

A Cute Inflammation

The Setting

Inflammation is the body's response to a traumatic event.

The inflammatory response is an attempt to:

- mitigate the attack,
- destroy the invading organisms or chemicals,
- repair the damage, and
- return the area to a state of homeostasis.

Creates:

- Redness = *rubor*,
- Swelling = *tumor*
- Heat = *calor*
- Pain = *dolor*, and
- possibly Loss of Function = *functio laesa*.

1. The Defensive Line-up

The First Line of Defense

- Mechanical Barriers: Skin, mucous membranes, hair
- Chemical Barriers: mucus, tears and saliva (all of which contain lysozymes), sweat and the lactic acid mantle, stomach acids.
- Hyaluronic acid beneath the epithelial tissues

All are components of non-specific innate immunity

The Second Line of Defense

Phagocytosis and the inflammatory response = non-specific innate immunity.

The Third Line of Defense

Specific learned immune response = acquired immunity

Cellular activation is specific to the nature of the attack

Involves cells like Natural Killer, T & B Cells and learned antibody reactions

2. The Offensive Line-up

Infection = Pathogenic invasion by parasites, bacteria, viruses, fungi

Chemical trauma = radiation, toxins, environmental chemicals, allergens

Physical trauma = extremes of temperature incl. heat, cold; extremes of pressure, rupturing of, or damage to, tissues incl. blunt and/or penetrating impacts

Foreign Bodies = splinters, dirt, basically anything that gets in that does not belong there incl. surgical staples, stitches, adhesives from band-aids.

Necrosis = tissue death from physical or chemical injury (incl. infarction episodes)

3. The Defense Players

These are the **Leukocytes**, a.k.a White Blood Cells, the **Macrophages** and the **Mast Cells**

Leukocytes:

- **Basophils:** Are granulocytes that create a chemical trail for other leukocytes to follow. They secrete **leukotrienes**, which attract and activate neutrophils and eosinophils; **histamine**, which acts as a vasodilator; and **heparin**, which inhibits blood clotting. =0.5% WBC's.
- **Neutrophils:** Are granulocytes that spend their time in the connective tissues killing bacteria. They do this in one of two ways: i) simple **phagocytosis**, ii) the **respiratory burst**, by degranulation of enzymes into the surrounding tissues, which in turn produces superoxide, H₂O₂, and HClO (hyperchlorite) ions, which then creates a killing zone around the neutrophil. This event is an indiscriminate killing event...think of these guys like suicide bombers...they don't care what the kill (self-included) provided they get bad guys too! = 60-70% WBC's.
- **Eosinophils:** Are granulocytes that **protect against parasites and allergens**. They kill by producing superoxide, H₂O₂, and neurotoxic proteins. Like Neutrophils, these guys tend to be self-destroying, indiscriminate chemical killers in the local area. They also stimulate basophil and mast cell activity, phagocytize antigen-antibody complexes, and enzymically control the effect of histamine. = 2-4% WBC's.
- **Monocytes:** Are agranulocytes and represent the **progenitors of macrophages**. They circulate in the blood until they are needed at which point they leave the blood vessels and transform into macrophages = 2-8% WBC's.
- **Lymphocytes:** Are agranulocytes and **incl. NK, T & B cells**. They are mostly involved in specific immunity. They present antigens to activate other cells involved in the immune response. Natural Killer Cells are part of the immune surveillance, patrolling the body looking for trouble. When NK cells find an enemy cell they secrete perforins, which basically create a hole in the enemy cell, which is often enough to kill it, if that doesn't do the job the NK cells secrete granzymes, which destroy the enemy cell enzymes and trigger apoptosis. Lymphocytes also stimulate production of and also produce Interleukin. = 25-33% WBC's.

Macrophages: Are what monocytes become once they migrate into the connective tissue and transform into phagocytes. Dendritic cells are macrophages that are already resident in the connective tissues, but they are derived from different stem cells. Dendritic cells capture foreign materials and present them to

an immune cell to mount an immune response. Macrophages are your **basic cellular clean-up crew**; they phagocytize invasive pathogens and bacteria, damaged tissues as well as spent leukocytes. Specialized macrophages occur in the CNS = microglial cells, in the lung tissue = alveolar macrophages, and in the liver = hepatic macrophages.

Mast Cells: Are granulocytes found in connective tissues that produce **histamine** and **heparin** (like the basophils), and are sentinel cells in the connective tissues. They are armed with IgE antibodies that are specific to environmental antigens. Once triggered they release the histamine and heparin.

4. The Chemical Mediators

Histamine: Powerful **vasodilator** secreted by Basophils and Mast Cells.

Heparin: **Anticoagulant** secreted by Basophils and Mast Cells.

Bradykinin: Secreted by mast cells, endothelial (gut) and peri-vascular tissues, stimulates a **pain** response, **vasodilation**, vascular permeability, and acts as a **neutrophil attractor**. Causes bronchial smooth muscle contraction, and lowers BP^o.

Cytokines: Secreted by WBC's, mast cells, and macrophages, incl. TNF, interleukins and interferons, they play **chemotactic** roles (esp. neutrophils, lymphocytes & eosinophils) in the inflammation response.

Interleukins: A group of ~20 **chemical messengers** btwn lymphocytes and antigen-presenting cells. Can be synthesized by leukocytes, macrophages, lymphocytes, epithelial cells and fibroblasts. Act as WBC activators.

