Psoriasis: Targets and Therapy

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REVIEW

Current knowledge on psoriasis and autoimmune diseases

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Abstract: Psoriasis is a prevalent, chronic inflammatory disease of the skin, mediated by crosstalk between epidermal keratinocytes, dermal vascular cells, and immunocytes such as antigen presenting cells (APCs) and T cells. Exclusive cellular "responsibility" for the induction and maintenance of psoriatic plaques has not been clearly defined. Increased proliferation of keratinocytes and endothelial cells in conjunction with APC/T cell/monocyte/macrophage inflammation leads to the distinct epidermal and vascular hyperplasia that is characteristic of lesional psoriatic skin. Despite the identification of numerous susceptibility loci, no single genetic determinant has been identified as responsible for the induction of psoriasis. Thus, numerous other triggers of disease, such as environmental, microbial and complex cellular interactions must also be considered as participants in the development of this multifactorial disease. Recent advances in therapeutics, especially systemic so-called "biologics" have provided new hope for identifying the critical cellular targets that drive psoriasis pathogenesis. Recent recognition of the numerous co-morbidities and other autoimmune disorders associated with psoriasis, including inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus suggest common signaling elements and cellular mediators may direct disease pathogenesis. In this review, we discuss common cellular pathways and participants that mediate psoriasis and other autoimmune disorders that share these cellular signaling pathways.

Keywords: psoriasis, autoimmunity, immunosuppression

Introduction

Psoriasis is a prevalent, chronic inflammatory skin disease that affects approximately 0.5%–1% of children and 2%–3% of the world's population.[1] Psoriasis is a bi-modally distributed disease with one major age of onset at 20–30 years of age as well as a later smaller peak of onset at 50–60 years.[2,3] Even though psoriasis etiology remains unknown, it is believed to be multifactorial with numerous key components including genetic susceptibility, environmental triggers in combination with skin barrier disruption and immune dysfunction.[4] There are five subtypes of psoriasis: vulgaris (plaque), guttate, pustular, inverse, and erythrodermic. The most common variation of psoriasis is plaque psoriasis, which affects approximately 85%–90% of psoriatic patients.[5]

Psoriasis confers significant physical and psychological distress and impairment usually resulting in a detrimental impact on patient quality of life.[6,7] Psoriasis patients often express feeling shame and guilt and are stigmatized by the disease.[8] Psoriasis has been reported to affect the interpersonal relationships of patients as well as impacting sexual well-being and capacity for intimacy.[9,10] In the work place, psoriasis has a negative social impact which may manifest as discrimination and difficulty finding

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employment. Nearly 60% of employed psoriasis patients reported lost time from work in the previous year due to psoriasis.[11]

Complications arising from psoriasis lead to numerous deaths in the United States annually.[12] Perhaps the most detrimental aspect of psoriasis is the concurrent physical comorbidities such as cardiovascular disease (CVD), obesity, diabetes, metabolic syndrome, inflammatory bowel disease (IBD), and psoriatic arthritis that contribute to decreased longevity.[13–16]

Skin phenotype and histology of psoriasis

Phenotype

Plaque psoriasis is the most common presentation of the disease. It is phenotypically characterized by red, scaly, well-defined, silvery-white, dry plaques that preferentially appear on elbows, knees, scalp, and the lumbar area. The often symmetrical plaques can be erythematous and are often categorized by patients as itching intensely. Severity of the plaques is quantified by two major scoring systems; the psoriasis area and severity index (PASI) and the physician's global assessment (PGA). The PASI scale allows quantification of the extent of disease as a measure of area and intensity (erythema, induration, desquamation, and body surface area). Given the complicated nature of the PASI calculation, the PGA was introduced as an alternative assessment measure. The PGA calculates either a static or dynamic global assessment of lesion severity.[17] Interestingly, and a key feature of chronic plaque psoriasis, is the normal appearing "uninvolved" skin immediately adjacent to psoriatic plaques of affected individuals. Several recent studies have demonstrated that uninvolved tissue may contain a unique signature of genes, that when activated may account for the conversion of uninvolved skin to involved plaque. However, given the myriad cell types known to participate in this conversion, isolation of a single triggering factor is unlikely (Figure 1).

Histological manifestation

Plaque psoriasis is characterized by pronounced keratinocyte and dermal vascular endothelial cell proliferation followed

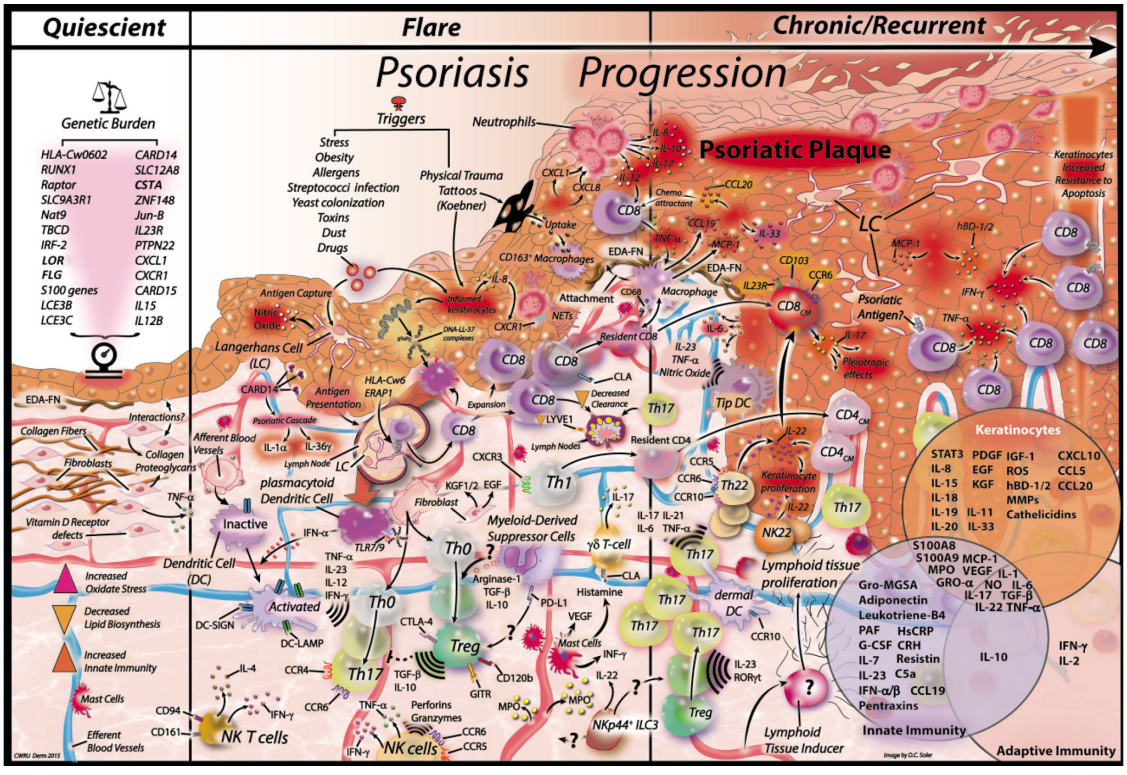

Figure 1 Key signals in psoriasis development.

Notes: Numerous cellular mediators and signaling pathways are activated in psoriatic lesions following diverse triggers. In the background of individuals expressing a favorable genetic predisposition toward a hyperactive immune response (quiescent panel), these mediators drive a proinflammatory response (flare panel). The proinflammatory state progressively overwhelms the immune counter-balancing mechanisms, and skin proliferation becomes uncontrollable by conventional regulatory cells and suppressive mediators (eg, Treg, IL-10, TGFβ; Chronic/recurrent panel). This exacerbated inflammation results in the progressive creation of resident memory self-reactive cells that in-turn contribute to recruiting inflammatory mediators that result in a life-long recurrent chronic inflammatory skin disease.

Abbreviations: CD8 CM, CD8 central memory; Treg, regulatory T cell; NK, natural killer; Th, T helper; TipDC, TNF-iNOS-producing DC; NETs, neutrophil extracellular traps.

by an inflammatory response. The classical histological manifestation includes marked epidermal thickening (acanthosis) due to keratinocytes' accelerated movement through the epidermis, thickening of stratum corneum (hyperkeratosis), retention of nuclei in upper layers of the skin which causes squamous cell layer thickening (parakeratosis), elongation of epidermal rete ridges, increase in the number and size of dermal blood vessels and an increased inflammatory cell infiltrate consisting mostly of neutrophils in the stratum corneum and epidermis (Munro's microabscesses and Kogoj pustules), significant mononuclear infiltrates in the epidermis as well as leukocyte infiltration (mostly T cells and dendritic cells [DCs]) into the dermis.

