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Arch Rheumatol 2025;40(1):144-156
doi: 10.46497/ArchRheumatol.2025.10934

REVIEW

Immune response and cytokine pathways in psoriatic arthritis: A systematic review

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Received: September 15, 2024
Accepted: January 03, 2025
Published online: March 17, 2025

Citation: Dilek G, Kalcik Unan M, Nas K. Immune response and cytokine pathways in psoriatic arthritis: A systematic review. Arch Rheumatol 2025;40(1):144-156. doi: 10.46497/ArchRheumatol.2025.10934.

ABSTRACT

Objectives: This review aims to focus on the role of innate and adaptive immune system cells and their molecular signaling pathways in the pathophysiology of clinical phenotypes of psoriatic arthritis (PsA).

Materials and methods: A systematic literature search was conducted in the PubMed database using the key words "psoriasis," "psoriatic arthritis," "pathogenesis," "adaptive immune system," "pathophysiology," "bone and cartilage damage," and "cytokine pathways."

Results: Clinical studies and *in vitro* studies on adaptive and innate immune system cells and mediators that cause activation of these cells in the pathogenesis of PsA were examined. The role of cytokine pathways affecting the pathogenesis of PsA on the most common clinical phenotypes of the disease were explained in detail.

Conclusion: In this article, we reviewed the cytokine pathways that may contribute to the immunological pathogenesis of psoriatic arthritis. We believe that this review will contribute to a better understanding of the pathogenesis of the clinical phenotypes of the disease and to disease management.

Keywords: Adaptive immune system, cytokine, innate immune response, psoriatic arthritis.

Psoriatic arthritis (PsA) is an inflammatory musculoskeletal disease with autoimmune and autoinflammatory characteristics. It is observed in approximately 30% of patients with psoriasis, and it was reported that it develops seven to 12 years after the psoriasis (PsO) clinic.[1] The vast majority of PsA patients have psoriatic lesions. However, it is thought that there is no correlation between the severity of cutaneous lesions and musculoskeletal symptoms. Accordingly, it was suggested that PsO and PsA, which have various phenotypic clinics, have different genetic arrangements or develop a different innate immune response to pathophysiological test factors.[2] It was stated that factors such as genetic predisposition, environmental triggers such as biomechanical stress, and natural and immune response interactions play a role in the development of this phenotypic diversity.[3]

In genetic studies, it was determined that the most dominant gene in PsO and PsA diseases is the MHC (major histocompatibility complex) region localized on chromosome 6p21.3, and it was revealed that this genetic component is affected by 30% in both diseases. Human leukocyte antigen (HLA) alleles at the MHC locus have also been associated with disease expression and prognosis of PsA.[4]

Significant genes identified by effective genome-wide association method in disease pathogenesis are interleukin (IL)-12B, IL-23R, TNIP1 (TNFAIP3-interacting protein 1), TRAF3IP2 (tumor necrosis factor-α [TNF]-alpha-derived protein 2), and REL (protooncogene c-Rel). It was stated that genetic variations identified in PsA studies and abnormalities in both adaptive and innate immune systems are important in the development

of the disease. The IL-23/IL-17 axis, RANK (receptor activator of nuclear factor-kappa B [NF-κB]), and NF-κB signaling pathways are critical in the pathogenesis of PsA.[5]

The subtypes of effector T cells in the disease area and the cytokine pathway pattern they cause determine the phenotype of the disease, the type of structural damage, and the response to treatment.[6]

This study aimed to focus on the role of innate and adaptive immune system cells and their molecular signaling pathways in the pathophysiology of clinical phenotypes of PsA.

MATERIALS AND METHODS

The PubMed database was searched for articles and reviews in the English language published between 2000 and 2024. A systematic literature search was conducted using the key words "psoriasis," "psoriatic arthritis," "pathogenesis," "adaptive immune system," "pathophysiology," "bone and cartilage damage," and "cytokine pathways" in clinical studies, clinical trials, reviews, and meta-analyses.

RESULTS

The article examined data from original and review studies on immune system elements and cytokine pathways affecting the pathogenesis and phenotypes of psoriatic arthritis. The reviews discussed genetic loci affecting cytokine pathways,[2] the role of innate immunity and innate immune cells in PsA pathophysiology,[3,7] acquired immune cells and cytokine pathways,[3,5,8-10] and bone damage in PsA, pathophysiology of entheseal inflammation, and biomarkers.[11-15] The original studies included in the article were as follows: a case-control study[5] on genetic loci affecting pathogenesis, clinical studies on the effect of the innate immune system and its cells on inflammatory response,[16-19] case-control studies[20-23] and a case study examining the effect of T cell activation of the adaptive immune system and chemokines on inflammation,[24] a case-control study on the role of T-helper (Th) 17 and Th22 cells in synovium inflammation,[25] clinical studies evaluating the effect of the IL-17/IL-23 pathway on inflammation,[26,27] and gene-targeted mouse studies examining the effect of the IL-23/IL-17/IL-22 cytokine pathway on proliferative and inflammatory processes.[8,26,28] The effect of PsA on bone turnover was evaluated by case-control studies,[29-33] clinical studies,[34,35] and mouse model studies[36-38] regarding cytokine pathways (e.g., IL-17, IL-23, IL-22, and TNF-α) and biomarkers (e.g., Wnt [Wingless-related integration site] pathway and DKK-1). A clinical study,[39] an *in vitro* study,[39] a mouse model study,[40] and a clinical study 60 were examined regarding the proliferative effects of the IL-22 pathway. The cytokine pathways related to the pathophysiology of PsA disease are detailed below under the following subject headings.

