Chapter 10: Innate and adaptive immune responses

Cellular responses to recognition of pathogens

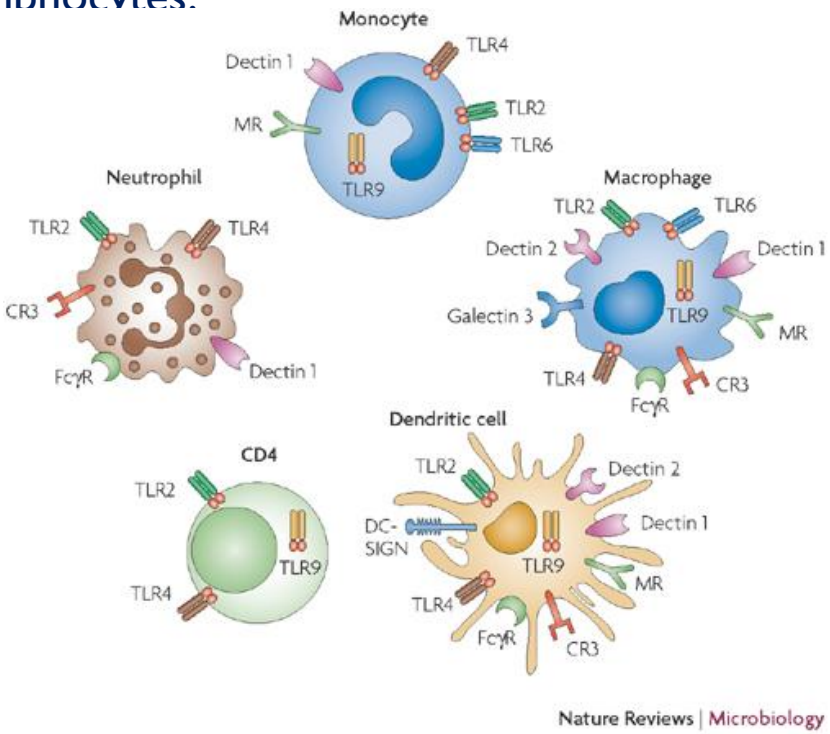
The most important cell types expressing PRRs are neutrophils, macrophages, dentritic cells and NK cells, but also CD4 T lymphocytes.

Phagocytic receptors: Fc receptor for antibodies (FcγR); C3b receptor (CR3); MR= mannose receptor (MR), dectins (CLR).

Activation receptors: TLRs, f-Met Receptor. They mainly activate production of soluble mediators.

Adhesion receptors: integrins and selectins.

Others: MHC class I and II



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PRRs have 3 functions: detect unusual molecular patterns, sense the extent of tissue damage and determine the **class** of immune response. Specialized cells of central immunity such as dendritic cells and T and B cells are principle players in integrating these TLR signals into a specific immune response.

Proinflammatory signaling pathways

Proinflammatory signaling pathways induced by PRRs, activate the innate immune response. To initiate these responses, the transcription factors **NF-κB**, and **IRF3/7** play pivotal roles due to their capacity to stimulate the production of proinflammatory mediators, including cytokines and IFNs respectively.

NF-κB-Inducible Proinflammatory Mediators:
– proinflammatory cytokines: IL-1, IL-6 and TNF-α, chemokines including IL-8
– upregulation of adhesion molecules (selectins)
– Upregulation of immunoreceptors: cytokine and chemokine receptors, TLRs.

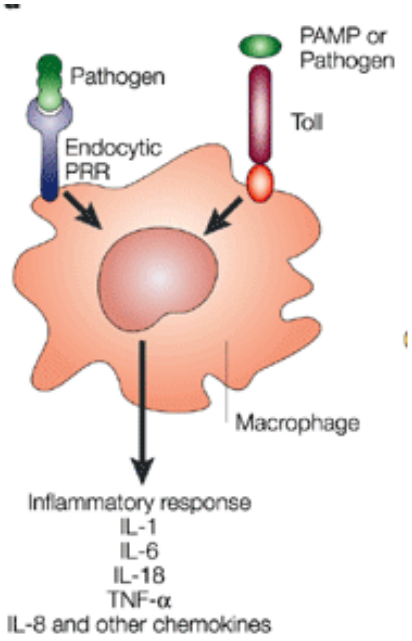
Activation and recruitment of leukocytes to sites of infection (inflammation),
Enhanced phagocytosis of microbes,
Activation of complement- or NK cell-mediated cellular lysis
Enhanced antigen presentation

tight regulation is essential to ensure the strong, albeit transient, nature of these responses, and this is achieved via amplification early during infection, as well as restriction and downregulation when needed at later stages.

