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REVIEW

IL-21 acts as a promising therapeutic target in systemic lupus erythematosus by regulating plasma cell differentiation

Xiao-Mei Deng, Shang-Xue Yan and Wei Wei

Plasma cells, which secrete auto-antibodies, are considered to be the arch-criminal of autoimmune diseases such as systemic lupus erythematosus, but there are many cytokines involved in inducing the differentiation of B-cell subsets into plasma cells. Here, we emphasize IL-21, which has emerged as the most potent inducer of plasma cell differentiation. In this review, we focused on the promoting effects of IL-21 on plasma cell differentiation and discuss how these effects contribute to B cell-mediated autoimmune disease.
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INTRODUCTION

Plasma cells (PCs), which act as double-edged swords in the immune system, are the unique source of auto-antibodies in autoimmune diseases such as systemic lupus erythematosus (SLE). Accumulation of auto-reactive PCs and auto-antibodies[1,2] has been reported in SLE patients and murine models. Thus, controlling PC differentiation from B cells may be a promising strategy to inhibit autoimmune disease development.

Recently, high IL-21 serum levels were detected in SLE patients and animal models. Studies indicated that IL-21 is important in the pathogenesis of murine lupus.[3–6] All of this evidence indicated that IL-21 may act as a promoter of PC differentiation,[7] which results in PC and auto-antibody accumulationand leads to autoimmune disease. Therefore, a better understanding of the function of IL-21 networks in PC differentiation will be helpful in developing treatments to control SLE development.

In the following sections, we review the process of B cells differentiating into PCs, and discuss the relative IL-21 network involved in that process.

PC DIFFERENTIATION: THE IMPORTANCE OF T CELLS, CYTOKINES AND TRANSCRIPTION FACTORS

After completing their early development in the bone marrow, immature B cells migrate to secondary lymphoid organs, whereby they further differentiate into marginal zone or follicular B cells.[8,9] When activated in the secondary lymphoid organs, marginal zone B cells expand and differentiate into short-lived PCs, which rapidly undergo apoptosis to exert a rapid and temporary protection of organs.[10–12] Together, marginal zone B cells and B1-B cells participate in the early immune response against T-independent antigens.[13] In contrast, portions of follicular B cells undergo an extra-follicular response and produce short-lived unmutated PCs, which act as an early defense against foreign threats.[14–18] Additionally, a portion of follicular B cells migrate to the perimeter of the follicles to form germinal centers (GCs)[14,19](Figure 1). In the GC, the follicular B cells differentiate into centroblasts, which proliferate to form the GC dark zone. Moreover, the centroblasts proliferate and undergo somatic hypermutation and class switching. Clones with weak affinity or that auto-react die of apoptosis or experience further rounds of somatic hypermutation in the dark zone.[20] The other cells, however, migrate into the light zone where the proliferation speed is decreased. Here, GCs undergo a reaction to increase Ig affinity with the help of T cells to produce either memory B cells or affinity-matured long-lived PCs, (Figure 2) which migrate to specialized niches in the bone marrow that help maintain survival.[21] PCs can be divided into two subsets, namely short- and long-lived PCs, according to their life spans.[22,23] Both short- and

