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Review

T-cells interact with B cells, dendritic cells, and fibroblast-like synoviocytes as hub-like key cells in rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory synovitis-based systemic disease characterized by invasive joint inflammation and synovial hyperplasia, which can lead to arthrentasis and defunctionalization. Previous research has shown that T cells, B cells, dendritic cells (DCs), and fibroblast-like synoviocytes (FLSs) play vital roles in the regulation of RA. Both T follicular helper (Tfh) cells and helper T (Th) 17 cells play immunomodulatory roles in RA. Moreover, interleukin-23 (IL-23), and IL-17 are vital to the pathogenesis of RA. T cells behave as a hub, in that B cells, DCs, and FLSs can interact with T cells to inhibit their activation and interfere with the process of RA. T cells cooperate with B cells, DCs, and FLSs to maintain the stability of the immune system under physiological conditions. However, under pathological conditions, the balance is disrupted, and the interaction of T cells with other cells may intensify disease progression. This review focuses on the interaction of T cells with B cells, DCs, and FLSs in different tissues and organs of RA patients and animal models, and highlight that the interplay between immune cells may underline the unique function of T cells and the application prospect of targeting T cell treatment for RA.

1. Introduction

Rheumatoid arthritis (RA) is a common autoimmune disorder, and is characterized by chronic and progressive organ inflammation, particularly the synovium of joints, causing joint destruction, decreased life expectancy, and reduced quality of life [1]. RA is characterized by infiltration of the synovial membrane by T cells, B cells, and monocytes, a process preceded by endothelial cell activation. Neovascularization is another hallmark of RA synovitis, and the expansion of synovial fibroblast-like and macrophage-like cells results in synovial lining proliferation. This expanded synovium, often referred to as “pannus,” invades the periarticular bone at the cartilage-bone junction, causing bone erosion and cartilage degradation [2]. In the periarticular phase of RA, subclinical inflammation in the small joints of patients with

Abbreviations: ADP, adenosine 5′-diphosphate; AMP, adenosine 5′-monophosphate; ATP, adenosine 5′-triphosphate; ACPAs, anticitrullinated peptide antibodies; APCs, antigen presenting cells; APS, apoptotic cells; AhR, aromatic receptors; BLIMP-1, B lymphocyte induced maturation protein1; BCL-6, B-cell lymphoma 6; CCR6, C-C chemokine receptor type 6; CCL20, chemokine (C-C motif) ligand 20; CXCL13, chemokine (C-X-C motif) ligand 13; (CXCL9), chemokine (C-X-C motif) ligand 9; cDCs, classical dendritic cells; CIA, collagen-induced arthritis; CIA-B cells, collagen-induced arthritis mice; CXCR3, C-X-C chemokine receptor type 3; CXCR5, C-X-C chemokine receptor type 5; CXCL10, C-X-C motif chemokine 10; CXCL11, C-X-C motif chemokine 11; Tc, cytotoxic T cells; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DCs, dendritic cells; EAE, experience-autoimmune encephalomyelitis; FLSs, fibroblast-like synoviocytes; FAK, focal adhesion kinase; Tfh, Follicular helper T; Foxp3, forkhead box P3; GCs, germinal centers; HLA, human leukocyte antigen; ITAM, immune receptor tyrosine-based activation motifs; ITIM, immuno-receptor tyrosine-based inhibitory motif; IA, inflammatory arthritis; IBD, inflammatory bowel disease; ICAM-1, intercellular adhesion molecule – 1; IL, Interleukin; JIA, juvenile idiopathic arthritis; LFA-1, leukocyte function-associated antigen; LAG-3, lymphocyte activating gene-3; KAT7, Lysine acetyltransferase 7; MHC-II, major histocompatibility class II; MMPs, matrix metallo proteinases; IgV, immunoglobulin variable; MDR1, multidrug-1; MS, multiple sclerosis; NK, natural killer cells; Nrp-1, neuropilin 1; NFAT, nuclear factor of activated T-cells; pDCs, plasma dendritic cells; PDGF, platelet-derived growth factor; Treg, regulatory T cell; RA, Rheumatoid arthritis; RA-FLS, rheumatoid arthritis fibroblast-like synoviocytes; RF, rheumatoid factor; RNs, rheumatoid nodules; RUNX1, runt-related transcription factor 1; STAT5, signal transducer and activator of transcription 5; SHP-2, Src homology 2 domain–containing protein tyrosine phosphatase 2; STIM, stromal interaction molecule; TBX21, T-box transcription factor; TL1A, TNF-like protein 1A; TGF, transforming growth factor; TILs, tumor infiltrating lymphocytes; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor

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arthralgia is predictive of inflammatory arthritis (IA) development [3]. Moreover, auto-antigens (e.g., anti-citrullinated peptide antibodies [ACPAs]), antibodies to IgG (rheumatoid factor [RF]), nuclear antigens, or auto-antigens that cross-react with bacterial or viral antigens, which develop before symptoms appear, can form immune complexes that may activate complement, exacerbating inflammatory responses. This stage is called “pre-RA” and it can last for < 1 year, or as long as 10 years [4].

