Regulating Protective Immunity in Atherosclerosis

Jan Nilsson

Atherosclerosis is a disease characterized by chronic inflammation. Looking back it is almost embarrassing how long it took for us to realize that the presence of these innate immune responses also was associated with activation of adaptive immunity. The first hints of an involvement of adaptive immunity in atherosclerosis came from studies performed by Göran Hansson and his coworkers about 20 years ago demonstrating the presence of activated T cells and expression of class II molecules in atherosclerotic plaques. This finding provoked an intense interest in the role of immunity in atherosclerosis, and it is now generally recognized that adaptive immune responses have a key role in determining the balance between disease progression and regression. It also focused attention on the immune system as a target for prevention and treatment of cardiovascular disease. Mice with defective adaptive immunity, such as SCID and Rag-1, develop less atherosclerosis indicating that adaptive immune responses are primarily proatherogenic. Oxidized LDL has been identified as one of the most important autoantigens in atherosclerosis. A large fraction of the T cells present in atherosclerotic plaques are specific for oxidized LDL, and oxidized LDL IgG is prevalent in the circulation of both humans and atherosclerosis-prone animals. However, studies evaluating the role of immune responses against oxidized LDL by immunizing animals with in vitro oxidized LDL unexpectedly revealed a protective effect. Although it still remains to be established whether naturally occurring autoimmune responses against oxidized LDL also have atheroprotective effects, these observations suggest the fascinating possibility of developing an immunomodulatory therapy for atherosclerosis.

However, manipulating the immune system in complex diseases does not come without risk, and if the development of an immunomodulatory therapy for atherosclerosis is to become successful it will require detailed characterization of both disease-related and protective immune responses. The article by Zhou et al published in the present issue of Circulation Research provides important new information in this respect. Knowing that the protective effect of immunization with oxidized LDL is associated with expression of specific T cell–dependent IgG, they postulated that CD4+ T cells play a critical role in orchestrating both atherogenic and protective immune responses. CD 4 is expressed on a subset of T cells and facilitates binding of the T cell receptor to MHC class II molecules on antigen presenting cells (Figure). To test their hypothesis they immunized control apolipoprotein E knockout (apoE KO) and CD4-deficient apoE KO mice with MDA-modified LDL. Because the adjuvant they used (Freund) is known to have antiatherogenic properties in itself they included two control groups; one given adjuvant alone and one left completely untreated. Some of the results were well in line with expectations whereas others were more surprising. At 18 weeks of age the CD4-deficient apoE KO mice showed a 70% reduction in aortic sinus lesion size and a decreased plaque expression of the activation marker I-A<sup>d</sup> as compared with control apoE KO mice. This observation is in accordance with the above mentioned studies in SCID and Rag-1 mice and also with recent studies by Buono et al demonstrating that B7-1/B7-2 (costimulatory molecules expressed by antigen-presenting cells and required for T cell activation) deficiency reduces atherosclerosis in LDL receptor KO mice. It favors the notion that the atherosclerotic disease process involves a scavenger receptor–mediated uptake of modified lipoproteins and possibly other antigens leading to presentation of peptide antigens on MHC class II molecules. Recognition by antigen-specific CD4+ T cells results in expansion of INF-γ producing Th1 cells promoting inflammation and plaque development (Figure). The activation of this pathway appears to be promoted by a concurrent stimulation of Toll-like receptors as well as by a CD1-mediated presentation of lipid-antigens to NKT cells. However, it is likely that this model is too simplistic and that the role of CD4+ T cells in atherosclerosis is much more complex. In a recently published study by Elhage et al no difference was observed in aortic sinus lesion size between apoE KO mice and CD4/apoE double KO mice. The reason responsible for this difference remains unclear because both groups used the same strain of CD4 KO mice, similar diet, and studied the same time point. The latter study even observed a marked increase in development of atherosclerosis in the aorta of CD4-deficient mice both at 18 weeks and 1 year. Unfortunately, there is no information available regarding the effect of CD4 deficiency on aortic atherosclerosis in the mice studied by Zhou and coworkers.

