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Progress in understanding the immunopathogenesis of psoriasis

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Abstract

This review emphasizes how translation from bench research to clinical knowledge and vice versa has resulted in considerable progress in understanding the immunopathogenesis of psoriasis. First, the journey in understanding the pathogenic mechanisms behind psoriasis is described. The roles of different components of the adaptive and innate immune systems involved in driving the inflammatory response are explained. Discovery of new immune pathways i.e. the IL23/Th17 axis and its subsequent impact on the development of novel biological therapies is highlighted. Identification of potential targets warranting further research for future therapeutic development are also discussed.

Keywords

psoriasis; immunopathogenesis; T cells; adaptive/innate immune response

Psoriasis is a common and stigmatising chronic inflammatory skin disease affecting about 2 % of the population worldwide [1]. This condition may cause significant morbidity due to the possible co-existence of psoriatic arthritis and association with a large number of systemic diseases [2]. A recent cohort study [3] has also shown that severe psoriasis (defined as psoriasis patients with a history of systemic therapy) is associated with an increased risk of mortality as male and female patients in the study died 3.5 and 4.4 years younger respectively than those without psoriasis (even after adjustment for classical risk factors of mortality). Hence psoriasis is a major public health problem. On an individual basis, it has a negative impact on patients' quality of life. Therefore, psoriasis poses a major social and economic burden on society. Current existing therapies only relieve symptoms but cannot cure disease. Therapeutic costs are expensive with treatments carrying substantial side effects. Therefore better understanding of the immunopathogenesis of psoriasis remains at the forefront of both basic and translational research as this is essential for the development of improved therapies. The immunological and inflammatory basis for psoriasis has been extensively reviewed in the literature [4-7]. Although considerable progress has been made in understanding the immunopathogenesis of psoriasis [1], many fundamentally important questions regarding the functional roles of cells and molecules implicated in psoriasis remain unanswered. The aim of this review is to summarise the important findings from clinical studies and experimental models that have led to a better understanding of the immunopathogenesis of psoriasis with emphasis on how the transfer between knowledge acquired from basic research to clinical studies and vice versa is crucial for rapid progression in both areas. Important areas for future research directions will also be highlighted.

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Clinical subtypes, histological features and associated comorbidities

Different clinical subtypes of psoriasis exist with psoriasis vulgaris, the commonest type of psoriasis, accounting for 90 % of all cases. About 50 % of psoriasis patients have psoriatic nail disease with nail pitting as the most common change. Psoriatic arthritis is a seronegative inflammatory arthritis with a prevalence of up to 25 % [8] and in the vast majority (90 %) of psoriasis patients with psoriatic arthritis, the skin manifestations precede arthritis.

Psoriasis is thought to be a complex condition resulting from a combination of genetic predisposition and environmental triggers. The acute forms of psoriasis, guttate and generalised pustular psoriasis (von Zumbusch psoriasis), are both associated with infections. The former usually occurs about 2 weeks after a b-haemolytic streptococcal infection such as tonsillitis or pharyngitis, or a viral infection. Apart from infection, other triggering factors which may elicit psoriasis in genetically predisposed individuals include trauma (Koebner phenomen) [9], HIV infection [10], hypocalcaemia in generalized pustular psoriasis [11], psychogenic stress [12,13] and certain drugs including lithium, beta-blockers, antimalarials, interferon, NSAIDs and rapid tapers of high dose corticosteroids [14]. Increased alcohol consumption and smoking have been associated with psoriasis but neither has been shown to be a major risk factor.

The 3 main histological features of psoriasis are epidermal hyperplasia, dilatation and proliferation of dermal blood vessels and accumulation of inflammatory cells, particularly neutrophils and T lymphocytes in the dermis. It now transpires that the first two features are caused by inflammatory cell infiltrates. The increased vascularity in the dermis seen histologically is driven by angiogenic factors. One of these factors, vascular endothelial growth factor (VEGF), is found at high levels in psoriasis plaques [15]. The interaction between VEGF and the angiopoietin/Tie signalling pathway is modulated by tumour necrosis factor a (TNFa), a key pro-inflammatory cytokine in psoriasis [16,17].

Psoriasis is also associated with a number of systemic disorders [2] including Crohn's disease, diabetes mellitus (notably type 2) [18], metabolic syndrome [19], obesity, cardiovascular disease [20], depression [21] and cancer. It is uncertain whether cancers particularly lymphoma and skin cancer, are related to psoriasis or to its treatment. Psoriasis has been identified as an independent risk factor for cardiovascular disease [22]. Potential mechanisms may include the presence of circulating pro-inflammatory factors and endothelial activation [22].