RA is closely associated with a variety of immune cells, with each cell type contributing differently to disease pathogenesis. Several types of immunomodulatory molecules, mediated by immune cell-secreted cytokines, influence the pathogenesis of RA, complicating disease treatment and management. T cells, B cells, and pro-inflammatory cytokines play pivotal roles in RA pathogenesis [5]. Additionally, other immune cells, such as dendritic cells (DCs) and fibroblast-like synoviocytes (FLSs), are reported to mediate RA pathophysiology [6]. B-cells secrete proteins such as RFs, ACPA, and pro-inflammatory cytokines, and mediate T-cell activation through expression of co-stimulatory molecules. T cells secrete pro-inflammatory cytokines, including TNF-α, IL-1, and IL-17, typically exceed the protective effects of anti-inflammatory cytokines such as IL-4, IL-10, and IL-13, causing cytokine-mediated inflammation [7]. In RA, $CD4^+$ T cells (Th cells), B cells, and macrophages can infiltrate the synovium, which is normally a cellular with a delicate intimal lining, and subsequently organize into discrete lymphoid aggregates with germinal centers (GCs). T cells interact with B cells, DCs, and FLSs in peripheral blood, spleen, and joint cavities, interfering with RA [8] (see also Fig. 1).

In this review, we discuss the interaction of T cells with B cells, DCs, and FLSs in different tissues and organs of RA patients and animal models, and explore a newly developed therapeutic target of T cells.

2. T cells interact with B cells in rheumatoid arthritis

During the RA immune response, B cells in the peripheral blood of patients can identify and present antigens to T cells. B cells provide co-stimulatory signals to aid in T cell activation, secrete inflammatory factors, produce rheumatoid factors and anti-cyclic citrullinated peptide antibody, and participate in the formation of GCs [9]. A murine airway inflammation model has been used to demonstrate the significance of T/B cooperation in lymph nodes, as well as in inflamed peripheral tissues for local antibody responses to infection and autoimmunity [10]. Meanwhile, the B cell activation pathway in synovium of RA patients achieves an abnormally active immune response through a T cell-dependent mechanism (CD40-CD40L), in combination with a non-T cell dependent mechanism, resulting in immune damage [11]. Moreover, it was found that B cells from collagen-induced arthritis (CIA) mice promoted regulatory T cell (Treg) differentiation, proliferation, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression [12]. Research involving the animal models mentioned above demonstrate that T-B cell interactions may be relevant to the arthritis process.

2.1. T cells interact with regulatory B cells (Bregs)

B cells perform essential roles in autoimmune diseases by presenting antigens and producing antibodies. In the GC of the spleen, B cells are divided into two major subpopulations, namely B1 and B2 cells [13]. B1 cells are considered innate immune cells, which react rapidly and independent of T cells. B2 cells are mature B cells, primarily found in the secondary lymphoid organs, from which Bregs are derived from them [14].

Bregs secrete anti-inflammatory cytokine IL-10, which can block the activity and formation of Th1 and Th2 cytokines, thereby reducing the number of Th cells [15]. Human regulatory B cells, which are predominantly identified based on their production of IL-10, exhibit a phenotypic and functional heterogeneity similar to that of mouse IL-10-producing regulatory B cells. Human regulatory B cells were enriched in both transitional ($CD24^{hi}CD38^{hi}$) and memory ($CD24^{hi}$ $CD27^+$) B cells [16]. Mauri and colleagues showed that $CD24^{hi}CD38^{hi}$ regulatory B cells from normal controls inhibited differentiation of $CD4^+CD25^-$ T cells into Th1 and Th17 cells and promoted their conversion into regulatory T cells, partially through IL-10 production. By contrast, $CD24^{hi}CD38^{hi}$ regulatory B cells from RA patients failed to suppress Th17 differentiation through IL-10, and convert naive T cells into functional regulatory T cells [17]. Moreover, Bregs, which were derived from peripheral blood $CD24^{hi}CD27^+$ B cells, play a role in immune regulation, and participate in immune and inflammatory responses [18]. Adoptive transfer of $IL\text{-}10^+$ regulatory B cells strongly reduced circulating leukocyte numbers and inflammatory monocytes. In addition, they decreased $CD4^+$ T cell activation and increased $IL\text{-}10^+$ $CD4^+$ T cell numbers [19]. So, regulatory B cells may contribute to suppression of the disease in RA patients, although their function may be attenuated.

