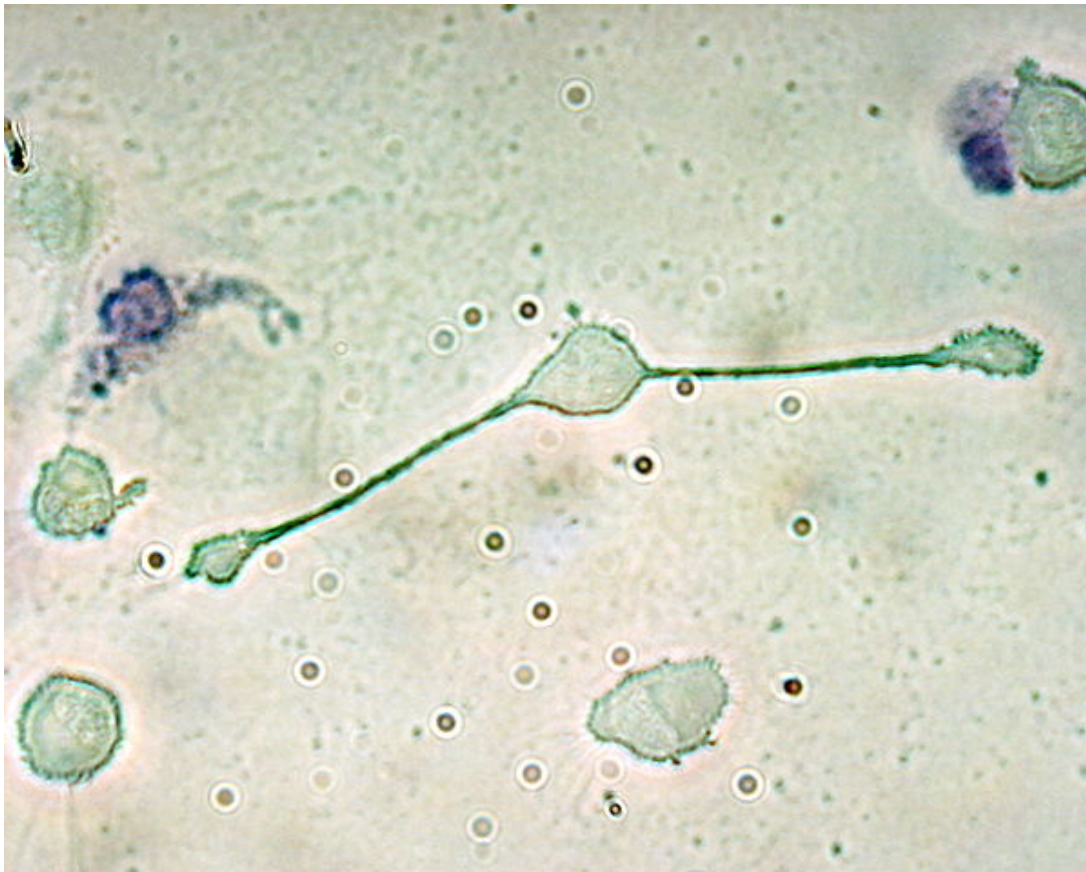


Innate Immune System: Components and Complement System

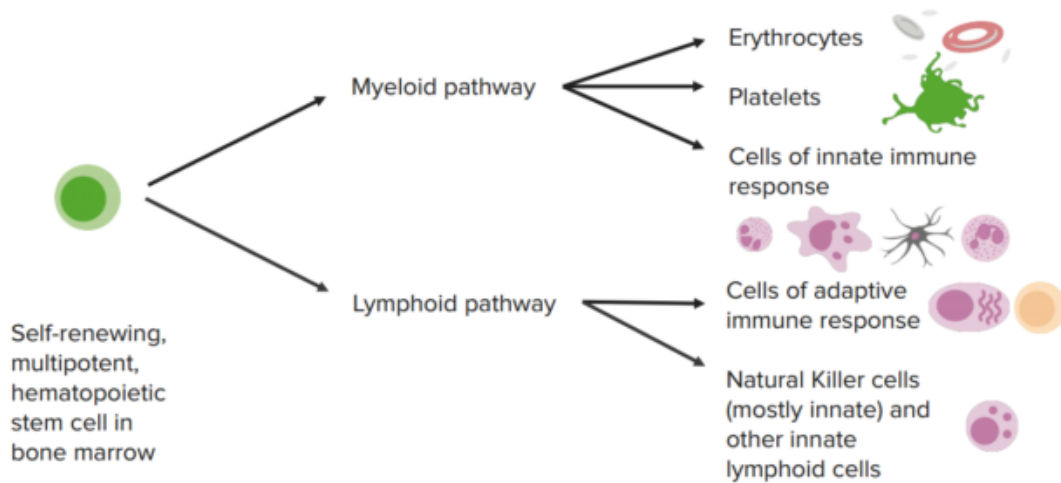
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The immune system is essential for our organism to survive. Without the ability to distinguish friend and foe, we would not stay alive for very long.

Functionally we can differentiate between specific and non-specific immune responses. The unspecific immune response is like our body's first protective shield against pathogens. In the following article, you will get to understand the mechanisms of this immune response in a quick overview.



Hematopoiesis



Features and Components

Nonspecific immune response has three important features that differentiate it from specific immune response: Nonspecific immune response is innate, is unspecific against pathogens, and has no immunological memory. Thus, nonspecific immune response also is called **innate immunity**. Innate immunity is determined by the genome and therefore cannot adapt to environmental changes. Phylogenetically (in terms of evolution), innate immunity is older than adaptive immunity.

Furthermore, **the innate immune system can recognize antigens as a whole, which means that antigens do not have to be degraded and presented first.** Nonspecific defense is especially **fast** and takes place within seconds or minutes after the first contact with an antigen.

Nonspecific immune response is made up of numerous cell types with different functions. However, the response involves different noncellular (humoral) components, which are messengers that are able to cause local or systemic reactions. One such component is the **complement system**. The complement system is part of the nonspecific immune response, but because it can also be activated by components of the specific immune response, the complement system serves as a connection between both systems.

Remember: The nonspecific immune response:

- Is innate (not acquired).
- Is unspecific against pathogens.
- Has no immunological memory.