Journey in understanding the immunopathogenesis of psoriasis

Genetics of psoriasis

A complete overview of the genetics of psoriasis is beyond the scope of the current article but has been extensively reviewed elsewhere [23,24]. Twin and family studies have shown that psoriasis has a strong genetic component although the inheritance pattern is still unclear. 71 % of patients with childhood psoriasis have a positive family history [25]. Siblings [26] and first-degree relatives [27] of psoriasis patients show a four-fold or more increased risk in developing psoriasis. Analysis of concordance rates in twin studies [28-31] show a threefold increased risk of psoriasis in monozygotic twins compared to dizygotic twins, being approximately 72 % and 15-23 % respectively for northern European individuals, and 35 % and 12 % respectively for Australian individuals. These data further support genetics as a major influence in psoriasis.

At least ten chromosomal loci have been identified showing statistically significant evidence for linkage to psoriasis (PSORS 1-10). However, the only region that has consistently been identified in genetic screens of families with psoriasis is the major-histocompatibility complex (MHC) region on chromosome 6 named PSORS1 [32,33] and markers within this region have repeatedly been shown to have the greatest association with psoriasis in different genome wide

association scans [34,35]. This region is considered to be responsible for up to 50 % of genetic susceptibility to psoriasis. Within PSORS1 is the human leukocyte antigen-C (HLA-C) gene which is the strongest candidate gene for psoriasis identified to date [32], with its allele HLA-Cw6 (HLA-Cw*0602) shown to be the predominant risk allele. A new psoriasis susceptibility gene ZNF313/RNF114, which may regulate T cell activation through ubiquitin ligase activity, has been identified [34]. This further supports the notion that multiple gene products share a role in the immune regulation of psoriasis, contributing to disease pathogenesis. Other novel psoriasis susceptibility genes that have been identified from genomewide association scans have been summarized in a recent review [1] and include the IL-23R, CDKAL1 and the IL-4/IL-13 gene cluster [1].

HLA-Cw6 and psoriasis

HLA-Cw6 is seen in up to 60 % of psoriasis patients compared to 15 % in the general population. Individuals carrying this allele have a 10-20-fold increased risk of developing psoriasis [36]. A dosage effect of HLA-Cw*0602 has been observed, where homozygous individuals have a 2.5-fold increased risk of developing psoriasis compared to HLA-Cw6 heterozygous individuals [37]. Homozygous individuals also experience an earlier onset but disease severity is not affected [37]. The HLA-Cw6 allele is present in 90 % of patients with early onset psoriasis, in 50 % of those with late onset psoriasis, and only 7.4 % of a control population. HLA-Cw6 positive and negative psoriasis patients may exhibit distinctive clinical phenotypes. Some clinicians have designated patients with early onset psoriasis, a positive family history of psoriasis and the expression of HLA-Cw6 as having Type I psoriasis and those with late onset disease, no family history and a lack of expression of HLA-Cw6 as Type II psoriasis [38]. Guttate psoriasis, both acute onset and persistent eruptive subtypes, are mostly confined to HLA-Cw6 positive patients. Meanwhile, psoriatic nail disease, palmoplantar pustulosis and psoriatic arthritis are more common in HLA-Cw6 negative patients [39,40]. Apart from significantly earlier disease onset, HLA-Cw*0602 is associated with more widespread and recurrent psoriasis [39]. Partial or total remission during pregnancy is much more frequent in HLA-Cw*0602 positive women whilst HLA-Cw*0602 negative women are more likely to have unchanged or worsening psoriasis during pregnancy [39]. Koebner's phenomenon is also more common in HLA-Cw6 positive patients [39,40].

Gene to function perspective on HLA-Cw6

The strong association of HLA-Cw6 with psoriasis further supports psoriasis as an immune-mediated disorder. Despite this strong association, the functional role of HLA-Cw6 remains unknown. Both the adaptive and the innate immune systems are important in defence against pathogens, the former generates a highly specific response for a particular pathogen whilst the latter confers immediate non-specific defence against infection. Figure 1 illustrates that HLA-Cw6 may exert its effect via the adaptive or the innate immune system. HLA-Cw6 may act via the adaptive immune system by its antigen presenting capacity. This hypothesis is supported by the fact that guttate psoriasis, which is strongly associated with HLA-Cw6, is triggered by streptococcal pharyngitis [41,42]. HLA-Cw6 may also exert an innate immune response via its interaction with a class of killer immunoglobulin-like receptors (KIRs) expressed on natural killer (NK) and natural killer T (NKT) cells, which are important components of the innate immune system and are implicated in the pathogenesis of psoriasis [43]. NK cells produce predominantly IFN-g and may cause cytolysis of target cells. NK cell activity is up-regulated by IL-2, IL-12 and IL-15; which are all found at increased levels in psoriatic plaques. NK cells can mediate both activating and inhibitory immune responses as they express both activating and inhibitory killer immunoglobulin-like receptors. KIRs recognise different types of HLA-C molecules leading to either an overall activating or inhibitory immune response. KIRs have been associated with psoriasis and psoriatic arthritis [44]. HLA-Cw6 is a natural ligand for KIR2DL1 (an inhibitory receptor) and it is possible that interaction between HLA-Cw6 and

KIR2DL1 would lead to aberrant function of lymphoid cells in the immunopathogenesis of psoriasis. A better understanding of the functional role of HLA-Cw6 is important for both elucidating the immunopathogenesis of psoriasis and development of improved treatments for psoriasis.

