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Low-dose Interleukin-2: Biology and therapeutic prospects in rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic aggressive arthritis that is characterized with systemic inflammation response, the production of abnormal antibodies, and persistent synovitis. One of the key mechanisms underlying the pathogenesis of RA is the imbalance of CD4 + T lymphocyte subsets, from T helper (Th) 17 cells and regulatory T (Treg) cells to T follicular helper (Tfh) cells and T follicular regulatory (Tfr) cells, which can mediate autoimmune inflammatory response to promote the overproduction of cytokines and abnormal antibodies. Although the treatment of RA has greatly changed due to the discovery of biological agents such as anti-TNF, the remission of it is still not satisfactory, thus, it is urgently required new treatment to realize the sustained remission of RA via restoring the immune tolerance. Interleukin-2 (IL-2) has been discovered to be a pleiotropic cytokine to promote inflammatory response and maintain immune tolerance. Low-dose IL-2 therapy is a driver of the imbalance between autoimmunity and immune tolerance towards immune tolerance, which has been tried to treat various autoimmune diseases. Recent researches show that low-dose IL-2 is a promising treatment for RA. In this review, we summarize the advances understandings in the biology of IL-2 and highlight the impact of the IL-2 pathway on the balance of Th17/Treg and Tfh/Tfr aiming to investigate the role of IL-2-mediated immune tolerance in RA and discuss the application and the therapeutic prospect of low-dose IL-2 in the treatment of RA.

1. Introduction

Rheumatoid arthritis (RA) is a relatively common chronic aggressive arthritis, characterized with systemic autoimmune inflammation response, the overproduction of abnormal antibodies and persistent synovitis [1], which can cause the damage of cartilage and bone leading to disability in the final [2,3]. Genetics, environmental risk factors and epigenetic modification have been confirmed to be involved in the pathological process of RA [4–7]. However, the etiology of RA remained unclear. It has found that macrophages, which have been identified into two different polarization states including classically activated macrophages (M1) and alternatively activate macrophages (M2), have a key role in leading to autoimmune inflammation response [8,9]. M1 macrophages can promote osteoclastogenesis in synovial tissue by secreting a large number of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-1 to cause joint erosion [8].While M2 macrophages can produce anti-inflammatory cytokines mainly IL-10 to exert anti-inflammation effect [8,9]. Present systematic review indicates that in blood and in the synovial tissue of RA patients, there is an imbalance between the M1 macrophage and M2 macrophage [9]. Basis on this, the first biological agent, anti-TNF, after conventional synthetic disease-modifying anti-rheumatism drugs (csDMARDs) was born to antagonize the inflammatory factor TNF and inhibit the polarization of macrophage. However, some patients have to discontinue anti-TNF therapy due to loss of response or intolerance, for these patients who have not achieved remission, the advantages and disadvantages of early use of alternative biological drugs need to be further weighed, so it is necessary to find other effective new treatment strategies for RA from the pathogenesis of it [10].

It has been confirmed that the breakdown of immune tolerance in patients with RA caused by dysfunctional CD4 + T cells is one of the key mechanisms to promote the pathogenesis and progression of RA. Naïve CD4 + T cells can be activated upon interactions with antigen present cells (APC) to differentiate into several different subsets of cells and the imbalance of the number and function of some cells can contribute to the abnormal activation of cells and the dysfunction of humoral immune [11,12],which is the central mediators of the autoimmune pathology of RA [11].On the one hand, the systemic

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autoimmune inflammation response of RA mediated by the abnormal activation of innate immune cells including dendritic cells, mast cells, and innate lymphoid cells, and adaptive immune cells including T helper (Th) 17 cells, T follicular regulatory(Tfr) cells, B cells and plasma cells, can lead to the overproduction and overexpression of pro-inflammatory cytokines such as TNF,IL-6,IL-17and so on, finally result in the damage of cartilage and bone [13–16].On the other hand, the dysfunction of humoral immune of RA caused by the aberrant autoantigen presentation and the excessive activation of antigen-specific T and B cells can lead to the overproduction of abnormal antibodies including rheumatoid factors (RF) and anti-cycle citrullinated peptide antibody (anti-CCP) [17,18],which are able to recognize the antigens in joints to form immune complexes deposited on synovial tissue leading to the persistent synovitis even in the pre-RA phase [19] and the destruction of joints in the final [17,20,21].It has been confirmed that Th17 cells (a subpopulation of T cells characterized with the secretion of IL-17) can promote synovial inflammation by producing many pro-inflammatory cytokines, while Tregs cells can suppress inflammation response and maintain immune tolerance [22–24]. T follicular helper (Tfh) cells and Tfr cells (a new subset of CD4 + T cell) can exert an opposite effect in the regulation of humoral immunity [25].Intensive researches have showed that the imbalance of Th17/Treg cells and Tfh/Tfr cells are related to the pathogenesis and development of RA [26,27], reversal of which appears to be a potential therapeutic targets for RA.

With the full understanding on the biological characteristics and function of IL-2, it has been gradually discovered that IL-2 can exert different effects by activating different cells in immune system [28–31], uncovering the pleiotropic function of IL-2: on the one hand, it acts as a pro-inflammatory factor to promote autoimmune inflammatory response; on the other hand, it induces the differentiation of Treg cells and inhibits Th17 cells to maintain immune tolerance as an anti-inflammatory factor. The dose of IL-2 is a driver of the imbalance between autoimmunity and immune tolerance. High-dose of IL-2 can activate effector T cells to promote autoimmunity, while low-dose of IL-2 can exert essential function to control immune responses and maintain self-tolerance, which has been tried to treat various autoimmune diseases such as type 1 diabetes (T1D) [32,33], HCV-induced vascuitis [34],graft - versus - host disease (GVHD) [35,36] and systemic lupus erythematosus(SLE)[37]to rebuild the immune tolerance. Recent researches show that low-dose IL-2 is also a promising treatment for RA [38]. However, low-dose IL-2 therapy is still a new field with some challenges. For example, there is no conclusion about the optimal dose and treatment scheme for low-dose IL-2 administration, and the long-term efficacy and safety of it remains to be determined, in addition, it is necessary to consider the risk of the activation of the effector arms of immune system due to the relatively low selectivity of IL-2 for Treg cells. Thus, the clinical application of low-dose IL-2 in autoimmune diseases needs further exploration. In this review, we focus on the biology of IL-2 and introduce the effects of IL-2 on Th17/Treg and Tfh/Tfr in patients with RA to explore the role of it in influencing the immune tolerance of RA, and then recognize the clinical use and report the progress of therapy with low-dose IL-2 to clarify its therapeutic prospect in the treatment of RA, in order to provide a new therapy for the targeted treatment of RA in the future.

2. The biology of IL-2

2.1. IL-2 and IL-2R

As early as 1976, a cytokine named T cell growth factor with the unique ability to promote the development, proliferation, survival and differentiation of T cells was discovered [39] and then was confirmed to be IL-2 [40,41]. IL-2,which is mainly produced by activated CD4 + T cells but can also be secreted by CD8 + T cells, NK cells and activated dendritic cell (DCs) to a lesser extent, exerts effects via interacting with IL-2 receptors (IL-2Rs) [28–31]. T cell receptor (TCR) on the surface of T cells combined with foreign- and self-peptide–major histocompatibility complex(MHC) on antigen-presenting cells (APC) can stimulate the expression of IL-2 and IL-2R [42].In addition, various transcription factors can also regulate the expression of IL-2 and IL-2R, such as nuclear factor of activated T cells (NFAT) family members [43], activator protein 1 (AP-1), nuclear factor- κB (NF-κB) [44], forkhead box protein P3(FOXP3) [45] and B lymphocyte-induced maturation protein 1(Blimp-1) [46], signal transducer and activator of transcription(STAT) [28]. It has been confirmed that NFAT can promote the expression of IL-2, but FOXP3 can inhibit it [45–47]. Therefore, the production of IL-2 is regulated positively and negatively [30].And there is a positive feedback loop provided by STAT5 and FOXP3, which bind to the IL-2Rα gene locus to make the more expression of IL-2Rα [28], which is important in the application of IL-2.

IL-2R consists of three subunits including IL-2Rα (also known as CD25), IL-2Rβ (also known as CD122), and IL-2Rγ (also known as CD132) [28,30]. In the subsequent years of researches, a great deal of understandings on the structure of the IL-2R has been acknowledged. It has been confirmed that IL-2Rα lacks the cytoplasmic signal transduction domain [29] and is absent or rarely expressed on resting T cells [30],but the combination of APC and TCR on the surface of T cells can trigger the expression of IL-2Rα and the initially binding of IL-2 and IL-2R can increase the level of IL-2Rα through a STAT5-dependent feedback loop [28] to enhance the affinity of IL-2R and result in the recruitment of IL-2Rβ [48,49], but IL-2Rα cannot transmit signal even the addition of IL-2β, leading to the discovery of IL-2Rγ [29]. IL-2Rγ, considered to be the common cytokine receptor γ- chain (γc),plays an important role in the signal transduction, which can not only response to IL-2 but can also response to the γc family of cytokines including IL-4, IL-7, IL-9, IL-15, and IL-21 [50]. Furthermore, even in the absence of IL-2Rα, IL-2 can bind with dimer IL-2R and lead to signal transduction [51]. Thus, IL-2R can be divided into three categories: low affinity receptor (only IL-Rα), intermediate affinity receptors (containing IL-2Rβ and IL-2Rγ), as well as high affinity receptors (containing IL-2Rα, IL-2Rβ and IL-2Rγ).The intermediate affinity receptor is mainly constitutively expressed on resting NK cells and CD8 + T cells, whereas the low affinity and high affinity receptor are expressed on the activated lymphocyte [30]. In addition, some cells can inductively express high affinity receptor because the expression of IL-2 Rα is induced by the stimulation of antigen and cytokines [29], but the removal of antigens down-regulates the expression of IL-2Rα-related genes leading to the disappearance of high-affinity IL-2R from the cell membrane and a state that is not responsive to IL-2. Therefore, based on the different expression of IL-2R subunits on different T cells, it achieves the flexible regulation of different types of T cells by different concentration of IL-2, which is the important basis for the application of it to treat different disease. For instance, resting NK cells and CD8 + T cells, as important cells to exert cytotoxic effects to promote the immune response and kill tumor cells, express intermediate affinity receptors, which are slightly less sensitive to IL-2 and can only be activated by high-dose IL-2.Conversly, the cells expressing high affinity receptors are sensitive to IL-2 and can be activated by low-dose IL-2, especially Treg cells, as a critical factor to maintain immune tolerance, constitutively express high affinity receptors, which confers Treg cells dominance at low-dose IL-2, so Treg cell has superior efficacy to compete with other cells to bind IL-2 [29,42].

The signal transduction of IL-2 combined with IL-2R occurs through three major pathways including [28–30] JAK-STAT signaling pathways (JAK: Janus kinase), PI3K/AKT/mTOR signaling pathways (PI3K: phosphatidylinositol 3 kinase; mTOR: mammalian target of rapamycin; AKT: protein kinase B) and MAPK/ERK signaling pathway (MAPK: mitogen-activated protein kinase; ERK: extracellular regulated protein kinases) to regulate the development, proliferation, survival and differentiation of cells. Pro-inflammatory cytokine activation of the JAK/STAT signal transduction pathway is a critical event in the pathogenesis and progression of RA [52].

