Lipid Mediators-Role in Resolution of Inflammation

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ABSTRACT:

The host response to injury, inflammation and infection leads to generation of a range of chemical mediators. This integrated response of the host is very important in both maintenance of state of health and disease. It is important to achieve a more complete understanding of the molecular and cellular events governing the formation and actions of endogenous mediators of resolution that appear to control the duration of inflammation.

Key words: Inflammation, Host response, Chemical mediators.

Introduction:

In the recent years inflammation has emerged as playing a key role in many prevalent diseases including Alzheimer's disease and cardiovascular disease as well as cancer.[1,2] These deadly diseases have now joined the community of well known inflammatory disorders like periodontitis. Resolution of inflammation is the reduction or removal of leukocytes and debris from inflamed sites, enabling the return to homeostasis. The resolution of inflammatory leukocytic infiltrates was previously considered to be a passive process. Recent findings indicate that resolution is not merely a passive process but is initiated after acute challenges by cellular pathways that actively biosynthesize local, specialized, dual-acting anti-inflammatory and pro-resolution lipid mediators, such as the lipoxins, resolvins and protectins.[3,4] These molecules bind to distinct receptors on the cells which alter the function of the cells leading to resolution and healing.

Biosynthesis and actions

The term 'resolvins' or 'resolution-phase interaction products' was coined by Professor Charles Serhan and was introduced to emphasize that these are endogenous products possessing anti inflammatory properties. Protectins are distinguished by the presence of a conjugated triene double bond and by their potent bioactivity. They are biosynthesized via a lipoxygenase-mediated pathway. Lipoxins were the first mediators recognized to have dual anti-inflammatory and pro-

resolution activities. Lipoxins (such as lipoxin A4 and lipoxin B4) are unique structures derived from arachidonic acid that have potent actions *in vivo* and *in vitro* (Figure-1). It is well established that short-lived mediators derived from arachidonic acid (AA) regulate various events related to innate-immunity, coagulation, inflammation and uncontrolled cell growth.[5] Fatty acid precursors are transformed into potent bioactive mediators, eicosanoids, which play a role during inflammation and its resolution. The main bioactive products derived from AA can be inflammatory mediators, such as prostaglandins (PG) and leukotrienes (LT) or anti-inflammatory mediators, such as lipoxins (LX). Previous studies have demonstrated that human and animal cells convert ω-3 polyunsaturated fatty acids (PUFAs) into resolvins.[6-8] These lipid mediators were originally identified by Serhan and colleagues in a self-limited model of acute inflammation and have provided new insights indicating that resolution of inflammation is an active process (Figure 2).[9]

Role in resolution of inflammation

Counter-regulatory substances, such as lipoxins, are generated during the resolution of acute inflammation to serve in healthy termination of an acute response. It is important to note that these chemical mediators serve as agonists for endogenous anti-inflammatory and pro resolving mechanisms. Acute inflammation is a physiological mechanism that protects the host against local injury.[10] Under normal physiological conditions, the inflammatory response is cleared to a non inflammatory stage, leading to restoration of normal tissue architecture and function.[11,12] Defects in these clearance mechanisms appear to be associated with persistent tissue inflammation and autoimmunity to cellular contents.[13,14] Tissue damage resulting from uncontrolled acute inflammatory responses causes discomfort and severely compromises normal tissue function.[15]

In both acute and chronic models of inflammation, endogenous resolvins have been shown to accelerate resolution of inflammation. Resolvins (resolution-phase interaction products) are short-lived autacoids, belonging to a novel family of aspirin-triggered (AT) bioactive lipids, which are synthesized during the resolution of inflammation. They exhibit both anti-inflammatory and pro-resolving actions demonstrating the protective effects of ω-3 fatty acids.[16] Resolvin sub types include the E series (RvE1-3, derived from EPA), the D series (RvD1 and RvD2, derived from DHA) and AT forms (AT-RvD1-6) .[17]

Resolvins are produced in resolving exudates *in vivo* as a byproduct of transcellular biosynthesis with human leukocytes, endothelial or epithelial cells. The first step in resolvin biosynthesis involves the release of ω-3 PUFA from membrane phospholipids by phospholipase A2, which has been demonstrated to be responsible for DHA and EPA release in neural and retinal-pigmented cells.[18,19] However, in acute inflammation, it was demonstrated that DHA from peripheral blood enters the inflammatory exudate as a free fatty acid that is converted by resolving exudates to resolvins and protectins.[20,21]

In humans, initial oxygenation of arachidonic acid via 15-lipoxygenase type I and then by 5lipoxygenase is one route of lipoxin biosynthesis that has been observed in mucosal tissues, such as the respiratory tract, gastrointestinal tract and oral cavity, and that results from the interactions between epithelial cells and leukocytes. The blood vessels represent another main site where lipoxin biosynthesis occurs in humans.[22]

Resolvins regulate the immune system by controlling functions of specific cell types. For instance, RvD1 differentially modulates primary human macrophage responses to lipopolysaccharides, depending on the context in which this molecule is presented to the macrophage. Resolvins and protectins have been shown to stimulate innate killing mechanisms to manage bacterial loads and stimulate clearance of bacteria. RvE1 is a potent inhibitor of leukocyte infiltration, dendritic cell migration, IL-12 production and PMN transendothelial migration. Furthermore, RvE1 was found to negatively regulate the development of an allergic inflammation *in vivo*. Other studies demonstrated that RvE2 stimulates host-protective actions throughout initiation and resolution of the innate immune responses.[23,24] Resolvins block excessive inflammatory responses and promote resolution of inflammation as follows: (a) blocking cytokine production; (b) reducing PMN transendothelial migration and (c) increasing macrophage activity resulting in the clearance of apoptotic cells and debris from inflamed areas. RvE1 can reduce neuropathic pain by several mechanisms, which include inhibition of the following: (a) TNF-α synthesis release and downstream signaling (b) transient receptor potential ion channel signaling

and (c) peripheral inflammation via enhancing the phagocytic activity of macrophages.[25-27]