Potential causes/triggers of psoriasis

Genes

Genetics studies have shown that psoriasis patients have diverse gene polymorphisms related to immune and skin barrier function.[18] Analyses of psoriasis incidence demonstrated 70% probability of monozygotic twins to be affected by psoriasis and 20% probability in dizygotic twins.[19] Pedigree studies have shown that children have a 20% chance of developing psoriasis if one parent is affected and 65% if both parents are affected. More than 30 single nucleotide polymorphisms (SNPs) have been associated to contribute to psoriasis risk but only two gene mutations have been found to independently induce psoriasis (*IL36RN* and *CARD14*) by affecting both the skin and immune system.[20]

PSORS1

The first associated psoriasis susceptibility (PSORS) locus was PSORS1 on chromosome 6p21. This region has been shown to have the greatest impact on psoriasis heritability but the identity of its gene is controversial. PSORS1 is located within the major histocompatibility complex class 1 region with a consensus of HLA-C being the most likely PSORS1 gene.[21] HLA-haplotypes that have been described as over-represented in psoriasis patients are encoded within this susceptible locus, including HLACw6, the most popular and strongest disease loci associated haplotype.[22] More than 60% of psoriatic individuals carry the HLA-Cw0602 allele, which confers a 20-fold increased risk of developing psoriasis.[23] However, even when there is a strong genetic association, the exact role of HLA-C and HLA-Cw6 in psoriasis development remains uncertain. Furthermore, HLA-C accounts for only 50% of the familial clustering observed in psoriasis.

PSORS2/CARD14 mutations

Genome-wide linkage scans and family association mapping identified PSORS2 on chromosome 17q25.[24,25] Recently, next generation sequencing of patients with familial psoriasis found a gain-of-function mutation in CARD14 on this locus.[26,27] Furthermore, several missense CARD14 mutations were found among psoriatic individuals[26] as well as 2.7-fold increase of CARD14 mRNA in psoriasis transcriptome[27] and CARD14 SNP.[28] CARD14 mutations may cause psoriasis through increased induction of NF-kβ, which leads to enhanced expression of key psoriatic chemokines including CCL20, CXCL8/IL-8, and IL-36γ/IL-1F9.[20] However, an additional environmental trigger is also suspected to be necessary to initiate the psoriatic cascade[27] (Figure 1).

IL36RN mutations

IL36RN, also known as *IL-1F5,* encodes for the anti-inflammatory protein IL-36Ra (IL-1F9), a natural IL36R antagonist. IL-36 family members have been demonstrated to be highly upregulated in psoriasis.[29,30] The three IL-36 stimulating cytokines (IL-36α, IL-36β, and IL-36γ) belong to the IL-1 family, and they bind to IL-36R and activating NF-kβ. Mutations in IL-36Ra lead to loss of active protein which results in unrestrained proinflammatory effects of the IL-36 stimulating cytokines. Absence of IL-36Ra then leads to excessive neutrophil accumulation as observed in pustular psoriasis.[31] In the case of psoriasis vulgaris, IL-36Ra has been shown to be abundant, which may possibly attenuate agonist activity.[29,31]

SNPs

SNPs are substitutions of one base pair for another in more than 1% of the population.[32] SNPs are usually found in non-coding regions of the genome.[32] Using high-throughput technologies and statistical methods, large genome-wide association studies (GWAS) have compared the frequencies of hundreds of thousands different SNPs in psoriasis patients and healthy control individuals.[33] GWAS had identified significant SNPs in psoriasis, several of which are associated with the IL-23/IL-17 axis.[33] A recent publication identified an SNP in the *IL23* locus that may have functional importance because of its IL-17 response gradient to T cell stimulation by IL-23 in control and psoriasis patients.[34] Furthermore, a recent meta-GWAS analysis confirmed 21 SNPs and identified 15 new SNPs in psoriasis patients and controls.[28] These SNPs were associated with numerous immunological processes implicated in psoriasis pathogenesis including keratinocyte differentiation, T cell and natural killer (NK) cell proliferation,

cytokine responses, JAK-STAT cascade, T helper (Th)1 and Th17 cell regulation and leukocyte adhesion.[28]

Environmental triggers of psoriasis

Several environmental factors including physical trauma, drug reactivity, infection as well as modifiable variables such as psychological stress, obesity, smoking, and alcohol have been associated with a predisposition toward psoriasis development and exacerbation of the disease.

Physical trauma

Heinrich Koebner first described physical trauma as a trigger and exacerbating factor for psoriasis in 1872.[35] He observed the development of psoriatic lesions after a direct cutaneous injury, such as excoriation, tattoos, burns, and animal or insect bites, in previously normal-appearing skin (Figure 1, "Flare"). The new psoriatic lesion was characterized morphologically as identical to the injury site, known as an isomorphic response. The Koebner response has been observed with other dermal diseases such as vitiligo and lichen planus, but the frequency for its manifestation is higher among psoriasis patients. The prevalence of Koebner response in psoriasis patients ranges from 24%–51%.[36]

Psoriasis onset following an injury may take anywhere from 3 days to 2 years to develop, and may be dependent on seasonal variation (more frequently in winter) as well as disease severity (pre-existing and stability of psoriasis).[37,38]

Drug-induced psoriasis

Several medications have been associated with psoriasis onset as well as exacerbation of disease. The most commonly reported drugs to trigger psoriasis are lithium, beta-blockers, anti-malarials, tetracyclines, and non-steroidal anti-inflammatory medications.[39–42] In recent years, TNFα blockers, IL-6R blockers, and medications against IFNs (alpha, beta, gamma) as well as the TLR7 agonist imiquimod, have all been reported to induce or exacerbate psoriasis.[43–49]

Other reported medications that exacerbate psoriasis include ACE inhibitors, calcium channel blockers, and IL-2 among others.[50–52]

Infections

Considerable data suggest that infections are an important trigger for psoriasis, especially among children. Guttate psoriasis has been associated with *Streptococcus pyogenes* infection through both pharyngeal and skin routes.[53–55] A recent publication reports that streptococcal throat infections can trigger psoriasis onset and exacerbate chronic psoriasis. Additionally, patients with psoriasis are more prone to develop sore throats than non-psoriatic patients. Furthermore, *Staphylococcus aureus, Malassezia and Candida albicans* colonization in the gut and/or skin have also been linked to psoriasis exacerbation.[56–58] In addition, several researchers have observed an association between disease severity as measured by PASI with status regarding infection with *Helicobacter pylori*.[59–61] Given the relationship of these infections and psoriasis, the exotoxins of these microorganisms as well as peptidoglycans derived from bacterial sources have been reported as possible candidates for activating T cells and leading to psoriasis development through an abnormal immunological response.[62–65]

Stress

Psychological stress is known to aggravate psoriasis by altering the immune system. Numerous authors have suggested that increases in stress hormone levels due to activation of the hypothalamus–pituitary–adrenal axis may cause psoriasis exacerbation.[66–69] Corticotrophin-release hormone (CRH) is a central component of the hypothalamus–pituitary–adrenal axis that is important in the coordination of systemic stress responses as well as modulation of inflammatory response. Cutaneous CRH and CRH-receptor 1 have been shown to regulate local homeostasis in the skin and in psoriasis, expression of CRH is significantly increased.[70] Currently, the proinflammatory effects of CRH on skin are not clear, CRH may stimulate production of IL-6 or IL-11 in keratinocytes during cutaneous stress, therefore, it is possible that CRH is acting on keratinocytes to further exacerbate psoriasis.[71]

Alcohol and smoking

The association between alcohol consumption and psoriasis is complex and controversial. Studies indicate that the prevalence of psoriasis among patients who abuse alcohol is increased. Furthermore, a recent meta-analysis of case control studies showed that alcohol consumption is associated with increased risk of psoriasis. Epidemiological studies suggest that patients with moderate to severe psoriasis have an increased incidence of alcohol-related diseases and mortality.[72–74] The mechanism(s) by which alcohol consumption might trigger psoriasis remain unknown. However, in vitro studies have shown that 0.05% ethanol can activate T cells and induce keratinocyte hyperproliferation by directly stimulating TGFα, IL-6, and IFNα production. Furthermore, ethanol and acetone have been demonstrated to upregulate mRNA expression of ITGA5, cyclinD1, and keratinocyte growth factor

receptor leading to non-tumorigenic human keratinocytes to proliferate in vitro.[75]

Previous reports have shown a strong correlation between smoking and risk of psoriasis. One study indicates that this risk is higher among women than men, while another study showed that the risk for developing psoriasis is higher in former and current smokers than in those individuals who have never smoked.[76,77]

Genetic susceptibility to psoriasis has been linked to smoking. Based on a recent study, smokers with HLA-Cw6 haplotype have an 11-fold increased risk of developing psoriasis compared to non-smokers without the HLA-Cw6 haplotype.[78] A separate study demonstrated that SNP genetic variants in the genome-wide psoriasis-associated loci *CSMD1* and *TNIP/ANXA6* increase the risk for psoriasis when combined with smoking and alcohol use.[79]

Obesity

Obesity has been shown to be a risk factor for psoriasis. Correlation between obesity and psoriasis severity has been observed although the mechanism by which obesity promotes psoriasis is not well understood.[80,81] It is possible that the mechanism involves the adipocyte-derived cytokines, leptin and resistin. Previous publications have reported that leptin and resistin are found in high concentrations in psoriasis patients.[82,83] Furthermore, these adipokines can induce monocytes to produce proinflammatory cytokines including IL-8, TNFα, and IL-1β. Using an ex vivo organotypic culture system these investigators reported that exogenous addition of leptin induced psoriatic skin to produce AREG, an EGF family member that has been shown to cause keratinocyte proliferation in vitro and to promote inflammatory hyperplasia in transgenic mice that overexpress dermal leptin. Interestingly, psoriasis improvement after bypass surgery has been observed, however, worsening of psoriasis after weight loss as well as weight-loss surgery has also been observed.[84–86] Therefore, more studies are needed to improve our understanding of the effect of obesity and weight loss on psoriasis.

