Psoriasis: from pathogenesis to novel therapeutic approaches

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ABSTRACT

Psoriasis is one of the commonest chronic inflammatory disorders. Its cause is unknown, but a wealth of studies indicate that the disease results from a complex and dynamic interplay between genetic and environmental factors that trigger an excessive inflammatory response in the skin. Dendritic cells and effector T-cells are central in the development of the psoriatic lesion, and cytokines produced by these cells stimulate keratinocytes to proliferate and increase the migration of inflammatory cells into the skin, promoting epidermal hyperplasia and inflammation. Understanding the immunology of the psoriatic plaque has led to new therapeutic options and novel candidates for immunomodulation, and has changed the ways psoriatic patients are managed.

INTRODUCTION

Psoriasis is an immune-mediated skin disease that affects 1–3% of the population worldwide, with an equal sex distribution [1]. The common form of the disease, termed ‘plaque psoriasis vulgaris’, is observed in more than 80% of patients and is characterized by erythematous scaly plaques, typically on elbows, knees, scalp and buttocks (Figure 1A). Plaque size can vary from minimal to the involvement of the entire skin surface (erythrodermic psoriasis) [2]. Psoriasis causes a high degree of morbidity and decreased quality of life, largely due to clinical flare-ups and disfiguring lesions in visible areas of the skin, systemic manifestations and drug-related side effects.

Histological examination of psoriatic plaques reveals keratinocyte hyperproliferation with parakeratosis and elongation of rete ridges, increased angiogenesis and dermal infiltration of inflammatory cells, including T-cells, neutrophils, macrophages and DCs (dendritic cells) (Figure 1B). Psoriasis is probably a complex multifactorial disease, where various environmental triggers (e.g. trauma, stress, infections and drugs) promote, in genetically predisposed individuals, the activation of an exaggerated and poorly controlled immuno-inflammatory response in the skin, which leads to excessive keratinocyte proliferation.

GENETIC BACKGROUND

The incidence of psoriasis is greater in relatives of patients than among the general population [3,4], even though segregation analyses show no clear pattern of inheritance [5]. Disease concordance rates are much higher in...
Figure 1 Clinical presentation of severe plaque psoriasis (A) and histochemical staining of a plaque biopsy (B)

(A) Clinical presentation of a patient with severe plaque psoriasis, the commonest form of psoriasis. Multiple erythematosquamous sharply demarcated plaques are evident on the back and on extensory surface of the upper limbs. Obesity is commonly found in psoriatic patients. (B) Haematoxylin and eosin staining of a psoriasis plaque biopsy in which all key features are present: hyperproliferation and parakeratosis of the epidermis, neutrophil accumulation in stratum corneum, elongation of rete-ridges, vasodilation of venules and capillaries, and intense inflammatory infiltrates in the dermis.

Figures 2 and 3 show... (Figure 2).

INNATE IMMUNITY

DCs, the most potent APCs (antigen-presenting cells), are sentinels of the immune system. In normal skin, DCs are found in the epidermis (LCs (Langerhans cells)) and dermis (myeloid and plasmacytoid DCs) [18]. LCs reside in the suprabasal layers of the epidermis in close contact with keratinocytes. After activation, LCs up-regulate chemokine receptors on their surface and migrate to skin-draining lymph nodes, where they present antigenic peptides they have encountered in the skin to naïve T-cells [18–20]. Conflicting findings have been reported on the frequency of LCs in psoriasis. The mobilization of LCs into draining lymph nodes in response to stimuli that normally induce migration [e.g. chemical allergen, TNF (tumour necrosis factor)-α and IL-1β] is largely absent in psoriasis [21]. These findings raise the possibility that LCs retained within the epidermis present antigens locally and exacerbate the ongoing inflammatory reaction.