2.2. The pleiotropic functions of IL-2

Since the discovery of IL-2, it has been considered to be a pro-inflammation factor, which plays an essential role in activating the effector arms of the immune system by stimulating varieties of cells including effector T cells, memory cells and NK cells [28]. Based on the ability of IL-2 to induce and enhance the number and function of NK cells and CD8 + Tcells to exert the cytotoxicity effects to promote immune response and kill tumor cells, it has been extensively developed as a potential immunotherapy for the treatment of cancer [53–55]. And because resting NK cells and CD8 + T cells are slightly less sensitive to IL-2 and can only be activated by high-dose IL-2, therefore, the earliest therapeutic application of IL-2 in clinical practice was to treat cancer at high-dose and some patients had benefited remarkably [53,54,56].However, the further clinical application of it was greatly limited because of vascular leakage syndrome (VLS) and manifestations of cytokine storms,which were caused by the toxic effect of high-dose IL-2 [31].

After decades of in-depth researches on the function of IL-2, it has gradually been discovered that IL-2 is not only a pro-inflammatory factor, but can also act as an anti-inflammatory factor to exert the pleiotropic effects. In 1993, Sadlack et al. [57] reported that knockout-IL-2 -gene mice would lead to severe lymphocyte proliferation and suffered from autoimmune disease rather than immune deficiency, which first pointed that IL-2 could act as an anti-inflammatory cytokine and revealed the pleiotropic function of IL-2. Further studies began to question the main or only function of IL-2 is to stimulate the inflammatory response in autoimmune inflammation and with the continuous researches on the structure and function of IL-2 in the past years, the immunotherapy of IL-2 has re-entered research field of people [28–31]. Subsequent studies of rodent models with IL-2 or IL-2 receptor deficiency highlighted the key role of IL-2 in protective immunity and the particular effectiveness of Treg-mediated immune tolerance [30,42,51].Especially, the discovery of the opposite effects of IL-2 on the Th17 and Treg cells(IL-2 can promote the differentiation of Treg cells while inhibiting the differentiation of Th17) has further clarified the role of IL-2 in exerting anti-inflammatory effects and maintaining immune tolerance [30].

All these findings showed the pleiotropic function of IL-2, and high-dose IL-2 can activate effector T cells to promote autoimmunity, while low-dose IL-2 can exert essential function to control immune responses and maintain self-tolerance, meaning that the dose of IL-2 may be a driver of the imbalance between autoimmunity and immune tolerance [58]. The role of IL-2 has shifted from a cytokine that can activate effector T cells to fight cancer to a cytokine that can control autoimmune inflammatory response [31,59,60], and the latter is much more important. More and more studies attach importance to the essential function of low-dose IL-2 to control autoimmune responses and maintain self-tolerance, which can be a potential therapy in treating autoimmune disease including RA.

3. The role of IL-2 -mediated immune tolerance in RA

With the understanding of the pleiotropic function of IL-2, especially its anti-inflammatory effect, more and more studies have found that it can be used as an immunomodulatory drug to treat autoimmune diseases, which is also expected to be applied in the treatment of RA. Therefore, exploring the role of IL-2 in mediating immune tolerance and its therapeutic prospect in RA has become a research hotpot.

3.1. IL-2 and the balance of Th17/Treg

Studies have proved that Th17 cells and Treg cells can exert different effects [22,23].Th17 cell has the ability to enhance the influx of inflammatory cells such as neutrophils leading to systemic inflammatory response and stimulate specific B lymphocytes to produce autoantibodies which can promote auto-immune response [61,62], and the pro-inflammation factor IL-17 secreted by Th17 cells plays a critical role in autoimmune disorders [63,64] and has been shown to be a key factor in collagen-induced arthritis (CIA), an animal model of RA [65,66]. High levels of serum IL-17 and increased number of Th17 cells in peripheral blood have been reported in RA [64]. Treg cell is defined as CD4 + CD25 + Foxp3+ Treg cell, which includes thymus-derived Tregs (tTregs) and peripherally derived Tregs (pTregs) [67], based on the anatomical origin. Treg cells can maintain the immune tolerance by inhibiting the stimulatory capacity of antigen-presenting cells and producing anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β) to inhibit immune responses [67–69],and the decreased number of Treg cells in patients with autoimmune diseases is significantly negatively correlated with disease activity [70,71] suggesting that the breakdown of immune tolerance mediated by decreased Treg cells may be an important factor in the pathogenesis of RA. It has been confirmed that, as with other autoimmune diseases, the proportion of Th17/Treg in peripheral blood is indeed increased in patients with RA [12,26,72], which can be a therapeutic target [73,74].

Treg cells and Th17 cells share a common precursor cell and signaling pathway mediated by TGF-β [75], but the differentiation of the common precursor into pathogenic Th17 cells or into Treg cells is a different fate choice which may be associated with IL-2. IL-2R on the surface of Treg cells is sensitive to IL-2 providing a basis for IL-2 to affect the development of Treg cells, and there have been many observations confirmed that IL-2 can regulate the differentiation, development and expression of Treg cells and Th17 cells [31,51,57,76,77]. Sadlack et al. [57] found that Treg cells do not exist in mice with IL-2-deficient or IL-2R-deficient, which suggested that IL-2 can promote the differentiation of Treg cells. On the contrary, Laurence et al. [76] found that blocking IL-2 in the spleen cell culture of mice could increase the proportion of cells that produce IL-17, but the addition of exogenous human IL-2 reversed this effect, which revealed that the presence of IL-2 strongly discourage the differentiation of Th17. It has been confirmed that Th17 and Treg cells have different cell markers: FOXP3 is the marker of Treg cells while acid-related orphan receptor γt (RORγt, known as RORc in human) is the marker of Th17 cells. TGF-β is an essential factor for inducing the expression of FOXP3 and RORγt [78–80], but the two transcription factors, STAT5 and STAT3 [81,82], control the expression of FOXP3 and RORγt, respectively. Foxp3, which can induce the expression of IL-2Rα, is only expressed on the Treg cells, and the expression of it is regulated by the JAK-STAT5 signaling pathway [83–86]. The expression of programmed cell death protein 1(PD-1) and cytotoxic T-lymphocyte-associated protein 4(CTLA-4) on the Treg cells inhibit the PI3K-AKT-mTOR signaling pathway making Treg cells more dependent on IL-2-mediated JAK-STAT5 pathway [87–89]. Thus, after IL-2 interacts with IL-2R on Treg cells, the complex will activate JAK and preferentially induce the phosphorylation of STAT5 to bind to the promoter and introns in the Foxp3 gene leading to the expression of Foxp3 to promote the maturation and differentiation of Treg cells [52,85,90].However, IL-2 can inhibit the phosphorylation of STAT3, which is required for the expression of RORγt. STAT3 can be activated by IL-6 and IL-23, and then the activated STAT3 can promote the expression of RORγt and derive cells towards to the Th17 subsets [76,91,92]. In summary, the combination of IL-2 and TGF-β can induce naive T cells to differentiate into Treg cells by STAT5 and the addition of TGF-β together with IL-6 leads to the differentiation of Th17 by STAT3. Therefore, IL-2 is able to inhibit the development of Th17 cells and promote the development of Treg cells (See Fig. 1).

Considering that IL-2 can exert an opposite role in regulating the differentiation of Th17 and Treg cells, thus providing an important cell therapy targeted to Th17 and Treg cells in RA. Compared with biological agents such as anti-TNF targeting to pro-inflammation factor, low dose IL-2 therapy achieves remission of autoimmune disease activity from a higher level to reduce the production of pro-inflammation factor by expanding Treg cells and promoting the balance between Th17 and

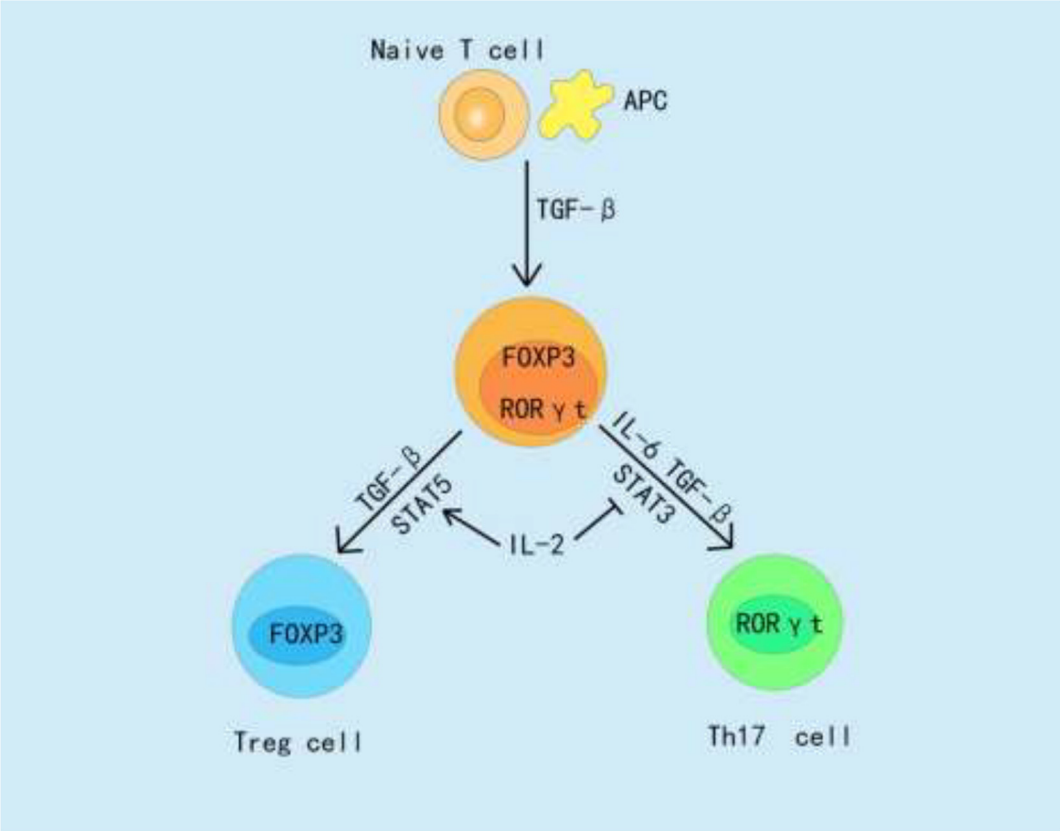

Fig. 1. Treg cells and Th17 cells have the common precursor cell, but they have different cell marker on the surface.FOXP3 is the marker of Treg cells while RORγt is the marker of Th17 cells. TGF-β is an essential factor for inducing the expression of FOXP3 and RORγt, but STAT5 and STAT3 control the expression of FOXP3 and RORγt respectively. Foxp3 is regulated by the JAK-STAT5 signaling pathway by IL-2.But RORγt is induced by the JAK-STAT3 signaling pathway by IL-6,and STAT3 can be suppressed by IL-2.Therefore,the presence of IL-2 can promote the differentiation of Treg cells via STAT5 mechanism while inhibit the differentiation of Th17 cells by preventing the activation of STAT3.

Treg cells to induce immunomodulatory and maintain immune tolerance. Therefore, IL-2 represents a higher advantage in the treatment of autoimmune diseases [60].

