Vaccines for atherosclerosis - A brief review

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Abstract:
The treatment of atherosclerosis is currently based on lipid lowering drugs that retard the progression of atherosclerosis. Innate and adaptive immunity of individual play a definite role in atherogenic process. Immune-modulation therapy is an emerging treatment modality for cardiovascular atherosclerosis. Atherosclerosis vaccines are based on targeting of lipid antigens, inflammation-derived antigens, and cell-based vaccination strategies.

Key words:
Atherosclerosis, vaccine immunity, heat shock proteins

Introduction
Atherosclerotic plaques contain components of both innate and adaptive immunity. They are dendritic cells (DCs), B and T lymphocytes, macrophages, Toll-like receptors (TLRs), immunoglobulin, cytokines and complements. The role of inflammation in atherosclerotic process is well established. This has focused attention on the immune system as a novel target in prevention and treatment of atherosclerotic cardiovascular disease.

Innate immunity produces rapid inflammatory and toxic response to invading microorganisms. Pattern recognition receptors on macrophages and dendritic cells detect pathogen associated molecular patterns and bind to a wide range of proteins, carbohydrates, lipids, and nucleic acids. The two most important receptors are scavenger receptors (SRs) and the Toll-like receptors (TLRs). Adaptive immunity is more specific and may take few days to become fully active. It leads to generation of a large number of T and B cell receptors and immunoglobulins, which can recognize foreign antigens.

Several antigens have been identified in the initiation of atherosclerotic immune responses including exogenous pathogens, such as Chlamydia pneumoniae, cytomegalovirus, endogenous proteins like heat shock proteins and b2-glycoprotein-Ib. Oxidized low-density lipoprotein (oxLDL) is the most important endogenous antigen. Lipoproteins in the arterial intima undergo oxidation, which are engulfed by macrophages and lead to foam cell formation. Oxidation of LDL results in structural changes in apoB-100 and leads to the generation of neo-epitopes, which renders the modified LDL immunogenic and leads to both a cellular and humoral response. A number of studies in animal models revealed that immunization against oxLDL reduces atherosclerosis. Various other immunogens used are malondialdehyde (MDA)-low-density lipoprotein, apolipoprotein B-100 peptides, phosphorylcholine head group on oxidized phospholipid cholesteryl ester transfer protein (CETP).

Dendritic cells (DCs) are the most potent antigen-presenting cells. Oxidized LDL induces several changes for DC maturation, including a higher expression of co-stimulatory molecule and the increased ability to stimulate T cells. Due to their potent capacity to stimulate T cells, DCs are being investigated in vaccine and therapy approaches. Vaccination against atherosclerosis- mainly 3 strategies

1. Lipid-based vaccination strategies
   a. Cholesteryl ester transfer protein
   b. Vaccination against oxidized LDL
   c. ApoB100 p210 peptide vaccination

2. Inflammation-based vaccination strategies
   a. Heat shock proteins
   b. Cytokines/growth factors
   c. Endothelial cells
   d. Metabolic factors

3. Dendritic cell-based vaccination strategies
Lipid-based vaccination strategies:

1. **Cholesteryl ester transfer protein:**
   Modulation of cholesteryl ester transfer protein (CETP) activity raises HDL levels. CETP vaccination in rabbits\(^\text{[19]}\) resulted in inhibition of atherosclerotic lesion formation, associated with increased CETP antibodies, decreased CETP activity and modified lipoprotein profiles. Intramuscular DNA vaccination targeting CETP has been shown to be effective in atherosclerosis.\(^{20}\)

2. **Vaccination against oxidized LDL:**
   Oxidative modification of LDL transforms the lipoprotein into an immunogenic form. Antibodies directed against ox-LDL are able to bind to ox-LDL in atherosclerotic lesions. Immunization with native LDL significantly inhibits atherosclerotic lesion formation.\(^{21,22}\)

3. **ApoB100 p210 peptide vaccination:**
   Immunization with ApoB100 peptide sequences p143 and p210 inhibited atherosclerotic lesion in the descending aorta of cholesterol-fed ApoE deficient mice.\(^{23}\)

Inflammation-based vaccination strategies:

1. **Heat shock proteins:**
   Heat shock proteins (HSP) mediated autoimmunity is important in atherosclerosis. HSP are regulated in endothelial cells and macrophages. The protective effect of oral HSP60 administration is due to enhanced regulatory T cell expansion and function, rather than the induction of HSP-specific antibodies.\(^{24-26}\)

2. **Endothelial cells:**
   DNA vaccination targeting vascular endothelial growth factor receptor-2 (VEGFR-2) produces anti-angiogenic effects and inhibits both initiation and progression of carotid artery atherosclerotic lesions. DNA vaccination against endothelial cell markers, CD99 and TIE2, inhibited atherosclerotic lesion formation both in the carotid arteries and the aortic root, which was mainly due to cell-specific lysis.\(^{27-28}\)

3. **Dendritic cell-based vaccination strategies:**
   DCs pulsed with the antigen elicit a specific humoral immune response. Ox-LDL pulsed dendritic cells are used as an immunotherapy for atherosclerosis. Vaccination with intravenous ox-LDL pulsed DCs attenuate atherosclerotic lesion formation in carotid artery atherosclerosis.\(^{29}\)

Conclusion

Immune modulatory responses to atherogenesis by active or passive immunization is a novel approach to the prevention of atherosclerotic cardiovascular disease. Different types of antigens have been shown to have great potential to be incorporated into vaccine formulations to reduce atherosclerosis. Selection of a specific antigen target is the most important difficulty in developing vaccination strategies for atherosclerosis. Vaccination strategies are based on targeting of lipid or inflammation-derived antigens, as well as cell-based vaccination approaches.

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Overview of different vaccination strategies

<table>
<thead>
<tr>
<th>Circulation</th>
<th>Atherosclerosis</th>
<th>Lymphoid Organs</th>
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<tbody>
<tr>
<td>CETP</td>
<td>EC cell</td>
<td>DC cell</td>
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<tr>
<td>LDL ox LDL</td>
<td>ox LDL MDA-LDL</td>
<td>IL-12</td>
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<tr>
<td>Apo-B100</td>
<td>MDA-LDL Apo-B100</td>
<td>Th1 cell HSP</td>
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<td>IL-12</td>
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Vaccination strategies: three main location sites for targeting: the circulation (lipid antigens), the atherosclerotic lesion (lipid and inflammatory antigens) and lymphoid organs (inflammatory antigens).

References:

13. Chyu KY, Zhao X, Reyes OS, et al.: Immunization using an Apo B-100 related epitope reduces atherosclerosis and...


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