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Review Article

Recent genetic advances in innate immunity of psoriatic arthritis

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A B S T R A C T

Psoriatic arthritis (PsA) is a heterogeneous disease that affects multiple organ systems including the peripheral and axial joints, entheses and nails. PsA is associated with significant comorbidities including cardiovascular, metabolic, and psychiatric diseases. The pathogenesis of PsA is complex and involves genetic, immunologic and environmental factors. Recent evidence suggests the heritability for PsA to be stronger and distinct from that of PsC. Prominent genes identified via GWAS for PsA include *HLA-B/C*, *HLA−B*, *IL12B*, *IL23R*, *TNP1*, *TRAF3IP3*, and *REL*. We review the genetics of psoriatic arthritis and discuss the role of the innate immune system as important in the pathogenesis of PsA by focusing on key signaling pathways and cellular makeup. Understanding the candidate genes identified in PsA highlights pathways of critical importance to the pathogenesis of psoriatic disease including the key role of the innate immune response, mediated through IL-23/IL-17 axis, RANK and NFκB signaling pathways.

1. Introduction

Psoriatic arthritis (PsA) is a chronic, debilitating immune-mediated disease that occurs in up to 30% of patients with cutaneous psoriasis (PsC) [1]. Psoriatic skin is characterized by well-demarcated erythematous plaques on extensor surfaces. Characteristic histological findings in the skin include acanthosis (thickening of the epidermis), hyperkeratosis (thickening of the stratum corneum), parakeratosis (retention of nuclei in the stratum corneum), Kogoj's spongiform pustule and Munro's microabcesses (neutrophil granulocytes within the epidermis), and mixed dermal inflammatory infiltrates consisting of T cells, dendritic cells, macrophages and neutrophils. The arthritis of PsA targets the spine, peripheral joints and entheses (attachment sites of ligament to bone). PsA can lead to destructive, erosive bone disease causing significant morbidity [1].

Almost all patients with PsA develop PsC, and in the majority, cutaneous lesions precede development of joint disease (70–80%) with a lag time of about 7–12 years from onset of psoriasis to diagnosis of PsA [1–4]. PsC and PsA are both associated with significant comorbidities including metabolic syndrome, cardiovascular disease, autoimmune and psychiatric disorders, and studies have shown that PsA poses a higher risk than PsC disease alone [5–9]. The majority of individuals with PsA also have psoriasis, suggesting these diseases share a common pathophysiologic mechanism. However, the severity of cutaneous manifestations does not predict or correlate with the musculoskeletal manifestations. Possible explanations for the variable phenotypes of psoriasis and psoriatic arthritis include differences in genetic makeup or differences in innate immune responses to physiologic triggers [10–12].

It is well known that psoriatic arthritis is a highly heritable polygenic disease. Mounting evidence suggests that PsA has a genetic component that is stronger and distinct from that of PsC. Twin studies of psoriatic arthritis in European populations have reported a greater concordance in monozygotic twins (80–100%) than in dizygotic twins [13]. Additionally, an Icelandic study calculated the heritability risk ratio (risk of first-degree relatives compared to unrelated population controls) of psoriatic arthritis to be 40 [14], substantially higher than the risk ratio of psoriasis [14,15]. In this article we review the genetics of psoriatic arthritis and discuss the role of the innate immune system in the pathogenesis of PsA. The IL-23/IL-17 axis, RANK and NFκB signaling pathways are critical mediators of psoriatic disease; further research will clarify their pathogenic roles and how they differ between PsA and PsC.

2. Genetic association within the MHC region

Genetic investigations have revealed the most dominant genetic effect of PsC and PsA is located on chromosome 6p21.3 within the MHC region, accounting for one-third of the genetic contribution of both diseases [16]. Genetic variants within the class I HLA allele as well as non-HLA genes within the MHC region also were identified.

