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Mini review

The function of BAFF on T helper cells in autoimmunity

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ABSTRACT

B cell-activating factor belonging to the TNF family (BAFF) exerts its pathogenic role in supporting the survival and proliferation of B cells, regulating class switch recombination as well as the selection of autoreactive B cells. Overexpression of BAFF induces a dramatic expansion of activated B cells, particularly marginal zone B cells, as well as hypergammaglobulinemia, autoantibody production and immune complex deposition. However, in addition to its effect on B cells, recent work has also demonstrated that BAFF can promote T cell activation, proliferation and differentiation. In this review, we have discussed the recent progress on the function and role of BAFF on T cells and T cell-mediated diseases.

1. Introduction

In the periphery the B cells maturation depends on the BCR signal, the surrounding stromal micro-environment including appropriate growth factors, and their ability to respond to them. One of the tumor necrosis factor superfamily members, BAFF (B cell-activating factor belonging to the TNF family) (also termed BLyS, zTNF4, TANK, TALL-1 and TNFSF-13b), is an important B-cell survival factor, being primarily expressed by monocytes, macrophages, dendritic cells, neutrophils and mast cells, and functioning to stimulate B cell proliferation, differentiation, and survival [1,2]. Three BAFF receptors have been identified, including transmembrane activator and calcium-modulating and cyclophilin ligand interactor (TACI, also known as TNFRSF13b), B cell activating factor-receptor (BAFF-R, also known as BR3 and TNFRSF13c) and B cell maturation molecule (BCMA, also known as TNFRSF17). The binding and downstream signaling of BAFF and BAFF receptors are essential for B cells survival and maturation [3]. BAFF-R is the predominant BAFF receptor expressed on peripheral B cells and activated/memory T cells. BCMA and TACI express on a more confined cell subsets. BCMA is mainly expressed on germinal center B cells, plasmblasts and plasma cells whereas TACI is basically expressed by transitional type 2 precursor B cells, marginal zone B cells and activated B cells [4]. BAFF or its receptor BAFF-R deficiency results in immature transitional type-1 stage B cells, and BAFF or BAFF-R knock out mice appeared to have almost none of follicular and marginal zone B cells, although the development of B-1 B cells remains to be unaffected [5,6]. Furthermore, BAFF plays an important role in regulating class switch recombination as well as in the selection of autoreactive B cells. Blocking BAFF signaling with anti-BAFF-R mAb *in vivo* also dramatically reduced the follicular and marginal zone B cell numbers [7]. Overexpression of BAFF in mice induces a dramatic expansion of activated B cells, marginal zone B cells and activated T cells, as well as hypergammaglobulinemia, autoantibody production and immune complex deposition [8,9]. Thus, BAFF and its receptors signaling play an important role in promoting the survival and maintenance of follicular and marginal zone B cells and B cell function.

BAFF also plays a critical role in many autoimmune and other diseases. Increased concentrations of soluble BAFF are found in

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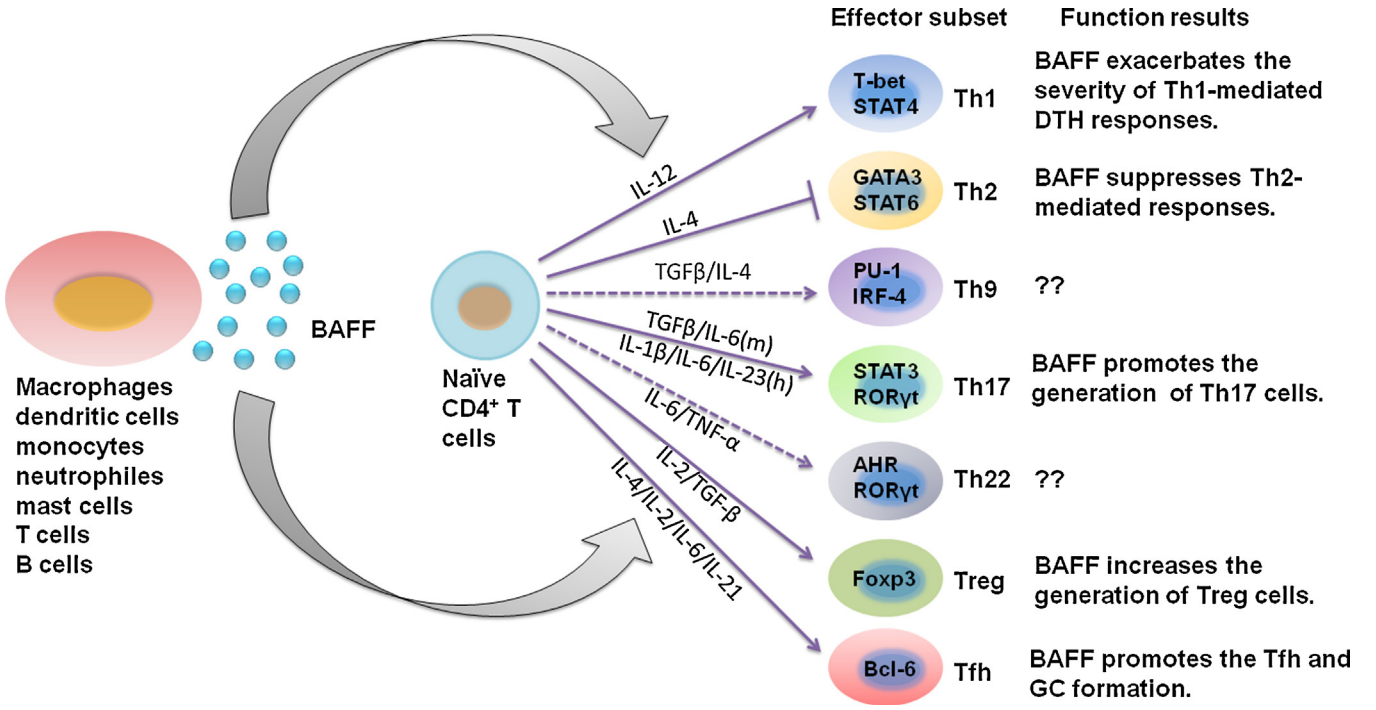

