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Review

The resolution of inflammation: Principles and challenges

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ABSTRACT

The concept that chemokines, cytokines and pro-inflammatory mediators act in a co-ordinated fashion to drive the initiation of the inflammatory reaction is well understood. The significance of such networks acting during the resolution of inflammation however is poorly appreciated. In recent years, specific pro-resolving mediators were discovered which activate resolution pathways to return tissues to homeostasis. These mediators are diverse in nature, and include specialized lipid mediators (lipoxins, resolvins, protectins and maresins) proteins (annexin A1, galectins) and peptides, gaseous mediators including hydrogen sulphide, a purine (adenosine), as well as neuromodulator release under the control of the vagus nerve. Functionally, they can act to limit further leukocyte recruitment, induce neutrophil apoptosis and enhance efferocytosis by macrophages. They can also switch macrophages from classical to alternatively activated cells, promote the return of non-apoptotic cells to the lymphatics and help initiate tissue repair mechanisms and healing. Within this review we highlight the essential cellular aspects required for successful tissue resolution, briefly discuss the pro-resolution mediators that drive these processes and consider potential challenges faced by researchers in the quest to discover how inflammation resolves and why chronic inflammation persists.

1. Introduction

Inflammation is a dynamic tissue response mechanism that has developed throughout evolution to defend the host against invasion by pathogens. All animals have innate mechanisms for dealing with pathogen invasion and injury, and even simpler organisms such as protozoans are able to phagocytose infective agents [1]. In the past few decades bacterial defense against bacteriophages and plasmids by clustered, regularly interspaced short palindromic repeats (CRISPRs) was discovered. These sequences represent an adaptive, but also heritable record of past infections and encode small RNAs that target invasive nucleic acids, providing evidence that all kingdoms of life develop protection from other invading organisms [2]. Higher organisms, especially those with developed vasculature, are not only able to sense and react to pathogen presence, but also to detect host injury and initiate complex tissue repair programs, returning the organism to the pre-inflamed phenotype. Dysregulated or persistent inflammation is a driver in the pathogenesis of many diseases, and its untimely resolution represents a process which if targeted could provide new therapeutic avenues for the treatment of a multitude of diseases.

Acute inflammation is the process by which invading pathogens or tissue injury are dealt with in an orchestrated manner to eliminate the source of insult. The initial insult is sensed by tissue macrophages or mast cells (usually by pattern recognition receptors) activating a program of proinflammatory cytokine, chemokine, vasoactive amine and eicosanoid secretion to amplify the immune response. These mediators increase vascular permeability leading to the influx of plasma containing antibodies and other soluble components, such as complement that is required for the opsonisation of bacteria (the humoral immune response), and the dilution of injurious factors. Chemokines produced by resident cells form gradients on the intraluminal surface of the microvascular endothelium, to capture and recruit circulating neutrophils via their chemokine receptors. Activated neutrophils transmigrate through the endothelium into the inflamed tissue and exert potent antibacterial killing mechanisms such as degranulation and the generation of reactive oxygen species (ROS) through oxidative burst [3]. Monocytes follow neutrophils and link the innate and adaptive immune responses, governing whether the insult can be overcome with or without the aid of the adaptive immune system.

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2. Principles of resolution

In order to prevent the progression from acute-resolving to persistent-chronic inflammation, the inflammatory reaction must be actively resolved, inhibiting further tissue damage. Historically, it was believed that the resolution of inflammation was a passive process involving the dilution of chemokine gradients over time, thus circulating leukocytes would no longer sense gradients and be recruited to the site of injury. However, extensive work over the past few decades has revealed that the resolution of inflammation is a carefully managed active process, and deficiency in any of its components may lead to over-active, uncontrolled chronic inflammation.

The resolution of inflammation occurs in overlapping phases governed by the spatial and temporal production of pro-resolving mediators. The processes fundamental to resolution include the limitation or cessation of neutrophil tissue infiltration, the counter-regulation of chemokines and cytokines, the induction of apoptosis in spent neutrophils and their subsequent efferocytosis by macrophages [4], the transformation of macrophages from classically activated to alternatively activated cells, the return of non-apoptotic cells to the vasculature or lymphatics and finally the initiation of healing processes. These events culminate in a return to tissue homeostasis [5]. Macrophages and neutrophils are important cellular components of the resolution process associated with acute inflammation, and increasing evidence suggests that eosinophils play important functions during the resolution of chronic, adaptive inflammatory processes. An effective inflammatory response in turn feeds in to an appropriate resolution response of the host (Fig. 1).

