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B-lymphocyte depletion for the treatment of multiple sclerosis: now things really get interesting

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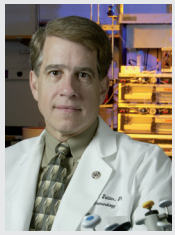

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"...pan-B-cell-depletion therapies may actually represent a double-edged sword in the treatment of some autoimmune individuals."

Conventional wisdom is that B lymphocytes are a major driving force behind autoantibody-dependent autoimmune diseases, such as systemic lupus erythematosus, and the autoimmune blistering diseases, such as pemphigus vulgaris. Other autoimmune diseases have been classically viewed as predominantly T-cell-dependent, such as multiple sclerosis (MS), rheumatoid arthritis, systemic sclerosis and Type 1 diabetes. This conclusion derives from the finding that adoptive transfer of T cells from diseased animals can initiate disease symptoms in healthy recipients. Recent assessments of the role of B cells in the immune system have demonstrated that B cells serve essential functions in regulating immune responses that were not previously appreciated [1,2]. B cells contribute to disease pathogenesis not only by the production of autoantibodies, but through their function as cellular adjuvants for $CD4^+$ T-cell activation [3] and their ability to regulate T-cell function and inflammation through cytokine production [4]. Clinically, pan-mature B-cell depletion in humans using a CD20 monoclonal antibody (mAb; rituximab) is effective for treating various autoimmune disorders in some patients, such as rheumatoid arthritis [2]. Furthermore, recent Phase I and II trials using rituximab suggest clinical efficacy in MS patients [5,6]. The human clinical trial findings have been reviewed extensively [7,8], so they will not be discussed here. Nonetheless, the mechanisms underlying the effect of pan-mature B-cell depletion on disease activity in humans remains predominantly unknown.

"A phenotypically unique spleen $CD1d^{high}CD5^+$ regulatory B-cell subset has recently been identified that is responsible for most B-cell IL-10 production."

CD20 is a B-cell-specific cell surface molecule first expressed during the pre-B to immature B-cell transition and fully expressed by mature B-cell subsets, but is lost upon plasma cell differentiation in humans and mice [9]. In mice, CD20 mAb depletes normal and malignant B cells *in vivo* through antibody-dependent cellular cytotoxicity, without detectable contributions from the complement system [10–12]. Unexpectedly, B-cell depletion by CD20 mAb also significantly inhibits T-cell function in mouse autoimmune disease models, including collagen-induced arthritis and Type 1 diabetes [13–15]. CD20 mAb does not deplete T-cell or other non-B-cell leukocyte subsets in mice. In most cases, serum antibody and established autoantibody levels are also not affected by $CD20^+$ B-cell depletion [16]. Moreover, the rapid therapeutic benefit of B-cell depletion in MS patients is unlikely to be explained by a reduction in pathogenic autoantibodies [5,6]. Rather, in these models and with other antigens, B cells are necessary for optimal $CD4^+$ T-cell but not $CD8^+$ T-cell activation during immune responses to low-dose antigens, with dendritic cells sharing this

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duty [3]. Thereby, the therapeutic effect of B-cell depletion in mice is attributable in part to reduced autoreactive $CD4^+$ T-cell activation. Studies in humans have suggested similar effects [17,18].

B cells not only activate T cells, but appear to also have opposing negative regulatory properties that can significantly inhibit autoimmune disease and inflammation [19–22]. A phenotypically unique spleen $CD1d^{high}CD5^+$ regulatory B-cell subset has recently been identified that is responsible for most B-cell IL-10 production [23,24]. We call these cells 'B10 cells', since other regulatory B-cell subsets may exist. Although B10 cells only represent 1–2% of spleen B cells, they dramatically inhibit the induction of antigen-specific inflammatory reactions and autoimmunity [22]. Thereby, B cells may regulate multiple components of the immune system and causes of autoimmune disease through combinations of their multipurpose cellular and humoral functions [2].

> "...the balance of at least two opposing B-cell functions shapes the normal course of experimental autoimmune encephalomyelitis immunopathogenesis."

