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Review

The resolution code of acute inflammation: Novel pro-resolving lipid mediators in resolution

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ABSTRACT

Studies into the mechanisms in resolution of self-limited inflammation and acute reperfusion injury have uncovered a new genus of pro-resolving lipid mediators coined specialized pro-resolving mediators (SPM) including lipoxins, resolvins, protectins and maresins that are each temporally produced by resolving-exudates with distinct actions for return to homeostasis. SPM evoke potent anti-inflammatory and novel pro-resolving mechanisms as well as enhance microbial clearance. While born in inflammation-resolution, SPM are conserved structures with functions discovered in microbial defense, pain, organ protection and tissue regeneration, wound healing, cancer, reproduction, and neurobiology-cognition. This review covers these SPM mechanisms and other new omega-3 PUFA pathways that open their path for functions in resolution physiology.

1. Introduction

The origins of resolving inflammation trace to the 11th century in the Canon of Medicine [1] as a *resolvent* promotes the disappearance of inflammation. For historical perspective on resolution, interested readers are directed to Ref. [1] for a recent review. Barrier break, trauma and microbial invasion each create the host's need to neutralize invaders, clear the site, remodel and regenerate tissue (Fig. 1A); the inflammatory response is a terrain where lipid mediators (LM) such as eicosanoids (prostaglandins (PG) and leukotrienes (LT)) [2] and novel pro-resolving mediators uncovered [3,4] play pivotal roles. The acute inflammatory response is divided into initiation and resolution phases (Fig. 1A).

Leukocyte traffic from circulation forms inflammatory exudates traditionally viewed as a battlefield. The first responders, neutrophils (PMN), swarm like sharks to defend the host along chemotaxic gradients, e.g. LTB_4 [5,6], exiting venules governed by PGE_2 and PGI_2 and influx to form the exudate. The main events in resolution are cessation of PMN influx and macrophage clearance of debris. *But how does the host return the system to homeostasis and what are the roles of chemical mediators and the inflammatory exudate in timely resolution?*

Excessive inflammation is widely appreciated as a unifying component in many chronic diseases including vascular diseases, metabolic syndrome, neurological diseases, and many others, and thus a significant public health concern. Since the acute inflammatory response is protective, evolved to permit repair of injured tissues and eliminate invading organisms, it is *ideally self-limited* and leads to complete resolution enabling return to homeostasis (Fig. 1A). Although resolution of disease is appreciated by clinicians, resolution was considered a *passive* process [7], passive in that the chemoattractant and other chemical mediators involved in mounting the inflammatory response would just dilute and

Abbreviations: 17R-HDHA, 17*R*-hydroxy-4*Z*,7*Z*,10*Z*,13*Z*,15E,19*Z*-docosahexaenoic acid; AT, aspirin-triggered; AT-RvD3, 4*S*,11*R*,17*R*-trihydroxydocosa-5*Z*,7*E*,9*E*,13*Z*,15*E*,19*Z*-hexaenoic acid; GPCR, G protein-coupled receptor; LC–MS–MS, liquid chromatography–tandem mass spectrometry; LM, lipid mediator; LT, leukotriene; LTB_4, leukotriene B_4, 5*S*,12*R*-dihydroxy-6*Z*,8*E*,10*E*,14*Z*-eicosatetraenoic acid; LXA_4, lipoxin A_4, 5*S*,6*R*,15*S*-trihydroxy-7*E*,9*E*,11*Z*,13*E*-eicosatetraenoic acid; LXB_4, lipoxin B_4, 5*S*,14*R*,15*S*-trihydroxy-6*E*,8*Z*,10*E*,12*E*-eicosatetraenoic acid; MaR1, maresin 1, 7*R*,14*S*-dihydroxy-docosa-4*Z*,8*E*,10*E*,12*Z*,16*Z*,19*Z*-hexaenoic acid; MΦ, macrophages; PD1/NPD1, protectin D1/neuroprotectin D1, 10*R*,17*S*-dihydroxy-4*Z*,7*Z*,11*E*,13*E*,15*Z*,19*Z*-docosahexaenoic acid; PMN, polymorphonuclear neutrophil; PG, prostaglandin; PGE_2, prostaglandin E_2, 9-oxo-11*R*,15*S*-dihydroxy-5*Z*,13*E*-prostadienoic acid; PUFA, polyunsaturated fatty acid; Rv, resolvin; RvD1, resolvin D1, 7*S*, 8*R*,17*S*-trihydroxy-4*Z*, 9*E*, 11*E*, 13*Z*, 15*E*, 19*Z*-docosahexaenoic acid); RvD2, resolvin D2, 7*S*, 16*R*, 17*S*-trihydroxy-4*Z*, 8*E*, 10*Z*, 12*E*, 14*E*,19*Z*-docosahexaenoic acid; RvD3, resolvin D3, 4*S*,11*R*,17*S*-trihydroxydocosa-5*Z*,7*E*,9*E*,13*Z*,15*E*,19*Z*-hexaenoic acid; RvD5, Resolvin D5, 7*S*,17*S*-dihydroxy-4*Z*,8*E*,10*Z*,13*Z*,15*E*,19*Z*-docosahexaenoic acid; RvE1, resolvin E1, 5*S*,12*R*,18*R*-trihydroxy-6*Z*,8*E*,10*E*,14*Z*,16*E*-eicosapentaenoic acid; RvE2, resolvin E2, 5*S*,18*R*-trihydroxy-6*E*,8*Z*,11*Z*,14*Z*,16*E*-eicosapentaenoic acid; SPM, specialized pro-resolving mediators; TRP, transient receptor potential.