Institute of Clinical Pharmacology of Anhui Medical University, Key Laboratory of Anti-inflammatory and Immune Medicine, Ministry of Education, Hefei, China
Correspondence: Dr W Wei, Institute of Clinical Pharmacology, Anhui Medical University, Hefei 230032, China.
E-mail: wwei@ahmu.edu.cn
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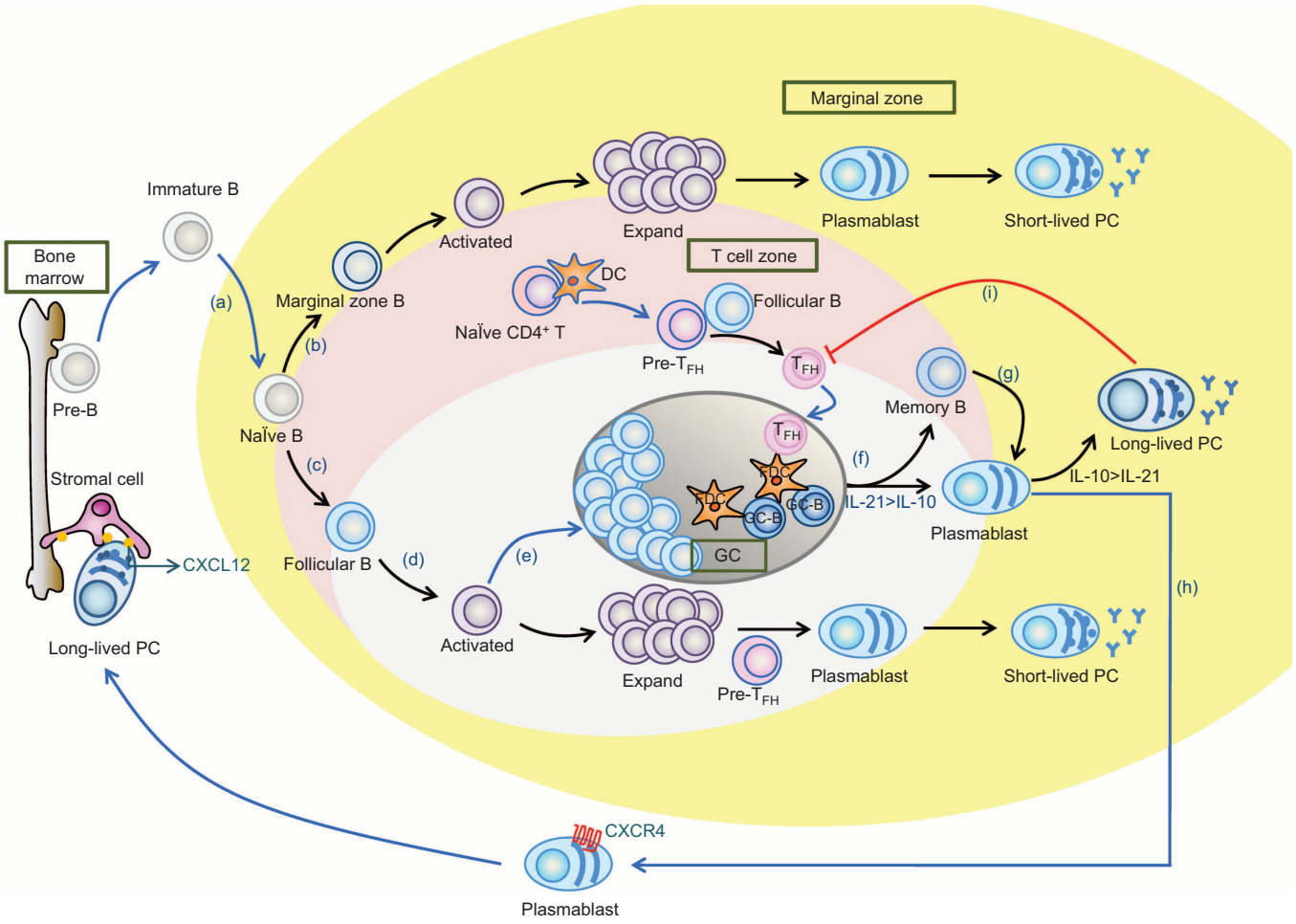

Figure 1 PC development in lymphoid tissues. (**a**) Immature B cells leave the bone marrow and migrate to the lymphoid tissues. In the spleen, immature B cells can mature into either marginal zone B cells (**b**) or follicular B cells (**c**). (**b**) When activated at the T/B border, the marginal zone B cells rapidly differentiate into IgM-secreting plasmablasts and short-lived PCs in a T-independent manner to participate in the early immune response. (**d**) After being activated, follicular B cells with intrinsically higher affinity will preferentially migrate to the extrafollicular area, where they undergo rapid expansion and become short-lived PCs with the help of pre-follicular helper T (pre-T_{FH}) cells. (**e**) Follicular B cells with lower affinity receptors enter the follicular foci to form the GC. (**f**) Within the GC, T_{FH} cells continue providing assistance to the B-cell development, maintain the GC reaction, and facilitate the production of long-lived PCs and memory B cells. (**g**) When an antigen is present for a second time, memory B cells can rapidly differentiate into PCs to help resist an infection. (**h**) A portion of plasmablasts developed in the GC migrate to the bone marrow under the control of CXCL12 to find survival niches that ensure the steady survival of long-lived PCs. (**i**) PCs negatively regulate T_{FH} cells. IL-21 has a potent effect on centroblasts differentiating into plasmablasts, and IL-10 has a greater impact on the differentiation of PCs from plasmablasts than does IL-21. GC, germinal center; PC, plasma cell; T_{FH}, follicular helper T.

long-lived PCs have critical humoral immunity roles in the defense against foreign pathogens.

