Molecular Aspects of Medicine xxx (2017) 1–9

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Does promoting resolution instead of inhibiting inflammation represent the new paradigm in treating infections?

Jesmond Dalli, PhD *

Lipid Mediator Unit, Biochemical Pharmacology, William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University of London, London, EC1M 6BQ, United Kingdom

ARTICLE INFO

Article history:
Received 20 February 2017
Received in revised form
27 March 2017
Accepted 28 March 2017
Available online xxx

ABSTRACT

Infections arise when the host response is overwhelmed by pathogens leading to organ dysfunction. In some instances patients progress to more severe conditions, including septic shock, that are associated with increased mortality. Current strategies in treating infections aim at either blocking inflammation using inhibitors to pro-inflammatory molecules and/or inhibiting bacterial growth using antibiotics. These approaches find their origins in studies conducted by Joseph Lister who demonstrated that applying carbolic acid to wounds promoted wound healing without suppuration, reducing both the necessity of amputation and mortality. While this approach is still applicable to certain infections, inhibition of the immune response is also associated with increased mortality, especially in septic patients. In many instances sepsis survivors succumb later to persistent, recurrent, nosocomial and secondary infections. This, together with a rise in resistance to many frontline antibiotics, has prompted a search for alternative ways to treat infections. Recent studies investigating processes engaged by the host response during self-resolving infections identified a novel group of mediators, termed as specialized pro-resolving mediators (SPM). These molecules, produced via the enzymatic conversion of essential fatty acids, actively *reprogram* the immune response to promote clearance of invading pathogens, and counter-regulate the production of inflammation-initiating molecules. Furthermore, recent studies also demonstrate that these mediators promote tissue repair and regeneration, essential processes in the re-establishment of barrier and prevention of re-infection. The scope of the present review is to discuss the evidence underpinning the endogenous protective roles of these novel mediators, as well as the evidence demonstrating that dysregulation in their production and actions contribute to disease pathogenesis in infections. This review will also discuss the potential of resolution pharmacology-based approaches in developing new therapeutics for combatting infections that do not interfere with the immune response.

1. Introduction

A significant proportion of cells making up our body are of foreign origin. Indeed, these are derived from the vast number of microorganisms that we carry around every day that form part of our microbiome (Lynch and Pedersen, 2016). To ensure that our interactions with these organisms are not of detriment and to maintain a status of homeostasis the body has evolved a number of mechanisms. The identification of a several of these intricate processes has shed new light onto some of the reasons why organisms with which we co-exist for years at one point become pathogenic. In addition, these new observations provide insights into how pathogenic organisms manage to breach our defence systems causing harm.

Together with the epithelium, where the majority of these host-microbiome interactions occur, the immune system is at the frontline in keeping microbes at bay. In this context both the innate and adaptive arms of the immune system play central roles in ensuring that the myriad of organisms we are in contact with are kept in check. Innate immune cells in particular are the focus of studies investigating how our body maintains this status of homeostasis and clears any invading pathogens. Among the processes that recently received significant attention is the identification of a novel genus of molecules termed as specialized pro-resolving mediators (SPM) that are produced by cells of the innate immune

* William Harvey Research Institute, John Vane Science Centre, Charterhouse Square, London, EC1M 6BQ, United Kingdom.
E-mail address: j.dalli@qmul.ac.uk.

http://dx.doi.org/10.1016/j.mam.2017.03.007

system. These mediators are formed via the stereoselective conversion of essential fatty acids that include arachidonic acid, eicosapentaenoic acid (EPA), n-3 docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA). They are grouped into four families, the resolvins, protectins, maresins and lipoxins. Interested readers are referred to (Serhan, 2017; Serhan et al., 2015) for detailed review of the biosynthetic pathways.

These mediators share fundamental biological actions in the regulation of host responses, which include their ability to counterregulate the production of pro-inflammatory cytokines and chemokines, including TNF-α and IL-1β (Serhan, 2017; Serhan et al., 2015). They also promote the downregulation of inflammation-initiating eicosanoids, including the prostaglandins and leukotrienes, regulate leukocyte trafficking and stimulate macrophages phagocytosis of apoptotic cells, bacteria and cellular debris (Serhan, 2017; Serhan et al., 2015). Recent studies demonstrate that G-protein coupled receptors are responsible for mediating the biological actions of these protective molecules (Serhan and Chiang, 2013). The aim of the present review is to discuss the evidence underpinning the role of SPM in maintaining the homeostatic balance between our body and the trillions of microorganisms that interact with it on a daily basis. This article will discuss the mounting evidence for the role of SPM in directing host responses to various types of pathogens.

2. What is the evidence that SPM are relevant to human disease?

Pro-resolving lipid mediators are evolutionarily conserved chemical signals identified in a diverse number of organisms including planaria (flatworms) (Dalli et al., 2014), tunicates (Knight et al., 1999), frogs (Gronert et al., 1995), mice (Chiang et al., 2012, 2013; Dalli et al., 2015a) and humans (Colas et al., 2014; Dalli et al., 2017b). In humans these mediators are present at bioactive concentrations (i.e. within the fM-nM ranges) in many tissues and organs. In patients with tuberculosis (TB) production of D-series resolvins (RvD) is upregulated potentially as part of the host response to infections. RvD1, 17R-RvD1 and RvD2 were increased in plasma from TB patients when compared with non-TB patients (Frediani et al., 2014). Studies investigating the expression of enzymes involved in SPM biosynthesis found that polymorphisms in the Leukotriene A_4 Hydrolase (LTA_4H), which is involved in the formation of the leukocyte chemoattractant leukotriene (LT) B_4 as well as the EPA-derived SPM resolvin E (RvE) 1, are related to disease severity and outcome in tuberculosis (Tobin et al., 2010).

