Inflammation, immunity and allergy

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Abstract

Injury or foreign invasion will instigate a cascade of events directed at eliminating the intruder and augmenting the healing process. This involves the unification of two separate processes (inflammatory and immune processes) to provide an effective host defence. Chemical mediators converge on the site of tissue damage and exert local and distant effects. The immune response is divided into innate and acquired immunity. The immediate, non-specific innate response, combined with the specifically targeted acquired response, provide our major defence mechanisms. Lymphocytes and immunoglobulins are the hallmark of acquired immunity. Regulation of these interlinked systems provide cohesion and a group of soluble proteins called cytokines have a major role. Protective immune mechanisms can sometimes cause detrimental effects to the host. We discuss and classify allergic reactions, in particular, the most severe and potentially life threatening form – anaphylaxis.

Keywords Allergy; cytokines; immunity; immunoglobulins; inflammation; macrophages; neutrophils

Royal College of Anaesthetists CPD Matrix: 2C00; 3I00

Learning objectives

After reading this article, you should be able to:

- describe the acute inflammatory response that occurs following local tissue damage
- differentiate the innate from acquired, and cellular from humoural immune responses
- highlight the multiple regulatory mediators involved, defining their functions and looking at their roles in the critically ill patient
- discuss immunomodulation and its potential role in critical care
- classify allergic reactions and describe the management of an acute anaphylactic reaction

The inflammatory response

Inflammation is a necessary defencive and reparative response when tissue is injured by pathogens or trauma. The aim is ultimately to eliminate causative micro-organisms and initiate a healing process that is appropriate and controlled. The inflammatory process is designed to transport the necessary components of the body's response to the site of injury, where a regulated cascade of events can occur.

The main features of the inflammatory response are:[1]

- **Vasodilation**, thereby increasing blood flow to the affected area.
- **Increased vascular permeability** to facilitate diffusion of components to the injured site.
- **Cellular infiltration** by inflammatory mediators.
- **Activation** of immune and enzyme systems.

In health, extracellular fluid is typically void of pro-inflammatory mediators and the cells required to fight pathogen invasion. Inflammation therefore promotes the migration of these components to where they are required. Vasodilation occurs soon after the initial insult, with histamine from mast cell release being the predominant influence. The increased capillary capacity promotes the movement of leucocytes to the site of injury and the increase in vascular permeability, also facilitated by histamine, allows them to enter damaged tissue. Fluid exudate consequently forms in the interstitium due to changes in the colloid osmotic pressure.

Cellular infiltration by neutrophils and macrophages then occurs via a process of margination where blood flow in the site of injury actually slows and leucocytes leave the central axial blood stream to come into contact with the endothelium. The leucocytes then begin a process of rolling whereby they align themselves with the endothelial wall forming bonds. This stage is mediated by the selectin family of transmembrane adhesion receptors, with P-selectin the most prominent. The process of cellular adhesion to the endothelium is dependent on leucocyte integrins interacting with endothelial ICAMS (intercellular adhesion molecules) and VCAMS (vascular cell adhesion molecules). Once adhered to the endothelium they emigrate through it, down a chemotactic gradient in a process called diapedesis. This involves the leucocyte assuming a flattened form and using pseudopodia to negotiate between the much smaller vascular pores and into the extravascular space. The activation of leucocytes is triggered by multiple immune and enzymatic processes that ultimately result in suppuration, healing and repair of the injured site.[2] These regulatory processes also help ensure that an excessive response is inhibited thus preventing further tissue and organ destruction.

Immunity

Immunity is the balanced state of having an adequate system to fight infection, while having adequate tolerance to avoid inflammation, allergy and autoimmune dysfunction.[2] There are two types of immunity; innate and acquired (or adaptive).

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Innate immunity

Innate immunity consists of anatomical, physiological, cellular and molecular barriers to pathogens. Importantly it is immediate, non-specific and does not require previous exposure to antigen. These barriers include body surfaces (skin, mucous membranes), antibacterial secretions (unfavourable gastric pH, salivary lysozymes and lactoperoxidase) and stasis prevention (mucociliary activity, coughing, sneezing, vomiting and diarrhoea). In addition, the innate immune system comprises the complement protein system along with active immune cells and interferon.

The receptors associated with the innate immune system are encoded on the genome and have the ability to detect threats via expression of families of pattern recognition receptors (PRRs).[3] These include Toll-like receptors (TLRs), Nod-like receptors (NLRs), Rig-I-like receptors (RLRs), C-type lectin receptors (CLRs) and cytosolic DNA receptors. The localization of PRRs reflects the specific ligands they sense. When activated these receptors lead to production of inflammatory mediators that coordinate further recruitment of immune cells to the site of injury.