These differentiation events are also partly mediated by T follicular helper (T_{FH}) cells. These cells are a specific T-cell subset with unique surface markers, cytokines, and transcription factors that are different from other $CD4^+$ T-cell subsets. Phenotypically, T_{FH} cells can be characterized by the high expression of chemokine (C–X–C motif) receptor 5 (CXCR-5), programmed death-1, CD40L and inducible costimulator (ICOS). Additionally, B-cell lymphoma 6 (Bcl-6) acts as a transcription factor for T_{FH} cells.[24] These markers contribute to the location and function of T_{FH} cells and direct the interaction of T_{FH} cells with B cells to promote a T cell-dependent B-cell response.[25] It is now known that T_{FH} cells, localized in the B-cell follicle, are essential for the formation of GCs and the selection of mutated GC B cells. They can interact with B cells through CD28/CD86, CD40L/CD40, ICOS/ICOS-L and instruct their differentiation into memory cells or long-lived PCs (Figure 2). Purified T_{FH} cells that were cocultured with purified tonsil PCs resulted in increased tonsillar PC immunoglobulin production. Additionally, this effect was impaired when T_{FH} cell-derived IL-21 was blocked.[26] Additionally, IgE and other immunoglobulin isotypes were observed to be switched under the influence of T cell-derived cytokines.[24]

