Reactive Oxygen Species in Psoriasis and Psoriasis Arthritis: Relevance to Human Disease

Ia Khmaladze Kutty Selva Nandakumar Rikard Holmdahl

Division of Medical Inflammation Research, Department of Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden

Key Words

Psoriasis · Inflammation · Keratinocytes · Mouse models · Reactive oxygen species

Abstract

Psoriasis (Ps) is a chronic, immune-mediated, skin inflammatory disease affecting up to 3% of the population worldwide. Different environmental triggers initiate this complex multifactorial syndrome. Many individuals affected by Ps (6–26%) develop inflammatory disease in other organs, often in the joints as in psoriasis arthritis (PsA). Animal models that reflect the typical Ps syndrome, including both skin and joint pathology as in Ps and PsA, are valuable tools for dissecting disease pathways leading to clinical manifestations. In this context, we developed a new acute Ps and PsA-like disease model that appears after exposure to *Saccharomyces cerevisiae* mannan in certain mouse strains. The disease was found to be triggered by mannan-activated macrophages, leading to the activation of a pathogenic interleukin-17 pathway involving innate lymphocytes. Interestingly, the production of reactive oxygen species protected the mice from the triggering of this pathway and ameliorated Ps and PsA development.

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Introduction

Psoriasis (Ps) is a chronic, immune-mediated, skin inflammatory disease affecting up to 3% of the worldwide population with an equal sex distribution [1]. Different environmental triggers like infection (from bacteria, fungi and viruses) [2, 3], medications (lithium, antimalarials and nonsteroidal anti-inflammatory drugs) [2, 4, 5], obesity [6] and stress [7] initiate or worsen this complex, multifactorial syndrome in genetically prone individuals. Ps patients are at a great risk of developing a number of comorbid conditions including diabetes mellitus, hypertension, coronary heart disease, inflammatory bowel disease, lymphoma and depression [8]. In addition, disorders involving musculoskeletal structures, the eyes and the gut are also common in these patients [9, 10].

Clinical Characteristics

Ps is usually manifested as erythematous, thickened plaques with silvery scales in the skin. Histopathologically, it is characterized by acanthosis (epidermal thickening) due to increased proliferation of keratinocytes with

Fig. 1. Ps histopathology. Ac = Acanthosis; EPI = epidermis; ERR = elongated rete ridges; PK = parakeratosis. The dashed line indicates the border between the epidermis and the dermis.

elongated rete-like ridges protruding downward into the dermis. Incomplete maturation of epidermal keratinocytes results in an abnormal retention of nuclei in the stratum corneum, denoted as parakeratosis (the presence of nuclei in the cornified layer) and inflammatory infiltrates in the epidermis (fig. 1) and the dermis [11]. Erythema of Ps skin lesions is due to the increased dilation of elongated blood vessels in the papillary dermal region. Endothelial cells are also activated in Ps lesions via mechanisms dependent on ICAM-1 (intracellular adhesion molecule), VCAM-1 (vascular cell adhesion molecule) and E-selectin (CD62E) [12].

Genetics

Population-based studies show higher disease inheritance in first- and second-degree relatives compared to in the general population [13]. However, the concordance rate reaches 70% in monozygotic twins [14], arguing for the influence of environmental factors on disease manifestations. Classic genome-wide linkage analysis has mapped the PSORS1 (psoriasis susceptibility 1) locus as a major genetic determinant [15]. PSORS1 is located on chromosome 6 in the major histocompatibility complex (MHC) region spanning within the class I telomeric

part of HLA-B. It accounts for up to 50% of the inheritability of Ps [16]. HLA-Cw6, an associated variant of HLA-C, was identified as the susceptibility allele within the PSORS1 region [17]. In 1985, nonpustular Ps was suggested to be divided in two subtypes: type 1, which usually develops before 40 years of age and has a strong family history associated with the HLA-Cw6 haplotype, and type 2, which is noninheritable and develops after 40 years of age [18–21]. The presence of the HLA-Cw*0602 allele is correlated with an early onset and more severe Ps, and was found in 100% of patients with guttate Ps [22, 23]. Lately, a loss-of-function mutation in the gene encoding the interleukin (IL)-36 receptor antagonist (*IL36RN*) was found to be associated with pustular Ps [24]. Genome-wide association studies have identified loci with *IL23R*, *LCE3C/3D*, *IL13*, *TNIP1/ANXA6*, *IL12B*, *CDKAL1*, *HLA-C*, *TNFAIP3*, *IL23A/STAT2* and *ZNF313* to be common risk variants for Ps development. However, only 11.6% of Ps heritability was associated with these loci and, most importantly, the most dominant risk locus was *HLA-C* which has a predictive capability stronger than that of the other 9 non-MHC loci combined, as discussed by Johnson-Huang et al. [14]. Moreover, sequence variants in the gene of IL-23R and its ligand IL-12B conferred protection against Ps [25].