In agreement with most previous studies Zhou and coworkers demonstrate a reduction in atherosclerosis in apoE KO mice treated with Freund adjuvant alone as compared with the untreated control. Interestingly, Freund adjuvant did not have this effect in the CD4-deficient apoE KO mice. This suggests that CD4+ T cells can be manipulated to activate also atheroprotective immune responses. Because the adjuvant in this case was given without coadministration of an antigen it is possible that it functioned by shifting the CD4+ T cell response against an atherosclerosis-relevant autoanti-
In the absence of CD4/H11001 mice as in the control apoE KO mice. It has been described that MDA-LDL was almost as strong in the CD4/apoE double KO mice not to turn out to be the case. A protective effect of MDA-LDL immunization was observed also in mice lacking CD4/H9253+/CD8/H11001 as alternative mediators of the protective effect of CD4/H11001 KO mice to a similar extent as active immunization.17,18 Modulation of immune responses represents an attractive novel possibility for prevention and treatment of cardiovascular disease. Our understanding of potential target mechanisms is rapidly increasing, and the present studies by Zhou and coworkers expand our understanding of the role of CD4–/CD8– T cells or by direct effects on B cells, and inhibition of disease. MDA-LDL immunization may act by a similar mechanism by activation of MHC class II–restricted CD4–/CD8– T cells or by direct effects on B cells or regulatory T cells (Treg).

As postulated by Zhou and coworkers it appeared logical to assume that the protective effect of immunizing with MDA-LDL is mediated by CD4+ T cells. Unexpectedly, this did not turn out to be the case. A protective effect of MDA-LDL immunization was observed also in mice lacking CD4+ T cells. Moreover, the IgG response to immunization with MDA-LDL was almost as strong in the CD4/apoE double KO mice as in the control apoE KO mice. It has been described that immunoglobulin class switching may occur also in the absence of CD4+ T cells. However, it should be kept in mind that the findings by Zhou and coworkers demonstrate that MDA-LDL immunization is effective in the absence of CD4+ cells, but do not exclude the involvement of other MHC class II–restricted T cells. Indeed, it has been shown that in CD4 KO mice several class II–restricted T cells emerge from the thymus as CD4 lineage cells that express neither CD4 nor CD8.15,16 These CD4–/CD8– double negative CD4 lineage T cells constitute 10% to 20% of the peripheral T cell pool and could potentially mediate the effect of immunization in a manner similar to that of CD4+ T cells. The authors also suggest γδT cells (T cells expressing a different type of T cell receptor and lacking both CD4 and CD8) as alternative mediators of the protective effect of MDA-LDL immunization. In this context it is interesting to note that absence of γδT cells did not influence the development of atherosclerosis in the studies by Elhage et al.11 Immunized CD4 deficient mice generated a strong IgG1 and IgG2a but no IgM response suggesting that the protective effect could be mediated by specific IgG. This is in accordance with recent studies demonstrating that treatment with recombinant IgG against MDA-modified peptide sequences in apoB-100 reduces plaque size and inflammatory activity in apoE KO mice to a similar extent as active immunization.17,18

Modulation of immune responses represents an attractive novel possibility for prevention and treatment of cardiovascular disease. Our understanding of potential target mechanisms is rapidly increasing, and the present studies by Zhou and coworkers expand our understanding of the role of CD4+ T cells in atherosclerosis and as possible mediators of protective immunity. They suggest that in the absence of CD4+ T cells the MHC class II restricted activation of T cells is impaired to such an extent that endogenous proatherogenic immune responses are significantly reduced. The atheroprotective effect of Freund adjuvant is similarly inhibited by CD4 deficiency clearly involving activation of CD4+ T cells in protective immunity possibly by switching the T cell response toward a less proinflammatory phenotype. In contrast, the protective effect of MDA-LDL immunization is independent of CD4. One possible explanation is that the response to immunization is sufficiently strong to overcome the impairment of MHC class II–dependent T cell activation caused by CD4 deficiency. Alternatively, immunization may act directly on B cells or regulatory T cells.


Key Words: T cells • adaptive immunity • lipoproteins • oxidation
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doi: 10.1161/01.RES.0000159183.88730.79

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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