Microbiota in psoriasis

Given that the skin acts as a barrier that is also in contact with the outside environment, it is colonized by different microorganisms including bacteria, fungi, viruses, and mites.[87–89] An estimated 1 million different bacterial species inhabit one square centimeter of skin.[90] Several factors including age, genetics, immune reactivity, climate, and hygiene influence the composition of the microbiota communities of the skin. Also, differences in skin thickness, density of hair follicles and skin invaginations cause different habitats with differential microbiota composition. Under healthy conditions, symbiotic relationships develop that permit skin protection against invasion by more pathogenic and harmful microorganisms to the host as well as by educating and priming resident T cells.[91] Therefore, alterations in microbial communities of the skin have been associated with disease.

Using 16S-based genomic sequencing, differences in the composition of the bacterial[92,93] and fungal[94,95] communities in lesional and non-lesional psoriatic skin have been observed.

Psoriatic lesional skin has been shown to have increased bacterial diversity including increased *S. pyogenes*[93] and *S. aureus*[96] when compared to healthy and non-lesional skin. Three studies on skin microbiome in psoriasis, one using biopsies[92] and the other two using swabs[93,97] have been performed. *Streptococcus* was the most common species found in biopsies,[92] while the most common bacterial species detected using swabs were *Corynebacteria*.[93,97] As previously stated, tonsil infections have been shown to be a possible trigger for psoriasis development. A study performed by Diluvio et al comparing T cell receptor (TCR) β-chain rearrangements in psoriatic skin lesions, blood, tonsils, and tonsillar T cells fractions showed that psoriatic lesions were dominated by clonal T cell expansions, which might be the link between *Streptococcus* tonsillitis and inflammation in psoriasis.[98] The authors suggest that *S. pyogenes* infections prime and select tonsillar T cells to migrate into the skin, where they are reactivated and expand promoting psoriatic skin lesion formations.[98] This mechanism was supported by long-term remission of psoriatic skin inflammation for more than 3 years after tonsillectomy.[98] However, this study was performed using a small number of patients (n=3), therefore the significance of the findings needs further evaluation.

Fungal composition differences have also been shown in psoriasis. Several studies suggest the *Malassezia* yeasts as possible triggers for elicitation,[99–102] as well as for exacerbation of psoriatic plaques.[103–106] Furthermore, several studies have shown improvement of scalp psoriasis after antifungal agent ketoconazole treatment.[101,107,108] Given that *Malassezia* yeasts are part of the healthy human cutaneous flora, it is important to determine what causes them to become aggravators of psoriasis.

Another commensal yeast species that has been associated with psoriasis is *Candida* spp. Significantly higher prevalence of *Candida* spp. colonization in both the oral cavity,[109,110] as well as in lesional skin[109] on psoriasis patients have been

described. Furthermore, super-antigens and toxins released from *Candida* spp. have been associated with exacerbation of psoriasis by activating T cells and keratinocytes cytokines secretion.[111] The most common *Candida* spp. found in oral cavity and psoriatic lesional skin is *C. albicans.*[109] *C. albicans* is one of the most common commensal yeasts and it is the most prevalent to cause different diseases under predisposing conditions.[112]

Even when microbiota has been shown to be differential between psoriasis and homeostasis, an association between microbiome and psoriasis has yet to be established. Furthermore, recent studies have shown that skin microbiota varies in dry, moist and sebaceous sites but how this variation might affect psoriasis development remains unknown.[91]

Cellular participants in psoriasis

The skin is a dynamic organ that serves as a front line defense against insults, injuries, and microbial pathogens. Given its constant exposure to the environment, immune surveillance and immune tolerance are key roles of the skin. The skin consists of the epidermis, dermis, and adipose tissue or subcutis layers. The epidermis is mainly composed of keratinocytes and Langerhans cells (LCs).[20]

Keratinocytes

Keratinocytes are the main components of the epidermis, where they maintain a mechanical barrier and participate in the initiation and maintenance of the skin's immune response. Keratinocytes interact with immune cells during the development of psoriasis. Psoriatic skin is characterized by increased proliferation and abnormal differentiation of keratinocytes.[3] In psoriasis, keratinocyte differentiation is incomplete and keratinocyte stem cell proliferation pathways are dysregulated, causing preferential activation and proliferation of rapidly matured cells with reduced lipids and keratohyalin granules.[3]

Neutrophils

Neutrophils or polymorphonuclear leukocytes are the most abundant circulating leukocytes in humans.[113] Cellular infiltration in psoriasis includes neutrophils from dermal papillae towards the epidermis and accumulation of neutrophils in the stratum corneum (Munro microabscesses).[114] Neutrophils are attracted to the skin by an array of chemotactic factors including IL-8, gro-MGSA, complement product C5a, leukotriene B4 and platelet activating factor.[115–117] Stimulation of neutrophils by GM-CSF[118,119] results in rapid upregulation of surface integrin CD11b/CD18 which causes extravasation and localization via ICAM1 expressing activated epidermal keratinocytes.[120]

A previous publication described rapid improvement of long-standing psoriasis during agranulocytosis wherein, after blood neutrophil recovery, psoriatic plaques reappear.[114] Therefore, blood neutrophil counts and agranulocytosis may be correlated with psoriasis activity, which might indicate a requirement for neutrophils in psoriatic plaques development.

Furthermore, the "flaky skin" psoriasis mouse model (fsn/fsn) exhibits prominent neutrophil infiltration and microabscesses within a hyperproliferative epidermis. In this model, neutrophil depletion caused dramatic reduction of epidermal thickening, neutrophil infiltration into the skin, down regulation of TNFα and IL-1β as well as elimination of microabscesses.[121]

Moreover, neutrophils can produce extracellular traps, which are composed of DNA and antimicrobial peptides.[122] Their physiological function is to kill invading microorganisms while preventing tissue damage.[122] These neutrophil extracellular traps are induced by IL-23 and IL-1β and during their formation neutrophils release IL-17, a major cytokine associated with psoriasis development.[123] This is particularly important because although IL-17 production by T cells is widely studied, appreciation of innate immune cells producing IL-17 is a fairly new area of research, which requires further studies.

Mast cells

Early psoriatic skin lesion has been reported to typically include degranulated mast cells.[124,125] The number of mast cells[126–129] as well as histamine concentration[130,131] are increased in psoriatic skin. A particular subset of mast cells, tryptase and chymase producers (MC_{TC}s), have been shown to be enriched in the papillary dermis of psoriatic skin.[127,132] Mast cells have been termed "ghost cells" in early psoriasis lesions because they are frequently activated and degranulated. Furthermore, approximately 70% of mast cells in psoriatic skin are IFNγ positive, which suggests an important role for triggering psoriasis.[132]

In an early study, initial phases of psoriasis triggered by Koebner phenomenon showed that mast cells were significantly increased at day 4 when compared to control skin. Mast cells' increased peak was at day 14 which was simultaneous with the manifestation of psoriasis.[133] Also, mast cells' numbers decrease in psoriasis lesions after successful therapy with anthralin, psoralen plus UVA light therapy and cyclosporine.[129,134,135]

A recent article demonstrated that mast cells and neutrophils increased number in psoriasis contribute to the release of IL-17 through the formation of extracellular traps, which may be triggered by IL-23 and IL-1β.[123] More recently, mast cells have been shown to be major producers of IL-22 in psoriasis and atomic dermatitis.[136] Therefore, innate immune cells' release of IL-17 is a new and exciting topic that needs further evaluation for determining how it may be triggering psoriasis.

DCs

DCs are antigen presenting cells (APCs) crucial for efficient T and B cell activation. In the skin, there are three main DC populations: epidermal LCs, resident dermal myeloid DCs (mDCs), and plasmacytoid DCs (pDCs). During inflammation, a fourth population, inflammatory DCs, can be observed.[137]

In psoriasis, an overall increase in DCs has been reported in the epidermis and dermis.[138,139] High numbers of pDCs, immature as well as mature DCs, iNOS- and TNF-producing DCs (TipDCs), and inflammatory epidermal DCs have been observed in psoriatic lesional skin.[140]

LCs

LCs are resident conventional DCs present in the suprabasal layers of the epidermis, in close contact with keratinocytes.[137] Activation of LCs (eg, antigen acquisition) causes their migration out of the epidermis toward draining lymph nodes where T cell activation can be initiated[20] (Figure 1). LCs represent approximately 3% of the epidermal cells[141] and are characterized by expression of CD207, CD1a, e-cadherin, and EpCAM.[137] It was recently shown that LCs have two subtypes, short-term and long-term LCs, which are present in the steady state and during inflammation, respectively.[142]

The functional role of LCs in psoriasis is not fully understood. Previous studies have shown LC reduction in psoriatic skin, which can be restored to normal levels after therapy.[143]