During inflammation, regulation of the gene-expression network is controlled by microRNAs (miRs) via interference with key inflammatory checkpoints [26]. It was shown that a distinct miRNA expression profile exists in Ps skin compared to healthy skin. For example, miR-203, miR-125b, miR-424 and miR-99a [26–29] regulate keratinocyte proliferation and differentiation and miR-21 is upregulated in psoriatic skin and suppresses T-cell apoptosis events [30]. The suppression of miR-31 (an miRNA overexpressed in Ps keratinocytes) in Ps skin alleviated inflammation by interfering with the cross-talk between keratinocytes and immune cells [31].

Psoriasis Arthritis

Ps arthritis (PsA) is an inflammatory skin disease with the additional involvement of the joints [32]. Due to the clinical similarities between PsA and rheumatoid arthritis, and between PsA and Ps (in the initial phase), it is important to have specific criteria for the diagnosis of PsA. The most widely used classification criteria for PsA are CASPAR (Classification Criteria for Psoriatic Arthritis), for which signs of inflammatory articular disease are required [32, 33]. One of the CASPAR is that PsA is sero-

negative (lacking high titers of rheumatoid factors) and occurs in 6–26% of patients with chronic plaque-type Ps [32, 33]. In 1973, Moll and Wright [34] described 5 distinct patterns of PsA based on the clinical presentation and distribution of the joint disease: (1) asymmetric polyarthritis is the most common form, affecting the distal joints in an asymmetric fashion and involving only few joints (oligoarthritis), (2) symmetric polyarthritis is the peripheral joint disease, which is symmetrically distributed, (3) spondyloarthropathy includes sacroiliitis and ankylosis spondylitis, (4) predominant distal interphalangeal joint disease involves distal interphalangeal joints and may develop into (5) arthritis mutilans, with distal joint desorption [34].

In recent years, extensive research has provided novel insights into the mechanisms involved in both skin and joint inflammation. The main pathological changes in PsA are associated with skin inflammation, synovial inflammation, enthesitis (enthesis inflammation), tenosynovitis (tendon-sheath inflammation) and bone abnormalities. Until recently, it was thought that the genes susceptible to Ps without arthritis (PsO) and to PsA are the same, but recent studies have shown the existence of a distinct genetic make-up between these two diseases. Different HLA alleles like HLA-B*08, HLA-B*27, HLA-B*38 and HLA-C*06 have been found to be associated with PsA rather than with PsO [35]. In addition, the frequency of HLA-C*06:02 was shown to be lower in PsA patients than in PsO patients [36]. Recent association studies show that MICA*016 is linked with increased risk of Ps, while homozygosity for MICA*00801 is associated with PsA development in Ps patients independently of HLA [37]. Moreover, PsA individuals with HLA-B*27 or DQB1*02 were shown to have an increased risk of developing the most severe form of PsA, arthritis mutilans [38]. Recent studies of the single-nucleotide polymorphism +489A allele of the tumor-necrosis factor (TNF) α gene shows a trend of association with the response to PsA treatment with neutralizing antibodies to TNF α (etanercept), suggesting a role for the SNP +489A allele in the susceptibility and severity of PsA [39]. Moreover, gene-expression profiling of peripheral blood cells suggests that innate immunity may be important in the pathogenesis of PsA, involving Toll-like receptor (TLR) signaling, NF- κ B, and various chromatin-remodeling complexes, and potential biomarkers of PsA in Ps patients being identified, such as *NOTCH2NL*, *HAT1*, *CXCL10* and *SETD2*, which were associated with PsA irrespective of clinical differences between patients [40].

Animal Models of Ps and PsA

Spontaneous Models

Some inbred mouse strains tend to develop joint lesions that could resemble some aspects of PsA, in particular when challenged under stress conditions. Male mice of the DBA/1 strains, when grouped after puberty, develop stress due to intermale aggressiveness and then develop a severe arthritis characterized by swollen joints, inflammation and enthesitis, a disease believed to be caused by an exaggerated healing response [41, 42]. There are also a number of spontaneous mutations causing Ps phenotypes. The flaky-skin mouse (*Ttcfsn/Ttcfsn*) [43] has a spontaneous mutation that induces increased squamous-cell proliferation, but these mice are unresponsive to corticosteroid treatment. However, their lesions do not express all the features of Ps [44]. Similarly, a spontaneous mutation in CPD (chronic proliferative dermatitis) in *Sharpin^{cpdm}/Sharpin^{cpdm}* mice [45] induces skin lesions at the age of 5–6 weeks that are characterized by epidermal hyperplasia, hyperkeratosis, parakeratosis and necrotic keratinocytes; the dermis and epidermis are infiltrated by granulocytes and macrophages [45]. This model is mainly dependent on Th2 cytokines (IL-4, IL-5 and IL-13), but the mice responded to IL-12 treatment [46].