3.2. IL-2 and the balance of Tfh/Tfr

Tfh cells and Tfr cells (newly discovered CD4 + T cells localized in the germinal centers) play an extremely critical role in the formation of lymphoid follicular germinal centers (GC) [93,94], which is important for B cells to finish a series of reactions including affinity maturation and class switch recombination and achieve the proliferation and differentiation of B cells leading to the production of high-affinity antibodies. And the two cells can exert an opposite effect in the regulation of humoral immunity: Tfh cell can promote the proliferation and differentiation of B cells and produce high affinity antibodies such as RF and anti-CCP to mediate the destruction of cartilage and bone in patients with RA [95,96], but Tfr cells, a kind of negative regulatory cell, have the potential to maintain immune tolerance by inhibiting the GC response and suppressing the production of these high-affinity antibodies [97–99]. The dysregulation of the number and function of Tfh cells and Tfr cells can lead to the aberrant GC response and over-production of abnormal autoantibodies, eventually causing autoimmune diseases including RA [100–102].

Tfh cells are defined as Bcl-6^{hi}CXCR5^{hi}IL-2Rα^{low}CD4^{+}T cells (CXCR5: CXC Chemokine Receptor 5, Bcl-6: B-cell lymphoma 6 protein) [29,103,104].It has been confirmed that the absence of Bcl-6 can make CD4 + T cell fail to differentiate into Tfh cell showing that the master transcription factor Bcl-6 is required for the development of Tfh cell [105–107].Bcl-6 is induced and activated by the JAK-STAT3 mediated pathway [108] under the stimulation of the IL-21 and IL-6 [109].IL-21 and IL-6 can activate JAK leading to the phosphorylation and activation of STAT3, and then the pSTAT3 binds to the locus gene of Bcl-6 to drive the differentiation of Tfh cell [109,110]. Bcl-6 and Blimp-1 are mutually exclusive [111] and the latter is activated by IL-2 via the JAK-STAT5 pathway [112]. However, low expression of IL-2Rα on the surface of Tfh cells can reduce the synthesis of Blimp-1 caused by STAT5 signal transduction, making it possible for the differentiation of Tfh cell to mostly depend on Bcl-6 [113]. In view of the expression characteristics of Bcl-6, the use of IL-2 can effectively inhibit the differentiation of Tfh cell [29,114,115]. It may be based on the following mechanisms: on the one hand, IL-2 can preferentially activate STAT5 and inhibit STAT3, resulting in a decrease in binding to the locus gene of Bcl-6 [113]; on the other hand, IL-2 can promote the expression of Blimp-1 to reduce the expression of Bcl-6 [114]. In addition, Tfh cells have minimal mTOR activity, so IL-2 can activate AKT and mTORC1 (mechanistic target of rapamycin complex 1) in CD4+ T cells to promote the differentiation of Th1 cells instead of Tfh cells [116](See Fig. 2).

Tfr cells are special subpopulation of T regulatory cells, which not only express characteristic surface molecules of Tfh cells, such as CXCR5, Bcl-6 [93], but also express related surface molecules of Treg cells, such as Foxp3 and CTLA-4 [98].It has been confirmed that FOXP3 and Bcl-6 are both important transcription factor for the differentiation of Tfr cells. In addition, the mTORC1-pSTAT3-TCF-1-Bcl-6 transcription axis has been showed to be essential for the regulation of Tfr cell differentiation from conventional Treg precursors [117]. The mTOR, a serine/threonine protein kinase, has the impact on the growth, proliferation, and survival of cells [118], and is activated in rheumatoid

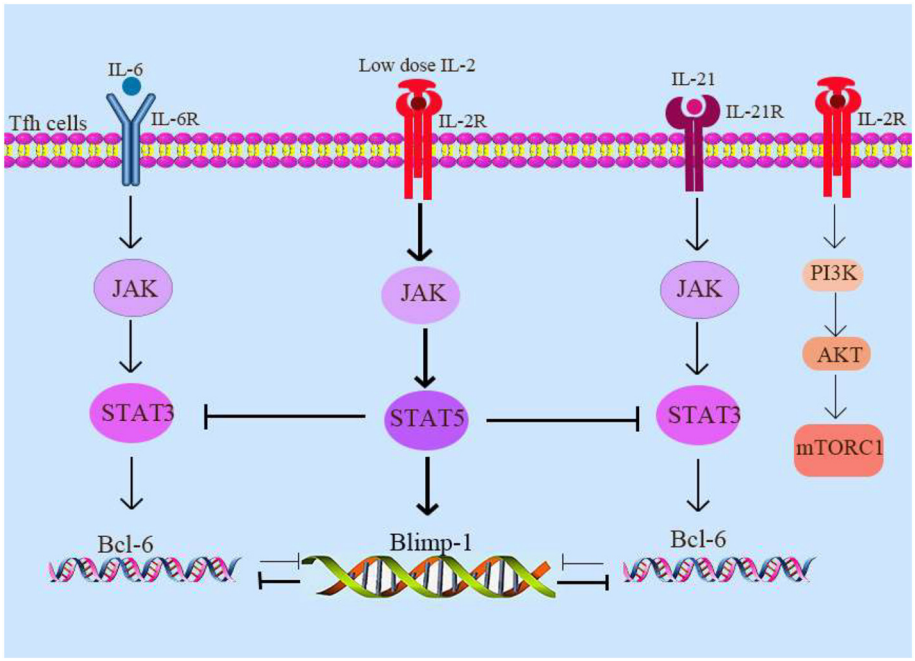

Fig. 2. Bcl-6 is required for the development of Tfh cells, which is induced and activated by the JAK-STAT3 mediated pathway under the stimulation of the IL-21 and IL-6. Bcl-6 and Blimp-1 are mutually exclusive and the latter is activated by IL-2 via the JAK-STAT5 pathway. IL-2 can effectively inhibit the differentiation of Tfh cell by preferentially activating STAT5, which can inhibit STAT3 resulting in a decrease in binding to the locus gene of Bcl-6, but promoting the expression of Blimp-1 to further reduce the expression of Bcl-6. In addition, Tfh cells have minimal mTOR activity, and IL-2 can activate AKT and mTORC1 in CD4+ T cells to promote the differentiation of Th1 cells instead of Tfh cells.

diseases [119].And mTOR forms two functionally distinct complexes: mTORC1 and mTORC2 (mechanistic target of rapamycin complex 2), which have distinct scaffolding subunits, Raptor and Rictor, respectively [120]. Xu et al. [117] found that mTORC1 but not mTORC2 had a positive regulatory effect on the differentiation and function of Tfr cell by deleting Raptor or Rictor. And their study demonstrated that mTORC1induced the expression of the transcription factor T cell factor 1(TCF-1) by the phosphorylated STAT3, and subsequently TCF-1 combined with Bcl-6 promoter to induce Bcl-6 expression and initiate the differentiation of Tfr cells. The effect of IL-2 on the differentiation of Tfr cells is not very clear at present. Some think IL-2 can positively influence the differentiation of Tfr cells in the GC [29]. Because Tfr cells derive from Treg cells [93,121], and Treg cell is up-regulated by IL-2, which may in turn positively increase the directed transformation of Tfr cells. In addition, IL-2 can promote the expression of FOXP3 to promote the differentiation and function of Tfr cell. While others think IL-2 inhibits the conversion of Treg cells into Tfr cell [100,122]. First, the IL-2-JAK-STAT5 signal pathway can promote the expression of Blimp-1, which suppresses the level of Bcl-6 and leads to the down-regulation of Tfr cells. Second, there are many factors to inhibit the PI3K/mTOR signal pathway such as PD-1, CTLA-4 and Roquin [87,123], thus, it is difficult for IL-2 to influence Tfr cells by activating the PI3K/AKT/mTORC1 signaling pathway. Interestingly, high concentration of IL-2 at the peak of influenza virus infection prevents Treg cells from differentiating into Tfr cells through a Blimp1-dependent mechanism, but with the level of IL-2 decrease, Treg cells up-regulate the expression of Bcl-6 and differentiate into Tfr cells [124].Therefore, the effect of IL-2 on Tfr cells is complex, which may be related to the comprehensive environment, the source of cells,multiple signaling mechanisms and different diseases of body(See Fig. 3).

Studies have shown that the number of Tfh cell in the peripheral blood of RA patients was significantly higher than that of the normal control groups [125,126],and the presence of Tfh cell in RA synovial tissue is closely related to the severity of synovial pathology [127,128], indicating that Tfh cell was involved in the progression of RA. The decreased number of Tfr cells in patients with RA has been described [108,129]. And Ding et al. [130] found that the number of Tfh and auto-reactive B cells was decreased, and the level of IL-21 and the concentration of RF in serum was also decreased after transferring Tfr cells into model mice, which revealed the protective role of Tfr cells. But, the increased Tfr cells in patients with RA have also been reported [27,131]. So the role of Tfr cells in RA is controversial. However, it is believed that the imbalance between Tfh cells and Tfr cells in circulatory and synovial tissue are involved in the pathogenesis and progression of RA [27,100,108,132].Therefore, the therapy targeted to restore the balance between Tfh cells and Tfr cells to prevent self-reactive Tfh cell responses can become a potential method for treating RA [100]. Due to the regulatory effect of IL-2 on Tfh cells and Tfr cells, it may be valuable for improving the outcome of patients with RA by reversing the imbalance of Tfh/Tfr cells [133,134].

4. The therapeutic prospect of low-dose IL-2 in treating RA

In the past years, treatment strategies for RA have dramatically changed [135,136].The drugs commonly used in the international treatment of RA have developed from non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids to DMARDs, these methods have achieved a certain effect [1–3], but the remission rate is not satisfactory [137,138]. Recently a Chinese cross-sectional observational study [137], including a total of 1945 RA patients who had taken at least one DMARDS from 40 large hospitals, showed that the proportions of patients who fulfilled the 28 Joint Disease Activity Score (DAS28), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI) and American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) remission criteria was only 10.90%, 6.17%, 5.04% and 1.75%, respectively. The result indicated that the rate of disease activity remission of RA treatment is extremely low. Although the development of biological agents targeting to pro-inflammatory factors involved in the pathogenesis of RA has profoundly improved the treatment strategies of the disease [139], the risk of infection and malignant tumors after long term immunosuppression and the huge economic burden have limited the wide application of it [140], and in addition some patients discontinue biological agents due to loss of response or intolerance, it is necessary to weigh the advantages and disadvantages of early use of alternative biological drugs [10]. Accordingly, new and economically available therapies are urgently required to realize the sustained remission of RA.