Janeway et al. observed that the lack of Bregs in B10/PL mice resulted in abnormally severe chronic autoimmune encephalomyelitis (EAE), demonstrating that Bregs affect the development and progression of autoimmune diseases by producing IL-10 [20]. In addition, Gray et al. believe that apoptotic cells (APS) can also act as an endogenous signal to trigger the production of IL-10 and improve CIA [21]. Moreover, apoptosis can also induce spleen cells to produce IL-10. Enhanced secretion of IL-10 by T cells can play an immunosuppressive function. Therefore, Bregs can mediate immune tolerance and inhibit excessive inflammatory responses [22]. If sufficient evidence is accumulated to prove that interaction between T cells and Bregs can attenuate T cells activity, this may provide a new avenue for the treatment of RA.

2.2. Follicular helper T cells interact with B cells

T follicular helper (Tfh) cells are a T-cell subset, named for their location in GCs. Tfh cells are critical for the production of GCs, a unique structure in which antigen-primed B cells undergo proliferation, immunoglobulin (Ig) class switching, somatic hypermutation, and differentiation [23]. To prevent excessive B-cell and auto-antibody production, PD-1 on T cells interacts with its ligand PD-L1 on B cells in GC. CD40-CD40L, PD1-PDL1, and the storage of CD40L in GC Tfh all promote T-B cell interactions, ensuring that T cells and B cells play their respective roles and activities in the immune response of RA [24].

An important characteristic of Tfh cells is the production of high levels of IL-21, which promotes Tfh cells differentiation in a positive autocrine feedback loop [25]. Data from RA patients indicates that they have higher IL-21 serum levels than controls [26]. At the time of diagnosis early-stage RA patients, in whom the disease duration has been less than six months, had significantly increased IL-21 plasma levels as compared to both late-stage RA patients (disease duration > 8 years) and healthy controls (HCs). The levels increased from baseline to 3 months after diagnosis, but declined at 12 months after diagnosis. Late-stage RA patients did not have increased IL-21 plasma levels as compared to HCs [27]. In addition, Shoda et al. have found that IL-21 plasma levels correlate to disease activity and radiological progression in RA, and that the IL-21-producing Tfh cells are increased in the blood and synovial fluid of these patients. IL-21is thought to exert key functions in controlling and directing the T and B cell responses leading to formation of antibodies and auto-antibodies alike [28].

Moreover, in the model of CIA, C-X-C chemokine receptor type 5 (CXCR5) was identified as an essential factor for the induction of inflammatory autoimmune arthritis, as CXCR5-deficient mice and mice with selective CXCR5 deficiency on T cells are resistant to CIA [29]. In another model (self-reactive $CD4^+$ cells transferred from KRN-T cell antigen-receptor transgenic mice to recipient animals), $CD4^+$cell defect-protected mice with lymphocyte activation-related protein (SAP) signaling were observed to be protected against developing arthritis [30]. The above data indicate that persistent interactions between T