A recent publication demonstrated that LCs are reduced in lesional psoriatic skin of patients as well as in the skin of the KRT5 specific deletion of Jun and JunB (DKO) psoriatic mouse model.[144] LC depletion can aggravate psoriatic-like inflammation in DKO mice in an IL-10 and PD-L1 dependent manner.[144]

pDCs

pDCs account for less than 0.1% of PBMCs; however, they are the primary source of IFNα.[145] In contrast to other DC subsets, pDCs do not express TLRs 2–5 on their surface; instead they uniquely express endosomal TLR7 and TLR9, which respond to their respective ligands single stranded RNA and unmethylated CpG.[146] Hence, IFNα secretion in response to in vivo CpG changes has been shown to be exclusively mediated by pDCs.[145] This is particularly important because CpG methylation has been demonstrated to change in psoriatic involved skin.[147]

pDCs have been shown to be highly expressed within lesional psoriatic tissue[148] and their presence in non-lesional skin has also been reported by some investigators,[148] but not observed by others.[144] Blockade of IFN production by pDCs has been shown to inhibit psoriatic lesional development in a xenograft skin mouse model.[148] Furthermore, it was found that pDCs were necessary for the initiation of psoriatic disease in the DKO psoriatic-like inflammation mouse model but not for the sustainability of their chronic inflammation.[144]

In psoriasis, keratinocytes produce elevated levels of the antimicrobial peptide LL-37, which forms complexes with self-DNA/RNA released by stressed/damaged cells. This causes activation of pDCs in a TLR7 and 9 dependent manner.[149] Also, pDC activation causes release of IFNα which in combination with IL-1β, IL-6, and TNFα are thought to activate conventional DCs (cDCs) causing their migration to cutaneous lymph nodes where they can prime Th17 and Th22 differentiation[149] (Figure 1).

mDCs

Although pDCs are believed to be initiators of psoriatic skin development, myeloid DCs (mDC) are thought to have an important role in the maintenance and amplification of psoriasis.[150]

The first report of mDCs in psoriasis demonstrated that dermal DCs derived from lesional skin could stimulate T cell responses by producing IL-2 and IFNγ, thereby contributing to Th1-type responses.[151]

Dermal mDCs are identified by CD11c expression.[152] Skin inflammation in psoriasis causes a 30-fold increase in $CD11c^+$ DCs in the dermis, which is nearly equivalent to the number of lesional T cells.[137]

Two populations of mDCs have been identified: classical resident mDCs ($CD11c^+$ $BDCA\text{-}1^+$) and inflammatory mDCs ($CD11c^+$ $BDCA\text{-}1^{neg}$). BDCA or CD-1c is part of the major histocompatibility complex that participates in lipid antigen presentation to T cells;[153] the absence of BDCA expression is the current phenotype for classifying inflammatory mDCs.

$CD11c^+$ BDCA-DCs are present in high numbers in psoriatic lesional skin[154] and include TipDCs[138] as well

as IL-20- and IL-23-producing DCs.[150] TipDCs appear to be important in the pathogenesis of psoriasis (Figure 1); rapid down-modulation of the TipDC products TNF, iNOS, IL-20, and IL-23 are observed after effective TNF-blocking therapy.[155] Furthermore, TipDCs are immunostimulatory and capable of Th17 polarization[154] as well as IL-12p40, IL-23p19, and IL-20 production in psoriatic skin.[156] A recent publication proposed that mDCs expressing 6-sulfo-LacNac (Slan DC) are the inflammatory DCs' precursors in psoriasis capable of driving Th1 and Th17 responses.[157]

T cells

Teff and memory cells

One of the known characteristics of psoriasis is the recurrence of lesions at the site of initial onset after therapy has been discontinued. Although the ultimate cause for this phenomenon is not clearly understood, the involvement of different types of cells, including sessile effector memory T cells is suspected[158–160] (Figure 1). More specifically, there have been reports that the effector memory T cells responsible for this phenomenon could be IL-17-expressing skin-resident CD8 T cells.[161] However, the presence of these IL-17-expressing CD8 T cell clones would suggest that an auto-antigen must exist, a contentious point in the field of psoriasis.[162–166] The presence of tissue-resident memory T cell clones that live permanently in the skin[160] could explain the recurrence phenomenon observed in psoriasis patients. Since psoriasis patients can go into remission following biologic therapy, new treatments focusing on eliminating these skin-resident memory T cells could foreseeably accomplish permanent skin clearance in psoriatic patients even after treatment discontinuation.

Suarez-Farinas et al[167] recently reported numerous genes that did not return to normal levels following psoriatic skin improvement with anti-TNFα therapy. This list of genes suggests that there may be factors beyond skin-resident auto-reactive T cells. For example, the *LYVE1* gene participates in lymph vessel drainage. In normal skin, the presence of this gene was reported in wide-open lumens of lymphatic channels located in the upper reticular dermis. This could be an important factor contributing to the failure of healed psoriatic skin to clear infiltrating cells, since down regulation of LYVE1 may contribute to the collapsed morphology of draining lymphoid vessels present in psoriatic healed skin.[167,168] This decreased draining capacity could contribute to leaving pathogenic T cells that would be de-mobilized otherwise.

Th17 cells: protective and pathogenic

Recent exciting advances in cellular immunology have provided new targets for therapy in immunological diseases, including pathogenic Th17 cells,[169] which are associated with initiation of autoimmune and inflammatory conditions[170] including psoriasis.[154,171–174] The complex interplay among regulatory T cell (Treg), effector memory T cells (Tmem)/Teff, DC/APC, Th1 and Th17 cells ultimately defines the skin's immune response at rest, during challenge, and in diseases such as psoriasis.

The Th1/Th2 paradigm proposed by Mosmann et al established the two canonical subsets of helper T cells.[175] Th1 cells are classically defined by activation of the transcription factors STAT4 and T-bet, secretion of IFNγ, and participation in directed immune responses to pathogens as well as coordination of cell mediated immune response. Th2 cells, conversely, are controlled by the transcription factor Gata-3, produce IL-4, IL-5, and IL-13, and mediate humoral immunity. Recently however, the discovery of a new, distinct Th-subset has been revealed;[176] termed Th17 cells, these cells were demonstrated to occur in the absence of Th1- or Th2-specific transcription factors and cytokines.[177,178] Several groups have implicated cytokines in the differentiation of Th17 cells, including TGFβ, IL-6, IL-1, and IL-21, and have shown the necessity of IL-23 for maintenance and proliferation of established Th17 cells (Figure 1). IL-23R expression on Th17 cells is directed by TGFβ and, in combination with IL-6 and IL-21, signals through STAT3 to direct Th17 differentiation. TGFβ and IL-1 plus IL-6 or IL-21 act on Th17 cells as differentiation factors and IL-23 promotes growth and stabilization. STAT3, ROR-γt, and ROR-α have been identified as transcription factors active in Th17 development, and these are activated by the cytokines discussed (Figure 1). The relationship between TGFβ and Th17 cells likely indicates a further connection to $CD4^+CD25^+Foxp3^+$ Tregs since TGFβ also induces differentiation of naïve T cells into $Foxp3^+$ Tregs in the absence of IL-6 or IL-23.

Cytokines secreted from Th17 auto-reactive cells include IL-17A, IL-17F, IL-22, TNFα, and IL-6, which in combination with IL-19, IL-20 and IL-24 from mononuclear cells, likely participate in the pathogenesis of psoriasis.[179] The complex interplay of proinflammatory cytokines, chemokines, growth factors, and chemical mediators initiated by Th17 cells may well be critical for inducing the keratinocyte hyperplasia, angiogenesis and influx of neutrophils that ultimately culminates in excess keratinocyte proliferation and characteristic features of psoriatic plaques.[162,180]

Tregs

We previously examined Tregs' function in psoriasis patients using cells isolated from both PBMC and skin biopsy tissue.[181] Selection of Treg cells by negative CD4 bead selection, followed by positive CD25 bead selection after resting the cells to allow non-constitutive CD25 to become negative, allowed us to utilize a population of Treg cells that was identical between normal and psoriatic samples in terms of numbers and Foxp3 expression. Treg cells isolated from both blood and lesional skin of psoriasis patients exhibited significantly less effective suppression of allogeneic Teff cells than Tregs isolated from normal (healthy) individuals. Our observation of psoriatic Treg dysfunction included "criss-cross" experiments demonstrating that psoriatic Tregs were deficient in suppressing both psoriatic and normal Teff cells. In addition, as shown in our previous paper, Teff cells obtained from psoriasis patients are hyperproliferative in response to allo-antigen. This likely contributes to the escape of Tmem/eff psoriatic T cells and to the decreased restraint observed in psoriatic T cell co-culture experiments. Our recent work indicates that there is a defect localized in the psoriatic Treg subset that expresses CCR5, the high potency subset of Treg cells that chemo-attracts to MIP1, 2.

NK T cells

The exact role for NK T cells in psoriasis pathogenesis remains controversial, however at least one study has demonstrated $CD56^{+}$ cells infiltrating psoriatic tissue.[182] In addition to immature $CD56^{hi}$ $CD16^{neg/lo}$ cells mature $CD56^{lo}$ $CD16^{+}$ cells are also present, and each population can produce IFNγ contributing to the proinflammatory loop.[183] Keratinocytes secrete chemokines known to attract NK T cells including CXCL10, CCL5, and CCL20. Secretion of these chemokines results in the recruitment of NK T cells to the skin where upon activation the NK T cells may contribute to the inflammatory skin milieu.