In the inflamed dermis of psoriatic patients, there is a marked increase in myeloid CD11c+ DCs. These cells, probably derived from circulating DC precursors, migrate into the skin in response to chemotactic signals and synthesize high levels of pro-inflammatory cytokines (e.g. IL-12 and IL-23) [18–20]. The dermal CD11c+ DCs which make TNF-α and iNOS (inducible nitric oxide synthase) (TIP-DCs) are thought to be the human equivalent of a similar DC subset which is needed for the clearance of some pathogens in mice [22]. There are also increased numbers of plasmacytoid DCs in psoriatic skin compared with normal skin. These express TLR (Toll-like receptor) 9 and produce large...
Both environmental triggers and genetic defects (e.g. LCE3B/LCE3C1), which alter the skin barrier, may contribute to the molecular events that, through the formation of self-DNA/RNA and LL37 complexes, lead to the synthesis of IFN-α by plasmacytoid DCs (pDC) and maturation of myeloid DCs (mDC) into mature DCs. Mature DCs in turn produce multiple cytokines that promote differentiation and expansion of Th1 (i.e. IL-12), Th17 (i.e. IL-6, TGF-β1 and IL-23) and Th22 (i.e. TNF-α and IL-6) cells. Both Th1 and Th17 cytokines induce keratinocytes to produce CCL20, a chemoattractant for CCR6-expressing DCs and T-cells, thus promoting the accumulation of these cells in the psoriatic skin. Th17-related cytokines stimulate DCs and proliferating keratinocytes to make IL-20, a cytokine that promotes keratinocyte proliferation. Keratinocytes produce inflammatory cytokines, such as IL-1β, IL-6 and TNF-α, thus contributing to enhance DC activation and expand the local inflammation.

Keratinocytes can be viewed as an integral part of the skin-resident immune system, because they may act as APCs, produce innate immune mediators, and contribute to the skin homing and local activation of immune cells. Keratinocytes express TLRs and respond to microbial stimuli by producing large amounts of cytokines (e.g. TNF-α, IL-1α, IL-6 and IL-18), chemotactic chemokines [e.g. IL-8 and CCL20 (CCL20)], and antimicrobial peptides [e.g. HBD (human β-defensin)-2, HBD-3, LL37] [19, 32, 33].

NK (natural killer)-T-cells, a subset of T-cells bearing typical NK cell markers (CD161+ and CD94+), but which typically utilize only a restricted range of T-cell receptors, play an immunoregulatory role in the recognition of self and foreign antigens and have been implicated in the pathogenesis of many autoimmune and inflammatory skin diseases.
inflammatory diseases. NK-T-cells generally recognize glycolipid antigens in the context of the MHC class I-like antigen-presenting molecule CD1d, which interestingly is overexpressed in the epidermis of psoriatic plaques [34]. They also rapidly secrete IFN-γ and IL-4 following activation [35]. Psoriatic keratinocytes can activate NK-T-cells, but their role in the pathogenesis of human psoriasis is still unclear [38]

Other cellular elements of innate immunity, which are increased in the lesional skin of psoriatic patients, include neutrophils, γδ T-cells and mast cells [34]. The role these cells play in the pathogenesis of psoriasis remains to be ascertained.

T-CELLS AS MEDIATORS OF SKIN INFLAMMATION IN PSORIASIS

In the skin, the vast majority of activated T-cells express CLA (cutaneous lymphocyte-associated antigen), a carbohydrate epitope of P-selectin glycoprotein 1, which guides T-cell skin homing [19]. The psoriatic plaque is characterized by a marked infiltration of activated CD4+ and CD8+ T-cells. CD4+ T-cells infiltrate mainly the dermis, whereas CD8+ T-cells are present in the epidermis [19]. The different anatomical distribution is in part dictated by a selective expression of integrins on T-cells. More than two-thirds of epidermal CD8+ T-cells (but not dermal T-cells) express CD103 (αEβ7), an integrin that binds to E-cadherin and facilitates migration of CD8+ T-cells to the epidermis [36]. Another checkpoint for entry of T-cells into the epidermis is the heterodimeric integrin α1β1 (also known as very late antigen 1), a receptor for collagen IV. Increased numbers of integrin α1β1-expressing T-cells are observed in the epidermis, but not dermis, of lesional skin of psoriatic patients. These cells exhibit the phenotype of effector memory T-cells [CD45RO+ and CCR (CC chemokine receptor) 7+] and produce IFN-γ [37,38], but some of these also produce IL-17, IL-21 and/or IL-22, three critical cytokines in the psoriatic plaque [45,46]. T-cells might also recognize PG (peptidoglycan) a component of streptococcal cell wall, and PG could interact with various receptors of innate immunity, including TLRs, NOD (nucleotide-binding oligomerization domain) 1 and NOD2 [48–50].

