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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

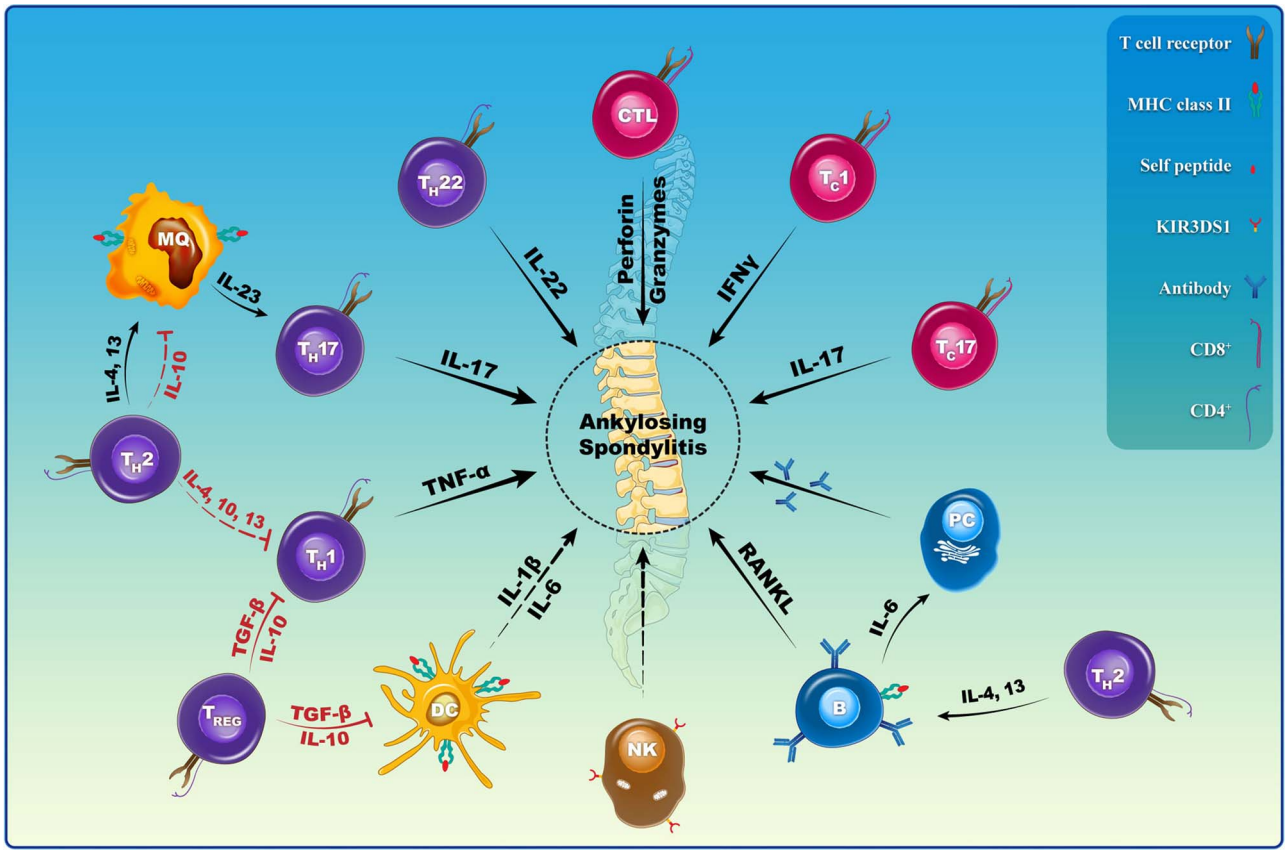

Fig. 1. Immune cells involved in the initiation, progression, and regulation of ankylosing spondylitis. B: B cell; CTL: cytotoxic T lymphocyte; DC: dendritic cell; IFNγ: interferon gamma; IL: interleukin; KIR3DS1: killer cell immunoglobulin like receptor, three Ig domains and short cytoplasmic tail 1; MQ: macrophage; NK: natural killer cell; PC: plasma cell; TC: cytotoxic T cell; TH: T helper ce6ll; TNF-α: Tumor necrosis factor alpha.

more progressive [61].

Since chemokines are essential mediators of T cell recruitment to inflamed sites, Wang et al. evaluated the level of IP-10 (IFN-γ-inducible protein-10/CXCL10) in sera of AS patients, which attract Th1 cells. They found a significant increase in IP-10 level which can lead to more IFN-γ and TNF-α production and aggravate inflammatory conditions in these patients [62].