Innate and Adaptive Immune System Dysregulation and Immune Response in Psoriatic Arthritis Pathophysiology

Environmental factors, microbiota, and genetic predisposition are thought to affect the pathogenesis of PsA. Genetic variation in HLA class 1 alleles affects the phenotypic features of PsA. As a result of dysregulation of the immune system, clinical findings such as cutaneous involvement, synovial inflammation, cartilage damage, joint erosion, osteoproliferation, and new bone formation are observed in PsA. The major inflammatory pathway in PsA pathogenesis is thought to be the IL-17/IL-23 axis.[41]

Stimulation of the IL-23/IL-17 cytokine axis of antigen presenting innate immune cells in the enthesis, skin, and gastrointestinal system creates the proliferation of CD4+, CD8+, Th, and Th17 cells and the release of IL-23, IL-12, IL-17, and TNF. This initiates a cascade that finally forms an inflammatory clinical response (Figure 1).[41] To understand this inflammatory process, it is necessary to analyze the role of the innate and acquired immune system in the pathogenesis of PsA. In the course of the article, the precursor cells of the innate and acquired immune system that are dysregulated in PsA disease and the production of inflammatory cytokines and their consequences will be discussed.

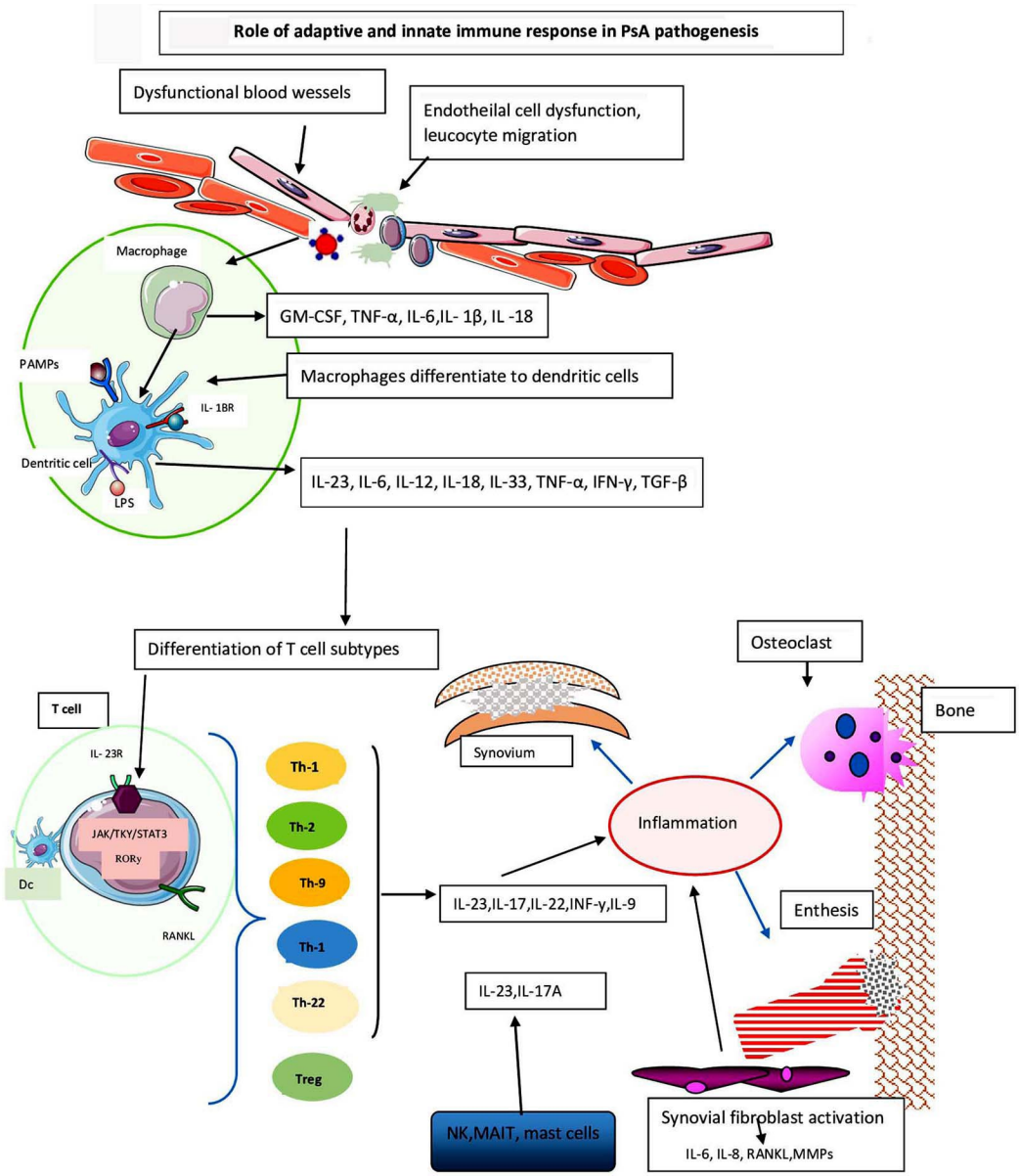

Figure 1. Role of adaptive and innate immune response in PsA pathogenesis. Dysfunctional angiogenesis and activation of endothelial cells cause inflammatory cell infiltration, and the resulting release of cytokines, primarily GM-CSF, causes macrophages to differentiate into DCs. Pathogen-associated molecular patterns, lipolysaccharides, and IL-1 activate the inflammatory response. IL-23 released from DCs plays a role in T cell differentiation. IL-23 binds to JAK2 and Tyk2 receptors and phosphorylates STAT3 to induce RORγ and causes the differentiation of Th-17 cells, resulting in IL-17A and IL-17F gene expression. The increase in TNF-α, IFN-β, IL-2, and IL-23 released from DCs in PsA causes differentiation of T cells into Th1 and Th17 subtypes. NK, MAIT, and mast cells are alternative sources of IL-17. Mediators such as IFN-β, IL-2, IL-4, TNF-α, IL-17-A, and GM-CSF, which are the main inflammatory cytokines released by T cells, contribute to inflammation in the PsA synovium. Th17 cells release proinflammatory cytokines such as IL-17A, IL-17B, IL-21, IL-22, IL-25, IL-26, and TNF-α. RANKL expression is regulated by cytokines such as IL1, IL6, and TNF-α. Increased expression in mesenchymal cells causes osteoclast activation, resulting in bone destruction. With the release of IL-17 and IL-22, new bone formation is stimulated, and enthesitis develops. Macrophages release matrix methyloproteinase inducible nitric oxide synthetase and present antigen to T and B cells that contribute to bone resorption. Synovial fibroblasts secrete matrix-degrading enzymes and RANK.

PsA: Phenotypes of psoriatic arthritis; GM: Granulocyte; CSF: Colony stimulating factor; DCs: Dendritic cells; IL: Interleukin; JAK2: Janus kinase 2; STAT3: Signal transducer and activator of transcription 3; RORγ: Related orphan receptor gamma; TNF-α: Tumor necrosis factor alpha; IFN-β: Interferon-gamma; Th: T-helper; NK: Natural killer; MAIT: Mucosal-associated invariant T; RANKL: Receptor activator of nuclear factor kappa-b ligand; MSC: Mesenchymal stem cells.