Proinflammatory signaling pathways leads to release proinflammatory cytokines

Proinflammatory signaling pathways leads to release **proinflammatory cytokines** and other mediators that set up a state of inflammation in the tissue:

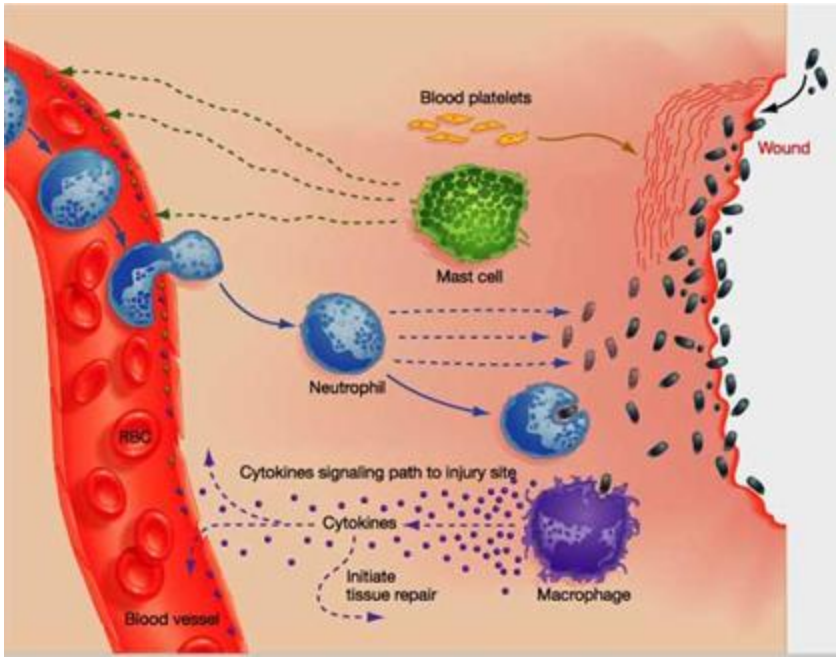
Cytokines: small proteins (~25 kDa) released by various cells in the body, usually in response to an activating stimulus.
They mainly act in an **autocrine** and **paracrine** manner affecting the behavior of adjacent cells. by binding to specific receptors.
Main cytokines secreted in response to PRRs stimulation: interleukin-1 **IL-1**, interleukin-6 **IL-6** and tumor necrosis factor (**TNF-α)** and many others (IFNγ, interleukins IL-4, IL-10, IL-12, IL-18 and TGFβ.)



Chemokines: cytokines that have **attractant properties**, inducing cells with the appropriate receptors to migrate towards their source: interleukin-8 (**IL-8**).
Other factors (**vasoactive peptides**) increase vascular permeability.

Inflammatory responses and recruitment of leukocytes to the site of infection

Inflammatory responses are characterized by: **increased permeability of the blood vessels** leading to increased local blood flow and the leakage of fluid. (pain, redness, heat, and swelling at the site of an infection). **Mast Cells:** secrete factors that mediates vasodilation and delivery of blood factor. **Platelets** from blood release blood-clotting proteins at wound site.

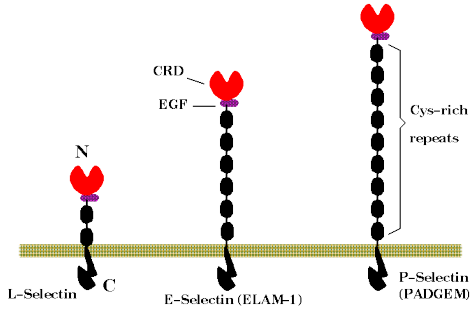


Released cytokines (IL-1, TNFα) and chemotactic factors (chemokines, C3a C5a). cause the endothelial cells of blood vessels near the site of infection to express cellular adhesion molecules**. Increased adhesive properties** of the endothelium cause circulating leukocytes to stick to the endothelial cells of the blood vessel wall and migrate between them to the site of infection, to which they are attracted by chemokines.

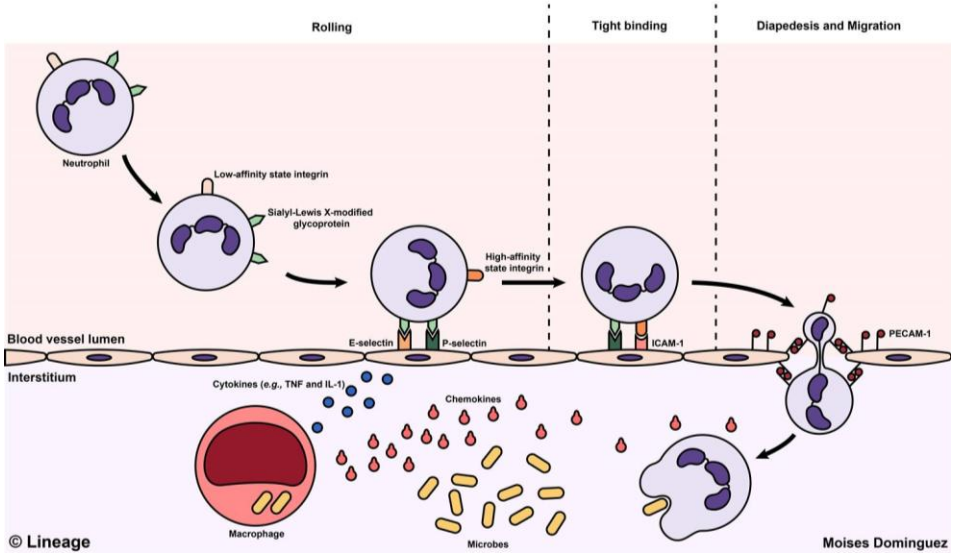
Neutrophils, which are recruited into the infected tissue in large numbers in the early phase are the principal cells that engulf and destroy the invading micro-organisms.