3.2. T helper 2 cells (Th2)

Previous studies demonstrated that the percentage of CD4+/CCR4+ T cells were increased in active AS, RA, and SLE. Overexpression of CCR4 on CD4+ T cells, as a chemokine receptor of Th2 cells, demonstrates that Th2 responses could be enhanced in AS, although the immunoregulatory function of Th2 cells may be incompleted to regulate enhanced Th1 responses. Furthermore, the number of CD4+/CCR4+ T cells have a positive correlation with the BASDAI in AS [63]. Thymus and activation-regulated chemokine (TARC/CCL17) and macrophage-derived chemokine (MDC/CCL22) play a particular role in the migration of Th2 cells. High serum concentrations of TARC and MDC in AS patients have been demonstrated. While the serum level of IL-4 was not significantly elevated in AS patients. High levels of these chemokines may be caused by an adaptive reaction to attract higher Th2 cells to restore a balance of Th1/Th2 [64]. Some of the studies showed atopic disorders slightly increased in AS compared with RA patients [65]. Also, genome-wide association studies (GWAS) of this genetic disease have involved specific immune pathways, including the IL-23/17 pathway, regulation of NF-κB activation, amino acid trimming for MHC antigen presentation and other genes controlling CD8 and CD4 T cell populations [66]. In conclusion, these results recommend that Th2 cells and chemokines may be involved in the progress of AS [64].

3.3. T helper 17 cells (Th17)

Th17 cells are one of the subsets of CD4+ T cells that can produce proinflammatory cytokines such as IL-6, IL-26, IFN-γ but they considered as the main source of IL-17 production. Th17 differentiation is controlled by transcription factors signal transducer and activator of transcription (STAT) 3 and STAT5. Co-stimulation of Th17 cells with IL-6 and transforming growth factor beta (TGF-β) Induce STAT3, and as a result, STAT3 causes IL-17 promoter activation. In contrast, IL-2 upregulates STAT5 and inhibit Th17 differentiation. IL-23 is also necessary for expansion and maintenance of Th17 cells [67].

IL-17 is a proinflammatory cytokine that was identified in 1993. There are several isoforms of IL-17 named IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F. It has been shown that proinflammatory IL-17 involves the pathophysiology of several autoimmune diseases. The primary function of Th17 cells is protection against pathogenic bacteria such as *staphylococcus, mycobacteria, klebsiella* or fungal pathogens but excess secretion of IL-17 from activated T cells can cause autoimmune diseases. Uncontrolled IL-7 production induces secretion of inflammatory mediators from fibroblasts, endothelial cells, dendritic cells, and macrophages. Excretion of such factors leads to inflammatory state and joints destruction that is seen in rheumatoid arthritis and ankylosing spondylitis [35,67].

Recent findings show that IL-23/17 pathway has an important role in the pathogenesis of AS. IL-23 is critical for amplification and maintenance of Th17 cells [68]. Different studies revealed that serum levels of IL-17 and IL-23 as well as the percentage of Th17 cells in AS patients have increased [69–71]. Targeting Th17 responses is a promising approach for the treatment of AS. Several clinical trials to target Th17

responses have been done using monoclonal antibodies including secukinumab and ixekizumab (both against IL-17A), ustekinumab (a monoclonal antibody that targets IL-23) and brodalumab (directing against IL-17RA receptor). Secukinumab has been shown effective outcome to treatment AS [72–75]. In 2013 Baeten et al. used Secukinumab in a randomized, double-blind study and achieved improvement in assessment of spondyloarthritis international society criteria for improvement (ASAS20) response in the treatment group compared with placebo [76]. Ustekinumab also has therapeutic potency for AS patients. In a trial, ustekinumab groups have shown improvement in ASAS40 response and BASDAI score in comparison to placebo [77].

3.4. T helper 22 cells (Th22)

Th22 cells are a novel subset of CD4+ T cells distinct from other T helper subsets. They were defined by Trifari et al. in 2009 as a T cell subset that secrete cytokines such as IL-22, IL-13, and TNF-α [78]. Th22 cells do not produce IL-17, IFN-γ and IL-4 cytokines (as Th17, Th1, and Th2 markers, respectively). IL-6 and TNF-α can induce differentiation of naïve CD4+ T cells into Th22 cells. Transcription factors involved in Th22 differentiation are not fully elucidated, but it seems that aryl hydrocarbon receptor (AHR) is the key transcription factor in the regulation of Th22 expansion [79].