The Role of the Innate Immune Response In the Pathogenesis of Psoriatic Arthritis

The pathophysiological process in PsA begins with the disruption of self-tolerance, the disruption of the endothelial barrier, and dysfunctional angiogenesis. This results in an immunological response that includes neutrophil migration, macrophage activation, and activation of the adaptive immune system by antigen-presenting cells.[5]

As a result of the deregulation of the innate immune system, macrophages play a key role in the transition from cutaneous inflammation to joint inflammation in PsA.[16] Natural killer (NK) cells in the PsA synovium play a key role in the transformation of monocytes into dendritic cells (DCs).[20] Innate immune system cells and their effects on PsA pathogenesis will be explained in detail in the following sections.

Dendritic cells

Dendritic cells are antigen-presenting cells with heterogeneous subsets that are in contact between the innate and adaptive immune system. Cytokines released from activated macrophages play a role in the differentiation of T cells into subtypes. TNF-κ, interferon-gamma (IFN-γ), IL-2, and IL-23 cytokines released from DCs in PsA stimulate toll-like receptors, and as a result, T cells differentiate into Th1 and Th17 subtypes.[21] In addition, it is thought that immature DCs exacerbate the disease by giving an inflammatory response to the synovial environment and arythronegic peptides.[22] CD141+ DCs are cells that cross-present antigens to CD8+ T cells and are known to express CLEC9. CD141+ DCs are important in the chronic inflammatory process in PsA patients. In the study by Ramos et al.,[42] it was determined that CLEC9A expression in serum and synovial tissue of PsA patients was reduced with adalimumab treatment. Another DC subtype expressing ATG16L1 (autophagy related 16 like 1) and NADPH (nicotinamide adenine dinucleotide phosphate) oxidase molecule transferred to the cell endosome in PsA activates toll-like receptors and causes proinflammatory cytokine release.[43] DCs expressing the CLEC9A molecule in PsA are increased in psoriatic skin and present exogenous antigen to native CD8+ T cells in a significant way. CLEC5A (MDL-1) is known to trigger activation of osteoclasts through both the RANK ligand (RANKL) and IL-23 pathways.[42]

Monocytes and macrophages

Activated macrophages activate proinflammatory cytokines in the synovium. M1 macrophages are proinflammatory and have an active role in host defense against infection. M2 macrophages are anti-inflammatory and play a role in tissue remodeling. In inflammatory arthritis, macrophages with M1 dominant phenotype can induce matrix metalloproteinase (MMP) and release nitric oxide synthetase, present antigen to T and B cells, and contribute to bone resorption.[44] Histological studies indicated that macrophages were the leading cells in the PsA synovium. The role of polarization in M1 and M2 phenotypic macrophage ratios in the pathogenesis of PsA has still not been fully elucidated.[45]

