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REVIEW

Boosting Inflammation Resolution in Atherosclerosis

The Next Frontier for Therapy

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Defective inflammation resolution is the underlying cause of prevalent chronic inflammatory diseases, such as arthritis, asthma, cancer, and neurodegenerative and cardiovascular diseases. Inflammation resolution is governed by several endogenous factors, including fatty acid–derived specialized proresolving mediators and proteins, such as annexin A1. Specifically, specialized proresolving mediators comprise a family of mediators that include arachidonic acid–derived lipoxins, omega-3 fatty acid eicosapentaenoic acid–derived resolvins, docosahexaenoic acid–derived resolvins, protectins, and maresins. Emerging evidence indicates that imbalances between specialized proresolving mediators and proinflammatory mediators are associated with several prevalent human diseases, including atherosclerosis. Mechanisms that drive this imbalance remain largely unknown and will be discussed in this review. Furthermore, the concept of dysregulated inflammation resolution in atherosclerosis has been known for several decades. Recently, there has been an explosion of new work with regard to the therapeutic application of proresolving ligands in experimental atherosclerosis. Therefore, this review will highlight recent advances in our understanding of how inflammation resolution may become defective in atherosclerosis and the potential for proresolving therapeutics in atherosclerosis. Last, we offer insight for future implications of the field. *(Am J Pathol 2017, 187: 1211–1221; http://dx.doi.org/10.1016/j.ajpath.2017.01.018)*

The Ideal Outcome of the Inflammation Resolution Response Is Tissue Repair and Regeneration

Acute inflammation, coupled with a timely inflammation resolution response, is a protective process.[1] When there is a defect in the inflammation resolution program, inflammation persists and collateral tissue damage ensues.[1,2] However, most inflammatory processes are self-limiting, which implicates the existence of endogenous proresolution pathways.[1] Although it was previously thought that proinflammatory mediator catabolism was sufficient for inflammation to cease, it is now known that the resolution of acute inflammation is an active, highly coordinated process.[1] The process is controlled by a variety of endogenous mediators that include the following: i) specialized proresolving mediators (SPMs), such as lipoxins, resolvins, protectins, and maresins[1,3,4]; ii) protein/peptide mediators, such as annexin A1[5] and IL-10; iii) gases, such as carbon monoxide and hydrogen sulfide[6,7]; and iv) nucleotides, such as adenosine and inosine.[8] As an example, SPMs are actively biosynthesized in local tissue microenvironments at the onset of acute inflammation to counterbalance the numerous proinflammatory signals,

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which controls the magnitude and duration of inflammation.[1] SPMs each have distinct chemical structures and bind and activate specific G-protein–coupled receptors.[1] The concentration of SPMs needed to activate these receptors is achieved at their local sites of biosynthesis.[1] As an example, the concentration of resolvin D1 (RvD1) in local blister exudates from humans is approximately 85 pmol/L.[9] In a separate study with human macrophages, RvD1 enhanced efferocytosis in the dose ranges of 10 to 100 pmol/L,[10] thus supporting that low concentrations of SPMs detected in humans are capable of evoking significant biological activity. Furthermore, deletion of key SPM receptors, such as ALX/FPR2 or GPR18, leads to exacerbated inflammation and defective resolution.[11–13] These findings provide strong evidence that SPMs are essential endogenous mediators of the inflammation-resolution response. Furthermore, emerging evidence has revealed that the balance of proinflammatory mediators and SPMs during acute inflammation regulates the duration of the inflammatory response and the timing of tissue resolution.[14,15] SPMs, which are biosynthesized through the actions of lipoxygenases (LOXs), are protective *in vivo*, and act locally to control leukocyte trafficking and enhance efferocytosis.[1] As such, SPMs stimulate the host to repair and regenerate tissue and are thus protective in several disease models, including injury-induced neointimal hyperplasia,[16,17] myocardial infarction,[18,19] and atherosclerosis,[20–24] to name a few. This panoply of work suggests that lipid mediator balances and tissue repair/regeneration (rather than a simple blockade of proinflammatory signals) are critical to thwart disease. Moreover, as will be illustrated in the following section, an imbalance between proresolving and proinflammatory mediators has been linked to a number of diverse chronic inflammatory diseases in humans, including atherosclerosis.[25–27] Furthermore, this review will highlight recent advances in our understanding of how inflammation resolution may become defective in atherosclerosis and the potential for proresolving therapeutics in atherosclerosis.