Genetically Engineered Models

K5.Stat3C is a genetically manipulated strain in which the signal transducer and activator of transcription 3 is constitutively activated in basal keratinocytes under the control of the keratin 5 (K5) promoter [47]. Ps-like skin inflammation in this model is dependent on keratinocytes and T cells, but as interdependent participants. In these mice, an external stimulus such as tape-stripping exaggerated Ps symptoms, similar to the 'Koebner phenomenon' [47]. CD18 β 2 integrin hypomorphic mice have a reduced expression of common β 2-chain of lymphocyte integrin adhesion molecules. On a PL/J strain background, PL.129S7-*Itgb2*^(tm1Bay) mice develop Ps-like skin inflammation with infiltrating lymphocytes, and have nonpsoriasisiform epidermal hyperplasia together with a condition similar to PsA that is dominated by enthesitis [48–50]. The JunB/c-Jun epidermal inducible double-knockout mouse represents another model targeting epidermal keratinocytes. JunB is a component of the AP-1 transcription factor. The JunB gene is localized in the Ps susceptibility region PSORS6, and c-Jun is considered as an antagonist to JunB. Epidermal deletion of both JunB and c-Jun leads to the development of a Ps-like disease phenotype and arthritic lesions in mice, and T and

B cells play a minor role in the etiology of the disease. Additionally, the deletion of TNFR-1 in JunB/c-Jun double-mutant mice does not prevent the development of the skin phenotype, suggesting that TNFR-1 signaling might be dispensable for the induction of the disease [51]. Zenz et al. [51] proposed a possible mechanism in which the abrogation of the JunB/activator protein 1 in keratinocytes triggers chemokine/cytokine expressions that are responsible for neutrophil and macrophage recruitment to the epidermis, leading to various PsA phenotypes. Thus, epidermal alterations are sufficient to initiate both cutaneous and articular diseases. Another PsA model by Bardos et al. [52] described and characterized PsA-like disease in 'humanized' (HLA-transgenic) mice lacking their own MHC. Animals of 4 transgenic lines (HLA-DR2.Ab⁰, DR4.Ab⁰, DQ6.Ab⁰ and DQ8.Ab⁰) developed severe PsA-like symptoms, such as hyperkeratosis and parakeratosis, nail deformities and bone resorption associated with significantly fewer CD4⁺ cells in the peripheral blood as well as reduced NK cell activity when they were compared to disease-resistant HLA-DR3.Ab⁰ transgenic mice. Mice overexpressing VEGF epidermally via the K14 promoter develop Ps-like inflammation including vascular, epidermal and inflammatory features with an increased infiltration of mast cells in the upper dermis as well as increased leukocyte rolling and adhesion in the postcapillary skin venules. This study showed that VEGF in the epidermis is sufficient to induce skin inflammation, and it provides a new insight by linking angiogenesis, mast-cell accumulation and leukocyte recruitment to the sites of inflammation [53]. In the epidermal-specific IKK2 knockout mouse, the deletion of IKK2, the catalytic subunit of the I κ B kinase complex necessary for NF- κ B activation through proinflammatory signals, causes Ps-like cutaneous inflammation dependent on TNF signaling but not on $\alpha\beta$ T cell-mediated inflammatory responses. This study suggests the important function of IKK2-mediated NF- κ B activity in the epidermal keratinocytes for the maintenance of immune homeostasis in the skin [54].

In another model, epithelial growth factors, such as TGF α , KGF and TGF β were genetically targeted via the K14 or K5 promoters to the basal epidermis, which resulted in acanthosis but with no inflammatory cell infiltrations. For this reason, growth-factor transgenic mice are not considered as optimal models of Ps pathogenesis, but are useful for understanding epidermal growth and differentiation events [55]. The keratin 14 promoter amphiregulin (AR) gene (K14-ARGE) was shown to induce early-onset and severe skin pathology characterized by

hyperkeratosis with focal parakeratosis, acanthosis, lymphocyte and neutrophilic infiltration and vasodilation, suggesting that the aberrant epidermal expression of AR might play a critical role in the development of psoriatic lesions [56]. The K14-IL-17A^{ind/+} mouse is a relatively new Ps animal model, in which transgenic IL-17A expression is targeted to the skin after crossing the IL-17A^{ind} allele with the K14-Cre strain. These mice develop skin inflammation with many hallmark characteristics of human Ps including the dermal infiltration of effector T cells, the formation of neutrophil microabscesses and hyperkeratosis. IL-17A expression in the skin resulted in upregulated granulopoiesis and the migration of IL-6R-expressing neutrophils into the skin [57]. Involucrin enhancer/promoter-dependent expression of human AR (INV-AR) in the suprabasal epidermis of transgenic mice also depicted Ps-like features. Histopathologically, the INV-AR mouse had epidermal hyperkeratosis, parakeratosis, acanthosis, an exaggerated dermal vasculature and infiltrated neutrophils and CD3⁺ T lymphocytes in the lesions [58]. Thus, epidermal AR expression is a possible mediator of cutaneous inflammation and also a potential trigger of both cutaneous Ps and PsA (fig. 2).

