Expression of Interlukin-1 and Interlukin-1 Receptor Antagonist in Ox-LDL-treated Human Aortic Smooth Muscle Cells and in the Neointima of Cholesterol-fed Endothelia-denuded Rabbits.

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摘要

Abstract

The migration of vascular smooth muscle cells (VSMCs) from the media to the intima and the proliferation of intimal VSMCs are key events in restenotic lesion development. These events, which are preceded and accompanied by inflammation, are modulatedby the proinflammatory cytokine, interleukin-1 beta (IL-1 beta), which induces vascular smooth muscle cells to express adhesion molecules and to proliferate. IL-1 beta action is complex and regulated, in part, by its naturally occurring inhibitor, the IL-1 receptor antagonist (IL-1ra). Whether there was a temporal and spatial correlation between IL-1 beta and IL-1ra expression in, and release by, oxidized low density lipoproteins (oxLDL)-stimulated human aortic smooth muscle cells (HASMCs) wasdetermined by using ELISA and Western blot. In addition, IL-1 beta and IL-1ra expression was detected in the neointima of endothelia-denuded cholesterol-fed New Zealand white rabbits by immunohistochemistry and Western blot. In HASMCs, oxLDL inducedIL-beta and IL-1ra expression and release in a dose- and time-dependent manner. Treatment with 20 microg/ml oxLDL resulted in increased IL-1 beta release after 6 h, which peaked at 24 h, and in increased IL-1ra release, first seen after 12 h, but continuing to increase for at least 48 h. In the cells, IL-beta expression showed a similar pattern to release, whereas IL-1ra expression was seen in unstimulated cells and was not increased by oxLDL treatment. Confocal microscopy showed colocalizationof IL-beta and IL-1ra expression in oxLDL-stimulated HASMCs. oxLDL caused significant induction of nuclear factor kappa B and activator protein-1 DNA binding activity in HASMCs (6.6- and 3.3-fold, respectively). In cholesterol-fed endothelia-denudedrabbits, the notably thickened intima showed significant IL-1 beta and IL-1ra expression. These results provide further support for the role of IL-1 system in the pathogenesis of restenosis. This is the first demonstration of IL-1 beta and IL-1ra expression and secretion of oxLDL-treated HASMCs and their expression in the rabbit neointima, suggesting that the smooth muscle cells of the intima are an important source of these factors.