Innate Immunity in Human Atherosclerosis and Myocardial Infarction: Role of CARD8 and NLRP3

av

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Akademisk avhandling

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Abstract

Atherosclerosis is complex inflammatory disease of the arterial wall with progressive accumulation of lipids and narrowing of the vessel. Increasing evidence suggest that inflammation plays an important role in plaque stability and often accelerate cardiovascular events such as myocardial infarction (MI). Among the vast number of inflammatory cytokines, IL-1β is known to be a key modulator in vessel wall inflammation and acceleration of the atherosclerotic process. The biologically active IL-1β is regulated by a multiprotein complex known as the NLRP3 inflammasome complex. In this thesis, we have focused on polymorphisms in the NLRP3 and CARD8 genes and their possible association to atherosclerosis and/or MI. We have also investigated the expression of inflammasome components NLRP3 and CARD8 in atherosclerosis and the role of genetic variants for the expression of these genes. The expression of NLRP3, CARD8, ASC, caspase-1, IL-1β, and IL-18 were found significantly upregulated in atherosclerotic lesions compared to normal arteries. Human carotid plaques not only express the NLRP3 inflammasome, but also release IL-1β upon exposure to lipopolysaccharide (LPS), adenosine triphosphate (ATP) and cholesterol crystals, which suggest NLRP3 inflammasome activation in human atherosclerotic lesions. Also, CARD8 was found to be important in the regulation of several inflammatory markers in endothelial cells, like RANTES, IP10 and ICAM-1. We further assessed the potential association of a CARD8 polymorphism and polymorphisms located downstream of the NLRP3 gene to the risk of MI in two independent Swedish cohorts. The CARD8 variant exhibited no association to risk of MI in either of the two cohorts. Some of the minor alleles of NLRP3 variants were associated with increased IL-1β levels and to NLRP3 mRNA levels in peripheral blood monocytic cells (PBMC). Taken together, the present thesis shows that NLRP3 inflammasome activation and increased expression of CARD8 in the atherosclerotic plaque might be possible contributors to the enhanced inflammatory response and leukocyte infiltration in the pathophysiology of atherosclerosis.

Keywords: Atherosclerosis, Inflammasome, NLRP3, CARD8, Myocardial infarction, Endothelial cells, Polymorphism, IL-1β, Cytokines, Innate immunity.

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