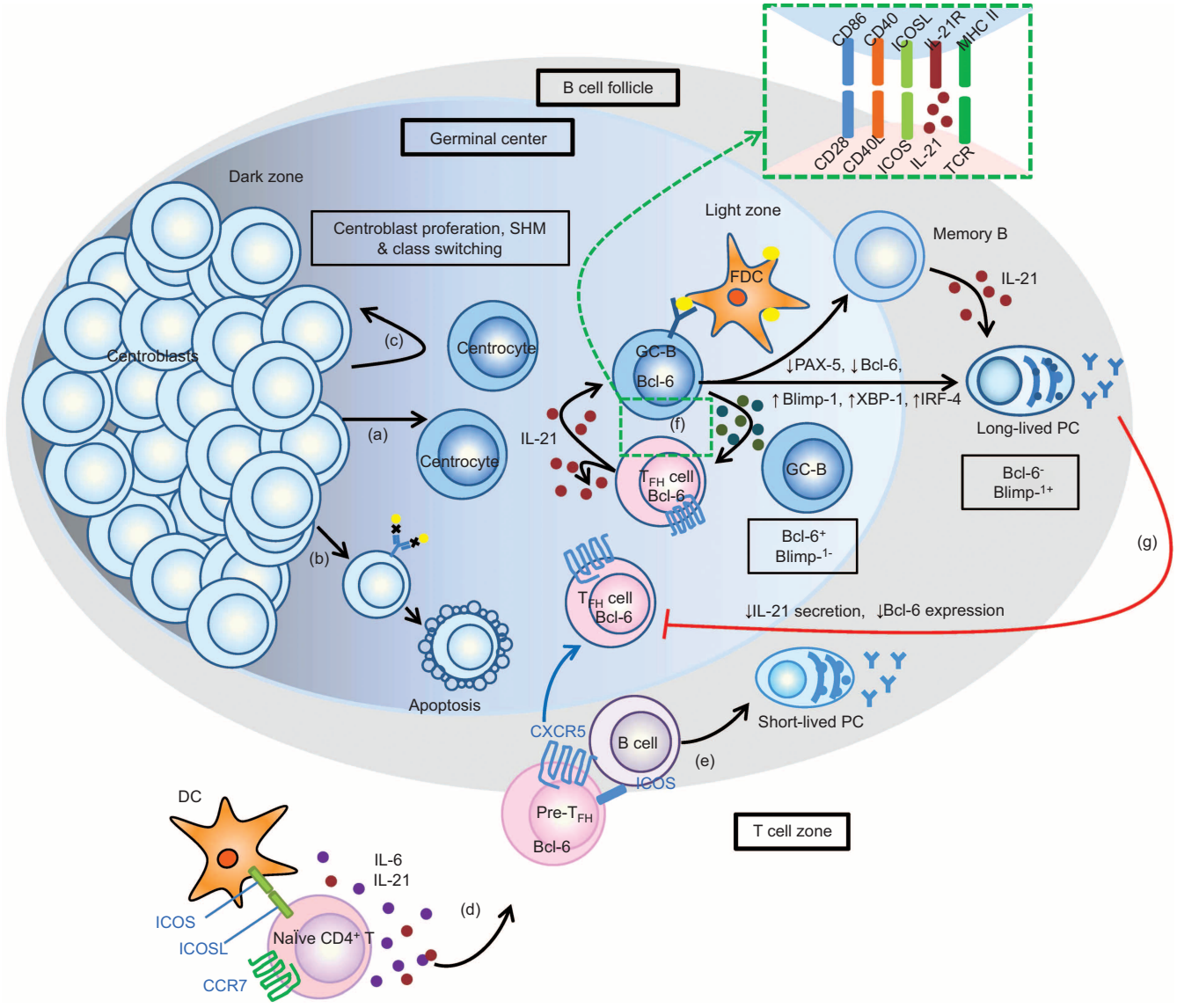

Figure 2 IL-21 signaling regulates germinal center formation and reactions and maintains T_{FH} cell development. Antigen-activated follicular B cells enter the follicular foci. In the dark zone, they differentiate into centroblasts. (**a**) The centroblasts proliferate and undergo SHM and class switching. Then, they migrate into the light zone and differentiation is facilitated for increased Ig affinity. In this stage, they are called centrocytes. Clones with weak affinity or with auto-reaction die of apoptosis (**b**) or experience further rounds of SMH in the dark zone (**c**). (**d**) At the same time, in T-cell zone, naive $CD4^+$ T cells are activated after recognizing peptide–MHC class II complexes on DCs and develop into pre-T_{FH} cells with the downregulation of CCR7, upregulation of CXCR5 and increased Bcl-6 expression (under the regulation of IL-6 and IL-21), which allows them to migrate to the B cell follicle. (**e**) In the extra-follicular area, the pre-T_{FH} cells aid the follicular B cells, which results in the differentiation of short-lived PC. The interaction between T and B cells drives the full development of T_{FH} cells. (**f**) Within the GC, T_{FH} cells continue supporting the B cell development in the GC through T- and B-cell interactions, such as with CD28/CD86, CD40L/CD40, ICOS/ICOS-L and cytokine interactions (including IL-21). IL-21 secreted by T_{FH} cells can also maintain T_{FH} cell development in an autocrine manner. The GC reaction will result in the formation of memory cells and long-lived PCs, which express high levels of Blimp-1. The process of PC differentiation requires the downregulation of PAX-5 and Bcl-6 as well as Blimp-1, XBP-1 and IRF-4 upregulation. (**g**) PCs have a negative regulatory effect on T_{FH} cells by shutting down their capacity to secrete IL-21 and decreasing their Bcl-6 expression. Bcl-6, B-cell lymphoma-6; Blimp-1, B lymphocyte induced maturation protein-1; DC, dendritic cell; GC, germinal center; ICOS, inducible costimulator; IRF-4, IFN-induced regulatory factor 4; PAX-5, paired box-5; PC, plasma cell; SHM, somatic hypermutation; T_{FH}, follicular helper T; XBP-1, X-box binding protein-1.

For instance, IL-10 was identified as the switch factor for IgG4,[27] and IL-21 was shown to be the switch factor for human IgG1 and IgG3.[28] The precise control of T_{FH} cell numbers is necessary to produce affinity-matured antibody responses with the absence of self-reactivity.[29] Moreover, T_{FH} cell differentiation and functions are precisely regulated in a complex temporospatial manner.[30] IL-21 is also an important regulator for the generation of T_{FH} cells in an autocrine manner.[31] However,

studies[32] have shown that IL-21 is required for T_{FH} expansion or persistence, rather than for their appearance, localization or their ability to support GC formation. Furthermore, IL-21 was found to directly impact B-cell function and promote PC development in secondary lymphoid organs.[33] Therefore, the critical regulatory functions of IL-21 on GC and T_{FH} cells may provide an inspiration in future PC differentiation studies.

The differentiation of activated B cells into PCs is regulated by transcriptional programs and networks that are affected by numerous microenviromental factors. In addition to IL-21, the key transcription factors involved in regulating PC differentiation include B lymphocyte-induced maturation protein-1 (Blimp-12) and the transcriptional repressor Bcl-6. There exists an interesting reciprocal repression capacity between Blimp-1 and Bcl-6. The balance between the Blimp-1 and Bcl-6 axes also involves the participation of other important transcription factors such as paired box-5 (PAX-5), X-box binding protein-1 (XBP-1), and IFN-induced regulatory factor 4[12,34] (Figures 2 and 3b). Blimp-1 is a crucial promoting transcription factor in PC differentiation[35,36] for both short and long-lived PCs.[37] Bcl-6, which is expressed in GC B and T_{FH} cells, is required for T_{FH} cell formation and supports GC formation and reactions.[18,38,39] Additionally, it blocks PC differentiation and directs GC B-cell fate by suppressing Blimp-1 expression.

IL-21 IS THE MOST POTENT PC DIFFERENTIATION INDUCER

Where does IL-21 come from?

Initially, IL-21 was reported to be produced by activated $CD4^+$ T cells.[40] Subsequently, it was shown that Th2 cells and not Th1

