Seminars in Immunology 27 (2015) 161–168

Contents lists available at ScienceDirect

Seminars in Immunology

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

Review

New insights into the resolution of inflammation

Derek Gilroy*, Roel De Maeyer

Centre for Clinical Pharmacology and Therapeutics, Division of Medicine, 5 University Street, University College London, London WC1E 6JJ, United Kingdom

ARTICLE INFO

Article history:
Received 24 March 2015
Received in revised form 6 May 2015
Accepted 13 May 2015

Keywords:
Adaptive immunity
Eicosanoids
Chronic inflammation
Macrophages

ABSTRACT

The goal of treating chronic inflammatory diseases must be to inhibit persistent inflammation and restore tissue function. To achieve this we need to improve our understanding of the pathways that drive inflammation as well as those that bring about its resolution. In particular, resolution of inflammation is driven by a complex set of mediators that regulate cellular events required to clear inflammatory cells from sites of injury or infection and restore homeostasis. Indeed, it may be argued that dysfunctional resolution may underpin the aetiology of some chronic inflammatory disease and that a novel goal in treating such diseases is to develop drugs based on the mode of endogenous pro-resolution factors in order to drive on-going inflammation down a pro-resolution pathway. And while we are improving our understanding of the resolution of acute and chronic inflammation, much remains to be discovered. Here we will discuss the key endogenous checkpoints necessary for mounting an effective yet limited inflammatory response and the crucial biochemical pathways necessary to prevent its persistence and trigger its resolution. In doing so, we will provide an update on what is known about resolution of acute inflammation, in particular its link with adaptive immunity.

1. Introdution

Inflammation is a key pathophysiological component of a wide range of diseases, including rheumatoid arthritis, asthma, inflammatory bowel disease atherosclerosis and cancer. Over the past 50 years knowledge concerning the mediators that cause inflammation in various preclinical models and clinical settings has developed to the point that the current mainstay for treating many inflammation-mediated diseases is based on inhibiting the synthesis or activities of these mediators. While non-steroidal anti-inflammatory drugs (NSAIDs), steroids and monoclonal antibodies are effective at treating disease symptoms in specific clinical settings, none of these approaches are curative, and many of them have undesirable side effects. Rather than just focusing on the initiation of the inflammatory response, recent years have seen increasing attention on the other end of the inflammatory spectrum – the resolution of the inflammatory response. Inflammatory resolution is increasingly viewed as an active process involving a number of key mediators, with dysregulation of this process possibly predisposing individuals to the development of chronic inflammatory diseases [1]. While understanding resolution biology will provide important insights into the aetiology of chronic inflammatory diseases, it will also provide new targets for the development of novel anti-inflammatory drugs based on triggering and driving pro-resolution pathways. Such approaches provide the exciting potential to reverse the underlying disease processes of a wide range of inflammatory conditions that have high and unmet medical needs. In this review we will attempt to define "inflammatory resolution" and place it in the context of the broader inflammatory response. This will provide a solid basis for understanding the potential clinical utility of compounds, which can modulate inflammatory resolution processes.

2. What is 'resolution of inflammation'?

It is important to distinguish between inflammatory resolution and inflammatory onset. At onset, local release/activation of soluble mediators (e.g. complement, vasoactive amines, cytokines, lipids) from histiocytes and stromal cells and up-regulation of cell adhesion molecules on the microvascular endothelium collectively facilitate extravascular leucocyte accumulation manifesting in Celsus' cardinal signs of inflammation – heat, redness, swelling and pain (Rudolph Virchoff added loss of function in the 19th century) [2]. This well-characterised phase of the inflammatory response is routinely targeted using drugs including NSAIDS and anti-TNFα that inhibit or antagonise the action of these inflammatory drivers forming the mainstay for treating chronic inflammatory disease. Resolution, however, switches inflammation off. In-as-much as

* Corresponding author. Tel.: +44 020 7679 6933; fax: +44 020 7679 6351.
E-mail address: d.gilroy@ucl.ac.uk (D. Gilroy).

http://dx.doi.org/10.1016/j.smim.2015.05.003
1044-5323/

onset is orchestrated by a host of sequentially released mediators, resolution is an active process that is no longer considered a passive event where the response was hitherto thought to simply fizzle out [3,4]. For instance, a critical requirement for the inflammatory response to switch off is the elimination of the injurious agents that initiated it in the first place. Failure to achieve this first step will lead to chronic inflammation as exemplified by chronic granulomatous disease, which results from a failure of the phagocytic NADPH oxidase enzyme system to produce superoxide and kill invading infections leading to a predisposition to recurrent bacterial and fungal infections and the development of inflammatory granulomas [5]. Successfully dispensing with the inciting stimulus will signal a cessation of pro-inflammatory mediator synthesis and lead to their catabolism. This will halt further leucocyte recruitment and oedema formation. These are probably the very earliest determinants for the resolution of acute inflammation, the outcome of which signals the next stage of cell clearance. The clearance phase of resolution, be it polymorphonuclear leucocyte (PMN)- or eosinophil-driven or adaptive (lymphocyte mediated) in nature, also has a number of mutually dependent steps. The clearance routes available to inflammatory leukocytes include systemic recirculation or local death by apoptosis/necrosis of influxed PMNs, eosinophils or lymphocytes followed by their phagocytosis or efferocytosis by recruited monocyte-derived macrophages. Once phagocytosis is complete, macrophages can leave the inflamed site by lymphatic drainage with evidence that a small population may die locally by apoptosis [6].

