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Specialized pro-resolving mediators in renal fibrosis

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ABSTRACT

Inflammation and its timely resolution play a critical role in effective host defence and wound healing. Unresolved inflammatory responses underlie the pathology of many prevalent diseases resulting in tissue fibrosis and eventual organ failure as typified by kidney, lung and liver fibrosis. The role of autocrine and paracrine mediators including cytokines, prostaglandins and leukotrienes in initiating and sustaining inflammation is well established. More recently a physiological role for specialized pro-resolving lipid mediators [SPMs] in modulating inflammatory responses and promoting the resolution of inflammation has been appreciated. As will be discussed in this review, SPMs not only attenuate the development of fibrosis through promoting the resolution of inflammation but may also directly suppress fibrotic responses. These findings suggest novel therapeutic paradigms to treat intractable life-limiting diseases such as renal fibrosis.

1. Introduction

Inflammation plays a critical role in host defence and tissue and wound repair. The trafficking of leukocytes to sites of injury involves integration of elaborate signals generated by proteins, peptides [chemokines and cytokines] and lipid mediators. The infiltrating cells and inflammatory signals drive the subsequent proliferative and maturation stages of the healing response, promoting regeneration and recovery (Nathan, 2002). Therefore, an essential component of effective host defence and restitution of homeostasis is effective and timely resolution of inflammation. Conventionally, the dissipation of inflammatory responses was presumed to reflect a decline in production and degradation of pro-inflammatory mediators including prostaglandins and leukotrienes. It is now clear that distinct mediators acting in an autocrine or paracrine fashion can promote the maintenance of homeostasis (Fullerton and Gilroy, 2016). A major advancement in our understanding of the regulators of resolution of inflammation has been made by investigation of lipid mediator biosynthesis along the continuum of inflammation and its resolution (Serhan et al., 2008). These studies have identified distinct, stereoselective pro-resolving bioactions of lipoxins (Maderna and Godson, 2009), and more recently, resolvins, protectins and maresins (Spite et al., 2014). Such mediators attenuate leukocyte migration, promote macrophage efferocytosis of apoptotic cells at an inflammatory focus, regulate proinflammatory gene expression and promote IL-10 production. The final processes in physiologic wound healing include fibrogenesis, characterised by the production of new extracellular matrix components to replace damaged tissue providing the scaffold for wound closure, remodeling and repair. Failure of resolution can result in persistent fibrogenesis, and collateral tissue damage includes abscess formation, scarring, fibrosis and eventual organ failure. The subversion of resolution may be reflected in many prevalent chronic diseases such as arthritis, diabetes and atherosclerosis associated with chronic, low-level 'sterile' inflammation, characterised by macrophage infiltration and localised cytokine/chemokine production (Libby, 2007; Tabas and Glass, 2013).

Fibrotic disorders represent a leading cause of morbidity and mortality and, with the exception of the liver, fibrosis is typically considered to be an irreversible process. Fibrotic disorders are estimated to contribute to 45% of all-cause mortality in the USA. Effective therapies are of very limited value and the majority of clinical trials have failed (Rockey et al., 2015; Thannickal et al., 2014). The mechanisms underlying the development of fibrosis are shared across multiple organs with subtle but significant differences in the relative contribution of different cell types. Renal fibrosis is the final pathological manifestation of chronic kidney disease (CKD) of diverse aetiologies reflecting an unsuccessful wound healing response to chronic, sustained injury (Duffield, 2014). An estimated 10% of the population worldwide is affected

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by CKD (Jha et al., 2013). Renal fibrosis is characterised by glomerulosclerosis, tubular atrophy and interstitial fibrosis, leading to eventual end-stage renal disease, organ failure and a requirement for renal replacement therapy (i.e. dialysis or transplantation). Diabetic kidney disease (DKD) is the leading cause of renal failure accounting for over 50% of cases of end-stage renal disease (de Boer et al., 2014). DKD reflects the convergence of inflammatory responses to the metabolic and hemodynamic stresses of diabetes in susceptible individuals (Forbes and Cooper, 2013). Current therapies for CKD rely on blockade of the renin angiotensin-aldosterone system (RAAS) (Cravedi et al., 2010; Ruggenenti et al., 2010). However, at best these interventions slow CKD progression, but cannot reverse fibrosis. Therefore, there is an urgent need to develop safe and effective therapeutics for CKD (Forbes and Cooper, 2013). However, while significant improvements in the management of risk factors for diabetic complications such as hyperlipidemia and glycemia have resulted in decreased incidence of stroke, myocardial infarction and amputation, it is noteworthy that renal complications persist, reflecting inadequate therapeutic options and increased survival (Gregg et al., 2014). Therefore, CKD and associated renal fibrosis present a major healthcare burden. Here we will review the potential of specialized pro-resolving lipid mediators [SPMs] in renal inflammation, repair and fibrosis to address this significant unmet need.

