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B cell-targeted therapies in autoimmunity: rationale and progress

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Abstract

B cells are recognized as main actors in the autoimmune process. Autoreactive B cells can arise in the bone marrow or in the periphery and, if not properly inhibited or eliminated, can lead to autoimmune diseases through several mechanisms: autoantibody production and immune complex formation, cytokine and chemokine synthesis, antigen presentation, T cell activation, and ectopic lymphogenesis. The availability of agents capable of depleting B cells (that is, anti-CD20 and anti-CD22 monoclonal antibodies) or targeting B cell survival factors (atacicept and belimumab) opens new perspectives in the treatment of diseases such as systemic lupus erythematosus, rheumatoid arthritis, type I diabetes, and multiple sclerosis.

Introduction and context

B cell depleting agents are currently available and the most used is definitely rituximab. Rituximab is a glycosylated immunoglobulin G (IgG) chimeric mouse/human antibody that binds to the CD20 antigen present on the majority of circulating B cells [1]. Expression of CD20 is restricted to the B cell lineage from the pre-B-cell stage until terminal differentiation into plasma cells. Treatment with rituximab induces a notably rapid (within hours) and prolonged (more than 3 months) depletion of circulating B cells. Interestingly, naïve B cells appear to recover faster than memory B cells. The manner and speed of action of rituximab could potentially suggest an effect related to antibody-independent B cell function, whereas an antibody-mediated effect would not have been so fast since plasma cells are CD20-negative and thus not directly affected by rituximab [2]. Although this has been nicely demonstrated in autoimmune diseases, in the case of immune-mediated thrombocytopenia, Bussel [3] has defined three different phenotypic responses with very different kinetics of clinical response. In diseases such as pemphigus vulgaris, it has been clearly demonstrated that the mechanism of rituximab action is through eradication of the anti-keratinocyte IgG4 autoantibody [4]. However, many issues, such as the persistence of memory B cells or the ability of this drug to induce an in-depth depletion, remained to be defined.

Major recent advances

B cells and rheumatoid arthritis

Significant evidence arising from experimental models indicates that autoantibodies play a key role in the pathogenesis of inflammatory arthritis; moreover, B cell depletion therapy with rituximab provides evidence that B cells play a major role in rheumatoid arthritis (RA) [5]. In addition to autoantibody production, B cells efficiently present antigen to T cells. Rheumatoid factor (RF)-producing B cells are particularly effective in presenting immune complexes to T cells [6]; they produce soluble factors, including cytokines and chemokines, that can modulate dendritic cell migration and function [7] and form tertiary or ectopic lymphoid tissue, which ranges from loose aggregates of T and B cells to distinct follicle-like structures in close contact with the synovial membrane of RA patients, amplifying autoimmune responses and inflammation [8].

B cells and systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by formation of pathogenic

autoantibodies, immune complex deposition, and organ damage and failure [9]. A central role for B cells is evident and is confirmed by the therapeutic potential of B cell depleting treatment in humans [10,11]. Autoantibody production contributes to SLE development by inducing immune complex-mediated type III hypersensitivity and type II antibody-dependent cytotoxicity. Moreover, antibody deposition can instruct innate immune cells to produce pathogenic cytokines such as interferon-alpha (IFNα), tumor necrosis factor (TNF), and interleukin-1 (IL-1) [12]. Several abnormalities of B cells have been related to an SLE-like phenotype; Bolland and colleagues [13] demonstrated how some of the genes involved in lupus may downregulate B cell receptor signaling at the immature stage, impairing B cell tolerance. Alterations in B cell longevity can also cause an SLE-like phonotype; transgenic expression of BAFF (B cell activator of the TNF family), a cytokine promoting B cell survival, leads to a lupus-like phenotype with high mature B cell and plasma cell numbers, spontaneous germinal center reactions, autoantibodies, and Ig deposition in the kidney [14]. Moreover, administration of soluble BAFF receptor ameliorates disease progression and survival; in human serum, elevated BAFF correlates with serum IgG and autoantibody levels [15] and excessive BAFF promotes the survival of autoreactive B cells in the periphery [16]. The breakdown of B cell tolerance occurs at a very early stage of development in both mice and humans [17] and may precede or trigger other immune abnormalities, as shown by the expression of antinuclear antibodies in SLE patients several years before the onset of clinical disease [18].