Leukocytes extravasation

Leukocyte rolling occurs due to transient interactions between **E-selectins** present on endothelial cells and **selectin ligands** (sialyl-Lewis^x) expressed on leukocytes.
Tight binding: some high affinity state **integrins** on the surface of leukocytes bind to members of the Ig superfamily (ICAM-1) on the surface of endothelial cells. This arrests the motion of the rolling cells.



The selectins are a family of mammalian adhesion proteins, with three members.



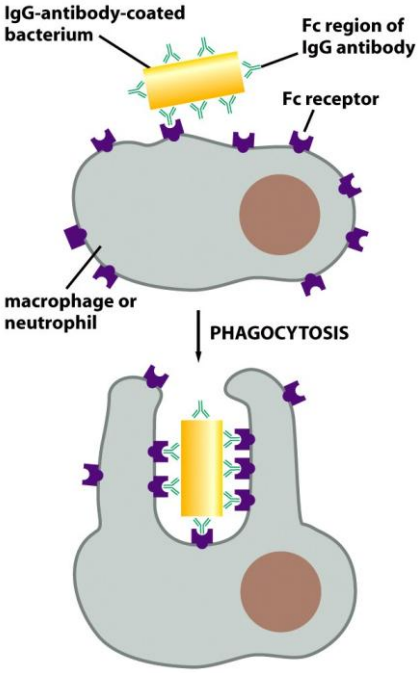
https://step1.medbullets.com/pathology/106005/leukocyte-extravasation

Leukocytes enter the tissues by secreting proteases to breach the endothelial basement membrane (diapedesis). The influx of neutrophils is followed a short time later by monocytes that rapidly differentiate into macrophages.

The adhesion defects result in poor leukocyte chemotaxis: Leukocyte adhesion deficiency (LAD)

Receptor-activated phagocytosis

Phagocytosis is a remarkably complex and versatile process: it contributes to innate immunity through the ingestion and elimination of pathogens.



Antibody-activated phagocytosis

Phagocytes have several PRRs that bind specifically to certain PAMPs inducing the phagocytosis (mannose receptor, dectins).

Opsonins, can be deposited onto foreign surfaces and serve as adaptors that bind and activate potent phagocytic receptors (Fc receptor, C3b receptor,).

Membrane protrusions surround the bacteria and absorb the bacteria into the phagosome, which is formed by the fusion of cell membranes. Actin cytoskeleton governs particle engulfment. A variety of signaling cascades can be activated during this process.

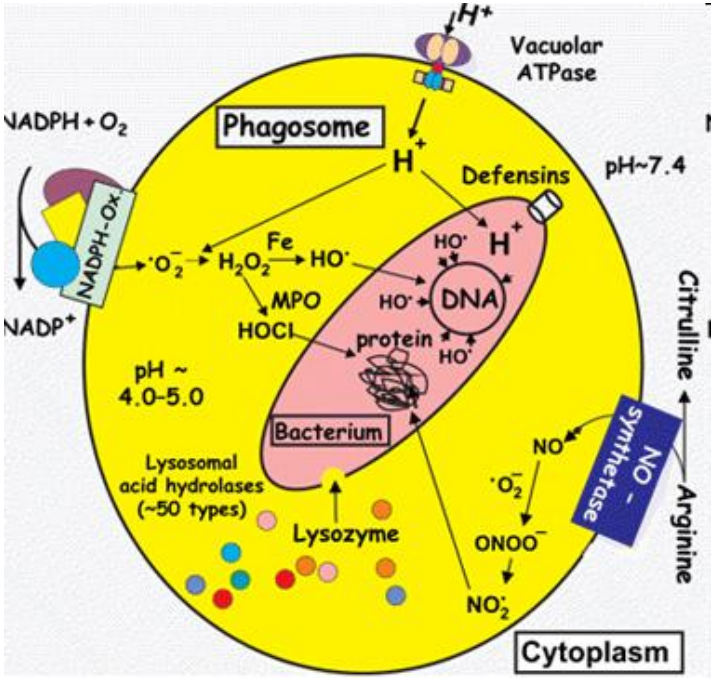
The macrophages and neutrophils produce many toxic compounds

Once the pathogen has been phagocytized, macrophages and neutrophils have an impressive armory of weapons to kill it. The phagolysosomes contain:

non oxidative killing effectors: lysozyme and acid hydrolases to degrade bacterial cell walls and proteins, antimicrobial peptides.

oxidative killing mechanisms: **NADPH oxidase complex** that catalyzes the production of highly toxic oxygen-derived compounds: superoxide anion ($\bullet O_2^-$), hypochlorous acid (HOCl), hydrogen peroxide (H_2O_2), hydroxyl radicals ($HO\bullet$.) *NO* synthase for the production of nitric oxide (NO).

competitors: Fe^{2+} binding proteins.