We have introduced that IL-2 can regulate the balance of Th17 / Treg and Tfh / Tfr to exert the anti-inflammatory effect and maintain immune tolerance as a potential method for the treatment of RA aiming

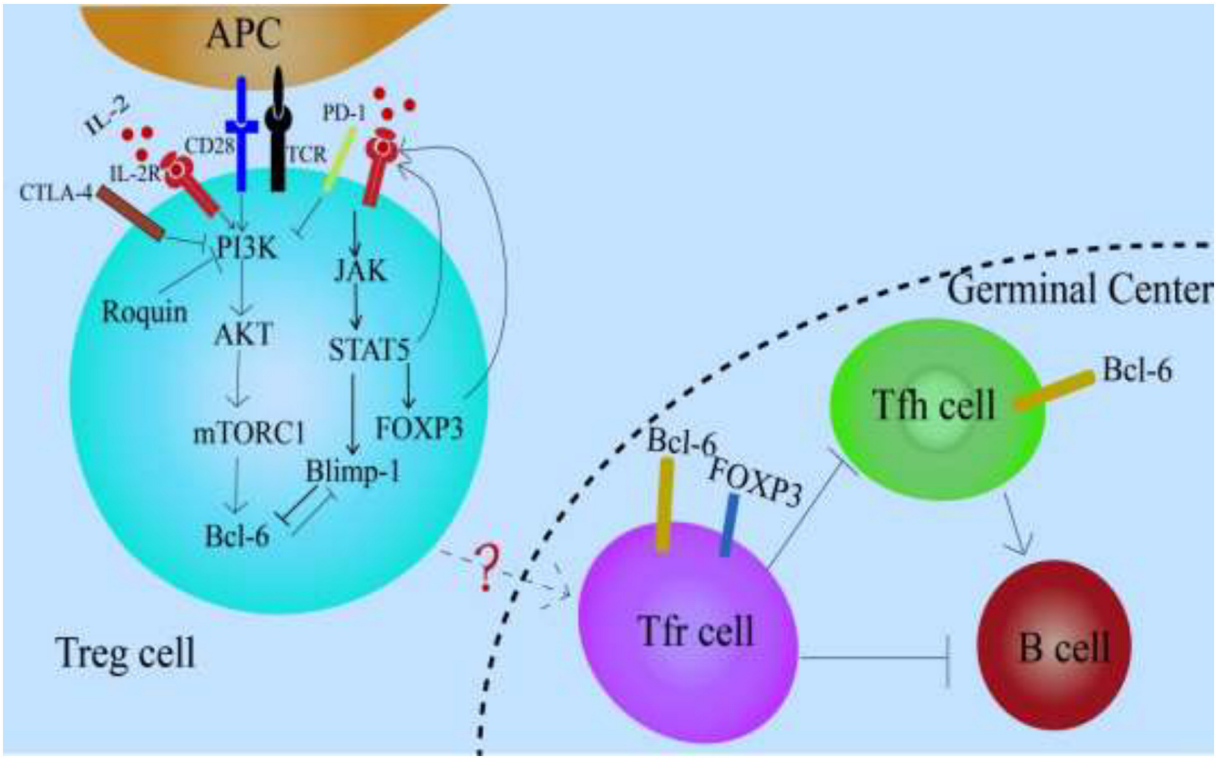

Fig. 3. Tfr cells exert important effects to maintain immune tolerance by inhibiting the Tfh cells and B cells to suppress GC response and the production of high-affinity antibodies. The effect of IL-2 on the differentiation of Tfr cells is not very clear. On the one hand, Treg cells are considered to be precursors of Tfr cells, and IL-2 can promote the development of Treg cells to increase the level of Tfr cells, and IL-2 can up-regulate the expression of FOXP3 to promote the function of Tfr cells. On the other hand, the mTORC1-pSTAT3-TCF-1-Bcl-6 transcription axis is essential for the regulation of Tfr cell differentiation from conventional Treg precursors, but PD-1, CTLA-4 and Roquin inhibit the PI3K/mTOR signal pathway, thus, it is difficult for IL-2 to promote the conversion of Treg cells into Tfr cells. The regulatory mechanism of Treg cells needs further exploration.

to provide a new way to achieve targeted treatment of rheumatoid arthritis by low-dose IL-2.

4.1. The clinical application of low-dose IL-2

Because of its potent to induce and enhance the number and function of NK cells and CD8 + Tcells to exert the cytotoxicity effects leading to the autoimmune response, IL-2 has been developed as a potential immunotherapy for the treatment of cancer at high dose, however, the use of it was limited by serious adverse reactions, thus, to avoid the severe side effects of the activation of effector T cells (Teff) caused by high-dose IL-2, it was thought that low-dose IL-2 could be the solution to reduce the toxic effect of IL-2. And an in vitro IL-2 sensitivity test on Teff and Treg cells found that IL-2 has dual regulatory functions on Teff and Treg cells: the high-dose IL-2 can increase the content of Teff cell to exert the pro-inflammatory effect, in contrast, the low-dose IL-2 can increase the number of Treg cell to exert the anti-inflammatory effect [42], further confirming that low-dose IL-2 are an important factor to drive the imbalance between autoimmunity and immune tolerance towards immune tolerance. The mechanism is that Treg cells constitutively expresses high affinity receptors, meaning that the surface of Treg cells expresses a large amount of IL-2Rα which can enhance the affinity of IL-2R for IL-2 and effectively compete with other cells to bind IL-2,thus Treg cells are sensitive to IL-2 and low-dose IL-2 can activated Treg cells preferentially [29,42,89,141]. Moreover, the signaling induced by low-dose IL-2 is sufficient to support the development of Treg, while it is not sufficient to support the response of Teff [142]. Several observations have supported that low-dose IL-2 can also be used to treat disease including type 1 diabetes (T1D) [32,33], HCV-induced vascuitis [34] and graft - versus - host disease (GVHD) [35,36], which have achieved significant clinical efficacy in recent years.

It has been confirmed that the use of low-dose IL-2 can increase the number of CD4 + CD25 + Foxp3+ Treg cells leading to a significantly reduced ratio of Th17 / Treg cells in patients with SLE [37], primary Sjögren's syndrome [143] and dermatomyositis/polymyositis [144], proving that the clinical efficacy of low-dose IL -−2 can increase the selectivity of Treg cell to realize the balance of Th17 / Treg. IL-2 can also regulate the balance of Th17 / Treg and Tfh / Tfr to exert the anti-inflammatory effect and maintain immune tolerance as a potential method for the treatment of RA. Kosmaczewska et al. [145] found the combination of IL-2 and biological agents can promote the growth of Treg cells in the peripheral blood of patients with RA to conver the Th17 cell-mediated immune imbalance into the Treg cell-mediated immune tolerance, revealing the potential clinical therapeutic application of IL-2 in patients with RA. Recently, Rosenzwajg et al. [38] assessed the safety and clinical efficacy of low-dose IL-2 therapy in 46 patients with autoimmune disease (including 4 patients with RA) via a single and open clinical trial, and all patients received low-dose IL2 (1 million IU/day) for 5 days, and followed by injected every two weeks for 6 months. Finally, it was found that under the induction of this dose and treatment scheme, the Treg cells were selectively activated and expanded without impacting on the level of Teff cells, and although some patients experienced mild allergic reactions during the treatment process, but did not observe serious adverse events, further to demonstrate the protective role of low-dose IL-2 and highlight that low-dose IL-2 might be effective and well tolerated in the treatment of RA.

Therefore, the low-dose IL-2-based immunotherapies have potential clinical therapeutic implications in patients with RA by selectively targeting on Treg cells to induce immunomodulatory and maintain immune tolerance. Despite of the promising clinical application of low-dose IL-2 therapy, it is still a new field with some challenges. First, the optimal dose, timing and treatment schedule of low-dose IL-2

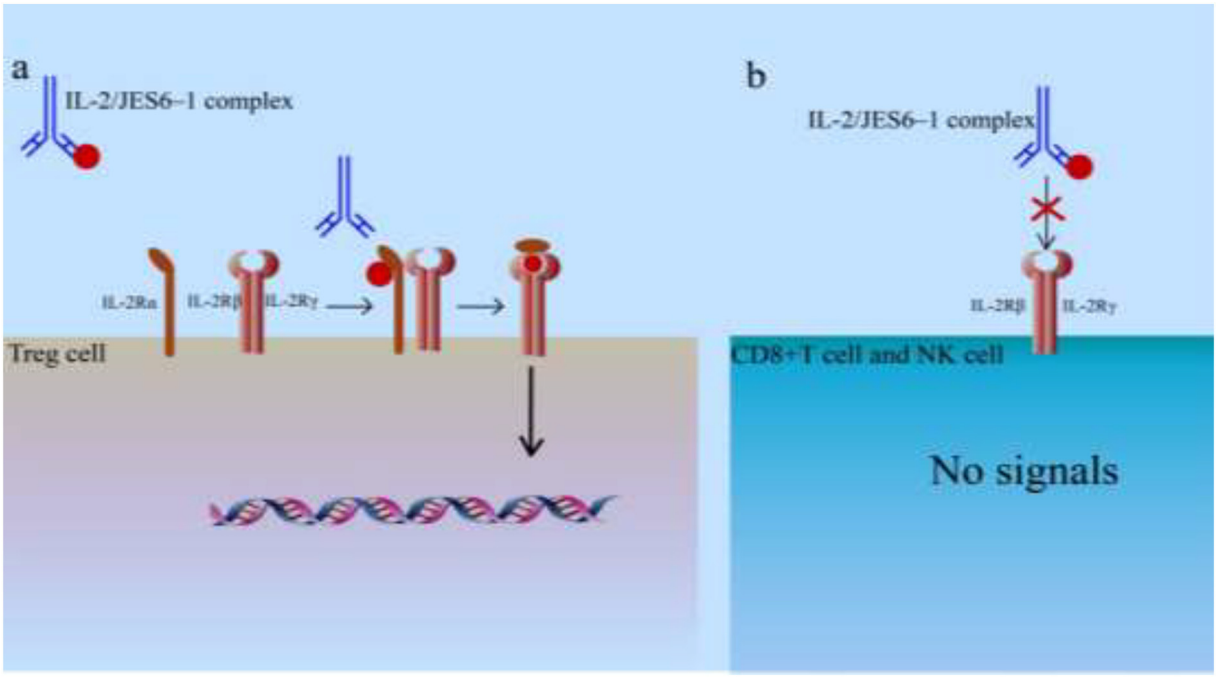

Fig. 4. JES6–1 binds to the region of IL-2 forming the IL-2/JES6–1 complex, and after encountering with cells expressing sufficient IL-2Rα on the surface (such as Treg cells) JES6–1 will be replaced by IL-2Rα.Then IL-2Rα recruits IL-2Rβ and γc to form the functional complexes to conduct the signals. In addition, IL-2/JES6–1 complex fails to interact with the IL-2Rβγ on the cells of expressing no IL-2Rα (such as CD8 + Tcells and NK cells) because of the steric hindrance. It guarantees that IL-2 can selectively activate Treg cells without affecting effector T cells.

administration to achieve disease remission without other adverse reactions is still inconclusive, and needs more abundant clinical data to support it. Second, given the pleiotropic function of IL-2, there is still a risk of activation of the effector arm of the immune system, what results from the relatively low selectivity of IL-2 to Treg cells, and the long-term efficacy and safety of it remains to be determined in animal and clinical trials. In addition, due to the short half-life of IL-2, it may be necessary to increase the dose or shorten the interval between doses to achieve the remission of disease, which will also increase the toxic effect of IL-2 at the same time and is unavoidable to influence the number and function of Teff cells in a dose-dependent manner leading to the off-target effects and inflammation response. Therefore, the therapeutic application of low-dose IL-2 in the treatment of RA has some problems, and it is worthy to be explored other novel IL-2-related therapies such as IL-2/antibody complexes and IL-2 muteins which more selectively expand Treg cells to increase the selectivity of Treg cell stimulation and to extend the time duration of IL-2 in the circulation as well as reduction of the toxicity of IL-2 to minimize the associated risks, which have emerged as important applications in autoimmune diseases.

