Role of Inflammasomes in Atherosclerosis

Chronic inflammation, as seen with gout, silicosis and asbestosis, is thought to result from the inability of cells to destroy crystalline triggers. Inflammasomes, a component of the innate immune system characterised by caspase-1 activating multiprotein complexes, play a key role in this process. Cholesterol crystals are also the hallmark of atherosclerosis; however, until recently it was thought that their appearance typically late in atherogenesis precluded them as the primary inflammatory stimulus. The availability of novel microscopic techniques subsequently disproved this, commented Professor Eicke Latz, Institute of Innate Immunity, Bonn, Germany. Minute cholesterol crystals, coinciding with the first appearance of inflammatory cells, were shown to be present early in diet-induced atherosclerotic lesions.

In vitro studies showed that human cells treated with cholesterol crystals had active inflammasomes and secreted interleukin-1β (IL-1β), whereas sham-treated controls did not. Blocking inflammasome activation also inhibited IL-1β production in response to the presence of cholesterol crystals. In vivo, Apo lipoprotein E knockout mice fed a high-cholesterol diet for 2 weeks were examined for the presence of early atherosclerotic lesions in the aortic sinus using a combination of laser reflection and fluorescence confocal microscopy. There was evidence of minute cholesterol crystals, as well as recruitment of macrophages to the sites of crystal deposition.

A member of the Nod-like receptor (NLR) family, the NLRP3 inflammasome, was implicated in the pathogenesis of atherosclerosis. Activation of NLRP3 by cholesterol crystals led to their phagocytosis, with resultant uptake promoting lysosomal damage and rupture. These findings suggest that crystalline cholesterol acts as an endogenous danger signal with deposition in arteries an early cause rather than a late consequence of inflammation.

What are the clinical implications of these findings?

From a clinical perspective, these findings may offer new potential molecular targets for the management of atherosclerosis. Agents under investigation include anti-IL-1β strategies, treatments involving solubilisation of cholesterol crystals (based on studies with cyclodextrin), and reconstituted HDL. However incomplete understanding of the upstream mechanisms of NLRP3 activation remains an obstacle to development.

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