γδ T cells

T cells express 1 of 2 major TCR subtypes composed of heterodimeric alpha/beta (αβ) or gamma/delta (γδ) proteins. The majority of T cells in the blood and draining lymph nodes are of the αβ type while γδ T cells are increased in epithelial tissues and exhibit less TCR variability, however, this characterization has been largely surmised from murine studies. In humans, the isolation and characterization of γδ T cells is vastly less. Nevertheless, there are reports of γδ T cells found in human psoriatic tissue and a concomitant reduction in circulating cells.[184]

Monocytes, macrophages, and myeloid-derived suppressor cells

Monocytes

Monocytes are known precursors for DCs and macrophages and as such, they have been described to be important cellular contributors to psoriatic pathology. It has been suggested that psoriatic monocytes engulf low density lipoprotein leading to overproduction of inflammatory cytokines.[185] Additionally, psoriatic monocytes have also been described to possess increased phagocytic capabilities due to an imbalance in the ratio of cAMP/cGMP found in lesional skin.[186] More recently an increase in $CD14^{+}$ $CD16^{+}$ intermediate monocytes – termed Mon2 – has been described in a cohort of human psoriatic patients.[187,188] Interestingly, Mon2 monocytes also have been shown to be linked to an increased risk of CVD and to be predictive of myocardial infarction and death.[189–191]

Macrophages

Infiltration of macrophages at the dermal epidermal junction is a well-known characteristic of psoriasis (Figure 1).[192,193] Although there is general agreement classifying psoriasis as a T cell mediated pathology, the role for macrophages in disease pathology has been described recently in psoriasiform mice models.[180,194,195] Research has shown that downregulation of CD18 in mice spontaneously creates chronically inflamed skin resembling human psoriasis that contains large numbers of TNFα–releasing macrophages. Interestingly, when macrophages were depleted using clodronate liposomes, the skin showed a significant improvement in inflammation.[195] Similarly, a deletion of IKK2 in mice leads to chronic skin inflammation with psoriasis-like characteristics. The inflamed skin contained large amounts of macrophages and the inflammation was reported to be T cell independent.[194] Macrophages have also been identified as a major source of the proinflammatory cytokine MCP-1 and mature $CD163^{+}$ macrophages have been shown to react to tattoo chemicals in psoriasis-prone patients potentially contributing to the initiation of a psoriatic flare (Figure 1).

Myeloid-derived suppressor cells (MDSCs)

Under healthy physiologic circumstances myeloid progenitor cells are created in the bone marrow and egress to the peripheral blood supply. In particular, neutrophils and monocytes are in turn recruited into local tissues where they either undergo activation or in the case of monocytes, differentiate into macrophages, DCs, and other myeloid effector subtypes. However, under pathological conditions, this differentiation

step is halted and either neutrophils or monocytes stay undifferentiated for longer periods of time, becoming the so-called MDSCs. These cells are currently considered a heterogeneous cell population divided into $CD33^{+}$ $CD11b^{+}$ $CD15^{+}$ $CD14^{neg}$ $HLA\text{-}DR^{neg/low}$ granulocytic MDSC and $CD14^{+}$ $CD15^{neg}$ $HLA\text{-}DR^{neg/low}$ monocytic MDSC (Mo-MDSC), such as the ones described in Figure 1. While both granulocytic MDSCs and Mo-MDSCs have the ability to display suppressive mechanisms such as inhibiting the proliferation of CD8 T cells,[196–198] only Mo-MDSCs have been shown to possess the ability to induce Tregs.[199] Mo-MDSCs express several regulatory molecules such as ARG1, IL-10, CTLA4, and nitrous oxide. Although MDSCs were first described in cancer patients and the "MDSC" designation was coined in 2007,[200] their role in autoimmune diseases has begun to be described recently.[201,202]

Topical and systemic therapeutics in psoriasis

Topical treatments

Mild psoriasis is typically treated with topical therapy alone or in combination with other agents.[203] Moderate to severe psoriasis patients are usually treated with phototherapy and systemic biologics but the use of topical in combination with these therapies may be helpful in reducing the amount of other therapies required to achieve disease control. The six principal classes of topical therapies in psoriasis are coal tar, dithranol (anthralin), vitamin D analogs, corticosteroids, keratolytics, calcineurin inhibitors, and retinoids.

Coal tar has been used as a psoriasis treatment for more than a hundred years. However, its mechanism of action remains unknown, although anti-proliferative actions have been shown.[204] Adverse effects of coal tar include poor tolerance in patients due to its odor and staining, skin irritation, contact dermatitis, folliculitis and photosensitivity[203] and potential carcinogenicity in humans as well as in several animal models.[203,205,206]

Dithranol or anthralin is an anthracycline that has been used as psoriasis treatment for a long time. However, its use has declined due to more cosmetically acceptable therapies.[203,206] The response rate for dithranol has been shown to vary from 30%–70% but it is not recommended as long-term therapy.[207] Some of its side effects include irritation and discoloration of skin, as well as blistering and necrosis when used in excess.[206]

Vitamin D analogs are used for the treatment of mild to moderate psoriasis.[203] The global estimate of efficacy showed that between 30%–50% of patients treated significantly improved or had complete clearance after 4–6 weeks of use.[203,206] Vitamin D analogs bind to intracellular vitamin D receptor; upon binding, downstream effects include direct regulation of genes involved in epidermal proliferation, inflammation, and keratinization.[204] Currently, the vitamin D analogs available for treating psoriasis are calcitriol, tacalcitol, and calcipotriol.[204] Skin irritation and photosensitivity are the most common side effects of vitamin D analogs.[203,206]

Corticosteroids include the most important and frequently used topical medications for psoriasis. They are used for all grades of plaque psoriasis as monotherapy or complementary to systemic therapies. Corticosteroids are classified into four groups depending on their efficacy: super-potent, potent, moderately potent, and mild.[204] Given the wide range of corticosteroids used, their effect on cellular metabolism varies. However, their therapeutic response is mediated by vasoconstriction, anti-inflammatory, and immunosuppressive effects.[204] Their efficacy and side effects depend on the potency, vehicle, occlusion, and patient compliance.[203] The higher the potency, the more efficacy is observed, but to minimize side effects, typically the strength of the corticosteroid is decreased after improvement of psoriasis begins.[206] Some systemic side effects observed after corticosteroid therapies include hypertension, osteoporosis, cataracts, glaucoma, and diabetes, among others.

Keratolytics agents such as salicylic acid, urea, propylene glycol, and glycolic acids are another important group of topical treatment in psoriasis. When used in conjunction with other topical treatments they show increased efficacy but also increased toxicity.[203,207,208]

Calcineurin inhibitors such as tacrolimus and pimecrolimus have been used off-label to treat facial and intertriginous lesions.[203,208] Calcineurin is a protein phosphatase essential for lymphocyte proliferation through upregulation of IL-2.[209] Therefore, inhibition of calcineurin causes immunosuppression. Their most common side effects include self-limited pruritus, burning sensation at site of application, and breakdown products found in breast milk.[203,208]

Topical retinoids such as tazarotene were developed after association of oral retinoids with several adverse effects such as teratogenicity, serum lipid and transaminase elevations, mucocutaneous toxicity, hair loss, and skeletal changes.[210] Approximately half the patients have 50% improvement after 0.1% tazarotene gel application for 12 weeks.[203,206]

Also, these medications work best when combined with topical vitamin D analogs or topical steroids.[207,208] The mechanism of action of retinoids is through binding of the retinoic acid receptor (RAR) preferentially binding RAR-α, RAR-β and RAR-γ[211] but not to retinoid X receptor.[212] The

engagement of these receptors causes reduction of epidermal hyperproliferation, decrease of inflammation, and decrease of keratinocytes' differentiation.[213] The most common adverse effects include local inflammation and photosensitization.[207]

Phototherapy

Phototherapy is commonly used as treatment for moderate to severe psoriasis. The use of UV light developed from the observation that natural and artificial light has beneficial effects over psoriasis severity. Phototherapy consists of UVB and psoralen plus UVA (PUVA).

UVB light is used for mild to moderate psoriasis and can be used as a broadband or a narrowband.[214] The efficacy of both types of UVB therapy fluctuates from 50%–70% of patients achieving at least 75% PASI improvement after 4–6 weeks.[204] Often it is combined with additional topical or systemic therapeutics.[215] Some of the side effects seen with acute UVB treatment are itching, burning, and erythema, while chronic exposure to UVB may cause photoaging, carcinogenesis, solar lentigines, and telangiectasias.[204]

UVA light is more effective than UVB for treating psoriasis. However, it is more carcinogenic and causes more photoaging.[207] UVA is also frequently used as photochemotherapy (PUVA), where it is administered in combination with photosensitizing psoralen compounds. Improvement with PUVA therapy can be seen within a month and clearance within several months.[214] However, increased incidences of cutaneous malignancies and increased risk for melanoma have been observed among long-term patients receiving high dose PUVA therapy.[216]

Retinoids

Oral retinoids have also been used as a treatment for psoriasis since the early 1980s.[217] They can be administered alone or in combination with UV light treatment, the latter has been shown to be more effective in patients with psoriasis vulgaris.[218] Retinoids are natural and synthetic analogs of vitamin A that inhibit epidermal proliferation and differentiation.[219] These anti-psoriatic traditional compounds are non-specific, exhibit diverse side effects and relatively high toxicity, therefore more specific therapeutics have been developed.

More narrowly targeted specific biologic compounds were developed based upon the response to immunosuppressive agents observed in psoriasis patients. Anti-psoriatic biological agents include antibodies, soluble cytokine receptors, and fusion proteins that inhibit psoriasis immuno-pathogenesis by interfering with signaling of specific proinflammatory pathways and/or receptors, cytokines or antigens.