4.2. Therapeutic prospect for the application of IL-2 therapy

A more elaborate approach to increase the selectivity of Treg cell stimulation and inhibit the activation of the effector arm of the immune response is to independently block the effector arm by neutralizing IL-2/monoclonal antibody (IL-2/mAb) complexes. One kind of the IL-2 / mAb complexes, produced by the combination of IL-2 and anti-IL-2 antibodies JES6–1(like antibody 5344 in human), can activate Treg cells preferentially to maintain the biological function of Treg cells [146–148],which has showed in several autoimmune diseases, including type 1 diabetes in non-obese diabetic mice (NOD mice) [149], experimental autoimmune encephalomyelitis (EAE) [150] and experimental myasthenia [151].There are also studies investigating the interaction of the IL-2 complex with CIA mice. They found that after injecting the IL-2/JES6–1 complexes into CIA mice, the expansion of CD4 + Foxp3 + Treg cells in the peripheral blood can boost largely [152] and the development of autoimmune inflammatory responses can be suppressed [153]. It may also be beneficial for RA. The mechanism of IL-2 / JES6–1 complexes to selectively increase the number of Treg cells is that JES6–1 binds to the region of IL-2 that contacts with the other two IL-2R subunits and JES6–1 can be replaced by IL-2Rα after encountering with cells expressing sufficient IL-2Rα on the surface (such as Treg cells), and then recruits IL-2Rβ and γc to form the functional complexes to promote the expression of gene in Treg cells [154–156]. In addition, the binding between IL-2/JES6–1 complex and IL-2Rβγ was suppressed by steric hindrance which blocks the binding site of the IL-2Rβ leading to the failure to target cells mainly expressing IL-2Rβγ (such as NK cells and CD8 + Tcells). Similar IL-2 / mAb complexes also include IL-2/F5111.2 complex [157] and IL-2/mAb fusion-JY3 IC [158] (See Fig. 4).In contrast, the mouse monoclonal antibody against mouse IL-2 named S4B6 has distinct functions from JES6–1. Complexes of IL-2 with the S4B6 monoclonal antibody can expand effector T cells expressing high level IL-2Rβγ by blocking the interaction between IL-2 and IL-2Rα, which leads to a strong stimulation and expansion of CD8 + T cells and NK cells [146]. Thus, some IL-2/mAb complexes like IL-2/JES6–1 complexes can be applied as an IL-2/mAb complexes-based immunotherapy to preferentially expand Treg cells without affecting the number or function of effector T cells in mice to induce specific immune tolerance, which have a great application prospect and are worthy to be explored in human patients.

The half-life of IL-2 is very short, and the complex formed by binding to the high-affinity IL-2R on the cell surface is quickly internalized ($t_{1/2}$10–20 min) [28]. To solve the problem, fusions of IL-2 with carrier proteins, such as the Fc domain of IgG antibodies have been applied [159,160]. In addition, it has been confirmed that some IL-2 muteins(such asN88D and N88R) can greater selectivity target to Treg cells with relatively mild efficacy and low toxicities by modulating IL-2-mediated immune response than wild-type IL-2 [161,162].

5. Conclusions and perspectives

The understanding of IL-2 has shifted from pro-inflammatory

cytokines that induce effector cell reactions to anti-inflammatory cytokines that maintain immune tolerance, and the latter effect makes it possible to apply low-dose IL-2 to treat autoimmune disease, but the application for autoimmune diseases is still a new attempt especially for the treatment of RA. It is difficult to achieve and maintain the balance between the efficacy and pleiotropic function of IL-2, and the risk of IL-2 to activate the effector arms of the immune system cannot be ignored, so it is important to pay attention to which function dominates when using IL-2 to treat diseases, and ensuring safety is the primary problem we should address. It needs further exploration to turn challenges into opportunities. On the one hand, it is necessary to explore the optimal dose, timing and treatment scheme of low-dose IL-2 administration in patients with RA by the clinical application to minimize the toxicity of IL-2 at the greatest extent and ensure safety. On the other hand, it also needs to evaluate the safety and the clinical benefits of IL-2/mAb complexes and other novel therapy in animal and clinical trials to provide new therapeutic ideas. Future studies will be needed to better understand the biology of IL-2 in order to realize the targeted treatment to RA and it is expected that IL-2 can be the potential targeted treatment for RA more effective and safer in the future as the new revolution in immunoregulation.

Author contributions

RW drafted the manuscript, drew illustrations, and discussed the content with the other authors. CW conceived the topic of the manuscript and revised the content of the manuscript. NL, XZ, TD and HW revised the manuscript.CG, and XL also critically revised the content of the manuscript. All authors approved the publication of the manuscript.

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Declaration of Competing Interest

The authors declare no financial or commercial conflict of interest.

References

[1] Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. Lancet 2010;376:1094–108. https://doi.org/10.1016/S0140-6736(10)60826-4.
[2] Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. The Lancet 2016;388(10055):2023–38. https://doi.org/10.1016/s0140-6736(16)30173-8.
[3] Kumar LD, Karthik R, Gayathri N, Sivasudha T. Advancement in contemporary diagnostic and therapeutic approaches for rheumatoid arthritis. Biomed Pharmacother 2016;79:52–61. https://doi.org/10.1016/j.biopha.2016.02.001.
[4] Karami J, Aslani S, Jamshidi A, Garshasbi M, Mahmoudi M. Genetic implications in the pathogenesis of rheumatoid arthritis; an updated review. Gene 2019;702:8–16. https://doi.org/10.1016/j.gene.2019.03.033.
[5] Generali E, Ceribelli A, Stazi MA, Selmi C. Lessons learned from twins in autoimmune and chronic inflammatory diseases. J Autoimmun 2017;83:51–61. https://doi.org/10.1016/j.jaut.2017.04.005.
[6] Deane KD, Demoruelle MK, Kelmenson LB, Kuhn KA, Norris JM, Holers VM. Genetic and environmental risk factors for rheumatoid arthritis. Best Pract Res Clin Rheumatol 2017;31(1):3–18. https://doi.org/10.1016/j.berh.2017.08.003.
[7] Arend WP, Firestein GS. Pre-rheumatoid arthritis: predisposition and transition to clinical synovitis. Nat Rev Rheumatol 2012;8(10):573–86. https://doi.org/10.1038/nrrheum.2012.134.
[8] Benedettoa PD, Ruscittib P, Vadaszc Z, Toubic E, Giacomellib R. Macrophages with regulatory functions, a possible new therapeutic perspective in autoimmune diseases. Autoimmun Rev 2019;18(102369). https://doi.org/10.1016/j.autrev.2019.102369.
[9] Tardito S, Martinelli G, Soldano S, Paolino S, Pacini G, Patane M, et al. Macrophage M1/M2 polarization and rheumatoid arthritis: a systematic review. Autoimmun Rev 2019;18(102397). https://doi.org/10.1016/j.autrev.2019.102397.
[10] Rubbert-Roth A, Szabo MZ, Kedves M, Nagy G, Atzeni F, Sarzi-Puttini P. Failure of anti-TNF treatment in patients with rheumatoid arthritis: the pros and cons of the early use of alternative biological agents. Autoimmun Rev 2019;18(12):102398. https://doi.org/10.1016/j.autrev.2019.102398.
[11] Rao DA, Gurish MF, Marshall JL, Slowikowski K, Fonseka CY, Liu Y, et al. Pathologically expanded peripheral T helper cell subset drives B cells in rheumatoid arthritis. Nature. 2017;542(7639):110–4. https://doi.org/10.1038/nature20810.
[12] Wehrens EJ, Prakken BJ, van Wijk F. T cells out of control–impaired immune regulation in the inflamed joint. Nat Rev Rheumatol 2013;9(1):34–42. https://doi.org/10.1038/nrrheum.2012.149.
[13] Chen Z, Bozec A, Ramming A, Schett G. Anti-inflammatory and immune-regulatory cytokines in rheumatoid arthritis. Nat Rev Rheumatol 2019;15(1):9–17. https://doi.org/10.1038/s41584-018-0109-2.
[14] McInnes IB, F.R.C.P., Schett G.. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365(23):2205–19. https://doi.org/10.1056/NEJMra1004965.
[15] McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol 2007;7(6):429–42. https://doi.org/10.1038/nri2094.
[16] Zhang Y, Li Y, Lv TT, Yin ZJ, Wang XB. Elevated circulating Th17 and follicular helper CD4(+) T cells in patients with rheumatoid arthritis. APMIS 2015;123(8):659–66. https://doi.org/10.1111/apm.12399.
[17] Derksen V, Huizinga TWJ, van der Woude D. The role of autoantibodies in the pathophysiology of rheumatoid arthritis. Semin Immunopathol 2017;39(4):437–46. https://doi.org/10.1007/s00281-017-0627-z.
[18] Lee KH, Ahn BS, Cha D, Jang WW, Choi E, Park S, et al. Understanding the immunopathogenesis of autoimmune diseases by animal studies using gene modulation: a comprehensive review. Autoimmun Rev 2020;102469. https://doi.org/10.1016/j.autrev.2020.102469.
[19] Deane KD, Holers VM. The natural history of rheumatoid arthritis. Clin Ther 2019;41(7):1256–69. https://doi.org/10.1016/j.clinthera.2019.04.028.
[20] Pozsgay J, Szekanecz Z, Sármay G. Antigen-specific immunotherapies in rheumatic diseases. Nat Rev 2017. https://doi.org/10.1038/nrrheum.2017.107.
[21] Burkhardt H, Sehnert B, Bockermann R, Engstrom A, Kalden JR, Holmdahl R. Humoral immune response to citrullinated collagen type II determinants in early rheumatoid arthritis. Eur J Immunol 2005;35(5):1643–52. https://doi.org/10.1002/eji.200526000.
[22] Littman DR, Rudensky AY. Th17 and regulatory T cells in mediating and restraining inflammation. Cell 2010;140(6):845–58. https://doi.org/10.1016/j.cell.2010.02.021.
[23] Noack M, Miossec P. Th17 and regulatory T cell balance in autoimmune and inflammatory diseases. Autoimmun Rev 2014;13(6):668–77. https://doi.org/10.1016/j.autrev.2013.12.004.
[24] Bilate AM, Lafaille JJ. Induced CD4+Foxp3+ regulatory T cells in immune tolerance. Annu Rev Immunol 2012;30:733–58. https://doi.org/10.1146/annurev-immunol-020711-075043.
[25] Zhu Y, Zou L, Liu YC. T follicular helper cells, T follicular regulatory cells and autoimmunity. Int Immunol 2016;28(4):173–9. https://doi.org/10.1093/intimm/dxv079.
[26] Wang W, Shao S, Jiao Z, Guo M, Xu H, Wang S. The Th17/Treg imbalance and cytokine environment in peripheral blood of patients with rheumatoid arthritis. Rheumatol Int 2012;32:887–93. https://doi.org/10.1007/s00296-010-1710-0.
[27] Wang X, Yang C, Xu F, Qi L, Wang J, Yang P. Imbalance of circulating Tfr/Tfh ratio in patients with rheumatoid arthritis. Clin Exp Med 2018;19(1):55–64. https://doi.org/10.1007/s10238-018-0530-5.
[28] Malek TR. The biology of interleukin-2. Annu Rev Immunol 2008;26:453–79. https://doi.org/10.1146/annurev.immunol.26.021607.090357.
[29] Spolski R, Li P, Leonard WJ. Biology and regulation of IL-2: from molecular mechanisms to human therapy. Nat Rev Immunol 2018;18(10):648–59. https://doi.org/10.1038/s41577-018-0046-y.
[30] Liao W, Lin JX, Leonard WJ. Interleukin-2 at the crossroads of effector responses, tolerance, and immunotherapy. Immunity 2013;38(1):13–25. https://doi.org/10.1016/j.immuni.2013.01.004.
[31] Abbas AK, Trotta E, Simeonov DR, Marson A, Bluestone JA. Revisiting IL-2: Biology and therapeutic prospects. Science Immunology 2018;3:eaat1482. https://doi.org/10.1126/sciimmunol.aat1482.
[32] Hartemann A, Bensimon G, Payan CA, Jacqueminet S, Bourron O, Nicolas N, et al. Low-dose interleukin 2 in patients with type 1 diabetes: a phase 1/2 randomised, double-blind, placebo-controlled trial. The Lancet Diabetes & Endocrinology 2013;1(4):295–305. https://doi.org/10.1016/s2213-8587(13)70113-x.
[33] Rosenzwajg M, Churlaud G, Mallone R, Six A, Derian N, Chaara W, et al. Low-dose interleukin-2 fosters a dose-dependent regulatory T cell tuned milieu in T1D patients. J Autoimmun 2015;58:48–58. https://doi.org/10.1016/j.jaut.2015.01.001.
[34] Saadoun D, Rosenzwajg M, Joly F, Six A, Carrat F, Thibault V, et al. Regulatory T-cell responses to low-dose Interleukin-2 in HCV-induced Vasculitis. N Engl J Med 2011;365(22):2067–77. https://doi.org/10.1056/NEJMoa1105143.
[35] Matsuoka K, Koreth J, Kim HT, Bascug G, McDonough S, Kawano Y, et al. Low-dose interleukin-2 therapy restores regulatory T cell homeostasis in patients with chronic graft-versus-host disease. Sci Transl Med 2013;5(179):179ra43. https://doi.org/10.1126/scitranslmed.3005265.
[36] Koreth J, Matsuoka K-I, Kim Haesook T, SM McDonough, Bindra B, et al. Interleukin-2 and regulatory T cells in graft-versus-host disease. N Engl J Med 2011;365(22):2055–66. https://doi.org/10.1056/NEJMoa1108188.
[37] He J, Zhang X, Wei Y, Sun X, Chen Y, Deng J, et al. Low-dose interleukin-2 treatment selectively modulates CD4(+) T cell subsets in patients with systemic lupus erythematosus. Nat Med 2016;22(9):991–3. https://doi.org/10.1038/nm.4148.
[38] Rosenzwajg M, Lorenzon R, Cacoub P, Pham HP, Pitoiset F, El Soufi K, et al. Immunological and clinical effects of low-dose interleukin-2 across 11 autoimmune diseases in a single, open clinical trial. Ann Rheum Dis