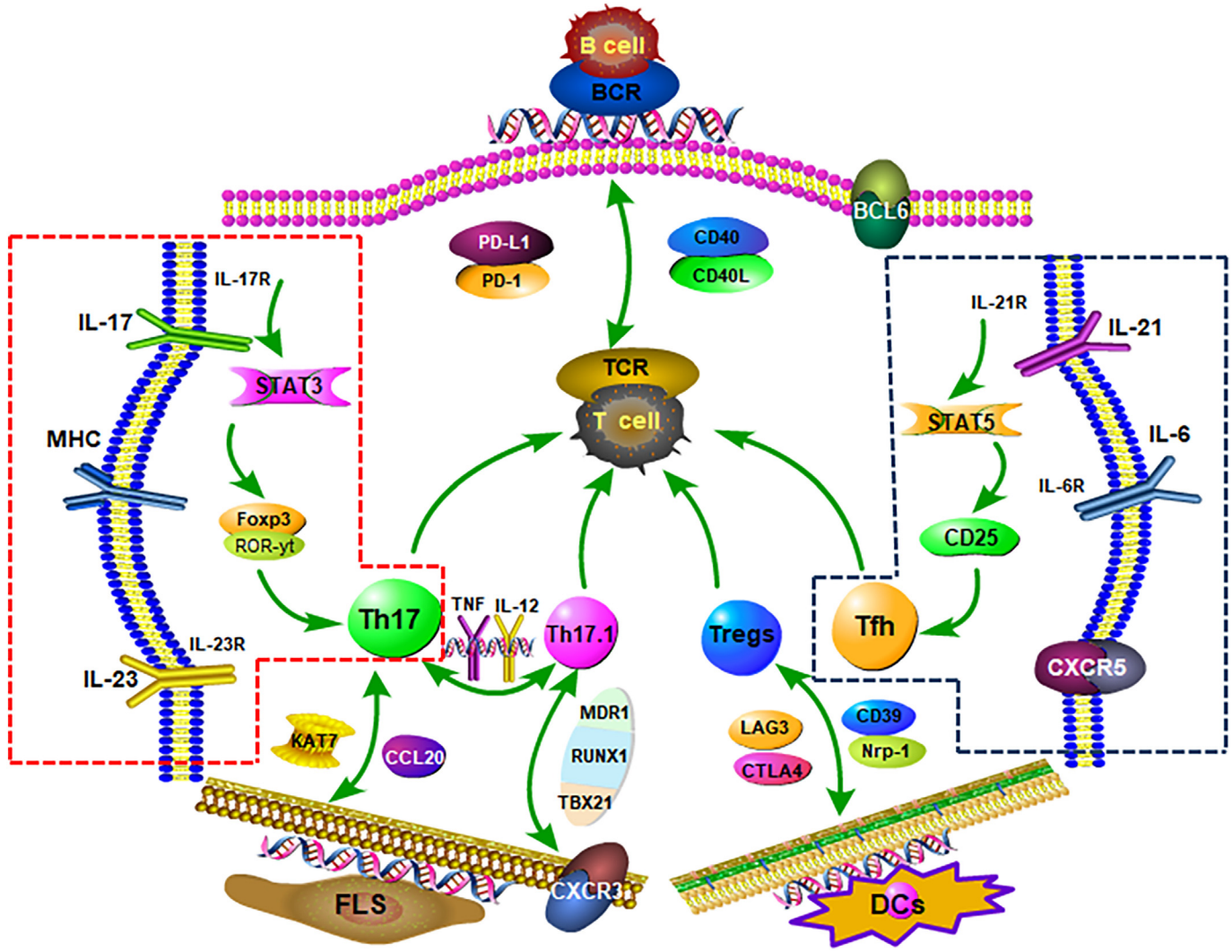

Fig. 1. The interaction process of T cells involved in immune cells and molecules in rheumatoid arthritis.
The interaction among T Cells and B cells, fibroblast-like synoviocytes (FLSs), dendritic cells (DCs) are important in rheumatoid arthritis (RA). Th17 cells, mainly secrete IL-17, downstream signals of STAT3 along with ROR-γt mediates Th17 cell differentiation and cytokine expression. An important characteristic of T follicular helper (Tfh) cells is the production of high levels of IL-21. To prevent excessive B-cell and auto-antibody production, PD-1 on T cells interacts with its ligand PD-L1 on B cells in GC. IL-2/CD25/signal transducer and activator of transcription 5 (STAT5) signaling attenuates the formation of Tfh by inducing B lymphocyte-induced maturation protein1 (BLIMP-1) and inhibitingBCL-6. CD40-CD40L, PD1-PDL1, and the storage of CD40L in GC Tfh all promote T-B cell interactions, ensuring that T cells and B cells play their respective roles and activities in the immune response of RA. Meanwhile, DCs are congenital APC, which can activate initial Th cells. Some markers of Tregs (CD39, LAG-3, CTLA-4 or Nrp-1) can interact with DCs, they were co-expressed in Tregs and expressed in different ways in RA synovium. In addition, Th17 and Th17.1 cells are both present in the synovial fluid of patients with RA, the interaction between Th17 cells and FLSs can stimulate FLSs to express the pro-inflammatory mediators such as IL-6, CCL20. FLSs can promote the differentiation and migration of Th17 cells through KAT7. Moreover, Th17.1 differentiation from Th17 cells can be enhanced by exogenously produced IL-12, or as a consequence of autocrine TNFαproduction.Th17.1 cells express multidrug-1 (MDR1), T-box transcription factor (TBX21) and runt-related transcription factor 1 (RUNX1). In contrast to Th17 cells, Th17.1 cells are highly resistant to FLS-mediated suppression of proliferation and cytokine expression. In a conclusion, T cells are hub-like key cells interact with B cells, DCs and FLSs, and play an important role in the process of RA.

and B cells and GC formation are essential for disease progression in RA.

