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Review

Are psoriasis and psoriatic arthritis the same disease? The IL-23/IL-17 axis data

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ABSTRACT

Psoriatic arthritis (PsA) is a psoriasis (Ps)-associated inflammatory joint disease that affects peripheral joints, entheses, spine, and eyes. PsA and Ps are likely to be the same disease. PsA develops in nearly 70% of patients with Ps, and the hallmark of the disease is bone erosions and bone formation. Both innate and adaptive immunity appear to contribute to pathogenesis of PsA and Ps. Trauma may be a trigger factor for both PsA and Ps. The same T cell clones were reported to be present in both synovial tissues and skin lesions suggesting that a common antigen drives T cell immune response in the joints and skin lesions of patients with PsA. The IL-23/IL-17 axis plays a critical pathogenic role for both PsA and Ps, and biologics neutralizing IL-17A or IL-23/IL-12 are effective therapies for PsA and Ps. The differential expression of Th17 cytokines IL-17 and IL-22 at various sites could explain the different manifestations of the disease. IL-17 is highly expressed in peripheral joints and skin lesions and causes bone erosions. IL-22 is highly expressed in skin lesions and entheses, not peripheral joints, and cause bone formation. Finally, mannan from baker's yeast caused PsA-like arthritis and Ps-like skin lesions that were blocked by IL-17 treatment. These data suggest that PsA and Ps are likely to be the same disease exhibiting different manifestations depending on the local cytokine production.

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1. Features of psoriatic arthritis

Figs. 1 and 2.

Psoriatic arthritis (PsA) has been defined for years as an inflammatory arthritis associated with psoriasis in a patient without rheumatoid factor. In 2006, the CASPAR classification criteria for PsA were published, with 91% sensitivity and 99% specificity, and these are most commonly used [1]. According to CASPAR criteria, a person with inflammatory articular disease (joint, entheseal, spine) is said to have PsA if he/she has at least 3 points from the following categories: (a) current psoriasis (2 points), personal history of psoriasis or family history of psoriasis in first- or second-degree relative (1 point), (b) psoriatic nail dystrophy (1 point); (c) absence of rheumatoid factor (1 point); (d) dactylitis, current or past (1 point); (e) juxta-articular new bone formation on radiograph of hands or feet (1 point) [1]. The introduction of anti-

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citrullinated peptide antibodies (ACPAs) with high specificity for rheumatoid arthritis (RA) are likely to be incorporated in future updates of the PsA classification criteria [2–3].

Clinically, PsA belongs to spondyloarthropathies and, as such, it may manifests with peripheral arthritis, enthesitis, dactylitis, uveitis, and spondylitis (sacroiliitis, syndesmophytes and fusion in the spine). Joint manifestations may include arthritis mutilans, oligoarthritis, or polyarthritis, the latter resembling RA. PsA commonly affects distal interphalangeal joints of the hands, which are rarely affected in RA. However, a defining radiographic feature that distinguishes peripheral joint involvement of PsA from RA is the development of juxta-articular new bone formation, in addition to bone loss (erosions), which is common for both diseases. This radiographic feature makes PsA look like erosive osteoarthritis rather than RA.

The pathogenesis of psoriatic arthritis (PsA) is incompletely understood. It is logical to assume that psoriasis contributes to the pathogenesis of PsA entirely or partly. Psoriasis is a common inflammatory skin disease affecting 2%–13% of the general population [4]. PsA most commonly develops in patients with preceding psoriasis or concomitantly with psoriasis, and with all arthritic manifestations considered, such as enthesitis, PsA affects up to70% of patients with psoriasis (review in [5]). Uveitis may also be another manifestation associated with Ps. In a national cohort study of the Danish population, there was a bidirectional association between uveitis and Ps or PsA [6]. In fact, for patients with uveitis, the incidence rate ratios (95% CI) were 1.59 (1.32–1.91) for mild Ps, 2.17 (1.40–3.38) for severe Ps, and 3.77 (2.66–5.34) for PsA, respectively [6]. Genetic factors, such as HLA-class I alleles, and IL-23/IL-17 axis genes are implicated in psoriasis and PsA [7]. Environmental factors, such as infections, physical or emotional traumas are also implicated [7]. Psoriasis often develops at sites of injury (Koebner phenomenon), and joint trauma is frequently a triggering event for PsA [8].

1.1. Pathology

Lesional skin from patients with psoriasis exhibits epidermal hyperplasia, and infiltration with neutrophils, CD4(+) T cells, CD8(+) T cells, B cells, dendritic cells, and mast cells [9–10]. Also, innate lymphoid cells type 3 (ILC3) and γδT cells are increased in psoriatic skin lesions [11–13] and uninvolved skin [11–12]. In synovial membrane from patients with PsA, there are infiltrations with lymphocytes and macrophages. Furthermore, ectopic lymphoid tissues were found frequently in PsA synovial membrane with microanatomical features for germinal center formation capable of antibody production [14].