The most notable haplotype within the MHC region is the psoriasis susceptibility region 1 (PSOR1). Studies have confirmed that *HLA-Cw*0602* is the risk variant for PsC within the MHC region [17], and has been correlated with early age of onset, higher likelihood of familial heritability, guttate psoriasis, Koebner phenomenon, and decreased activity during pregnancy [18]. HLA-Cw*0602 is more strongly

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associated with PsC than PsA, and interestingly HLA-Cw*0602 PsC carriers are less likely to develop arthritis or have a delayed onset of PsA. PsA has been associated with other HLA antigens including HLA−B13, HLA−B27, HLA-B38/39, HLA-B57 and HLA-DRB1*04 [19], with HLA-C*12/B*38, HLA-B*27, and HLA-C*06/B*57 alleles seeming to be most relevant [20].

HLA alleles have also been associated with disease expression and prognosis of PsA. HLA-B38 and HLA-B29 are associated with peripheral polyarthritis, while axial involvement is associated with HLA-B27 [21]. HLA-B27 occurs more frequently in patients with dactylitis [22]. In addition, non-HLA alleles within the MHC region have been implicated in susceptibility to PsA including regions in the *TNFA* promotor region [23].

3. Genome-wide association strategies

Genome wide association studies (GWAS) are used to identify susceptibility determinants across the entire genome in order to identify novel genes. Single-nucleotide polymorphism (SNP)-based GWAS have identified approximately 2000 robust associations with > 300 complex diseases [24]. Prominent genes identified via genome-wide association studies (GWAS) in PsA cohorts include *IL12B*, *IL23R*, *TNIP1* (TNFAIP3-interacting protein 1), *TRAF3IP2* (tumor necrosis factor, Alpha-induced protein 2), and *REL* [25]. Candidate genes identified in PsA studies highlight pathways of importance in psoriatic disease including abnormalities in both the adaptive and innate immune system.

The *IL12B* gene encodes the shared p40 subunit of IL-12 and IL-23, and is involved in both the IL-12/Th1 pathway and the IL-23/Th17 pathway, both of which are prominent signaling pathways in psoriasis pathogenesis [26]. The *IL23R* gene encodes the IL-23R subunit of the heterodimeric IL-23R/IL-12Rβ1 receptor complex in which IL-23 signals through. Binding of IL-23 to IL-23R/IL-12Rβ1 leads to STAT3 phosphorylation and IL23-dependent gene expression. IL-23 promotes expansion and maintenance of Th17/Tc17 cells, a subset of T cells that are critical mediators of inflammation in psoriasis and PsA.

TN1P1 and TNFAIP3 work together in inhibition of NFκB signaling, via prevention of NEMO polyubiquination and subsequent degradation of the NFκB inhibitor, IκB [27,28]. TNIP1 inhibits NFκB signaling through several receptors including TNFα receptor, the EGF receptor, and Toll-like receptors [27,29]. In addition, a noncoding variant of *TNIP1* is associated with psoriasis, suggesting that reduced ability to suppress NFκB signaling is important in the elicitation of psoriasis [30].

REL encodes one of five subunits found in NFκB dimers and belongs to the Rel/NFκB family of transcription factors. With the exception of c-Rel, most Rel/NFκB family members are constitutively expressed in multiple cell types, whereas c-Rel is expressed primarily in lymphoid tissues by lymphoid and myeloid cells [31]. c-Rel appears to play a specific role in T cell function as c-Rel$^{-/-}$ mice are immunodeficient and have defects in response to immune signals. Bunting et al. identified c-Rel targeted genes including the known PsA susceptibility locus *TNFAIP3* [32]. TNFAIP3 controls the ubiquination and degradation of IκB-a, which inhibits NFκB transcription by retaining it in the cytoplasm [11]. c-Rel also mediates differentiation of CD4^{+}FoxP3^{+} regulatory T cells which have the ability to develop into IL-17 producing cells in psoriasis [33]. Further, it promotes IL-12 and IL-23 expression, by which Th1 and Th17 immune responses might be evoked [34,35].

4. Genes involved in innate immunity

Novel insights into important immune pathways are corroborated by genetic evidence and support an important role for the innate immune system in the initiation of psoriatic disease, amplification by triggering adaptive immunity, and tissue destruction and remodeling.

