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Review Article

Cytokines as regulators of proliferation and survival of healthy and malignant peripheral B cells

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ABSTRACT

Adaptive immunity depends on the production and maintenance of a pool of mature peripheral lymphocytes throughout life. The signals regulating the survival of mature splenic B cells have become a major focus in recent studies of B cell immunology. Lasting B cell persistence in the periphery is dependent on survival signals that are transduced by cell surface receptors. Cytokines have been shown to play a critical role in maintaining lymphocyte homeostasis. This review focuses on the role of cytokines and their receptors in the regulation of peripheral B cell survival, with an emphasis on those that have received relatively less attention in the literature.

1. Introduction

In normal individuals, the pool of peripheral lymphocytes is constant in size. The control of lymphoid homeostasis is the result of a very fine balance between lymphocyte production, survival, and proliferation. Survival factors have been shown to play a critical role in maintaining lymphocyte populations of the correct size.

B cell development is a highly regulated process that is initiated in the bone marrow (BM). BM B-lineage precursors proliferate and progress through differentiation steps that result in the production of immature, surface immunoglobulin (Ig)-expressing B-lymphocytes. B cell receptor signaling guides the selection of immature B cells in the bone marrow. A portion of these nascent immature B-lymphocytes then migrate into the spleen to complete maturation, and are incorporated into the long-lived peripheral lymphocyte pool. After migrating from the bone marrow to the spleen, immature B cells pass through two transitional stages, which are known as transitional type I (T1; newly formed B cells) and transitional type II (T2), before differentiating into naïve mature B cells [1]. It is likely that the T1 → T2 → mature follicular B cell pathway is the most universal [2]. Upon antigen recognition, B cells differentiate into the plasma cells (PCs), which specialize in Ig secretion. Some PCs then return to and colonize the BM as long-lived PCs (LLPCs), which migrate to and persist in the BM. Other activated B cells become memory B cells, which mediate immunological memory and are more sensitive to antigen than naïve cells (summarized in Fig. 1).

Expression of a functional B-cell receptor (BCR) is a key condition for peripheral B-cell survival, and for many years, BCR signals were thought to be sufficient to maintain survival [3]. However, in recent years, cytokines have emerged as key components essential for the maintenance of immunocompetent pools of B cells. This review will discuss the regulation of peripheral B cell proliferation and survival by cytokines (summarized in Fig. 2).

2. TNF family

Tumor necrosis factor (TNF) is a prototypic member of a family of cytokines whose activity is largely determined by the cell type to which it binds, and the presence of other protein regulators [4]. Members of the TNF cytokine family fulfill crucial roles in the immune system, and are critically involved in the regulation of infection, inflammation, autoimmune disease, and tissue homeostasis [5]. TNF family ligands are primarily expressed as trimeric type II transmembrane proteins and are often processed into soluble variants that maintain the trimeric structure. Thus, these ligands can act in an autocrine, paracrine, or endocrine manner [5,6]. The structural hallmark of the ligands of the TNF family is a

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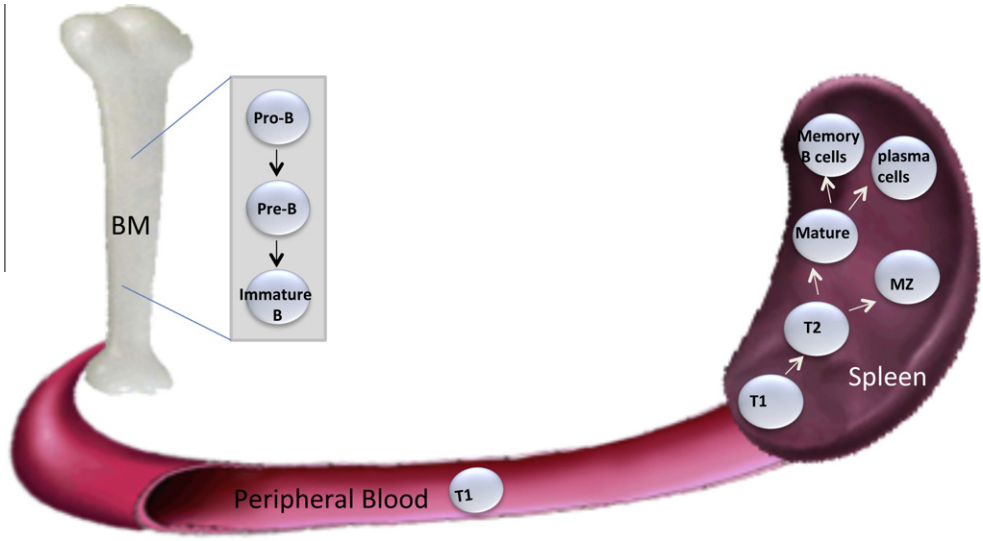

Fig. 1. B cell differentiation stages in the BM and periphery.

