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New immune cells in spondyloarthritis: Key players or innocent bystanders?

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The central role of the inflammatory cytokines such as TNF-α, IL-23, and IL-17 in the disease pathogenesis of spondyloarthritis (SpA) is unquestionable, given the strong efficacy of anti-cytokine therapeutics used in the treatment of SpA patients. These cytokines are produced by a diverse range of immune cells, some extending beyond the typical spectrum of lineage-defined subsets. Recently, a number of specialized cells, such as innate-like T-cells, innate lymphoid cells (ILCs) and natural killer receptor (NKR)-expressing T cells, have been marked to be involved in SpA pathology. In this chapter, we will elaborate on the unique characteristics of these particular immune subsets and critically evaluate their potential contribution to SpA disease, taking into account their role in joint and gut pathology.

Introduction

Spondyloarthritis (SpA) refers to a cluster of inflammatory conditions which share clinical genetic and pathophysiological characteristics [1] Disease classification by the recently established Assessment

List of abbreviations: SpA, Spondyloarthritis; AS, ankylosing spondylitis; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; IL, interleukin; CIA, collagen-induced arthritis; RORγt, retinoic acid receptor-related orphan receptor-γt; Th, T helper; iNKT, invariant natural killer T cells; UPR, unfolded protein response; PBMC, peripheral blood mononuclear cells; KIR, killer cell immunoglobulin-like receptor; ILC, innate lymphoid cells; MAIT, mucosal-associated invariant T cells.

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of Spondyloarthritis International Society (ASAS) criteria [2] is based on clinical outcome of patients, with subdivision in axial SpA (including both non-radiographic and radiographic axial SpA, also known as ankylosing spondylitis (AS)) and peripheral SpA. Typical symptoms include rheumatic/articular features (arthritis, dactylitis, sacroiliitis, and spinal inflammation) next to extra-articular manifestations, such as anterior uveitis, psoriasis, and inflammatory bowel disease (IBD). Interestingly, about 50% of SpA patients present microscopic signs of ileum (and colon) inflammation without showing overt GI symptoms [3–5]. Notably, for axial SpA patients, predictive factors including (younger) age, progressive disease, male sex, and higher disease activity as measured by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) are associated with an increased likelihood of presenting this subclinical inflammatory gut signature [6]. In addition, it was shown that SpA patients with chronic gut inflammation display a higher degree of bone marrow edema of the sacroiliac joints (visible by magnetic resonance imaging (MRI)) as compared to those with normal gut architecture [7]. Eventually, on average 6.5% of SpA patients develop clinically established IBD in the 5-year follow-up [8]. These data further underscore the existence of a significant gut–joint axis in SpA pathology.

In contrast to rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), being typical autoimmune diseases, SpA is generally considered to be autoinflammatory in nature [9]. In this regard, it is postulated that primary triggers induced by bacterial components (microbial antigens, Toll-like receptor ligands) and/or exposure to biomechanical stress (mechanical strain) can lead to dysregulated innate inflammatory processes in targeted tissues of susceptible individuals [10–12]. Inflammatory cytokines play a crucial role in these disease processes as shown by the marked efficacy of biologicals directed against tumor necrosis factor (TNF)-α [13,14] and more recently interleukin (IL)-23/IL-17 pathway mediators [15–17].

These cytokines can be produced by a diverse range of immune cells, some extending beyond the classical spectrum of lineage-defined subsets. Indeed, with the recent advances in multicolor flow cytometry and imaging techniques, specific new subsets of immune cells such as innate-like T cells, innate lymphoid cells (ILCs), and myeloid subsets have been identified, of which some have been suggested to play a key role in SpA. Especially, cells showing an IL-17 signature (the so-called Type-17 cells) have acquired increased attention in recent years [18,19]. In this chapter, we will provide an overview of the emerging new immune subsets and critically evaluate their potential contribution to SpA disease pathology (Fig. 1).

KIR3DL2$^+$ and KLRG1$^+$ T cells

As established for over more than four decades now, HLA-B27, an MHC class I gene, shows the strongest genetic association with SpA, accounting for roughly 30% of heritance [20–22]. Although from an immunological perspective, CD8-restricted T lymphocytes, potentially autoreactive toward joint-associated self-antigens, would be apparent candidates in the disease processes, solid evidence for this “arthritogenic peptide” hypothesis was never established [23,24]. It rather seems that the unusual biochemical properties of HLA-B27 molecules provide a better rationale for their link with SpA. Specifically, HLA-B27 molecules show an increased tendency to misfold and to form aberrant disulfide-linked heavy chain homodimers [25]. HLA-B27 misfolding can potentially initiate an unfolded protein response (UPR) in the endoplasmic reticulum (ER) and/or can activate autophagy pathways, processes responsible for the degradation and recycling of cellular organelles [23]. Interestingly, in HLA-B27 transgenic rats presenting marked SpA disease features, it was shown that HLA-B27 misfolding and UPR activation can be responsible for an enhanced IL-23 expression by myeloid cells. Direct evidence for this condition in SpA patients is currently lacking [26–29].

Alternatively, B27 dimers can activate a particular subset of T helper cells (and natural killer (NK) cells) which express the killer cell immunoglobulin-like receptor (KIR)3DL2 [30,31]. Paul Bowness and his colleagues have shown increased numbers of circulating KIR3DL2$^+$ CD4 T cells and NK cells in SpA patients [32]. Moreover, KIR3DL2$^+$ CD4 T cells survive, proliferate, and produce IL-17 (next to e.g., interferon (IFN)-γ and TNF-α) upon stimulation with cells expressing B27 dimers, and particularly this IL-17$^+$ cell subset is expanded and enriched in peripheral blood and knee joint aspirates of SpA patients [31].

Apart from a clear association with HLA-B27, other T cells also expressing natural killer receptors (NKRs) were associated with SpA pathology. Melis et al. showed that T cells positive for killer cell lectin-like receptor G1 (KLRG1) are enriched in the synovial fluid (SF) of SpA but not crystal-induced arthritis