Immune response

Epidermal keratinocytes are able to recruit and activate T cells. Most T cells infiltrating psoriatic skin are divided into T helper 1 (Th1; CD4 +) and T cytotoxic (Tc1; CD8 +) subsets [45]. Two further T cell subtypes, Th17 cells [46] and regulatory T cells (Treg) [47] have been identified as important contributors to the pathogenesis of autoimmune diseases including psoriasis. Figure 2 illustrates the different T cell subtypes implicated in psoriasis. Involvement of both innate (keratinocytes, dendritic antigen-presenting cells, neutrophils, macrophages, natural killer (NK) and natural killer T (NKT) cells) and adaptive (CD4+ and CD8+ T lymphocytes) immune responses are important in mediating the inflammatory cascade [1,48] and this is summarized in figure 3.

Characterization of cells and cytokines showed that elevated levels of T helper (Th) 1 cytokines IFNg, T N F a and IL-12 are present in psoriasis, but not the T helper (Th) 2 cytokines IL-4, IL-5 or IL-10 which appeared to be protective against psoriasis. The use of Th2-type cytokines IL-4 [49] and IL-10 [50] in clinical trials as treatment for psoriasis suggest that a shift of the cytokine milieu from Th1 to Th2 response may reverse psoriasis inflammation. These observations led to the view that psoriasis is a Th 1-type disease [51]. The crucial role of TNFa in psoriasis has become evident from three distinct TNFa inhibitors etanercept [52], infliximab [53] and adalimumab [54] which block the interaction of soluble TNFa with TNFa receptors on target cells and are highly effective in the treatment of psoriasis. By studying the progressive changes in inflammatory cytokines and chemokines induced by etanercept in psoriatic lesions, it has been suggested that TNFa may strongly regulate early cytokine production and support the inflammation driven by IFNg and the signal transducer and activator of transcription (STAT) pathways, thereby encouraging chemokine production that regulates T cells and DC interactions in the skin [7]. TNFa has been linked to fatigue and depression [55] which are co-morbidities associated with psoriasis and TNFa receptors have been detected in the central nervous system. [55] Hence biological therapies targeting TNFa may also improve these psoriasis associated co-morbidities in the long term [56].

Role of T cells

Until the 1990s, psoriasis was thought to be a disease of disordered keratinoctye proliferation and differentiation [57] especially as epidermal hyperplasia was the most prominent clinical and histological feature. This initial view of psoriasis resulted in the use of antimetabolites including methotrexate which limit epidermal hyperproliferation. However, subsequent evidence from clinical studies, *in vitro* and *in vivo* experimental models support the concept that psoriasis is a T cell-mediated inflammatory skin disease [51] affecting genetically predisposed individuals and the observed epidermal hyperplasia is a result of cellular immune infiltration. The first piece of evidence resulting in psoriasis being widely considered as a T-cell mediated autoimmune disease came from the success of T-cell-targeted therapies such as cyclosporin [58,59] and tacrolimus [60] in the treatment of psoriasis [61]. Monoclonal antibodies specific for CD3 and CD4, which are more selective biological T-cell antagonists, produced clinical improvement in some patients with severe psoriasis. A pivotal study involved the testing of interleukin-2 (IL-2)-diphtheria-toxin fusion protein in psoriasis patients [62]. This agent was proposed to selectively deplete activated T cells expressing IL-2 receptors from psoriasis skin lesions and resulted in clinical and histopathological remission of psoriasis vulgaris. These studies stimulated further research into the development of T-cell-targeted drugs for psoriasis treatment. Subsequently, administration of another fusion protein, cytotoxic

T-lymphocyte antigen 4 (CTLA4)-immunoglobulin, was shown to reverse the clinical and cellular features of psoriasis [63]. This agent blocks T cell co-stimulation mediated by dendritic cells (DCs) but does not directly deplete T cells. Its effectiveness indicated that continuing T-cell co-stimulation is required to sustain psoriasis disease activity, including the excessive infiltration of T cells and DCs into the skin [64]. These clinical studies all provided evidence that lesion-associated T cells are central to sustaining disease activity in psoriasis vulgaris. Further evidence highlighting the importance of T cells in psoriasis pathogenesis have been reviewed [1] including the appearance of clonal T cells in psoriatic lesions [65], the development of psoriasiform phenotype within symptomless (nonlesional) psoriatic skin after transplantion onto the xenotransplantation AGR 129 mouse model again highlights the importance of epidermal T cells in the development of psoriasis [66]. The immune response involved in psoriasis pathogenesis is explained further below.