2.3. PD-1^{hi}CXCR5-CD4^{+} T cells interact with B cells

The pathogenesis of autoimmune and inflammatory disorders is not fully understood. It is, however, well known that T cells are the central mediators of autoimmune disorder pathology, and that the expression of activated T cells mediates the development of chronic arthritis [31]. The marked expansion of PD-1^{hi} cells specifically in seropositive RA, a disease characterized by autoantibody production and frequent synovial T–B-cell aggregates, led us to consider whether synovial PD-1^{hi} cells might be Tfh cells. Tfh cells, often identified as CXCR5^{+} PD-1^{+}, are uniquely adapted to promote B-cell recruitment and differentiation in lymph node follicles through production of IL-21, IL-4, CD40L, and CXCL13, the ligand for CXCR5 [32]. While, seropositive RA synovial tissue samples contained few PD-1^{hi}CXCR5 $^{+}$ Tfh cells, which clustered separately from PD-1^{hi} CXCR5^{-} cells. By contrast, 85% of PD-1^{hi} CD4^{+} cells in synovial tissue lacked CXCR5, as did almost all PD-1^{hi} CD4^{+}cells in synovial fluid. Measurement of CXCR5 transcript levels in sorted PD-1^{hi} CXCR5^{-} and PD-1^{hi} CXCR5^{+} cells from synovial tissue, synovial fluid, and blood confirmed that PD-1^{hi}CXCR5^{-} cells from all three sources contained little, if any, CXCR5 mRNA [33]. Thus, seropositive RA synovium contains abundant PD-1^{hi}CXCR5-CD4^{+} T cells that are distinct from Tfh cells.

Federica et al. have assessed the function of synovial PD-1^{hi}CXCR5^{-}

cells. Surprisingly, despite a lack of CXCR5 expression, PD-1^{hi}CD4^{+} T-cell sorted from seropositive RA synovial fluid showed over 100-fold increase in IL21 mRNA expression and a > 1000-fold increase in CXCL13 mRNA expression. High IL-21 and CXCL13 production by synovial fluid PD-1^{hi}CXCR5^{-} CD4^{+} T cells indicates that these cells are not globally exhausted, and instead suggests a possible B-cell helper function [34]. CXCL13 is a steady-state B-cell chemo attractant that is induced in RA, and is associated with the development of B-cell follicles and GC responses in synovial bone marrow. Its plasma levels have been found to be related to disease activity. CXCL13 is often characterized by the absence of follicular-assisted T cell markers CXCR5 and BCL-6 protein, and the production of Th cells through terminal differentiation [35]. In vitro experiments showed that T cell receptor-CD28 has potent effect on the production and secretion of CXCL13 in primary cells. CXCL13 can be expressed directly by T cells, inducing binding to antigen presenting cells and T cell receptors [36]. These findings demonstrate the significant function of CXCL13, and suggest that it may be plastically regulated during the immune response, acting as a direct signal transducer for T-B cell interactions.

Therefore, great importance is attached to PD-1^{hi} cells. The specificity of PD-1^{hi} cells in seropositive RA patients, characterized by the auto-antibodies and frequent synovial T-B cell aggregates produced [37].

3. T cells interact with DCs in rheumatoid arthritis

DCs are highly efficient antigen presenting cells that have the unique function of initiating an initial immune response. Immature or subcultured DCs are derived from CD34^{+} hematopoietic progenitor cells ingesting antigens, and then become more conducive to the presentation of antigens as mature DCs [38]. Mature DCs present antigens to Th cells, which then activate T cells, B cells, and macrophages, eliciting specific immune responses.

3.1. Th17 cells and cytotoxic T cells (Tc) interact with DCs

DCs are generally divided into two subtypes, namely, classical dendritic cells (cDCs) and plasma dendritic cells (pDCs). DCs regulate the immune response and immune tolerance, and are the most important antigen-presenting cell that binds to T cells, and especially to Th cells [39]. Th17 cells were initially characterized by the production of IL-17A, but now have been shown to coproduce a group of cytokines (IL-17A, IL-17F, IL-21, and IL-22), which act in a coordinated manner to mediate tissue inflammation [40]. Initial studies suggested that IL-23 is the differentiation factor for Th17 cells. IL-23 from DCs activates IL-17 production in Th17 cells, and it has been speculated that DCs might also play a role in the pathogenesis of rheumatoid nodules (RNs) through the production of IL-23 [41]. To investigate this question, Saito-Sasaki et al. examined the distribution of IL-23 positive cells in the skin. Consistent with the above results, the number of IL-23 positive cells in RNs was found to be significantly increased compared to numbers in healthy subjects, and in non-RN skin from RA patients [42]. To examine the possible role of the IL-23/IL-17 axis more precisely, the correlation between IL-17 positive and IL-23 positive cells in RN and healthy subjects was also analyzed. A significant positive correlation was found between the number of IL-17 positive cells and the number of IL-23-positive cells. These findings indicate that IL-23 and IL-17 might be also necessary to the pathogenesis of RA [43].

The recent discovery of IL-23, which shares the p40 chain with IL-12, indirectly led to the discovery of Th17 cells [44]. Pioneering studies utilizing IL-12 and IL-23-deficient mice demonstrated that it was the loss of IL-23, and not of IL-12, that made mice resistant to the development of EAE and CIA. The mice deficient in IL-23 lacked the expression of IL-17-producing T cells in the target organ, which led to the suggestion that IL-23 might be critical for the generation of pathogenic IL-17 producing T cells. Furthermore, it suggested that the loss of Th17 cells is responsible for autoimmune disease resistance in IL-23-deficient mice [45]. The above animal models show that the association between IL-17 and IL-23 really affects the pathogenesis of RA. Therefore, the interaction between Th17 and DCs is crucial for RA.