Toxic oxygen- and nitric-derived compounds are generated in a process known as the "*respiratory burst*"

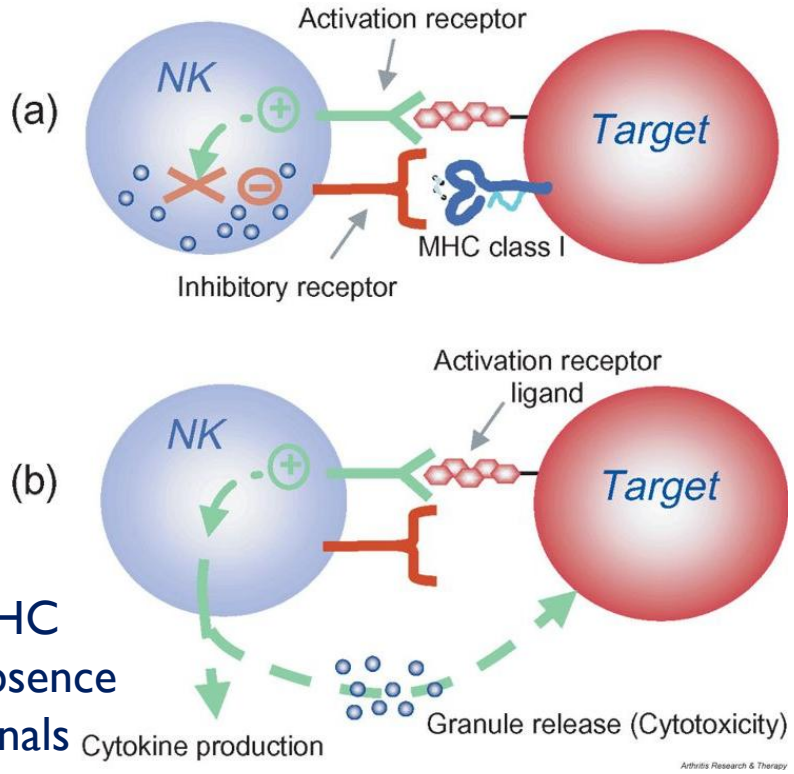
Chronic Granulomatis Disease (CGD), a primary immunodeficiency that affects phagocytes, defects in NAPDH oxidase

Fuctions of Natural killer cells

Natural killer (NK) cells are large, granular, bone marrow-derived lymphocytes that do not express T or B cell receptors.

Rapid response to infected or transformed cells either by killing the abnormal cells or by releasing chemokines and cytokines.
NK functions must be carefully regulated to prevent damage to normal tissues

NK cell responses result from the integration of signals from both cytokine receptors and germline-encoded NK cell inhibitory and activation receptors.



(a) Inhibitory NK cell receptors recognize self MHC class I and restrain NK cell activation. **(b)** In the absence or downregulation of MHC class I, stimulatory signals are no longer suppressed, resulting in NK cell responses