Neutrophils

The IL-23/IL-17 pathway is activated by the induction of the NF-kB pathway, and the G-CSF (granulocyte colony stimulating factor), GM-CSF (granulocyte macrophage colony stimulating factor), CXCL1, CXCL2, CXCL5, and CXCL8/IL-8 chemokines cause migration of leukocytes. IL-17 enhances leukocyte mobilization by increasing endothelial P-selectin, E-selectin, and integrin molecules, including ICAM-1 and VCAM-1. There is evidence of neutrophil extracellular traps in the PsA synovium, and it was suggested that anti-IL-37 antibodies in synovial fluid correlate with disease activity. It was reported that chronic neutrophil activation contributes to the pathogenesis of PsA by causing a chronic acquired immune response.[7]

Innate immune cells

Innate immune cells are less common in the immune cell population but are effective in psoriatic skin lesions because they play a key role in epithelial proliferation and cytokine production. Type 3 immune cells are richer in the PsA synovium than in rheumatoid arthritis. When compared to the healthy controls in PsA, it was detected that there is an increase in type 3 lymphoid cells (IL-17 and IL-22) and a decrease in type 2 immune cells (IL-4, IL-5, IL-9, and IL-13). 7 Furthermore, joint inflammation and bone

damage was associated with the ratio of immune cells.[46]

Mucosal-associated invariant T cells and natural killer cells

Knowledge of the role of mucosal-associated invariant T (MAIT) cells in the pathogenesis of PsA is limited, and it was suggested that MAIT cells increase inflammation and are associated with disease activity in animal models of arthritis. It was reported that IL-17-producing CD8+ MAIT cells are present in the psoriatic skin and synovium of PsA patients. It was suggested that MAIT cells are an alternative source of IL-17 at the site of inflammation.[17]

Natural killer cells have both protective and pathogenic roles, which are regulated by inhibitory and activator receptors. NK cells secrete GM-CSF and activate the transformation of monocytes into DCs, which is one of the most important links between the innate and adaptive immune response. In PsA, NK cells contribute to cell proliferation and synovial inflammation by expressing ligands such as CD69 and NKp44. The increase in circulating CD16+ and CD56+ NK cells during etanercept treatment was associated with good clinical response in PsA patients.[18]

Mast cells

It was detected that the PsA synovium contains mast cells expressing IL-17A. Mast cells in the synovial membrane can secrete prostaglandins (PGs) and leukotrienes together with proteases, histamines, growth factors such as platelet-derived growth factor, basic fibroblast growth factor, and vascular endothelial growth factor (VEGF), and cytokines such as TNF and IL-1.[23]

Adaptive Immune System

In this section, the IL-17/IL-23 axis, which is the major cytokine pathway of PsA, will be examined in detail. It was stated that T cells play a key role in the pathogenesis of PsA through cytokines. Mediators such as IFN-γ, IL-2, IL-4, TNF-α, IL-17A, GM-CSF, which are the main inflammatory cytokines released by T cell, have been shown in the PsA synovium.[19] There is strong evidence that the role of T cells in the pathogenesis of PsA is genetically linked to MHC class I and II molecules.[24] MHC class I-associated CD8+ T cells play a dominant role in the pathogenesis of PsA, and they respond to self or pathogenic antigen by clonal expansion in the PsA synovium and contribute to inflammation. Th17 cells, IL-23, and IL-17 are emphasized in immune pathogenesis. Naive T cells differentiate into Th17 cells with the activation of IL-23, TGF-β, IL-6, IL-21, and IL-1b. Th17 cells release proinflammatory cytokines such as IL-17 A, IL-17 B, IL-21, IL-22, IL-25, IL-26, and TNF-α.[25]

Interleukin-23 pathway

Interleukin-23 is a heterodimeric cytokine containing subunits from p19 and p40. These subunits bind to the IL-23 receptor (IL-23R)/ IL-12 receptor β1 subunit. IL-23R is expressed on the surface of myeloid cells (DCs), macrophages, and monocytes, including lymphoid cells, innate lymphoid cells, and DCs.[47]

Interleukin-23 binds to JAK2 (Janus kinase 2) and Tyk2 (tyrosine kinase 2) receptors and phosphorylates STAT3 (signal transducer and activator of transcription 3) to induce RORγ (RAR-related orphan receptor gamma) and causes differentiation of Th17 cells, resulting in IL-17A, IL-17F gene expression. IL-23 also stimulates the innate immune system by causing NF-kB activation.[26]

Interleukin-17 pathway

The IL-17 family are proinflammatory glycoproteins involved in the pathogenesis of PsA.[8] There are six members of the IL-17 family (IL-17A-IL-17F). IL-17A and IL-17F are the most potent proinflammatory cytokines of this family. The IL-17 cytokine binds to the IL-17 receptor (IL-17R) expressed on the cell surface of keratinocytes, fibroblasts, lymphocytes, lymphoid tissue cells, and monocytes.[48] IL-17RA and IL-17C signaling is mediated by the IL-17R adaptor protein (Act1) and fibroblast growth factor-like expression (SEFIR) genes.[49] Act1 is the key adaptor protein for the IL-17 receptor, and after IL-17 is stimulated, it forms a complex with inducible kinase (IKKi), causing the formation of TRAF2-Act1 and TRAF5-Act1 complexes and stabilization of CXCL1 mRNA, which is a neutrophil chemokine. Act1 also binds to TRAF6, activating the AP-1 (NF-κB activator protein 1) or C/EBP (CCAAT-enhancing binding protein) cascade.[28]

