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Vaccination for heart attack: promise for the future?

- **European Consortium aims to develop a vaccine for atherosclerosis**

'It is highly likely that targeting the immune response may lead to an additional therapy for atherosclerosis' – Professor Johan Kuiper, Professor of Therapeutic Immunomodulation, Leiden University, The Netherlands

Atherosclerosis is a multifactorial, chronic inflammatory condition evolving over several decades and culminating in clinical events such as heart attack. The disease process is initiated by both lipid accumulation and inflammatory responses.

Currently, treatment of atherosclerosis focused on targeting modifiable risk factors, including elevated low-density lipoprotein (LDL) cholesterol – the primary lipid target - high blood pressure and high blood glucose. Statins represent the cornerstone of LDL-lowering therapy to reduce cardiovascular risk,¹ and also have other important effects which may be relevant to maintaining the stability of the atherosclerotic plaque, and preventing thrombus formation.² Despite the availability of effective therapies, however, cardiovascular disease remains the leading cause death in Europe and other highly developed regions.

Would targeting inflammation offer further benefit?

On-going studies are evaluating the potential of anti-inflammatory therapy as a treatment for atherosclerosis. For example, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) is evaluating canakinumab, an antibody that inhibits the endogenous pro-inflammatory protein interleukin-1-beta (IL-1 β) in patients with stable coronary artery disease.³ A second trial, the Cardiovascular Inflammation Reduction Trial (CIRT) is evaluating the use of low-dose methotrexate on top of the current standard of care (including high-dose statin therapy) in patients who been stabilised after a heart attack.⁴

An alternative approach, however, might be to prevent atherosclerosis by vaccination. Indeed, vaccination is already accepted as an effective strategy in other diseases where the body is challenged by a protein or micro-organism leading to a highly specific humoral immune-response. However, this is somewhat more complicated for atherosclerosis as it is a multifactorial disease.

Potential targets?

One of the difficulties in developing effective vaccination strategies for atherosclerosis is the selection of a specific antigen to target. So far vaccination strategies have been based on targeting of lipid or inflammation-derived antigens, as well as cell-based vaccination approaches. Studies showing protective effects associated with vaccination with oxidised LDL, have led to antibody approaches targeting apolipoprotein B100, the main protein component of LDL.⁵

Recent insights into the responses of immune cells that lead to atherosclerotic plaque formation suggest alternative approaches. Retention and accumulation of cholesterol-containing lipoproteins, in particular LDL, in the artery wall is a key step driving the development of atherosclerosis.

Modification of lipoproteins and the subsequent activation of endothelial cells results in an increased expression of inflammatory mediators such as chemokines (small proteins that stimulate recruitment of leucocytes), and adhesion molecules, leading to the attraction of monocytes and their subsequent entry into the arterial vessel wall. The monocytes ingest the modified lipoproteins and differentiate into foam cells. These foam cells produce chemokines and cytokines that enhance the recruitment of more monocytes and also T cells (a type of leucocyte or white blood cell), thereby aggravating atherosclerosis.

T cells play a key role in the initiation and progression of atherosclerosis. Most T effector cell responses are thought to aggravate atherosclerosis, via their effect on released mediators, which modulate inflammation and systemic lipid metabolism. However, recent studies have identified another category, regulatory T cells (Tregs), which have been shown to dampen inflammatory responses in several autoimmune diseases.^{6,7} Based on these findings, a number of prototype vaccines active against inflammatory proteins that play a role in cardiovascular disease have been investigated in mice. These studies showed a reduction in atherosclerosis, which was mediated via induction of the Treg response.^{8,9} Furthermore, the use of an oral tolerance induction approach on these studies offers advantages, by obviating the need for adjuvants or immune-modulatory components, and is also less costly than antibody strategies.

'A vaccine offers a way to change the immune response in patients with cardiovascular disease. Studies have shown that we can change the immune response in an experimental mouse model by changing the way T cells react during atherosclerosis. By enhancing the Treg response you can diminish atherosclerosis. Therefore, Tregs may hold promise for the future development of a vaccine for atherosclerosis. ' – Professor Kuiper

The next step is to translate such findings to the clinical setting. Funded by a grant from the European Union, Professor Kuiper is working with a European funded Consortium, called VIA (vaccination in Atherosclerosis) involving 8 University hospitals and 5 companies to develop a vaccine for atherosclerosis. Preclinical studies are nearing completion, with the first in man studies, anticipated in the next 2-5 years.

For further information: <http://www.research.leiden.edu/news/developing-a-vaccine-against-arteriosclerosis.html>

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