However, it is noteworthy to say that there may not be an autoantigen in psoriasis. The T-cells in lesions may be reacting to a group of antigens, or they are memory T-cells that are proliferating in response to cytokines in an antigen-independent manner.

Several other lines of evidence support a major role for T-cells in psoriasis. First, psoriasis improves in patients taking T-cell-targeting drugs (e.g., cyclosporine, or being given antibodies against CD3 or CD4), or following allogeneic bone marrow transplantation from psoriasis-free donors [51,52]. Psoriasis has arisen de novo in patients who underwent bone marrow transplantation from donors with psoriasis [53]. Secondly, compounds which block the recruitment of T-cells in the skin have been used with success in psoriatic patients [54]. Thirdly, the clinical benefit of PUVA (psoralen combined with UVA) therapy is in part due to the impairment of T-cell function [55]. Fourthly, psoriasis can be associated with other T-cell-mediated immune diseases, such as inflammatory bowel diseases and coeliac disease [56–58]. Fifthly, in vitro studies show that lesional skin-infiltrating CD4+ T-cells release factors that increase keratinocyte proliferation [59]. Finally, experimental findings from murine models of psoriasis indicate that T-cells are essential for the development of psoriatic-like skin changes [60]. In this context, major insights have been provided by studies in AGR129 mice, which are deficient in type I and type II IFN receptors and lack T- and B-cells (i.e. Rag-null mice). In this model, explants of uninvolved skin from psoriatic patients engrafted onto the skin of AGR129 mice became lesional after 4–5 weeks. A marked proliferation of the T-cells in the graft precedes the development of the psoriatic lesion [60]. In the human psoriasis xenograft mouse model, dermal T-cell infiltration precedes accumulation of T-cells in the epidermis, and histological features of psoriasis
plasmas only occur when T-cells accumulate in the epidermal compartment. In this model, blockade of integrin α1β1 inhibits the increase in numbers of epidermal T-cells and prevents development of psoriasis [60].

**THE CONTRIBUTION OF POLARIZED T-CELLS AND T-CELL-DERIVED CYTOKINES IN THE DEVELOPMENT OF THE PSORIATIC PLAQUE**

Th1 and Th2 are the best understood effector CD4+ T-cells formed during immune responses. Th1 cells produce IFN-γ and TNF-α, and mediate immune responses against intracellular bacteria, viruses and tumour cells [61,62]. Th2 cells make mostly IL-4, IL-5 and IL-13, and stimulate humoral responses against extracellular parasites [61,62]. Another subset of Th cells, termed Th17 cells, which are predominantly CD161-expressing cells [63], secrete IL-17A and IL-17F, and are involved in the activation of neutrophils and immunity to bacteria and fungi [64,65].

TGF-β1 (transforming growth factor-β1) concentration and the concomitant presence of at least one pro-inflammatory cytokine are key factors in human Th17 differentiation. In fact, low concentrations of TGF-β1 synergizes with pro-inflammatory cytokines, such as IL-1β, IL-6, IL-21 and IL-23 [66,67], to promote IL-23R expression, thus favouring the differentiation of naive cells into the Th17 effector lineage, whereas high levels of TGF-β1 and the absence of inflammatory cytokines would rather inhibit Th17 differentiation, shifting the balance toward regulatory T-cell development [66]. They are differentiated from naive T-cells following the stimulation by specific cytokines (TGF-β1, IL-6 and IL-23) [66,67].