The role of pro-resolving mediators in controlling infections is further supported by the observation that lipid mediator profiles in human septic patients are correlated with outcome (Dalli et al., 2017b). Increases in plasma levels of select SPM including RvE2, lipoxin (LX) B_4 and RvD2 associate with patients that survive for 28 days post admission to the Medical Intensive Care Unit. In healthy human volunteers increasing the endogenous production of pro-resolving mediators including 17R-PD1 with essential fatty acid and aspirin supplementation correlates with an improved ability of peripheral white blood cells to clear bacteria (Colas et al., 2014). An association between pro-resolving mediator levels and disease outcome was also reported in cystic fibrosis patients where *Pseudomonas aeruginosa* infections are a main cause of demise (Yang et al., 2012). Patients with elevated sputum RvE1 demonstrate improved lung function when compared with patients where RvE1 levels were lower. Furthermore, a correlation was recently found between circulating levels of LXA_4 and disease activity in tuberculosis patients where the levels of this mediator were elevated in patients with active infections when compared with those having latent infections (Lee et al., 2015b). Thus, these findings suggest a protective role for SPM in controlling the host responses to infection and indicate that disease may arise when these pathways are inadequately engaged.

3. What is the experimental evidence for a role of SPM in infections?

Animal models and *in vitro* experiments have provided a wealth of information on the mechanisms activated by SPM. These studies shed light onto how SPM orchestrate the host response to counterregulate the inflammation arising from the recognition of a pathogen by the immune system and to clear the invading organism allowing the host to regain function. The aim of the next section is to review our current understanding of these mechanisms, assessing the tissue specific and pathogen specific responses engaged by the host during infections. The pharmacological actions of the SPM will also be reviewed to highlight their potential utility as novel therapeutics for the treatment of infections.

3.1. Peritoneal infections

Escherichia coli is a coliform bacterium found in the mammalian lower gastrointestinal tract. The majority of *E. coli* strains are harmless and some may be beneficial for example by producing vitamin K_2. However, certain serotypes can become pathogenic leading to, amongst others, urinary tract infections, peritonitis and haemolytic-uremic syndrome. Studies investigating the mechanism engaged by the host response in the clearance of infections have identified several points of regulation for different pro-resolving mediator families. At a tissue level the central nervous system is now appreciated to exert a pivotal role in maintaining tissue resolution tone. Recent studies demonstrate that the vagus nerve promotes the formation of the immunoresolvent *protectin conjugate in tissue regeneration* (PCTR)1 (16R-glutathionyl, 17S-hydroxy-4Z,7Z,10Z,12E,14E, 19Z-docosahexaenoic acid) by group 3 innate lymphoid cells (ILC-3), which in turn regulates peritoneal macrophage responses to bacterial infections (Dalli et al., 2017a) (Fig. 1). The biosynthesis of PCTR1 is initiated by leukocyte 15-LOX in human leukocytes that convert DHA to 17S-hydroxydocosaexaenoic acid, that is converted to 16S, 17S-epoxy-PD and then to PCTR1. This mediator is an immunoresolvent since it actively promotes the termination of bacterial infections, stimulating the uptake and killing of bacteria as well as the repair and regeneration of damaged tissues (Dalli et al., 2015c). Disruption of the vagus reflex dysregulates PCTR1 formation and macrophage phenotype leading to an impaired ability of the recruited leukocytes to efficiently clear pathogens resulting in delayed resolution of infectious inflammation (Dalli et al., 2017a).

Leukocyte recruitment, especially neutrophils, to the site of infection is an essential aspect in the containment and clearance of the invading pathogen. It is now well appreciated that events occurring immediately after recognition of the pathogen by the immune system have a strong influence on outcome (Dalli et al., 2015a; Serhan and Savill, 2005). Recent studies demonstrate that during the early stages of self-resolving *E. coli* infections (i.e. when the host is able to clear the bacterium and turn off inflammation) a novel family of pro-resolving mediators termed *thirteen series resolvins* (RvT) was identified (Dalli et al., 2015a). The formation of these molecules is initiated by the activated vascular endothelium whereby endothelial cyclooxygenase-2 converts n-3 docosapentaenoic acid to 13-hydro(peroxy)-7Z,10Z, 14E,16Z,19Z -docosapentaenoic acid, that is most likely rapidly hydrolysed to 13(R)-hydroxy-7Z,10Z,13R,14E,16Z,19Z-docosapentaenoic acid (Fig. 2). This intermediate is then donated to neutrophils where it is converted to RvT1 (7,13,20-trihydroxy-8,10,14,16Z,18-docosapenta-

Please cite this article in press as: Dalli, J., Does promoting resolution instead of inhibiting inflammation represent the new paradigm in treating infections?, Molecular Aspects of Medicine (2017), http://dx.doi.org/10.1016/j.mam.2017.03.007