Systemic therapeutics

Traditional systemics

Early therapeutic modalities for the treatment of psoriasis included methotrexate and cyclosporine, which induce general immunosuppression by preventing T cell activation. Although these therapies were effective, given their non-specificity, long-term use is very toxic and therefore resulted in diminished enthusiasm for their continued therapeutic use. Methotrexate is a synthetic analog of folic acid which acts as an anti-inflammatory therapeutic as well as an immunosuppressant by reducing T cell activation as well as other non-specific components of the immune system.[220] Liver toxicity is the main side effect of long-term use of methotrexate; however a recent review concluded that the incidence of hepatic fibrosis due to methotrexate treatment according to the literature does not give precise risk quantification.[221]

Another traditional first line systemic therapy is cyclosporine. As with methotrexate, even though effective for treating psoriasis,[222] several toxicities have been implicated in its long-term use.[219] Cyclosporine inhibits T cell activation and cytokine expression, which causes general immunosuppression. Furthermore, cyclosporine usage can cause hypertension, hyperkalemia, hypomagnesemia, hypercalcinuria, acidosis,[223,224] as well as nephrotoxicity with reduced renal transplant function, arteriolopathy and interstitial fibrosis.[225]

T cell transmigration and activation receptors

The first US Food and Drug Administration-approved biologic for the treatment of psoriasis was alefacept, which targeted T cell activation, followed by efalizumab, which targeted T cell transmigration.[214] Currently, both of these biologics have been discontinued. Alefacept was discontinued by the manufacturer in 2011, although no specific safety concerns were indicated. Efalizumab, a monoclonal antibody that blocked CD11a, the alpha subunit of LFA-1, which is selectively used by T cells for migration and activation was discontinued due to severe adverse events associated with fatal brain infections.[226,227] However, it was during studies examining the mechanism of action of efalizumab that the inflammatory Tip-DCs were discovered in psoriasis lesions.[138]

TNFα

The largest group of approved biologic therapeutics for psoriasis is TNFα inhibitors including etanercept, infliximab, and adalimumab. Biologics targeting TNFα revolutionized psoriasis therapy due to their greatly improved effectiveness compared to more global immunosuppressants. Different

TNF therapeutics have been used for the treatment of psoriasis including neutralizing antibodies and TNF receptor fusion proteins. Treatment with anti-TNF antibodies such as adalimumab or infliximab has been shown to improve the PASI score of psoriasis patients by up to 75%.[228,229] Furthermore, 34%–49% of patients achieved PASI-75 after treatment with the TNF receptor fusion protein, etanercept.[230] However, paradoxical development of psoriasis has been linked to anti-TNFα treatments in rheumatoid arthritis (RA) patients[231] and to worsening of the disease in psoriasis patients.[232] Also, serious side effects such as lymphoma, infections, congestive heart failure, demyelinating diseases, induction of autoantibodies, lupus-like syndrome, and systemic side effects have also been reported.[233]

IL-12/IL-23p40

Early research showing IL-23 and Th17 related cytokines in skin lesions and serum of psoriasis patients, as well as the association of IL23R gene variants in psoriasis and functional role of Th17 cells in autoimmunity, raised interest in the IL-23/Th17 axis as a potential target for psoriasis immunotherapy.[234] Ustekinumab is an approved psoriasis biologic that neutralizes the p40 subunit shared by IL-23 and IL-12. Therefore this neutralization also partially inhibits Th17 and Th1 responses. More than 65% of patients treated with ustekinumab show a PASI-75 response at 12 weeks post-therapy.[235] Thus far, serious infections, malignancies or adverse cardiovascular events have not been observed in patients treated with ustekinumab.[236]

IL-23/IL-17

Skin biopsies from psoriatic lesions show increased levels of IL-17A and T cells as well as higher IL-17A mRNA expression when compared with healthy control skin.[161,237] IL-17 receptors are constitutively expressed on keratinocytes throughout the epidermis and on some dermal cells such as DCs, dermal fibroblasts, and endothelial cells.[174] Stimulation by IL-17A causes keratinocytes to express multiple chemokines including CCL20 which may directly recruit $CCR6^+$ cells, such as Th17 and DCs to the skin, which elicit a positive loop for inflammatory cell maintenance in psoriatic lesional skin.[237] Th17 cells in peripheral circulation and lesional psoriatic skin have been shown to positively correlate with psoriasis disease severity.[238] Several IL-17A inhibitors are in clinical Phase III trials in the United States such as the monoclonal antibodies for IL-17A neutralization secukinumab[239] and ixekizumab[240] and the antibody for binding IL-17A receptor, brodalumab.[241] Recently, the European Medicines Agency (EMA) has approved secukinumab as a first line systemic treatment for moderate-to-severe plaque psoriasis in adults. However, even though IL17-A neutralizing antibodies have been successful, their side effects remain unknown. Additionally, several IL-23 inhibitors are currently in Phase III of clinical trials in the United States including antibodies directed against the p19 subunit of IL-23, such as guselkumab (CNTO1959) and MK-3222/SCH-900222.[242]

JAK inhibitors

Several important cytokines in psoriasis such as IL-2, IL-6, IL-22, IL-23, and IFNγ use the janus kinase (JAK/STAT) signaling pathways.[243,244] Therefore, JAK inhibition may interfere with key cytokine signaling causing suppression of immune cell activation and subsequent inflammation.[245,246] A clinical JAK inhibitor, tofacitinib, has been approved for RA;[247] oral and topical formulations are being tested for psoriasis.[248,249] Early results show significant response rates but the long-term safety of JAK inhibition remains unknown.

Biomarkers of psoriasis

The US National Institutes of Health Biomarkers and Surrogate Endpoint Working Group defines biomarkers as biological characteristics that are objectively measured and evaluated as indicators of specific processes either under homeostasis, pathogenesis or pharmacologic responses.[250] Biomarkers can be disease-related for diagnosis and prognosis or drug-related based on pharmacokinetics and pharmacodynamics. Therefore, biomarkers play an important role in diagnosis assessment, disease processes, and treatment response.[250] Evaluation of biomarkers in psoriasis may help to establish severity and therapeutic response. Biomarkers can be categorized into several distinct biologic classes including genetic biomarkers, serum (blood)/soluble biomarkers, tissue biomarkers, and transcriptional markers of activation associated with disease. Herein, we address only examples of serum (blood)/soluble biomarkers.

Inflammatory biomarkers

TNF

Psoriasis patients have increased levels of proinflammatory cytokines, such as TNF. TNFα is a 17 kD polypeptide that regulates innate immune responses. TNF can stimulate proinflammatory cytokines and enhance cell adhesion thereby increasing the phagocytic index for innate defense cells such as macrophages. TNF ligation through membrane-bound receptors (TNF-R1 [p55] and TNF-R2 [p75]) induces apoptosis machinery following phagocytic activation. TNFα

can be produced by a plethora of cells including lymphocytes, monocytes, keratinocytes, mast cells, and APCs such as macrophages and DCs of the skin. In psoriasis, TNFα promotes innate immune cell activation and trafficking to the skin which results in accelerated keratinocyte proliferation. Targeted therapeutics, designed to inhibit TNFα activity are currently in use to treat several autoimmune conditions including psoriasis and psoriatic arthritis. Thus, monitoring the level of TNFα activity can be used as a "biomarker" for psoriasis activity, although it is not specific to only psoriasis and should be viewed as a non-specific marker of general inflammation, as are all of the outlined markers in this section.

Adiponectin

This adipose tissue specific cytokine is known to inhibit inflammatory response by reducing the production of TNFα, IL-6, IFNγ, adhesion molecules in monocytes, phagocytic activity by macrophages, and increases insulin sensitivity and repair of the vasculature.[81,251–253] However, the role of adiponectin in psoriasis is controversial. Some reports indicate a reduction of adiponectin in overweight/obese psoriatic patients,[254–256] which was inversely correlated with PASI score;[257] while others have shown increased adiponectin concentration that positively correlates with PASI score.[258] Therefore, further studies are warranted for determining adiponectin's role in psoriasis.

Resistin

Resistin is expressed by macrophages and peripheral monocytes in the stromal compartment of the adipose tissue. Resistin is involved in proinflammatory responses by causing an increase in the expression of TNFα and IL-6.[259] Resistin levels have been found to be elevated in psoriasis as well as being associated with disease severity.[83,254,257,260] Recent studies have shown that the more severe the psoriasis the higher the levels of resistin found in the serum[254] and plasma.[261]

MPO

MPO is a proinflammatory protein that can be stored in leukocytes and secreted upon activation of the cells during inflammatory processes. The conversion of chloride and hydrogen peroxide to hypochlorite – a strong reactive oxygen species is catalyzed by MPO. Although several cell types can produce MPO, including monocytes, macrophages, Kupffer cells, and microglial cells, nearly all of the circulating MPO is produced by polymorphonuclear neutrophils. MPO has emerged as a biomarker for CVD as well as generalized stress and inflammation.