Induced Models

Imiquimod (IMQ), a topical application targeting TLR7/8, can induce and exacerbate IL-23/IL-17 axis-dependent Ps in mice. IMQ-induced, inflamed, scaly skin lesions resemble plaque-type Ps and show increased epidermal proliferation, abnormal differentiation, CD4⁺ T cells, CD11c⁺ dendritic cells (DCs), plasmacytoid DCs and neutrophil infiltration, along with neoangiogenesis. Epidermal expression of IL-23, IL-17A and IL-17F and an increase in splenic Th17 cells were noted [59]. Recently, in an IMQ-induced Ps-like model, Ps disease was partially reduced and delayed but not abolished in the absence of IL-17RA with persisting signs of inflammation such as neutrophil and macrophage infiltrations within the skin [60]. Moreover, Shibata et al. [61] demonstrated IL-27-activated Th1-mediated responses in IMQ-induced Ps-like skin lesions. More recently, Yoshiki et al. [62] showed that IL-23 from Langerhans cells (LCs) was required for the development of IMQ-induced Ps-like dermatitis by the induction of IL-17A-producing $\gamma\delta$ T cells.

Very recently, we developed a new disease model, in which a single intraperitoneal injection of *Saccharomyces cerevisiae* mannan induced Ps-like and PsA-like symptoms in mice. Reactive oxygen species (ROS) determined the nature of the developed disease. Erythema and edema

Fig. 2. Mouse models of Ps and PsA grouped as spontaneous, genetically engineered, induced, human skin transplant and in vitro models.

of joints started 1 day after the injection and reached maximum severity on days 4–5, while skin scaling appeared from day 3. This model depicts the inflammatory phase of PsA, where macrophages, $\gamma\delta$ T cells and IL-17A are the major contributors. Treatment with clodronate liposomes, anti-Ly6G and the neutralization of IL-17A and TNF α either completely blocked or significantly attenuated both joint and skin inflammation [63].

Human Skin Transplant Models

In human skin transplant models (xenotransplants), skin biopsy from Ps patients or in vitro cultured skin is transplanted into severe combined immunodeficient (SCID) mice. These mice lack T and B cells but contain functional neutrophils and mature natural killer (NK) cells [64]. In SCID mice, grafted tissues were well tolerated and psoriatic characteristics were maintained for several months in the transplants. AGR129 mice tolerated xenogenic grafts better than the SCID mice. AGR129 mice also lack T and B cells, but unlike SCID mice, they have immature NK cells [65]. Transplant rejection was reduced in these mice. Boyman et al. [65] demonstrated that human uninvolved psoriatic skin grafted onto AGR129 mice spontaneously developed psoriatic plaques. In fact, skin grafts developed a psoriatic phenotype in 90% of the grafted mice. The grafted-skin histopathology

was comparable to Ps lesions. Inhibition of T cells with monoclonal antibodies, anti-CD3 and anti-TNF α treatments diminished Ps phenotypes [65]. Thus, activation and proliferation of skin-resident T cells are necessary and even sufficient to drive Ps inflammation (fig. 2).

In vitro Models

An alternative approach for studying Ps pathogenesis is by using in vitro models. In the in vitro system, epidermal keratinocytes obtained either from psoriatic or healthy individuals are grown at an air-liquid interface where they differentiate and mimic the morphology of the stratified squamous epidermis. Keratinocytes are then treated with different cytokines, such as IL-20 and IL-22, in order to develop psoriatic epidermis characteristics. This system enables the study of keratinocyte behavior towards different stimulation agents [55, 66] (fig. 2) and possible cross-talk events between keratinocytes and immune cells. Recent investigation of the interactions between keratinocytes and T cells in a three-dimensional microenvironment showed CD4⁺ T cell migration into the dermis, which initiated keratinocyte activation within 2 days [67]. The psoriasiform inflammation was also observed using Th1-polarized and Th17-polarized CD4⁺ T cells. Treatment with anti-inflammatory drugs reduced the expression of proinflammatory

cytokines and chemokines, leading to the suppression of the psoriasiform inflammation [67]. In vitro keratinocyte coculture also allowed for the characterizing of the cross-talk of cytokines and growth factors, where perostin tuned the magnitude of keratinocyte proliferation and differentiation by interacting with the paracrine IL-1 α /IL-6 loop [68].

Immunopathology of Ps and PsA

Both innate and adaptive immunity play a functional role in Ps pathology and in their interactions with keratinocytes. Keratinocytes have a key function in balancing skin homeostasis. Targeted deletion of cJun/JunB; K5.Stat3C in mice deregulates keratinocyte functions, leading to pathological immune responses resulting in different skin and/or joint pathologies. They also serve as sentinels of the skin and as a protective layer for the body against several invading pathogens. They express many types of innate immunity receptors like TLRs (TLR1–6, TLR9 and TLR10) recognizing PAMPS, and NLRs recognizing PAMPs and DAMPs (irritants and toxins). Activation of keratinocytes via TLR/NLR leads to predominantly Th1-type immune responses and the secretion of type I interferons (IFNs) [69]. Keratinocytes closely interact with skin-resident immune cells and thus contribute to inflammatory reactions. They produce antimicrobial peptides like psoriasin (S100A7), human β -defensins 2 and 3 and cathelicidin (LL-37) [70, 71], which form chemotactic gradients to attract immune cells to the skin tissue. Keratinocytes can also potentially secrete proinflammatory cytokines and chemokines, such as IL-1, IL-6, CXCL8, CXCL10 and CCL20 [71]. Recently, IL-19 production was found to be induced in keratinocytes by IL-17A, and this was further enhanced by TNF α and IL-22. Interestingly, IL-19 amplified many IL-17A effects on keratinocytes, including the induction of β -defensins, IL-19, IL-23p19 and Th17 and neutrophil cells attracting chemokines [72]. In another study, keratinocyte overexpression of IL-17C promoted psoriasiform skin inflammation and Ps patients treated with etanercept rapidly decreased cutaneous IL-17C levels, likely suggesting the importance of IL-17C/TNF α -mediated inflammatory signaling in Ps pathogenesis [73]. A broad spectrum of cells that includes keratinocytes possesses binding sites for IL-8. Increased expression of epidermal IL-8 receptors has been observed in psoriatic skin [74]. Furthermore, keratinocytes are able to express MHC class II molecules induced by IFN- γ and might act as nonprofessional anti-

