

Summaries Rossi/Sawatzky: The Resolution of Inflammation

Moir K. B. Whyte, Christopher Haslett and Edwin R. Chilvers
Granulocyte apoptosis

Keywords: neutrophil, eosinophil, apoptosis

Derek Gilroy and Toby Lawrence

The resolution of acute inflammation: a ‘tipping point’ in the development of chronic inflammatory diseases

Summary

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Cell surface molecular changes associated with apoptosis

The mechanisms underlying control of programmed cell death and the functional consequences are beginning to be defined. In this chapter we discuss the implications of the heterogeneity of apoptotic cell phenotype for studies of phagocytosis of apoptotic cells. Delayed apoptotic cell clearance within tissues could potentially drive the progression to late apoptosis and secondary necrosis. Efficient clearance of apoptotic cells by macrophages may affect development of specific immune responses, with necrotic cells promoting activation of lymphocyte responses. Masking of apoptotic-specific membrane alterations may lead to the generation of anti-inflammatory signals, potentially overcoming tolerogenic responses to apoptotic cell uptake. Understanding the contribution that apoptosis-associated membrane receptor alterations make to the development of inflammatory and autoimmune diseases remains an important goal.

Keywords: apoptosis, neutrophil, phagocytosis, surface receptors, immune regulation

Summary

Mauro Perretti and Roderick J. Flower

Anti-inflammatory glucocorticoids and Annexin 1

Understanding the way our body switches off host defence responses has yielded some of the most innovative recent discoveries in inflammation research. In reality the concept is not new, and was already implicit in publications of late 1970s’ which showed that during inflammation, glucocorticoids are increased in the circulation and that these protect the host from over-shooting and ensuing self-inflicted injury. We cover here some of the well-established mechanisms of glucocorticoid efficacy and illustrate in detail one specific example, that of annexin 1. This 37-kDa glucocorticoid-regulated protein is endowed with important homeostatic roles crucial for regulating the inflammatory response. Work during the last 2-3 years has clarified its mechanism of action, identifying a specific G protein coupled receptor as its molecular target. Therefore, the picture that is emerging is of “the annexin 1 system” as a pivotal response in resolving anti-inflammation and maintaining tissue homeostasis after the host response has cleared the inflammogen.

Keywords: dexamethasone, prednisolone, corticosteroids, anti-inflammation, lipocortin 1, neutrophil, trafficking, gene induction, receptor

Summary

Paola Maderna and Catherine Godson

Beyond inflammation: Lipoxins; resolution of inflammation and regulation of fibrosis

Phagocytosis of apoptotic cells plays a pivotal role in developmental processes and in the resolution of inflammation. Failed or delayed clearance of apoptotic cells can result in chronic inflammation and potentially fibrotic disorders. Recent evidence has shown that such processes can be regulated by endogenous mediators, suggesting that specific mimetics may have therapeutic potential in chronic inflammation and in autoimmune disorders. Here we review the evidence that lipoxins and endogenously produced eicosanoids, stimulate phagocytosis of apoptotic cells, describing the underlying mechanisms and the downstream consequences.

Keywords: lipoxin, resolution of inflammation, phagocytosis, macrophages, neutrophils, mesangial cells, cytokines, growth factors, apoptotic cells, anti-fibrotic, annexin-1

Summary

Geoffrey J. Bellingan and Geoffrey J. Laurent

Fate of macrophages once having ingested apoptotic cells: lymphatic clearance or in situ apoptosis?

Macrophages can be removed from the inflamed site by apoptosis or necrosis locally or by emigration. Macrophages are usually seen as long-lived cells resistant to apoptosis, however changes in intracellular levels of anti-apoptotic agents can alter this resistance profile, facilitating apoptosis as the inflammatory process evolves. This may be important especially in relation to regulation of infection where macrophage apoptosis may be as important in pathogen killing as it is for macrophage clearance. In these circumstances, the process of clearing these apoptotic macrophages has not been delineated. Infection can also activate macrophages and inhibit apoptosis, indeed there may be several activation states or populations of macrophages at the inflamed site over time and the importance of this for macrophage clearance and resolution of inflammation are not clear yet. Using sterile inflammatory models macrophage emigration to the draining lymphatics, rather than local apoptosis, has been shown to be the major route for cell clearance. This is highly regulated and the ingestion of apoptotic cells dramatically enhances macrophage clearance. Macrophage adhesion to cells overlying entry to the draining lymphatic vessels is a major site controlling emigration; both β_1 and β_2 integrins are involved. Emigration occurs with resolution of inflammation at many sites including peritonitis, glomerulonephritis and pulmonary inflammation.