- Can recognize antigens as a whole.
- Occurs very quickly (within minutes).

Cellular components







Cells of the nonspecific immune system can be found **in all body tissues**, as well as in the blood and lymphatic fluid, ensuring that the cells can react quickly to invading pathogens at any time. Most of the cells take up antigens via phagocytosis (e.g., neutrophil granulocytes). Dendritic cells, monocytes, and macrophages are so-called antigen-presenting cells. Such cells can take up antigens, phagocytize them, then present them for other cells and initiate a specific immune response.

On the contrary, eosinophil granulocytes perform exocytosis and release vesicles containing toxic substances and enzymes in their surroundings. Natural killer cells are lymphocytes and kill cells that have been infected with a pathogen or show neoplastic changes. Natural killer cells do so by initiating natural cell death (apoptosis) via cell-surface molecules.

Remember: Cellular components of the nonspecific immune system are:

- Dendritic cells.
- Monocytes and macrophages.
- Neutrophil and eosinophil granulocytes.
- Natural killer cells.

Moreover, all cells that are part of **inflammatory processes** are part of the nonspecific immune response because those cells produce messenger substances (e.g., endothelial cells, fibroblasts, thrombocytes, keratinocytes).

Neutrophil		Phagocytosis
Monocyte and macrophage		Phagocytosis
Dendritic cell		Activation of T cells
Follicular dendritic cell		Activation of B cells
Eosinophil, basophil, and mast cell		Production of inflammatory mediators
Natural killer (NK) cell and other innate lymphoid cells (ILCs)		NK cell killing of infected cells; diverse functions of ILCs

Phagocytic cells

- **Neutrophils** are short-lived cells that leave blood and enter tissues.
- **Monocytes** leave blood to develop into relatively long-lived macrophages.

Neutrophils and monocytes bind to blood vessel endothelium using adhesion molecules and are attracted by a concentration gradient of chemotactic factors.