gen-presenting cells, thus contributing to the limitation of an ongoing inflammation by antigen-specific tolerization and/or activation of T cells [75].

Innate Immunity

Monocytes/macrophages are divided into three main populations based on their functional properties: proinflammatory M1, regulatory M2 and wound-healing macrophages [76]. Recently, Wang et al. [77] demonstrated that the inflammatory state in human blood monocytes could be stimulated by IL-17. In addition, IL-17 may also promote monocyte adhesion by inducing molecules such as ICAM-1, integrin α 4, platelet/endothelial cell adhesion molecule 1 and CD99. M1 macrophages have a key function in both acute and chronic skin inflammation in animal models of Ps and PsA (the IKK, PL/J CD18 β 2 and mannan-induced Ps/PsA models), where macrophage depletion leads to resolution of skin inflammation [63, 78, 79]. Psoriatic skin contains a large number of macrophage-secreting proinflammatory cytokines (IL-6, IL-12 and IL-23) [80, 81]. Macrophages are the major source of TNF α , which activates IL-17A-driven inflammatory pathways, leading to Ps/PsA-like inflammation in mice [63]. Hence, type I macrophages have good potential to be a therapeutic target in the future.

Neutrophils and mast cells are normally found in the infiltrations of psoriatic plaques, the main source for IL-17 in the human skin. IL-17-positive mast cells and neutrophils are found at higher densities than IL-17-positive T cells in Ps lesions [82]; however, it is still debatable whether the positive staining for IL-17 in these cell types is due to its secretion or uptake from the milieu. In the mannan-induced Ps/PsA model, granulocyte infiltration has been observed in psoriatic skin and in the peritoneal cavity. Anti-Ly6G treatment suppressed both dermatitis and arthritis [63].

DCs are also sentinels of the immune system that bridge innate and adaptive immunity. They are normally found in both the layers of the skin: as LCs in the epidermis and myeloid and plasmacytoid DCs in the dermis. Another specialized subgroup of dermal DCs called TIP-DCs, producing IFN- α and inducible nitric oxide synthase (iNOS) are also present in the skin. In human Ps tissue, the majority of CD11c+ cells produce iNOS [83]. Existing data on the frequency of LCs in Ps skin are inconsistent, but in the dermis, an increased number of CD11c+ myeloid DCs secreting the proinflammatory cytokines IL-12 and IL-23 can be found. These myeloid DCs

might be the immigrant cells derived from circulating DC precursors that migrate and are trapped in the skin in response to the chemoattraction [83] induced by antimicrobial peptides and chemokine production by keratinocytes [71]. The numbers of plasmacytoid DCs are also significantly increased in Ps skin and are mainly activated via TLR signaling pathways. Large amounts of IFN- α are produced by plasmacytoid DCs in response to self-DNA/LL-37 complexes targeting TLR9 or self-RNA/LL-37 complexes recognizing TLR7 and TLR8. Self-DNA/RNA fragments are released by the dying cells in the skin [84, 85]. Additionally, it was shown that alefacept (a CD2-binding fusion protein) therapy reduces activated DCs and inflammatory gene expression in the tissue; this finding supports the involvement of DCs in Ps pathogenesis [86].

In healthy human skin, $\gamma\delta$ T cells are very rare, and it is still under debate whether they play a role in skin homeostasis or pathology. There are different subsets of $\gamma\delta$ T cells residing in different compartments of the mouse skin. One subset of dermal $\gamma\delta$ T cells expresses IL-7R, CCR6 and retinoic acid-related orphan receptor γ t (ROR γ t), which is different from the classic V γ 5V δ 1+ DETC subset of $\gamma\delta$ T cells producing IFN- γ [87, 88]. Mouse IL-17-producing $\gamma\delta$ T cells were shown to be important in IMQ-induced Ps and mannan-induced Ps/PsA models [63, 89]. In the IMQ model, opposing effects of IL-15 and IL-15R α were shown in psoriasiform skin inflammation, where IL-15 was responsible for the expansion of IL-17-producing $\gamma\delta$ (and $\alpha\beta$) T cell populations and was inhibited by keratinocyte-derived soluble IL-15 receptor antagonist [90]. Furthermore, CCR6 was required for the epidermal trafficking of $\gamma\delta$ T cells in the IL-23-induced model of psoriasiform dermatitis [91]. Recent investigations show that IL-23 from LCs was necessary for the development of IMQ-induced Ps-like dermatitis via the induction of IL-17A-producing $\gamma\delta$ T cells [62]. Ps severity in CD18 β 2 integrin hypomorphic mice correlates with the loss of skin-resident V γ 5+ T cells and the concurrent skin infiltration of IL-17- and IL-22-producing dermal $\gamma\delta$ T cells. Thus, using different animal models of Ps, it is possible to clearly determine the important contribution of $\gamma\delta$ T cells in the inflammation of the skin.