These cells appear to lie at the very heart of the pathogenesis of psoriasis. Indeed, IL-17 produced by Th17 cells was shown to promote the production of IL-6, IL-8, GM-CSF (granulocyte/macrophage colony-stimulating factor) and ICAM-1 (intercellular adhesion molecule-1) in keratinocytes, synergizing with IFN-γ [68,69]. Th17 cell number is increased, together with that of Th22 and Th1 cells, in circulating blood of psoriatic patients [65], but in contrast with other potential Th17-type autoimmune diseases, such as coeliac disease [70], MS (multiple sclerosis) [71], systemic lupus erythematosus [72] and systemic sclerosis [73], no statistically significant differences in peripheral levels of IL-17A have been found in psoriatic patients when compared with that in controls [74].

This suggests that IL-17A production by Th17 cells only occurs in inflamed skin and not in circulating blood. They can also produce IL-21, IL-22 and IL-26 [75]. IL-21 acts on Th17 cells to amplify its own synthesis [76]. IL-21 also up-regulates IL-23R expression on T-cells, thus making Th17 cells responsive to IL-23 [76]. Altogether, these events generate a positive-feedback loop that helps amplify the Th17 lineage. More recently, it has been shown that the IL-22 expression profile may differ from that of IL-17A, and that IL-22-producing T-cells, termed Th22 cells, could represent a T-cell subset that is distinct from typical Th17 cells [77,78].

Traditionally, psoriasis has been classified as a Th1-associated disease, because T-cells infiltrating the lesional skin of psoriatic patients produce high levels of IFN-γ [79]. IL-12, the major Th1-inducing factor in humans, is also highly expressed (Figure 2) [80]. However, in the psoriatic plaque, there is also elevated synthesis of Th17-related cytokines, such as IL-17A, IL-17F, IL-21 and IL-22 (Figure 2) [40,41,81], as well as enhanced production of IL-23 [82], a heterodimeric cytokine composed of IL-23p19 and IL-12p40 subunits which amplifies Th17 cell responses [76] and causes psoriasis lesions when administered intradermally to mice [41]. A functional role of Th17 cells in psoriasis is suggested by the demonstration that both IL-21 and IL-22 induce keratinocyte hyperplasia [40,41] and that Th17 cytokine levels decrease during successful anti-TNF-α treatment [83]. IL-22 also triggers the production of antimicrobial peptides and expression of genes involved in epidermal differentiation and survival [84,85]. Studies in mice have shown that IL-22 induces keratinocyte hyperplasia and acanthosis, and that some biological effects of IL-22 are amplified by TNF-α, as a result of the ability of TNF-α to enhance IL-22 receptor expression [78,86–88].

Both Th1 and Th17 cytokines induce keratinocytes to produce CCL20, a chemoattractant for CCR6-expressing DCs and T-cells (Figure 2), thus providing a positive-feedback loop that sustains the accumulation of these cells in the psoriatic skin [89]. IL-17A and IL-22 are powerful inducers of IL-20 by DCs and proliferating keratinocytes [86] (Figure 2). IL-20 is highly produced in psoriasis, and its overexpression in transgenic mice causes epidermal thickening. Interestingly, the skin alterations in IL-20-transgenic mice occur without immune cell infiltration, suggesting that IL-20 is a downstream mediator in the psoriasis-associated immuno-inflammatory cascade [87].

Therefore the IL-23/Th17 pathway appears to be central in the pathogenesis of psoriasis, orchestrating both the induction and maintenance of skin inflammatory response by regulating the secretion of inflammatory cytokines and chemoattractants, and the proliferative response of psoriatic keratinocytes through the production of mitogenic cytokines (IL-22 and IL-21).

Naïve T-cells can also differentiate into a distinct subset of cells, termed Tregs (regulatory T-cells). Tregs express constitutively high levels of CD25 (the IL-2 receptor chain), the transcription factor FoxP3 (forkhead box P3) and the co-stimulation molecule CTLA-4 (cytotoxic T-lymphocyte antigen-4), and can suppress the activity of effector T-cells and promote resolution of inflammatory processes [76]. In psoriasis, blood
Efalizumab (anti-CD11a humanized antibody) inhibits the LFA1–ICAM-1 interaction therefore preventing full activation of T-cells by APCs and T-cell extravasation to inflamed tissues. Alefacept (an LFA3–IgG fusion protein) targets the CD2 molecule on the memory T-cell surface, inducing their killing by NK cells. Anti-TNF-α agents include two monoclonal antibodies (infliximab and adalimumab) that are able to bind and neutralize soluble TNF-α trimers. They also induce complement-mediated killing of cells expressing membrane TNF-α (not shown). Etanercept, a fusion protein composed of the extracellular domain of TNFR2 (TNF receptor 2) and the IgG Fc fragment, neutralizes soluble TNF-α trimers, but cannot induce lysis of TNF-α-expressing cells. Ustekinumab is an anti-IL12/23 monoclonal antibody targeting the p40 subunit shared by IL-12 and IL-23. Ustekinumab inhibits the differentiation of naive T-cells into pathogenic Th1 and Th17 cells.

