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Review

Immune cells involved in the pathogenesis of ankylosing spondylitis

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ABSTRACT

Ankylosing spondylitis (AS) is an inflammatory autoimmune disease. AS is a prototype form of spondyloarthropathies (SpA). The precise etiology of AS has not been fully understood. But Inflammation has a critical role in the pathogenesis of the disease. The immune system by various cells, secreted-mediators and markers manage and regulate the immune responses and inflammation. Every factor which disturbed this regulation and hemostasis can cause chronic inflammation. In this review, we discussed the role of several innate and adaptive immune cells involved in the triggering, initiation, development, and regulation of AS.

1. Introduction

Ankylosing spondylitis (AS)- a type of spondyloarthropathies (SpA) group- is the most common form of chronic inflammatory arthritis [1] that occurs in the third decade of life and mostly affects the lower spine, and sacroiliac joints although other areas of the body such as peripheral joints, enthesitis, and extra-skeletal (eye, gut, skin) and rarely the lungs and heart can be affected [2,3]. Like other autoimmune diseases, although the precise cause of ankylosing spondylitis is unknown, It is believed to involve a combination of genetic and environmental factors that make inflammation [4]. Genetic risk is attributable to the MHC-encoded class I allele, HLA-B27, endoplasmic reticulum aminopeptidase 1 (ERAP1) and IL-23R [5–7].

Chronic inflammation in spinal joints (vertebrae) leads to severe, chronic pain and stiffness in patients that finely can cause -ankylosis- new bone formation in the spine [8]. However, dysregulation or overactivation of immune system seems to be important because several studies showed that various immune cells, secreted-mediators, and markers which play an important role in the pathogenesis of AS [9,10].

In the current review, we discussed the immune cells involved in ankylosing spondylitis in the initiation, progression, and regulation steps. Based on the immune system classification, we first described the role of innate immune cells (dendritic cells, macrophages, and natural killer cells) in the pathogenesis of AS. Subsequently, the discussion is continued with the importance of adaptive immune cells (T helper cells, T regulatory, TCD8+ and B cells) in the disease.

2. Innate immunity

2.1. Dendritic cells (DC)

Dendritic cells (DC) are keepers of the immune system that have key roles in initiation and management of the immune responses. There are different types of dendritic cells depending on their location, surface markers and functions [11]. Human dendritic cells are located in the lymphoid and non-lymphoid organs and subdivided into $CD1c^+$ (conventional DC1) and CD141+ (conventional DC2) subsets [11–13]. $CD1c^+$ cells express myeloid antigens CD11b, CD11c, CD13, CD33, CD172 (SIRPa) and CD45RO markers. In return, CD141+ DCs express less CD11b and CD11c markers [14]. Other types of DC are nominated monocyte-derived DC (Mo-DC, or MD-DC) [15]. These cells play a key role in innate and adaptive immunity, due to their ability to stimulate CD4+ and CD8+ T-cell responses, as well as they are involved in the immunoglobulin production by B cells [15]. Another subset is plasmacytoid dendritic cell (pDC) expressing CD56+ which they have plasma cell morphology and express CD4, derived dendritic cell antigen-2 (BDCA-2), HLA-DR, CD123, Toll-like receptor (TLR) 7 and TLR9. But they are negative for CD14 and CD11c, that discerns them from monocytes and conventional dendritic cells, respectively [16]. Langerhans cells and inflammatory DC are the other subsets that were

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defined [11,12]. Some of these are involved in the immunity to nonself-antigens, and the others are promoting tolerance to self-antigens [12]. Langerhans cells lack some important TLRs, but they can induce regulatory T cells and IL-22 production. Likely, CD14+ monocytes are the precursors of inflammatory DCs [14].

As has been shown previously, DCs play a key role in ankylosing spondylitis. The disease can be transferred by bone marrow transplantation, and apparently, DCs are the main involved cells [17]. Human $CD1c^+$ DCs can induce Th1, Th2 responses. As has been reported in the previous studies, the number of circulating $CD1c^+$ DCs has reduced in AS patients that have been accompanied by an increased number of CD14- CD16+ mononuclear cells capable of inducing CC chemokine receptor (CCR) 6-expressing T cells, and consequently, the production of interleukin (IL)-1b and IL-6. These events may contribute to the Th17 immune responses and therefore associated manifestations of AS [11,18].

Other studies have shown altered properties of the function and gene expression in MD-DCs from human leukocyte antigen (HLA)-B27+ axial SpA patients. Moreover, some signaling pathways of MD-DCs apparently have dysregulated in SpA that can cause inflammatory responses associated with Th17 cells [19,20]. The MDDCs from AS patients express decreased levels of class II major histocompatibility complex (MHC) molecules (HLA-DR) that likely cause their impaired activity [21].

2.2. Macrophage cells (MQ)

Macrophage as a phagocyte and antigen presenting cells play a critical role in innate immunity and host protection. Macrophages have a key role in wound repairing with the turnover regulation of extracellular matrix [22]. In response to various signals and environments, macrophages can be classified into two main populations: classic (M1) or alternative (M2) macrophages [23].