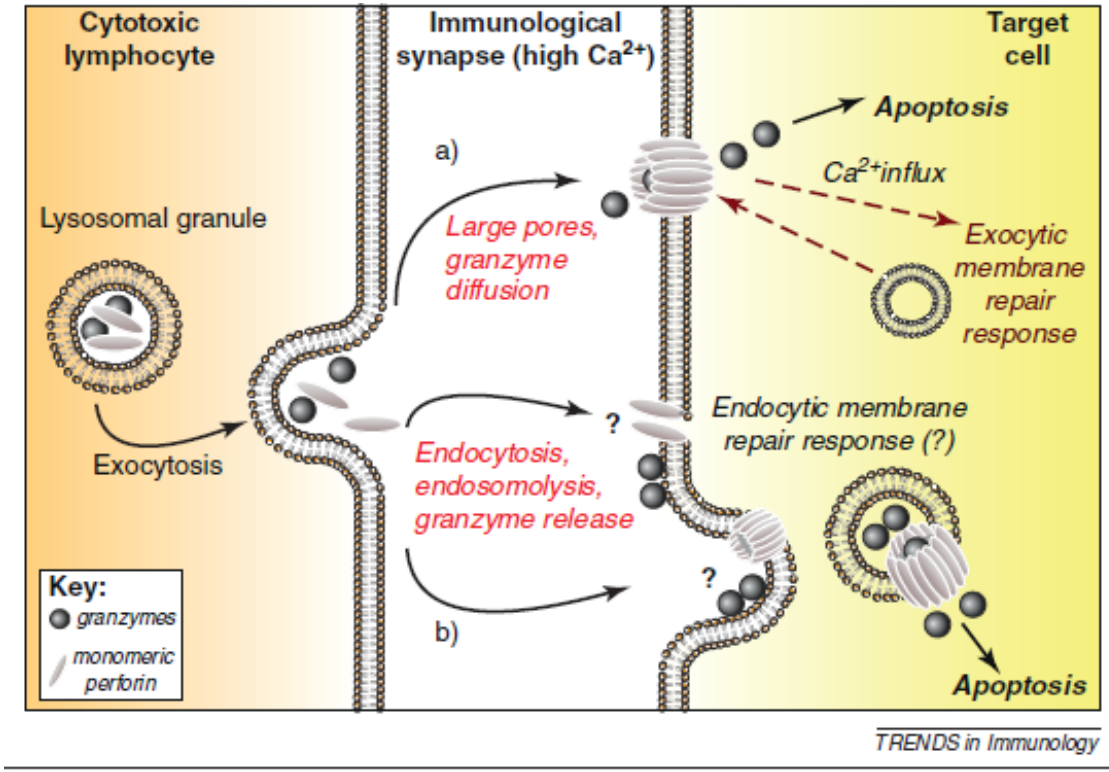
Cytotoxic mechanism of NK cells

NK cells and CTLs (cytotoxic lymphocytes) use a common mechanism of cytotoxicity, involving the regulated exocytosis of toxic effector molecules

Cytotoxic lymphocytes use the highly toxic pore- forming protein **perforin** to eliminate dangerous cells, while remaining refractory to lysis.

Following exocytosis, perforin delivers the proapoptotic protease, **granzyme B**, into the target cell by

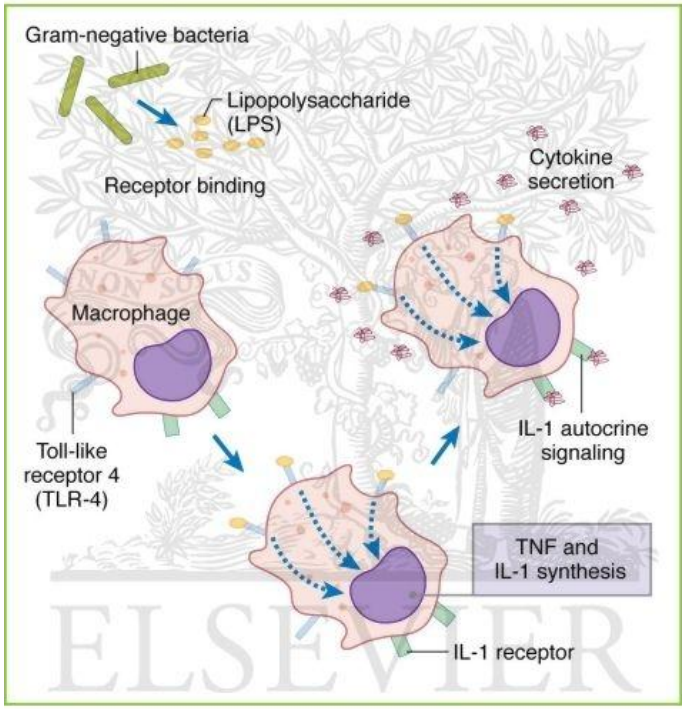
a) and b) Putative mechanisms of synergy between perforin and granzymes



The dark side of the innate defenses: septic shock

Inflammatory responses, which are so effective at controlling local infections, can have disastrous consequences when they occur in a disseminated infection in the bloodstream, a condition called ***sepsis.***

Bacterial LPS has the ability to induce a dramatic systemic reaction known as septic shock. This syndrome is the result of **overwhelming secretion of cytokines**, particularly of **TNF-α** and **IL-1**, often as a result of an uncontrolled systemic bacterial infection. The systemic release of proinflammatory signaling molecules into the blood causes dilatation of blood vessels, loss of plasma volume, and widespread blood clotting, which is an often fatal condition known as ***septic shock.***



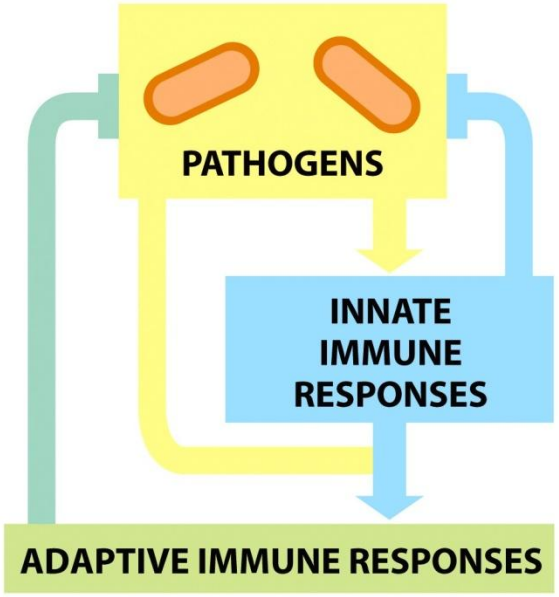
Mutant mice that **lack TLR-4** function; although resistant to septic shock, they are highly sensitive to LPS-bearing pathogens such as *Salmonella typhimurium*

Bridging Innate and Adaptive Immune Defenses

Whereas the innate immune responses are general defense reactions, the adaptive responses are **highly specific** to the particular pathogen that induced them, and they provide long-lasting protection.