The role of the IL-17 pathway in the pathogenesis of psoriatic arthritis

T-helper 17 cells release proinflammatory cytokines such as IL-17A, IL-17B, IL-21, IL-22, IL-25, IL-26, and TNF-β. It was found that there is an increase in Th17 cells in the inflamed synovium, blood, and psoriatic lesions of PsA patients.[9] Recently, it was emphasized that the proportional change or shift in cellular IL-17 sources in PsO and PsA is a situation that needs to be clarified. Other important cellular sources of IL-17 have been reported as mast cells, κδ T cells, αβ T cells, and native lymphoid cells.[10]

It is thought that IL-17 can be released through neutrophil extracellular traps, which neutrophils use in host defense and inflammatory events. Similarly, mast cell extracellular trap formations induced by IL-23 and IL-1β are thought to be associated with IL-17 release.32 The effect of TNF-α inhibition on the IL-23/IL-17A axis is a complex situation. IL-17 and TNF-α are thought to synergistically coregulate keratinocyte-associated downstream genes. It is accepted that the IL-23/IL-17A axis plays a key role in the pathogenesis of PsO and PsA. Furthermore, it is thought that TNF-α creates synergy with IL-17A by promoting inflammation and maturation and development of the myeloid DC.[50]

Pathophysiology of bone and cartilage damage in psoriatic arthritis

As a result of the interaction between the immune response and bone cells, osteoproliferation, osteoporosis, and cartilage damage may occur, which forms the basis of the pathogenesis of PsA. This pathophysiological event not only determines the treatment targets but also helps identify patients at risk of developing structural damage.[11]

Bone remodulation in psoriatic arthritis

Osteoclases are derived from the monocyte-derived hematopoietic stem cells stimulated by M-CSF (macrophage colony stimulating factor) released from synovial mesenchymal cells and Th1 cells and are under the influence of RANKL signaling. RANKL, which is a member of the TNF superfamily, is expressed in activated fibroblast-like synoviocytes, particularly in T cells of the Th17 subtype. RANKL's expression increases with the effect of proinflammatory cytokines such as IL-1, IL-6, and TNF from mesenchymal stem cells (MSCs). With the increase of RANKL expression, osteoclastogenetic activity increases. IL-17 increases RANK expression in osteoclast precursors and stimulates osteoclast differentiation, a process downregulated by osteoprotegerin (OPG). IL-17 can interact with astromal cells and macrophages and increase the expression of IL-1, IL-6, and TNF, providing positive feedback to osteoclastonenesis.[29]

Interleukin-23 promotes osteoclastogenesis by triggering differentiation of Th17 cells and expression of RANK in osteoclast precursors. However, it was reported in the study that IL-23 inhibited osteoclastogenesis by stimulating GM-CSF expression of Th17 cells.[36] However, it was suggested that the net effect of IL-23 on osteoclastogenesis depends on its role on IL-17 and RANKL expression.[36]

Dickkopf-related protein 1 (Dkk-1) is a negative regulator of the Wnt signaling pathway produced from fibroblast-like cells. TNF upregulates Dkk-1 and sclerostin expression and inhibits Wnt pathway and, accordingly, new bone formation. There is evidence of an association between increased expression of Dkk-1 and sclerostin proteins and erosive bone damage in patients with PsA. It is also possible that the inhibition of the Dkk-1-mediated Wnt signaling pathway is lost by the disruption of the binding of the Dkk-1 protein to the Wnt coreceptor LRP6, and the stimulation of the bone formation pathway is also possible.[30]

A resolution of bone erosion was reported when anti-Dkk-1 was given in a mouse model of inflammatory arthritis. Data suggests that the Dkk-1 protein has a two-way mechanism of action on both osteoblasts and osteoclasts (Figure 2).[37]

Proinflammatory cytokines such as IL-1, TNF, IL-6, and IL-7 induce the production of MMPs and aggrecanases (ADAMTS [ADAM metallopeptidase with thrombospondin type 1 motif]) from cells such as chondrocytes, fibroblast-like synoviocytes, and neutrophils. These enzymes cause joint erosion and narrowing by damaging the extracellular matrix of bone and cartilage.[12]

