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Review

Interaction between microbiome and host genetics in psoriatic arthritis

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ABSTRACT

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease, seen in combination with psoriasis. Both genetic and environmental factors are responsible for the development of PsA, however little is known about the different weight of these two distinctive components in the pathogenesis of the disease. Genomic variability in PsA is associated with the disease and/or some peculiar clinical phenotypes. Candidate genes involved are crucial in inflammation, immune system, and epithelial permeability. Moreover, the genesis and regulation of inflammation are influenced by the composition of the human intestinal microbiome that is able to modulate both mucosal and systemic immune system. It is possible that pro-inflammatory responses initiated in gut mucosa could contribute to the induction and progression of autoimmune conditions. Given such premises, the aim of this review is to summarize immune-mediated response and specific bacterial changes in the composition of fecal microbiota in PsA patients and to analyze the relationships between bacterial changes, immune system, and host genetic background.

Contents

1. Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease, seen in combination with psoriasis (PsO). It is considered that about 30% of patients affected by PsO develop PsA [1]. The overall prevalence of PsA has been reported to range from 0.01% in the Middle East to 0.19% in

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Europe [2]. PsA belongs to the family of spondylarthritis (SpA) because it shares with SpA several clinical features, as enthesitis, dactylitis, peripheral arthritis and axial involvement [2]. These clinical features were included in 2006, by Taylor and collaborators in the new classification criteria, CASPAR (ClASsification criteria for Psoriatic Arthritis) [3]. Characteristic extra-articular manifestations of PsA include psoriasis, nail psoriasis, uveitis and inflammatory bowel disease (IBD), which may be frequently unrecognized or undertreated [4]. The extra-articular concomitant diseases, also called comorbidities, such as obesity, dyslipidaemia, type II diabetes, liver disease and cardiovascular disease, are increased in PsA patients and their role in the progression and the clinical response to treatment remains under investigations [5]. The disease pathogenesis is multifactorial: both genetic and environmental factors are responsible for the development of PsA, however little is known about the different weight of these two components in the pathogenesis of the disease [6].

1.1. Pathogenetic pathways in PsA

Several pathogenic mechanisms have been deeply investigated in the last three decades, revealing a crucial role of both adaptive and innate immunity. Enthesitis seems to be the *primum movens* of the disease, as well as the prominent clinical feature at presentation in up to 38% of PsA patients [7]. The immune activation may be triggered by various mechanisms including the presence of self-molecules identified as auto-antigens by autoreactive CD4+ and CD8+ T cells [8].

Psoriasis skin inflammation is driven by multiple immune circuits amplified by keratinocytes that recruit T cells, neutrophils, dendritic cells (DCs), and other immune cells, producing chemokines and AMPs acting as chemoattractants [8,9].