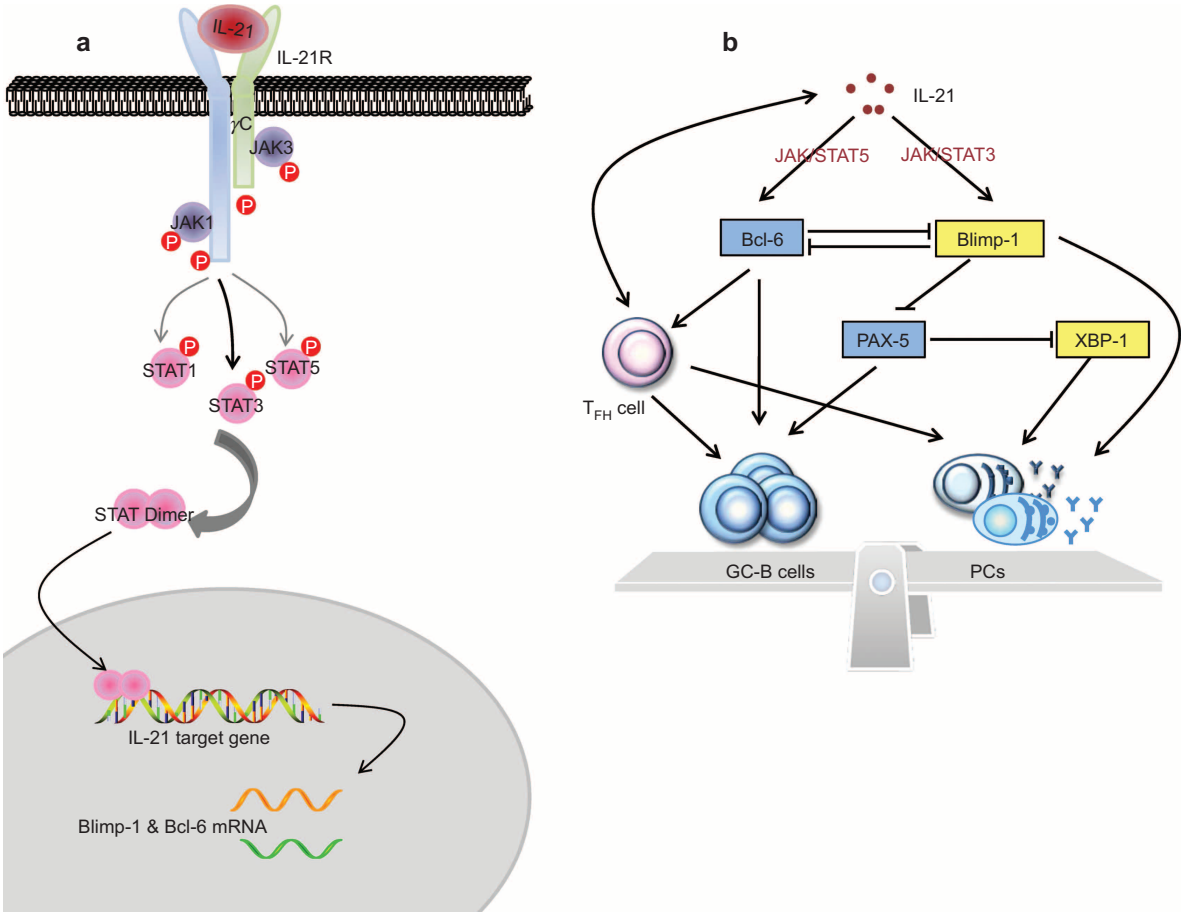

Figure 3 The IL-21 signaling network involved in PC differentiation. (**a**) When IL-21 binds to the IL-21R, JAK1 and JAK3 are activated and strongly phosphorylate STAT1 and STAT3 and weakly phosphorylate STAT5 proteins through interactions with IL-21Rα and γc, respectively. Then, the STATs dimerize and are subsequently shuttled to the nucleus, where they bind to their target gene regulatory elements. (**b**) This signaling event introduces the transcriptional factors that mutually affect GC B-cell development and PC differentiation. IL-21 can induce the expression of Blimp-1 and Bcl-6 through JAK/STAT signaling. These two transcriptional factors mutually repress with each other, and there is a balance between the two. Bcl-6 and PAX-5 are highly active in GC B cells to promote GC B-cell differentiation and repress plasmacytic development. Blimp-1 and XBP-1, however, promote PC differentiation. Additionally, IL-21 acts on T_{FH} cells in an autocrine manner, and Bcl-6 is an important transcription factor in T_{FH} cell development. T_{FH} cells are the primary cells that aid B-cell development in the GC. Moreover, they also assist the differentiation of GC B cells into long-lived PCs, which is similar to their ability to help follicular B cells differentiate into short-lived PCs. Thus, IL-21 also regulates GC B-cell development and PC differentiation through T_{FH} cells. Bcl-6, B-cell lymphoma-6; Blimp-1, B lymphocyte induced maturation protein-1; GC, germinal center; PAX-5, paired box-5; PC, plasma cell; T_{FH}, follicular helper T; XBP-1, X-box binding protein-1.