2. Specialized pro-resolving lipid mediators

2.1. Lipoxins

Lipoxins (LXs) are endogenously produced eicosanoids with potent anti-inflammatory and pro-resolving effects. They were discovered in 1984 by Serhan *et al* when examining mixed fractions of human leukocytes and were named “lipoxins”, an acronym for lipoxygenase interaction products (Serhan et al., 1984). LipoxinA_4 (LXA_4: 5(*S*)-6(*R*)-15(*S*)-trihydroxy-7,9,13-*trans*-11-*cis*-eicosatetraenoic acid) and Lipoxin B_4 (LXB_4: 5(*S*)-14(*R*), 15(*S*)- trihydroxy-6,8,10,12- eicosatetraenoic acid) are the principal species found in mammals. Serhan and colleagues have shown LXs are generated from the omega-6 fatty acid, arachidonic acid, in a trans-cellular manner by the sequential action of 5-lipoxygenase (5-LO) and either 12-lipoxygenase (12-LO) or 15-lipoxygenase (15-LO) (Serhan et al., 1987). LXs are produced at local sites of inflammation between neutrophils, platelets and resident tissue cells, such as epithelial cells, where they are active within the pico-to nanomolar range. It is reported that LX formation can also be induced by low-dose aspirin which, under cytokine primed conditions, can acetylate cyclooxygenase (COX)-2 and thus shift its activity from that of an endoperoxidase to a lipoxygenase (Claria and Serhan, 1995). The initial consensus that LXs are ‘made local and act local’ as conventional paracrine mediators within inflammatory exudates has recently been challenged by evidence that LXs and other SPMs can be detected in peripheral blood (Colas et al., 2014), human breast milk (Arnardottir et al., 2016), and placenta (Jones et al., 2013) at concentrations consistent with biological responses.

Synthetic LX analogues resistant to enzymatic transformation have been generated and tested for their efficacy as mimetics of native LXs. 15-epi-16-(*p*-fluoro)-phenoxy-LXA_4, [also referred to as ATLa; aspirin-triggered lipoxin analogue] has been demonstrated to preserve renal function in models of ischemic injury (Kieran et al., 2003; Leonard et al., 2002), and was protective in models of lung injury (Martins et al., 2009). A second generation of LX/ATLa analogues, resistant to β-oxidation, have also been generated through insertion of a 3-oxa group. These analogues have similar biologic activity as the 15-epi analogues and displayed efficacy on oral dosing in a model of colitis (Fiorucci et al., 2004). A third generation of analogues features a benzo-fused ring system (O'Sullivan et al., 2007; Petasis et al., 2008). These have proven to be efficacious in promoting resolution and suppressing fibrosis in experimental models of renal and adipose inflammation as will be discussed below (Borgeson et al., 2011, 2015; Brennan et al., 2013).

The original observations on the bioactions of LXs focused on their role as ‘braking signals’ in acute inflammation. This attribution reflected attenuation of prototypic inflammatory responses such as polymorphonuclear leukocyte adhesion and transmigration and eosinophil activation. Importantly, and in contrast to other anti-inflammatory agents, responses to LXs do not compromise host defence (Basil and Levy, 2016; Chiang et al., 2012). Furthermore recent data show that LXA_4 increases host defence and decreases pathogen virulence by inhibiting quorum sensing in Pseudomonas Aeruginosa (Wu et al., 2016). A significant advance in our understanding the continuum of effective physiologic inflammation and a restoration of homeostasis was our discovery that LXs stimulate macrophage efferocytosis of apoptotic leukocytes (Godson et al., 2000; Mitchell et al., 2002). Efferocytosis of apoptotic cells is coupled to numerous processes associated with promoting resolution. In addition to clearance of apoptotic cells pre-empting destructive cellular necrosis, efferocytosis is associated with altering macrophage activation status prompting the release of ‘anti-inflammatory’ cytokines and the biosynthesis of specialized lipid mediators (Dalli and Serhan, 2012; Maderna and Godson, 2009). The LX-mediated response of phagocytic macrophages to apoptotic polymorphonuclear leukocytes was coupled to actin cytoskeletal rearrangement (Maderna et al., 2002; Reville et al., 2006), and mediated through a specific G-protein coupled receptor (GPCR) designated ALX/FPR2 (Maderna et al., 2010).

2.2. Resolvins, protectins and maresins

In studies of exudates over the course of temporally defined inflammation and its resolution, Serhan and colleagues used LC-MS-MS lipidomics to detect a switch in lipid mediator biosynthesis from established proinflammatory agents typified by prostaglandins and leukotrienes to LXs and several families of novel mediators including resolvins, protectins and maresins (Serhan, 2014). Collectively these omega-6 [LXs] and omega-3 [resolvins, protectins, maresins]-derived polyunsaturated fatty acids (PUFA) metabolites are termed SPMs. The stereochemistry and organic synthesis of the SPMs has facilitated investigation of their activities in various experimental systems including animal models and isolated human leukocytes, supporting their role as immunoresolvents, re-establishing homeostasis in physiological responses. Deficits in the generation of, or response to, SPMs may be associated with several pathologies characterised by unresolved inflammation. These include atherosclerosis where plaque instability is associated with decreased levels of SPMs (Fredman et al., 2016), severe asthma (Levy et al., 2005), and increased inflammation in cystic fibrosis airways (Karp et al., 2004).

Resolvins, protectins and maresins are generated from the omega-3 PUFA: eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA). EPA forms E-series resolvins (RvE) by a series of enzymatic reactions involving cytochrome P450, followed by conversion to 18R-hydroxy-5Z,8Z,11Z,14Z,16E-eicosapentaenoic acid (18*R*-HEPE), which can be further transformed by enzymatic epoxidation and 5-LO in leukocytes to form RvEs. Endogenous DHA generates D-series resolvins (RvDs), protectins and maresins. DHA is converted into RvDs by the sequential activation of 15-LO, enzymatic epoxidation and 5-LO, where 17(*S*)-hydroxy Docosahexaenoic Acid (17*S*-HDHA) is the intermediate product. Protectins are generated from DHA via a separate pathway involving 15-LO and enzymatic epoxydation and hydrolysis where 17S-

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