The innate immune system is important in the initiation of psoriatic inflammation. As in many autoimmune diseases, various triggers result in initiating events that lead to a common interaction and inflammatory cascade resulting in characteristic clinical manifestations. Several triggering factors have been associated with psoriasis exacerbations, including skin breakdown, wounds, stress and medications. The resulting inflammation may be in part dependent upon activation of the innate immune system [36–38]. Cutaneous triggers result in keratinocyte damage which upregulates inflammatory mediators such as type I IFN, tumor necrosis factor (TNF)- α, interleukin IL-1 and IL-6 by resident keratinocytes or infiltrated plasmacytoid dendritic cells. These inflammatory mediators further recruit cells from the adaptive immune system. An important example of this process is the Koebner phenomenon, or the development of psoriatic lesions after physical trauma [39,40]. Self-nucleic acids can be released from keratinocytes or from neutrophil extracellular traps released from infiltrating neutrophils [41], which trigger TLR7/8 signaling in plasmacytoid dendritic cells (pDCs) and subsequent IFN production [39,40]. Skin breakdown from injury or stress also causes increased production of antimicrobial peptides, such as cathelicidin (LL-37), which initiate inflammation through TLR7/8 activation [17,18]. Notably, systemically administered IFN for treatment of diseases such as hepatitis, multiple sclerosis and melanoma have been shown to exacerbate psoriatic disease [42–44]. Preventing immune activation may therefore be the key to preventing psoriatic flares. However, the role of innate immune activation in progression to chronic PsA is not well understood.

Amplification of psoriatic inflammation is a complex process that involves interaction of the innate and adaptive immune systems. Inflammatory signals activate other dendritic cell populations to migrate to the skin-draining lymph node and activate naïve T cells to differentiate into Th1 and Th17 cells, which have well established roles in psoriasis. These cells also play important roles in perpetuation and amplification of the inflammatory reaction in the skin. Molecular signaling pathways such as IL-17, IL-23, TNF, RANK and NFκB lead to effector cytokine signals that simulate epidermal hyperplasia and abnormal keratinocyte differentiation as well as destructive bone remodeling that leads to joint inflammation and damage. Genetic associations with molecular pathways important in PsA pathogenesis will be discussed below followed by discussion of the aberrations in innate immune cell function.

5. Molecular pathways in PsA pathogenesis

5.1. IL-23/IL-17 pathway

Genetic studies provided the first evidence that interleukin (IL)-23 is involved in the pathogenesis of psoriatic arthritis. Variants in several genes involved in the IL-23/IL-17A proinflammatory cytokine pathway have been associated with the disease, with *IL12B* (IL-12p40), *IL23R*, and *TRAF3IP2* (Act1) achieving genome-wide significance [45–47]. Is it increasingly recognized that the IL-23/IL-17 pathway plays a major role in PsA immunopathogenesis with therapies targeting the IL-23/IL-17A axis showing clinical efficacy for both PsA and PsC [48–50]. Notably IL-23/IL-17, and RANK/RANKL pathways act through NFκB to promote inflammation and bone resorption that is the hallmark feature of PsA.

5.2. IL-23 and IL-23 receptor

IL-23 is a heterodimeric cytokine composed of the p19 and p40 subunits that bind to the heterodimeric IL-23R/IL-12Rβ1 receptor. Both subunits are secreted primarily by innate immune cells, macrophages, and dendritic cells [51]. IL-23R is expressed on surface of lymphoid cells, innate lymphoid cells and myeloid cells including dendritic cells (DCs), macrophages and monocytes [52]. Janus kinases (Jak)2 and Tyk2 bind to IL-23R and induce phosphorylation of signaling through signal transductor and activator (STAT)3 to induce RORγ, resulting in Th17 specific cell differentiation as evidenced by increased gene expression of IL-17A, IL-17F and IL-23R [53,54]. IL-23 also stimulates degradation of the inhibitory subunit of nuclear factor kappa B (IκBα)

to induce activation of nuclear factor of kappa light chain enhancer of activated B cells (NFκB), an essential factor in activation of innate immune responses [55].

