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Introduction

The changing face of atherosclerotic plaque inflammation

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In August 2014 the Journal of Internal Medicine organized a symposium to discuss vascular inflammation as a pathogenic mechanism underlying the development of acute ischemic cardiovascular events. This concept has gained considerable support from experimental studies over the last two decades but the question whether these processes represent possible targets for clinical intervention remains to be finally resolved. Analyses from large genome-wide association studies consortia has identified three major networks associated with coronary artery disease; lipid metabolism, inflammation and repair, and immune cell trafficking (reference Ohro-Melander). These observations were well in line with the idea that atherosclerosis is the result of inflammatory and immune responses to lipoprotein lipids accumulated in the arterial wall. Additional support has come from epidemiological studies of associations between HLA-type, lipoprotein autoantibodies, inflammatory biomarkers, immune cell subsets and cardiovascular disease (CVD), but results has not been as clear and straightforward as in the experimental studies [1]. Moreover, the first large randomized clinical trials directly targeting plaque inflammation by inhibition of lipoprotein-associated phospholipase A2 had failed to reduce the incidence of cardiovascular events [2, 3].

Accordingly, although there is persuasive evidence that plaque inflammation plays a key role in the development of acute cardiovascular events it remains to be revealed how this knowledge can be used to improve patient risk prediction and treatment.

The review articles in this volume cover some of the controversies regarding the role of plaque inflammation in CVD today. Over the last couple of decades there has been growing support for the concept that inflammation-induced plaque vulnerability is the major cause of acute cardiovascular events [4-6]. According to this hypothesis accumulation of lipoprotein-derived lipids cause cell death and inflammation in atherosclerotic lesion. Matrix metalloproteinases released from activated macrophages will degrade the extracellular matrix and since many of the smooth muscle cells in the plaque have died this tissue will not be replaced. As a consequence the plaque fibrous cap will become degraded increasing the risk for plaque rupture to occur. The process is further aggravated by a loss of immunological tolerance against modified lipoproteins resulting in activation of a detrimental attack of Th1 cells on the plaque. However, it is now becoming increasingly clear that the processes responsible for development of acute cardiovascular events are much more complex than so. General anti-inflammatory therapy, such as the non-steroidal anti-inflammatory drugs, tends to increase cardiovascular risk, general matrix metalloproteinase inhibitors have shown little or no effect in experimental models of atherosclerosis and an increasing number of acute cardiovascular events are linked to thrombotic occlusion on top of plaques with an intact fibrous cap, so called endothelial erosions. In addition, there is evidence from examination of atherosclerotic plaques harvested during endarterectomy that there has been a change towards a more stable plaque structure over the last decade possibly as a result of improved risk factor management [7]. Other studies performed on endarterectomy specimens have indicated that the increased atherosclerotic plaque vulnerability in subjects with diabetes today is associated with impaired fibrous repair rather than by an increased plaque inflammation [8]. Again, this

may be the result of improved risk factor management and in particular of reduced plaque inflammation in response to statin treatment. The increased interest of the role of fibrous repair in atherosclerosis is interesting from an historical perspective since this was the core of the original “response to injury” hypothesis of atherosclerosis put forward by Russell Ross and John Glomset in their landmark paper in *New England Journal of Medicine* in 1976 [9]. While Ross and Glomset described the pathogenic role of exuberated tissue repair responses in development of early atherosclerotic lesions of fibromuscular phenotype we now know that the similar repair responses are of critical importance for maintaining the integrity of more advanced plaques [10]. Consequently, there is today a growing interest in the biology of the plaque extracellular matrix. It has become clear that this role is much more complex than originally anticipated and that atherosclerosis research may benefit from a closer interaction with scientists involved in matrix biology. In this volume of the journal Hultgårdh-Nilsson et al (reference Hultgårdh-Nilsson et al) have reviewed the role of small leucine-rich repeat proteoglycans in atherosclerosis and discuss recent evidence that these matrix proteins are of importance not only in maintaining collagen integrity but that they also are involved in regulation of inflammation and repair responses. Another concept that has received increasing attention during recent years is that it may not be the activation of plaque inflammation that is the major problem in atherosclerosis but rather the lack of proper resolution of the inflammatory process. This issue is being addressed by several of the review articles in this volume. It has been found that lipoxygenase metabolism of polyunsaturated fatty acids can give rise not only to pro-inflammatory lipid mediators but also to potent anti-inflammatory mediators such as the lipoxins and the resolvins (reference Bäck et al). Both act through the FPR2/ALX receptor and the observation that LDL receptor-deficient mice lacking this receptor have increased atherosclerosis suggest that it represents an interesting novel target for intervention. Defective efferocytosis (phagocytic clearance of apoptotic cells) is another

cardinal sign of impaired inflammation resolution (reference Hansson et al). It is widely recognized that delayed clearance of apoptotic cells leads to secondary necrosis triggering inflammation and autoimmunity. Moreover, several lines of evidence have implicated cleavage and shedding of the macrophage efferocytosis receptor MerTK as a key factor in reduced resolution of plaque inflammation and expansion of the necrotic core. The potential role of a defective clearance of apoptotic cells in aggravation of atherosclerosis also represent an interesting common feature with systemic lupus erythematosus (SLE), an autoimmune disorder associated with an up to 50-fold increased risk of cardiovascular events (reference Wigren et al). The mechanisms responsible for development of autoimmunity in SLE remains to be fully clarified and most likely involve multiple factors but defective efferocytosis is considered as one of the most important causes. It is likely that a closer collaboration between scientists involved in SLE and cardiovascular research would not only help to elucidate the mechanisms responsible for cardiovascular complications in SLE but also to gain a better understanding of the role of autoimmune responses in atherosclerosis.

The identification of the important role of adaptive immune responses against plaques antigens in atherosclerosis along with the realization that these may both aggravate and counteract the disease process has paved the way for development of entirely new types of cardiovascular interventions. These involve vaccines to induce tolerance against heat shock proteins and LDL antigens as well as specific antibodies to interfere with different components of cellular immunity or to facilitate an anti-inflammatory removal of oxidized LDL particles (reference Nilsson et al). Most of these therapies are still at the experimental stage but can, if translational hurdles are overcome, offer entirely new opportunities for prevention of CVD that are likely to work on top of current intervention strategies. A critical factor in the success of this work is the development of better plaque imaging techniques that

can be used to monitor the response to intervention in early clinical studies. Fortunately, this is an area that has made impressive progress over the last decade (reference Goncalves et al).

Conflict of interest statements

Jan Nilsson and Göran Hansson are signed as co-inventors on patents describing immune-modulatory therapy for atherosclerosis.

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