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 uniting of two separate process (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 immunoglobulinsr 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

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Learning objectives

After reading this article, you should be able to:

- describe the acute inflammatory response that occurs following tissue damage of local infection
- compare and contrast the innate and acquired immune responses
- explain the specific roles of the regulatory mediators involved in the inflammatory and immune systems
- classify allergic reactions and describe the initial management of an acute anaphylactic reaction

The inflammatory response

Inflammation involves the integration of a series of biological processes with the ultimate goal being destruction of the invading pathogen, removal of debris and commencement of healing and repair of the host. The inflammatory response follows a similar pathway regardless of the initial trigger (micro-organism invasion, trauma, etc.), which leads to the release of several proteins causing a cascade of events resulting in the inflammatory response.

Main features of inflammatory response include:[1]

- vasodilation (increasing blood flow to affected area)
- increased vascular permeability (allowing diffusion of mediators to the site)
- cellular infiltration (by inflammatory mediators)
- activation (of immune and enzymatic systems)

Localized *vasodilation* occurs after the initial insult, increasing blood flow to the affected area. This is predominantly caused by histamine released from mast cells. The result is an influx of phagocytic leucocytes and plasma proteins, both involved in the defence response. Histamine will also *increase vascular permeability* (enlarging capillary pores) at the site allowing further inflammatory mediators to enter the damaged tissue.[1] These mediators are now in the interstitial space and cause a change in the colloid osmotic pressure, resulting in tissue oedema.

Cellular infiltration results in large numbers of leucocytes (neutrophils and macrophages) congregating at the inflamed area within an hour. The movement of leucocytes to the injured site requires adhesive interactions between leucocytes and the endothelium. Once adhered to the endothelium they must cross into the tissues in a process called diapedesis.[2] This involves the leucocyte assuming a flattened form to move through the much smaller pore. Four to five times the normal amount of neutrophils will congregate within a few hours. Macrophages arrive slower but have a longer lasting presence at the site of injury.

The *activation* of these leucocytes will elaborate various mediators and directly trigger a number of enzymatic processes (elaborated below; immune response), which provides a co-ordinated response to injury or infection. This process may ultimately result in suppuration, healing and repair, and even chronic inflammation states. The final result depends on the type of tissue involved and the extent of tissue destruction that has occurred, which are in turn related to the cause of the injury and the immune response to it.[3] In addition, it is important to note that inflammation must be tightly regulated to avoid injury to normal tissue or an excessive inflammatory response, which can result in organ injury.

Immunity

Immunity is the balanced state of having adequate biological defences to fight infection, disease or other unwanted biological invasion, while having adequate tolerance to avoid inflammation, allergy and autoimmune diseases. There are two types of immunity: innate and acquired.

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Innate immunity

Innate immunity is a non-specific, rapid response, which does not require previous exposure to the offending antigen and is the first line of defence. Examples include mechanical barriers (skin), antibacterial secretions (low gastric pH) and stasis prevention (coughing, vomiting). The main components include inflammation (described above), the complement system, natural killer cells and interferon.[2]

The complement system is an enzymatic system comprising of two pathways: the classical and the alternate. The classical pathway is initiated by exposure to antibodies produced against a specific foreign invader (acquired), whereas the alternate pathway is initiated by exposure to the carbohydrate chains found on microorganisms (innate). Both pathways lead to the production of membrane attack complexes (MAC), which fragment the microorganisms and cause cellular lysis. The complement system also augments and reinforces the inflammatory process.[3]

Natural killer (NK) cells target virus-infected cells and tumor cells. They recognize the features of these cells by a means that is yet not completely understood. Destruction is by release of chemicals causing cell lysis and death. They provide an immediate non-specific response before the acquired system is activated.

The release of interferon is a viral-related defence mechanism. Interferon is composed of a group of three related cytokines.[2] A virally infected host cell releases interferon which interferes with the replication of the same or even unrelated viruses. It binds to the plasma membrane of neighbouring and distant cells warning them of a potential viral attack. It does not have direct anti-viral effects but triggers the host cells to produce anti-viral enzymes.

Acquired immunity

Acquired Immunity requires prior exposure to an antigen and involves antibodies and lymphocytes. Acquired immunity requires that the host recognize's the microorganism as being foreign, initiate a specific response and ultimately eliminate it. It can be further classified into cellular and humoral immunity.

Cellular immunity

Cellular immunity is provided by T-lymphocytes, which provide defence against most viral infections and play an important regulatory role in immune mechanisms. T cells defend against invaders that infiltrate into cells where antibodies and complement systems cannot reach. They are antigen specific and possess unique receptor proteins, T-cell receptors (TCR), on their plasma membrane.

Activation of T cells requires the presence on the cell surface of both foreign antigen and self-antigen, also known as major histocompatibility complex (MHC) molecules. After exposure to a novel antigen it can take several days for activated T cells to launch a cell-mediated attack.[2] Lymphoid tissue initiates a primary non-specific response. Memory T cells move to all areas of the body ready to commence an immediate secondary response if the same antigen is encountered in future.

The two main types of T cells: cytotoxic (killer) and helper.

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[3] (inflammatory mediators). 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. They are the most abundant of the T cells accounting for 70% of circulating T cells.

Neutrophils

Neutrophils are the 'initial responders' against infectious agents. They are recruited to the site of injury within minutes and are the hallmark of acute inflammation. Released into the bloodstream in a non-activated state from bone marrow they marginate (position themselves adjacent to blood vessel endothelium) in tissue pools and have a half-life of 1–2 days (in activated form). Measuring on average 12–15 micrometers in diameter they are the most abundant leucocytes in humans. Neutrophils contain cytoplasmic granules full of cytotoxic substances, proteinases, hydrolases and cytoplasmic membrane receptors.[4] The production of free radicals (reactive oxygen and nitrogen intermediates) plays an important role in how neutrophils cause cell destruction. They also engulf pathogens by phagocytosis. Reactive oxygen species produced by neutrophils are involved in pathological conditions including acute respiratory distress syndrome (ARDS). Chemotaxis describes a process whereby neutrophils migrate towards a site of infection or inflammation. Cell surface receptors detect inflammatory mediators (e.g. interleukin-8, interferon) present at these sites. A recently discovered mechanism of binding pathogens, involves the expulsion of the neutrophil's nuclear contents, to form neutrophil extracellular traps[5] (NET's). The released nuclear contents are largely composed of DNA and form extracellular fibres.

Phagocytosis

Phagocytosis is a complex process composed of several morphological and biochemical steps.[1]

1. Identification and binding to phagocyte surface: reasonably effective for bacteria and viruses but less so for proteins and encapsulated bacteria. To overcome this antibodies are directed against the capsule allowing the organism to be ingested by the Fc receptors.
2. Engulfment: pseudopodium formation, which is protrusion of membranes to surround the target-when the target is fully enclosed by membrane a 'phagosome' is formed.
3. Fusion with lysosome: the phagosome moves deeper into the cell and fuses with a lysosome, forming a phagolysosome. Lysosomes contain hydrogen peroxide, oxygen free radicals, peroxidase, lysozyme and hydrolytic enzymes.
4. Release of hydrolytic enzymes leading to destruction of ingested cells. This is known as an oxidative burst resulting in digestion of the phagolysosomal contents.
5. Release of destroyed material: termed exocytosis, with subsequent pus formation.

Opsonization is a term used to describe the coating of organisms by molecules, which speeds up the phagocytic process. Examples include the Fc portion of antibody and complement (C3).