

## **Human Resistin in atherosclerosis progression.**

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Resistin is an adipokine first identified as a mediator of insulin resistance in murine obesity models. But, its role in human pathology is under debate. Although a few recent studies suggested the relationship between resistin and atherosclerosis in human, the causal relationship and underlying mechanism have not been clarified. We investigated the effects of human resistin on atherosclerosis progression and clarified its underlying mechanisms. To evaluate direct role of resistin on atherosclerosis, rabbit carotid artery collar model was used. Homology of resistin between rabbit and human was higher than that between mouse and human. Rabbit resistin was expressed by macrophages of the plaque in the three different atherosclerotic models. Peri-adventitial resistin gene transfer induced macrophage infiltration and expression of various inflammatory cytokines, resulting in the acceleration of plaque growth and instabilization. In vitro experiments elucidated that resistin increased monocyte-endothelial cell adhesion by up-regulating VLA-4 on monocytes and their counterpart VCAM-1 on endothelial cells. Resistin augmented monocyte infiltration in collagen by direct chemoattractive effect as well as by enhancing migration toward MCP-1. Administration of Connecting Segment-1 peptide, which blocks VLA-4-VCAM-1 interaction, ameliorated neointimal growth induced by resistin in vivo. Our results indicate that resistin aggravates atherosclerosis by stimulating monocytes, endothelial cells and vascular smooth muscle cells to induce vascular inflammation. These findings provide the first insight on the causal-relationship between resistin and atherosclerosis.