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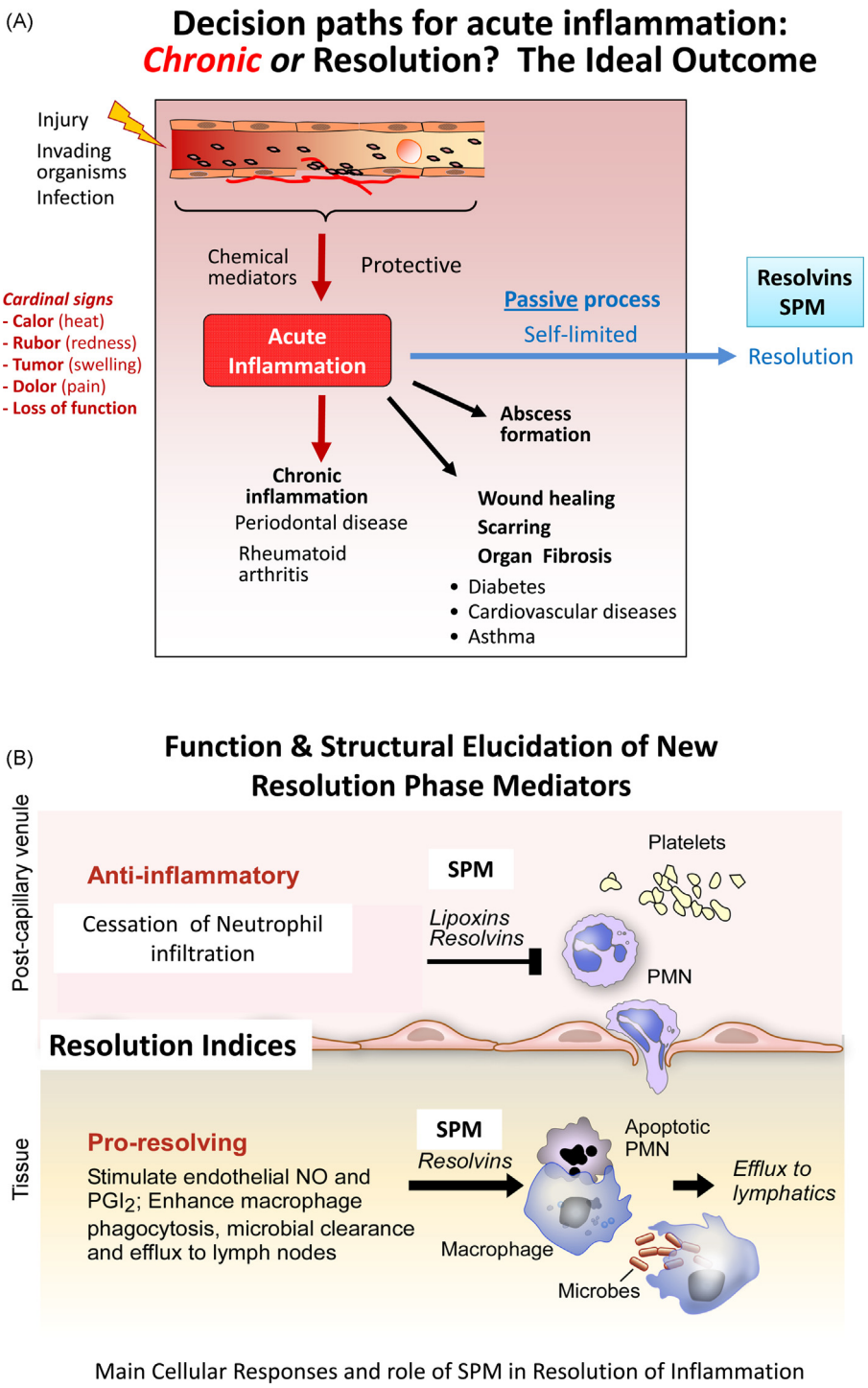

Fig. 1. Lipid mediators in the acute inflammatory response and its outcomes. Panel A: LM play pivotal roles in the vascular response and leukocyte trafficking, from initiation to resolution. Eicosanoids are critical in initiating the cardinal signs of inflammation, and the specialized proresolving mediators (SPM), illustrated above, play key roles stimulating resolution (Panel B). Depicted are some roles of resolvins, protectins and maresins, SPM, in leukocyte trafficking, lipid mediator class switching, efferocytosis, resolving exudates to homeostasis and signaling to adaptive immunity via lymphocytes. Failed resolution can lead to enhanced prostaglandin and leukotriene production and chronic inflammation that can lead to fibrosis. SPM (lipoxins, resolvins, protectins and maresins) counterregulate pro-inflammatory chemical mediators, reducing inflammation, and stimulate reepithelialization, wound healing, and tissue regeneration (see text for details).

dissipate [8,9]. With identification of proresolving mediators, we obtained evidence *that resolution of self-limited inflammation is an active programmed response* that *is "turned on" and not simply a process of diluting chemoattractant gradients*. Unexpectedly, $n-3$ PUFA present in marine oils are precursors of proresolving mediators (Fig. 1A and B).

Since $n-3$ PUFA EPA and DHA have cardioprotective and anti-inflammatory effects, they were held earlier to simply compete with arachidonic acid for eicosanoid biosynthesis, preventing pro-inflammatory eicosanoids, a process readily discernible in vitro [10]. Utilization of $n-3$ PUFA by resolving exudates to biosynthesize novel pro-resolving local mediators – resolvins, protectins