Keywords: macrophage, emigration, adhesion, apoptosis, resolution, inflammation

Summary

Charles N. Serhan

Novel lipid mediators in resolution and their aspirin triggered epimers: lipoxins, resolvins, and protectins

Increasing evidence now provides a link between inflammation and many diseases afflicting Western societies that have not been traditionally recognized as having an etiologic basis in aberrant inflammatory responses. The emergence of this new evidence emphasizes the importance of natural resolution. Systematic analysis of contained *in vivo* models of inflammation that undergo spontaneous resolution, using a multidisciplinary approach, demonstrate that resolution of acute inflammation is a highly coordinated program of active responses rather than, as once thought, a passive response. Polyunsaturated fatty acid-derived mediators have specific tasks in resolution: providing local signals that orchestrate leukocyte trafficking and resolution at the tissue level. This chapter highlights the role of anti-inflammatory mediators, lipoxins, and the newly uncovered resolvins and protectins that are generated from ω -3 essential fatty acids during resolution. Identification of these new pathways and potent resolvins and protectins underscores the importance of appreciating the cellular and molecular mechanisms involved in resolution. Moreover, these findings may provide insight into the control of these responses in humans as well as potential leads towards new therapeutic modalities that take advantage of novel pro-resolving mechanisms.

Keywords: Leukocyte, lipid mediator lipidomics, second organ injury, lipoxin, resolvins, protectin, arachidonic acid, ω -3 PUFA, eicosapentaenoic acid (EPA), lipid mediator, resolution, inflammation, DHA, docosatriene, neuroprotectin, lipoxygenase, leukotriene B₄, neutrophil, prostaglandin, anti-inflammatory, inflammatory bowel disease, aspirin

Summary

John L. Wallace and Philip M. Sherman

Resolution of Mucosal Inflammation

Inflammation is a common occurrence in the gastrointestinal tract, partly because of the continual exposure of the mucosal lining to erosive substances and partly because of the large numbers of microbes within the lumen. Regulation of inflammatory processes is, therefore, of crucial importance for the maintenance of mucosal integrity. Not surprisingly, therefore, many of the chemical mediators that play important roles in the resolution of mucosal inflammation are also well known for contributing to the resistance to damage. For example, prostaglandins are potent 'gastroprotective' substances, increasing the resistance of the gastric mucosa to damage induced by substances such as aspirin. These substances are also powerful anti-inflammatory factors. Suppression of prostaglandin synthesis leads to increased susceptibility of the mucosa to injury and to enhancement of acute inflammatory reactions. This review includes a discussion of numerous other endogenous substances that contribute to resolution of inflammatory reactions, and to preservation of mucosal integrity, in the gastrointestinal tract.

Keywords: Ulcer, Inflammatory Bowel Disease, Enteric microbes, Prostaglandins, Nitric oxide, Cytokines, Healing, Enteritis, Gastritis

Summary

Garry M. Walsh and Catherine M. McDougall

The resolution of airway inflammation in asthma and COPD

It is now widely accepted that airway inflammation is the key factor underlying both the pathogenesis of asthma and exacerbations of symptoms in chronic obstructive pulmonary disease (COPD). Inhaled corticosteroids remain the most important anti-inflammatory

treatment for asthma. However, they are relatively non-specific in their actions and their use raises concerns over side effects and compliance issues, particularly in children and adolescents. Moreover, a significant sub-group of asthmatic patients responds poorly or not at all to high-dose inhaled or systemic steroid treatment. In COPD, inhaled corticosteroids have proved to be largely ineffective in preventing long-term decline in patients' lung function. Therefore, much effort is being made to develop novel, more effective, specific and safer therapy for both asthma and COPD. This chapter will consider some of the developments that are targeting airway inflammation, the most significant element of asthma and COPD pathogenesis.

Keywords: Asthma, COPD, corticosteroids, mediator antagonists, phosphodiesterase inhibitors, Protease inhibitors, cytokines, chemokines, neutrophils, eosinophils, adhesion molecules, apoptosis, phagocytosis

Summary

David C. Kluth and Jeremy Hughes

Resolution of glomerular inflammation

Glomerulonephritis is initiated by a wide range of immunological triggers. It is typified by infiltration by inflammatory cells with progression to fibrosis and loss of renal function. However glomerular inflammation can resolve both spontaneously and in response to immunosuppressive treatment. The precise sequence of events remains uncertain but a number of mechanisms are important. These include removal of the initiating insult, modulation of the glomerular cytokine milieu, the removal of injurious leucocytes, altering the phenotype of infiltrating macrophages to favour resolution, clearance of apoptotic cells, prevention of fibrosis and restoration of resident glomerular cell population. This chapter will review the primary drivers of glomerular inflammation, our current understanding of the mechanisms of its resolution and how this can be translated into therapy.

Summary

Andrew Devitt and Christopher D. Gregory

Innate immune mechanisms in the resolution of inflammation

Recruitment of inflammatory cells to a site of infection or tissue damage is an important defence mechanism that is tightly controlled to ensure that an affected tissue returns to its pre-inflamed state following challenge. Removal of inflammatory cells that have infiltrated any tissue is an important step in the resolution of inflammation that requires inflammatory cell death and phagocytic removal of cell corpses by viable resident cells or infiltrating macrophages. Components of the innate immune system - including CD14 - have been firmly implicated in phagocytic clearance of dead and dying cells. This chapter reviews the published role of innate immune factors in this efficient clearance process.

Keywords: Resolution of Inflammation, apoptosis, innate immune system, phagocyte, macrophage, CD14, complement

The Resolution of Inflammation

Rossi, A.; Sawatzky, D.A. (Eds.)

2008, XII, 240 p., Hardcover

ISBN: 978-3-7643-7505-8

A product of Birkhäuser Basel