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INFLAMMATORY DISORDERS: A REVIEW

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ABSTRACT

Acute inflammation is a short-term response that usually results in healing: leukocytes infiltrate the damaged region, removing the stimulus and repairing the tissue. The processes by which acute inflammation is initiated and develops are well defined, but much less is known about the causes of chronic inflammation and the associated molecular and cellular pathways. Inflammatory abnormalities are a large group of disorders which underlie a vast variety of human diseases.

INTRODUCTION

Inflammation is the body's immediate response to damage to its tissues and cells by pathogens, noxious stimuli such as chemicals, or physical injury. Chronic inflammation, by contrast, is a prolonged, dysregulated and maladaptive response that involves active inflammation, tissue destruction and attempts at tissue repair. Such persistent inflammation is associated with many chronic human conditions and diseases, including allergy, atherosclerosis, cancer, arthritis and autoimmune diseases. This Insight highlights recent advances in our knowledge of the exogenous and endogenous inducers of chronic inflammation, as well as the inflammatory mediators and cells that are involved. We hope that these articles will contribute to a better understanding of inflammatory responses, and ultimately result in the design of more effective therapies for the numerous debilitating diseases with a chronic inflammatory component.(1,2)

The immune system is often involved with inflammatory disorders, demonstrated in both allergic reactions and some myopathies, with many immune system disorders resulting in abnormal inflammation. Non-immune diseases with etiological origins in inflammatory processes include cancer, atherosclerosis, and ischaemic heart disease.(3)

A large variety of proteins are involved in inflammation, and any one of them is open to a genetic mutation which impairs or otherwise dysregulates the normal function and expression of that protein.

Examples of disorders associated with inflammation include:

- Acne vulgaris
- Asthma
- Autoimmune diseases
- Celiac disease
- Chronic prostatitis
- Glomerulonephritis
- Hypersensitivities
- Inflammatory bowel diseases
- Pelvic inflammatory disease
- Reperfusion injury
- Rheumatoid arthritis

- Sarcoidosis
- Vasculitis
- Interstitial cystitis

Atherosclerosis

Atherosclerosis, formerly considered a bland lipid storage disease, actually involves an ongoing inflammatory response. Recent advances in basic science have established a fundamental role for inflammation in mediating all stages of this disease from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis. These new findings provide important links between risk factors and the mechanisms of atherogenesis. Clinical studies have shown that this emerging biology of inflammation in atherosclerosis applies directly to human patients. Elevation in markers of inflammation predicts outcomes of patients with acute coronary syndromes, independently of myocardial damage. In addition, low-grade chronic inflammation, as indicated by levels of the inflammatory marker C-reactive protein, prospectively defines risk of atherosclerotic complications, thus adding to prognostic information provided by traditional risk factors. Moreover, certain treatments that reduce coronary risk also limit inflammation. In the case of lipid lowering with statins, this anti-inflammatory effect does not appear to correlate with reduction in low-density lipoprotein levels. These new insights into inflammation in atherosclerosis not only increase our understanding of this disease, but also have practical clinical applications in risk stratification and targeting of therapy for this scourge of growing worldwide importance. Clinical Cardiology: New Frontiers (Inflammation and Atherosclerosis)

Allergies

An allergic reaction, formally known as type 1 hypersensitivity, is the result of an inappropriate immune response triggering inflammation. A common example is hay fever, which is caused by a hypersensitive response by skin mast cells to allergens. Pre-sensitised mast cells respond by degranulating, releasing vasoactive chemicals such as histamine. These chemicals propagate an excessive inflammatory response characterised by blood vessel dilation, production of pro-inflammatory molecules, cytokine release, and recruitment of leukocytes.Severe inflammatory response may mature into a systemic response known as anaphylaxis.

Other hypersensitivity reactions (*type 2* and *type 3*) are mediated by antibody reactions and induce inflammation by attracting leukocytes which damage surrounding tissue.(3)

Myopathies

Inflammatory myopathies are caused by the immune system inappropriately attacking components of muscle, leading to signs of muscle inflammation. They may occur in conjunction with other immune disorders, such as systemic sclerosis, and include dermatomyositis, polymyositis, and inclusion body myositis.(3)

Leukocyte defects

Due to the central role of leukocytes in the development and propagation of inflammation, defects in leukocyte function often result in a decreased capacity for inflammatory defense with subsequent vulnerability to infection.(3) Dysfunctional leukocytes may be unable to correctly bind to blood vessels due to surface receptor mutations, digest bacteria (Chediak-Higashi syndrome), or produce microbicides (chronic granulomatous disease). Additionally, diseases affecting the bone marrow may result in abnormal or few leukocytes.

Pharmacological

Certain drugs or exogenic chemical compounds are known to affect inflammation. Vitamin A deficiency causes an increase in inflammatory responses,(4) and anti-inflammatory drugs work specifically by inhibiting normal inflammatory components. Certain illicit drugs such as cocaine and ecstasy may exert some of their detrimental effects by activating transcription factors intimately involved with inflammation (e.g. NF-κB).(5,6)

Cancer

Inflammation orchestrates the microenvironment around tumours, contributing to proliferation, survival and migration. Cancer cells use selectins, chemokines and their receptors for invasion, migration and metastasis.(7) On the other hand, many cells of the immune system contribute to cancer immunology, suppressing cancer.

Resolution of inflammation

The inflammatory response must be actively terminated when no longer needed to prevent unnecessary "bystander" damage to tissues.(3) Failure to do so results in chronic inflammation, and cellular destruction. Resolution of inflammation occurs by different mechanisms in different tissues. Mechanisms which serve to terminate inflammation include.(3,8)

- Short half-life of inflammatory mediators *in vivo*.
- Production and release of Transforming growth factor (TGF)

- Production and release of Interleukin 10 (IL-10)(12)
- Production of anti-inflammatory lipoxins(11)
- Downregulation of pro-inflammatory molecules, such as leukotrienes.
- Upregulation of anti-inflammatory molecules such as the Interleukin 1 receptor antagonist or the soluble tumor necrosis factor receptor (TNFR)
- Apoptosis of pro-inflammatory cells(14)
- Desensitization of receptors.
- Increased survival of cells in regions of inflammation due to their interaction with the extracellular matrix (ECM)(15,16)
- Downregulation of receptor activity by high concentrations of ligands
- Cleavage of chemokines by matrix metalloproteinases (MMPs) might lead to production of anti-inflammatory factors.(17)
- Production of resolvins, protectins or maresins.

Acute inflammation normally resolves by mechanisms that have remained somewhat elusive. Emerging evidence now suggests that an active, coordinated program of resolution initiates in the first few hours after an inflammatory response begins. After entering tissues, granulocytes promote the switch of arachidonic acid–derived prostaglandins and leukotrienes to lipoxins, which initiate the termination sequence. Neutrophil recruitment thus ceases and programmed death by apoptosis is engaged. These events coincide with the biosynthesis, from omega-3 polyunsaturated fatty acids, of resolvins and protectins, which critically shorten the period of neutrophil infiltration by initiating apoptosis. Consequently, apoptotic neutrophils undergo phagocytosis by macrophages, leading to neutrophil clearance and release of anti-inflammatory and reparative cytokines such as transforming growth factor-β1. The anti-inflammatory program ends with the departure of macrophages through the lymphatics.(18)

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