5.3. IL-17 and IL-17 receptor

The interleukin 17 family is a newer group of proinflammatory glycoproteins that have been implicated in the pathogenesis of psoriasis. The IL-17 family consists of six members (A-F), the most proinflammatory being IL-17A and IL-17F. IL-17A is produced as a homodimer or heterodimer with IL-17F by T cells, innate lymphoid cells, mast cells and neutrophils [56,57]. IL-17 binds to IL-17R which is expressed in monocytes, lymphocytes, lymphoid tissue inducer cells, fibroblasts and keratinocytes [58,59]. IL-17RA and IL-17RC signals through similar expression to fibroblast growth factor (SEFIR) genes and IL-17R with the adapter protein Act1 [60]. Act1 is a key adapter protein for the IL-17 receptor and forms a complex with the inducible kinase IKKi after stimulation with IL-17 and leads to the formation of tumor necrosis factor associate factor (TRAF)2-Act1 and TRAF5-Act 1 complexes [61] and stabilization of CXCL1 mRNA, a neutrophil chemokine [62]. Act1 also binds TRAF6 to activate the NFκB activator protein 1 (AP-1) or the CCAAT-enhancer- binding protein (C/EBP) cascade [63,64]. Independently of IKKi, Act1 ubiquitinates TRAF6 leading to the activation of NFκB [65].

5.4. RANKL and RANK receptor

Psoriatic arthritis is characterized by pathologic bone remodeling and extensive bone resorption induced by receptor activator of nuclear factor kappa (RANK) and its ligand RANKL. A recent study showed an association with single-nucleotide-polymorphism (SNP) rs8092336 within the *RANK* gene locus in ankylosing spondylitis but its susceptibility in PsA is less clear [66]. Assmann et al. studied the association between susceptibility of PsC and PsA in genes encoding *RANK*, *OPG* and *RANKL* but noted only nonsignificant trends for SNP rs1054016 for psoriasis arthritis [67].

RANKL is a homotrimeric transmembrane protein expressed by bone-forming osteoblasts under physiological conditions; upon proteolytic cleavage RANKL is secreted as a soluble protein [68]. RANK is a transmembrane receptor located on monocyte derived osteoclast precursors and dendritic cells. Interaction of RANK and RANKL results in differentiation of these cells to multinucleated, bone-resorbing osteoclasts and hence promotes bone remodeling observed in PsA [68,69]. The RANK receptor recruits TRAF adaptor proteins (TRAF2,5,6) to induce NFκB and mitogen-activated kinases such as Jun N-terminal kinase, nuclear factor of activated T-cell cytoplasmic 1 (NFATc1) and AP-1 [70] leading to secretion of bone matrix degradation enzymes, matrix metalloproteinase 9 (MMP) and cathepsin K (CatK) [71]. RANK is elevated in synovial fluid of psoriatic arthritis patients and both IL-23 and IL-17 upregulate its expression [72–74]. IL-20 secreted by keratinocytes and monocytes is also increased in PsA synovial fluid and upregulates RANK and RANKL [75,76]. In skin, IL-20 promotes keratinocyte proliferation and may therefore be an important link between skin inflammation and arthritis [67].

5.5. NFκB pathways

IL-23, IL-17A and RANKL all activate the NFκB pathway to upregulate response genes that are critical to the pathogenesis of PsA, shown in Fig. 1d. NFκB is a transcription factor that regulates a large number of genes in response to infection and inflammation. Inappropriate NFκB activity has been linked with many autoimmune and inflammatory conditions, including PsA [77]. NFκB represents a family of structurally related proteins (p100 or NFκB2, p105 or NFκB1, p65 or RelA, RelB, or c-Rel), which exist as homo- or heterodimers. Effects of NFκB are mediated through three pathways 1) the canonical, 2) the p105 and 3) the alternative (p100) pathway (reviewed in [78]). In the canonical pathway, phosphorylation of inhibitory IκB proteins (IkBa) leads to release of NFκB and its nuclear translocation to promote inflammation and cell survival. The p105 pathway is dependent on phosphorylation of p105 proteins, leading to nuclear translocation of p52 heterodimer complexes to promote inflammation. Unlike the canonical and p105 pathways, the alternate p100 pathway does not depend on the NFκB essential modulator (NEMO)-IKKa-IKKb (NEMO-IKK) complex for phosphorylation, but rather on NFκB inducing kinase (NIK) and IKKa heterodimers phosphorylate p100 and allows nuclear translocation of p52/RelB heterodimers.

