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IL-1, quo vadis ?

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Commentary

The build up of lipids and immune cells in the subintimal space of arteries is termed atherosclerosis. This slow, but progressive process occurs in the majority of humans. Atherosclerosis remains undetected until changes in the atherosclerotic vessel cause decreased blood flow, or result in luminal thrombotic occlusion.

It is generally accepted that elevated blood cholesterol levels play a causative role in the pathogenesis of atherosclerosis. Why the excessive lipid deposition in atherosclerotic lesions is accompanied by an elaborate inflammatory response however, is far less understood. A myriad of cytokines, chemokines and other factors have been shown to influence the inflammatory reaction towards the buildup of lipids and some of these factors can modulate the ensuing architectural changes of the arteries[1].

Interleukin (IL)-1 cytokines play a pivotal role in triggering vessel wall inflammation. The biological activity of IL-1 cytokines is controlled by a naturally occurring IL-1 receptor antagonist (IL-1ra). IL-1ra binds to the IL-1 receptor (IL-1R) but does not induce its activation. IL-1ra counterbalances the proinflammatory activity of IL-1 cytokines by competing with IL-1α and IL-1β for binding to the IL-1R. Genetic studies have highlighted the importance of a finely tuned IL-1R activation for the arterial vascular system. The absence of IL-1ra leads to a prolific, and ultimately, a lethal arterial inflammation which is most pronounced in areas of high blood flow turbulences[2]. This suggests that physical stress, such as shear stress, leads to the induction of an IL-1 response in the vessel wall, which is normally counterbalanced by IL-1ra. Of note, the same areas that show persistent and damaging inflammation in the IL-1ra deficient mice are the predilection sites for the development of cholesterol-induced inflammation in atherosclerosis. Recent work sheds light on yet another inducer of IL-1 in the vessel wall, namely the inflammasome.

The activity of IL-1 activity is regulated not only at the level of its receptor. IL-1β cytokines lack signal peptides and are expressed as inactive zymogens in the cytosol of cells. Unlike most other cytokines, IL-1β as well as the IL-1β cytokine family member IL-18, require cleavage by caspase-1 to become biologically active[3]. In addition, activated caspase-1 promotes IL-1β family cytokines as well as IL-1α secretion from cells[4]. The activity of caspase-1 itself is controlled by several inflammasomes, which sense microbial products or danger signals including crystalline and aggregated materials[5]. Crystalline cholesterol in atherosclerotic lesions activate the NLRP3 inflammasome and promote IL-1 mediated inflammation. This mechanism could link elevated blood cholesterol levels to the observed inflammatory response in atherosclerotic lesions[6].

The pro-atherogenic effects of IL-1 cytokines are well established in mouse models of diet-induced atherosclerosis. Both IL-1α and IL-1β promote inflammatory responses to Western

diets in murine models of atherosclerosis, and deficiency in IL-1ra leads to enhanced disease[7]. However, until now, it was unclear which cells in the vessel wall are targeted by IL-1 cytokines. The report by Shemesh and colleagues provides novel insight into local IL-1 activity[8]. The authors utilized the well-characterized bone marrow transplantation model of atherosclerosis to answer the question of whether myeloid or resident vessel cells respond to the locally produced IL-1 in murine atherosclerosis. ApoE KO mice reconstituted with apoE/IL-1R dKO bone marrow showed equivalent levels of Western diet-induced atherosclerosis as mice reconstituted with apoE KO bone marrow sufficient in IL-1R. This suggests that bone marrow derived cells do not need to sense IL-1 cytokines to promote atherogenesis. In the reciprocal experiment, in which apoE/IL-1R dKO mice hosted apoE deficient bone marrow, a reduction of almost 50 % aortic sinus lesions was observed compared to apoE KO mice fed on a Western diet. These data suggest that vascular resident cells act as sentinels for IL-1 cytokines and significantly contribute to atherogenesis. Therefore, interplay between activated myeloid cells and resident vessel wall cells appear to be very important for the pathogenesis of atherosclerosis. The study further provides pharmacological evidence that IL-1 activity is important in the vascular endothelial to upregulate adhesion molecules as well as chemotactic factors. While no genetic data were provided that the endothelial cells are indeed the main cell population that relay the information of locally produced IL-1 to the blood compartment, the authors provide some evidence that this may actually be the case. Macrophage markers, adhesion molecules as well as chemokines were indeed substantially reduced in the DKO mice compared to apoE single KO mice.

These data and many others document the pro-atherogenic role of IL-1 cytokines in Western-diet induced murine atherosclerosis. However, it should also be noted that IL-1 has pro-fibrotic effects in a number of chronic inflammatory diseases and that this ‘repair’ function could be important for the stability of atherosclerotic plaques. It is known that IL-1 can be mitogenic for smooth muscle cells and fibroblasts[9]. Since these cells are important for the architectural changes in the atherosclerotic vessel wall, lack of IL-1 signaling, or blockade of IL-1 could lead to differences in the plaque architecture. Indeed, a detailed analysis of late Western-diet induced vessel changes in IL-1R/apoE dKO mice recently demonstrated evidence for such an IL-1 function. IL-1R/apoE dKO generally had less atherosclerosis, but it was also noted that later lesions had reduced outward vessel remodeling with concomitant narrowing of the vessel lumen and reduction of smooth muscle cells and collagen deposition[10]. In light of current efforts of the pharmaceutical industry to intervene with IL-1β activity in cardiovascular diseases[11], the profibrotic effects of IL-1 cytokines should be taken into account as potential confounding factors.

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