B cells and type 1 diabetes

Type 1 diabetes (T1D) is an autoimmune disease characterized by T-cell mediated destruction of insulin-producing pancreatic β cells [19]. T1D involves the interaction of different subsets of lymphocytes and antigen-presenting cells; in particular, B lymphocytes, because of their highly efficient ability to internalize β cell antigens through Ig and subsequently present them to autoreactive CD4 T-cells, they serve as a preferential subset of diabetogenic antigen-presenting cells in non-obese diabetic (NOD) mice and possibly in humans [20]. Indeed, B cell-deficient NOD mice have been shown to be protected from autoimmune diabetes [21] and to be deficient in the development of the major autoantigen T-cell response (such as glutamate decarboxylase) [22]. These findings have made B cell targeting a new and attractive strategy for the treatment of T1D. Work by Hu and colleagues [23] showed the positive effects of an anti-CD20-based B cell depleting strategy, preventing autoimmune diabetes and reversing established diabetes, in transgenic NOD mice expressing the humanized CD20 receptor on B cells. The actual use of B cell depletion as a therapy for human autoimmune disease, including its use in patients with new-onset T1D, is ongoing [24]. Recent work by our group suggested a novel approach: a newly developed reagent, anti-CD22 calicheamicin-conjugated monoclonal antibody (mAb) [25], which has been previously tested in humans, both for the immunoregulatory properties of CD22 engagement and for the possibility of depleting mature B cells. It has had promising results in the fields of autoimmune disease [26] and B cell malignancies [27], but had not been tested in diabetes until recently. The study shows how anti-CD22 calicheamicin-conjugated mAb treatment can delay diabetes onset in prediabetic NOD mice and, more importantly, can restore normoglycemia in new-onset hyperglycemic NOD mice. Moreover, for the very first time, data highlight that re-emerging B cells in NOD mice display a different phenotype from naïve B cells; they are functionally impaired in their ability to present antigen and can regulate the autoimmune response, resulting in long-term tolerance to autoantigens *in vivo* [25].

B cells and multiple sclerosis

In addition to T cell responses, B cell and antibody responses may contribute to the pathogenesis of multiple sclerosis (MS) [28]. Antimyelin autoantibodies such as those directed against myelin basic protein and myelin oligodendrocyte glycoprotein can target damage in both animal and human inflammatory central nervous system diseases [29]. B cells are also able to internalize and present antigens through the B cell receptor at least 10,000 times more efficiently than professional antigen-presenting cells, and can activate T cells, produce cytokines such as IL-6 and IL-10 that affect the local environment, play a role in the formation and maintenance of lymphoid-like follicles in the ventricular-meningeal compartment [30], and harbor the Epstein-Barr virus in a chronically activated state.

Future directions

New approaches to targeting the B cell compartment are under investigation. Trials with anti-CD20 mAbs have been published recently in MS [2], RA [5], and SLE [10,11] and should be published soon for T1D. Whereas anti-CD20 therapy for MS and RA has been successful, many limitations appear to be evident when it is used for SLE and T1D, possibly due to the presence of highly specialized memory B cells resistant to depletion, or to the potential inability of anti-CD20 to deplete B cells in the pancreas or in tertiary lymphoid tissue.

None of the published trials for SLE are controlled, and work presented at the 2008 American College of

Rheumatology annual meeting showed negative data from a placebo-controlled trial on the use of rituximab in nonrenal SLE (EXPLORER). Thus, another negative trial of rituximab in lupus nephritis (LUNAR) would suggest that anti-CD20 mAb might be inefficacious in human SLE.

