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Structural elucidation and physiologic functions of specialized pro-resolving mediators and their receptors

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ABSTRACT

The acute inflammatory response is host-protective to contain foreign invaders. Many of today's pharmacopeia that block pro-inflammatory chemical mediators can cause serious unwanted side effects such as immune suppression. Uncontrolled inflammation is now considered a pathophysiologic basis associated with many widely occurring diseases such as cardiovascular disease, neurodegenerative diseases, diabetes, obesity and asthma, as well as the classic inflammatory diseases, e.g. arthritis, periodontal diseases. The inflammatory response is designated to be a self-limited process that produces a superfamily of chemical mediators that stimulate resolution of inflammatory responses. Specialized pro-resolving mediators (SPM) uncovered in recent years are endogenous mediators that include omega-3-derived families resolvins, protectins and maresins, as well as arachidonic acid-derived (n-6) lipoxins that stimulate and promote resolution of inflammation, clearance of microbes, reduce pain and promote tissue regeneration via novel mechanisms. Here, we review recent evidence from human and preclinical animal studies, together with the structural and functional elucidation of SPM indicating the SPM as physiologic mediators and pharmacologic agonists that stimulate resolution of inflammation and infection. These results suggest that it is time to develop immunoresolvents as agonists for testing resolution pharmacology in nutrition and health as well as in human diseases and during surgery.

Introduction

Phagocytes in the innate immune system play a central role to protect the host from invading organisms and foreign objects. The repertoire and cell trafficking of the acute inflammatory response is protective, and the cardinal signs of inflammation – heat, redness, swelling, and eventual loss of function – were recognized by physicians of ancient civilizations (Majno, 1975; Cotran, 1999). It is now clear that excessive or uncontrolled inflammation is associated with many widely occurring diseases. The therapeutic approach to treating excessive inflammation and the resulting collateral tissue damage has not significantly changed since ancient practitioners of folk medicine used willow bark (Yedgar et al., 2007); namely, therapeutic approaches to inflammation have focused on suppressing, blocking or inhibiting pro-inflammatory mediators of inflammation (Serhan, 2017). Many of these are effective, relieving gross signs and symptoms, but can give rise to immune suppression and infections (Dinarello and Joosten, 2016; Delano and Ward, 2016). Therefore, new therapeutic interventions need to be developed to address infection, inflammatory diseases, aging and the tissue damage-evoked inflammation associated with surgery (Nathan, 2012).

Temporal events in many physiologic inflammation or self-limited acute inflammatory responses are recognized to resolve at the histologic level (Fig. 1) with the loss of inflammatory infiltrates from these tissues with the return of function or catabasis (Robbins and Cotran, 1979; Serhan et al., 2004). The cellular steps and tissue histology of the stage were, for example, viewed clinically in the resolution of lung inflammation (Henson, 1991; Savill et al., 1989) yet the role and function of resolution phase mediators remained to be uncovered. Focus on the fundamental mechanisms in the resolution response using a modern systems approach, in the authors' laboratories, led to the isolation and complete structural elucidation of several novel families of pro-resolving mediators of inflammation that together constitute a superfamily of structurally distinct bioactive mediators. These are biosynthesized from

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Abbreviations

CTR	conjugate in tissue regeneration
DHA	docosahexaenoic acid
eicosanoid	arachidonic acid-derived carbon-20-containing structure
EPA	eicosapentaenoic acid
GPCR	G protein-coupled receptor
HDHA	hydroxy-docosahexaenoic acid
HEPE	hydroxy-eicosapentaenoic acid
HETE	hydroxy-eicosatetraenoic acid
HpETE	hydroperoxy-eicosatetraenoic acid
LC-MS-MS	liquid chromatography tandem mass spectrometry
LM	lipid mediators
LOX	lipoxygenase
LTB_4	leukotriene B_4, (5*S*, 12*R*-dihydroxy-eicosa-6*Z*, 8*E*, 10*E*, 14*Z*-tetraenoic acid)
LX	lipoxin
LXA_4	lipoxin A_4 (5*S*, 6*R*, 15*S*-trihydroxy-eicosa-7*E*, 9*E*, 11*Z*, 13*E*-tetraenoic acid)
LXA_5	lipoxin A_5 (5*S*, 6*R*, 15*S*-trihydroxy-eicosa-7*E*, 9*E*, 11*Z*, 13*E*, 17*Z*-pentaenoic acid)
LXB_4	lipoxin B_4 (5*S*, 14*R*, 15*S*-trihydroxy-eicosa-6*E*, 8*Z*, 10*E*, 12*E*-tetraenoic acid)
Maresin	macrophage-derived resolution mediator of inflammation
MaR1	maresin 1 (7*R*, 14*S*-dihydroxy-docosa-4*Z*, 8*E*, 10*E*, 12*Z*, 16*Z*, 19*Z*-hexaenoic acid)
PD	protectin
PD1	protectin D1 (10*R*, 17*S*-dihydroxy-docosa-4*Z*, 7*Z*, 11*E*, 13*E*, 15*Z*, 19*Z*-hexaenoic acid), also known as neuroprotectin D1 (NPD1)
Rv	resolvin
RvD1	Resolvin D1 (7*S*, 8*R*, 17*S*-trihydroxy-docosa-4*Z*, 9*E*, 11*E*, 13*Z*, 15*E*, 19*Z*-hexaenoic acid)
RvD2	Resolvin D2 (7*S*, 16*R*, 17*S*-trihydroxy-docosa-4*Z*, 8*E*, 10*Z*, 12*E*, 14*E*, 19*Z*-hexaenoic acid)
RvD3	Resolvin D3 (4*S*, 11*R*, 17*S*- trihydroxy-docosa-5*Z*, 7*E*, 9*E*, 13*Z*, 15*E*, 19*Z*-hexaenoic acid)
RvD5	Resolvin D5 (7*S*, 17*S*-dihydroxy-docosa-4*Z*, 8*E*, 10*Z*, 13*Z*, 15*E*, 19*Z*-hexaenoic acid)
RvE1	Resolvin E1 (5*S*, 12*R*, 18*R*-trihydroxy-eicosa-6*Z*, 8*E*, 10*E*, 14*Z*, 16*E*-pentaenoic acid)
RvE2	Resolvin E2 (5*S*, 18*R*-dihydroxy-eicosa-6*E*, 8*Z*, 11*Z*, 14*Z*, 16*E*-pentaenoic acid)
RvE3	Resolvin E3 (17*R*,18*R*-dihydroxy-eicosa-5*Z*, 8*Z*, 11*Z*, 13*E*, 15*E*-pentaenoic acid)
SPM	specialized pro-resolving mediator (Rv, MaR, PD)