Given the role of key-cytokines such as IL-22, TNFα, and IFN-γ drive pathogenic pathways, which are upregulated in both PsO and PsA, mounting evidence has proved the crucial role of the IL-23/IL-17 axis [8,9]. IL-17 indeed, has been proposed as a key player in the most relevant pathogenetic circuits, acting in synergy with TNF [9]. IL-17 is mainly produced by a subset of T cells identified in 2005, Th17 cells [10,11]. In 2008, it was reported that a combination of TGF-b, IL-1b and IL-6, IL-21 or IL-23 in serum-free conditions is necessary and sufficient to induce IL-17 expression in naïve human CD4+ T cells from human cord blood [12]. Th17 cells, initially implicated in an animal model of multiple sclerosis [13], have been proved to be involved in the pathogenesis of type I INF-driven systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis, PsO and PsA [14]. Although type I INFs have been shown to antagonize Th17 responses, it is also evident from the observations made in diseases such as PsO or SLE that type I INF and Th17 responses can coexist to drive inflammation and disease [15]. Studies on animal models of autoimmune arthritis (collagen-induced arthritis, CIA), demonstrated that the IL-23/IL-17 axis plays a critical role in the development of autoimmune arthritis, in fact, mice deficient for IL-23 are protected against the development of CIA; moreover, IL-17 knockout mice develop less severe arthritis [16]. IL-17 helps in osteoclastogenesis and bone resorption by inducing the expression of receptor activator of NF-kB ligand (RANKL) [17], it also induces cartilage collagen breakdown and has a regulatory role on synovial cells (1), acting in combination with other proinflammatory cytokines [18]. In PsA, IL-17 seems to influence all critical events of inflammation such as, induction of adhesion molecules (ICAM-1), upregulation of interleukines (IL-6, IL-8) and angiogenesis. IL-17 has also been shown to induce the expression of RANKL in osteoclasts in vitro [19]. Thus, the regulatory role of IL-17 on fibroblasts, osteoblasts and chondrocytes has an impact in both synovial inflammation and joint destruction. In a study from Sherlock et al. IL-23 was essential in enthesitis acting on previously unidentified entheseal resident T cells (CD3 + CD4-CD8-) [20]. These cells allowed entheses to respond to IL-23 in vitro in the absence of further cellular recruitment and to elaborate inflammatory mediators including IL-6, IL-17, IL-22 and chemokine (C-X-C motif) ligand 1 (CXCL1). The presence of these entheseal resident cells and their production of IL-22, which activates signal transducer and activator of transcription 3 (STAT3)-dependent osteoblast-mediated bone remodeling, explains why dysregulation of IL-23 results in inflammation at this precise anatomical site [20]. Several studies demonstrated in psoriatic skin lesions high levels of p40, subunit of IL-12. The p40 subunit is also shared by IL-23. The role of IL-23 in the induction of PsO has been confirmed by injecting IL-23 in the skin of the ears of a mouse model resulting in epidermal hyperplasia and inflammatory cellular infiltration similar to psoriasis, which was mediated by TNF-α, IL-22, IL-17A and IL-17F [21]. Th1 and Th17 cells contribute to PsO pathophysiology by secreting inflammatory cytokines, including INF-γ, IL-17 and IL-22, that activate keratinocytes to proliferate and secrete additional inflammatory mediators [22]. Recently, significant sources of IL-17, IL-22 and INFα in PsO, have been identified in several CD8+ T cell subsets, named Tc17, Tc22 and Tc1 respectively. Besides, Th17 and Tc17, mast cells, and neutrophils, appearing within the early phases of psoriatic lesions formation, were reported to produce large amount of IL-17. IL-17 induces in keratinocytes the production of antimicrobial peptides, proinflammatory cytokines, chemoattractants, including CCL20, CXCL3, CXCL5. The secretion of CCL20 recruits CCR6+ cells, such as DCs and effector T cells (Th17, Th22, Tc17) and creates reverberating circuits [22]. The immune cell infiltration into the skin and the consequent inflammatory processes result in psoriasis skin pathology. One of the most striking features of PsA synovium is the marked tortuosity of blood vessels at the macroscopic level, plasma-cell infiltration with extra-lymphoid neogenesis and mononuclear cell infiltration [23]. These histological findings are associated with monocyte-derived cytokines [24]. Several monocyte-derived cytokines have been implicated in the pathogeneses of PsA [25]. Myeloid-related proteins (S100A8/A9) seem to play a role in the propagation and perpetuation of the inflammatory process in patients with psoriasis and PsA, because of an activated monocyte/macrophage system involved in the “enthesal-complex” [26]. Myeloid-related protein 8 (MRP8; S100A8) and 14 (MRP14;S100A9) are calcium-binding proteins belonging to the S100 protein family that are involved in both intracellular and extracellular functions [27]. Elevated S100A8 and S100A9 levels are found in synovial fluid from PsA patients, strengthening the hypothesis that these molecules are important inflammatory factors [28]. We have recently demonstrated in skin biopsies from PsA patients that S100A8 and S100A9 were present at visibly higher levels in psoriatic plaques compared with normal skin samples. Moreover, S100A8 and S100A9 RNA levels were significantly higher in the peripheral region of plaques compared with the central region. The strong nuclear staining for S100A8/A9 is consistent with the hypothesis that these proteins are involved in psoriasis plaque initiation and amplification through their direct binding, transcriptional activation of genes of the complement system and recruitment of inflammatory cells via secreted cytokines [29].

Innate Lymphoid Cells (ILCs) are a newly described immune cell subtype that still needs to be fully characterized both morphologically and functionally. Indeed, they are thought as precursors of NK cells, as bearing NK markers (such as NKp44). Functionally, three ILC subtypes may be distinguished based on their cytokine production: ILC1, producing IFN-γ, ILC2, producing IL-4, and ILC3, producing IL-17 and IL-22, and expressing IL-23R. This latter subtype is found increased in both blood and lesional skin of psoriatic patients [30–32]. Although these innate-like T cells are present only at low frequencies and often with a specific tissue distribution, it is proposed that they could play a vital function in the development or progression of SpA-related pathology [33]. They could also link the joint pathology to the gut inflammation [34,35]. Resident ILCs at the enthesis might explain the anatomical localization of SpA [36]. Many studies have indicated that ILCs could contribute to local cytokine-driven immune alterations in SpA and RA [37]. Authors demonstrated that synovial fluid from PsA patients is enriched for group 3 ILCs that express CCR6 and NKp44, which distinguishes the

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