cells produce IL-21.[41] More recently, it was reported that IL-17-producing $CD4^+$ T cells (Th17) produce higher levels of IL-21 than Th2 cells and that IL-21 acts as an autocrine growth factor for Th17 cells.[42–45] However, in a study that established the intracellular cytokine staining of IL-21, it was observed that a considerable number of IL-21-producing $CD4^+$ T cells were negative for intracellular IL-17A and IL-17F under Th17-polarizing conditions.[46] This provided new insight and guidance into the cellular source of IL-21 in activated $CD4^+$ T cells. Even more recent research showed that IL-21 was a potential product associated with Th17 and T_{FH} cells.[47] A recent study[6] argued strongly that IL-21, which was associated with SLE symptoms in BXSB-Yaa mice, was not a product of Th17 cells but appeared to be generally produced by $ICOS^+CD4^+$ T splenic T cells. A similar study defined anatomically distinct extrafollicular cells that were specialized humoral effector T cells akin to T_{FH} cells that regulate PC differentiation *via* IL-21 production in MRL/MpJ-Fas^{lpr} (MRL/lpr) mice.[48] Additionally, there is considerable evidence indicating that T_{FH} cells are a robust source of IL-21.[31,47]

The effects of IL-21 in regulating PC differentiation in mice and humans

IL-21 is involved in the development, differentiation, and death in the late B-cell development stage in mice. It can induce mature B cells to differentiate into Ig-secreting PCs.[7] Additionally, in IL-21 receptor (IL-21R)-deficient mice, B-cell development for the most part was normal but the IgG1 was lower after immunization; however, IgE was higher than the wild-type animals.[49,50] The former mice were found to have a severely impaired IgG response.[49,50] Additionally, MRL/lpr mice that were treated with IL-21R.F*c* fusion protein had reduced circulating ds-DNA auto-antibody and total sera IgG1 and IgG2a levels.[51]

In humans, IL-21 is the major cytokine that induces B-cell activation, PC differentiation, and Ig production. Moreover, it can induce PC differentiation and Ig secretion in human $CD19^+$ peripheral blood and splenic B cells when combined with anti-CD40.[52,53] IL-21, however, inhibits anti-IgM and IL-4-induced proliferation.[40] Additionally, activation with IL-21 and/or TLR-9 induced $CD19^+CD27^+$ memory B cells and $CD19^+CD38^{high}IgD^-$ PC levels in active SLE patients and healthy controls.[4] These studies indicated that T-cell-derived IL-21 may exert different effects on B-cell differentiation depending on the presence of different stimuli during immune responses. Moreover, another study investigated the effect of IL-21 and IL-10 on the different PC development stages in the GC. IL-21 preferentially converted $CD77^+$ centroblasts into $CD20^-CD38^{high}$ plasmablasts in the early stage; however, IL-10 had a more potent effect on the terminal differentiation of $CD20^-CD38^{high}$ plasmablasts into $CD138^+$ PC in the later stage[54] (Figure 1).

The IL-21 mechanism of action

On the one hand, IL-21 acts directly on B cells and controls GC B-cell formation in a B cell-intrinsic fashion.[55] IL-21 maintains the expression of Bcl-6 in GC B cells and sustains the GC[32,55] (Figure 3b). Many murine model studies have shown that the spontaneous generation of GCs correlated with autoimmune disease development,[56,57] which suggests that the GC may be a pathogenic hot spot in autoimmune disease due to its production of auto-PCs and auto-antibodies.[58] On the other hand, IL-21, which is produced mainly by T_{FH} cells,[59] is also essential for T_{FH} cell development. Events that occur in the GC are all dependent on the assistance of T_{FH} cells, including the maintenance and the activity of the GC. GC dysregulation is often due to the aberrant accumulation of hyperactive and/or dysfunctional T_{FH} cells.[60,61] (Figure 3b) IL-21 plays an essential role in T_{FH} cell development, and IL-21-deficient T cells are not able to induce T_{FH} cell development, GC formation or antibody production in K/BxN mice.[62] However, an excessive number of T_{FH} cells appears to lower the selection threshold in the GC reaction and allows for the survival of low affinity or self-reactive clones.[29] Based on the above, the IL-21 signaling pathway profoundly affects the B-cell response to antigens, maintains GC persistence and function, and promotes PC formation.[32,63]

