EDITORIAL

Potential for an Atherosclerosis Vaccine

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English physician Edward Jenner two hundred years ago made a remarkable discovery. He created vaccine. Today immunization can be credited for saving approximately 9 million lives a year all around the world, bringing seven major human diseases under control to some extent, i.e., smallpox, diphtheria, tetanus, yellow fever, whooping cough, polio, and measles. So far only smallpox has been completely eradicated, saving approximately 5 million lives annually. A further 16 million deaths a year can be prevented if effective vaccines against rest of them are deployed efficiently. Another 17 million can be saved if Atherosclerosis can be vaccinized.

Today cardiovascular disease is the major cause of mortality. More than 17 million men and women die from acute myocardial infarction (acute MI or Heart attack) each year, worldwide and this figure will raise to nearly 289 million people by the year 2020. Secondly, heart attack is crushing the national economies by overwhelming health care expenditure; it is a battle we are losing fast. WHO estimates that the medical and human costs of heart attack have already reversed social and economic development in many developing countries. Only a vaccine can end the ischemic heart disease pandemic.

Researchers have been working for more than a decade to find a vaccine for atherosclerosis, the main cause of ischemic heart disease including acute MI. This disease process has been found to be governed by immune-mediated inflammatory mechanisms.[1] Atherosclerosis, an arterial chronic inflammatory disease, leads to myocardial infarction (MI), heart failure, stroke and claudication. Ever since, there are advances in molecular biology and vaccine innovations for other diseases, vaccine for atherosclerosis has become a promising pursuit. In this regard the name of Dr. Göran K Hansson truly stands out as a pioneer in this field. His contributions from experimental atherosclerosis to its physiological relevance and potential clinical applications have greatly enhanced the knowledge toward the development of vaccine for atherosclerosis.[2]

Currently, the treatment is based on lipid lowering drugs in combination with anti-inflammatory therapies to slow down the progression of atherosclerosis, which is not fully successful with an efficacy of 30% to 40% only. A number of different strategies focusing recent advances in atherosclerosis immunotherapy are being investigated and explored to protect people against atherosclerosis or to treat patients with clinical symptoms. Advances in molecular biology and vaccine discoveries for other diseases have made this pursuit a reachable goal. The ultimate achievement of the eradication of heart attack therapy is only in the development of a vaccine.

Atherothrombosis appears to be the major mechanism behind atherosclerosis occurring through the activation of immunological system, proinflammatory LDL receptor cytokines and chemokines. These are the components of cholesterol-carrying low-density lipoprotein which trigger inflammation, T cell activation and antibody production during the course of disease. Several vaccination strategies have been developed targeting this mechanism. Hanson and coworkers[3] in 2010 published their research on vaccination strategy that target LDL receptor, the point where T cells react to oxidize LDL. This vaccine against LDL receptor can inhibit the immune reaction and reduce the disease by between 60 to 70 per

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cent in animal model. The researchers are quite hopeful about the future prospects of this vaccine in treating patients with a high risk of myocardial infarction and stroke. Despite the vast amount of experiments, showing protective effects of oxidized LDL vaccination on atherosclerosis, the underlying mechanisms remain obscure.

Another approach is through aiming at cellular and humoral immune response elements. Zhou in 2001 showed that immunizing apolipoprotein E (ApoE)-deficient mice with MDA-LDL or atherosclerotic plaque homogenates (in CFA) results in decreased lesion formation.[4] After various clinical studies, it was found that immunization of apoprotein E- (ApoE-) deficient mice with MDA-modified fibronectin resulted in a 70% decrease in plaque area. Immunization also resulted in conversion of a weak naturally occurring Th1 antibody response against MDA-fibronectin into a Th2 and reduction in plasma fibronectin levels[5] Activation of B-cell was another area which was being explored which in principle should provide protection against atherosclerosis Ait-Oufella and coworkers[6] presented contrary findings that instead of increase in B-Cell, depletion of mature B-cell induces a significant reduction of atherosclerosis in various mouse models. Looking at the role of GAG on atherogenesis, Soto[7] and his colleagues worked on a chimeric monoclonal antibody that binds sulfated molecules, such as PG-contained GAG. The antibodies recognize proatherogenic GAG that interfere with LDL retention and which are also capable of inducing autologous antibodies with similar properties in the immunized animals, acting as idiotypic vaccines. Further, research is awaited on antibodies against oxidized forms of cardiolipin, aOxCL and also antibodies against oxidized phosphatidylserine (aOxPS) which have been found to be negatively associated with atherosclerosis development.[8]

After exploring vaccination for many aspects of lipid metabolism over the past years the interest has turned to an indirect approach. Taking advantage of "Human Microbiome Project (HMP)" the atherosclerosis/CVD has been explored in connection to the intestinal bacterial flora.[9] (HMP)" was launched in 2008 by the National Institutes of Health, USA with the mission of comprehensive characterization of the human microbiota and its role in human health and disease.[10] The AA-derived molecules produced by intestinal bacteria affect host health by regulating either host immunity and cell function or microbial composition and metabolism. Emerging evidence shows Intestinal microbiota metabolism of choline and phosphatidylcholine produces trimethylamine (TMA), which is metabolized to proatherogenic trimethylamine-N-oxide (TMAO). Recently, it was demonstrated that metabolism by intestinal microbiota of dietary lcarnitine in red meat produces TMAO and accelerates atherosclerosis in mice. This finding suggests another interesting link between gut flora and atherosclerosis.[11]

In the near future, it is anticipated that DNA and protein state of art vaccines will be developed for atherosclerosis, thoroughly tried and tested on animal models causing blockade of the molecule such as proatherosclerotic cytokines. Discussed here were a few of the many studies suggesting different ways of vaccination that could become potential mode of preventing atherosclerosis. These ongoing researches all around the world strongly suggest that the myth of atherosclerosis vaccine will soon become a reality.

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