Dispensing with the injurious agent leads to the next phase of pro-inflammatory mediator catabolism where levels of cytokines, chemokines, eicosanoids, cell adhesion molecules, etc. must revert back to that expressed during the pre-inflamed state. For prostaglandins (PGs), for instance, the first step in their catabolism (reviewed in detail in Ref. [7]) is the oxidation of the 15(S)-hydroxyl group by a 15-hydroxyPG dehydrogenase, which metabolises E-series PGs as well as other eicosanoids including Lxs, 15-HETE, 5,15-diHETE, and 8,15-diHETE to the corresponding 15-keto compounds. The second step involves the reduction of the $\Delta 13$ double bond by an NADPH/NADH dependent $\Delta 13$–15-ketoPG reductase. Further catabolism of PGs some HETES and Lxs occurs by the beta-oxidation pathway common to fatty acids in general, i.e. via the carboxyl end of the molecule leading to the formation of short-chain metabolites, which are excreted in the urine. Some of these eicosanoids are also excreted following glucuronidation. 5-HETE and LTs undergo beta-oxidation from the omega-terminus following an initial omega-hydroxylation. In terms of chemokines, the atypical chemokine receptors such as D6 possess the inability to initiate classical signalling pathways after ligand binding thereby acting as a type of scavenging system for pro-inflammatory signals such that in TPA-induced skin inflammation D6-deficient mice exhibit an excess concentration of chemokines resulting in a notable inflammatory pathology with similarities to human psoriasis, for review see [8]. In addition, the work of Ariel et al. showed that CCL3 and CCL5 were increased in peritoneal exudates of Ccr5−/− mice during the resolution of acute peritonitis. Transfer of apoptotic PMNs resulted in CCR5-dependent scavenging of CCL3, CCL4 and CCL5. It transpires that CCR5 surface expression on apoptotic PMNs was reduced by pro-inflammatory cytokines and was increased by pro-resolution lipid mediators including lipoxin (Lx)A4 [9]. Thus, endogenous systems exist to facilitate pro-inflammatory mediator clearance and whose function, when it becomes dysregulated, may lead to chronic inflammation. If all of these pathways of stimulus removal, inhibition of granulocyte trafficking, pro-inflammatory mediator catabolism, appropriate cell death/efferocytosis (phagocytosis of apoptotic cells), etc. are followed then acute inflammation will resolve without causing excessive tissue damage and give little opportunity for the development of chronic, non-resolving inflammation.

Each stage of the resolution cascade represents an opportunity to be harnessed to drive ongoing inflammatory diseases down a pro-resolution pathway. Yet, we caution that this will not be a panacea for all diseases driven by ongoing inflammation. We suspect that resolution processes may vary from tissue to tissue and be dependent of the nature of the injurious stimulus. Thus, designing pro-resolution drugs will have to be organ and disease specific. With that comes the need for more appropriate animal models of ongoing inflammation that best reflect the intended human condition. In addition more studies must be focused on examining resolution pathways in healthy and diseased humans.

3. Inflammatory onset

Inflammation is a reaction of the microcirculation; it is a protective response initiated after infection or injury. While both local and systemic responses can be activated, inflammation is an essential biological process with the objective of eliminating the inciting stimulus, promoting tissue repair/wound healing and in the case of infection, establishing memory such that the host mounts a faster and more specific response upon a future encounter. The acute inflammatory response is a complex yet highly coordinated sequence of events involving a large number of molecular, cellular and physiological changes. It begins with the production of soluble mediators (complement, chemokines, cytokines, eicosanoids [including PGs], free radicals, vasoactive amines, etc.) by resident cells in the injured/infected tissue (i.e. tissue macrophages, dendritic cells, lymphocytes, endothelial cells, fibroblasts and mast cells) concomitant with the up-regulation of cell adhesion molecules on both leukocytes and endothelial cells that promote the exudation of proteins and influx of granulocytes from blood [10]. Upon arrival these leukocytes, typically PMNs in the case of non-specific inflammation or eosinophils in response to allergens, primarily function to phagocytose and eliminate foreign microorganisms via distinct intracellular (superoxide, myeloperoxidase, proteases, lactoferrins) and/or extracellular (neutrophil extracellular traps) killing mechanisms [11]. It is likely that the magnitude of the infectious load and its eventual neutralisation signal the next phase of active anti-inflammatory and pro-resolution [12].

In terms of signalling pathways that regulate this very early response to injury/infection, most of our earlier knowledge was garnered from work done on studying members of interleukin 1 (IL-1) and tumour necrosis factor (TNF) receptor families and the Toll-like microbial pattern recognition receptors (TLRs) which in fact belong to the IL-1R family. IL-1 and TNFα represent the archetypal pro-inflammatory cytokines, which are rapidly released upon tissue injury or infection. TLRs recognise microbial molecular patterns, hence the term pattern recognition receptor (PRR) and therefore TLRs represent a germline encoded non-self recognition system that is hard-wired to trigger inflammation. However, there is some suggestion that endogenous ligands may trigger TLRs during tissue injury and certain disease states which may act to promote inflammation in the absence of infection [13]. Although structurally different, these receptors use similar signal transduction mechanisms. Receptor engagement results in recruitment of adaptor proteins, that possess either Toll-IL-1 receptor (TIR) domains in the case of TLRs and IL-1R or death domains (DD) in the case of the TNFR family, linked to the regulation of cell survival [14]. Once recruited these adaptors recruit further signalling proteins that belong to the TRAF family [15,16] and various protein kinases, including IRAK1 and 4 in the case of TIR signalling [17] and RIP kinases in the case of TNFR signalling [18,19]. These