Interferons: Produced by T-cells to **inhibit viral reproduction**, and act as a chemotactic pathway for recruitment of macrophages, **activate macrophages and NK cells**. Also produced by infected leukocytes and act as 'last-gasp chemotactic message' to surrounding cells.

Tumor Necrosis factor: A cytokine which is produced by lymphocytes and macrophages esp., recruits and **activates macrophages** and **causes apoptosis in cancer** cells. Promotes blood clotting.

Leukotrienes: Produce by many types of cells, **vasodilators** that also promote **neutrophil chemotaxis**. Also stimulate smooth muscle contraction esp. in allergic response.

Prostaglandins: Secreted by platelets, endothelial and peri-vascular tissues, promotes neutrophil diapedesis, chemotactic to neutrophils. A class of chemicals with opposing properties, some are **vasodilators**, others are **vasoconstrictors**. Stimulators for both **pain** and inflammation.

Serotonin: Produced by platelets, causes smooth muscle contraction, **attracts neutrophils**.

Fibrinogen: Soluble component of blood plasma, **plasma-clotter** that forms fibrin, **keeps pathogens localized**, forms **transient scaffolding** for repair tissues.

Platelet Activating Factor: Produced by basophils, causes platelets to aggregate. **Chemotactic** to other leukocytes, and promotes degranulation. Enhances adhesion of WBC's.

5. The Repair Team

Fibroblasts: Structural connective tissue repair cells that secrete collagen, ground substance for tissue growth.

Platelets: Aka Thrombocytes are fragments of megakaryocytes in the bone marrow that get shed into the blood stream via thrombopoiesis. They secrete i) neutrophil & monocyte chemotactic compounds, ii) vasoconstrictors, iii) clotting factor and iv) platelet-derived growth factor, which stimulates mitosis in fibroblasts.

6. The Timeline of Events

There is a distinct sequence of events that begins with a triggering event and ends with repair of the injury site.

- **Trigger**
- **Release** of defense agents, WBC's, immune responders
- **Amplification** of response by recruiting more WBC's and initiating clean-up and repair until healing has occurred
- **Stop** once the threat has been contained and eliminated.

Phase 1:

At the site of injury, the first response is vasoconstriction (lasting only a few seconds) followed by vasodilation. The first stage is controlled by nervous stimulation, chemical mediators and cytokines. The chemical mediators begin to lay down a chemotactic trail that will attract leukocytes to the site of the injury. Some mediators will stimulate smooth muscle contraction especially in the bronchi and the gut.

Vasodilation has several effects. It slows down blood flow in the area of the injury, therefore promoting settling of the WBC's. WBC's then undergo margination and attach to the vascular wall as they roll along looking for a point of egress. WBC's leave the blood vessels via a process called diapedesis.

The whole point of vasodilation and increase vascular permeability is to induce the delivery of WBC's.

Phase 2:

Phase 2 is the stage of the acute inflammation. It is at this stage that the four (or five) signs appear at the injury site. One of the most important aspects of the inflammation is to sequester and contain any invading pathogen, such that it is unable to spread. It is in this role that fibrinogen creates a wall of sorts adjacent to the injury site, while heparin prevents blood clotting in the immediate area of the injury.

Once in the connective tissues, the WBC's go to work on mitigating the nature of the injury. At the same time, fluids from the blood leak into the connective tissue as 'exudate', which creates the inflammation and a local edema. The exudates may be clear, red or yellow. When yellow, the exudates is called pus. It contains WBC's, pathogens, degraded tissues and the debris created by phagocytosis.

Ongoing recruitment of leukocytes peaks ~6 to 24 hrs post-injury. The neutrophils are the first responders and they hit peak concentrations first. The macrophages hit peak concentrations up to 48 hrs post-trauma, and initiate the healing response.

The pathogen is attacked by phagocytes and antibodies, particularly the neutrophils in the case of a bacterial insult. It is the bradykinins and leukotrienes that help to guide the leucocytes to the injury site via chemotaxis. Each phagocyte can engulf as many as ~100+ foreign bodies before they trigger their own apoptosis. *Note: In phagocytosis, the microbe/foreign body is engulfed as an endocytic engulfment. The resulting vacuole containing the engulfed microbe/foreign body, is then fused with a lysosome, which then digests the contents of the vacuole without damaging the cell contents of the phagocyte.*

The process of resolution involves the clearing away of all injurious stimuli, plus all the chemical mediators used in the response process, the cellular debris caused by the injury and resultant phagocytosis. Much of the clearing-up process is completed by macrophages. It is the macrophages that trigger tissue repair, inform the third line of defense about the potential infection present and secrete inflammatory chemical mediators.

The injured cells are then replaced in the best structure possible (if original architecture is lost, scarring, associated with permanent loss of function = fibrosis, will occur). If possible, normal function is restored.

Initially fibrin is laid down as protein strands that trap the platelets to form a basic wall. The repair process is performed in the extracellular matrix as fibroblasts lay down collagen as a structural scaffold upon which tissues can be generated. Integrin molecules bind the collagen fragments together as granulation tissue and epithelial regeneration and proliferation occurs.

Sources:

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Saladin: Anatomy & Physiology

Fox: Human Physiology

Talaro and Chess; Foundations in Microbiology

Wikipedia and NIH websites.