Imbalances in Proinflammatory and Proresolving Mediators Drive Atheroprogression and Arterial Tissue Injury

The concept that imbalances in lipid mediators are associated with disease originated shortly after the discovery of thromboxane A_2 and prostacyclin.[28] In this regard, an imbalance in the thromboxane A_2/prostacyclin ratio was thought to provide an explanation for some of the changes occurring in various pathological situations.[28,29] Another piece of the puzzle was added when Serhan and colleagues[30] found that angioplasty increased the levels of proresolving lipoxins (eg, lipoxin A_4, LXA_4) and proinflammatory leukotrienes (LTs; eg, LTC_4, LTD_4) in human coronary arterial blood, indicating that coronary arterial cells could perform LT and SPM biosynthesis and thereby affect the balance of mediators. Correlations were reported for high levels of plasma LTs and plaque instability in humans,[31] and other studies indicated that LTB_4 increased recruitment of monocytes and their differentiation to foam cells,[32] as well as intimal hyperplasia.[33] Furthermore, cysteinyl LTs have been shown to enhance the recruitment of leukocytes into the arterial wall and to contribute to thrombosis and vascular remodeling.[34,35] In humans, the incidence of atherosclerosis, stroke, and myocardial infarction in certain populations has been linked to variants of the genes that encode proteins and enzymes required for LT biosynthesis, such as 5-lipoxygenase (5-LOX), 5-LOX–activating protein, and leukotriene A_4 (LTA_4) hydrolase.[36–39] Furthermore, on treatment with a 5-LOX–activating protein inhibitor, C-reactive protein was reduced in one population of patients who had both a history of myocardial infarction and one of the enzyme gene variants mentioned above.[40] Diet gene interactions have also been extensively studied.[41,42] For example, individuals with a specific 5-LOX variant who also ingested a diet rich in AA had increased carotid atherosclerosis compared to individuals with nonvariant 5-LOX, whereas those with the same mutation but who ingested a diet rich in omega-3 fatty acids had less carotid atherosclerosis compared with the control population.[41] More recent work indicated a trend between eicosapentaenoic acid and a 5-LOX variant in lowering cardiovascular disease (CVD) risk ($P = 0.06$).[43] Further studies need to be performed to determine the functions of these single-nucleotide polymorphisms and to reconcile the results of a few clinical trials that failed to show a protective effect of dietary fish oils.[42] For example, this variability may be because of a lack of uniformity and quality control of the fish oils being tested, different doses and types of fish oils used, and/or the difficulty of showing beneficial effects on subjects already being treated with other CVD or diabetes drugs. Furthermore, fish oils contain a mixture of substances, only a fraction of which represent n-3 polyunsaturated fatty acids. This is the case particularly for marine oils that can also contain fish steroids. In this regard, fish oils should not be considered synonymous with eicosapentaenoic acid and docosahexaenoic acid. Also, there is an absence of data on the uptake and kinetics of eicosapentaenoic acid and docosahexaenoic acid into human tissues.

Although much of the earlier attention was focused on proinflammatory LTs, new results highlight SPMs in CVD (see more details below). For example, support for a role of endogenous biosynthesis of SPMs in limiting atherosclerosis was suggested by a study showing that overexpression of a key SPM biosynthetic enzyme, 12/15-LOX, in chow-fed *Apoe*$^{-/-}$ mice was atheroprotective.[20] Furthermore, low levels of SPMs in the plasma, including aspirin-triggered LXA_4, were reported in patients with vascular disease.[44,45] As another example, human vulnerable atherosclerotic plaque regions had significantly less 5-LOX–derived SPMs and a significant imbalance between these SPMs and LTs compared with stable plaque regions.[22] These human plaque findings were also corroborated in murine plaques, where there was a marked imbalance between SPMs and LTs as