Phagocytic cells use pattern-recognition receptors (PRRs) to recognize pathogen-associated molecular patterns (PAMPs). Pathogens also can become coated with substances (opsonins), which are additionally recognized by phagocytic cells.

Once engulfed by phagocytic cells, a pathogen is destroyed by reactive oxygen intermediates generated by a respiratory burst, as well as by a number of non-oxygen-dependent killing mechanisms.

Phagocytosis

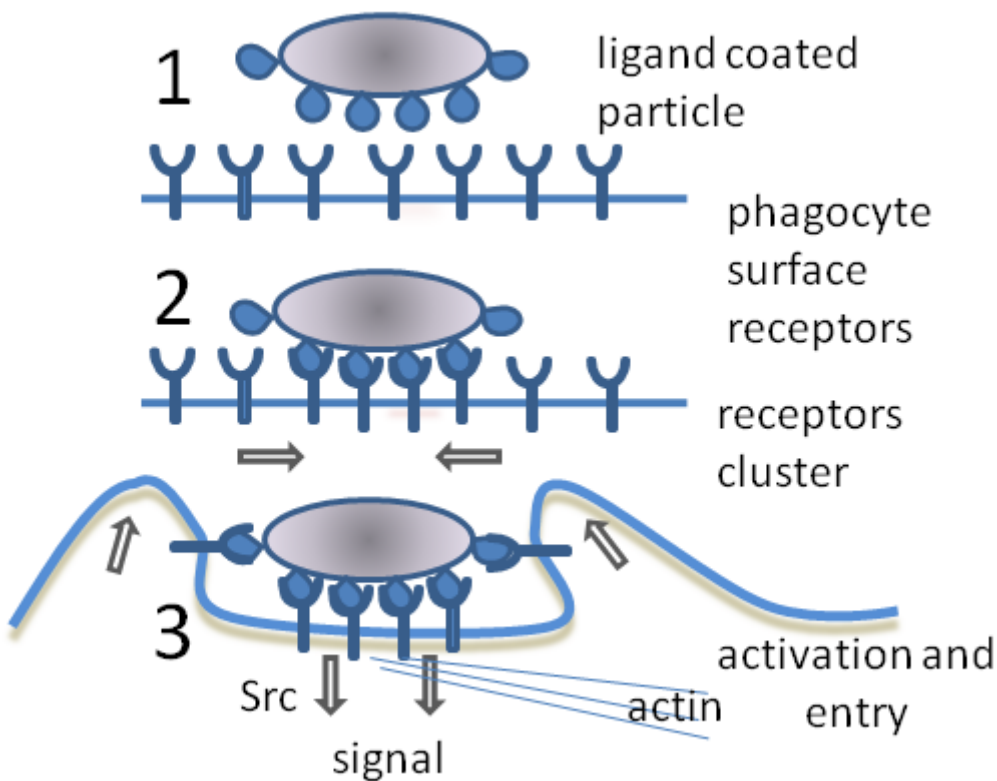


Image: "Phagocytosis in three steps: Unbound phagocyte surface receptors do not trigger phagocytosis. Binding of receptors causes them to cluster. Phagocytosis is triggered and the particle is taken up by the phagocyte," by Graham Beards. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

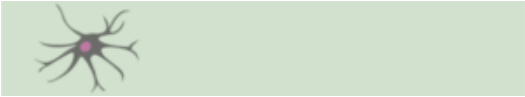
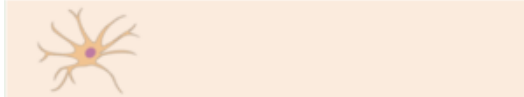
Microbicidal activity of phagocytic cells

Oxygen-dependent	Oxygen-independent
O ₂ ⁻ (superoxide)	Lysozyme: cleaves peptidoglycan
1O ₂ (singlet oxygen)	Defensins: form channels in bacterial membranes
·OH (hydroxyl radical)	Lactoferrin: chelates iron
H ₂ O ₂ (hydrogen peroxide)	Proteases (e.g., elastase)
HOCl (hypochlorite)	




NO (nitric oxide)	
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Note: In addition, neutrophils can extrude their DNA and granule contents to produce neutrophil extracellular traps (NETs) containing lysozyme, elastase, defensins, etc.