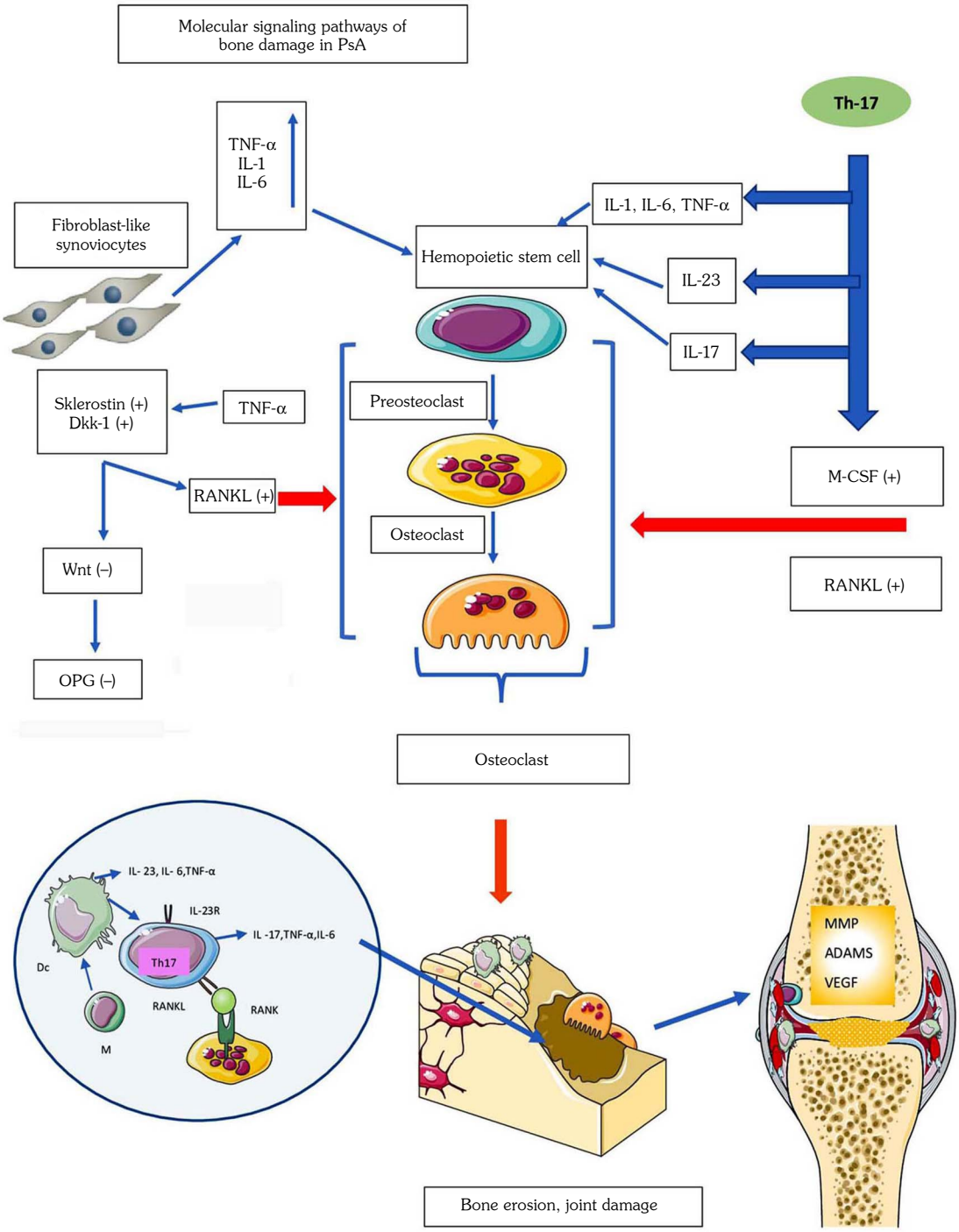

Figure 2. Molecular signaling pathways of bone damage in PsA.
Osteoclases derive from monocyte-derived hematopoietic stem cells stimulated by M-CSF and are under the influence of RANKL signaling. Cytokines such as TNF-α, IL-1, IL-6, IL-17, IL-23 released from Th-derived cells (Th-1, Th-17) and fibroblast-like synoviocytes increase RANKL expression. Therfore; an increase in osteoclastogenesis, in which the hemopoietic stem cell transforms into preosteoclast and osteoclast. TNF-α; It inhibits the Wnt pathway by up-regulating the expression of Dkk-1 and sclerostin, reducing the OPG level. As a result of this inflammatory process, bone erosion occurs as an increase in osteoclastogenesis. Pro-inflammatory cytokines such as IL-1, TNF-α, IL-6 and IL-7 induce the production of VEGF, MMPs, and ADAMTS enzymes from cells such as chondrocytes, fibroblast-like synovocytes and neutrophils.

PsA: Phenotypes of psoriatic arthritis; OPG: Osteoprotegerin; M-CSF: Macrophage-colony stimulating factor; RANKL: Receptor activator of nuclear factor kappa-b ligand; TNF-a: Tumor necrosis factor alpha; IL: Interleukin; Th: T-helper; Dkk-1: Dickkopf-1; VEGF: Vascular endothelial growth factor; MMPs: Matrix metalloproteinases; ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs.

