The B Cell
A Good Guy in Vascular Disease?
Göran K. Hansson

Inflammatory cells and molecules have largely been considered bad guys in the pathogenesis of atherosclerosis and other vascular diseases. This is particularly true for macrophages, T cells, and mast cells. In contrast, the role of B cells has remained unclear. Recent studies suggest that this cell type may inhibit the development of vascular pathology in models of atherosclerosis and restenosis. The Table summarizes some experiments addressing the effect on atherosclerosis of cells involved in adaptive immunity.

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The case for the monocyte-derived macrophage is particularly strong. It can oxidize lipoproteins, express scavenger receptors, and accumulate cholesteryl esters. It is also capable of producing tissue factor, and it is a major source of matrix metalloproteinases and proinflammatory cytokines. All of these factors and phenomena are considered proatherogenic. Direct support for the conclusion that macrophages promote atherosclerosis was obtained in studies of mice deficient in interferon-γ. This indicates that the immune system can mount protective as well as detrimental activities during the course of atherosclerosis.

Antigenic challenge in mice deficient in interferon-γ tumor necrosis factor-α and lymphotoxin. ApoE-/-/- mice, the offspring developed little, if any, atherosclerosis. This implies that monocyte differentiation into macrophages is a necessary step in the development of atherosclerosis.

T cells as well as B cells can respond to athero-antigens such as oxidized LDL and heat shock proteins. The predominant T cell subtype in atherosclerotic lesions, the CD4+ Th1 cell, responds to antigenic challenge by releasing proinflammatory cytokines including interferon-γ, tumor necrosis factor-α and lymphotoxin. ApoE-/-/- mice that lack adaptive immunity, ie, T and B cells, develop significantly less atherosclerosis than immunocompetent apoE-/-/- mice (Table 1). Reconstitution of such apoE-/-/-× SCID (severe combined immunodeficiency) mice with CD4+ T cells increases atherosclerosis dramatically. This indicates that the CD4+ T cell subset contains proatherogenic immunity.

Additional evidence suggests that such proatherogenic activity is exerted at least partly through secretion of the cytokine, interferon-γ. ApoE-/-/- mice that lack interferon-γ or its receptor develop significantly smaller lesions, implying a proatherogenic role for this cytokine. Interferon-γ has also been identified as a key promotor of transplant vascular sclerosis (transplant arteriosclerosis, chronic vascular rejection).

All these data point to a proatherogenic role for cell-mediated, inflammatory immunity that involves macrophages and T cells at its core. Paradoxically, activation of the immune system with the athero-antigen, oxidized LDL, reduces rather than aggravates the disease process. Such an effect was first demonstrated by Palinski et al using oxidized LDL (Ox-LDL) immunization of Watanabe LDL receptor-deficient rabbits. Protective effects of immunization with modified LDL has been demonstrated in several models including apoE and LDL receptor knockout (KO) mice and suggest that the immune system can mount protective as well as detrimental activities during the course of atherosclerosis.

Protective immunity seems to correlate with development of IgG antibodies to Ox-LDL, although this remains controversial. A role for antibodies in atheroprotective immunity was also suggested by a study showing that infusions of immunoglobulins (ivIg preparations) could reduce atherosclerosis in apoE KO mice.

A report in the March 15 issue of the Journal of Clinical Investigation has provided more direct evidence for an atheroprotective role of B cells. In it, Caligiuri et al demonstrate that transfer of B cells from atherosclerotic apoE KO mice to young, disease-prone apoE KO mice could protect the latter from developing advanced disease. Protection to a lesser extent was observed when B cells from young apoE-deficient donors were transferred, implying a role for development of adaptive immunity in the protective response. The reduction in atherosclerosis was paralleled by an increase in the titers of IgG-anti-Ox-LDL, but it remains to be formally demonstrated whether transfer of antibodies can actually protect recipients from disease. Alternatively, protection may depend on cell-cell interactions involving B cells.

In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Dimayuga et al present further evidence for a protective role of B cells in vascular disease. They have used a periadventitial cuff to induce intimal hyperplasia in the carotid artery of mice and assessed the role of adaptive immunity by comparing immunodeficient Rag-1 KO mice with immunocompetent C57BL/6×129/S controls. Interestingly, lesions were approximately 3- to 5-fold larger in the Rag-1 KO mice, which lack T and B cells. This is in line with previous studies that we have performed in T cell–deficient nude rats, which also exhibit enhanced lesion formation after mechanical injury. In the latter model, injection of the T cell cytokine interferon-γ reduced smooth muscle proliferation and lesion formation. Therefore, T cells may inhibit restenotic lesions. By inference, one would assume that T cells could

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destabilize atherosclerotic plaques by inhibiting the formation of smooth muscle caps.

In their study, Dimayuga et al\(^3\) attempted to protect the immunodeficient mice by infusing B cells from immunocompetent mice 48 hours before injury. This procedure had a remarkable effect on the lesions, which did not develop beyond the size of those in immunocompetent animals. In other words, B cell transfer reduced lesions \(\approx 3\)–4-fold. The protective effect could be demonstrated even under conditions when lesion formation was accelerated by a high-fat diet.

The mechanism by which B cells reduce neointimal formation remains unclear. The authors speculate that IgM antibodies might mediate the protective effect. A previous study from the same group showed a protective effect on neointimal hyperplasia by immunization with Ox-LDL\(^34\) and it could be speculated that antibodies to this antigen might inhibit neointimal formation. However, the mechanism by which such protection might operate is unknown. One can envisage how antibodies to Ox-LDL could protect against atherosclerosis by eliminating oxidized lipoprotein particles from the circulation or preventing their uptake by macrophages. In contrast, it is difficult to see how anti–Ox-LDL antibodies might prevent neointimal hyperplasia. Because the antigens are not known in this condition, it is unclear how antibodies could protect against neointimal post-injury hyperplasia. The alternative possibility should also be considered that B cells themselves can inhibit lesion formation either by cell-cell contact or by secreting a factor other than an immunoglobulin. It will obviously be important to test whether immunoglobulin preparations or specific antibodies can affect neointimal proliferation. Similarly, they should be tested in models of atherosclerosis to follow up the report of B cell protection in this disease.

Although several questions remain, the two articles by Caligiuri et al\(^2\) and Dimayuga et al\(^3\) put B cells in the limelight of vascular research for the first time. And after the identification of one bad guy after another, it is about time for a good guy to appear on the scene.

### References

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