Genome-wide association studies (GWAS) have revealed several PsA susceptibility genes associated with the NFκB pathway. Next to SNPs for genes involved in IL-23 signaling, loci including TNF induced protein 3 (*TNFAIP3*) showed a strong association with psoriasis [79]. *TNFAIP3* encodes the A20 cytoplasmic zinc finger protein, which induces degradation of NEMO to negatively regulate NFκB [80]. Interestingly, A20 (*Tnfaip3*) deficient mice exhibit sustained NFκB activity and enhanced osteoclastogenesis, and A20 deficiency in keratinocytes promotes hyperkeratosis, but not psoriasis [81]. Other significantly related genes involved in the NFκB pathway include *TNIPI*, *TRAF3IP3*, *NFKBIA* and *REL* (c-Rel) [82–85]. Tumor necrosis factor receptor-associated factor 3-interacting protein interacting protein 2 (*TRAF3IP2*) is also known as Act1 [86]. Act1 deficient mice develop skin inflammation and Act-1 mediated signaling is required for the pathogenesis of arthritis [87,88].

6. Role of innate immune cells in PsA pathogenesis

6.1. Dendritic cells

Dendritic cells (DCs) are a heterogeneous subset of antigen presenting cells that are an important link between the innate and adaptive arms of the immune system. DC have been implicated in numerous inflammatory and autoimmune diseases, including PsA. DCs activate adaptive immune response through antigen presentation and secretion of proinflammatory cytokines and result in T cell differentiation. In PsA, DCs secrete TNFα, IFN-γ, IL-12, and IL-23 following Toll-like receptor stimulation which results in differentiation of T cells to the Th1 and Th17 subtypes that have been shown to be important mediators of PsA inflammation [89]. Interestingly, the synovial fluid of patients with psoriatic arthritis has an increased ratio of immature myeloid to plasmacytoid dendritic cells which have upregulation of TLR2, but not TLR4 expression. A recent study identified TLR2 gene rs5743708 as a susceptibility factor for developing psoriatic arthritis and reported an associated 10-fold increased risk. This missense mutation reduces activation of the NFκB pathway and compromises intracellular signaling. Given that NFκB also serves as a risk factor for PsA there may be other effects of this polymorphism that also contribute to PsA risk.

In vitro studies of dendritic cells from patients with PsA show impaired secretion of proinflammatory cytokines from dendritic cells following stimulation with Toll-like receptor 2 as well as increased intracellular expression of suppressor of cytokine signaling 3 (SOCS3) and TNF Alpha induced protein 3 (TNFAIP3) [90]. SOCS3 inhibits cytokine signaling by acting as a kinase inhibitor to JAKs or as a competitive binder for docking sites with STAT. TNFAIP3 is involved in the cytokine-mediated immune and inflammatory response and has been identified as a prominent gene in psoriatic arthritis hereditability [91]. DCs in psoriatic arthritis also express molecules such as ATG16L1 and NADPH oxidase that are transported to endosomes to activate Toll-like receptors causing production of proinflammatory cytokines [90,92].

Another subset of dendritic cells that express CLEC9A have recently been shown to be a crucial link to the innate and adaptive immune system in psoriatic arthritis through their colocalization and cross-presentation to $CD8^+$ T cells [93]. CLEC9A expression is specific to $CD141^+$ dendritic cells and has been shown to be increased in psoriatic skin compared to control [93]. CLEC9A cells colocalize with $CD8^+$ T