Furthermore, IL-21 mediates the differentiation and function of T, B and Natural Killer cell (NK) through binding of its receptor, IL-21R, which consists of a common γ-chain and a cytokine-specific α-chain.[64] When IL-21 binds to IL-21R, JAK1 and JAK3 interact with the IL-21Rα- and γ-chains, respectively. Then, STAT1, STAT3 and STAT5 are phosphorylated. These transcription factors contribute to the activation of multiple different downstream genes in B and T cells.[65] Additionally, IL-21 has been shown to mainly activate STAT3 signaling and to a lesser extent STAT1 and STAT5 signaling.[64] (Figure 3a) STAT5 signaling induces Bcl-6 expression, which blocks PC differentiation and promotes proliferative self-renewal signaling in human B cells.[66] STAT3, in contrast, upregulated Blimp-1 gene expression to promote PC differentiation in a murine model.[67] These studies demonstrate the ability of IL-21 to upregulate Blimp-1 and Bcl-6 expression. Another study, however, proposed that IL-21 positively regulates Bcl-6 expression through the activation of AP-1 and STAT3.[68] Although many studies have investigated the IL-21-induced Bcl-6 expression levels, the mechanism still remains ambiguous.[52,69] Studies have shown that in addition to IL-21, IL-10 and IL-6 were also required for PC survival by inducing STAT3 phosphorylation.[70] In addition to the JAK/STAT pathway, the MAPK and PI3K pathways are also associated with IL-21 signaling, which were reported to be crucial for IL-21-mediated cell proliferation.[65,71,72]

Based on the above, the IL-21 signaling pathway activates the JAK/STAT pathway, which is followed by Blimp-1 and Bcl-6 gene expression induction in the nucleus. In other words, IL-21 that is produced by T_{FH} cells acts directly on B cells to maximize the expression of Bcl-6 to promote GC B-cell development and survival. Additionally, it also promotes Blimp-1 expression, which facilitates PC differentiation.[73] (Figure 3b) The reciprocal repression between Blimp-1 and Bcl-6 exists during the overall B cell differentiation process. Specifically, these proteins

decide whether naïve B cells will differentiate into GC B cells (under the regulation of Bcl-6) or into extra-follicular PCs (under the regulation of Blimp-1). Moreover, Bcl-6 mRNA and protein are highly expressed in GC B cells during the GC reaction. At the end of the GC reaction, Bcl-6 expression is downregulated and Blimp-1 expression is upregulated to facilitate the differentiation into long-lived PCs.[74] When the balance favors PC differentiation, Blimp-1 is derepressed from Bcl-6 and suppresses PAX-5; this leads to the XBP-1 de-repression, which promotes PC differentiation. Bcl-6 and PAX-5 promote B-cell proliferation and the GC reaction by repressing Blimp-1 and XBP-1 (Figure 3b). The mutual repression between these two transcriptional factors prevents the unlimited formation of PCs in the GC and prevents the reversion of the PC back into an earlier B-cell stage.[75]

Studies have shown that mice lacking Bcl-6 contained elevated Blimp-1^+ PCs level.[67] In humans, reducing Bcl-6 expression by RNA interference resulted in an increase in Blimp-1.[76] It is thought that Bcl-6 suppressed PC differentiation because of its negative regulation on Blimp-1.[77] However, a study also reported that the inhibitory effect of Bcl-6 on Blimp-1 was not absolute because the elevated Blimp-1 expression was observed in Bcl-6^+ B cells exposed to STAT3 activation either directly or *via* IL-21 stimulation.[78] Therefore, the upregulation of Blimp-1 alone was not sufficient for primary human B cells to differentiate into PCs. Additionally, the downregulation of Bcl-6 was also required for the complete PC differentiation process.[77] However, Bcl-6 deficient mice that lacked GCs had impaired T_{FH} cell formation, which consequently developed damaged T cell-dependent antibody responses.[58] As shown previously, GC reactions produce long-lived PCs and memory cells. Because Bcl-6 is essential for the GC development and reactions, Bcl-6 may also prepare GC B cells for differentiation into long-lived PCs. The promoting or inhibiting effect of Bcl-6 on PC differentiation is dependent on the different stages of B-cell differentiation, and whether the cells enter into the follicular to facilitate the GC reaction or to differentiate into short-lived PC in extrafollicular.

Although the functions of Blimp-1 and Bcl-6 in B cells have been investigated intensively for nearly 15 years, the impact on T cells remained relatively unknown until recently.[79] $CD4^+$ T cells play an essential role in helping B cells differentiate into PCs. The balance between Blimp-1 and Bcl-6 expression is also critical for T_{FH} cell differentiation. A series of studies have demonstrated that Bcl-6 is the master regulator for T_{FH} cell development and that Blimp-1 is a critical antagonist of T_{FH} differentiation because of its antagonistic relationship with Bcl-6.[38] Specifically, $CD4^+$ T cells can be divided into four subsets: Th1 cells, Th2 cells, Th17 cells and regulatory T cells. These subsets have a powerful ability to clear a given infection or inflammatory state.[80] Interestingly, T_{FH} cells express high levels of Bcl-6,[81] and the remaining $CD4^+$ T cells (non-T_{FH} cells) possess high Blimp-1 expression levels,[38,82,83] which suggests that Bcl-6 *versus* Blimp-1 expression might decide the direction of $CD4^+$ T cell differentiation. Bcl-6 expression leads to T_{FH} cell differentiation. Once the development of T_{FH} cells is established, these cells assist with GC formation and activity, which also provides an environment for the subsequent differentiation of GC B cells into post-switched PCs (Figure 3b).