Therefore, there is a need for new agents targeting memory B cells/plasma cells and agents selective for autoreactive B cells. Selective modulation of B cells has been achieved recently with a humanized mAb against the B cell surface marker CD22. This antibody (epratuzumab) has been reported to be effective, with the same safety profile, in two prototype autoimmune diseases, SLE and primary Sjögren syndrome [31,32]. Other drugs, such as atacicept (a fully human recombinant fusion protein that blocks the activity of B-lymphocyte stimulator [BLyS] and of a proliferation-inducing ligand [APRIL]) and belimumab (LymphoStat-B®, a human mAb that specifically recognizes and inhibits the biological activity of BLyS), inhibit specific B cell survival factors, resulting in reductions in B cells and plasma cells [33]. These drugs are undergoing clinical evaluation in phase II and III studies in patients with relapsing MS, SLE, lupus nephritis, RA, and several B cell malignancies. The use of these drugs induces a reversible decrease in circulating Ig concentration and a reduction in mature B cells in the peripheral blood and lymphoid tissues [34]. Unfortunately, the lupus nephritis trial involving atacicept was stopped earlier this year due to increased frequency of severe infections. The other studies of atacicept in SLE, RA, and MS are proceeding. For the sake of completeness, we would like to mention the development of anti-CD19 mAbs, as well as the single-chain CD20-binding polypeptides that are being co-developed by Trubion Pharmaceuticals Inc (Seattle, WA, USA) and Wyeth (Madison, NJ, USA). Finally, a lupus trial using abetimus (a double-stranded oligodeoxyribonucleotide thylene glycol that was developed to induce tolerance in B cells directed against double-stranded DNA) was recently stopped because of an interim analysis showing futility.

Two recent papers show a new regulatory role for specific subsets of B cells in MS and T1D, confirming that B cells can abrogate T cell immune response when co-adoptively transfered with autoreactive T cells or can halt disease progression [25,35].

The paper from Tedder and colleagues [35] showed that B cells play critical positive and negative regulatory roles in a murine model of MS [experimental autoimmune encephalomyelitis (EAE)]. B cell depletion had two opposing effects on disease [35]. Early B cell depletion exacerbated not only EAE induction, but also the recovery phase of disease [35]. Moreover, the adoptive transfer of IL-10-producing regulatory B10 cells, but not other B cells, normalized EAE pathogenesis [35]. Therefore, investigators proposed that increased EAE severity following total B cell depletion before disease induction results from depletion of the B10-cell subset [35]. Regulatory B cells may be critical during disease induction and for resolving disease. In contrast, B cell depletion after the onset of EAE symptoms ameliorated disease progression [35], making this strategy applicable for treating human MS after disease onset.

Anti-CD20 mAb treatment depletes memory cells in mice but does not deplete long-lived plasma cells [32]. Thus, $CD20^+$ B-cell depletion may be most beneficial when carried out before the long-lived plasma cell pool is established.

Therefore, future studies will investigate selectivity and specific depletion/targeting of autoreactive B cells and expansion of regulatory B cells.

Abbreviations

APRIL, a proliferation-inducing ligand; BAFF, B cell activator of the tumor necrosis factor family; BLyS, B-lymphocyte stimulator; EAE, experimental autoimmune encephalomyelitis; EXPLORER, a randomized, double-blind, placebo controlled, multicenter, phase II/III study to evaluate the efficacy and safety of rituximab in subjects with moderate to severe SLE; Ig, immunoglobulin; IL, interleukin; IFNα, interferon-alpha; LUNAR, a phase III, randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy and safety of rituximab in subjects with class III or IV lupus nephritis; mAb, monoclonal antibody; MS, multiple sclerosis; NOD, nonobese diabetic; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; TNF, tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

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