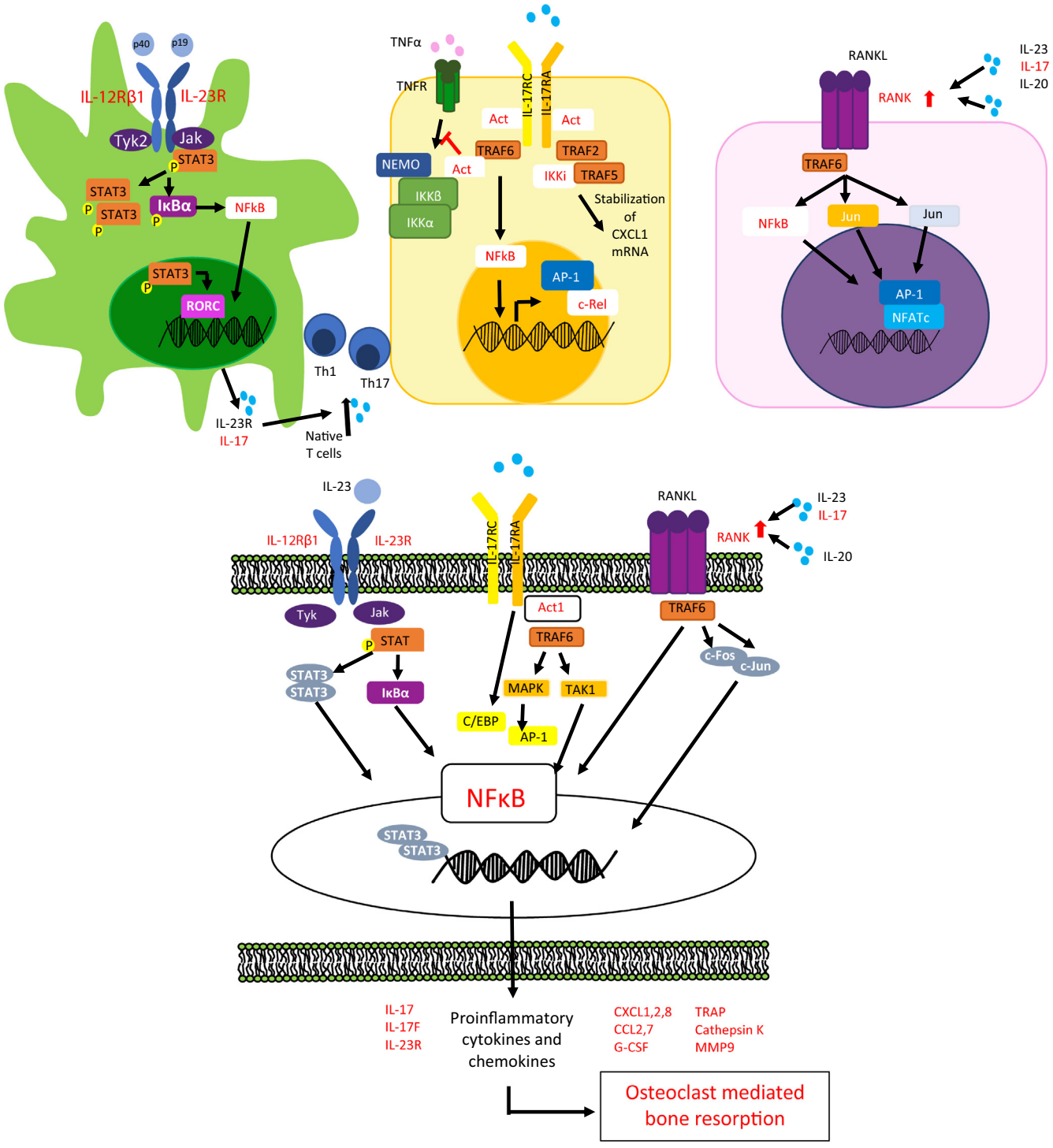

Fig. 1. (a) IL-23 signaling. IL-23 subunit p40 and p19 binding to respective subunit IL-12Rβ1 and IL-23R. Signaling pathway is present on dendritic cells (as in figure) but also innate lymphoid cells, myeloid cells, macrophages and dendric cells. IL-23 signals through Jak2/Tyk2 to induce phosphorylation of STAT3 and induce RORC gene resulting in Th17 and Th1 cell differentiation. (b) IL-17 signaling through IL-17 receptor expressed monocytes, lymphocytes, lymphoid tissue inducer cells, fibroblasts and keratinocytes (shown in figure). IL-17 signals through IL-17RA and IL-17RC to recruit Act adaptor to in turn recruit TRAF2,5,6. TRAF2 and 5 lead to stabilization of CXCL1 mRNA whereas TRAF6 leads to activation of NFkB and AP-1. (c) RANK/RANKL signaling pathway also leads to activation of NFkB pathway. (d) Highlights IL-23, IL-17 and RANK signal through NFkB to induce crucial chemokines and cytokines that lead to bone resorption in PsA. PsA susceptibility genes are in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