Adaptive Immunity

T cells are considered to be the major mediators of Ps, where T-cell-mediated pathomechanisms lead to a large spectrum of regulatory mediators including cytokines,

growth factors and lipid mediators, which are abnormally expressed in psoriatic skin [92]. Both lymphocyte inhibition and T-cell-specific immunosuppressive (cyclosporine) treatment lead to the clinical improvement of patients [93, 94]. Some patients do not respond to treatment with T-cell-immunosuppressive medications, which might argue for different T cell-independent pathways in Ps development. This statement is supported by recent findings using mannan-induced inflammation, where $\alpha\beta$ T cells had a negligible role in joint pathology [63]. The presence of IL-12 cytokines in the psoriatic plaques suggested dominant Th1-driven pathological events. However, another cytokine, IL-23, discovered later, was found to be crucial for disease development. This cytokine has a p19 protein paired to the IL-12 p40 subunit. In psoriatic skin, levels of the IL-23 p19 and p40 subunits, but not the IL-12 p35 subunit, increase significantly [95]. Ustekinumab binds specifically to IL-12/IL-23p40 and thus effectively neutralizes their biological activity. Recent findings imply that ustekinumab treatment improves Ps without suppressing tumor antigen-specific cytotoxic T lymphocytes, supporting clinical trials showing no increased incidence of malignancies with ustekinumab treatment [96]. IL-23 has been shown to activate T cells expressing a different cytokine profile such as IL-17A and IL-17F (termed Th17 cells) and an IL-22-expressing T-cell subset (called Th22). Both Th17 and Th22 cells require IL-23 for their expansion/maintenance and are implicated in Ps pathogenesis [97–99]. Thus IL-23-mediated skin inflammation is IL-17A-dependent, which in turn activates keratinocytes and leads to further production of inflammatory mediators; this all helps in maintaining the psoriatic lesions [99]. Th17 cells are rarely found at inflammatory sites in comparison with other T-cell subsets; this can be explained by the finding that Th17 cells rapidly shift into the Th1 phenotype in the presence of IL-12 and/or TNF α and they also possess self-regulatory mechanisms limiting their own expansion [100]. Different models of Ps are available to understand such disease pathology. The IL-22-overexpressing transgenic mouse has aberrant skin phenotypes mimicking Ps [101] and epidermal hyperplasia and macrophage infiltration in the dermis. It was shown that in the absence of IL-22, IL-23-mediated dermal inflammation was reduced significantly [102]. Recently, in the IMQ-induced psoriasiform skin inflammation model, skin pathologies were found to be almost absent after daily applications of IMQ in IL-22-deficient mice and also in mice treated with blocking anti-IL-22 antibodies [103]. Since IL-22

neutralization does not induce considerable improvements in the majority of Ps patients [104], the precise therapeutic potential of this cytokine for these patients has still to be clarified.

Recently, a novel type of Th cells, designated as Th9, was identified, but little information is available about these cells in humans. Recently, Schlapbach et al. [105] showed that most of the memory Th9 cells are skin-tropic or skin-resident. Human Th9 cells coexpress TNF α and granzyme B, lack coproduction of Th1/Th2/Th17 cytokines and are specific to *Candida albicans*. IL-9-producing T cells are increased in the skin lesions of Ps, suggesting that they may contribute to human inflammatory skin disease. IL-9 is necessary for the efficient production of IFN- γ , IL-9, IL-13 and IL-17 by skin-tropic T cells. This study suggests that human Th9 cells may have a protective function against extracellular pathogens, but anomalous activation of these cells may contribute to inflammatory diseases of the skin.

ROS in Psoriasis

ROS and reactive nitrogen species (RNS) are oxygen-derived reactive molecules, free radicals and nitrogen-containing oxidants with one or more uncoupled electrons. ROS generation as a byproduct occurs with mitochondria, peroxisomes, cytochrome P450 and other cellular elements. The phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase was the first identified example of a system that generates ROS not as a byproduct, but rather as the primary function of the enzyme system. The phagocyte NOX family of NADPH oxidases consists of NOX complexes (NOX1–5) and dual oxidase complexes (DUOX1–2) [106]. These enzymes participate in ROS generation by transporting electrons across the plasma membrane. It was originally thought that only phagocytic cells were responsible for ROS production as part of the defense mechanism against invading pathogens, but it has also been demonstrated that ROS have a role in cell signaling including apoptosis, gene expression and the activation of cell signaling cascades [107]. Overproduction or inadequate removal of ROS can result in oxidative stress, leading to cell and tissue pathological changes due to damage to lipids, proteins and DNA [108]. In 1957, Berendes et al. [109] described a rare syndrome, triggered by pyogenic infections, now referred to as chronic granulomatous disease (CGD), caused by the absence of respiratory burst in the phagocytes. Patients with this genetic disorder suffer from life-threatening

