

Atherosclerosis Progression is Associated With a Decrease in Pro-Resolving Mediators and Can Be Mitigated With Restoring Resolvin D1

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Background: Chronic unresolved inflammation plays a causal role in the development of advanced atherosclerosis. However, the mechanisms that prevent resolution of inflammation in atherosclerosis remain unclear. During acute inflammation, the balance of pro-inflammatory and pro-resolving mediators regulates the duration of the inflammatory response and the timing and extent of resolution.

Methods and Results: Using targeted mass spectrometry, we identified specialized pro-resolving lipid mediators (SPMs) in histologically-defined stable regions of human carotid atherosclerotic plaques. Most importantly, the levels of SPMs, particularly resolvin D1 (RvD1), and the ratio of SPMs to pro-inflammatory leukotriene B4 (LTB4) were significantly decreased in the vulnerable regions of these plaques. To determine whether these human data might be applicable to further experimentation in an animal model, we conducted targeted LC-MS/MS analysis in lesions of Ldlr^{-/-} mice fed a Western-type diet (WD) for 8 weeks (early lesions) or 17 weeks (advanced lesions). A similar decrease in lesional SPMs was observed in advanced atherosclerotic plaques compared with early lesions of WD-fed Ldlr^{-/-} mice. Using metaboanalyst software, RvD1 decreased (~87 fold) from early to advanced lesions, and that the magnitude of this change was larger than any other lipid mediator. Because RvD1 was decreased in advanced plaques, we next questioned whether restoring RvD1 in Ldlr^{-/-} mice with established atherosclerosis could decrease plaque progression. In this model, restoration of RvD1 significantly decreased lesional OS and plaque necrosis, and significantly improved lesional efferocytosis and fibrous cap thickness. Levels of LTB4 were significantly lower in RvD1-restored plaques, which was mechanistically linked to reduced nuclear localization of 5-lipoxygenase. Furthermore, RvD1 treatment restored the advanced lesional ratio of RvD1:LTB4 to that of early lesions.

Conclusions: These findings add a critical new molecular link to the concept that resolution of inflammation is defective in advanced atherosclerosis and provide a rationale for developing "SPM-restoration" therapy to help prevent the formation of clinically dangerous plaques.

Disclosure Block:

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