Accumulating evidence suggests that both adaptive and innate immunity are involved in the pathogenesis of psoriasis and PsA, and the IL-23/IL-17 axis is central to the pathogenesis of both conditions.

1.2. Adaptive immunity

The adaptive immune response appears to be involved in PsA [15]. T cells are activated in PsA joints, and synovial fluid T cells exhibit oligoclonal expansions, as detected by β-chain CDR3 length analysis. Most of these clones were CD8(+) T cells rather than CD4(+) T cells, and sequence analysis of some T cell clones suggested clonal selection, i.e., clonal expansion driven by antigens [16]. Oligoclonal expansions of T cells, as detected by β-chain CDR3 length analysis, were also found in psoriatic skin lesions [17]. In two other PsA studies, some T cell clones were common in synovial membrane and skin lesions [18], suggesting that a common antigen drives the T cell immune response in joints and skin lesions. These findings go along a report that CD4(+) and CD8(+) T cells infiltrating skin lesions recognize the cationic antimicrobial peptide LL37 overexpressed in psoriatic keratinocytes and produce IFNγ and Th17 cytokines (IL-17, IL-22, IL-21) [19].

The role of B cells in PsA is unknown. Yet, a recent study reported that autoantibodies against a peptide that shares sequence homology with skin and entheseal autoantigens were detected in 85% of patients with PsA [20]. Other autoantibodies have been reported [21]. Ectopic lymphoid structures, detected in PsA synovial membrane [14], by allowing interaction among T cells, B cells and dendritic cells, and antigen recognition, imply that B cell differentiation to antibody production may take place in PsA synovial membrane. This has been shown for RA synovial membrane, where anti-citrullinated protein antibodies are produced locally [22]. Furthermore, analysis of immunoglobulin heavy chain variable region (IgVH) genes of synovial membrane from 5 patients with PsA showed identical amino acid replacements, which is indicative of antigen-driven activation of B cells [23]. All these findings support the concept for an adaptive immune response in joints and skin lesions.

1.3. Innate immunity

Innate immunity is involved in psoriasis and PsA as innate cells, such as neutrophils, γδT cells, NK cells, and mast cells are activated in psoriasis and PsA, and will be discussed later in the IL-23/IL-17 section. The cationic peptide LL37 overexpressed in psoriatic keratinocytes in response to infections and mechanical stress, forms complexes with self DNA/RNA and activates dendritic cells via toll-like receptor (TLR) 7/8/9 [24]. One hypothesis suggests that entheses are the initial sites that drive innate immune response in PsA [5,25].

2. IL-23/IL-17 axis

IL-17 is the defining cytokine produced by Th17 cells. There are several IL-17 family members (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F). IL-17A (also known as IL-17) most closely relates to IL-17F, and these isoforms form homodimers or heterodimers. IL-6 and TGFβ promote the initial differentiation of Th0 to Th17 cells while IL-23 stabilizes and expands Th17 cells [26]. IL-23 (p19/p40), produced by dendritic cells and macrophages, is a heterodimer consisting of p19 and p40 subunits, the latter being shared with IL-12 (p35/p40) cytokine. The orphan nuclear receptor RORγt is the key transcription factor of Th17 cells. Upon binding to its receptor complex, consisting of IL-23R and IL-12β1R, IL-23 activates RORγt and STAT3 in Th17 cells [27]. Th17 cells, apart from IL-17A and IL-17F, also produce IL-21 and IL-22. IL-17 is also produced by CD8(+) T cells, innate lymphoid cells type 3, γδT cells, and mast cells. IL-17C shares 23% homology with IL-17A and is produced mainly by epithelial cells. IL-17C acts in an autocrine manner and its functions overlap with those of IL-17A [27]. IL-17 receptor family has five members: IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE [28]. IL-17A, as well as IL-17F, binds to its receptor, the IL-17RA/IL-17RC heterodimer, and recruits the nuclear factor κB (NFκB) activator 1 (ACT1) adaptor protein which then activates mitogen-activated protein kinases (MAPKs) including p38 MAK. IL-17 also activates other signaling pathways, such as c-jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), Janus kinase (JAK), signal transducer and activator of transcription (STAT), and phosphoinositol 3 kinase (PI3K) and induces several pro-inflammatory cytokines (IL-1β, IL-6, TNFα, CCL2), antimicrobial peptides (β-defensin), and matrix metalloproteinases (reviewed in [29]. IL-17C signals through the IL-17RA/IL-17RE heterodimer.

An important cytokine produced in the IL-23/IL-17 axis is IL-22. Apart from Th17 cells, IL-22 is also produced by Th22 cells, γδT cells in response to IL-23 [30], and NK cells in response to IL-23 [31]. γδT cells, upon IL-23 stimulation, produced IL-17 and IL-22 but also prevented the conversion of T cells into Foxp3+ Tregs and made T cells refractory to Tregs suppression [32].

2.1. The IL-23/IL-17 axis in psoriasis and PsA

Studies on IL-23/IL-17 axis in psoriasis and PsA have revealed that innate immunity is heavily involved in the pathogenesis of these