Mediators of new bone formation in psoriatic arthritis

Ankylosing spondylitis is the prototype of axial proliferative diseases. Axial PsA has a similar axial proliferative spectrum. Additionally, new bone formation is an important feature of PsA with peripheral involvement. However, there are some differences compared to ankylosing spondylitis. Data regarding the role of IL-17 in osteoblastogenesis and new bone formation are conflicting.[51] It is hypothesized that human IL-17RA-expressing MSCs and Th17-derived IL-17 cytokines may stimulate osteoblast differentiation. Therefore, it is thought that IL-17A or IL-17F may have both positive and negative effects on osteoblastogenesis at the differentiation stage of osteoblast precursors. An *in vitro* study has shown that γδ T cells producing IL-22, T cell subtypes such as Th17, Th 22, and type 3 innate lymphoid cells (ILC3) support the proliferation and migration of MSCs.[39]

It was suggested that TNF has both positive and negative effects on osteoblastogenesis. It is thought that this effect becomes clear in the differentiation phase of cells.[13] TNF can antagonize or induce Dkk-1 and sclerostin proteins by inhibiting the Wnt pathway or the bone morphogenic protein 2 (BMP-2) pathway.[52] TNF may also promote osteoblastogenesis by increasing NF-kB activation and BMP-2 expression.[34]

In a cross-sectional study, in which patients with mixed axial and peripheral PsA and only peripheral PsA were recruited, it was suggested that radiological progression was related to changes in markers of osteoproliferation.[31] In addition, no significant correlation was found between quantitative axial radiographic severity or osteoproliferation severity in PsA and the rates of OPG, Dkk-1, MMP-3, and M-CSF.[31] In three other studies on this subject, radiographic sacroiliac osteoproliferation (sacroiliitis) and MMP-3, RANKL, OPG, BMP-2, BMP-4, BMP-6, COMP (cartilage oligomeric matrix protein) or type 2 collagen biomarkers (C2C, C1-2C, or CPII) levels were not found to be significant; the results were reported as indeterminate for Dkk-1 and M-CSF.[32,33,35]

Enthesis pathophysiology

Areas of inflammation (enthesitis) of these tendons and ligament insertions are a hallmark of PsA. Biomechanical stress, prostaglandin E2 (PGE2)-mediated vasodilation, innate immune response, and some cytokines are thought to play a role in the development of enthesitis.[14] It was suggested that mesenchymal cells have the potential to differentiate into chondrocytes and osteoblasts due to environmental factors in integral structures.[53] Likewise, it was reported that there are T cells and type 3 native lymphoid cells located in the internal structures. It is thought that these cells trigger inflammation during the disease.[54] It is stated that mechanical stress is a trigger for the development of enthesitis. In a study, it was found that mechanical stress increased the local expression of chemokines such as CXCL1 and CXCL2 in the applied area, increasing the entry of innate immune cells into the area.[40]

Prostaglandin E2 is one of the earliest mediators of enthesitis. For this reason, nonsteroidal anti-inflammatory drugs can be effective in the treatment of enthesis. In a study, it was shown that the cyclooxygenase-2/PGE2 pathway increases IL-17 release from T cells independent of the IL-23 pathway (Figure 3).[55] IL-17 appears to be a major inflammatory mediator in the pathophysiology of enthesis, induces the release of other mediators such as granulocyte macrophage stimulating factor, PGE2, IL-8, and ensures the invasion of neutrophils into the enthesis region.[38] Studies have reported that TNF-α, like IL-17, is an important mediator in the pathophysiology of enthesitis by stimulating local mesenchymal cells.[56] IL-22 is thought to have a key role in the formation of new bone in enthesitis.[39]

Dactylitis immunopathogenesis

Dactylitis is accepted as one of the distinguishing features of PsA and is defined as diffuse swelling between the metacarpophalangeal, proximal, or distal interphalangeal joint and digital tuft (distal dactylitis) and soft tissue. The joints of the feet are affected more frequently than the joints of the hands, and the flexor tendons are predominantly affected.[57] Genetic, environmental, and immunological factors have been implicated in the pathogenesis of dactylitis. Various microtraumas