Dendritic cells

Dendritic cells	Follicular dendritic cells
	
Derived from hematopoietic stem cells	Derived from mesenchymal stem cells
Present throughout the body	Only present in germinal centers of secondary lymphoid tissues
Initially phagocytic	Never phagocytic
Posses MHC class II and costimulatory (e.g., B7) molecules	Lack of MHC class II and costimulatory molecules
Activate helper T cells	Do not activate helper T cells, but are specialized to show antigen to B cells

Production of inflammatory mediators

Eosinophil	Basophil	Mast cell
		
Present in blood and tissues	Present in blood	Present in mucosal and connective tissues
Characteristically releases major basic protein	Releases histamine, prostaglandins, and leukotrienes	Releases histamine, prostaglandins, and leukotrienes


Innate lymphoid cells




One type of ILC, the natural killer cell, induces apoptotic cell death in infected cells using:

- Fas/FasL caspase pathway
- Granzyme/perforin pathway

Other types of ILCs have functions similar to helper T cells and regulatory T cells of the adaptive response.

Cells of the adaptive immune response

Helper T cell		Helps activate macrophages, cytotoxic T cells, and B cells
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Regulatory T cell		Suppresses other cells of the immune response
Cytotoxic T cell		Kills infected cells
B cell and plasma cell		Produce antibodies

Humoral and Local Acting Messenger Substances

The noncellular components of the nonspecific immune system include a range of different **cytokines**. Cytokines are proteins that influence growth and differentiation of cells. Cytokines of the nonspecific immune system are interleukin (IL)-1, IL-6, tumor necrosis factor- α (TNF- α), and interferon- α (INF- α).

IL-1, IL-6, and TNF- α activate additional inflammatory cells and communicate with the specific immune system. As so-called endogenous pyrogens, those three cytokines also trigger an increase in body temperature. Fever ensures that immune cells can carry out their work in their **optimal operating temperature**, so the immune response becomes efficient. INF- α , which is produced by granulocytes and fibroblasts, inhibits the replication of viruses in the host cell and activates natural killer cells.

Another part of the humoral and local acting messenger substances are **acute-phase proteins**, which are produced in the liver after stimulation of cytokines. Acute-phase proteins support the nonspecific immune system and surround and confine the center of inflammation.

The blood concentration of acute-phase proteins increases thousandfold within hours. Examples of acute-phase proteins are **fibrinogen**, **procalcitonin**, and **C-reactive protein (CRP)**. Negative acute-phase proteins are substances whose serum levels decrease during acute inflammation (e.g., albumin, transferrin). Some serve as diagnostic inflammation markers, such as CRP.

Last but not least are defensins, substances produced by epithelial cells of the skin and mucosa as well as by different immune cells. They react with bacterial components and thus assist in destruction.

The Complement System

The complement system is a group of **plasma proteins** involved in defensive mechanisms against microorganisms and activated on the surface of plasma proteins. Most of the approximately 30 plasma proteins are produced in the liver.

Activation of the complement system triggers an enzyme cascade, which activates further functions of the immune system and boosts the nonspecific immune response. **Opsonization** is when the complement system covers the surfaces of pathogens with complement factors, with the aim of making pathogens recognizable for other cells, leading to elimination.

The complement system can be activated via direct or indirect pathways. Indirect activation is done via components of an antigen's cell wall. Direct activation serves as a connection to the specific immune response because it requires the formation of **antigen-antibody complexes**.

There is one more activation pathway of the complement system, enabled by the so-called **mannose-binding lectin**, which is a substance produced through immune reactions with bacteria and can be found within the plasma.

The joint final pathway of both activation methods is the conversion of complement factor 3 (C3) to C3a and C3b, which, in turn, cleaves C5 in its active parts and forms a membrane attack complex (**MAC**) together with the remaining factors. This complex lyses the target cell. For the detailed process, see the figure.

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