Medical Hypotheses (2008) **70,** 40—42

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medical hypotheses

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BAFF — an essential survival factor for B cells: Links to genesis of ITP and may be of therapeutic target

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Received 27 April 2007; accepted 1 May 2007

Summary Idiopathic thrombocytopenic purpura (ITP) is an organ-specific autoimmune disease characterized by the production of antiplatelet antibodies secreted by B cells resulting in enhanced destruction of platelets by macrophages. B cells have been demonstrated to play a critical role in the genesis of ITP.

Recently identified B cells activating factor of the TNF ligand family (BAFF) is essential in their physiology which can promote B cells development, survival, proliferation and maturation, then the secretion of more antibodies. In the pathological conditions of ITP, there is an overproduction of BAFF. Therefore, we propose that BAFF plays, at least in part, an important role in the pathogenesis of ITP and offers the opportunity to improve our therapeutic approach.

Introduction

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder in which platelets are opsonized by autoantibodies and destroyed by macrophages [1]. Therefore, ITP represents a prototype of a B-cell-mediated autoimmune disorder and B-cell depletion has become a reasonable option for ITP patients by decreasing the formation of autoantibody [2]. B-cell activating factor belonging to the tumour necrosis factor (TNF) family (BAFF) is an important regulator implicated in the survival, maturation and activation of peripheral B lymphocytes. BAFF binds to three different receptors: transmembrane activator and calcium modulating and cyclophilin ligand interactor (TACI), B-cell maturation antigen (BCMA) and BAFF-receptor (BAFF-R), whose expression is restricted to B cells. BAFF and BAFF-R-deficient mice showed a dramatic loss of peripheral B cells and a severely reduced immune response. In contrast, an enhanced BAFF expression leads to an enhanced B cells activation and the survival of pathologically active B cells in mice [3]. *In vivo*, administration of soluble decoy receptors for BAFF effectively decreases disease progression in some autoimmune diseases mouse models, such as lymphoid cancers [3], systemic lupus erythematosus (SLE) [4,5], rheumatoid arthritis [6] and sjogren's

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0306-9877/$ - see front matter
doi:10.1016/j.mehy.2007.05.005

syndrome [7]. These evidences render BAFF as a potentially new therapeutic target for autoimmune diseases. Recent study has shown that circulating level of BAFF significantly increased in ITP, which offers important new insights into the pathogenesis of ITP [1], therefore, BAFF might serve as a new rational therapeutic target for ITP.

Hypothesis

Taken together, these evidences have led us to hypothesize that BAFF, an essential survival factor for B cells, plays an important role in the pathology of ITP. Most probably, blocking the expression of BAFF may induce B cells depletion; therefore, it may be an effective therapeutic target molecule in patients with ITP.

Discussion

ITP is a well-defined autoimmune hematologic disorder characterized by thrombocytopenia of peripheral origin due to clearance of opsonised platelets by the macrophages [8,9]. In recent years, the central role for B cells in the pathogenesis of this disease has gained more prominence as a result of research in both mice and humans [10,11]. It can produce more autoreactive antibodies which opsonized the platelets and increased platelets destruction [12,13]. Research in recent years gave the first real proof that B cells depletion has the potential to induce disease amelioration by inhibiting autoantibody production and/or by interfering with other B cells pathogenic functions [14].

B cells require signals from multiple sources for their development from precursor cells, and differentiation into effector cells. Identification of the B cells survival factor, BAFF, was a key discovery in understanding the survival mechanism for mature B cells in the periphery [15]. BAFF belongs to the family of tumour necrosis factor ligands and is expressed by several cell types, including monocytes, macrophages, neutrophils, dentritic cells and T lymphocytes [16—18]. It binds to three receptors within the TNF receptor family, BAFFR/BR3, BCMA and TACI, the latter two also bind APRIL, which are primarily expressed on B lymphocytes [19]. BAFF plays a crucial role in B cells development, survival, and immunoglobulin-production [20]. It enhanced long-term B cells survival primarily through the alternative, but not the classical, NF-κB pathway, it promoted immunoglobulin class switching and generation of pathogenic antibodies through the classical pathway. Activation of the alternative NF-κB pathway resulted in integrin upregulation, thereby retaining autoreactive B cells in the splenic marginal zone, a compartment that contributes to their survival [21]. Therefore, BAFF is required for B cells hyperplasia and autoimmunity. Mice overexpressing BAFF display increased B cells numbers and immunoglobulin levels as well as clinical features similar to that observed in patients with autoimmune disorder [15]. Preliminary data on the treatment of SLE with belimumab, a fully human monoclonal antibody that specifically binds to and neutralizes the BAFF, are now available and meet primary efficacy endpoints [5]. All these suggest that the development of autoantibodies is linked to elevated BAFF levels.

Clinical study has showed that serum BAFF levels in patients with an active ITP were significantly higher than in healthy control group, whereas, in inactive patients, BAFF levels were observed to be similar to those of the healthy control group, Moreover, immunosuppressive treatment was associated with strongly suppressed BAFF levels. All these suggested that there is a correlation between BAFF levels and disease activity [1]. Therefore, ITP can be effectively treated by decreasing the level of BAFF. The targeting of BAFF with inhibitors has proven efficient in the control of autoimmunity in mouse models of SLE and rheumatoid arthritis [15,22]. Hence, selective targeting of BAFF in ITP patients with high levels of BAFF could be considered as a novel therapeutic strategy.

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