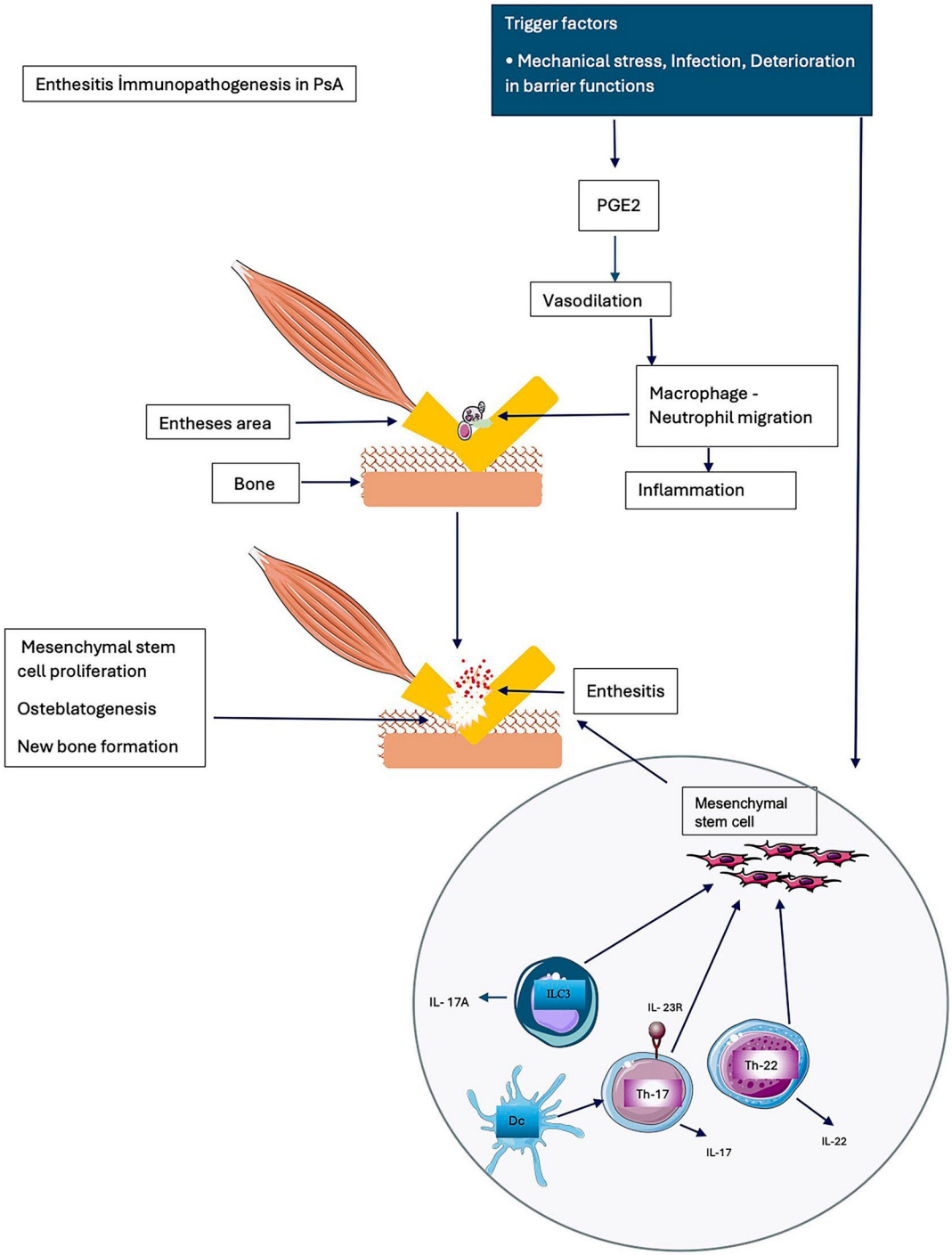

Figure 3. Enthesitis immunopathogenesis in PsA. Factors such as mechanical stress and impaired barrier functions trigger the development of enthesitis. PGE2 is the earliest mediator of enthesitis. PGE2 contributes to inflammation by making it easier for neutrophils and other innate immune cells to come from the bone marrow to the enthesitis area through vasodilation. IL-17 appears to be a major inflammatory mediator in the pathophysiology of enthesis; MSCs expressing IL-17 RA and Th17-derived IL-17 contribute to new bone formation by stimulating osteoblast differentiation. T cell subtypes such as Th17, Th22, and ILC3 stimulate mesenchymal stem cell proliferation by producing IL-22. Enthesitis develops as a result of mesenchymal stem cell proliferation, osteoblastogenesis, and new bone formation secondary to inflammation caused by the causative factors.

PsA: Phenotypes of psoriatic arthritis; PGE2: Prostaglandin E2; IL: Interleukin; MSCs: Mesenchymal stem cells; RA: Rheumatoid arthritis; Th: T-helper; ILC3: Lymphoid cells 3.

(deep Koebner phenomenon) are held responsible as key the triggering factor. Koebner phenomenon occurs as a result of biomechanical stress and may cause dactylitis in people with a genetic predisposition. It is reported that the HLA-B*2705 and HLA-B*0801 alleles were associated with dactylitis in PsA patients. The deep Koebner phenomenon activates innate immunity at the stress site. Proinflammatory cytokines are released from the innate immune cells such as neutrophils, macrophages, and γδ T cells in the stress region. T cells infiltrate the soft tissue, and TNF-α and IL 17-23 pathway are reported to be major cytokines in dactylitis immunopathogenesis.[58] In magnetic resonance imaging studies on PsA patients with dactylitis, it has been reported that tenosynovitis due to dactylitis develops as a result of inflammation in the form of microenthesitis of the tendon sheaths associated with the pulleys. Dactylitis is hypothesized to be a form of enthesitis involving soft tissue and bone in response to mechanical stress.[15,59] What is known about the pathogenesis of dactylitis in PsA is insufficient and remains an issue to be elucidated.

DISCUSSION

This review focused on the role of innate and adaptive immune system cells and their molecular signaling pathways in the pathophysiology of clinical phenotypes of PsA. The PsA gives clinical findings based on the phenotype and genotype of the individual, biomechanical and molecular environmental stress, local factors such as joints, skin, vertebrae, enthesis area, and the interaction of natural and acquired immunity. It interacts with antigen presenting cells, lymphoid cells, and naive T cells in the disease area such as skin and entheses, causing local expansion of Th 1, type 1 CD8+ T cells, and type 17 T cells. The subtypes of effector T cells in the disease area and the cytokine pathway pattern they cause determine the phenotype of the disease, the type of structural damage, and the response to treatment.

In conclusion, understanding the cytokine pathways of PsA clinical phenotypes such as dactylitis, enthesitis, and bone involvement will contribute to the treatment of the disease.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Concept design, preparing references was done: M.K.U.; Writing, and controls were done: G.D.; Literature review and critical review, idea presentation were done: K.N.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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