Atherosclerosis bears many similarities to inflammatory/autoimmune diseases like rheumatoid arthritis and multiple sclerosis (MS). Compelling data from experimental models show that such diseases may be treated by vaccination. Will it be possible to attack atherosclerotic cardiovascular disease with the same approach? Several studies have shown positive effects of immunization with antigenic LDL preparations, and a report in this issue of *Circulation* demonstrates a protective effect of oral and nasal immunization with another antigen, heat shock protein 65 (HSP65).

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Atherosclerosis is a complex disease that involves several different cell types and their molecular products. The immune system is even more complicated, with many cell types, hundreds of cytokines, and literally millions of different antigens. The work has just begun to sort out the ones involved in atherosclerosis among this myriad of molecules and cells. Two gene-targeted murine models of atherosclerosis, the apolipoprotein E– knockout and the LDL-receptor knockout mice, have proved to be useful for these investigations.

Several lines of evidence point to the CD4+ T cell as a “bad guy” in atherogenesis. If these cells are transferred from immunocompetent to immune deficient apolipoprotein E– knockout mice, disease increases drastically. The CD4+ cell is also the most prevalent T cell in the human atherosclerotic lesion, and exhibits reactivity to putative “athero-antigens.”

CD4+ T cells can be divided into at least 2 different subsets that counterbalance each other. The most prevalent type of CD4+ T cells is called Th1; it induces macrophage activation and promotes inflammation. Th1 cells accomplish this largely by secreting interferon-γ, an important proinflammatory cytokine, which is produced in the human atherosclerotic lesion and accelerates atherosclerosis in mice. Countering this subset, the Th2 cell suppresses inflammation and dampens macrophage activity. Several different cytokines may be responsible for this effect, including interleukin-4, interleukin-10 (IL-10), and transforming growth factor-β.

Interestingly, Th2 activation can be induced by oral or nasal administration of antigens. In experimental autoimmune conditions, such as experimental autoimmune encephalomyelitis and collagen-induced arthritis, the administration of myelin and cartilage proteins, respectively, can be used to successfully prevent development of disease. A similar mucosal vaccination is presently being tested in the human counterparts, MS and rheumatoid arthritis.

The key to inhibiting inflammation by mucosal vaccination is obviously to use the right antigen. In atherosclerosis, 2 major autoantigens are implicated: oxidized LDL (oxLDL) and heat shock protein 60 (HSP60). Oxidative or enzymatic modification of LDL generates new molecular structures, neoepitopes, that can be recognized as foreign by immune cells. Surprisingly, parenteral immunization with oxLDL inhibits rather than aggravates disease. This pivotal observation was first made by Palinski and associates, and has since been confirmed in several laboratories. It points to immunization with disease-associated autoantigens (eg, vaccination) as a possible strategy for treating atherosclerosis.

HSP60 is a chaperone that acts to protect nascent proteins during their intracellular maturation. It is released from injured cells during inflammation and elicits autoimmune responses in conditions such as rheumatoid arthritis. Because heat shock proteins are conserved in evolution, human HSP60 is highly homologous to and cross-reacts immunologically with mycobacterial HSP65 and chlamydial HSP60. It has therefore been speculated that at least part of the immune responses to HSP60 are caused by microbial infections. Such cross-reactivity may in fact explain why certain infections are associated with increased atherosclerosis.

Pioneering studies by Wick and colleagues have demonstrated antibody responses and cell-mediated immune reactivity to HSP65/60 in human and experimental atherosclerosis. In contrast to oxLDL, parenteral immunization with HSP65 aggravates atherosclerosis, and the transfer of HSP65-reactive cells also accelerates disease in hypercholesterolemic animal models. These effects might be explained by immune complex formation and induction of a Th1-biased immune response to the HSP60 autoantigen. However, the situation is more complex, both because immune reactions may be directed toward HSP65/60-expressing microbes in the artery wall and also because HSP60 can activate macrophages and promote inflammation even in the absence of adaptive immunity.

Maron et al have hypothesized that immune deviation of HSP65/60 reactivity toward a Th2 response may dampen atherosclerosis. In the present issue of *Circulation*, they...
report that mucosal vaccination with mycobacterial HSP65 decreases atherosclerosis in LDL receptor–deficient mice. Not only did administration of this preparation through the nasal mucosa reduce plaque size, but it also lowered the number of macrophages, CD4+ T cells, and the extent of interferon-γ staining in the plaques. In parallel, local and systemic production of IL-10 were increased by this treatment, and the authors concluded that mucosal treatment with HSP65 induces adaptive immune cells to produce antiinflammatory IL-10, migrate to the vessel wall, and inhibit plaque inflammation and thus the progression of atherosclerosis.