Contradictory roles for B cells have been demonstrated in experimental autoimmune encephalomyelitis (EAE), a mouse model of MS [25–28]. EAE studies using double-transgenic mice with myelin oligodendrocyte glycoprotein (MOG)-specific T- and B-cell antigen receptors have shown that B cells can function as antigen-presenting cells during EAE initiation [25,26]. More than 50% of these mice develop inflammatory demyelinating lesions in the CNS, while disease incidence is only approximately 5% in MOG-specific T-cell receptor-transgenic mice. By contrast, congenitally B-cell-deficient mice develop a severe nonremitting form of EAE [27,28]. B-cell production of IL-10 can also inhibit EAE development [28]. These apparently contradictory results suggest either multiple roles for B cells during EAE pathogenesis or the involvement of different B-cell subsets. Using CD20 mAb, we have found that EAE disease initiation and progression are differentially influenced by the depletion of B cells from mice with otherwise intact immune systems [24]. B-cell depletion before EAE induction significantly exacerbates disease symptoms and increases encephalitogenic T-cell influx into the CNS. Worsening disease results from depletion of the B10-cell subset since the adoptive transfer of splenic CD20-deficient B10 cells before EAE induction normalizes immunopathology in otherwise B-cell-depleted mice. Regulatory B10 cells are maximally effective during early EAE initiation, but have no obvious role during disease progression, potentially owing to the emergence of regulatory T-cell function. Rather, $CD20^+$ B-cell depletion during EAE progression dramatically suppresses disease symptoms. Specifically, B cells are required for CNS autoantigen specific-$CD4^+$ T-cell generation and encephalitogenic T-cell entry into the CNS during disease progression. Thus, the balance of at least two opposing B-cell functions shapes the normal course of EAE immunopathogenesis. The therapeutic benefit of B-cell depletion may thereby depend on the relative contributions and timing of these opposing B-cell functions during the course of autoimmune disease.

The amelioration of disease progression in mice when $CD20^+$ B cells are depleted after the onset of EAE symptoms may parallel the therapeutic benefit of rituximab for relapsing–remitting MS in humans. However, all immune-mediated inflammatory diseases may not behave the same after B-cell depletion, as rituximab treatment was recently suggested to exacerbate ulcerative colitis and trigger psoriasis, which predominately depend on T-cell-mediated mechanisms [29,30]. In addition, one case report suggests that B-cell depletion might have induced MS relapses in a patient with an 18-year history of MS who developed antimyelin-associated glycoprotein polyneuropathy that was treated with rituximab [31]. Although the B10-cell subset has yet to be definitively established in human disease, the available mouse studies raise the intriguing possibility that B10-cell depletion may induce or exacerbate autoimmunity in some susceptible individuals. In MS patients, B-cell IL-10 production is significantly lower than in healthy controls and is upregulated following therapy [32]. In addition, helminth infections induce regulatory B cells in MS patients and suppress disease activity [33], which may explain environment-related suppression of MS in areas with low disease prevalence. It therefore remains possible that pan-mature B-cell depletion may exacerbate MS occurrence in some undiagnosed cases or promote relapses. As a result, pan-B-cell-depletion therapies may actually represent a double-edged sword in the treatment of some autoimmune individuals [34].

> "These collective observations open the door to future therapies designed to augment, eliminate or impair B-cell subset-specific functions."

Although the currently recognized therapeutic benefit of pan-B-cell depletion using currently available drugs (rituximab) appears to outweigh the potential negative consequences of this therapy, additional mouse studies suggest that prolonged and complete B-cell depletion may also be required to induce optimal long-term therapeutic benefit [13,14]. These collective observations open the door to future therapies designed to augment, eliminate or impair B-cell subset-specific functions [35]. Currently, B-cell subset-directed therapies targeting CD22, BLyS and CD40 are in development, as well as other potential therapies directed at specific B-cell functions. It may also be possible to identify pathways that regulate B10-cell activation, expansion and function, which will allow this potent B-cell subset to be manipulated for therapeutic benefit. For example, the selective expansion of autoantigen-specific B10 cells may be sufficient to blunt the induction of autoimmune disease. One might even envision the use of this approach in preclinical autoimmune diseases, such as Type 1 diabetes. Alternatively, an approach that selectively depletes mature B cells while sparing regulatory B10 cells may offer a particularly potent therapy for MS and other immune-mediated inflammatory diseases. Now that the door for B-cell-directed therapies has been opened, new treatments addressing the regulatory complexity of the immune system appear more promising, with the likelihood that combination therapies directed at both the T- and B-cell arms of the immune system will be needed to address the complexity of autoimmune disease.

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