Chronic inflammation and healing

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Chronic inflammation results from persistent tissue insult, which may not always be preceded by an acute inflammatory response, particularly in cases of low-grade inflammation. Chronic inflammation is characterized by alterations in the inflammatory cell population, with a decrease in acute inflammatory cells and an increase in macrophages and lymphocytes, ongoing tissue damage, and tissue healing that involves fibrosis and scar tissue formation.

- **Alterations of the inflammatory cell population.** Chronic inflammation is characterized by a shift in the inflammatory cell population towards macrophages and lymphocytes, with a concomitant decrease in acute inflammatory cells such as neutrophils. Typically, at least three days are required for sufficient macrophages to accumulate, while lymphocyte infiltration may take up to 7-10 days. Plasma cells may also be present.
- **Ongoing tissue damage**
- **Tissue healing**. Fibrosis and the development of scar tissue.

Causes of chronic inflammation

Chronic inflammation can result from persistent tissue damage, which may not always be preceded by an acute inflammatory response, particularly in cases of low-grade inflammation. Common causes of chronic inflammation include foreign bodies, autoimmune diseases, persistent infections, and hypersensitivity/allergic reactions. **Foreign bodies** such as grass awns or inorganic materials like coal dust inhalation can result in a persistent nidus of irritation and consequential chronic inflammation. In **autoimmune diseases**, the immune system targets the host's own tissues, and the cause of inflammation is never cleared. **Persistent infections** can evade clearance by the immune system, allowing them to persist as a focus for inflammation. **Hypersensitivity/allergic reactions** occur when animals are exposed to environmental antigens, leading to chronic inflammation.

Forms of chronic inflammation

Chronic inflammation can take various forms and may overlap with acute inflammation.

Type of inflammation	Acute	Chronic
Fibrinous	+	-
Serous	+	-
Necrotizing	+	-
Eosinophilic	+	+
Suppurative/Purulent	+	+
Abscessation	+	+ (encapsulated)
Granulomatous	-	+
Lymphoplasmacytic	-	+

Lymphocytic/lymphoplasmacytic (also known as non-suppurative) inflammation

- Lymphocytic inflammation is characterized by the abundance of **lymphocytes**, including T lymphocytes and B lymphocytes, and plasma cells. This type of inflammation arises as a result of persistent antigenic stimulation, which triggers a predominance of lymphocytes. While other cell populations, such as neutrophils and macrophages, can also be present to a varying degree, the inflammation often develops perivascularly around blood vessels. In some cases, microscopic nodules of lymphocytes, called lymphoid follicles, may develop, especially in horses. Lymphocytic inflammation is most commonly seen in autoimmune and hypersensitivity diseases, but can also develop in infectious diseases, especially of viral origin.

Granulomatous inflammation

- Granulomatous inflammation is defined by **macrophages** as the predominant cell type, and is typically focal or multifocal. Granulomas appear as white-yellow nodules within tissues that may coalesce, and can be difficult to distinguish from neoplastic tumours. During chronic inflammation, macrophages secrete inflammatory mediators and phagocytose foreign material, presenting antigens to lymphocytes to induce adaptive immunity. Activated macrophages enlarge with abundant eosinophilic cytoplasm and are called epithelioid. In cases where the inflammatory insult is resistant to phagocytosis, macrophages fuse together to form giant cells.

- Several subtypes of granulomatous inflammation are recognized:
    - **Pyogranulomas** are characterized by the presence of central necrosis and neutrophils, with macrophages surrounding the necrotic tissue. This type of inflammation is often seen in cases of fungal and bacterial infections such as *Actinobacillus* and *Actinomyces* infections, as well as foreign bodies contaminated with bacteria, such as plant awns.
    - **Caseating granulomas/necrogranulomas** are characterized by central necrosis surrounded by macrophages, lymphocytes, plasma cells, and fibrovascular connective tissue peripherally. The necrotic centre may mineralize over time and has a cheesy appearance grossly, hence the name (caseous means cheesy). This type of inflammation is most commonly due to infectious agents such as *Mycobacterium tuberculosis* or parasites (often with eosinophils).
    - In some cases, **histiocytic inflammation** occurs instead of typical nodular granulomas, characterized by diffuse infiltration of macrophages into the tissue. Histiocyte is another term for macrophage, and while it is also acceptable to call it granulomatous inflammation, it is still different from nodular granulomas.

Eosinophilic inflammation

- Eosinophilic inflammation is characterized by an abundance of **eosinophils** and is frequently associated with parasitic disease, but can also develop in allergic disease such as asthma. It may appear green in colour in focal eosinophilic inflammation, such as parasitic nodules in tissues, as eosinophils contain green granules.

Chronic inflammation may persist beyond the acute stage, and neutrophil-dominant inflammation can become chronic-active inflammation. Chronic abscesses are typically surrounded by a dense fibrous capsule.

Tissue destruction in chronic inflammation

Chronic inflammation can lead to tissue damage due to the release of inflammatory mediators such as proteases and reactive oxygen species by leukocytes, direct cellular destruction by phagocytosis or induction of apoptosis, and tissue ischemia due to thrombosis or vascular damage.

Healing

Healing starts concurrently with the inflammatory process after tissue insult, but complete healing is usually unsuccessful until resolution of inflammation.

Most tissues heal through **regeneration** and **repair**. Some tissues, such as bone, have specific healing mechanisms.

