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Novel ω − 3-derived local mediators in anti-inflammation and resolution

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Abstract

The integrated inflammatory response of the host is essential in health and disease. Hence, it is important to achieve a more complete understanding of the local cellular and molecular events that govern the formation and actions of local mediators that can serve as endogenous local mediators of resolution. Because these compounds in experimental animal models of inflammation can control the duration and magnitude of inflammation, knowledge of their formation and actions may provide new avenues for appreciating the molecular basis of many inflammatory diseases. The first of these endogenous local counterregulators recognized were the lipoxins, which are trihydroxytetraene-containing mediators generated from arachidonic acid during cell-cell interactions via transcellular biosynthesis. Because this circuit of lipoxin formation appears to be of physiological relevance in resolution, therapeutic modalities targeting this and related systems should allow for the development of novel therapeutic agents (i.e., agonists of the important cellular and physiological responses required for timely resolution). This review offers a general overview of recent advances from studies by the author and colleagues on the biosynthesis and bioactions of the novel anti-inflammatory lipid mediators, resolvins, docosatrienes, and neuroprotectins as well as their endogenous aspirin-triggered epimeric counterparts. These previously unappreciated families of lipid-derived mediators were originally isolated from experimental murine models of acute inflammation captured during the natural spontaneous resolution phase. They possess anti-inflammatory, pro-resolving, and protective properties. Inappropriate resolution mechanism(s) may underlie our current appreciation of the inflammatory phenotype(s) that characterizes many prevalent human diseases where inflammation is now acknowledged to play an important role in the disease process. Moreover, these new pathways give opportunities to appreciate the complex roles of neutrophils in the generation of potent host protective lipid mediators that may be harnessed for the design of novel treatments for a wide range of diseases where inflammation contributes to the pathophysiology of the disorder.

Keywords: Leukocytes; Eicosanoids; Aspirin; Fish oils

Abbreviations: ATL, aspirin-triggered 15-epi-lipoxins; COX, cyclooxygenase; LOX, lipoxygenase; LX, lipoxin; PMN, neutrophils; resolvins, resolution phase interaction products; RvD, resolvins from docosahexaenoic acid; RvE, resolvins from eicosapentaenoic acid; TNF-α, tumor necrosis factor-α.

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1. Introduction

Pus bonum et laudabile. As early as the ancient Egyptian civilization, the major signs of inflammation were known by scholars of the time. This information on inflammation within hieroglyphics was decoded by the efforts of Dr. Guido Majno, a scholar, clinician, and investigator of significant stature that made many substantive contributions to our present understanding of the cellular events in inflammation (Majno, 1975). Since the early concepts on the importance of the phagocyte in host defense and inflammation as studied by Metchnikoff (Tauber & Chernyak, 1991) >100 years ago (for which he received a Nobel Prize), the focus of research in inflammation was maintained with the credo "elucidate the chemical mediators that evoke the cardinal signs of inflammation—heat, redness, swelling, pain, and loss of function (Vane, 1982; Winyard & Willoughby, 2003)—so that inhibitors could be prepared as new treatments to control the side effects of inflammation during disease."

Several hundred of these local chemical mediators have been identified, including the many protein-based mediators (i.e., cytokines, chemokines, growth factors, and inappropriately liberated enzymes) as well as the reactive oxygen species and the many other radicals derived from gases such as peroxynitrate, etc. (see Gallin et al., 1999; Nathan, 2002). There are also many lipid mediators: platelet activating factor, lysolipids, and the many eicosanoids from arachidonic acid considered "proinflammatory mediators" that include the classic prostanoids, leukotrienes (Samuelsson, 1982), and related compounds (Figs. 1 and 2). This review is not intended to discuss the >100 years of research into proinflammatory mediators. There are several recent books and excellent reviews for interested readers that cover each of these areas in depth (Gallin et al., 1999; Serhan & Ward, 1999; Lawrence et al., 2002; Nathan, 2002). This review briefly summarizes the production of novel protective mediators by neutrophils (PMN) and their ability to mount resolution and anti-inflammation.

Given the many mediators generated in host defense and their relative priority within the acute inflammatory response, many questions are raised that we need to address in current inflammation research and the quest for new approaches for treating the many diseases now recognized to have an inflammatory component. As depicted on the February 23, 2004 cover of *Time* magazine, inflammation has emerged as playing a central role in many prevalent diseases not believed previously to involve inflammation. These include Alzheimer's disease, cardiovascular disease (Helgadottir et al., 2004), and cancer (Erlinger et al., 2004; Pasche & Serhan, 2004) in addition to those well appreciated and associated with inflammation such as arthritis and periodontal disease (Gallin et al., 1999; Van Dyke & Serhan, 2003). Should we make each "proinflammatory mediator" a drug target? Should we try to selectively inhibit each of the hundreds if not thousands of important molecules? One clue in recent years from studies on phagocytes and endothelium comes from the work of Cotran and Majno, who were first to point to the endothelial role in inflammation, namely, that the vascular and cellular responses of both acute and chronic inflammation are mediated by endogenous chemical factors derived from plasma or cells and triggered by the inflammatory stimulus (Cotran, 1982; Majno, 1982). These endogenous chemical factors play important roles, not only initiating but also regulating the host responses. More recently, we have learned that this is also a setting, namely, the inflammatory exudate, for cell-cell interactions that promote transcellular biosynthesis of lipoxins (LX) and resolvins during inflammation and its resolution (Serhan et al., 1983; Levy et al., 2001; Serhan et al., 2000, 2002).

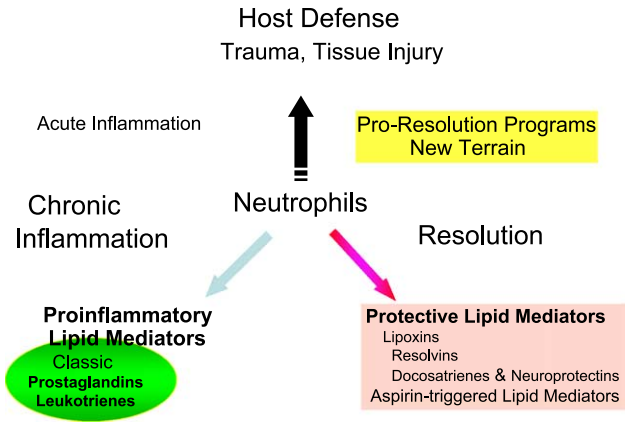

Fig. 1. PMN temporally switch from proinflammatory mediators to production of protective lipid mediators.