This concept fits with a Th1→Th2 deviation of the athero-immune response. Such an interpretation is also supported by the observation that nasal administration of HSP65 induced more IL-10, higher titers of Th2-dependent antibodies, and better protection against atherosclerosis than oral HSP65 treatment. At the same time, spleen T-cell proliferation in response to HSP65 was significantly reduced by nasal (or oral) HSP65 administration; proliferative responses are considered to be dominated by Th1 cells. Surprisingly, it was not possible to demonstrate any HSP65-specific IL-10 response in spleen cells of mice treated with HSP65 nasally. However, the bulk of data support the conclusion that nasal administration of HSP65 protects against atherosclerosis by inducing a Th2 deviation with concomitant production of antiinflammatory IL-10 in the vessel wall.

Is this protection due to modulation of an autoimmune response? This is not necessarily the case because the HSP65/60 family is well preserved throughout evolution and is the target for cross-reactions between microbial immunity and autoimmunity. One could theoretically argue that protection was caused by a neutralizing immune response against an HSP-producing, proatherosclerotic microbe in the LDL receptor–knockout mouse colony. The only way to formally rule out this possibility would be to repeat the experiment under completely germ-free conditions. However, there is very little difference in the extent of atherosclerosis between hypercholesterolemic mice kept under germ-free or dirty conditions. This suggests that atherosclerosis in such mice is not driven by microbes but by the metabolic condition. It would therefore be very surprising if the protection conferred by nasal HSP65 administration were a result of the neutralization of a microbe.

Another surprising aspect of HSP65/60 vaccination is that it seems to protect against several different immune/inflammatory diseases. A similar approach to the one used by Maron et al was recently shown to protect rats against experimental arthritis. Is HSP65 a magic potion against all kinds of diseases? Or is protection a laboratory artifact? The most likely explanation is that HSP60 autoimmunity is induced in many different inflammatory diseases and that modulation of the response therefore reduces the activity of several of them.

The authors conclude that their approach offers the potential for an antigen-specific therapy against atherosclerosis. This would be highly desirable because generalized immunomodulation achieved with immunosuppressive drugs can cause side effects that would be unacceptable in the treatment of atherosclerotic cardiovascular disease. For instance, general inhibition of proinflammatory immunity could increase the susceptibility to intracellular pathogens such as M tuberculosis and L monocytogenes. Such side effects might be acceptable in the treatment of lethal tumors or the prevention of rejection of organ grafts but will hardly be tolerated if the goal is to prevent myocardial infarction in a fraction of the treated individuals. In contrast, antigen-specific therapy—and prophylaxis—is narrowly targeted toward the pathogenic immune response and does not affect the resistance of the host against other pathogens or autoantigens.

For these reasons, antigen-specific immunomodulating therapy already tested in conditions that are more traditionally considered to be autoimmune. Mucosal administration of autoantigens has been tested in patients with diabetes, multiple sclerosis, and rheumatoid arthritis. Unfortunately, the experience is not entirely positive. For instance, attempts to treat MS by immunization with myelin proteins or peptides derived thereof have failed to produce any convincing improvement of the disease.19 Atherosclerosis may be even more difficult to treat by vaccination than other inflammatory/autoimmune diseases. Whereas insulin-dependent diabetes, MS, and rheumatoid arthritis each affect a few percent or less of the population, atherosclerosis affects the majority of individuals and will cause clinically manifest disease in ≥50% of them. Autoimmune reactions in such a large fraction of the population are likely to involve many different antigens. It may be quite some time before these questions have been sorted out and vaccination trials for atherosclerosis can begin.

These questions should not overshadow the fact that we now have encouraging results, in experimental models, of vaccination against atherosclerosis. Immunization with 2 different autoantigens, oxLDL and now also HSP65/60, can protect susceptible mice against advanced disease. These findings should encourage experimentalists and the biotechnological industry to pursue the vaccination approach vigorously; they should also stimulate epidemiologists to determine whether atherosclerosis is associated with HLA and other immune genes. Given the potential of an atherosclerosis vaccine, it will be important to embark on such studies sooner rather than later.

References


Key Words: Editorials • atherosclerosis • antigens • immunology
Vaccination Against Atherosclerosis: Science or Fiction?
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Circulation. 2002;106:1599-1601
doi: 10.1161/01.CIR.0000035275.64667.A3
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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