The IL-23/Th17 axis

The IL-23/Th17 axis is an exciting new area in psoriatic pathology because it has led to the development of promising new treatments for psoriasis which specifically target this axis. The development, characterization and function of Th17 cells and the role of IL-23 in Th17-cell-dependent chronic inflammation in psoriasis have been recently reviewed [67]. Briefly, IL-23 is a heterodimeric cytokine [68] and consists of the protein IL-23p19 combined with IL-12p40, an IL-12 subunit. Intradermal injection of IL-23 in mice resulted in the development of a psoriasiform phenotype with histopathological features [69]. IL-23 has been shown to mediate epidermal hyperplasia, acanthosis, hyperparakeratosis and orthohyperkeratosis via TNF-a, IL-20R2 and IL-22 [69,70]. These results are supported by findings in humans including an over-expression of IL-23p19 and IL-12p40 (precursors of IL-23) seen at the mRNA level in psoriatic skin lesions, compared to uninvolved skin. Further data indicate that production of IL-23 occurs at inflammatory skin sites and is mediated by tissue-resident and/or recruited immune cells, such as dendritic cells and possibly keratinocytes [71]. The pathogenic role of IL-23 in psoriasis is strongly supported by the clinical findings that anti-TNF-a agents can reduce IL-23p19 and IL-12p40 mRNA levels, and reduction of IL-23 level caused by cyclosporin A, UV therapy and biological agents correlates to clinical improvements in psoriasis patients [72-74].

Transforming growth factor (TGF)-b1, IL-6 and IL-21 are all required to transform naïve T cells into cells expressing the unique lineage-specific transcription factor, RORC variant 2 and IL-23 receptors with subsequent binding of IL-23 resulting in differentiation into Th17 cells. Th17 cells in turn produce IL-17A, IL-17F, IL-22 and IL-26 which are proinflammatory cytokines [75]. These cytokines activate keratinocytes leading to hyperproliferation and further production of proinflammatory cytokines, chemokines and antimicrobial peptides, which in turn recruit and activate other immune cells in the inflamed skin, leading to amplification of the inflammatory response and clinical features of the disease.

Support for a role of the IL-23/Th17 axis in psoriasis comes from whole genome studies showing that genetic variants of the IL-23 receptor and its ligand IL12B are associated with psoriasis [35].

Regarding the clinical relevance of the IL-23/Th17 pathway, targeting the common subunit p40 of IL-12 and IL-23 has demonstrated clinical improvement in psoriasis. Two anti-IL-12p40 monoclonal Abs, CNTO-1275/ustekinumab and ABT-874, have been recently developed as psoriasis treatments. Ustekinumab and ABT-874 are humanized IgG1 monoclonal antibodies that bind to the p40 subunit of human IL-12 and IL-23 and prevent interaction with IL-12Rb1. Phase I [76] and phase II [77,78] studies have supported the use of both antibodies as effective treatments for moderate to severe psoriasis. The safety profile of ustekinumab in psoriasis has been evaluated in 2 phase III studies. Of these, PHOENIX I assessed the efficacy and safety of ustekinumab 45 and 90 mg administered subcutaneously at weeks 0, 4, and then every 12

weeks over 76 weeks of treatment [79]. 67.1 % and 66.4 % of patients who received ustekinumab 45mg and 90mg respectively, achieved PASI-75 (improvement of PASI score by 75 %) at week 12 compared to placebo control (3.1 %). Efficacy increased over time and maximum effect was seen at week 24 with PASI-75 achieved in 76.1 % of patients treated with 45mg and in 85 % of patients treated with 90mg. The observed adverse events were mild, non-life threatening and not significantly different from the placebo group. The most commonly reported adverse events were upper respiratory tract infections, nasopharyngitis, headache, and arthralgia. The PHOENIX II trial [80] was conducted to further assess if dosing intensification would increase the response to treatment in partial responder patients (between PASI-50 and PASI-75). It was found that dosing intensification resulted in increased clinical efficacy only in patients receiving 90mg, but not 45mg, of ustekinumab every 8 weeks (PASI-75 in 68.8 % of patients receiving 90mg every 8 weeks versus 33.3 % of patients receiving 90 mg every 12 weeks). The incidence and type of adverse events observed did not differ between PHOENIX I and II studies. Ustekinumab is also effective in the treatment of psoriatic arthritis [81] and this study again confirmed that ustekinumab is well tolerated [81].

Regulatory T cells

Regulatory T (Treg) cells are characterized by their ability to suppress the activation and proliferation of CD4+ and CD8+ effector T cells via mechanisms that either require direct contact with antigen presenting cells [82] or by releasing IL-10 [83] or transforming growth factor beta 1 (TGF-b1) [84]. Treg cells express CD4, CD25 and the specific transcription factor Foxp3. They account for between 1-5 % of the total population of peripheral CD4+ cells. Dysfunction of Treg cells has been implicated in the pathogenesis of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and autoimmune polyglandular syndrome type II. In psoriasis, Treg function and proliferation are both defective [47]. This combination may result in a failure to constrain the activation and proliferation of pathogenic T cells, contributing to the ongoing inflammation seen in psoriasis. Hence strategies that correct Treg function or increase the Treg:pathogenic T cell ratio may be potential treatments for psoriasis [47]. Phototherapy may induce Treg type suppressor cells as well as eliminate pathogenic T cells [85], supporting a possible role of Treg cells in protection against psoriasis.