DCs promote the activation and proliferation of T cells by binding to the surface of the pMHC-II molecule and forming a peptide antigen. They then further induce the activation of Tc cells, resulting in cytotoxic effects [46]. In the autoimmune arthritis animal model, the percentage of native T cells decreases, while the proportion of activated T cells rises. DCs are considered to be congenital APCs, and are essential for activation of the initial Th and Tc cells [47]. They present an endogenous antigen and initiate a T cell response in inflammatory conditions (such as RA), and can also present an arthritic peptide to T cells and induce activation of the original T cells, thereby participating in the development of RA.

3.2. Tregs interact with DCs

Tregs are particularly important for the immunization of RA, and their interaction with DCs affects the development of RA. Tregs express cytotoxic surface molecules, CTLA-4, lymphocyte activating gene-3 (LAG-3), neuropilin 1 (Nrp-1), and CD39. Some markers of Tregs (CD39, LAG-3, or Nrp-1) can interact with DCs, and are co-expressed with forkhead box P3 (Foxp3) in Tregs and expressed in different ways in RA synovium. Specific interaction proteins on Tregs are as follows: 1) LAG-3: this protein has a very high affinity for MHC II of the CD4 homologue. By binding to MHC class II molecules, LAG-3 can induce immune receptor tyrosine-based activation motifs (ITAM), which can inhibit the ability of DCs to mature and affect immunosuppressive signaling pathways [48]; 2) CD39: this is the main immune system exonuclease capable of hydrolyzing adenosine 5′-triphosphate (ATP) or adenosine 5′-diphosphate (ADP) to adenosine 5′-monophosphate (AMP). Extracellular ATP promotes the maturation of DCs by up-regulating CD80/CD86 expression. In this way, Tregs along with CD39 can inhibit the maturation of DCs by reducing ATP; 3) Nrp-1: this transmembrane protein acts as a co-receptor for vascular endothelial growth factor (VEGF) and signal in 3A. Nrp-1 facilitates the long-term interaction between Tregs and DCs, and inhibits the function of DCs because of its high sensitivity to antigenic limits [49].

Meng et al. detected Foxp3-positive Treg cells in the large lymphoid aggregation area, as well as CD39-positive and LAG-3-positive Treg cells. Nrp-1-positive Treg cells were mostly distributed in the perivenular infiltration, lymphoid aggregation, and lining layer areas. DC-LAMP-positive or DEC-205-positive DCs were observed in co-localization with Foxp3-positive Treg cells in the RA synovium [50]. Therefore, the proteins described above have the effect of inhibiting the maturation of DCs, and thereby attenuate the interaction between DCs and T cells, eventually interfering with the development of RA.

4. T cells interact with FLSs in rheumatoid arthritis

In RA joint cavities, normal synovium is primarily comprised of two cell populations, which are termed type A and type B synoviocytes. Type A synoviocytes are monocyte/macrophage lineage cells, while type B synoviocytes are derived from mesenchymal cells known as FLSs [51]. The synovial tissue consists of an inner lining and a sublayer, mainly composed of T cells, which account for 30–50% of all cell types. The main type of T cells is Th cells, and changes in their quantity in the synovial intimae are reflective of changes associated with RA [52]. FLSs become the main factor that affect cartilage ring, owing to their unique invasion and protease production characteristics. Therefore, FLSs are critical in promoting inflammation and cartilage destruction in RA, and the interaction between T cells and FLSs is thought to facilitate T cells recruitment and FLSs activation [53].

4.1. Th17 and Th17.1cells interact with RA-FLSs

Expansive synovial tissue in the cartilage-bone interface covers and corrodes cartilage, known as “pannus”, and is characterized by local invasive tumors. RA-FLS are important mediators of joint destruction, since they are able to invade adjacent collagenous structures, including articular cartilage [54,55].

FLSs have been found to regulate their apoptotic responses through cell-cell interactions or secretion of soluble mediators, eventually participating in the accumulation of infiltrating T and B cells [56,57]. Previous studies have demonstrated that TNF-like protein 1A (TL1A) and IL-34 are capable of acting on FLSs to increase the expression of IL-6, expanding Th17 cells [58]. Interaction between FLSs and Th17 cells can stimulate FLSs to express IL-6, IL-8, chemokine (C-C motif) ligand 20 (CCL20), and other pro-inflammatory mediators of joint destruction [59]. Lysine acetyltransferase 7 (KAT7) over-expression induces IL-6 and transforming growth factor(TGF-β) expression through an epigenetic mechanism in cultured FLSs. In vitro, the polarization of cultured Th17 cells in these supernatants can promote cell differentiation [60]. Moreover, KAT7 over-expression in FLSs induces CCL20 expression via the p44/42 MAPK pathway, thereby promoting Th17 cell migration [61]. This confirms that the interaction between Th17 cells and FLSs indeed interferes with the pathogenesis of RA.

