experiments with PIM-1 knockout mice, therapeutic anti-IL-22 and small molecule inhibitors of PIM1. Developing inhibitors of this pathway offers potential therapeutic application to psoriasis patients.

Environmental factors

Psoriasis lesions can be induced by trauma (Koebner phenomenon), streptococcal pharyngitis (29), stress (30). and drugs including lithium and beta-blockers. These triggers are probably most relevant in patients with a genetic predisposition to developing psoriasis.

Skin microbiome

16s ribosomal RNA (rRNA) sequencing and total microbiome DNA sequencing have helped to characterise the diverse microbial population on the skin surface. As the skin is the primary interface between the environment and immune system, it is hypothesised that cutaneous microbiota may be vital in educating the immune system. Staphylococcus epidermidis, previously thought to be a harmless skin commensal, has been shown to be crucial for protective immunity against Leishmania Major in a T-cell dependent manner (31).

Dysregulation of immune responses to microbiota may contribute to inflammatory pathology. Analogous to this, defective immune tolerance to intestinal microbiota has been proposed to promote Crohn's disease – seen four times more commonly in psoriasis patients than in the general population (32).

Further investigation of the role of microbes in psoriasis etiology is supported by an altered microbial profile demonstrated in psoriasis patients and upregulation of antimicrobial peptides (33).

On a phylum level, Firmicutes were significantly overrepresented in psoriasis patients compared to non-lesional psoriasis skin and healthy volunteers (34). In these latter groups, Actinobacteriae were most prevalent and significantly underrepresented in the psoriasis group. Propionobacterium species were also underrepresented in psoriatic lesions. Alterations in the cutaneous microbiota of psoriasis patients also have been replicated in other studies (35, 36).

Immunopathogenesis of psoriasis

Psoriasis arises as a result of dysregulated interactions of the innate and adaptive immune system in the context of skin epithelium and connective tissue (Fig. 1) (2). It is within the spectrum of autoimmune-type inflammatory diseases. Innate immune cells induce a pro-inflammatory cytokine cascade. Interferon alpha released from plasmacytoid dendritic cells is a crucial cytokine in the initiation phase of psoriasis (37).

Keratinocytes are vital contributors in the immunopathogenesis of psoriasis, and are a rich source of antimicrobial peptides, including LL-37, beta defensins and S100A7 (psoriasin). LL-37 combines with host DNA to form DNA-LL-37 complexes stimulating plasmacytoid dendritic cells to produce interferon-alpha to act on the myeloid dendritic cells (38). Other key innate immune cell types also act on myeloid dendritic cells such as keratinocytes (mediated through IL-1, IL-6 and TNF-alpha), macrophages (mediated through TNF-alpha) and natural killer T-cells (mediated through TNF-alpha and Interferon gamma).

Dendritic cells are key immune system sentinels that drive the adaptive immune response in psoriasis. Their numbers are increased in psoriatic plaques and can induce auto-proliferation of T-cells when activated (39). Activated dendritic cells function as antigen-presenting cells and secrete cytokine mediators including IL-12 and IL-23 which drive differentiation of T-cells into Type 1 and Type 17 T-helper cells respectively. Th17 cells are particularly important and may have a role in epithelial immune surveillance (40). Activated Th17 cells produce cytokines including IL-17A, IL-17F and IL-22. IL-17 also may be released by innate lymphoid cells, mast cells, other T-