Regeneration

- Regeneration is dependent on cell type, preservation of connective tissue, and absence of necrotic debris or infection. It is the **replacement of damaged tissue** with the original cell type.
- More specialized tissues have a more limited capacity to regenerate. Cell populations can be classified into three broad categories for regenerative potential.
    - **Labile cells**, such as the epidermis, gastrointestinal epithelium, and hematopoietic cells, are constantly undergoing turnover and have the ability to fully regenerate as long as the tissue scaffold remains intact.
    - **Stable cells** have the ability to undergo mitosis if necessary and are capable of complete regeneration as long as the tissue scaffold remains intact. These cells are normally quiescent and include hepatocytes, osteocytes, and renal tubular epithelium.
    - **Permanent cells**, such as neurons and cardiac myocytes, are considered terminally differentiated and have minimal ability to replicate. Therefore, regeneration does not occur in these types of tissues.

Repair

- Repair is the process of **replacing damaged tissue with fibrous connective tissue**, commonly known as scar tissue. The normal function of the replaced tissue is lost, as fibrous tissue provides only structural support. Repair is the only means of healing in tissues composed of permanent cells, while in tissues with regenerative potential, it occurs in competition with regeneration. The initial repair of tissue deficits is through the formation of granulation tissue, which is a temporary, highly vascular, and densely cellular type of connective tissue.

Note: Granulation tissue and granulomatous inflammation are distinct processes. Granulation tissue is a type of temporary connective tissue formed during tissue repair, whereas granulomatous

inflammation is a chronic inflammatory response characterized by the presence of macrophages as the predominant cell type.

- Granulation tissue is a non-painful, soft, pink to red, moist, and bumpy tissue that is composed of loose, oedematous connective tissue containing fibroblasts and leukocytes, and immature blood vessels arranged perpendicularly to the surface. A coagulum of fibrin, which forms a protective barrier, typically overlies the surface. (A scab is a dried deposit of fibrin over a wound.)
- During the process of granulation tissue formation, the **inflammatory phase** begins with the clearance of debris and destroyed tissue by phagocytic leukocytes, including neutrophils and macrophages. The **proliferative phase** involves angiogenesis, which is stimulated by local hypoxia and the production of angiogenic cytokines by endothelial cells, macrophages, and platelets. These cytokines trigger endothelial cells to produce collagenases that break down basement membrane and disassociate pericytes, and the endothelial cells form into a bud which then canalizes and anastomoses with other branches to form vascular loops. Fibroplasia also occurs during the proliferative phase, which involves the migration of fibroblasts along the fibrin scaffold into revascularized tissue under the influence of growth factors. These fibroblasts secrete extracellular matrix, initially as a fine reticulin network, and connective tissue is remodelled along stress lines with further deposition of type I collagen. During the **maturation phase,** the granulation tissue becomes mature connective tissue, and collagen within the scar remodels and contracts, while atrophy of fibroblasts and microvasculature also occurs, leaving a relatively acellular, poorly vascular scar.

Examples of healing in tissues

Primary intention healing

- Primary intention healing occurs when wound edges are in direct apposition. The process begins with the formation of a blood clot that is replaced with granulation tissue, and then a thin fibrous scar. The steps include clearing tissue debris and wound contamination, epithelial covering of the wound, formation of granulation tissue, orientation of collagen fibres, and progressive maturation of granulation tissue into a fibrous scar over the course of approximately one month.

Secondary intention healing

- Secondary intention healing occurs in cases of extensive tissue loss, resulting in more intense inflammation, greater volume of granulation tissue, and more extensive contracture as the scar matures. This may restrict local movement or deform adjacent structures.

Factors affecting healing

The healing process may be impaired by a wide variety of factors, including:

- **Infection/necrosis**: Granulation tissue cannot form in the presence of necrotic tissue or persistent infections, as it requires viable tissue for development. Wound dehiscence is a common consequence of ongoing tissue damage and inflammation.
- **Nutrition**: Insufficient vitamin C intake hinders the maturation of collagen, while insufficient protein availability limits the substrate for repair.
- **Wound movement and pressure**: Granulation tissue is fragile and unable to handle excessive mechanical stress.
- **Foreign bodies**, including sutures: Act as a nidus for persistent inflammation and resultant tissue necrosis.
- **Impaired blood supply**: Hypoxia inhibits cellular viability, reducing healing.
- **Hormones**: Glucocorticoids are strong anti-inflammatory agents that also hinder collagen synthesis and promote the breakdown of connective tissue.
- **Concurrent disease**: Diabetes mellitus predisposes to infection and circulatory issues.
- **Age**: Wound repair is slower in older animals.

Examples of aberrant healing

Proud flesh

- Proud flesh is an excessive proliferation of granulation tissue that leads to formation of tumour-like masses, commonly seen in horses.

Keloid

- Keloids are excessive, dense formations of scar tissue that develop following some skin wounds. They are often unsightly and occur more commonly in individuals of African descent.

Potential complications of scarring

Strictures

- Scar tissue formation around hollow organs can cause obstruction by narrowing the internal lumen.

Adhesions

- Adhesions are fibrous tissue attachments that can develop between adjacent organs within body cavities, potentially entrapping organs or impairing normal function. They are particularly common following fibrinous inflammation.

Restriction of movement

- Scar tissue contraction can lead to reduced range of motion, especially in limbs.