Tregs exhibit a deficient regulatory activity, and effector T-cells appear to be resistant to their suppressive activity [90,91]. Taken together, these findings suggest that, in psoriasis, an altered balance between effector and counter-regulatory mechanisms can contribute to amplify the skin inflammatory immune response.

THERAPEUTIC APPROACHES IN PSORIASIS

Where do we stand?

Because of the wide range of clinical manifestations and the chronic nature of psoriasis, therapeutic approaches for these patients should be individualized taking into account the extent of skin lesions, the concomitant presence of arthritis and other co-morbidities, and triggering factors such as psychological stress or infections. In general, psoriasis can be treated with topical drugs (ointments, creams, lotions, foams and gels), phototherapy (UVB and PUVA) or conventional systemic therapy [92].

Patients with moderate-to-severe psoriasis (more than 10% of the body’s surface area) and/or associated psoriatic arthritis, and those who do not respond to topical agents and/or phototherapy are candidates for treatment with systemic agents, including methotrexate, cyclosporin, retinoids (e.g. acitretin) and fumarates, which can be prescribed as monotherapy, in combination or used sequentially even with biological agents [92]. Concomitant diseases (e.g. hypertension, impaired renal and/or liver function, infections, immunodeficiency and malignancies), breastfeeding and pregnancy are contraindications for these drugs. Since therapy with systemic agents can be complicated by severe side-effects, their use requires an accurate selection and monitoring of patients [92].

In the last decade, biological agents targeting molecules involved in the pathogenesis of psoriatic plaques has changed the management of patients (Figure 3). Five agents (i.e. infliximab, adalimumab, etanercept, ustekinumab, and alefacept) have been approved for psoriasis [93–96] (Figure 3). Efalizumab, a humanized
monoclonal antibody directed against the α subunit (CD11a) of LFA (lymphocyte function-associated antigen)-1 present on the T-cell surface (Figure 3), has recently been removed from the market because it has been associated with progressive multifocal leucoencephalopathy [97,98]. Infliximab is a chimeric monoclonal antibody that blocks TNF-α. Multicentre double-blind placebo-controlled phase III studies show the high efficacy and long-term disease-free maintenance of infliximab therapy [99]. Maintenance of the clinical response is more common in patients who do not develop infliximab antibodies [99]. Adalimumab, a fully-humanized monoclonal antibody that binds TNF-α and has long-term efficacy as a monotherapy in the treatment of moderate-to-severe psoriasis [99,100]. Etanercept is a human recombinant TNF receptor p75 protein that binds to TNF-α and lymphotoxin. It is administered subcutaneously, and is effective in the treatment of moderate-to-severe psoriatic plaques and psoriatic arthritis [99,101]. Although results emerging from clinical trials with these three compounds confirm the pathogenic relevance of TNF-α in psoriasis, it is highly likely that the therapeutic benefit of TNF inhibitors is due not only to the blockade of the soluble cytokine, but also to the neutralization of membrane-bound TNF-α. Indeed, both infliximab and adalimumab can bind pro-TNF on the cell surface and TNF in its receptor-bound forms, thus delivering pro-apoptotic signals to targeted cells [99,101]. In addition, based on recent findings on the synergistic activity of Th17-derived cytokines (e.g. IL-17A, IL-22 and IL-21) and TNF-α in the activation of psoriasis-specific inflammatory genes, we can hypothesize that anti-TNF-α may also act on the central IL-23–Th17 axis [77].