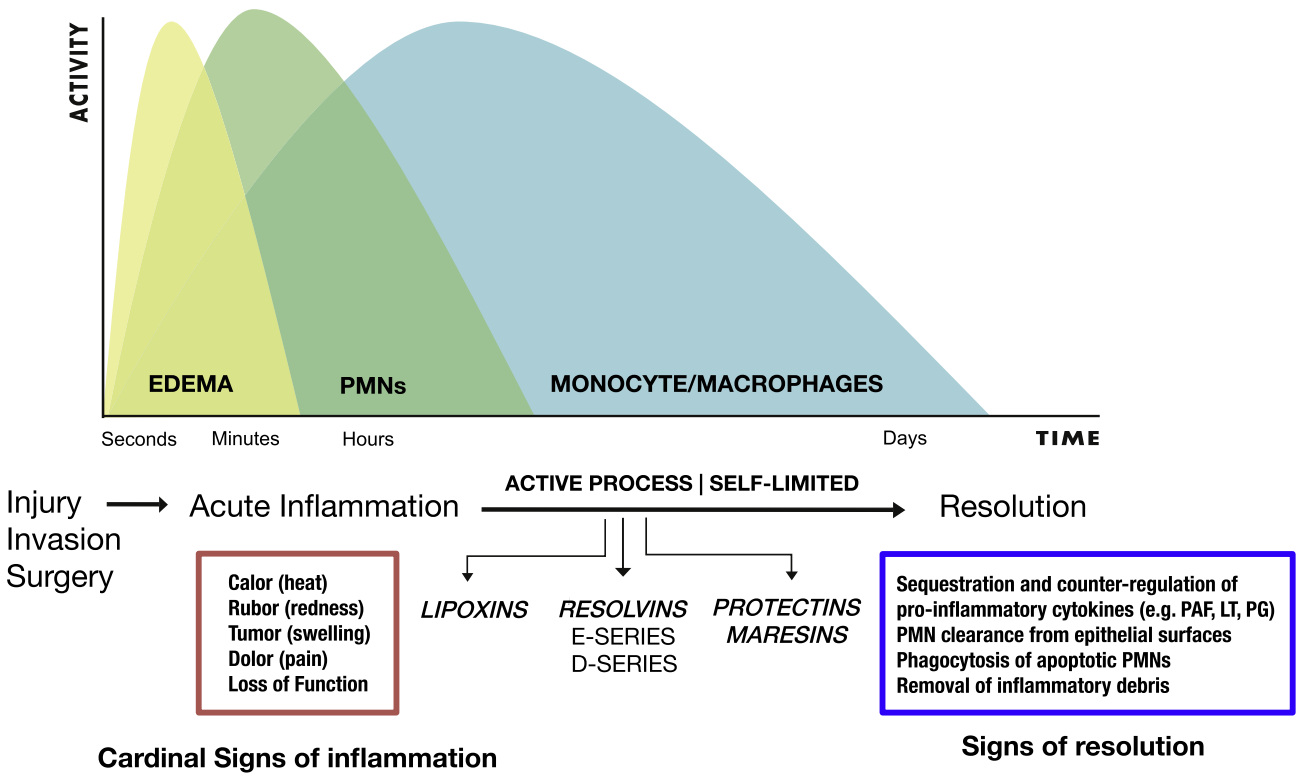

Fig. 1. The ideal outcome of inflammation: complete systems approach to mapping resolution. Injury, infection or surgery initiate acute inflammation that is normally a host-protective mechanism. The first event in acute inflammation is edema formation, followed by infiltration of PMN, and then monocyte and macrophages that clear PMN leading to resolution. Using the systems approach to map resolution, we demonstrated temporal biosynthesis of SPM in the resolution phase of self-limited inflammation. These SPM are a super-family of endogenous mediators, first identified in resolving exudates. They promote resolution of inflammation, wound healing and reduce organ fibrosis, leading to homeostasis. Based on these findings, we proposed the signs of resolution as listed. Identification and structure elucidation of these SPM provided the first evidence that resolution of inflammation is an active process.

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