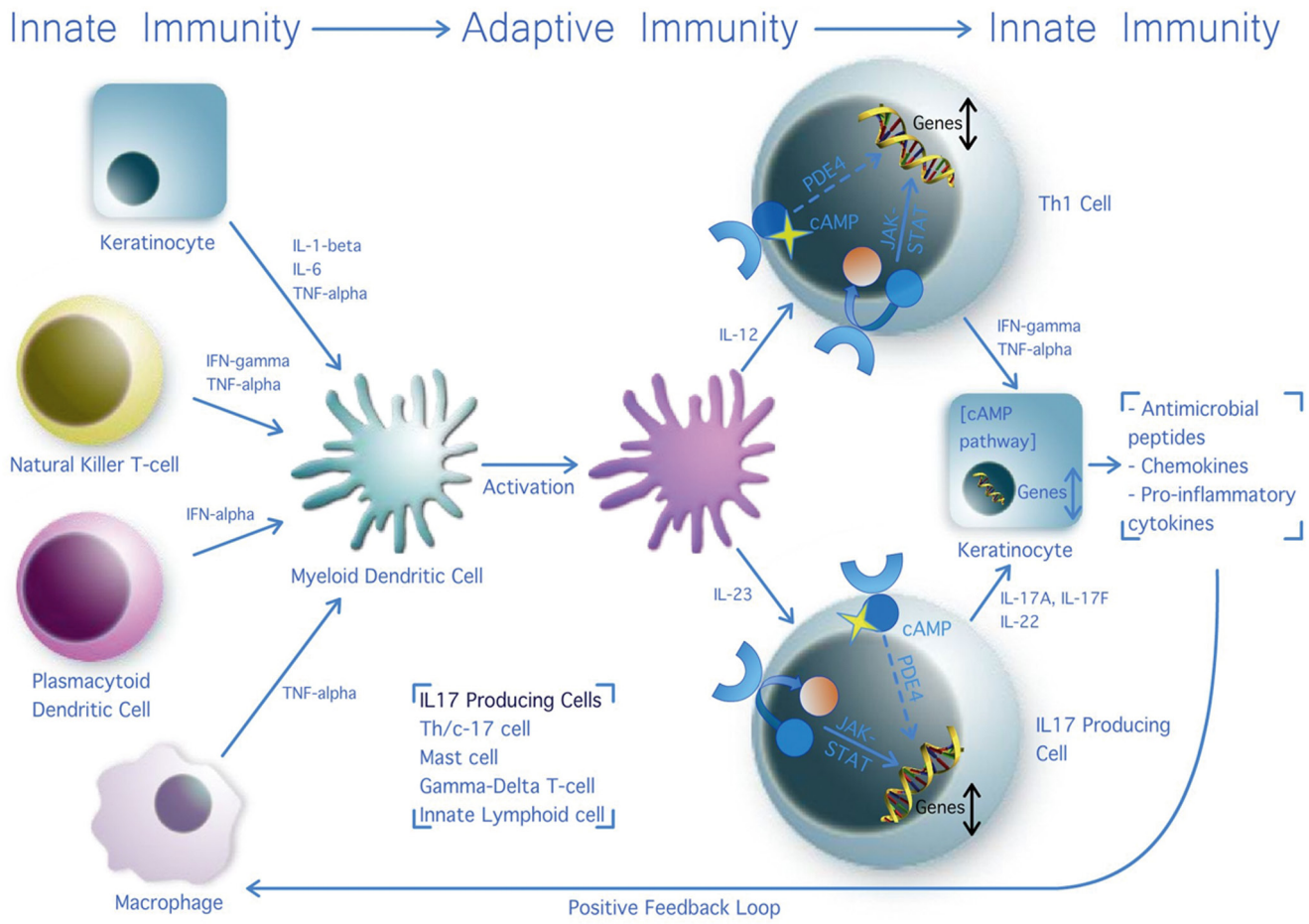

Fig. 1. Innate and adaptive immune effector cells, cytokines and pathways in psoriasis.
Plasmacytoid dendritic cells are potential initiators of the inflammatory cascade by releasing type I interferons which act by activation of myeloid dendritic antigen presenting cells. Keratinocytes, NK-T-cells and macrophages can also provide pro-inflammatory stimuli through the secretion of IFN-alpha, TNF-alpha, interleukins 1-beta and 6. Activated myeloid dendritic cells drive differentiation of T-lymphocytes into IFN-gamma producing Th1-cells through production of IL-12 and IL-17 producing cells through production of IL-23. IL-17 can be released from CD4 and $CD8^+$ T-lymphocytes (Th/c-17 cells), gamma delta T-cells,mast cells,innate lymphoid cells and possibly neutrophils. Cytokines exert their effect through activation of intracellular signal transducers such as JAK-STAT and cyclic AMP, which affect gene transcription for key cytokines and messengers. Cyclic AMP mediated anti-inflammatory activity is inhibited by hydrolysis of cAMP to AMP by the enzyme phosphodiesterase-4 (PDE-4). IL-17 producing cells act on keratinocytes via production of IL-17A, IL-17F, IL-22 and TNF-alpha. This drives keratinocyte proliferation and release of pro-inflammatory cytokines, chemokines and antimicrobial peptides that act via a positive feedback loop to further support the inflammatory process.
Adapted from Nestle et al, NEJM, 2009[2].

lymphocytes (*e.g.* gamma-delta T-cells and CD8 positive Tc17 cells) and potentially by neutrophils.

Keratinocytes are activated by IL-17A, IL-17F and IL-22 from the Th17-associated pathway and TNF-alpha and IFN-gamma from the Th1 pathway. These pathways lead to keratinocyte proliferation and production of pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha), chemokines and anti-microbial peptides. A positive feedback loop exists to attract other innate and adaptive immune cells and further potentiate the inflammatory process. The inflammatory cascade also activates mediators of angiogenesis (41), and induces endothelial adhesion molecules that stimulate further migration of immune cells into psoriasis lesions (42).

Intracellular signalling pathways

Cytokines exert their effects by activating intracellular signalling and transcription pathways. Type-1 interferons, IFN-gamma, IL-12, IL-22 and IL-23 activate the Janus kinases (JAK) and signal transducers and activators of transcription (STATs) pathway. Janus kinases are tyrosine kinases (JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2)) linked to cytokine receptors that can activate the STAT pathway. Activation results in phosphorylation, dimerisation and modulation of pro-inflammatory gene transcription (43). Inhibition of this pathway with drugs such as tofacitinib results in improvement in psoriasis (44, 45).