cells and have the ability to cross-present exogenous antigen to native $CD8^+$ T cells. Increased $CD8^+$ T cells in synovial fluid may be partly explained by inappropriate activation of dendritic cells [94]. Interestingly, TNF inhibition reduces CLEC9A expression in synovial tissue which correlates with a positive clinical response [93]. Additionally, CLEC5A (MDL-1) is known to play a role in the activation of osteoclasts via both RANKL and IL-23 pathways [95]. IL-23 upregulates RANK expression as well as MDL-1, a transcriptional target during myeloid differentiation that was recently identified to play a key role in myeloid progenitors, capable of osteoclast formation in inflammatory arthritis

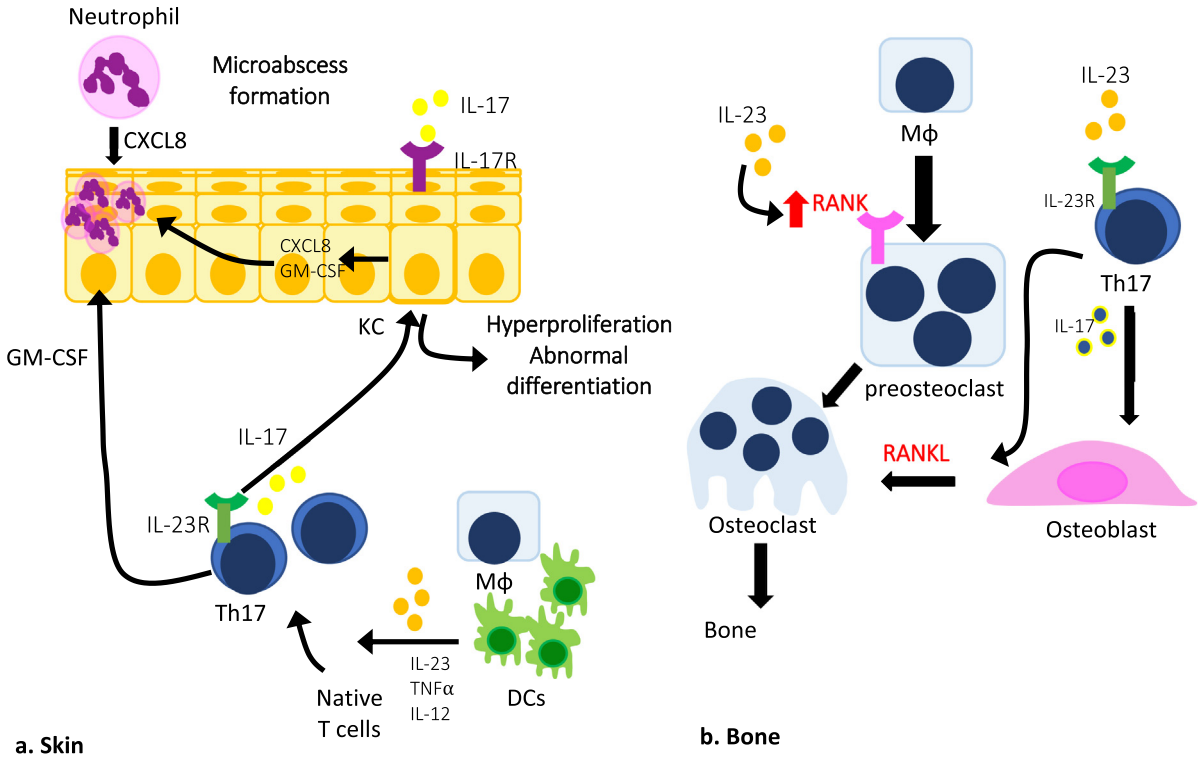

Fig. 2. (a) In the skin, macrophages and dendritic cells secrete IL-23 to induce Th17 differentiation and secretion of IL-17. IL-17 activates keratinocytes and leads to epidermal hyperplasia. Th17 cells also promote neutrophil recruitment through stimulation of GM-CSF. Neutrophil secrete CXCL8 which leads to microabscess formation. In the bone, IL-23 upregulates RANK on preosteoclasts. IL-23 secreted by macrophages induces IL-17 from TH17 cells which act on osteoblasts to secrete RANKL. Th17 cells also secrete RANKL to induce osteoclasts to secrete bone-degrading enzymes.