High-sensitivity CRP

In patients with psoriasis, there is sufficient systemic inflammation to raise hepatic-derived CRP, a risk factor for CVDs.[262,263] A number of systemic inflammatory diseases such as RA, systemic lupus erythematosus (SLE), and chronic gingivitis are associated with increased risk of CVDs and CRP elevation; although the mechanisms of this risk elevation are not elucidated.[264,265]

Emerging biomarkers

The new challenge in identifying biomarkers will be to increase the specificity of these markers for individual disease(s) rather than generic markers of inflammation. As such, genetic biomarkers are beginning to narrow the spectrum of which genes participate in different inflammatory diseases; however, many of these are also redundant to several disorders. The answer may lie in designing specific panels of markers, or molecular signatures that will be unique for each disease. Currently, the technology to accomplish this goal may slowly be reaching its potential. Increased use of sophisticated molecular, genetic, and cellular technologies such as multi-parameter flow cytometry analysis, mass spectrometry, "omics" data generated by next-generation technologies combined with computational algorithms mining the data sets will advance the comprehensive bioinformatics of diseases, allowing for improved profiling of different pathological subsets. Indeed, a systems biology approach examining immune cell interactions participating in skin disease is beginning to emerge. Employing these advanced methods should enhance the ability to design improved biomarkers for complex diseases.[266,267]

Psoriasis as an autoimmune disease

Autoimmune diseases are an amalgam of chronic conditions where the destruction or disruption of the body's own tissues by the immune system occurs.[268] Even when the specific etiology of the majority of the autoimmune diseases remains unknown, they are associated with a combination of genetic and environmental factors.

The current consensus regarding psoriasis etiology is that it constitutes an inherited and an immune-mediated disease. However, controversy exists to whether psoriasis should be considered a bona fide autoimmune disease given that no auto-antigen has been conclusively discovered that triggers the disease and no self-reactive T cells have been identified.[269]

Currently two theories about the nature of an antigen in psoriasis exist. The first one considers psoriasis to be an autoimmune disease caused by molecular mimicry,[270,271]

while the second one postulates that psoriasis is triggered by bacterial microbiota of the skin.[65]

Some evidence for considering psoriasis as an autoimmune disease include genetic predisposition as well as the overlap of several biochemical pathways with those altered in other autoimmune diseases such as Crohn's disease (CD), type I diabetes and RA, although the status of CD as "autoimmune" has also been recently questioned.[272] Also, molecular mimicry between streptococcal and keratin proteins, the existence of homologous peptides between these proteins and $CD8^+$ T cells' response to these homologous peptides have been shown in psoriasis.[271] Furthermore, several molecules in T cells that are associated with autoimmunity have been demonstrated in psoriasis. Some negative regulators of T cell activation such as CTLA4, PD1, SHP1, inhibitor of NF-κB (I-κB), PAG, and CSK have been shown to be involved in psoriasis animal models.[19]

Among the evidence for bacteria to trigger psoriasis is the finding of enhanced TLR2 on psoriatic keratinocytes.[273] TLR2 is involved in the recognition of Gram-positive bacteria products including lipoproteins[274] and peptidoglycans.[274] Furthermore, among the four known PGRPs with function in antibacterial immunity, polymorphisms of PGRP-3 and PGRP-4 gene on PSORS4 susceptibility site have been associated with psoriasis.[275,276] Not only streptococcal peptidoglycans have been found in APCs from psoriasis patients,[62] but also $CD4^+$ T cell lines established from psoriasis patients have been shown to respond to streptococcal and staphylococcal peptidoglycans.[62]

Psoriasis association with other autoimmune diseases

Association of psoriasis with other autoimmune diseases is an ongoing research area. Previous studies have shown that there is a higher frequency of autoimmune diseases among psoriasis patients than observed in the general population potentially stemming from cytokine pathways' dysregulation.[277,278] Based on a retrospective study using MEDLINE data from January 1, 1980 to June 1, 2011, the major autoimmune disorders associated with psoriasis include RA, celiac disease, IBD, especially CD, multiple sclerosis, SLE, and autoimmune thyroid disease.[279] However, anecdotal reports of other autoimmune diseases associated with psoriasis include Sjögren's syndrome (SS) and alopecia areata. In addition, a new meta-analysis of a single mutation of CD226, Gly307Ser (rs763361) has suggested that this modification is associated with an increased risk of developing various autoimmune disorders including psoriasis.[280]

Rheumatoid arthritis

RA and psoriasis are both chronic inflammatory autoimmune diseases. Even when clinical manifestation of these diseases is diverse, several parallel presentations have been observed. A genetic relationship between RA and psoriasis has been reported. One of the genetic associations is the expression of the *RUNX1* gene.[281] This transcription factor regulates differentiation of hematopoietic stem cells.[282] RUNX1 expression in psoriasis has been suggested to confer defective regulation of a phosphoprotein implicated in regulation of membrane dynamism for synapse formation and T cell activation (SLC9A3R1) or by NAT9, which is a new member of the NAT superfamily.[25]

Another genetic relationship is expression of the psoriatic susceptibility gene *PSORS1C1*, which has been shown to be significantly increased in blood cells from RA patients.[283] Importantly, this gene may be involved in IL-17 and IL-1β production in RA by increasing gene expression in synovial tissues. Additionally, IL-23R polymorphisms have been shown to control susceptibility to psoriasis as well as RA, which further emphasizes the importance of the Th17 pathway in both diseases.[284] Based on a retrospective cohort study, RA has the highest odds ratio with psoriasis among various autoimmune diseases evaluated, which included CD, SS, SLE, and others.[278]

Another gene that has been implicated in RA and psoriasis, as well as with celiac disease, CD, and SLE is *TNFAIP3*.[285] This gene encodes the intracellular ubiquitin-editing protein A20 (TNFAIP3) which is a negative regulator of TNFα-induced NFκβ signaling and TNFα-induced apoptosis.[285] Therefore, there is a clear genetic overlap between these diseases.

Immunological similarities have also been observed between psoriasis and RA. Activated auto-reactive T cells have been implicated to initiate and drive organ-specific inflammation in the synovium, in RA, and in the skin of psoriasis patients. Immune cell infiltration into the synovium and skin in RA and psoriasis respectively, is considered one of the principal characteristics of both diseases.[286]

In both diseases, an imbalance between Th17 and Tregs has been demonstrated, as well as limited functional capabilities by suppressive Tregs.[20,181,287] Key signaling molecules such as TNFα, IL-1β, IL-6, IL-17A, IL-17F, IL-21, and IL-23 have been implicated in pathogenesis of both diseases.[20,287] Hence, similar therapeutic approaches have been effectively used to treat both diseases, including methotrexate and neutralizing antibodies for TNFα. However, paradoxical psoriasis onset has been observed in RA patients after treatment with

neutralizing antibodies for TNFα[44,231,232] as well as with tocilizumab, an anti-IL-6 receptor specific antibody.[46,47,49] This paradoxical event is of interest considering both TNFα[288] and IL-6[289,290] have been shown to be key signals in psoriasis development. Therefore, further studies are required for better understanding of the role of TNFα and IL-6 inhibition in psoriasis.

Celiac disease

Celiac disease is an autoimmune disease triggered by gluten ingestion that affects the small intestine. Association of celiac disease with psoriasis remains controversial. Several small studies support the association by demonstrating significantly higher rates of celiac disease in psoriasis patients compared to controls and by elevated celiac disease-associated antibodies in psoriasis patients that correlate with their disease severity as well as improvement of psoriasis by implementation of a gluten free diet,[291–297] although other studies attempting to link celiac disease have shown no association.[298]

Previous publications[299,300] present several potential mechanisms regarding a positive association between psoriasis and celiac disease. Firstly, vitamin D deficiency is commonly seen in celiac disease[301] and is known to predispose patients to psoriasis development.[302,303] Secondly, patients with celiac disease who are exposed to gliadin may trigger a $CD4^+$ T cell response and subsequent proinflammatory cytokine cascade involving, for example, IFNγ[304] in both peripheral blood and skin, which might trigger or exacerbate psoriasis development.[305] Another potential mechanism is through common genetic factors such as the IL-2/IL-21 locus on chromosome 4q27, which has been previously linked with both psoriasis[306] and celiac disease.[307,308] Since the mechanisms for the positive association between celiac disease and psoriasis are not well understood, more studies to explore this association need to be performed.

Crohn's disease

CD is a chronic IBD that can affect the entire gastrointestinal tract but commonly affects the terminal ileum and colon. The prevalence of CD is seven cases per 1,000,000 adults in the United States.[309] Several genetic and immunopathological associations have been observed between CD and psoriasis.

