Acute inflammation

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Inflammation is a reaction to injury, irritation, or infectious agents, such as microbes. It involves various physiopathological processes, including vascular responses and the migration and activation of leukocytes. The reactions of blood vessels allow the distribution of inflammatory mediators and leukocytes to the site of inflammation, where they can exert their effects.

Acute inflammation is a swift and transient response that occurs within seconds or minutes and lasts for several minutes to a few days. It can result from a variety of factors, such as physical or chemical trauma, bacterial infections, or allergies to foreign proteins. Its primary aim is to flood the affected tissue with inflammatory exudate and convey proteins, fluid, and cells that mediate local defences. Neutrophils are the predominant leukocyte cell type involved in this initial response. The process includes the destruction and removal of biological agents and the breakdown of damaged tissues and debris.

The five cardinal signs of inflammation are:

- Redness (rubor),
- Swelling (tumor),
- Heat (calor),
- Pain (dolor)
- and loss of function (functio laesa).
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Mediators of inflammation

Autacoids

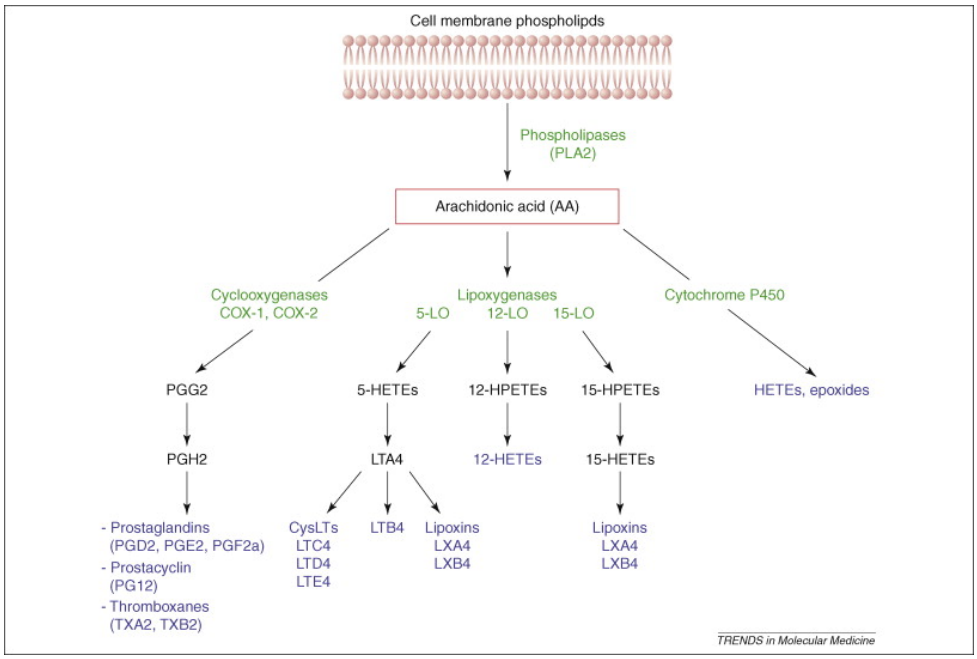
Autacoids are short-lived biomolecules that act as local hormones in the vicinity of their synthesis. Those implicated in inflammation are commonly referred to as inflammatory mediators. While their effects are mostly localised, they can be produced in large quantities and reach significant concentrations in the circulation, leading to systemic effects. These mediators have diverse biological actions, including modulation of the activity of smooth muscles, glands, nerves, and other tissues. They act as local hormones and therefore exhibit paracrine effects.

Some notable autacoids are:

- Mast cells release **histamine**, which is responsible for most acute allergy symptoms, including vasodilation, increased vascular permeability, bronchoconstriction, and increased mucus production.
- **Bradykinin** and **substance P** are peptides that also cause vasodilation, increased vascular permeability, itch, and pain. Substance P can also activate leukocytes.

Eicosanoids

Prostanoids and **leukotrienes** are mediators of inflammation that are derived from arachidonic acid (AA) liberated from cell membranes by phospholipase A2. They are synthesized by the enzymes cyclooxygenase (COX) and lipoxygenase (LOX), respectively. Prostaglandins, such as PGE2, cause vasodilation, pain, and fever. Inhibition of COX activity is a key therapeutic target in anti-inflammatory therapy.