The adaptive immune system is composed of many millions of **lymphocyte clones**, with the cells in each clone sharing a unique cell-surface receptor that enables them to bind a particular antigen.

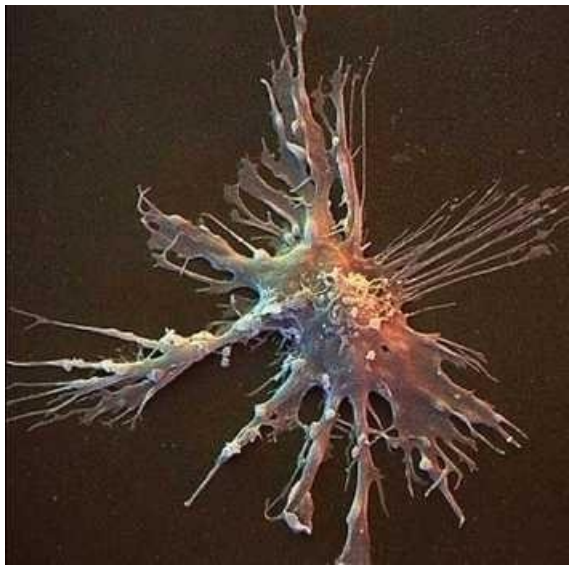
In vertebrates, pathogens, together with the innate immune responses activate, stimulate adaptive immune responses, which then work together with innate immune responses to help fight the infection.



The cells of the vertebrate innate immune system that respond to PAMPs and activate adaptive immune responses most efficiently are **dendritic cells.**

Dendritic cells a bridge between innate and acquired immunity

Dendritic cells (**DCs**) are the most important **antigen-presenting cells**.



http://www.realscience.us/2011/10/03/nobel-prize-in-medicine-goes-to-immunologists/

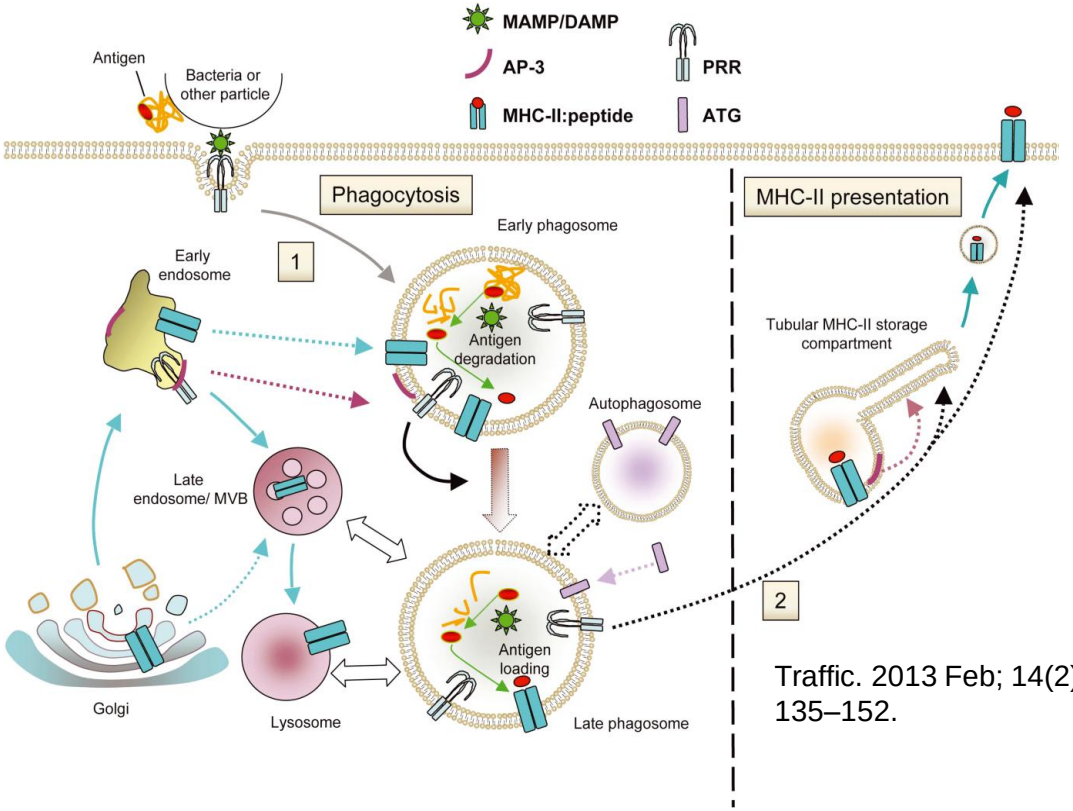
Immature DCs: are specialized phagocytic cells resident in most tissues, long-lived, turning over at a slow rate.

