Resolvins as New Fascinating Drug Candidates for Inflammatory Diseases

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New classes of lipids such as lipoxins, resolvins, protectins and maresin are found to promote the resolution of inflammation. The resolving actions of these endogenous lipids are mediated by membrane receptors such as lipoxin A4 receptor/formyl peptide receptor 2 (ALX/FPR2) and cysteinyl leukotriene receptor 1 (CysLT1). Further, there exists G protein-coupled receptor 32 (GPR32), chemokine receptor-like (CMLKLR), LTB4 receptor 1 (BLT1) and unidentified high-affinity surface binding receptors in human polymorphonuclear leukocytes (PMN). In particular, RX-10001 (resolvin E1) and RX-10004 (synthetic analog of resolvin, phase II) are being studied clinically in many inflammatory diseases including dry eye, retinal disease, asthma, inflammatory bowel diseases, rheumatic arthritis and cardiovascular diseases by Resolvyx Pharmaceuticals. These novel lipid classes of inflammation resolving mediators might offer new opportunities for candidates of drugs modulating chronic inflammatory diseases. Here, the progress of resolvins as new drug candidates is introduced and research on the resolution phase of inflammation is emphasized.

ACUTE INFLAMMATION AND RESOLUTION OF INFLAMMATION

Inflammation, which occurs in response to injurious stimuli such as microbes, physical insults and intracellular dysfunction is a beneficial and defensive event that leads to removal of the offending factor and restoration of tissue structure and function (Rajakariar et al., 2006). Symptoms of inflammation are characterized by rubor, calor and dolor, and aggravation of these symptoms leads to loss of function in tissues (Nathan and Ding, 2010). Acute inflammation is defined by an initial recruitment of polymorphonuclear granulocytes followed by monocytes, which differentiate locally into macrophages (Lawrence, 2007). Pattern recognition receptors (eg. TLRs) are involved in the activation of resident macrophages. This activation triggers the sequential release of proinflammatory mediators such as eicosanoids, cytokines, chemokines and proteases and these mediators drive leukocytes recruitment and activation (Lawrence et al., 2002).

Inflammation is involved in many chronic diseases such as arthritis, Alzheimer’s disease, cardiovascular diseases, autoimmune diseases and cancers. Therefore, many anti-inflammatory drugs are currently used in numerous chronic inflammatory diseases but such therapeutics have undesirable side effects. For example, steroids can cause osteoporosis and impair wound healing, whereas novel selective inducible cyclooxygenase (COX)-2 inhibitors might reduce protective vascular prostacyclin synthesis, leading to an increased risk of thrombosis (Bottone and Barry, 2009). Indeed, experience with tumor necrosis factor-α (TNF-α)-neutralizing therapy has also revealed several complications (Antoni and Braun, 2002). Therefore, continuing research on inflammation and new drug development to overcome the side effects of anti-inflammatory drugs is undergoing.
Recently, new findings on the initiation and resolution of inflammation (ex. inflammasomes and resolvins) have occurred (Lamkanfi and Dixit, 2011; Serhan, 2011). In particular, new knowledge on the resolution of inflammation increases the opportunities for new anti-inflammatory drugs. People understand that termination of acute inflammation due to passive dilution of proinflammatory signals and effectors (Levy, 2010). But, recent evidence suggests that resolution of inflammation is actively mediated by new resolving lipid classes such as resolvins, protectins, lipoxins and maresin (Fig. 1). Therefore, the failure of resolution is considered as one of the causes in chronic inflammatory diseases such as age-related macular degeneration, asthma, atherosclerosis, chronic pulmonary disease, inflammatory bowel disease, multiple sclerosis, rheumatic arthritis and cancer (Lawrence, 2007; Nathan and Ding, 2010).

NEW LIPID MEDIATORS IN RESOLUTION OF INFLAMMATION AND THEIR TARGETS

Resolvins, lipoxins, protectins and maresin are synthesized from arachidonic acid (AA) as well as omega-3 fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Enzymes involved in the biosynthesis of these mediators include COX-2, aspirin-induced acetylated COX-2 (COX-2/Aspirin), 5-lipoxygenase (5-LO), 12-LO and 15-LO (Fig. 2). These biosyntheses occur as transcellular events and the details are recently reviewed by Serhan (Serhan and Petasis, 2011).

Using an unbiased lipidomics and systems approach Serhan’s group identified, characterized and elucidated families of novel resolving lipid mediators from EPA and DHA, the enzymes responsible for oxygenation of omega-3 fatty acids. These include the E-series resolvins (RvE1 and RvE2) derived from EPA, as well as the D-series resolvins (RvD1-D6), the neuroprotectins/protectins (NPD1/PD1), and maresin (MaR1) which is derived from DHA (Serhan and Petasis, 2011). These pro-resolving mediators promote several actions such as arresting PMN recruitment, blocking of leukotrienes (LTs) and prostaglandins (PGs), reducing cytokine release and monocyte recruitment, as well as non-phlogistic removal of apoptotic PMN which leads to tissue homeostasis (Fig. 2). These diverse actions

Fig. 1. Structures of pro-resolving lipid classes of lipids.