Role in Periodontitis

Periodontitis is a chronic inflammatory disease caused by the release of immune mediators, resulting in destruction of the alveolar bone and periodontal connective tissue. The mechanism by which bone resorption is regulated involves different factors, including PGE2, which activates osteoclasts while influencing their number and function. In contrast, RvE1 was found to inhibit osteoclast growth and bone resorption by interfering with its differentiation.[28] A previous study indicated that topical application of RvE1 to rabbit periodontal tissue conferred dramatic protection against tissue and bone loss associated with periodontitis.[29] The main receptors for resolvins are the chemR-23 receptors expressed on macrophages and leukotriene-4-receptor-1 on neutrophils. This new family of chemical mediator- resolvins and protectins are defined by their potent bioactivity and novel chemical structures. Since the precursors of resolvins and protectins are derived from omega-3 polyunsaturated fatty acids, there is a clear link that omega-3 supplementation of diet reduces inflammatory disease.

Prevention of *P.gingivalis* induced periodontitis by topical application of resolvins was evaluated in a six week experiment by Hasturk H.et al. Teeth were ligatured at baseline and *P.gingivalis* was applied to the ligature *Porphyromonas gingivalis* colonies in a methyl cellulose slurry three times weekly to two groups of animals (New zealand white rabbit). One group received 5ul of a 1ug/ml solution of resolvin E1 in ethanol (topically) and other group received ethanol alone (placebo). At the end of six week treatment period, animals were sacrificed and periodontal disease progression was quantified morphologically and histologically. Significant progression of periodontal disease, including bone and attachment loss, was observed in the placebo group.[30] Resolvin E1 application prevented the onset and progression of periodontal disease in experiment group. Lipoxins can have a protective role in periodontitis, limiting further neutrophil recruitment and neutrophil - mediated tissue injury that can lead to loss of inflammatory barriers that prevent tissue invasion by periodontal pathogens. It has been further proposed that lipoxin generation and its relationship to PGE2 and LTB4 can be important markers in the pathogenesis of periodontal diseases. It has been shown that activated neutrophils from LAP patients produced Lipoxins whereas from healthy patients did not. The reasons for a reduction in the complexity of biofilm composition with RvE1 treatment remain unclear, given the absence of direct antibacterial properties. One possibility is that resolvin molecules promote the release of antimicrobial peptides, such as defensins and bactericidal/permeability-increasing protein, resulting in the destruction of select microorganisms.[29]

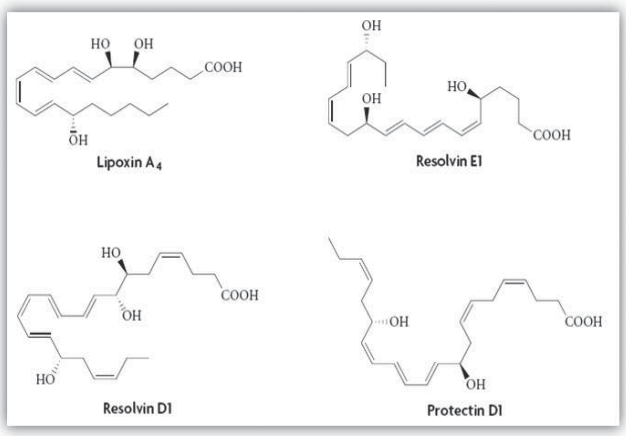

Figure 1: Structure of lipoxins

Conclusion

These lipid mediators open new avenues to design resolution-targeted therapies to control unwanted side-effects of aberrant inflammation. Given their potent bioactivity and specific actions

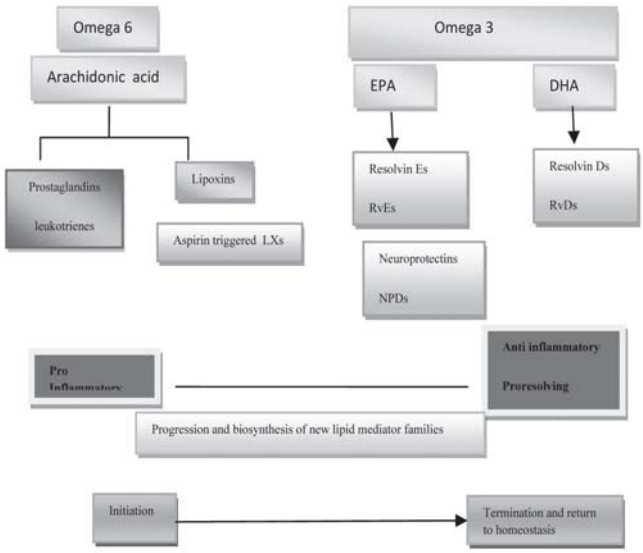

Figure 2: Synthesis of lipid mediators

within resolution, the lipoxins, resolvins and protectins and their mimetics now qualify as agonists for resolution in this new arena of resolution-modulation and tissue protection.

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