3. Pro-resolving mediators: master governors of resolution

Pro-resolving mediators can function at numerous steps of the resolution process outlined above. Substances which fall under this umbrella are diverse in nature including specialized lipid mediators (lipoxins, resolvins, protectins and maresins) [6], proteins (annexin A1) and peptides [7], gaseous mediators including hydrogen sulphide [8] and carbon monoxide [9,10], a purine (adenosine [11]), as well as neuromodulator (neurotransmitter/neuropeptide) release under the control of the vagus nerve [12,13].

Professor Charles Serhan led the major advancement in the research field of resolution, identifying several classes of specialized pro-resolving lipid mediators using an unbiased systems approach utilizing metabololipidomic analysis of resolution phase exudates. Lipoxins were the first to be identified, and neutrophils proved important for their biosynthesis. Depletion of neutrophils with antisera before the injection of TNF-α in murine air-pouches not only reduced the amount of neutrophils trafficking into the cavity but concomitantly decreased lipoxin A_4 levels by 30% [14]. During the time-course of inflammation, lipid mediator generation undergoes a class switch, whereby pro-inflammatory lipid mediators involved in the recruitment of leukocytes activate the translation of mRNAs encoding enzymes required for the production of potent pro-resolving mediators (lipoxins, protectins and resolvins). The generation of arachidonate-derived eicosanoids, such as prostaglandin-E_2, thromboxane A_2 and leukotriene-B_4 (that exert the classical pro-inflammatory actions of vasodilation, platelet aggregation and leukocyte chemotaxis, respectively) switches to the production of pro-resolution lipoxins [14]. In fact, prostaglandin E_2 plays an essential role by switching the

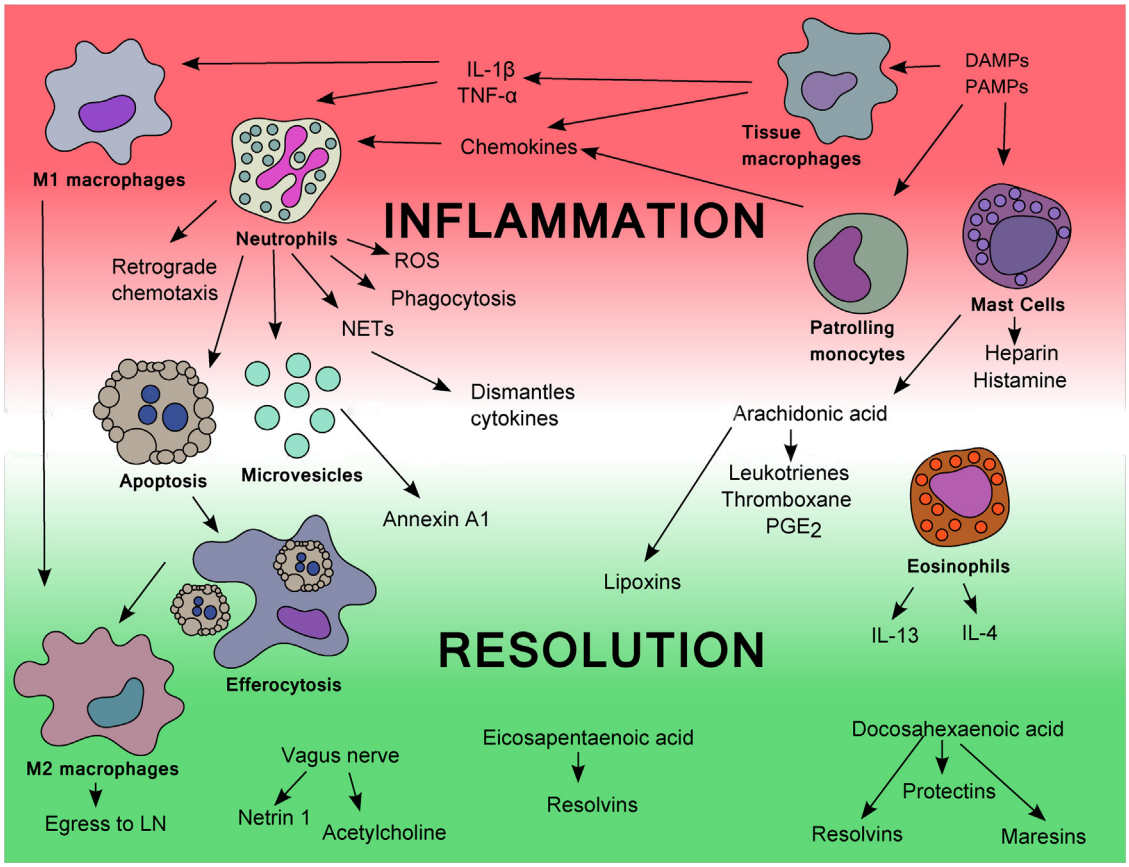

Fig. 1. Essential cellular components and mediators that govern inflammation and resolution.