Th17 and Th17.1 cells are both present in the synovial fluid of patients with RA and juvenile idiopathic arthritis (JIA). Th17.1 cells, in particular, are enriched in the synovial fluid in comparison to peripheral blood. Human Th17.1 cells are also highly enriched at inflammatory sites of patients with inflammatory bowel disease (IBD), multiple sclerosis (MS), and sarcoidosis, and correlates with disease activity [62,63]. The accumulation of Th17.1 cells at inflammatory sites may be mediated by the C-X-C chemokine receptor type 3 (CXCR3) ligands chemokine (C-X-C motif) ligand 9 (CXCL9), C-X-C motif chemokine 10 (CXCL10), CXCL11, and the C−C chemokine receptor type 6 (CCR6) ligand CCL20, which are all highly expressed in the inflamed RA joint synovium.

Th17.1 cells have various pathogenic properties distinct from Th17 cells, and express pathogenic gene characteristics, including increased expression of T-box transcription factor (TBX21), STAT4, and runt-related transcription factor 1 (RUNX1). Furthermore, they display decreased expression of aromatic receptors (AhR) and IL-10 [64]. Th17.1 differentiation from Th17 cells can be enhanced by exogenously produced IL-12, or as a consequence of autocrine TNFα production. Moreover, the addition of IL-12 to Th17 cell cultures, irrespective of the presence of IL-23, results in the induction of Th17.1 cells. In contrast to Th17 and Th1 cells, Th17.1 cells are highly resistant to FLS-mediated suppression of proliferation and cytokine expression. In addition, in contrast to Th17 cells, Th17.1 cells express multidrug-1 (MDR1), an ATP-dependent efflux pump that leads to Th17.1-specific anti-glucocorticoids [65]. Therefore, the interaction between Th17/Th17.1 cells and FLSs plays a crucial role in the development of RA.

4.2. Cytokine-activated T (Tck) cells interact with RA-FLS

The mechanism by which FLSs are converted to the inflammatory phenotype in RA is not fully understood, but the interactions between FLSs and invading lymphocytes (especially T cells) are considered a key component of this pathological process. Cells have been identified from a different population of RA synovium, usually similar to Tck cells, and it was observed that the rapid and firm adhesion of Tck and super antigen-activated T cells to FLSs could result in peristalsis on the surface of FLSs [66]. Src homology 2 domain–containing protein tyrosine phosphatase 2 (SHP-2) mediates cellular responses to various growth factors, hormones, and cytokines. SHP-2 enhances response and invasiveness to platelet-derived growth factor (PDGF) and TNF by activating focal adhesion kinase (FAK), thereby promoting the aggressiveness of RA-FLS and enhancing the survival of RA-FLS [67]. Therefore, an increase in the number of Tck cells will also increase the number of FLSs, thereby accelerating the interaction between T cells and FLSs, and ultimately interfering with the development of RA.

4.3. Intercellular adhesion molecule–1(ICAM-1) and leukocyte function-associated antigen (LFA)-1

In RA synovial tissue, besides previously described proteins associated with Tck and Th cells, there are two other special related proteins, namely intercellular adhesion molecule 1 (ICAM-1) and leukocyte function-associated antigen (LFA)-1. ICAM-1, a trans-membrane protein expressed in lymphocytes and endothelial cells, which is also known as CD54, plays a significant role in stabilizing cell-cell interactions and promoting the migration of white blood cells and endothelial cells. LFA-1 is one of the most important ICAM-1 receptors, expressed only in lymphocytes, and involved in the killing effects of Tc, natural killer cells (NK), and lymphocyte activated killer cells [68,69]. LFA-1 binds to ICAM on the surface of target cells and initiates signal transduction, enabling cells to perform their functions of adhesion, migration, and phagocytosis, while also playing a role in inflammatory immunity [70]. In addition to their other functions, ICAM-1 and LFA-1 play important roles in the interaction between T cells and FLSs. FLSs can present peptides derived from type II collagen and human cartilage glycoprotein to T-cell hybridomas specific to those peptides. These antigen-dependent interactions are contact-dependent, and can be blocked by neutralizing antibodies to class II major histocompatibility complex and LFA-1 or ICAM-1 [71]. In addition, Anderson et al. confirmed that the expression levels of ICAM-1, LFA-1, and cytokines IL-8 and IL-10 are higher in synovial tissue from RA patients than in tissue from healthy controls [72]. Therefore, ICAM-1 and LFA-1 play vital roles in the interaction between T cells and FLSs, further interfering with the development of RA.