infections [110, 111]. CGD patients have mutations in all of the subunits of NOX complexes [112, 113]. An insufficient antioxidant system, together with increased levels of ROS, leads to pathological changes in cells and tissues, i.e. in inflammatory skin conditions [114]. Oxidative stress is believed to be a key factor in the pathogenesis of Ps [108]. Polymorphonuclear infiltrates in the dermis of psoriatic lesions were observed previously [115]. ROS discharged by keratinocytes, fibroblasts and endothelial cells might have chemotactic effects on neutrophils [116], and their accumulation in psoriatic lesions may cause abundant superoxide (O_2^-) production during phagocytic processes [117].

The Phagocyte NADPH Complex

In a resting condition, the catalytic core of the phagocyte NADPH complex is composed of an enzymatic part, i.e. flavocytochrome b558, which consists of membrane integrated glycoprotein, gp91phox (NOX2) and p22phox protein. These jointly make up the central component of NADPH oxidase (fig. 3a) [118]. The phagocyte NADPH complex also contains four cytosolic components denoted as *Ncf1* (p47phox), *Ncf2* (p67phox), *Ncf4* (p40phox) and the small G-protein Rac1 (or Rac2) [119], which play a regulatory role (fig. 3a). In the resting state, this cytosolic Phox-protein complex is inactive due to *Ncf1* autoinhibited conformation. Upon activation (exposure to microbes or inflammatory mediators), there is an exchange of guanosine diphosphate for guanosine triphosphate on Rac, leading to its activation. In addition, p47phox becomes heavily phosphorylated, releasing autoinhibitory confirmation, which enables the whole Phox-protein translocation and binding to flavocytochrome b558 [120]. The active enzyme complex transports electrons from cytoplasmic NADPH to extracellular or phagosomal oxygen to generate ROS superoxide (O_2^-) molecules (fig. 3b).

ROS/RNS Generation

ROS and RNS are derived from the NOX/DUOX enzymes. O_2^- is generated by the NOX enzymes and can be converted to hydrogen peroxide (H_2O_2), either spontaneously or by the action of superoxide dismutase (SOD). Alternatively, it can react with NO to produce peroxynitrite ($ONOO^-$). H_2O_2 generated by the DUOX enzymes or by the dismutation of O_2^- can be scavenged by the an-

Fig. 3. The NADPH complex consists of the membrane flavocytochrome b558 (NOX2 and p22^{phox} protein) and the cytosolic components Ncf1, Ncf2, Ncf4 and the small G-protein Rac1 or Rac2 (a). Upon activation, there is an exchange of guanosine diphosphate (GDP) to guanosine triphosphate (GTP) on Rac, leading to

its activation. Phosphorylated Ncf1 releases the autoinhibitory confirmation and enables the whole complex translocation to flavocytochrome b558. The active enzyme complex transports electrons from cytoplasmic NADPH to extracellular or phagosomal oxygen to generate ROS.

tioxidants catalase (Cat) or glutathione peroxidase (GPx) and form H₂O and O₂, be partially reduced to generate hydroxyl radical (OH) by the Fe³⁺-catalyzed Haber-Weiss and Fenton reactions or react with chloride in a reaction catalyzed by myeloperoxidase, resulting in the formation of hypochlorous acid (HOCl; fig. 4) [121].

Cellular Antioxidants

Antioxidants are compounds that will provide electrons to free radicals to neutralize them. It has been suggested that there is an insufficient antioxidant system in the pathogenesis of Ps. SOD, GPx and Cat are the most important enzymes in the antioxidant system. SOD protects cells from the toxic effects of O₂ radicals. Various results have been obtained in earlier studies on SOD activity in psoriatic patients. Therond et al. [122] found substantial SOD activity in the fibroblasts and erythrocytes of Ps patients, while another study showed lower

Fig. 4. Schematic representation of ROS/RNS generation in macrophages, where O₂⁻, NO, peroxynitrite (ONOO⁻), H₂O₂, hydroxyl radical (OH) and hypochlorous acid (HOCl) are formed by the action of the NOX1–5, DUOX1/2 enzymes and antioxidants like SOD, Cat, GPx, myeloperoxidase (MPO) and Fe³⁺.

SOD activity in the psoriatic group and suggested that SOD activity is lower in Ps because of an insufficiency in the antioxidant system [123]. Several other studies have also reported suppressed SOD activity in neutrophils

[124, 125]. Extracellular SOD has antichemotactic activities and has been detected at low levels in Ps lesions. EC-SOD knockout mice develop severe IL-23-mediated skin inflammation. The infiltration of immune cells at IL-23 injection sites and the expression of proinflammatory cytokines and chemokines are more elevated in these mice [126]. Interestingly, the IQM-induced mouse model shows an aberrant antioxidant system, with increased levels of myeloperoxidase and oxidative stress but less SOD activity. This model may thus be useful for studying the pathogenic role of redox imbalance in Ps [127]. The clinical response to efalizumab correlates with the antioxidant enzyme GPx activity in the blood cells, suggesting high hydrogen peroxide levels with Ps persistence [128]. Similarly, decreased neutrophil GPx activity has been observed in chronic plaque-type Ps [129]. Notably, erythrocyte Cat activity is significantly higher in psoriatic subjects than in controls [123, 130]. All of these findings support the general hypothesis that disturbance in the oxidant-antioxidant system may play an important role in the pathogenesis of Ps.