2019;78(2):209–17. https://doi.org/10.1136/annrheumdis-2018-214229.
[39] Morgan DA, Ruscetti FW, Gallo R. Selective in vitro growth of T lymphocytes from Normal human bone marrows. Science 1976;193(4257):1007–8. https://doi.org/10.1126/science.181845.
[40] Smith KA. Interleukin-2: inception, impact, and implications. Science 1988;240(4856):1169–76. https://doi.org/10.1126/science.3131876.
[41] Gillis S, Ferm MM, Ou W. Smith Ka. T cell growth factor: parameters of production and a quantitative microassay for activity. J Immunol 1978;120(6):2027–32. https://doi.org/10.3168/jds.2009-2823.
[42] Klatzmann D, Abbas AK. The promise of low-dose interleukin-2 therapy for autoimmune and inflammatory diseases. Nat Rev Immunol 2015;15(5):283–94. https://doi.org/10.1038/nri3823.
[43] Muller MR, Rao A. NFAT, immunity and cancer: a transcription factor comes of age. Nat Rev Immunol 2010;10(9):645–56. https://doi.org/10.1038/nri2818.
[44] Kim HP, Imbert J, Leonard WJ. Both integrated and differential regulation of components of the IL-2/IL-2 receptor system. Cytokine Growth Factor Rev 2006;17(5):349–66. https://doi.org/10.1016/j.cytogfr.2006.07.003.
[45] Wu Y, Borde M, Heissmeyer V, Feuerer M, Lapan AD, Stroud JC, et al. FOXP3 controls regulatory T cell function through cooperation with NFAT. Cell. 2006;126(2):375–87. https://doi.org/10.1016/j.cell.2006.05.042.
[46] Kallies A, Xin A, Belz GT, Nutt SL. Blimp-1 transcription factor is required for the differentiation of effector CD8(+) T cells and memory responses. Immunity 2009;31(2):283–95. https://doi.org/10.1016/j.immuni.2009.06.021.
[47] Rudensky AY, Gavin M, Zheng Y. FOXP3 and NFAT: partners in tolerance. Cell 2006;126(2):253–6. https://doi.org/10.1016/j.cell.2006.07.005.
[48] Wang X, Rickert M, Garcia KC. Structure of the quaternary complex of interleukin-2 with its α, β, and γc receptors. Science 2005;310:1159–63. https://doi.org/10.1126/science.1117893.
[49] Su EW, Moore CJ, Suriano S, Johnson CB, Songalia N, Patterson A, et al. IL-2Ra mediates temporal regulation of IL-2 signaling and enhances immunotherapy. Science Translational Medicine 2015;7(311):311ra170. https://doi.org/10.1126/scitranslmed.aac8155.
[50] Leonard WJ, Lin J-X, O'Shea JJ. The γc family of cytokines: basic biology to therapeutic ramifications. Immunity 2019;50(4):832–50. https://doi.org/10.1016/j.immuni.2019.03.028.
[51] Boyman O, Sprent J. The role of interleukin-2 during homeostasis and activation of the immune system. Nat Rev Immunol 2012;12(3):180–90. https://doi.org/10.1038/nri3156.
[52] Malemud CJ. The role of the JAK/STAT signal pathway in rheumatoid arthritis. Ther Adv Musculoskelet Dis 2018;10(5–6):117–27. https://doi.org/10.1177/1759720X18776224.
[53] Rosenberg SA, Lotze MT, Muul LM, Leitman S, Chang AE, Ettinghausen SE, et al. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. N Engl J Med 1985;313(23):1485–92. https://doi.org/10.1056/NEJM198512053132327.
[54] Rosenberg SA, Lotze MT, Muul LM, Leitman S, Chang AE, Vetto JT, et al. A new approach to the therapy of cancer based on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2. Surgery. 1986;100(2):262–72. https://doi.org/10.1097/00006534-198608000-00103.
[55] Rosenberg SA. IL-2: the first effective immunotherapy for human cancer. J Immunol 2014;192(12):5451–8. https://doi.org/10.4049/jimmunol.1490019.
[56] Rosenberg SA, Lotze MT, Muul LM, Chang AE, Avis FP, Leitman S, et al. A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high-dose interleukin-2 alone. N Engl J Med 1987;316(15):889–97. https://doi.org/10.1056/nejm198704093161501.
[57] Sadlack B, Merz H, Schorle H, Schimpl A, Feller AC, Horak I. Ulcerative colitis-like disease in mice with a disrupted Interleukin-2 gene. Cell 1993;75:253–61. https://doi.org/10.1016/0092-8674(93)80067-O.
[58] Malek TR, Castro I. Interleukin-2 receptor signaling: at the interface between tolerance and immunity. Immunity. 2010;33(2):153–65. https://doi.org/10.1016/j.immuni.2010.08.004.
[59] Kosmaczewska A. Low-dose interleukin-2 therapy: a driver of an imbalance between immune tolerance and autoimmunity. Int J Mol Sci 2014;15(10):18574–92. https://doi.org/10.3390/ijms151018574.
[60] Malek TR, Bayer AL. Tolerance, not immunity, crucially depends on IL-2. Nat Rev Immunol 2004;4(9):665–74. https://doi.org/10.1038/nri1435.
[61] Yang J, Sundrud MS, Skepner J, Yamagata T. Targeting Th17 cells in autoimmune diseases. Trends Pharmacol Sci 2014;35(10):493–500. https://doi.org/10.1016/j.tips.2014.07.006.
[62] Kotake S, Yago T, Kobashigawa T, Nanke Y. The Plasticity of Th17 Cells in the Pathogenesis of Rheumatoid Arthritis. J Clin Med 2017;6(7). https://doi.org/10.3390/jcm6070067.
[63] Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. N Engl J Med 2009;361(9):888–98. https://doi.org/10.1056/NEJMra0707449.
[64] de Morales JMG Ruiz, Puig L, Dauden E, Canete JD, Pablos JL, Martin AO, et al. Critical role of interleukin (IL)-17 in inflammatory and immune disorders: An updated review of the evidence focusing in controversies. Autoimmun Rev. 2020;19(1):102429. https://doi.org/10.1016/j.autrev.2019.102429.
[65] Nakae S, Saijo S, Horai R, Sudo K, Mori S, Iwakura Y. IL-17 production from activated T cells is required for the spontaneous development of destructive arthritis in mice deficient in IL-1 receptor antagonist. Proc Natl Acad Sci U S A 2003;100:5986–90. https://doi.org/10.1073/pnas.1035999100.
[66] Lee B, Jo Y, Kim G, Ali LA, Sohn DH, Lee SG, et al. Specific inhibition of soluble gammac receptor attenuates collagen-induced arthritis by modulating the inflammatory T cell responses. Front Immunol 2019;10:209. https://doi.org/10.3389/fimmu.2019.00209.
[67] Josefowicz SZ, Lu LF, Rudensky AY. Regulatory T cells: mechanisms of differentiation and function. Annu Rev Immunol 2012;30:531–64. https://doi.org/10.1146/annurev.immunol.25.022106.141623.
[68] Notley CA, Ehrenstein MR. The yin and yang of regulatory T cells and inflammation in RA. Nat Rev Rheumatol 2010;6(10):572–7. https://doi.org/10.1038/nrrheum.2010.143.
[69] Wing K, Sakaguchi S. Regulatory T cells exert checks and balances on self tolerance and autoimmunity. Nat Immunol 2010;11(1):7–13. https://doi.org/10.1038/ni.1818.
[70] Zhang SX, Ma XW, Li YF, Lai NL, Huang ZH, Fan K, et al. The proportion of regulatory T cells in patients with systemic lupus erythematosus: a meta-analysis. J Immunol Res 2018;2018:7103219. https://doi.org/10.1155/2018/7103219.
[71] Morita T, Shima Y, Wing JB, Sakaguchi S, Ogata A, Kumanogoh A. The proportion of regulatory T cells in patients with rheumatoid arthritis: a meta-analysis. PLoS One 2016;11(9):e0162306https://doi.org/10.1371/journal.pone.0162306.
[72] Niu Q, Cai B, Huang ZC, Shi YY, Wang LL. Disturbed Th17/Treg balance in patients with rheumatoid arthritis. Rheumatol Int 2012;32(9):2731–6. https://doi.org/10.1007/s00296-011-1984-x.
[73] Fasching P, Stradner M, Graninger W, Dejaco C, Fessler J. Therapeutic potential of targeting the Th17/Treg axis in autoimmune disorders. Molecules 2017;22(1). https://doi.org/10.3390/molecules22010134.
[74] Miyara M, Ito Y, Sakaguchi S. TREG-cell therapies for autoimmune rheumatic diseases. Nat Rev Rheumatol 2014;10(9):543–51. https://doi.org/10.1038/nrrheum.2014.105.
[75] Lee GR. The balance of Th17 versus treg cells in autoimmunity. Int. J. Mol. Sci. 2018;19(730). https://doi.org/10.3390/ijms19030730.
[76] Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, Yao Z, et al. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. Immunity 2007;26(3):371–81. https://doi.org/10.1016/j.immuni.2007.02.009.
[77] Cheng G, Yu A, Malek TR. T-cell tolerance and the multi-functional role of IL-2R signaling in T-regulatory cells. Immunol Rev 2011;241:63–76.
[78] Li MO, Sanjabi S, Flavell RA. Transforming growth factor-b controls development, homeostasis, and tolerance of T cells by regulatory T cell-dependent and -independent mechanisms. Immunity 2006;25:455–71. https://doi.org/10.1016/j.immuni.2006.07.011.
[79] Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 2006;441:235–8. https://doi.org/10.1038/nature04753.
[80] Mangan PR, Harrington LE, O'Quinn DB, Helms WS, Bullard DC, Elson CO, et al. Transforming growth factor-beta induces development of the T(H)17 lineage. Nature 2006;441(7090):231–4. https://doi.org/10.1038/nature04754.
[81] Ju JH, Heo Y-J, Cho M-L, Jhun J-Y, Park J-S, Lee S-Y, et al. Modulation of STAT-3 in rheumatoid synovial T cells suppresses Th17 differentiation and increases the proportion of Treg cells. Arthritis Rheum 2012;64(11):3543–52. https://doi.org/10.1002/art.34601.
[82] Yang XP, Ghoreschi K, Steward-Tharp SM, Rodriguez-Canales J, Zhu J, Grainger JR, et al. Opposing regulation of the locus encoding IL-17 through direct, reciprocal actions of STAT3 and STAT5. Nat Immunol 2011;12(3):247–54. https://doi.org/10.1038/ni.1995.
[83] Bluestone JA. FOXP3, the transcription factor at the heart of the rebirth of immune tolerance. The Journal of Immunology 2017;198(3):979–80. https://doi.org/10.4049/jimmunol.1602060.
[84] Setoguchi R, Hori S, Takahashi T, Sakaguchi S. Homeostatic maintenance of natural Foxp3+ CD25+ CD4+ regulatory T cells by interleukin (IL)-2 and induction of autoimmune disease by IL-2 neutralization. J Exp Med 2005;201(5):723–35. https://doi.org/10.1084/jem.20041982.
[85] Fontenot JD, Rasmussen JP, Gavin MA, Rudensky AY. A function for interleukin 2 in Foxp3-expressing regulatory T cells. Nat Immunol 2005;6(11):1142–51. https://doi.org/10.1038/ni1263.
[86] Fontenot JD, Rudensky AY. A well adapted regulatory contrivance: regulatory T cell development and the forkhead family transcription factor Foxp3. Nat Immunol 2005;6(4):331–7. https://doi.org/10.1038/ni1179.
[87] Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543–53. https://doi.org/10.1128/mcb.25.21.9543-9553.2005.
[88] Shi H, Liu C, Tan H, Li Y, Nguyen TM, Dhungana Y, et al. Hippo kinases Mst1 and Mst2 sense and amplify IL-2R-STAT5 signaling in regulatory T cells to establish stable regulatory activity. Immunity 2018;49(5):899–914. e6 https://doi.org/10.1016/j.immuni.2018.10.010.
[89] Chinen T, Kannan AK, Levine AG, Fan X, Klein U, Zheng Y, et al. An essential role for the IL-2 receptor in Treg cell function. Nat Immunol 2016;17(11):1322–33. https://doi.org/10.1038/ni.3540.
[90] Mahmud SA, Manlove LS, Farrar MA. Interleukin-2 and STAT5 in regulatory T cell development and function. JAKSTAT 2013;2(1):e23154https://doi.org/10.4161/jkst.23154.
[91] McGeachy MJ, Bak-Jensen KS, Chen Y, Tato CM, Blumenschein W, McClanahan T, et al. TGF-beta and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain T(H)-17 cell-mediated pathology. Nat Immunol 2007;8(12):1390–7. https://doi.org/10.1038/ni1539.
[92] Kimura A, Kishimoto T. IL-6: regulator of Treg/Th17 balance. Eur J Immunol 2010;40(7):1830–5. https://doi.org/10.1002/eji.201040391.
[93] Chung Y, Tanaka S, Chu F, Nurieva RI, Martinez GJ, Rawal S, et al. Follicular regulatory T cells expressing Foxp3 and Bcl-6 suppress germinal center reactions. Nat Med 2011;17(8):983–8. https://doi.org/10.1038/nm.2426.

