Comment on "Conventional B2 B Cell Depletion Ameliorates whereas Its Adoptive Transfer Aggravates Atherosclerosis"

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Comment on “Regulatory T Cells Protect from Local and Systemic Bone Destruction in Arthritis”

We read the interesting paper by Dr. Zaiss and colleagues (1) on the role of regulatory T cells (Treg cells) in local and systemic bone destruction in arthritis. We suggest that effective targeting of Treg cells makes CD28 superagonist Abs (CD28 SA) a promising novel reagent to prevent arthritic bone destruction.

Bone destruction in rheumatoid arthritis (RA) is caused in part by the activation of osteoclasts (2). It is well known that Treg cells can inhibit osteoclast formation (3). So far, however, no therapeutic reagents have been available to directly target Treg cells to suppress osteoclast formation. Interestingly, CD28 SA has the unique property of being capable of increasing the numbers and functionality of Treg cells in many animal models with conditions similar to human autoimmune diseases, including autoimmune neuritis, autoimmune myocarditis, and graft-versus-host disease (4–6). Zaiss et al. (1) first correlated CD28 SA with osteoclast-mediated bone destruction in arthritis; they found that during TNF-mediated arthritis, CD28 SA strikingly increased Treg cell numbers, but decreased osteoclast numbers and osteoclast-covered bone surface. Moreover, their study data show that CD28 SA ameliorates TNF-induced arthritis and systemic bone loss.

Collectively, these observations suggest that CD28 SA treatment could be used in patients as a tool to control bone destruction in arthritis by activating and expanding Treg cells (7). Thus, understanding the role of CD28 SA in Treg cell-mediated osteoclast suppression could result in important innovative therapies for the treatment of bone destruction in RA, and the first clinical trial is eagerly awaited.

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Response to Comment on “Regulatory T Cells Protect from Local and Systemic Bone Destruction in Arthritis”

We appreciate the comments by Dr. Yuan and colleagues, who propose that fostering the activity of regulatory T cells may be an attractive strategy to treat autoimmune diseases such as inflammatory arthritis, multiple sclerosis, and systemic lupus erythematosus. Such strategies could indeed be based on pharmacological approaches, which allow a rise in the numbers of regulatory T cells in vivo. Treatment with superagonistic Abs against CD28 have been shown to increase the number of regulatory T cells in vivo and show promising effects in animal models of autoimmune disease and bone loss (1, 2). Stimulation of CD28 by CD80/86-expressing APCs is considered the classical receptor–ligand interaction for T cell costimulation. At the same time, activation of CD28 elicits a regulatory response as well, which is of key importance in limiting T cell activation. This latter response is at least partly mediated by the expression of CTLA-4 by T cells and the induction of regulatory T cells. CTLA-4 is part of the armamentarium of regulatory T cells to block immune activation via cell–cell contact-mediated mechanisms.

The strategy to increase the regulatory T cell pool and to inhibit autoimmune disease by CD28 superagonistic Abs is indeed attractive, as it mimics the classical process of T cell costimulation, which is followed by regulatory immune responses. However, this concept bears the danger that the initial costimulatory signal via CD28 dominates and induces spurious but massive T cell activation and inflammation. This scenario has been observed in a first-in-human trial with a CD28 superagonist Ab, resulting in an acute and dramatic cytokine burst and life-threatening inflammation (3, 4). Therefore, approaches aiming to augment the regulatory T cell pool through stimulation of CD28 should be regarded with caution and carefully examined for their potential to induce acute inflammatory responses.

Another strategy using the immunomodulatory principle of regulatory T cells in therapy is to mimic their immunosuppressive effect by pharmacological approaches. CTLA4, a key surface molecule on regulatory T cells, mediates the cell–cell
contact-based immunoregulatory role of these cells. Indeed, administration of a CTLA-4–Ig fusion protein (abatacept, beletacept) shows anti-inflammatory effects in humans and has been already approved for the treatment of rheumatoid arthritis (a systemic autoimmune disease affecting the joints) and will be soon approved for acute graft rejection after kidney transplantation (5, 6). In contrast, blockade of CTLA4 by neutralizing Abs is used to foster immune responses against tumors such as melanoma and the side effects of drugs such as ipilimumab and is indeed the induction of autoimmunity (7).