Protective Nature of ROS

Recent studies implicate ROS as playing an immunoregulatory role in inflammatory diseases; this is in contrast to the traditional view of their damaging effects. As described previously, CGD patients are more prone to the development of different autoimmune diseases. Elevated levels of ROS due to defects in GPx1 and Cat in GPx1^{-/-} × Cat^{-/-} mice conferred resistance to DSS-induced colitis. The administration of N-acetylcysteine reduced Treg functions and made these mice susceptible to colitis [131]. Similarly, GPx1 deficiency in mice attenuated allergen-induced airway inflammation by suppressing Th2 and Th17 cell development [132]. Ablation of peroxiredoxin (a nonenzymatic cellular antioxidant) in mice attenuated colitis by increasing Treg functions [133]. Most recently, lowered ROS levels were associated with chronic colitis in Ncf1/p47^{phox}-mutant mice, mediated by local accumulation of peroxynitrites, proinflammatory cytokines and lymphocytes and systemic immune deregulation, similar to in CGD patients [134]. These studies implicate an association of ROS level with T cell/Treg responsiveness. Previously, reduced ROS levels were associated with the development of autoimmune arthritis and encephalomyelitis using the Ncf1 gene-mutated mouse strain, in which the Ncf1/p47^{phox} subunit of the NOX2 complex was dysfunctional [135]. Ncf1 has

been identified as a regulator of autoimmune arthritis in rodents [136]. Decreased ROS levels in these animals have been associated with an increased number of cell surface thiol groups on T cells, significantly enhancing the arthritogenicity of the cells [137]. Most importantly, macrophage-specific ROS production has been reported to suppress T cell responses and arthritis development [138]. It was previously suggested that Tregs under reduced ROS conditions are hypofunctional [139], and recently, Treg hyperfunctionality in elevated levels of ROS in an IMQ-induced Ps dermatitis model was observed [140]. Treg hyperfunctionality with high levels of ROS is suggested to operate as a compensatory mechanism to overcome the damaging effects of ROS and thereby decrease Ps disease activity [140]. Thus, the restoration of impaired Treg functions could be a possible therapeutic strategy for Ps patients.

Similarly, successful treatment of psoriasis vulgaris patients by hyperbaric oxygen therapy, which increases cellular ROS [141], was demonstrated previously [142]. Furthermore, hyperbaric oxygen therapy attenuated IMQ-induced Ps dermatitis whereas N-acetylcysteine aggravated it [140]. Recent studies also demonstrated the effect of photo(chemo)therapy in increasing Treg functions and reducing circulating Th17 cells [143]. Since it is known that phototherapy generates elevated ROS levels [144], it can be considered that elevated ROS might be the driving mechanism for Treg hyperfunctionality.

Ncf1 as a Regulator of Mannan-Induced Ps/PsA in Mice

Recently, we observed the immunoregulatory role of monocyte/macrophage-derived ROS in Ncf1^{mlj/mlj}.MN+ mice, which expresses functional Ncf1 in macrophages [63]. We measured mannan-stimulated ROS/RNS at the cell (blood granulocytes) and organ (hind paws) levels in B10Q, B10Q.Ncf1^{mlj/mlj}.MN+ and B10Q.Ncf1^{mlj/mlj} mice, where secreted ROS correlated with relatively milder peripheral-joint arthritis phenotypes and ROS deficiency promoted a more aggressive disease. Similarly, β1,3-glucan of *Alcaligenes faecalis*-induced ROS from monocytes was also shown to suppress innate inflammation [145]. Moreover, the protective function of ROS has been shown in other human skin diseases like scleroderma [146].

Hence, the normal production of ROS by a functional NOX2 seems to be critical for attenuating Ps and arthritis phenotypes in mice [63], but the mechanism whereby

ROS protection operates at the cellular and molecular level needs to be investigated further. It is most likely different from in autoimmune arthritis where $\alpha\beta$ T cells play a critical role under the regulatory control of macrophage-produced ROS [138], and also different from the IMQ-Ps dermatitis model where the ROS-mediated prevention of Ps operates through enhanced expression of indoleamine 2,3-dioxygenase and Treg activity [140].

Concluding Remarks

PsA and PsO are common but complex diseases that have so far escaped a detailed understanding of their causative pathways. However, new genetic findings, the development of effective treatments of established disease and the establishment of useful animal models will be valuable for future research. Using these tools, understanding the cause and pathogenic mechanisms involved is within reach, and will facilitate the development of treatments to not only ameliorate but also prevent and cure these diseases.

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