[94] Nurieva RI, Chung Y, Hwang D, Yang XO, Kang HS, Ma L, et al. Generation of T follicular helper cells is mediated by Interleukin-21 but independent of T helper 1, 2, or 17 cell lineages. Immunity 2008;29:138–49. https://doi.org/10.1016/j.immuni.2008.05.009.
[95] Park HJ, Kim DH, Lim SH, Kim WJ, Youn J, Choi YS, et al. Insights into the role of follicular helper T cells in autoimmunity. Immune Netw 2014;14(1):21–9. https://doi.org/10.4110/in.2014.14.1.21.
[96] Crotty S. T follicular helper cell biology: a decade of discovery and diseases. Immunity 2019;50(5):1132–48. https://doi.org/10.1016/j.immuni.2019.04.011.
[97] Linterman MA, Pierson W, Lee SK, Kallies A, Kawamoto S, Rayner TF, et al. Foxp3+ follicular regulatory T cells control the germinal center response. Nat Med 2011;17(8):975–82. https://doi.org/10.1038/nm.2425.
[98] Sage PT, Sharpe AH. T follicular regulatory cells in the regulation of B cell responses. Trends Immunol 2015;36(7):410–8. https://doi.org/10.1016/j.it.2015.05.005.
[99] Sage PT, Sharpe AH. T follicular regulatory cells. Immunol Rev 2016;271:246–59. https://doi.org/10.1111/imr.12411.
[100] Deng J, Wei Y, Fonseca VR, Graca L, Yu D. T follicular helper cells and T follicular regulatory cells in rheumatic diseases. Nat Rev Rheumatol 2019;15(8):475–90. https://doi.org/10.1038/s41584-019-0254-2.
[101] Basso K, Dalla-Favera R. Germinal centres and B cell lymphomagenesis. Nat Rev Immunol 2015;15(3):172–84. https://doi.org/10.1038/nri3814.
[102] Vinuesa CG, Sanz I, Cook MC. Dysregulation of germinal centres in autoimmune disease. Nat Rev Immunol 2009;9(12):845–57. https://doi.org/10.1038/nri2637.
[103] Breitfeld D, Ohl L, Kremmer E, Ellwart J, Sallusto F, Lipp M, et al. Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production. J Exp Med 2000;192(11):1545–51. https://doi.org/10.1084/jem.192.11.1545.
[104] Crotty S. Follicular helper CD4 T cells (TFH). Annu Rev Immunol 2011;29:621–63. https://doi.org/10.1146/annurev-immunol-031210-101400.
[105] Qiu H, Wu H, Chan V, Lau CS, Lu Q. Transcriptional and epigenetic regulation of follicular T-helper cells and their role in autoimmunity. Autoimmunity. 2017;50(2):71–81. https://doi.org/10.1080/08916934.2017.1284821.
[106] Nurieva RI, Chung Y, Martinez GJ, Yang XO, Tanaka S, Matskevitch TD, et al. Bcl6 mediates the development of T follicular helper cells. Science 2009;325(5943):1001–5. https://doi.org/10.1126/science.1176676.
[107] Poholek AC, Hansen K, Hernandez SG, Eto D, Chandele A, Weinstein JS, et al. In vivo regulation of Bcl6 and T follicular helper cell development. J Immunol 2010;185(1):313–26. https://doi.org/10.4049/jimmunol.0904023.
[108] Niu Q, Huang ZC, Wu XJ, Jin YX, An YF, Li YM, et al. Enhanced IL-6/phosphorylated STAT3 signaling is related to the imbalance of circulating T follicular helper/T follicular regulatory cells in patients with rheumatoid arthritis. Arthritis Res Ther 2018;20(1):200. https://doi.org/10.1186/s13075-018-1690-0.
[109] Eto D, Lao C, DiToro D, Barnett B, Escobar TC, Kageyama R, et al. IL-21 and IL-6 are critical for different aspects of B cell immunity and redundantly induce optimal follicular helper CD4 T cell (Tfh) differentiation. PLoS One. 2011;6(3):e17739https://doi.org/10.1371/journal.pone.0017739.
[110] Vogelzang A, McGuire HM, Yu D, Sprent J, Mackay CR, King C. A fundamental role for interleukin-21 in the generation of T follicular helper cells. Immunity 2008;29(1):127–37. https://doi.org/10.1016/j.immuni.2008.06.001.
[111] Johnston RJ, Poholek AC, DiToro D, Yusuf I, Eto D, Barnett B, et al. Bcl6 and Blimp-1 are reciprocal and antagonistic regulators of T follicular helper cell differentiation. Science 2009;325(5943):1006–10. https://doi.org/10.1126/science.1175870.
[112] Gong D, Malek TR. Cytokine-dependent Blimp-1 expression in activated T cells inhibits IL-2 production. J Immunol 2007;178(1):242–52. https://doi.org/10.4049/jimmunol.178.1.242.
[113] Johnston RJ, Choi YS, Diamond JA, Yang JA, Crotty S. STAT5 is a potent negative regulator of TFH cell differentiation. J Exp Med 2012;209(2):243–50. https://doi.org/10.1084/jem.20111174.
[114] Choi YS, Kageyama R, Eto D, Escobar TC, Johnston RJ, Monticelli L, et al. ICOS receptor instructs T follicular helper cell versus effector cell differentiation via induction of the transcriptional repressor Bcl6. Immunity 2011;34(6):932–46. https://doi.org/10.1016/j.immuni.2011.03.023.
[115] Pepper M, Pagan AJ, Igyarto BZ, Taylor JJ, Jenkins MK. Opposing signals from the Bcl6 transcription factor and the interleukin-2 receptor generate T helper 1 central and effector memory cells. Immunity 2011;35(4):583–95. https://doi.org/10.1016/j.immuni.2011.09.009.
[116] Ray JP, Staron MM, Shyer JA, Ho PC, Marshall HD, Gray SM, et al. The Interleukin-2-mTORc1 kinase Axis defines the Signaling, differentiation, and metabolism of T helper 1 and follicular B helper T cells. Immunity 2015;43(4):690–702. https://doi.org/10.1016/j.immuni.2015.08.017.
[117] Xu L, Huang Q, Wang H, Hao Y, Bai Q, Hu J, et al. The kinase mTORC1 promotes the generation and suppressive function of follicular regulatory T cells. Immunity 2017;47(3):538–51. e5 https://doi.org/10.1016/j.immuni.2017.08.011.
[118] Zoncu R, Efeyan A, Sabatini DM. mTOR: from growth signal integration to cancer, diabetes and ageing. Nat Rev Mol Cell Biol 2011;12(1):21–35. https://doi.org/10.1038/nrm3025.
[119] Perl A. Activation of mTOR (mechanistic target of rapamycin) in rheumatic diseases. Nat Rev Rheumatol 2016;12(3):169–82. https://doi.org/10.1038/nrrheum.2015.172.
[120] Laplante M, Sabatini DM. mTOR Signaling in growth control and disease. Cell 2012;149:274–93. https://doi.org/10.1016/j.cell.2012.03.017.
[121] Aloulou M, Carr EJ, Gador M, Bignon A, Liblau RS, Fazilleau N, et al. Follicular regulatory T cells can be specific for the immunizing antigen and derive from naive T cells. Nat Commun 2016;7:10579. https://doi.org/10.1038/ncomms10579.
[122] Fonseca VR, Ribeiro F, Graca L. T follicular regulatory (Tfr) cells: dissecting the complexity of Tfr-cell compartments. Immunol Rev 2019;288(1):112–27. https://doi.org/10.1111/imr.12739.
[123] Essig K, Hu D, Guimaraes JC, Alterauge D, Edelmann S, Raj T, et al. Roquin suppresses the PI3K-mTOR signaling pathway to inhibit T helper cell differentiation and conversion of Treg to Tfr cells. Immunity 2017;47(6):1067–82. e12 https://doi.org/10.1016/j.immuni.2017.11.008.
[124] Botta D, Fuller MJ, Marquez-Lago TT, Bachus H, Bradley JE, Weinmann AS, et al. Dynamic regulation of T follicular regulatory cell responses by interleukin 2 during influenza infection. Nat Immunol 2017;18(11):1249–60. https://doi.org/10.1038/ni.3837.
[125] Ma J, Zhu C, Ma B, Tian J, Baidoo SE, Mao C, et al. Increased frequency of circulating follicular helper T cells in patients with rheumatoid arthritis. Clin Dev Immunol 2012;2012:827480. https://doi.org/10.1155/2012/827480.
[126] Yu M, Cavero V, Lu Q, Li H. Follicular helper T cells in rheumatoid arthritis. Clin Rheumatol 2015;34(9):1489–93. https://doi.org/10.1007/s10067-015-3028-5.
[127] Sage PT, Ron-Harel N, Juneja VR, Sen DR, Maleri S, Sungnak W, et al. Suppression by TFR cells leads to durable and selective inhibition of B cell effector function. Nat Immunol 2016;17(12):1436–46. https://doi.org/10.1038/ni.3578.
[128] Chu Y, Wang F, Zhou M, Chen L, Lu Y. A preliminary study on the characterization of follicular helper T (Tfh) cells in rheumatoid arthritis synovium. Acta Histochem 2014;116(3):539–43. https://doi.org/10.1016/j.acthis.2013.10.009.
[129] Chang AY, Bethony JM, Simon GL, Reid SP, Encinales L, Firestein GS. T follicular regulatory cells are decreased in patients with established treated rheumatoid arthritis with active disease: comment on the article by Liu et al. Arthritis Rheumatol 2018;70(11):1893. https://doi.org/10.1002/art.40664.
[130] Ding Y, Li J, Yang P, Luo B, Wu Q, Zajac AJ, et al. Interleukin-21 promotes germinal center reaction by skewing the follicular regulatory T cell to follicular helper T cell balance in autoimmune BXD2 mice. Arthritis Rheumatol 2014;66(9):2601–12. https://doi.org/10.1002/art.38735.
[131] Liu C, Wang D, Lu S, Xu Q, Zhao L, Zhao J, et al. Increased circulating follicular Treg cells are associated with lower levels of autoantibodies in patients with rheumatoid arthritis in stable remission. Arthritis Rheumatol 2018;70(5):711–21. https://doi.org/10.1002/art.40430.
[132] Kim YU, Lim H, Jung HE, Wetsel RA, Chung Y. Regulation of autoimmune germinal center reactions in lupus-prone BXD2 mice by follicular helper T cells. PLoS One. 2015;10(3):e0120294https://doi.org/10.1371/journal.pone.0120294.
[133] Ballesteros-Tato A. Beyond regulatory T cells: the potential role for IL-2 to deplete T-follicular helper cells and treat autoimmune diseases. Immunotherapy 2014;6(11):1207–20. https://doi.org/10.2217/imt.14.83.
[134] Ballesteros-Tato A, Leon B, Graf BA, Moquin A, Adams PS, Lund FE, et al. Interleukin-2 inhibits germinal center formation by limiting T follicular helper cell differentiation. Immunity 2012;36(5):847–56. https://doi.org/10.1016/j.immuni.2012.02.012.
[135] JAB Nies, Jong Z, AHM Mil, Knevel R, Cessie SL, TWJ Huizinga. Improved treatment strategies reduce the increased mortality risk in early RA patients. Rheumatology (Oxford) 2010;49(11):2210–6. https://doi.org/10.1093/rheumatology/keq250.
[136] Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. The Lancet. 2017;389(10086):2338–48. https://doi.org/10.1016/s0140-6736(17)31491-5.
[137] Zhu H, Li R, Da Z, Bi L, Li X, Li Y, et al. Remission assessment of rheumatoid arthritis in daily practice in China: a cross-sectional observational study. Clin Rheumatol 2018;37(3):597–605. https://doi.org/10.1007/s10067-017-3850-z.
[138] Ji L, Geng Y, Zhou W, Zhang Z. A study on relationship among apoptosis rates, number of peripheral T cell subtypes and disease activity in rheumatoid arthritis. Int J Rheum Dis 2013;19:167–71. https://doi.org/10.1111/1756-185X.12211.
[139] Favalli EG, Matucci-Cerinic M, Szekanecz Z. The giants (biologicals) against the pigmies (small molecules), pros and cons of two different approaches to the disease modifying treatment in rheumatoid arthritis. Autoimmun Rev 2020;19(1):102421. https://doi.org/10.1016/j.autrev.2019.102421.
[140] Edwards CJ, Galeazzi M, Bellinvia S, Ringer A, Dimitroulas T, Kitas G. Can we wean patients with inflammatory arthritis from biological therapies? Autoimmun Rev 2019;18(12):102399. https://doi.org/10.1016/j.autrev.2019.102399.
[141] Hirakawa M, Matos TR, Liu H, Koreth J, Kim HT, Paul NE, et al. Low-dose IL-2 selectively activates subsets of CD4(+) Tregs and NK cells. JCI Insight 2016;1(18):e89278https://doi.org/10.1172/jci.insight.89278.
[142] Yu A, Zhu L, Altman NH, Malek TR. A low interleukin-2 receptor signaling threshold supports the development and homeostasis of T regulatory cells. Immunity. 2009;30(2):204–17. https://doi.org/10.1016/j.immuni.2008.11.014.
[143] Miao M, Hao Z, Guo Y, Zhang X, Zhang S, Luo J, et al. Short-term and low-dose IL-2 therapy restores the Th17Treg balance in the peripheral blood of patients with primary Sjögren's syndrome. Ann Rheum Dis 2018;77(12):1838–40. https://doi.org/10.1136/annrheumdis-2018-213036.
[144] Zhang S-X, Wang J, Sun H-H, Zhang J-Q, Liu G-Y, Luo J, et al. Circulating regulatory T cells were absolutely decreased in dermatomyositis/polymyositis patients and restored by low-dose IL-2. Ann Rheum Dis 2019;0:1–3. https://doi.org/10.1136/annrheumdis-2019-216267.
[145] Kosmaczewska A, Ciszak L, Swierkot J, Szteblich A, Kosciow K, Frydecka I. Exogenous IL-2 controls the balance in Th1, Th17, and Treg cell distribution in patients with progressive rheumatoid arthritis treated with TNF-alpha inhibitors. Inflammation 2015;38(2):765–74. https://doi.org/10.1007/s10753-014-9987-x.
[146] Boyman O, Kovar M, Rubinstein MP, Surh CD, Sprent J. Selective stimulation of T cell subsets with antibody-cytokine immune complexes. Science 2006;311(5769):1924–7. https://doi.org/10.1126/science.1122927.