Additionally, a growing amount of recent evidence suggests[84] that a negative regulatory capacity of PCs to T_{FH} cells also existed (Figure 2). This report showed that T_{FH} cells accumulated in the absence of PCs and that the PCs could decrease IL-21 and Bcl-6 levels in T_{FH} cells. Therefore, we came to the conclusion that a balance between PC and T_{FH} cells exists and maintaining that balance is crucial in humoral immunity.[84]

In brief, IL-21 can regulate B- and T-cell development by moderating the Blimp-1 and Bcl-6 axis to regulate PC differentiation. On the one hand, IL-21 directly mediates B-cell proliferation and apoptosis in a context-dependent manner, but it also promotes immunoglobulin production and isotype class switching.[31,85,86] The effect of IL-21 on PC differentiation is derived from its capacity to increase Blimp-1 expression, whereas the increase of Bcl-6 may prepare GC B cells for their subsequent differentiation into post-switched PCs. On the other hand, IL-21 signaling in $CD4^+$ T cells is essential for the generation and differentiation of T_{FH} cells, which supports PC differentiation and antibody production in GCs.

IL-21/IL-21R AND SLE

The effects of IL-21 on B cell differentiation into PCs and on T-cell responses makes IL-21 an attractive candidate for SLE.[50,69] In humans, higher serum IL-21 and IL-21 mRNA levels were observed in SLE patients,[87,88] and population-based case–control association analyses suggest that allelic variation in the IL-21 gene was a risk factor for SLE.[87] In a study evaluating SLE patient autologous mixed $CD3^+$ T- and $CD19^+$ B-lymphocyte cultures, the exogenous addition of IL-21 and/or CpG-ODN2006 caused a significant increase in secreted IgG and the PC proportion reduced following IL-21R.F*c* treatment.[4]

In SLE murine models, the lupus BXSB-Yaa mouse showed increased IL-21 at the transcriptional and serum protein levels compared to wild-type mice[69] and the genetic deletion of IL-21R in these mice led to the disappearance of abnormal SLE characteristics, including hypergammaglobulinemia, autoantibody production and renal disease.[6] Deregulated production of IL-17 and IL-21 resulted in either a lupus-like disease state or in rheumatoid arthritis-like symptoms in a murine model.[89] The sanroque mouse bore a mutation that repressed T_{FH} cell development, which resulted in excessive IL-21 production and lupus-like symptom development.[90] MRL/lpr mice treated with IL-21R/Fc displayed reduced autoantibody levels and SLE-like symptoms.[91]

The downstream genes and proteins of the IL-21 signaling cascade were also altered in SLE patients and murine models. Additionally, elevated Blimp-1 expression, which correlated with increased PC levels, was detected in SLE patients and lupus murine models.[92] Moreover, Blimp-1 siRNA reduced serum anti-dsDNA antibody levels by eliminating anti-dsDNA antibody-producing PCs and thus impeded lupus development.[76] However, the changes in Bcl-6 expression in autoimmune

disease remain disputed. Studies have reported elevated Bcl-6 mRNA levels in the $CD4^+$ T cells of RA patients[26] and SLE-prone mice.[69] The breakdown of the Blimp-1 and Bcl-6 balance leads to auto-PC accumulation, which tends to cause autoimmune disease.

CONCLUSION, COMMENTS AND FUTURE PERSPECTIVES

B cells play fundamental roles in supplying protective immunity against infection by differentiating into PCs and secreting antigen-specific antibodies. On the contrary, the dysregulated production of excessive self-reactive antibody quantities can lead to autoimmune diseases, such as SLE. IL-21, secreted mainly by T_{FH} cells, has been proven to promote PC differentiation and antibody secretion. Although various mechanisms exist regarding the effects of IL-21 on PC differentiation, we focused on the IL-21 signaling network that is involved in the Blimp-1/Bcl-6 axis in this review. IL-21 has the capacity to regulate the Blimp-1 and Bcl-6 balance, which is also essential for T_{FH} cell differentiation and GC formation. Subsequently, with the help of T_{FH} cells, short-lived PCs develop and the GC reaction produces long-lived PCs and antibodies. In conclusion, proposed therapies that inhibit the action of IL-21 by either directly targeting IL-21 or indirectly targeting T_{FH} cells or the downstream signaling molecules of the IL-21/IL-21R cascade, such as Blimp-1 or Bcl-6, to block the differentiation of autoreactive B cells into PCs and provide practicable strategies for the treatment of SLE, have been partly evaluated in murine SLE models.[6,51,93,94] These findings will also offer a profound foundation and new insight into the development of new SLE drugs.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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