[96,97].

6.2. Monocytes and macrophages

Monocytes and activated macrophages are important mediators of inflammation and as well as bone resorption in PsA. Classically there are two main phenotypes of macrophages. M1 macrophages are proinflammatory and act as host defense against infection. M2 are considered anti-inflammatory and are associated with tissue remodeling. Characteristically, M1 phenotype predominates in PsA resulting in secretion of abundant proinflammatory cytokines, presentation of antigen to T and B cells, and increased bone resorption [98]. Reduction in macrophage numbers in the synovium of PsA correlates with treatment response emphasizing a pathogenic role for these cells [99].

Osteoclasts are terminally differentiated cells of the myeloid lineage and their precursors are mononuclear phagocytes that serve a specialized function to degrade bone. Osteoclasts have the ability to adapt to stimuli in the microenvironment, including cytokine milieu and cell-cell interactions with other innate immune cells. This suggests that the bone resorption by osteoclasts in PsA does not fit in the M1/M2 paradigm but rather these cells have a dual phenotype [100]. Additionally, activation of macrophage TLRs can lead to NFκB activation and inhibition of RANK expression, this leading to osteoclastogenesis [101].

GWAS studies have identified *IL12B* on locus 5q33.3 to be a key candidate gene linked to psoriatic arthritis pathogenesis [83]. The *IL12B* gene encodes the p40 subunit of IL-12 and IL-23, and is expressed by activated macrophages that serve as essential inducers of T-helper-1 cell development. IL-12 is produced by macrophages (and dendritic cells) and is increased in synovial tissue and synovial fluid of PsA [102].

6.3. Neutrophils

As discussed above, the IL-23/IL-17 axis results in induction of the NFκB pathway and this in turn results in amplified production of granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage stimulating factor (GM-CSF) and chemokines CXCL1, CXCL2, CXCL5, CXCL8/IL-8 that recruit the migration of neutrophils [103–105]. Additionally, IL-17 enhances neutrophil mobilization through increased endothelial expression of P-selectins, *E*-selectins and integrin ligands, including ICAM-1 and VCAM-1 [106]. GM-CSF also promotes myelopoiesis to generate monocytes and neutrophils [107] (Fig. 2).

Psoriatic skin lesions commonly contain neutrophilic microabscess in the stratum corneum. In murine models of psoriatic-like disease, depletion of neutrophils using antibodies against cell surface marker CD11b reduces epidermal thickening and microabscess formation [108,109]. However, the role of neutrophils in psoriatic arthritis is less well understood. As discussed in Suzuki et al, studies have noted novel roles in regulating hematopoetic cells in the bone marrow, which may indicate that neutrophils have the capacity to modulate hematopoietic precursors in tissues outside of the bone marrow and drive-cytokine mediated inflammatory precursors in diseases, such as PsA [110,111]. Evidence of neutrophil NETosis is found in PsA synovial fluid, and interestingly, the presence of anti-LL-37 antibodies in the synovial fluid correlates with disease activity [112]. This suggests that chronic neutrophil activation may contribute to chronic adaptive immune responses in PsA. The importance of neutrophils in treatment response is also emphasized by positive correlations with neutrophil number reduction and improvement in disease activity indices **[99]**.

7. Conclusions

Psoriatic arthritis is a highly heritable polygenetic disorder with inheritance that is stronger and distinct from that of cutaneous psoriasis. Genetic investigations have revealed dominant genetic effects of major histocompatibility complex (MHC) and non- HLA alleles within the MHC region. Genome wide association studies have been crucial in identifying prominent genes in signaling pathways, such as IL-23/IL-17, RANK and NFκB. These studies have highlighted the importance of these pathways, as well as provided novel insights into the role of the innate immune system initiation of psoriatic disease, amplification by the adaptive immune system, and tissue destruction and remodeling. Greater understanding of the pathways involved may accelerate development of novel therapeutics aimed at preventing disease initiation, amplification and tissue destruction in PsA.

Declaration of competing interest

None of the authors has any potential financial conflict of interest related to this manuscript.

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