From bone marrow iDCs migrate to their peripheral stations, their role is to survey the local environment for pathogens. They express **high levels of TLRs** and other PRRs.

iDCs become **mature** when they recognize PAMPs released from pathogens. During this process, DCs upregulate **antigen presenting molecules** such as **MHC class II** and **costimulatory molecules** (including CD80, CD86, and CD40), and secrete cytokines that influence both innate and adaptive immune responses, making these cells essential gatekeepers that determine whether and how the immune system responds to the presence of infectious agents.

Model of phagosomal antigen processing and presentation by MHC-II.

CDs engulf pathogens processing their antigens on the cell surface in association with MHC class II



Traffic. 2013 Feb; 14(2): 135–152.

MHC-II: molecules composed of 2 integral membrane chains, α and β. The peptide-binding pocket is comprised of the membrane distal domains of both chains.

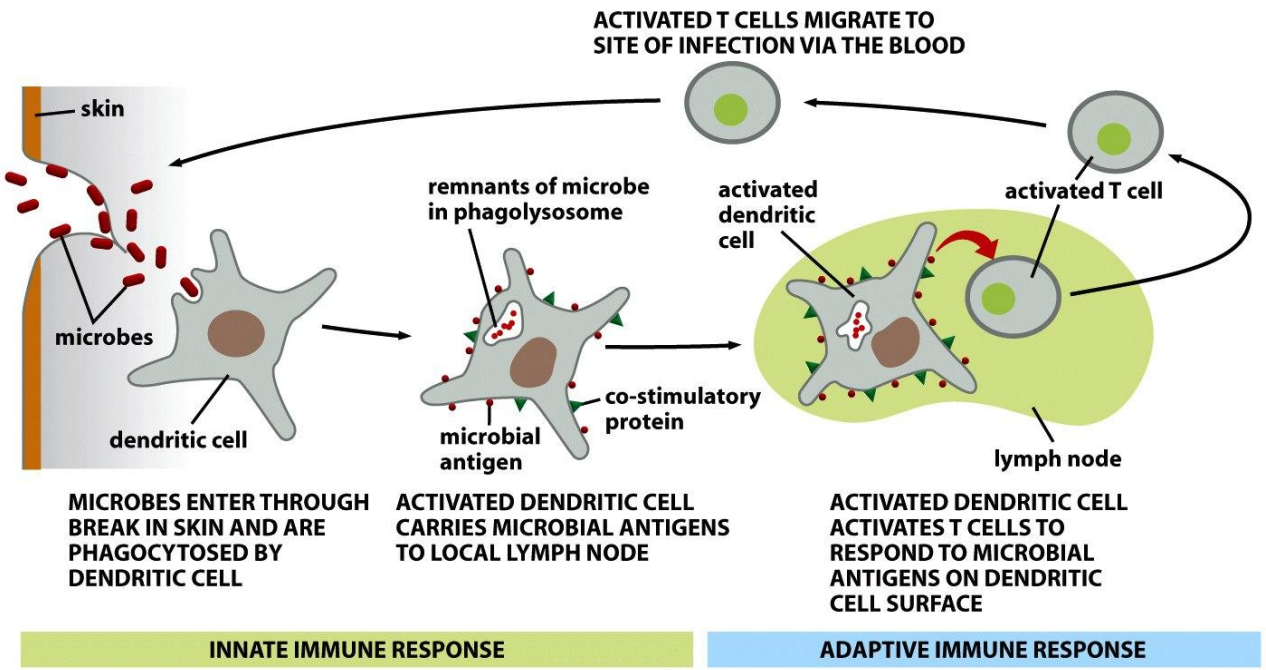
Phagocytozed antigen captured by APCs is degraded in phagosomes.

The phagosomes matures by the acquisition of content (including MHC-II) from early and late endosomes and lysosomes.

Antigen is loaded onto MHC-II molecules predominantly in late phagosomes.

From late phagosomes, peptide-loaded MHC-II molecules are delivered to the cell surface by mechanisms that are still poorly understood where they are available to stimulate antigen-specific T cells with cognate receptors.

