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Regulatory B Cells, Interleukin-10, and Atherosclerosis

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Activation of immune cells is increasingly credited as an important feature of atherosclerotic development. B lymphocytes play critical roles in the adaptive immune responses and their roles in mechanisms of atherosclerotic lesion formation have been studied extensively. This Bimonthly Update summarizes two recent publications [1**, 2**] that report conflicting results of B lymphocyte-specific interleukin (IL)-10 effects on atherosclerosis.

IL-10 is deemed to be an anti inflammatory cytokine [3–5]. Earlier studies by Mallat and colleagues demonstrated that secretion of IL-10 from regulatory T lymphocytes or macrophages reduced atherosclerotic development in both apolipoprotein E (*Apoe*)^{−/−} and low density lipoprotein receptor (*Ldlr*)^{−/−} mice [6–8]. Regulatory B lymphocytes also secrete IL-10. A recent study reported that reduced regulatory B lymphocytes in aortic tissues were accompanied by reductions of IL-10, and augmentation of atherosclerosis in *Apoe*^{−/−} mice [9]. On the basis of this premise, Strom et al. [1**] determined whether regulatory B lymphocytes would reduce atherosclerotic development in mice. B lymphocytes isolated from subiliac and para-aortic lymph nodes of mice were adoptively transferred into female *Apoe*^{−/−} mice fed a normal laboratory diet. Subsequently, left carotid artery injury was induced by placement of a perivascular collar. Adoptive transfer of lymph node-derived B lymphocytes led to a profound reduction of atherosclerotic development. Inhibition of IL-10 using a neutralizing antibody, or adoptive transfer of IL-10 deficient B lymphocytes, ablated the anti atherogenic effect of lymph node B lymphocytes. Further study demonstrated that CD21^{hi}CD23^{hi}CD24^{hi} regulatory B cells was attributed to this protective effects, which were also associated with increases of plasma IL-10 concentrations [1**]. Based on these data, it was concluded that regulatory B lymphocytes attenuate neointimal formation of atherosclerosis through an IL-10 mediated mechanism.

In contrast to the study of Strom et al. [1**], Sage and colleagues [2**] found that regulatory B lymphocyte-specific deficiency of IL-10 had no effects on the development of atherosclerosis. In this study, chimeric mice were generated using a conventional bone marrow transplantation approach [10]. Male *Ldlr*^{−/−} mice were irradiated and reconstituted with bone marrow-derived cells from μ MT mice (do not have mature B lymphocytes due to disruption of the membrane exon of the mu heavy chain gene) and IL-10 deficient mice to generate a chimeric system in which IL-10 deficiency was restricted to B lymphocytes as demonstrated previously [3]. Atherosclerotic lesions in both aortic root and aortic arch

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Conflicts of interest

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regions were assessed after 8 weeks of a saturated fat-enriched (21% wt/wt fat) diet feeding, which predominantly represented the early stage of atherosclerotic development. Despite marked reductions of IL-10 in regulatory B lymphocytes, the size and cellular contents of atherosclerotic lesions in either region was not different in mice repopulated with IL-10 deficient B lymphocytes compared to mice repopulated with IL-10 wild type B lymphocytes [2**].

There are several differences between these two studies, including: (1) different mouse strains (female *Apoe*^{-/-} mice fed a normal laboratory diet [1**] versus male *Ldlr*^{-/-} mice fed a saturated fat-enriched diet [2**]), (2) different mechanisms of atherosclerotic development (neointimal formation [1**] versus lesions with predominant presence of lipid-laden macrophages [2**]), and (3) different sources of regulatory B lymphocytes (lymph nodes-derived [1**] versus bone marrow-derived [2**]). Despite these many differences, their conflicting findings add another challenging layer to understand the complex mechanisms of regulatory B lymphocytes in the development of atherosclerosis. Of clinical relevance, it will also be interesting in determining how currently approved drugs (for example, rituximab and belimumab) for autoimmune diseases targeting on B lymphocytes markers contribute to atherosclerosis development [11].

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as

* of special interest

** of outstanding interest

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FURTHER RECOMMENDED READING

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