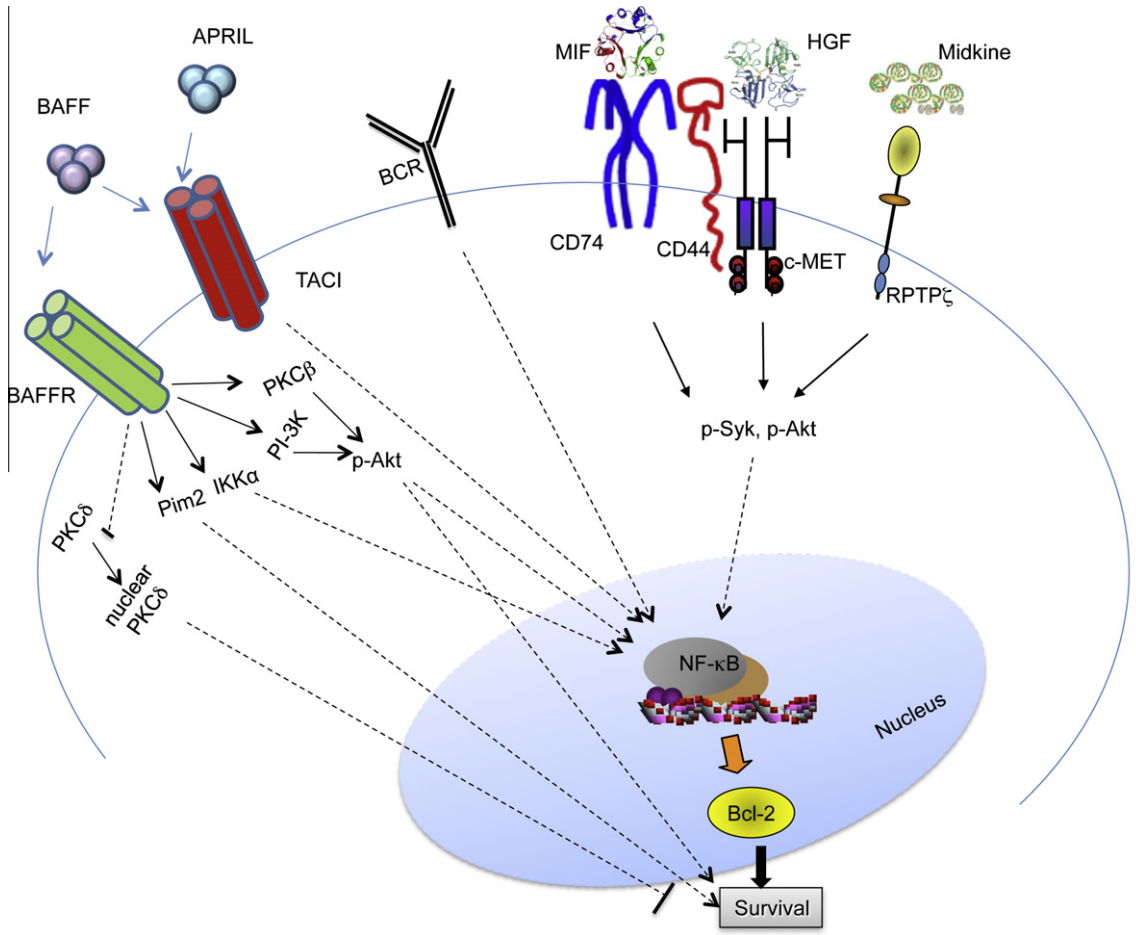

Fig. 2. Cytokines and their receptors regulating peripheral B cell survival.

conserved, 150-amino acid region in the carboxy-terminal, termed the 'TNF homology domain' (THD), which is included in both the transmembrane and soluble forms of TNF ligands. Trimeric ligands of the TNF family bind to three molecules of their corresponding receptor(s) creating a multivalent ligand, which is followed by secondary multimerization into supramolecular clusters [7,8]. The binding of the ligands to their respective receptors induces oligomerization, initiating downstream signaling events.

Here, we will focus on the ligands, BAFF (B cell activation factor of the TNF family, TNFSF 13b), also known as BlyS, TALL-1, zTNF4, or THANK [9,10], and on APRIL (a proliferation-inducing ligand, TNFSF 13a) also termed TALL-2 and TRAD-1. Both members are