Inflammation of synovial membrane shows same macroscopic appearance in rheumatoid arthritis (RA) and SpA. It has been reported that level of inflammation and frequency of infiltrated inflammatory cells to the synovial membrane is also similar in both diseases [24,25]. Some studies showed that CD163+ macrophages are predominant cells in inflamed peripheral joints in SpA patients [26,27]. Data demonstrated macrophages play a significant role in inflammation of synovial membrane and their frequencies correlate with disease activity. Furthermore, the number of macrophages is decreased, after efficient therapies in SpA [28]. In sacroiliac tissue sample from AS patients, abundant CD68+ macrophages and osteoclasts have been shown [29].

Animal arthritis models have revealed that depletion of macrophages has anti-inflammatory effects [30,31]. In a mouse AS model study, treatment with IL-4 inhibit the severity and incidence of arthritis. Also, mouse macrophages polarized from M1 subtype to a M2 subtype *in vivo* and *in vitro*. This treatment mediated attenuation of receptor activator of nuclear factor kappa-B ligand (RANKL) in macrophages [32].

Investigations on HLA-B27/human β2-microglobulin transgenic rats demonstrated a critical role of HLA-B27+ macrophages in entheses inflammation. In this content, macrophages produce pro-inflammatory cytokines, especially IL-23 [33]. Many studies showed a high amount of IL-23 in serum and tissues of AS patients [34]. It has been well-documented IL-23 can activate IL-23/17 axis, which is involved in the pathogenesis of ankylosing spondylitis [35].

2.3. Natural killer cells (NK)

Natural killer (NK) cells are critical components of innate immunity and provide surveillance at the front line defense against intracellular bacteria, virus and cancer cells. NK cells comprise 5–15% of the peripheral blood mononuclear cells and exist in secondary lymphoid tissues like spleen, tonsils and lymph nodes, as well as other organs such as the skin, liver, lung, and intestine [36,37]. NK cells can be recognized by the expression of CD56 and CD16 and the lack of the CD3 complex. They can be divided into two major subsets based on the expression of CD56 [38]. CD56 dim NK cells encompass approximately 90% of circulating peripheral NK cells and express perforin, and inhibitory killer immunoglobulin-like receptors (KIRs) [39]. However, CD56 bright NK cells more exist in secondary lymphoid tissues such as lymph nodes and tonsils [40].

Despite impaired function or decreased numbers of NK cells have been associated with autoimmune disorders like psoriasis, systemic lupus erythematosus (SLE), RA and multiple sclerosis [41–43], AS patients have a significantly higher percentage of NK cells of the subset of CD56dim CD16+ with a prominent increase in carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) expression [44,45]. Also, this increased number of NK cells are correlated with Bath AS Disease Activity Index (BASDAI) score of disease [46].

HLA molecules can interact with NK cells receptors. As the importance of HLA-B27 in the pathogenesis of AS [47,48], it has shown that among the KIR genes, the KIR3DL1/3DS1 locus is of particular interest on AS because it recognizes HLA-B27 [44,49]. NK cell lysis is inhibited when their inhibitory receptors interact with class I HLA molecules on target cells. Five subtypes of HLA-B27 including B*2701, *2703, *2704, *2705, and *2706 have potent inhibitory effects on NK cells, whereas the one subtype, B*2702 did not inhibit [50]. KIR3DL1 is an inhibitory receptor that interacts with HLA-Bw4 serotype (including HLA-B27) to suppress the cytolytic capacity of T or NK cells while KIR3DS1 is only activating the receptor.

However, the frequency of KIR3DL1 is 79%, several studies observed enrichment for KIR3DS1 in HLA-B27+ patients with AS [51,52] and KIR3DL1 was found to be underrepresented in patients with AS compared to HLA-B27+ healthy controls [53,54]. With regards to the ligand specificity of KIR3DS1, functional studies are needed to investigate a potential interaction of KIR3DS1 and HLA-B27 in the context of AS (Fig. 1).

Genetic polymorphisms of KIRs genes have also been studied by some research groups, finding that KIR2DL1, KIR3DL1, KIR2DS5, KIR3DS1, and KIR2DL5 are all associated with AS, though in different populations [54–57]. Finally, as the most recent evidence of the underlying role of NK cells in AS, we can imply the role of these cells as biosensors to respond to Etanercept therapy [58].

3. Adaptive immunity

3.1. T helper 1 cells (Th1)

The T helper cells (Th1 cells) are a subset of CD4+ T cells which are characterized by releasing cytokines like interferon gamma (IFN-γ), IL-2, and tumor necrosis factor alpha (TNF-α) to activate other immune cells and contribute to cellular immune responses. The number of T cell subsets and their roles in the pathogenesis of AS is still the subject of debate. Szanto et al. observed no significant difference in Th1 cell percentages and the Th1/Th2 ratio between 42 Hungarian AS patients and 52 healthy subjects. Moreover, the expression level of IFN-γ in sera of patients had no significant alteration in comparison to the control group [59].

However, another study by a group of Mexican scientists in 2012 indicated that IFN-γ producing T CD4+ cells (Th1) rose in the peripheral blood mononuclear cell (PBMC) of AS patients compared to healthy individuals. The frequency of Th1 cells and their prominent cytokine, IFN-γ, were significantly diminished after using TNF-α-blocker agents through impeding migration of immune cells from lymph nodes to peripheral tissues [60].

Wanxg et al. in 2015 detected a significant increase in Th1 frequency and Th1/Th2 ratio in two groups of patients with a mild and severe degree of AS. These imbalances in T cell subsets give rise to IFN-γ enhancement which may cause ongoing inflammation and make AS