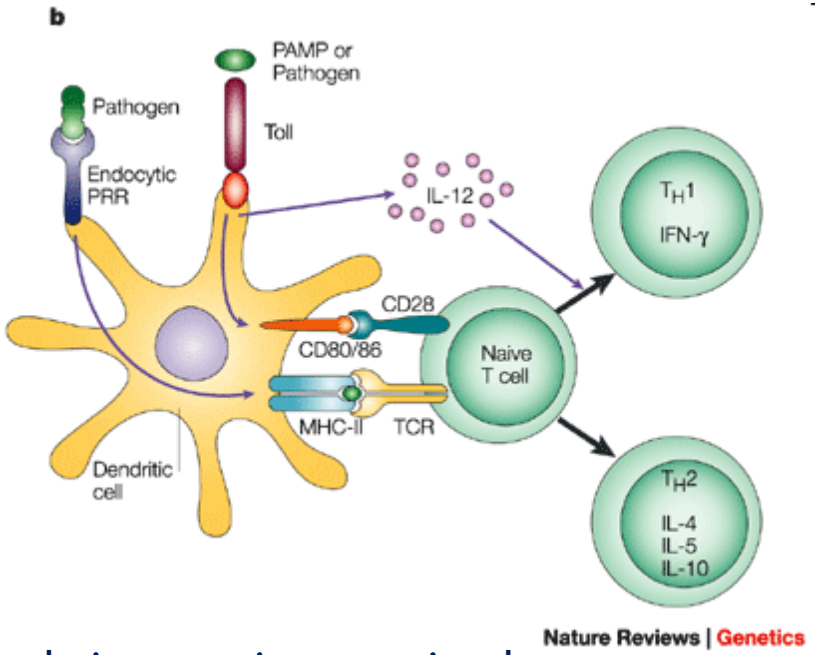
How the innate immune system can help activate the adaptive immune system.



Following antigen uptake by DCs, these cells become activated, express receptors for specific chemokines and are attracted to migrate to regional lymph nodes to present antigenic peptides in the context of relevant MHC molecules.

The microbial PAMPs activate the **DCs** so that they, in turn, can directly activate the **T cells** in peripheral lymphoid organs to respond to the microbial antigens displayed on the dendritic cell surface.

DCs present antigenic peptides in the context of relevant MHC molecules



DCs are endowed with the ability to stimulate naïve $CD4^+$ T lymphocytes into **T helper** (**Th**).

Each lymphocyte carries cell-surface receptors (**TCR**) of a single specificity, so that the total repertoire of receptors can recognize virtually any antigen

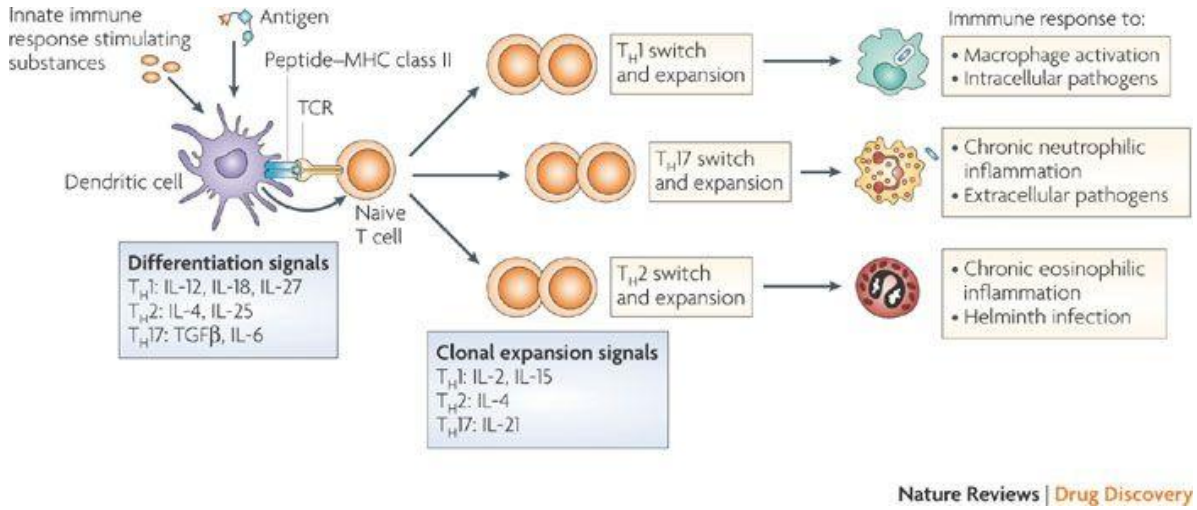
Stimulation require two signals:

1) an antigen-specific signal provided through the T cell receptor (**TCR**) which interacts with **antigen-MHC molecules** on the membrane of APC.

2) the co-stimulatory signal, an antigen-nonspecific signal and provided by the interaction between co-stimulatory molecules expressed on the membrane of APC and the T cell.

T cells interact with APC by releasing cytokines. APC also release cytokines.

Different subsets of DCs express different and nonoverlapping sets of PRRs, which together with the selective tissue distribution leads to release different of different set of cytokines.



Naive T cells differentiate into T_H1, T_H2 and T_H17 effector subsets

Th1 responses are important for protection against viruses and intracellular bacteria, whereas. **Th2 responses** mediate immunity to extracellular pathogens and protozoa at mucosal surfaces and are involved in allergic responses. **Th17** is necessary to combat extracellular pathigens.