Contribution of animal models in understanding the roles of resident T cells in the skin and the importance of plasmacytoid dendritic cells (PDCs)

A major hindrance in studying the immunopathogenesis of psoriasis and subsequent development of new therapies is the lack of disease relevant animal models. No naturally occurring disorder in laboratory animals can mimic the complex phenotype of psoriasis. After decades of research, a number of psoriasis mouse models have been developed, each with specific advantages and shortcomings. A number of comprehensive and critical reviews of different psoriasis mouse models have been published recently [86-88]. Criteria for an ideal psoriasis mouse model [86] should include:

1. Display of typical psoriasis clinical features and histopathology.
2. Feature the major role of T cells, due to overwhelming evidence in the literature.
3. Psoriatic lesions should clear with well established pharmacological treatments for the disease.
4. The pharmacologically validated model should reflect the clinical response in patients. There are two main approaches to the currently available mouse models: a) generation of mice with over-expression (transgenic) or deletion (knock out) of certain genes and gene products in specific tissue compartments such as the epidermis and b) xenotransplantation models involving transplantation of human skin onto

immunosuppressed mice to avoid graft rejection. The latter approach may overcome the problem of species difference which exists in the former approach.

Although no single model is perfect, the xenotransplantation AGR 129 mouse model [89] has been instrumental in understanding the early events of the immunopathogenesis of psoriasis. AGR 129 mice are deficient in type I (A) and type II (G) IFN receptors, in addition to lacking T and B cells (RAG-2 $^{-/-}$). In the AGR 129 mouse model, psoriatic phenotype develops spontaneously upon transplantation of symptomless non-lesional skin onto mice. No exogenous cells or factors are required to initiate the psoriatic lesions thereby allowing studies of early mechanisms in psoriasis immunopathogenesis. After transplantation of non-involved psoriatic skin onto the AGR 129 mouse, injection of the monoclonal anti-human CD3 antibody, which blocks T cell functions, results in inhibition of psoriasis development [89]. Furthermore, application of a neutralizing anti-human TNF-a monoclonal antibody, or TNF receptor fusion protein, leads to significant reduction of T cell numbers in the graft and inhibition of psoriasis phenotype development [89]. It was demonstrated that the source of TNF-a is local antigen presenting cells within the skin graft. Altogether, these data suggest that local TNF-a production is crucial for resident T cell proliferation and psoriasis development. These studies also provide evidence that local proliferation of effector T cells, rather than their recruitment, is important for induction of psoriasis.

Three types of DCs (Langerhans cells, dermal DCs and plasmacytoid DCs) play important roles in psoriasis. It has been demonstrated that plasmacytoid dendritic cells (PDCs) produce IFN-a, which results in the activation of many aspects of the innate immune system and helps drive the inflammatory process in psoriasis [90]. A role for IFN-a in psoriasis is supported by three observations [90]. First, an activated IFN-a signalling pathway is present in psoriatic skin lesion [91,92]. Secondly, continuous excessive IFN-a/b signalling results in an inflammatory skin disease in a mouse model that resembles psoriasis. Thirdly, administration of recombinant IFN-a to psoriasis patients for treatment of viral infections or tumours may worsen psoriasis. It has been demonstrated that PDCs accumulate in the skin of psoriasis patients and are activated to produce IFN-a early in the development of psoriasis [90]. PDCs are a rare cell population in peripheral blood and secondary lymphoid organs. They are the main effector cells in executing the antiviral activities of the innate immune system due to their unique ability to secrete large amounts of IFN-a in response to viral stimulation through their toll-like receptor (TLR)-7 and TLR-9. Through IFN-a production, PDCs drive the activation and expansion of the autoimmune T cell cascade leading to psoriasis [90], hence PDCs may provide a unique link between the innate and adaptive immune system in driving inflammation in psoriasis. In the same study, the number of PDCs were found to be increased in both plaque lesions and the nearby uninvolved skin of psoriasis patients but were completely absent in normal healthy skin or inflamed skin of atopic dermatitis. Activation of PDCs was demonstrated to occur locally in lesional psoriatic skin. IFN-a production by PDCs was increased early and transiently in the development of psoriasis and production declined as disease progressed. Intravenous ijection of an anti-BDCA-2 monoclonal antibody, which shared specific binding to human PDCs, led to a > 90 % reduction of IFN-a expression in the engrafted pre-psoriatic skin, resulting in complete inhibition of the subsequent pathogenic T cell activation and expansion and psoriatic phenotype development. Because human PDCs from the transplanted skin do not re-circulate in the AGR 129 mouse model, *in vivo* treatment with anti-BDCA-2 antibody selectively targeted human PDCs present in the engrafted pre-psoriatic skin, thereby confirming that PDCs represented the main IFN-a-producing cells. Administration of recombinant human IFN-a was found to be sufficient to reverse the anti-BDCA-2-mediated inhibition of T cell expansion and psoriasis development [90]. Hence, activation of PDCs and their IFN-a production represents an important proximal event in the psoriasis immune axis, highlighting the contribution of innate immunity towards autoimmunity in psoriasis. The pathogenic role of PDCs in psoriasis is further supported by the observation that the topical ILR 7/8 ligand imiquimod which activates