[147] Xu L, Song X, Su L, Zheng Y, Li R, Sun J. New therapeutic strategies based on IL-2 to modulate Treg cells for autoimmune diseases. Int Immunopharmacol 2019;72:322–9. https://doi.org/10.1016/j.intimp.2019.03.064.
[148] Krieg C, Letourneau S, Pantaleo G, Boyman O. Improved IL-2 immunotherapy by selective stimulation of IL-2 receptors on lymphocytes and endothelial cells. Proc Natl Acad Sci 2010;107(26):11906–11. https://doi.org/10.1073/pnas.1002569107.
[149] Tang Q, Adams JY, Penaranda C, Melli K, Piaggio E, Sgouroudis E, et al. Central role of defective Interleukin-2 production in the triggering of islet autoimmune destruction. Immunity 2008;28:687–97. https://doi.org/10.1016/j.immuni.2008.03.016.
[150] Webster KE, Walters S, Kohler RE, Mrkvan T, Boyman O, Surh CD, et al. In vivo expansion of T reg cells with IL-2-mAb complexes: induction of resistance to EAE and long-term acceptance of islet allografts without immunosuppression. J Exp Med 2009;206(4):751–60. https://doi.org/10.1084/jem.20082824.
[151] Liu R, Zhou Q, La Cava A, Campagnolo DI, Van Kaer L, Shi FD. Expansion of regulatory T cells via IL-2/anti-IL-2 mAb complexes suppresses experimental myasthenia. Eur J Immunol 2010;40(6):1577–89. https://doi.org/10.1002/eji.200939792.
[152] Yokoyama Y, Iwasaki T, Kitano S, Satake A, Nomura S, Furukawa T, et al. IL-2-anti-IL-2 monoclonal antibody immune complexes inhibit collagen-induced arthritis by augmenting regulatory T cell functions. J Immunol 2018;201(7):1899–906. https://doi.org/10.4049/jimmunol.1701502.
[153] Lee SY, Cho ML, Oh HJ, Ryu JG, Park MJ, Jhun JY, et al. Interleukin-2/anti-interleukin-2 monoclonal antibody immune complex suppresses collagen-induced arthritis in mice by fortifying interleukin-2/STAT5 signalling pathways. Immunology. 2012;137(4):305–16. https://doi.org/10.1111/imm.12008.
[154] Spangler JB, Tomala J, Luca VC, Jude KM, Dong S, Ring AM, et al. Antibodies to Interleukin-2 elicit selective T cell subset potentiation through distinct conformational mechanisms. Immunity. 2015;42(5):815–25. https://doi.org/10.1016/j.immuni.2015.04.015.
[155] Letourneau S, van Leeuwen EM, Krieg C, Martin C, Pantaleo G, Sprent J, et al. IL-2/anti-IL-2 antibody complexes show strong biological activity by avoiding interaction with IL-2 receptor alpha subunit CD25. Proc Natl Acad Sci U S A 2010;107(5):2171–6. https://doi.org/10.1073/pnas.0909384107.
[156] Rojas G, Cabrera Infante Y, Pupo A, Carmenate T. Fine epitope specificity of antibodies against interleukin-2 explains their paradoxical immunomodulatory effects. MAbs. 2014;6(1):273–85. https://doi.org/10.4161/mabs.27224.
[157] Trotta E, Bessette PH, Silveria SL, Ely LK, Jude KM, Le DT, et al. A human anti-IL-2 antibody that potentiates regulatory T cells by a structure-based mechanism. Nat Med 2018;24(7):1005–14. https://doi.org/10.1038/s41591-018-0070-2.
[158] Spangler JB, Trotta E, Tomala J, Peck A, Young TA, Savvides CS, et al. Engineering a single-agent cytokine/antibody fusion that selectively expands regulatory T cells for autoimmune disease therapy. J Immunol 2018;201(7):2094–106. https://doi.org/10.4049/jimmunol.1800578.
[159] Onur B, SC D, Jonathan S. Potential use of IL-2/anti-IL-2 antibody immune complexes for the treatment of cancer and autoimmune disease. Expert Opin. Biol. Ther 2006;6:1323–31. https://doi.org/10.1517/14712598.6.12.1323.
[160] Courtney LP, Phelps JL, Karavodin LM. An anti-IL-2 antibody increases serum halflife and improves anti-tumor efficacy of human recombinant interleukin-2. Immunopharmacology. 1994;28:223–32. https://doi.org/10.1016/0162-3109(94)90058-2.
[161] Shanafelt AB, Lin Y, Shanafelt M-C, Forte CP, Dubois-Stringfellow N, Carter C, et al. A T-cell-selective interleukin 2 mutein exhibits potent antitumor activity and is well tolerated in vivo. Nat Biotechnol 2000;18:1197–202. https://doi.org/10.1038/81199.
[162] Peterson LB, Bell CJM, Howlett SK, Pekalski ML, Brady K, Hinton H, et al. A long-lived IL-2 mutein that selectively activates and expands regulatory T cells as a therapy for autoimmune disease. J Autoimmun 2018;95:1–14. https://doi.org/10.1016/j.jaut.2018.10.017.