TNF-alpha acts in part via NF-κB which is a transcription factor important for cellular proliferation, differentiation and apoptosis (46). Phosphorylated (active) NF-κB is elevated in psoriasis. In addition to anti-TNF therapies, fumaric acid esters may also act by inhibition of this pathway (47).

The T-lymphocyte and potential keratinocyte response also is modulated by the intracellular messenger cyclic adenosine monophosphate (cAMP).

Table I. Selected biologic and small molecule inhibitors for treatment of moderate to severe psoriasis.

Drug	Target	Formulation
Etanercept	TNF-receptor	Human p75 Fc fusion protein
Infliximab	TNF-alpha	Chimeric monoclonal (IgG1)
Adalimumab	TNF-alpha	Human monoclonal (IgG1)
Ustekinumab	Anti-IL12, IL-23 (p40 subunit)	Human monoclonal (IgG1)
Brodalumab*	IL-17 receptor	Human monoclonal (IgG2)
Ixekizumab	IL-17A	Human monoclonal (IgG4)
Secukinumab	IL-17A	Human monoclonal (IgG1)
Apremilast	Phosphodiesterase 4 (PDE4)	Small molecule inhibitor (oral)
Tofacitinib	Janus Kinase (JAK-STAT pathway)	Small molecule inhibitor (oral)

*Brodalumab development is under review due to observations of suicidal ideation and behaviour during clinical trials (50).

cAMP is hydrolysed by the enzyme phosphodiesterase 4 (PDE-4). Drugs such as Apremilast inhibit this enzyme and increase levels of intracellular cAMP (48). This process reduces expression of proinflammatory cytokines TNF-alpha, IFN-gamma, IL-2, IL-12, and IL-23 and causes an increase in the anti-inflammatory cytokine IL-10 (49).

Therapeutic aspects

Mild psoriasis is amenable to topical therapy such as corticosteroids, coal tar preparations and vitamin D analogues. Severe psoriasis often necessitates treatment with phototherapy or systemic agents such as methotrexate, cyclosporine, fumaric acid esters or systemic retinoids. Advances in our understanding of disease pathogenesis has led to targeted immunomodulatory, or biologic, therapies that act on the upregulated cytokine pathways in psoriasis (Table I). Anti-TNF therapies, including infliximab, adalimumab and etanercept have been available for more than a decade.

Newer biological therapies have become available in recent years. Ustekinumab is a monoclonal antibody directed against the common p40 subunit shared between IL-12 and IL-23. The crucial role of the IL-23/Th17 axis is underlined by relatively superior efficacy compared to anti-TNF therapy in certain studies (51). Secukinumab is highly effective for psoriasis and psoriatic arthritis and also acts on the Th17 pathway by blocking an effector cytokine IL-17A (52). Ixekizumab also targets interleukin 17A and has shown promising results (53).

The small molecule inhibitors target enzymes within the psoriasis signalling pathways. These drugs are potentially advantageous compared to the biologics as they can be administered orally and topically rather than parenterally and may be less expensive.

Apremilast is licensed for moderate to severe psoriasis and acts through inhibition of phosphodiesterase-4, which leads to a reduction of proinflammatory cytokines (49). Inhibition of the JAK-STAT pathway with small molecule inhibitors such as Tofacitinib (inhibitor mainly of JAK 3, but also JAK 1 and 2) also is effective in the treatment of psoriasis (54).

Precision medicine

Considerable variability has been seen in an individual's response to immunomodulators. Characterisation of patient and disease specific immune and molecular features and selecting of appropriate targeted therapies is the essence of precision medicine and is a major research initiative for the future (55). Roederer *et al*. (56) recently published a unique bioresource highlighting the heritability of key aspects of our immune system and the impact risk-alleles may have on autoimmune disease (57, 58). Our group performed immunophenotyping of peripheral blood leucocytes analysing 78,000 immune traits in a 669 healthy twins specifically investigating immune cell subset frequency and cell surface protein expression levels. Comparing immune traits between monozygotic and dizygotic pairs, we were able to identify the 151 most heritable traits. A GWAS then identified 11 new genetic loci that explained up to 36% of the variation in 19 immune traits.

Many of the SNPs influencing immune traits mapped to loci associated with susceptibility to autoimmune and infectious diseases, for example SLE and inflammatory bowel disease. Particular SNP's (*i.e*. genotypes) can impact cell surface protein (*e.g*. CD32) expression on dendritic cells that have the potential to directly modulate immune responses and potentially alter the risk of developing autoimmune diseases. The dataset provides numerous novel pathways for investigation of common diseases, and in addition to molecular signatures from microbiomic data (59) represent an exciting development in precision medicine with the potential to benefit patients with psoriasis, as well as other chronic inflammatory diseases.

Conclusion

Psoriasis therapy has evolved as our understanding of the basic science has developed. Further characterising the key genomic, immune and microbiomic pathways involved will help to identify novel disease mechanisms and novel therapeutic targets. Ultimately, precision medicine based on these advances will help to reduce the patient morbidity associated with psoriasis and other inflammatory chronic diseases.

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