PDCs can exacerbate psoriasis [93]. Hence therapies that target PDCs and PDC-derived IFN-a may be valuable for both prevention and early treatment of psoriasis. IFN-a targeted therapies may be advantageous over anti-TNF-a therapy in that its production is highly specific, both spatially and temporally i.e. IFN-a is mainly produced by dermal PDCs during the early stage of psoriasis development unlike TNF-a which is produced by a broad range of cells including myeloid DCs, T cells and keratinocytes throughout different stages of psoriasis. Hence, IFN-a targeted therapies may facilitate prevention and early treatment of psoriasis, minimizing the need for long term administration and monitoring of existing psoriasis therapies with a number of potential adverse side effects. PDCs and IFN-a have also been implicated in a number of other autoimmune diseases including lupus erythematosus, rheumatoid arthritis and insulin-dependent diabetes mellitus [94]. Hence the role of PDC-induced innate activation via IFN-a production may also provide valuable insights into the pathogenesis of other autoimmune diseases and their treatment strategies.

Role of bacterial superantigen

Of the many environmental factors implicated in the immunopathogenesis of psoriasis, throat infection with a-haemolytic streptococci is an external trigger that has been associated with initiation and exacerbation of guttate psoriasis [95]. However, a specific antigen responsible for T cell activation in the skin has yet to be conclusively identified. It has been suggested that antigen presenting cells in the tonsillar tissue may ingest bacterial wall fragments and are then re-circulated into the skin where they may activate a T cell response, resulting in psoriatic lesions [96]. Molecular mimicry is another hypothesis where T cell clones originally generated in response to streptococcal tonsillitis or pharyngitis are subsequently reactivated in the skin because of a cross-reactive epitope derived from hyperproliferative epidermal keratinocytes such as keratin 16 or keratin 17[97]. In a recent review[98] the close correlation between global epidemiological variation in psoriasis prevalence with that of historical mortality from epidemics of invasive streptococcal infections was highlighted and the authors suggested that the psoriasis susceptibility genotype may confer protection from mortality in such epidemics. It is postulated that changes in immunological pathways including the adaptive and the innate immune response as well as the Th17 cell cytokine network all confer protection against mortality during epidemics of invasive streptococcal infections by increasing efficiency in internalizing streptococci but also increase predisposition to psoriasis development [98].

Psoriasis as an autoimmune disease

Although the presence of T-lymphocyte subsets in the early phase of the disease and the response to T-lymphocyte-targeting therapies strongly support the hypothesis of psoriasis as a T-lymphocyte-mediated autoimmune disease, there are still significant gaps in our understanding of this disease. Unlike a well characterized autoimmune skin disease such as pemphigus vulgaris, where the autoantigens and effector molecules (autoantibodies, complement) have been extensively defined using *in vitro* and *in vivo* model systems [99], no reproducible autoantigen has yet been defined in psoriasis.

Recent data suggest that LL37 may be a key activator of PDCs in psoriasis, converting self-DNA into an autoimmune trigger [100]. The role of PDCs as key mediators in the immunopathogenesis of psoriasis has already been discussed. PDCs can recognise bacterial and viral DNA through Toll-like receptors (TLR7 and TLR9) and release type 1 IFNs like IFN-a. Under normal circumstances PDCs do not respond to self-DNA. However, in autoimmune disease, the endogenous antimicrobial peptide LL37 may combine with and convert self-DNA into a potent autoimmune trigger which activates PDCs into producing IFN-a. The antimicrobial peptide LL37 is mainly expressed by keratinocytes and is released by keratinocytes in response to injury or infection. LL37 is also released by migratory inflammatory cells including neutrophils and is present in the dermal compartment in

association with PDCs. Increased expression of LL37 appears to be specific in psoriasis as it is found to be highly upregulated in psoriatic lesions but not normal skin, uninvolved skin of psoriasis patients or other skin disease lesions.

Data suggest that when coupled with DNA, LL37 is taken up by PDCs and these LL37:DNA complexes then activate PDCs through TLR9 and stimulate IFN-a production [100]. This may explain how self-DNA may trigger autoimmunity in psoriasis.

a1b1 integrin and epidermal T cell accumulation

Based on the findings that expansion of skin resident T cells is important in psoriasis development in the xenotransplantation AGR mouse model, the role of tissue-specific factors in activation and expansion of resident T cells has been further explored [66]. T cells need to pass through the dermo-epidermal junction in order to enter the epidermis and collagen fibrils are an essential part of the dermo-epidermal junction. The most important basement membrane collagen is collagen IV. Long-term activation of T cells results in the expression of a receptor for collagen IV, the heterodimeric integrin a1b1 (synonymous with CD49a-CD29 or very late antigen 1, VLA-1). It has been shown that epidermal accumulation of a1b1-positive Th1 and Tc1 cells correlate with psoriasis development. Blocking a1b1 with a neutralizing monoclonal antibody prevents epidermal T cell accumulation and subsequent psoriasis development in the xenotransplantation AGR mouse model. a1b1 expression may act as a checkpoint for entry of T cells into epidermis with a1b1-positive epidermal T cells potentially playing an important role in psoriatic lesion formation. Hence targeting of these integrins may offer new therapeutic approaches in psoriasis and possibly in other autoimmune disease.