When LFA-1 and ICAM-1 are co-localized at the Tck-FLS synapse, their interaction can increase the efficiency of Tck, accelerate the interaction between Tck and FLSs, and promote the production of inflammatory factors. However, antibody blocking of membrane TNF-α on the Tck surface was found to inhibit FLS cytokine [9]. It was also found that LFA-1 monoclonal antibodies can inhibit expression of various inflammatory factors, and thereby reduce the symptoms of inflammation [73]. Therefore, in recent years, production of LFA-1 monoclonal antibodies has resulted in new treatment prospects for RA.

5. Targeting T cell treatment for RA

Previous studies showed that T cells play a vital role in RA pathogenesis. Recently, there has been an increase in the number of drugs available for the treatment of RA. The most classic of these is biological disease-modifying anti-rheumatic drugs (DMARDs). For example, rituximab and abatacept play an essential role in RA treatment by targeting B cells and the interaction between antigen-presenting cells and T cells respectively. Anti-TNF agents, anti-IL-6 drugs like tocilizumab, and anti-IL-1 agents like anakinra have also been used for RA therapy [74]. Furthermore, Nakayamada et al. showed that different biological DMARDs resulted in different changes in immune cell subsets. For example, abatacept characteristically reduced Th subsets, mainly Tfh and Th17 cells, whereas TNF inhibitors reduced pDCs but increased Tfh and Th17 cells, and tocilizumab reduced double negative B cells but increased Treg cells [75]. In recent years, IL-17-related biological agents have been undergoing clinical trials, an example being LY2439821, the human monoclonal antibody of IL-17, which can alleviate symptoms of RA without causing serious adverse reactions in patients [76].

Francesco et al. recently identified a T cell- and NK cell-specific gene expressed on activated T cells, Tregs, and NK cells that encode a protein containing an immunoglobulin variable (IgV) domain, a transmembrane domain, and an immune receptor tyrosine-based inhibitory motif (ITIM), which we called TIGIT (for “T cell immunoglobulin and ITIM

domain") [77]. Similar to CTLA-4 and CD28, TIGIT shares ligands (CD155 and CD112) with its co-stimulatory counterpart, CD226. It has been shown that TIGIT is expressed on peripheral memory and regulatory $CD4^+$ T cells and NK cells, and that it can be up-regulated after activation of both these cell types, as well as naive T cells [78]. Moreover, Zhang et al. have shown that TIGIT contributes to immune tolerance by inhibiting not only immune responses mediated by T cells, but also those mediated by NK cells, by binding its ligand, CD155, on antigen-presenting cells or target cells [79]. In a mouse model of colon and breast cancer, expression of TIGIT was elevated in $CD8^+$ tumor infiltrating lymphocytes (TILs). Blockade of TIGIT and PD-L1 synergistically enhanced $CD8^+$ TIL function and resulted in tumor rejection. A study demonstrated that, in patients with advanced melanoma, TIGIT is up-regulated in tumor antigen-specific $CD8^+$ T cells of PBMCs and $CD8^+$ TILs. Importantly these TIGIT-expressing $CD8^+$ T cells co-express the inhibitory receptor PD-1, and combined blockade of TIGIT and PD-1 increased both their proliferation and cytokine production [80]. Joller et al. have shown that TIGIT also has T-cell-intrinsic inhibitory effects. Because Treg cells are the primary cell type that constitutively expresses TIGIT, they suspected that many of the DC effects that have been observed might be mediated by $TIGIT^+$ Treg cells [81]. These observations suggest that TIGIT is an important negative modulator of T cell responses, and thus may represent a new target for immunotherapy.

6. Conclusion

Previous studies have shown that, while T cells play a vital role in RA pathogenesis, interactions among T cells, B cells, DCs, and FLSs are also involved. Th17 and Tfh have been shown to contribute to the development of autoimmune diseases. B cells can deliver co-stimulatory signals and secrete inflammatory factors, therefore, the interaction between T cells and B cells helps to activate T cells. DCs are congenital APC, which can activate initial Th and Tc cells. T cells can stimulate FLSs to express the pro-inflammatory mediators such as IL-6, IL-8, and CCL20. FLSs can promote the differentiation and migration of Th17 cells. T cells behave more like a hub, in that B cells, DCs, and FLSs can interact with T cells to inhibit their activation and interfere with the process of RA. For these reasons, treatment of RA may benefit from increased focus on T cell-targeting treatment drugs.

Declarations of interest

None.

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Author contributions

XXH and YJW wrote and revised the manuscript. WW conceived and designed the study. All authors contributed to data preparation and drafting and revising the manuscript.

Competing interests

The authors declare no competing interests.

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