IL-22 is the main cytokine produced by Th22 cells. IL-22 belongs to IL-10 cytokine family and has a significant role in infections and inflammatory conditions [80,81]. Elevated IL-22 levels have been shown in several inflammatory diseases including psoriasis, crohn's disease, RA, AS and SLE [82–84]. In a study in 2012, Zhang et al. demonstrated that an absolute number of Th22 cells in peripheral blood and plasma IL-22 levels had elevated in AS patients, but there was no correlation between the number of Th22 cells and disease activity [84]. In the recent study of El-Zayadi et al., the involvement of IL-22 in human mesenchymal stem cell (MSC) osteogenesis was demonstrating another pivotal role of this cytokine in the mechanism of new bone formation in SpA [85]. Since this phenomenon remains under the influence of this cytokine even after the inflammatory condition has been resolved, and the new bone formation is the adverse effects of this disease. It can be a new window for research on Th22 cells role in AS.

3.5. T regulatory cells (Treg)

Several studies have been carried out to determine the frequency [86], the role of both naïve (CD4+ CD25 high CD39− CD45RO−) [87] and active (CD4+ CD25 high CD127 low/–) Treg cells [88] in the peripheral blood of patients with AS [89]. In the other hand, some studies focus on evaluate the polymorphism in inhibitory molecules including cytotoxic T-lymphocyte antigen 4 (CTLA-4) [90] or Treg cell–related cytokines IL-2, TGF-β, and IL-10 production with transcription factors forkhead box protein P3 (FoxP3) and STAT5 levels specially either in ileum tissue [89] or in co-culture with autologous dendritic cells [91].

Approximately 75.7 and 24.3% of patients were responders and non-responders to anti-TNF-α therapy, respectively. As a result, the ratios of both Th1/Th2 and Th17/Treg were significantly higher in patients with AS [61]. Also, findings showed a significant upregulation of Treg cells percent in PBMCs [86,89] especially in AS patients who had a poor disease functional index with higher levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), HLA-B27+ [91] and were found to be negatively correlated with BASDAI score [71]. However, some finding showed CD4+ CD25 high CD127 low/– Treg cells in AS patients were found to be significantly lower than in healthy controls and were inversely correlated with serum IgA levels. In addition, there was no significant correlation between CD4+ CD25 high CD127 low/– Treg cell numbers and BASDAI scores [88].

Levels of IL-2, TGF-β, FoxP3, STAT5, and IL-10, with a 5-fold increase in the proportion of active Treg cell response, mainly dominated by IL-10 production, occurs in the gut of AS patients as compared with healthy subjects and is probably responsible for the absence of a clear Th17 polarization in the ileum of AS patients [86] and it could be reversed by adalimumab therapy [89]. In addition, the beneficial effect of anti-TNF-α therapy in AS might not only neutralize the effects of TNF-α but also downregulate Th17 and Th17-related cytokines accompanied by upregulating the Treg/TGF-β axis in responders [71].

These findings suggest that Tregs may play a role in modulating the inflammatory process in AS. It is unclear and requires further study, whether Tregs can be taken as a predictor of disease activity or treatment outcome [89].

3.6. T CD8+ cells

T CD8+ cells are one of the important arms of the cellular (adaptive) immune system which have different roles in development or protection of autoimmune diseases [92]. Upon recognition of MHC class I-restricted Antigens by T-cell receptor (TCR), naïve T CD8+ cell can differentiate into effector and cytotoxic T lymphocytes (CTL) [92]. CD8 effector T cells are divided into Tc1, Tc2 and newly defined subset Tc17 based on surface markers and cytokines secretion pattern that is similar to their counterpart helper T cells. Tc1 and Tc17 mediate inflammatory responses by generating IFN-γ and IL-17, respectively. Like Th2, Tc2 has a protective role in autoimmune disease through production of IL-4, IL-5, and IL-10 [47]. Although CTLs can typically target viral-infected or cancerous cells, they can also attack self-antigens and cause organ-specific autoimmune diseases. However, these self-antigens are not well characterized yet [93].

In a study in 2005, Atagunduz et al. demonstrated that peptide derived from type II and IV collagen in cartilage site could stimulate T CD8+ cells in four of seven patients with ankylosing spondylitis which results in cartilage destruction [94]. Chondrocytes act as non-professional antigen presenting cells (APCs) which present some cartilage antigens to CD8+ effector T cells in an inflammatory milieu. Following IFN-γ enhancement in inflamed joints of AS patients, MHC-I was upregulated on the surface of chondrocytes which lead them more susceptible to CTLs [28,93].

T CD8+ cells mediate their pathogenic role through several different mechanisms. CTLs cause direct lysing of target cells by secreting perforin/granzyme or signaling through Fas/FasL pathway. Furthermore, CD8+ effector T cells produce inflammatory cytokines such as TNF-α, IFN-γ, IL-17 and support chronic immune responses in AS patients [25].