The complement enzymatic system is synthesized by the liver and is designed to enhance the activity of both the innate and the acquired immune responses. It is comprised of two pathways; the classical and the alternative. In the classical pathway, antibodies bind antigen during a foreign invasion and the subsequent complex is recognized by complement proteins that trigger a cascade of inflammatory events (acquired). The alternative pathway is initiated by exposure to carbohydrate chains found on the surface of micro-organisms (innate). During the complement cascade, each precursor is cleaved into two parts (C3 to C3a and C3b, C4 to C4a and C4b etc) until C9a and C9b are generated. All of these complement proteins help facilitate the three major functions of this system, which include:

- Chemotaxis and inflammation (C3a, C5a), thereby recruiting phagocytes to the site of injury,
- Opsonization of pathogens (C3b), where they are tagged for destruction by phagocytes,
- Development of membrane attack complexes (MAC) (C5-9b). These specialized peptides adhere to the cell surface, disrupting the phospholipid bilayer and cause cell lysis.

The cells of the innate immune system include granulocytes, mast cells, natural killer cells and monocytes, none of which require previous pathogen exposure to carry out their functions. Mast cells are typically found on mucosal surfaces and have a crucial role in allergic responses. Similarly, eosinophils and basophils also have a major role in allergy, releasing histamines, leukotrienes and heparins. Neutrophils are another group of granulocyte and comprise more than 50% of normal circulating white cells. They are the first to attack pathogens and form the body's most aggressive cellular response to infection. They will be discussed further below. Natural killer (NK) cells target virus-infected cells and tumour cells, releasing chemicals to promote cell lysis and death. It was initially thought that NK cells were non-specific and lacked immune memory recall, but it is now appreciated that the reverse may be true and that in some instances NK cell memory responses to viral infections are well established and so they play an active part in both innate and adaptive immune responses.[4]

Interferon is another defence mechanism against viral insult. It is composed of cytokines that are released by virally infected host cells. Currently there are three types of interferons classified by their nucleotide sequence, interaction with specific receptors, chromosomal location, structure and physicochemical properties.[5] A high level of antiviral protection is achieved by IFN-α, IFN-β and IFN-λ. Interferon essentially prevents viruses from binding to cells and disrupts viral mRNA. It is important to note that these molecules do not have actual anti-viral properties but instead act as signals to other cells to produce anti-viral agents.

Acquired/adaptive immunity

Acquired immunity requires a prior exposure to an antigen and involves antibodies and lymphocytes. It is dependent on memory and recognition of prior pathogens with antigen-specific memory cells generating a more forceful response on re-exposure. This system is therefore typically slower in its initial response to attack with 72–96 hours required to generate specific T cells and antibodies. Acquired immunity can be further divided into cellular and humoural immunity.

Cellular immunity

Cellular immunity is mediated by T lymphocytes that are produced in bone marrow but mature in the thymus. They provide defence against most viruses and have a regulatory role in immune mechanisms. T cells defend against organisms that infiltrate into cells where antibodies and complement cannot access.[2] They have a unique antigen T-cell receptor (TCR) on their cell membranes that recognizes specific peptide sequences bound to major histocompatibility complexes (MHCs) on antigen-presenting cells and infected cells. The TCR and MHC interaction allows T cells to activate and proliferate.

In humans, MHC is also known as human leucocyte antigen (HLA). There are two classes, MHC class 1 and MHC class 2, with numerous molecules per class. MHC class 1 molecules are present on all nucleated cells of the body and cytotoxic (killer) T cells are the main responders. In contrast, MHC class 2 molecules are only found on lymphoid tissue cells with T helper cells primarily activated.

Cytotoxic T cells destroy host cells harbouring any foreign antigen such as viruses, tissue graft cells and tumour cells. Helper T cells modulate responses of other immune cells. They have the ability to activate other lymphocytes and macrophages to upgrade the level of overall immune response by releasing cytokines.[6] Circulating helper cells are capable of unrestricted cytokine expression and are guided into a focused pattern of cytokine release based on signals received at the outset of infection.[1] Circulating helper cells account for 70% of circulating T cells.

Neutrophils

Neutrophils are the most abundant leucocyte in humans and their aggregation is the hallmark of acute inflammation. They are released into the circulation from bone marrow in an inactive form and remain in this state for 4–10 hours before marginating and entering into tissue pools where they will survive in an activated form for 1–2 days. As alluded to earlier, chemotaxis

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