Ustekinumab is a fully human monoclonal antibody that targets the p40 subunit of IL-12/IL-23 and prevents the interaction of both IL-12 and IL-23 with the common receptor subunit IL-12Rβ1 (IL-12 receptor β1) [102]. Multicentre randomized double-blind placebo-controlled phase III studies have shown that psoriatic patients receiving this agent experienced sustained clinical responses. Moreover, treatment was effective for at least 1 year when ustekinumab was administered every 12 weeks [103,104]. The long-lasting effect of this drug may be explained considering the fact that IL-23 acts upstream in the pathogenesis of psoriasis. A single ustekinumab injection may hamper the generation/polarization of T-cells to Th17 cells, a step that requires more time to be reactivated than the production of a cytokine from an already differentiated cell. Ustekinumab is also effective in psoriatic arthritis [105].

Alefacept is a fully human LFA3–IgG1 fusion protein that targets CD2 and inhibits T-cell activation and proliferation. Alefacept also promotes apoptosis of memory T-cells. Overall the available findings indicate that only a small portion of patients exhibit a partial clinical response after a single cycle of therapy, whereas multiple courses of treatment would appear to be more effective, particularly if alefacept is given in combination with other therapies such as topical agents, methotrexate, cyclosporine, systemic retinoids or UVB [106]. For a detailed description of the indications, therapeutic benefits and side-effects of biological agents, the reader is directed towards excellent reviews [92,107,108].

Where next?

The rapid advancement of molecular techniques, hard and obvious clinical end points objectively visualized and the relative ease of access to diseased skin have led to a better knowledge of factors that orchestrate the tissue-directed immune response in psoriasis. The near future should witness the use of novel therapeutic strategies to attenuate inflammation and to halt the progression of the tissue damage and loss of function associated with psoriasis, and hopefully improve co-morbidities associated with psoriasis. Blockade of cytokine synthesis and/or activity will probably be at the forefront of this new era, given the therapeutic success observed with inhibitors of TNF-α and IL-12/IL-23 (Figure 3). Golimumab, a new anti-(human TNF-α) antibody, has already been used with success in patients with psoriatic arthritis [109], whereas no results have been reported on the efficacy of certolizumab, another TNF-α blocker that is effective in other immune-mediated diseases, such as Crohn’s disease and rheumatoid arthritis [110,111]. A double-blind placebo-controlled trial has shown that ABT-874, a monoclonal antibody directed against p40, is effective in patients with moderate-to-severe plaque psoriasis, thus confirming the pathogenic role of IL-12/IL-23 in this disease [112]. However, unlike ustekinumab, ABT-874 treatment appears to associate with a higher percentage of adverse events, which are most commonly related to reactions at the injection site (erythema, pruritus and irritation), but also include nasopharyngitis, upper respiratory tract infections, bronchitis and viral infections [112]. Th17 cells will be targeted by AIN-457, an IL-17-specific monoclonal antibody and by AMG-827, a fully human monoclonal antibody blocking signalling via IL-17R (IL-17 receptor). IL-21 and IL-22 inhibitors could also be very promising options in the treatment of psoriasis, as pre-clinical studies have shown the pro-inflammatory role of these two cytokines in the skin [39,77,78]. A novel compound, termed CP-690550, which has been developed to selectively inhibit JAK3 (Janus kinase 3)/STAT (signal transducer and activator of transcription) signalling in immune cells, appears to be therapeutically useful in patients with psoriasis [113]. Anti-inflammatory cytokines (e.g. IL-10 and IL-4), anti-VEGF (vascular endothelial growth factor), inhibitors of PKC (protein kinase C) isoforms and MAPKs (mitogen-activated protein kinases), and blockers of activation and migration of T-cells to the inflamed skin could
represent additional options for dampening the psoriasis-associated immuno-inflammatory response. In designing such therapeutic interventions it would be, however, necessary to take into account not only the advantageous effects of these novel therapies, but also the potential risk of severe side effects, because many of the above pathways play an important role in inducing and sustaining immunity against pathogens and tumours.

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