Conclusion

Extensive progress has been made in understanding the immunopathogenesis of psoriasis, over the last 10 years. Transfer between knowledge acquired from bench research and clinical studies is crucial for rapid progression in both areas. The discovery of the IL23/Th17 pathway and the subsequent development of new treatments have been major breakthroughs and better insight into psoriasis immunopathogenesis does not only lead to improved treatments for psoriasis but may also provide better understanding of pathological mechanisms behind other autoimmune diseases such as Crohn's disease and better therapeutic treatments for these diseases.

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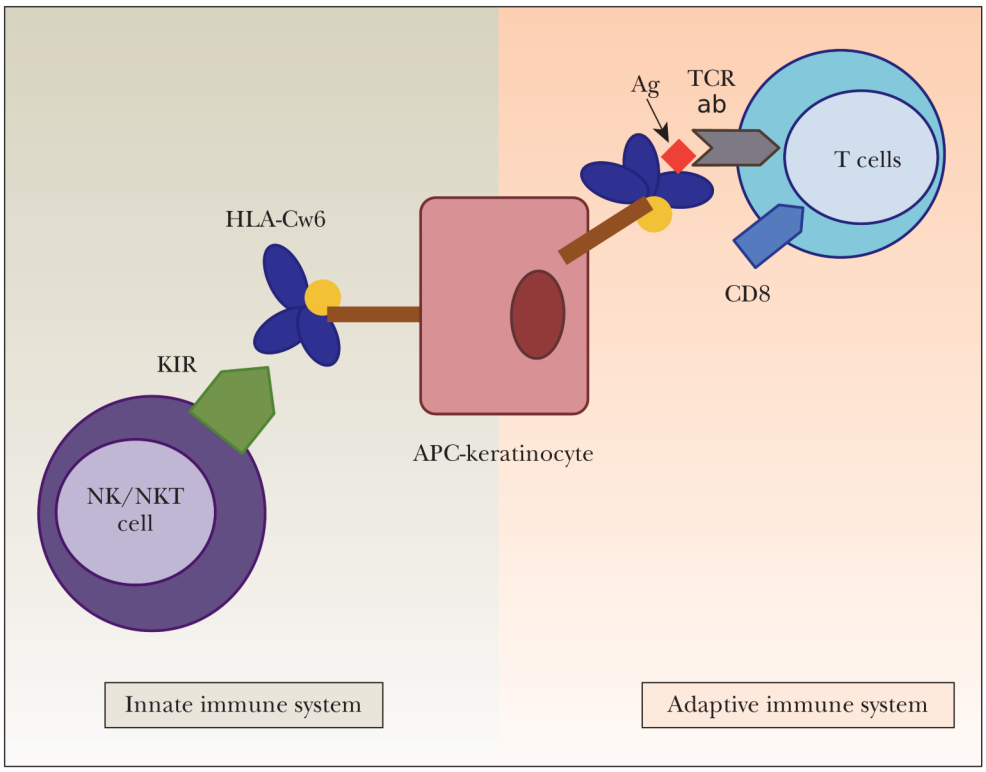

Figure 1.
Potential of HLA-Cw6 to regulate adaptive as well as innate immune responses. HLA-Cw6 expressed on antigen presenting cells (APCs) such as dendritic cells can trigger adaptive immune responses via presentation of processed antigen to the TCR of CD8+ T cells. In addition, innate immune response can be elicited by interaction of HLA-Cw6 with its natural Killer immunoglobulin-like receptors expressed on NK and NKT cells.