We thus agree with the comments by Yuan and colleagues that great potential lies in translating the molecular pathways of regulatory T cells into drug therapy for autoimmune disease. As the adoptive transfer of regulatory T cells into humans is not an easy task for several reasons, therapeutic developments will likely focus on the use of such molecular interventions, which either increase the pool of regulatory T cells or foster their immunosuppressive activity (8).

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Comment on “Conventional B2 B Cell Depletion Ameliorates whereas Its Adoptive Transfer Aggravates Atherosclerosis”

We read with interest the paper by Kyaw and colleagues (1), which used adoptive transfer of B cells into μMT Apoε−/− mice to determine if these cells were atherogenic in a model selectively deficient in B lymphocytes. When compared with PBS control, injection of 5 × 10^5 C57BL/6 splenic B cells resulted in a >3-fold increase in atherosclerosis, as determined by oil red O staining of cross sections at the aortic cusps following 8 wk of high-fat feeding. Although the degree of reconstitution was not provided in μMT Apoε−/− mice, we noted it was rather low, at 0.1–0.3% in triple knockout mice (Fig. 4). Recently, we adoptively transferred 60 × 10^6 C57BL/6 splenic B cells isolated by anti-CD43–negative selection (purity >98%) or PBS control into μMT Apoε−/− mice via tail-vein injection (n = 5 per group). Mice were then fed 16 wk of Western diet. We saw no aggravation of atherosclerosis, as determined by Sudan IV en face analysis of the entire aorta (B6 recipients 17.9 ± 2.4% versus sham 17.5 ± 1.9%; p = NS). Percent reconstitution was 1.4–7.9, nearly 20-fold greater than that of Kyaw et al. (1), suggesting the degree of reconstitution impacts the ability of B cells to modulate atherogenesis. In addition, use of chimeric mice of mixed genotype (transfer of Apoε+/− C57BL/6 B cells into μMT Apoε−/− mice) may confound interpretation. This is especially poignant because previous experiments demonstrating B-cell–mediated atheroprotection occurred when B cells from Apoε−/− mice were transferred to splenectomized Apoε−/− recipient mice (2).

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Response to Comment on “Conventional B2 B Cell Depletion Ameliorates whereas Its Adoptive Transfer Aggravates Atherosclerosis”

The comment by Lipinski et al. on our paper is interesting in that it highlights problems inherent in transfer experiments with B cells isolated from the spleen into different types of recipient mice. Given that the spleen contains a heterogeneous B cell population, the possibility exists that it includes not only proatherogenic B cell populations (as we have reported) but also anti-atherogenic
B cell populations. Indeed, we ourselves have found that transfer of 5 million unfractionated spleen C57BL/6 B cells (B220-positive selection, purity >95%) into lymphocyte-deficient triple knockout mice fed a high-fat diet for 8 wk failed to aggravate atherosclerosis at the aortic root, as assessed by lipid stain with oil red O (unfractionated B cell transfer: 0.02 ± 0.00 mm², n = 4; PBS control transfer: 0.02 ± 0.00 mm², n = 8). In contrast, as with conventional B2 cell transfer to triple knockout mice, we found that transfer of conventional B2 cells (purity >95%) into ApoE<sup>-/-</sup>, Rag-2<sup>-/-</sup> double knockout mice fed a high-fat diet for 8 wk also aggravated atherosclerosis, as assessed by lipid oil red O stain at the aortic root (conventional B2 cell transfer: 0.04 ± 0.01 mm², n = 4; PBS control transfer: 0.02 ± 0.00 mm², n = 8). Augmented atherosclerosis with this transfer tended to be greater than that seen with transfer to triple knockout mice, suggesting a possible contribution by proatherogenic NK cells. Lipinski et al. cited the paper by Caligiuri et al. (1) that reported B cell-mediated atheroprotection following transfer of 50 million unfractionated spleen B cells into splenectomized mice. It is possible that this outcome may have resulted from the action of anti-atherogenic B cells predominating over proatherogenic B cells in the mixed B cell population transferred. It is unlikely that the degree of reconstitution plays a role, given that we found significant proatherogenic effects with B2 cell reconstitution as low as 0.1–0.3% in the triple knockout lymphocyte-deficient mice. On the contrary, we argue that the data highlight the potency of the proatherogenic B2 population. Whether mixed genotypes may confound interpretation also seems unlikely, given that ApoE<sup>-/-</sup> mice are on a B6 background. It is possible that the divergent findings of Lipinski et al. are the result of feeding mice for 16 wk with a high-fat diet followed by en face analysis for lesions.

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