Data from a Chinese study in 2015 indicated that different subtypes of T cells were associated with AS progression. In cytotoxic T cell subsets, percentages of Tc1 and Tc17 and the expression level of their immune mediators, IFN-γ and IL-17 were significantly higher in AS patients compared to the healthy control group. However, the percentage of Tc2 had no considerable changes between the groups. Thus, the Tc1/Tc2 ratio was increased, and their cytokine imbalances might be helpful as a diagnostic factor for AS [95].

In order to treat autoimmune diseases, cell therapy can be a potential choice. Non-cytotoxic CD8+ regulatory cells could suppress immune responses via generating IL-10 in an IL-4 dependent manner. These regulatory T cells can be expanded by co-culture with lipopolysaccharide-activated DCs *in vitro*. By maintaining their regulatory capacity, they can be adoptively transferred in patients with inflammatory disorders for therapeutic purposes [24].

3.7. B cells

B lymphocytes play various roles in the immune system. These cells are not only involved in antibody production but also interact with T helper and APCs such as macrophages and dendritic cells, for producing multiple cytokines [96]. Recent studies have revealed that the pathogenesis of AS involves imbalances in the innate and adaptive immune

Table 1
Immune cells involved in the pathogenesis of ankylosing spondylitis.

Cell type	Main marker	Function in ankylosing spondylitis
M2 Macrophage (MQ)	CD163 +	- Production of IL-23 - Induction IL-23/17 pathway
Dendritic cells (DC)	CD14 − CD16 +	- Promotion of Th17 cells - Induction of IL-6 and IL-1β - Reduced expression of MHC II - Production of IL23 in high level
Natural killer cells (NK)	CD16 + CD56dim	- Recognition of HLA-B2 by KIR3DL1/3DS1
Th1	CD3 + CD4 +	- Mediating inflammatory responses by secreting IFN-Y, TNF-α
Th2	CD3 + CD4 + CCR4 +	- Production of IL-4, IL-10, IL-13 - Activation of MQ cells - Have a positive correlation with the BASDAI in AS
Th17	CD4 + IL- 17	- Mediating inflammatory response by secreting IL-17
Th22	CD4 + IL-22	- Mediating inflammatory response by secreting lL-22
Treg	CD4 + CD25highCD39-CD45RO-CD4 + CD25highCD127low/-	- production of TGFB, IL-10 - inhibition of MQ and DC - modifying of inflammation process
T CD8 +	CD3 + CD8 +	- Secreting inflammatory cytokines such as TNF-α, IFN-Y, IL-17. - CTLs directly kill target cells via secreting perforin/granzyme.
B cell	CD19 + CD86 + CD95 + CD27-	- Ectopic lymphoid structures formation - Autoantibody production - Immunomodulatory cytokines production such as IL-6 - Production of RANKL and may be involved in the progress of AS - Antigen-presenting to active T cells - Have a positive correlation with the BASDAI in AS

cells [97]. Many works have focused on T cell subsets in AS, while studies on B cells have been separated. Some studies illustrate frequencies and functions imbalances of B cells and its subtypes in SLE and RA [98]. Recent investigations provide many important insights into B cell pathobiology in AS patients. Findings demonstrated that the numbers of CD27 + B cells were decreased in AS patients, while CD86 + and CD27 − CD95 + B cells were increased. Also, it has been shown that the number of CD38 + And CD95 + B cells have a positive correlation with BASDAI. Therefore, CD27 − CD95 + CD19 + and CD86 + CD19 + B cells may be acceptable targets for the therapeutic intervention of AS [99]. Furthermore, data of other studies have shown that antibodies can serve as suitable biomarkers might supply to the improved for diagnosis and prognosis of ankylosing spondylitis. Altogether, higher prevalence of B cells, antigen-presenting to active T cells, immunomodulatory cytokines and RANKL production and ectopic lymphoid structures formation and autoantibodies existence are demonstrative of a role of B cells in AS [100].

The immune cells markers and functions in ankylosing spondylitis are described in Table 1.

4. Conclusions

However treatment for ankylosing spondylitis has considerably improved in the past years, an effective cure has not yet been established, and many patients suffer persistent disease or intolerable side effects from existing therapies. With progress in our findings of AS pathogenesis and use high-throughput techniques, the role of immune system and crucial cell types are increasingly recognized. This understanding can shed new light on the mechanisms underlying the targeting combinational therapies.

Conflicts of interests

There is no conflict of interest to declare.

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