Increased prevalence of psoriasis in CD patients has been previously demonstrated.[310–312] Five independent case control studies have shown that psoriasis prevalence is 8.9% in CD patients but only 1.4% in control individuals.[313] Furthermore, 10% of CD patients had relatives with psoriasis, while the prevalence among control patients was only 2.9%.[313] Also, some studies have shown that asymptomatic bowel inflammation may exist among psoriasis patients.[314]

Genetic overlap has been demonstrated between psoriasis and CD. Several genes that encode for IL-23-associated molecules including *IL23R, IL12B,* and *TYK2* have been associated with CD and psoriasis.[315–318] Furthermore, combined analysis of GWAS for both diseases has identified seven shared susceptibility loci between psoriasis and CD.[319]

Important immuno-pathologic associations have been demonstrated between psoriasis and CD. First, increased levels of TNFα have been shown in intestinal and other tissues from CD patients[320,321] as well as in psoriatic lesions in psoriasis patients.[322] TNFα inhibitors are effective in both diseases[229,322–324] however, paradoxical onset of psoriasis in patients treated with TNFα inhibitors has also been observed.[325,326] Second, both diseases present infiltration of T lymphocytes, macrophages, monocytes, DCs, and neutrophils as well as high levels of other cytokines such as IFNγ, IL-12, IL-6, and IL-17 into lesional tissue.[20,327]

Also, in both psoriasis[234] and CD,[328] Th17 cells have been reported to be key in establishing chronic inflammation. Imbalance between Tregs and Th17 cells by loss of $CD4^+CD25^{high}$ $Foxp3^+$ Tregs function,[181,329] as well as increased levels of proinflammatory Th17 cells,[234,330] have been associated with aberrant immune response in both diseases. Furthermore, recent studies have demonstrated IL-17 producing Tregs in inflamed intestinal mucosa of CD patients[331] as well as in lesional skin of psoriasis patients,[332] indicating a possible re-differentiation of Tregs towards a proinflammatory phenotype to further perpetuate the chronic inflammation stage of these diseases. Recently, a potential protective role for IL-17 in CD and IBD has also been proposed based upon adoptive transfer studies of colitis induction demonstrating exacerbation of disease in the absence of IL-17-producing cells.[333]

Another cytokine that appears to play an important role in both diseases is IL-6. In psoriasis, high levels of IL-6 have been detected in lesional plaques[289] and are responsible for phosphorylation of STAT3 which renders Teff cells refractory to Tregs inhibition.[290] In CD, IL-6 has been shown to be produced by lamina propria macrophages and T cells in the inflamed gut, which also results in IL-6-dependent STAT3 phosphorylation of Teff cells.[334] Studies blocking IL-6 signaling have shown beneficial effects in a pilot trial of CD patients;[335] however further studies to determine the clinical importance of IL-6 signaling blockade in both diseases need to be completed.

Atopic dermatitis

Atopic dermatitis (AD) and psoriasis are among the most common inflammatory skin diseases. However, AD patients suffer from frequent skin infections, while psoriasis patients exhibit relatively few skin infections. There are two forms of AD: extrinsic, characterized by elevated immunoglobulin E levels and eosinophils in peripheral circulation, and intrinsic which only affects ~20% of patients and presents with normal immunoglobulin E levels and eosinophils numbers.[336] Chronic phase AD shares many characteristics with psoriasis including epidermal hyperplasia, altered terminal keratinocyte differentiation and T and DC infiltrates.[337] Thus, even though phenotypically both diseases differ, histologically there are similarities between psoriasis and AD. In AD the epidermal differentiation process is disrupted due to primary genetic mutations in the epidermal differentiation complex localized on chromosome 1q21 that leads to deficiencies in epidermal barrier function.[337,338] The epidermal differentiation complex contains the *FLG* gene. FLG is an intracellular protein that promotes epidermal differentiation and hydration by aggregating keratin intermediate filaments within the corneocytes and drawing water into the stratum corneum.[338] Loss-of-function mutations in *FLG* have been associated with AD. In psoriasis, previous studies have shown no association between FLG mutations and early onset of psoriasis in childhood.[339] However, a recent publication demonstrated an association between rare mutations such as p.K4022X in the *FLG* gene with psoriasis in a Chinese population.[340] Therefore, a possible correlation between *FLG* gene mutations and both diseases remains to be further studied. Comparison of genomic overlap between psoriasis and AD revealed that nearly two thirds of the variants exhibit a risk profile for AD that is the opposite of those observed for psoriasis, however, one third revealed an association with the same allele. Thus both divergent and shared patterns occur between these common dermatological diseases.[341]

Using gene chip microarray, the innate immune response genes in AD and psoriatic skin were compared.[342] Decreased levels of HBD-3, HBD-2, iNOS, and IL-8 were observed in AD skin as compared to psoriasis.[342] Furthermore, TNFα and IFNγ are decreased in AD skin in comparison to psoriasis, which may be due to the previously mentioned down-regulation of the innate immune response genes.[342]

AD is characterized by significant barrier disruption as well as increased susceptibility to allergic sensitization and microbial colonization and infections.[343,344]

Previously the classical belief was that AD was a Th2 cell-mediated disease while psoriasis was a Th1 driven disease, however, the discovery and association of Th17 cells with epidermal activation has been shifting this hypothesis. Th17 cells are associated with several aspects of psoriasis pathogenesis including increased neutrophil chemotaxis and increased production of antimicrobial peptides. In acute AD, Th17 cells have also been demonstrated to be increased in both peripheral blood and skin lesions;[345] however, IL-17 production by Th17 cells has been shown to be decreased in chronic AD patients when compared to chronic psoriasis patients.[346] Therefore, it is possible that Th17 cells are not activated or may be inhibited by Th2 cytokines in AD.[347]

Systemic lupus erythematosus

SLE and psoriasis association has been reported as rare. A retrospective study evaluating published work from 1927 to 2007 established that only 22 reports of 111 cases presented coexistence of the two diseases,[348] while another report showed 0.6% of 520 SLE patients have concomitant psoriasis.[349] An independent separate investigation from 300 psoriatic patients found 17 (5.7%) SLE immunological characteristics.[348] Therefore, the exact incidence of SLE in psoriasis remains controversial. The strongest connection between psoriasis and SLE is the discovery that SLE, RA, and psoriasis share dysfunctional binding of the transcription factor RUNX1 to its binding site due to nucleotide polymorphisms.[25,350,351] RUNX1 binding on chromosome 2 is altered in many patients with SLE and psoriasis patients have an altered RUNX1 binding site on chromosome 17. Additional genetic similarities between psoriasis and SLE are also captured in polymorphisms associated with the Act 1 encoding gene TRAF3IP2 exhibited by SLE patients.[352] Previous work has identified TRAF3IP2 as a genetic susceptibility locus for psoriasis and a connection to IL-17 signaling.[353,354] A newly emerging role of Th17 and IL-17 in SLE has also been recently reported.[355–357] Finally, dysfunctional Treg control has also been described in both SLE and psoriasis[181,289,358,359] suggesting that common immune and genetic dysfunctions may direct similar responses in both SLE and psoriasis.

Sjögren's syndrome

SS is a chronic, autoimmune disease caused by mononuclear cell infiltrates and progressive damage to the exocrine glands.[360] A recent retrospective study demonstrated that psoriasis patients had an increased odds ratio of developing SS.[278] Several other case reports have identified SS patients who developed psoriasis, or vice versa.[361–366] The cellular determinant(s) driving psoriasis and SS have similar features including activated Teff cells, Th17 cells, and a role for Tregs

as well.[367] Although an increased risk of developing SS exists for psoriasis patients, no definitive genetic markers have been identified to date that link these respective diseases.

Vitiligo

Vitiligo is a common depigmentation of the skin disorder that affects around 1%–2% of the world population.[368] It is an autoimmune disorder caused by the selective destruction of skin melanocytes which results in the formation of white, depigmented skin patches.[368] Coexistence of psoriasis and vitiligo used to be considered very rare but this might be an underestimation. Several isolated case reports[369–371] as well as few retrospective studies have shown a possible association between psoriasis and vitiligo.[372–375] The biggest retrospective study using data from 2,441 vitiligo patients found that 23% of these patients had one or more autoimmune diseases and that psoriasis was the second most common comorbidity following thyroid-related disorders.[375]

Vitiligo and psoriasis share several immunological similarities including Th1 and Th17 signaling pathways[234,376] as well as dysfunction of Tregs.[289,290,329,332,377] Also, both diseases have been shown to be associated with NALP1 gene variations[378] as well as phenotype similarities such as Koebner phenomenon,[35] neuropeptides, and skin patches.[3,368] Furthermore, a recent report demonstrated the simultaneous presence of a family history of CVD with the presence of activated inflammatory pathways and the absence of organ-specific autoantibodies in both psoriasis and vitiligo.

Conclusion and future directions

Psoriasis patients have an increased risk of developing numerous other autoimmune diseases.[278] The increased risk for the various other diseases has been associated with an overactive immune response (eg, activated T cells, memory T cells, DCs, neutrophils, Th17, IL-17, TNFα),[4,149,158,181,299,357] genetic modifications (eg, RUNX1, SNPs,[25,28,281,350] CARD14),[26,27] decreased suppressive function (Treg,[181,289,290,327,328,332,358,359] IL-10) as well as potential environmental or epigenetic triggers. The autoimmune diseases associated with psoriasis often have a similar pattern of cellular responders suggesting that common signaling pathways may be implicated in the background of each autoimmune response. Despite numerous extensive GWAS studies, definitive causal loci for psoriasis or many of the other autoimmune disorders mentioned are still elusive. However, these studies have demonstrated that several common genes are present in various autoimmune disorders suggesting that convergent molecular pathways may mediate autoimmune response or susceptibility to autoimmunity. Given the striking similarities in the response elements, signaling pathways, cellular mediators, and genetic associations observed in autoimmune diseases associated with psoriasis, elicitation of additional autoimmune disorders in patients with psoriasis may have a low threshold that is readily overcome upon initiation of psoriasis immunopathogenesis. Targeted therapeutics addressing common elements in autoimmune disorders, such as anti-IL-17 therapies or TNFα inhibitors are beginning to cross platforms and be applied in several autoimmune diseases. Further research to refine the common autoimmune elements should lead to the development of more tailored therapies for all autoimmune disorders.

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The authors have no conflict of interest to disclose.

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