Fig. 1. The different function of BAFF on effector T cells. Several kinds of peripheral cells may secrete soluble BAFF as shown in the figure. BAFF then promote or inhibit the differentiation of naive $CD4^+$ T cells to Th1, Th2, Th17, T follicular helper T cells and Treg cells, resulting in corresponding consequences. Blue solid arrows represent stimulatory effect, and broken lines represent suppressive effect of BAFF.

different pathological conditions, including systemic lupus erythematosus (SLE) and multiple sclerosis (MS), B cell malignancies, and primary Ab deficiencies (PAD) [2,10,11]. A direct correlation between serum concentration of BAFF and severity of acute graft-*versus*-host disease (GVHD) after allogeneic hematopoietic stem transplantation has been identified [12]. Blocking BAFF signaling with TACI-Ig *in vitro* suppressed spontaneous T cell-dependent B cell anti-dsDNA antibodies production, which is possibly related to the effect on B cell survival [13]. It is helpful to define the mechanisms of BAFF on different immune cells, particularly on B cells [14,15], however, its function on T cells so far is less studied.

A proliferation-inducing ligand (APRIL), exhibiting structural similarity with BAFF, also plays an important role in the regulation of B-cell survival, differentiation and proliferation [16]. However, BAFF and APRIL display overlapping yet distinct receptor binding specificity. Both BAFF and APRIL bind BCMA (APRIL has higher affinity) although both bind the negative regulator TACI with similar affinity. In addition, BAFF-R exclusively binds BAFF with high affinity [16–18]. Furthermore, APRIL also has the capacity to bind heparin sulfate proteoglycans (HSPGs), which may help to retain to BCMA/TACI affinity [16,19]. Since T cells only express BAFF-R and hardly bind to APRIL, and only rBAFF induced cytokine secretion by $CD4^+$ and $CD8^+$ T cells *in vitro* [20,21], these data implicate that BAFF rather than APRIL could directly affect T cell differentiation and function. In this review, we will focus on the progress of role and function of BAFF in T cells and related diseases (Fig. 1).

2. Are T cells necessary for BAFF function on B cells?

BAFF transgenic (Tg) mice developed an autoimmune disorder similar to SLE [22]. BAFF-Tg mice show higher frequency of B cells and autoantibody production. Interestingly, in MHC class II-deficient mice which has few $CD4^+$ T cells, overexpression of BAFF did not expand splenic B cells albeit increased the numbers of antibody secreting cells as well as total IgM, IgG autoantibodies [23], indicating that $CD4^+$ T helper cells may play an important role in the expansion of B cells and increased autoantibodies by BAFF overexpression. Blocking BAFF signaling with BAFF-R-Ig or TACI-Ig treatment not only downregulates the B cell responses, but also decreases the frequency of activated and memory T cells [24]. However, BAFF transgenic mice with T cell deficiency still developed autoimmunity like SLE in a T cell-independent but toll-like receptor (TLR) signaling-dependent manner [22], suggesting that BAFF promotes autoimmunity independent upon T cells although T cells are required for BAFF to promote B cell expansion.

3. The differential expression of BAFF on T cell subsets

There are two distinct sources of BAFF in mice. The major one is from stromal cells, which is thought to regulate maturation of the peripheral B cells, and the second source comes from the secretion of myeloid cells during pathological conditions [25,26]. Although no evidence has showed that mouse T cells express BAFF, a low level of BAFF transcription has been detected in human T cells [27]. $CD4^+$ and $CD8^+$ T cells from peripheral blood of patients with active SLE or salivary glands from primary Sjogren's syndrome (pSS) patients expressed intracellular BAFF whereas those from normal subjects did not [13,28]. It has been identified that TCR stimulation with anti-CD3 antibody induced a robust expression of BAFF on T cells of SLE patients but not on T cells from health subject controls [29], implicating that the threshold to induce BAFF in T cells upon TCR stimulation is much lower under pathological conditions. Furthermore, TCR stimulation also triggers BAFF expression in the human T cell line Loucy *via* the mitogen-activated protein kinase (MAPK) (JNK/p38) cascade signal, and Furin, a membrane-bound protease of the subtilisin family, is responsible for the cleavage of BAFF to release sBAFF in Loucy cells [29].

4. BAFF contributes to T cell activation

BAFF co-stimulation promotes T cell activation with cytokine production *via* BAFF-R *in vitro* and *in vivo* [4,21]. BAFF co-stimulation