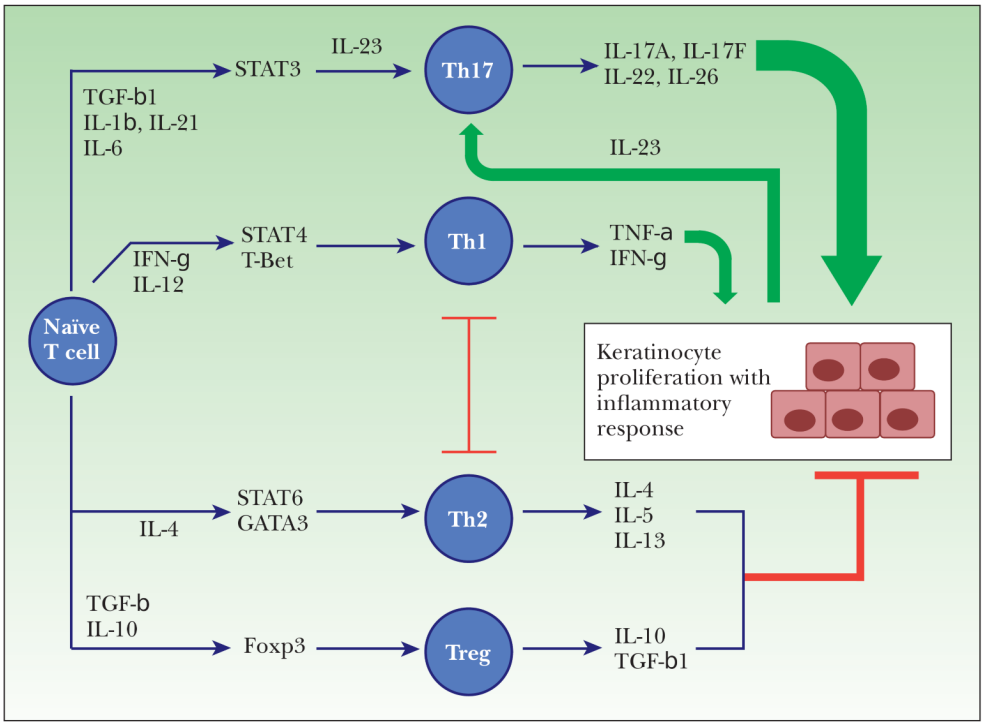

Figure 2.

Role of CD4 T cell subtypes in psoriasis. Pro-inflammatory cytokines produced from Th1 and Th17 dominate the cytokine profile in psoriasis. They mediate keratinocyte hyperproliferation and trigger a 'vicious cycle' of inflammation. IL-23 released by psoriatic keratinocytes and sentinel cells such as dendritic cells and macrophages, is critical for maintenance of Th17 function. Low levels of anti-inflammatory cytokines released by Th2 and Treg cells potentially counteract but cannot balance the effects of Th1/Th17 cytokines. Green arrows denote stimulatory actions, red blocking lines denote inhibitory actions.

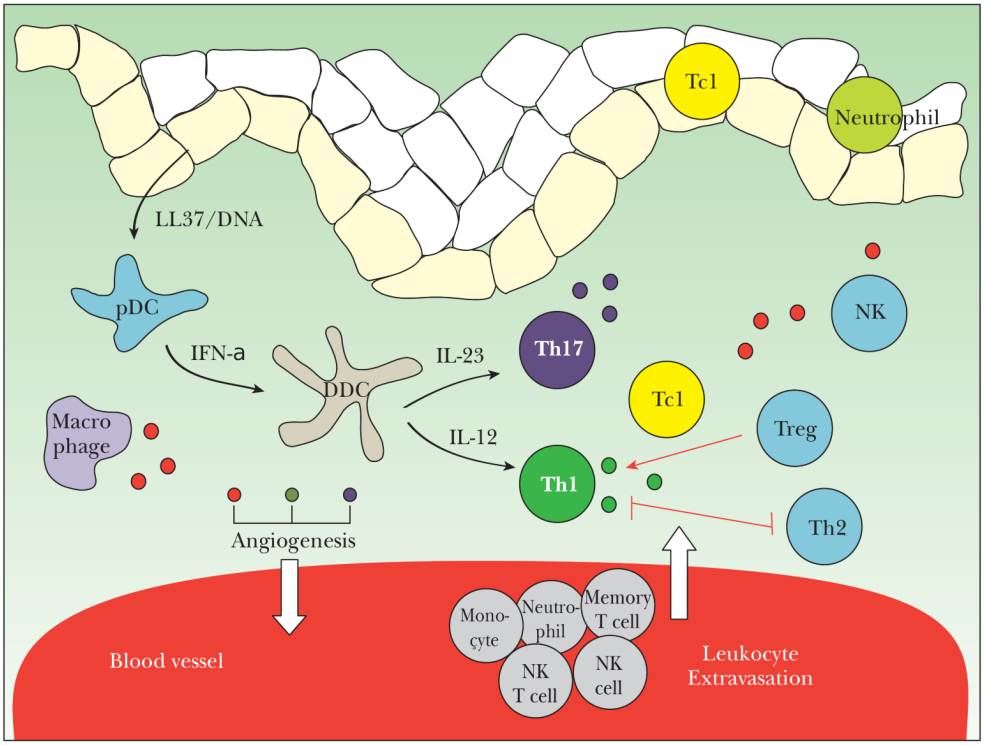

Figure 3.

Immune cell types and interactions implicated in psoriasis. Green dot denotes Th1 cytokines including IFNg and TNFa. Purple dot denotes cytokines produced by Th17 including IL17A, IL17F and IL22. Red dot denotes other inflammatory mediators such as IL-2 and IL-6. Low levels of anti-inflammatory cytokines released by Th2 and Treg cells potentially counteract but cannot balance the effects of Th1/Th17 cytokines. Th1 and Th2 cells have a mutually inhibitory effect as denoted by the red line. Treg inhibits Th1 actions as denoted by the red arrow.