Cytokines

Cytokines are small proteins produced mainly by leukocytes, endothelial cells, fibroblasts, and stromal cells. They direct the inflammatory response, stimulate or suppress it, and attract leukocytes to the site of inflammation (chemotaxis). The two main cytokines involved in acute inflammation are **tumour necrosis factor (TNF)** and **interleukin-1 (IL-1)**. These cytokines activate leukocytes and endothelial cells, and induce many of the systemic effects of illness, such as fever, malaise, and inappetence.

Processes of inflammation

Acute inflammation is characterized by three major physiological processes: **vasodilation, increase in vascular permeability,** and **emigration of leukocytes from the microcirculation.**

Vasodilation is induced by inflammatory mediators, such as histamine, prostacyclin, and nitric oxide, which lead to relaxation and widening of vessels, resulting in an increase in blood flow and the heat and redness of inflammation.

Structural changes in the microvasculature permit plasma proteins and leukocytes to leave the circulation, leading to an increase in vascular permeability.

Bacterial toxins, pro-inflammatory cytokines, and other mediators activate the endothelium, leading to the expression of cell adhesion molecules on the luminal surface. Leukocytes, mainly neutrophils in acute inflammation, stick to the endothelium and migrate through the vascular wall into the interstitial tissue, drawn in by increasing concentrations of specific cytokines called chemokines. Once in the tissues, neutrophils may release enzymes and oxygen free radicals, which can destroy microbes and foreign material but may also cause damage to bystander tissue and ultimately lead to loss of function.

Inflammatory fluid

Oedema is the leakage of relatively pure fluid into tissues. **Phlegmon**, on the other hand, refers to fluid leakage along with large amounts of inflammatory proteins and leukocytes (neutrophils). While oedema can be due to both inflammatory and non-inflammatory causes, phlegmon is always due to inflammatory causes. It is worth noting that the term phlegmon is not commonly used, and in most circumstances, the term for inflammation in the affected tissue is used (e.g. cellulitis in soft tissues, myositis in muscle).

Effusions are caused by increased vascular permeability and leukocyte recruitment. They are of two types: transudates and exudates. Transudates have minimal protein and cell content and occur in non-inflammatory conditions, while exudates occur in inflammatory conditions and have high protein and cell content. The type of effusion in body cavities depends on the degree of vascular permeability and leukocyte recruitment.

- **Transudates** are fluids with low protein and cell content that occur when there is minimal increase in permeability and leukocyte recruitment, which are uncommon in inflammatory diseases and more often found in non-inflammatory conditions such as congestive heart failure and protein deficiency diseases like liver and renal failure.
- When there is a significant increase in vascular permeability, a fluid called an **exudate** escapes into the tissues, along with plasma proteins and leukocytes. Exudates are primarily associated with inflammation.
- **Modified transudates** are fluids that contain low levels of protein and cells and can occur in both inflammatory and non-inflammatory disease. They result from a moderate increase in permeability that allows proteins to escape from the vessels, but with minimal leukocyte involvement.

Inflammatory fluids are composed of various constituents that play a role in the inflammatory process. These components include a fluid containing a mixture of salts that dilute toxins or pathogens and increase drainage from tissues to lymph nodes. Plasma proteins, including inflammatory mediators, antimicrobial molecules, antibodies, clotting factors, and fibrin, are also present. **Fibrin**, a polymerised form of fibrinogen, forms a meshwork in inflamed tissues, holding the damaged area together, blocking the migration of bacteria, and aiding the migration of leukocytes. Leukocytes, primarily neutrophils, exit vessels at the site of inflammation and release enzymes, free radicals, cytokines, and other inflammatory mediators. They also phagocytose and degrade foreign material, which can destroy microbes and foreign material, but may also cause damage to bystander tissue.

Pathological features of acute inflammation

Serous, catarrhal, fibrinous, and **suppurative inflammatio**n are four manifestations of increased vascular permeability due to inflammation.

- The least severe form of inflammation is **serous** inflammation, which manifests in a minimal increase in vascular permeability in a relatively mild inflammatory setting. Serous exudate, which may also be called modified transudate, contains only low molecular weight solutes and water, resulting in a yellow, straw-like colour and very low levels of protein and few cells. Examples of inflammatory responses that cause serous inflammation include burns injuries, skin blisters, and effusions into body cavities related to viral infections.

- **Catarrhal** inflammation is characterised by the formation of exudate on mucosal surfaces, such as the respiratory tract, pharynx, or intestine. Inflammation stimulates the glands at the surface to produce mucus, which combines with cell debris and inflammatory cells in the exudate.

- **Fibrinous** inflammation is a severe pattern that arises from greater vascular permeability due to injury. Fibrinogen, a high-molecular-weight plasma protein, can only exit through large defects in the blood vessel wall. When a vessel leaks due to injury, fibrinogen is cleaved to form insoluble fibrin, which coats all available surfaces. A fibrinous exudate is a hallmark of inflammation in body cavities such as the pericardium and pleura. Fibrin appears as an eosinophilic meshwork of threads or an amorphous coagulated mass. In these areas, inflammation typically has a mixed serofibrinous character, starting with a serous exudate that later becomes serofibrinous or fibrinous due to its component of large-molecular-weight fibrinogen.

- **Suppurative** or **purulent** inflammation is characterised by the production of pus, a fluid composed of neutrophils, necrotic tissue elements, and proteolytic enzymes that digest microbes and tissue components. It is a characteristic response to pyogenic bacteria. Neutrophils engulf microbes and become activated, releasing their proteolytic enzymes after they die.

- An **abscess** is a localised collection of pus caused by suppurative inflammation in response to pyogenic bacteria. It is characterised by the formation of a wall of fibrous tissue around the necrotic tissue and neutrophils. The wall is formed in an attempt to confine the abscess.

- **Empyema** is the accumulation of pus within a body cavity, particularly the pleura.

Other features of inflammation

- **Pain** is one of the hallmark symptoms of inflammation, which may be caused by damage or injury to peripheral nerve endings, pressure on nerve endings due to tissue swelling, and the effects of inflammatory mediators on nerve endings. Certain inflammatory mediators, such as cytokines and prostaglandins, can enhance the sensation of pain, acting on the peripheral nervous system and pain pathways in the spinal cord.

- **Pruritus**, or **itch**, frequently accompanies local skin inflammation. Inflammatory mediators, such as histamine and substance P, activate the itch pathway, which is mediated by a

different set of nerve fibres than those involved in pain sensation. Scratching the tissue can lead to self-trauma and further inflammation, and the reflex is to desire scratching rather than pulling away from the source of injury.

- **Fever**, or **pyrexia**, can be induced by inflammatory mediators circulating in the bloodstream. Activated leukocytes can release cytokines TNF and IL-1, which stimulate the hypothalamus, the brain's "thermostat" centre, causing an increase in the set-point temperature. Local production of prostaglandin E in the brain further increases the set-point, leading to stimulation of body processes that produce or conserve heat. Fever may be beneficial for some immune system processes, but excessive fever is harmful to the animal.

Resolution of inflammation

The resolution of the inflammatory process is a crucial aspect of tissue repair. The body can switch off inflammation through various mechanisms, including neutrophil apoptosis, reduction in chemokine signals attracting leukocytes, macrophage switch from pro-inflammatory to anti-inflammatory, and stop signals such as lipoxins. Failure to resolve inflammation can lead to chronic inflammation, which is associated with various diseases.

Systemic inflammation (sepsis)

Sepsis is a severe systemic inflammatory response that can result from various conditions that induce severe inflammation, such as intestinal torsion in horses. In this case, bacterial endotoxins that are released into the bloodstream from the damaged gut can cause the systemic release of inflammatory mediators, including cytokines and eicosanoids. These mediators can elicit a range of effects, including systemic vasodilation, activation of fibrin within vessels, and generalised activation of leukocytes. The net result of these effects is a marked decrease in circulation through tissues, as well as generalised tissue injury, which can lead to multiple organ failure and death.