Lecture 6 advance immunology
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The process of the immune response

Our immune system consists of multiple, co-operating systems which defend the body against the thousands of pathogens present in our environment. The first defence against invading pathogens, forming a physical and chemical barrier. Infections occur only when a pathogen crosses these barriers, as in the case of an injury. Although the gastrointestinal and respiratory tracts are exposed to a plethora of pathogens they are protected effectively by multiple mechanisms, such as mucus, coughing and sneezing, acidic environment, mucosal epithelium which consists of epithelial cells held together by tight junctions, epithelial cells can transport certain antibody isotypes (especially IgA which act by neutralizing effect). These have a number of protective functions, for example, it may prevent microorganisms from adhering to the epithelium.

Various immune cells ready for combat, such as macrophages, dendritic cells, effector T cells and B cell are all present in the subcutaneous or intraepithelial tissues. The invading pathogens are recognized first by the cells of the innate immune system (eg. macrophages and dendritic cells), expressing pattern recognition receptors.

They immediately trigger the well-known reactions of the innate immune system (elimination of pathogens, recruitment of other immunocytes) leading to induction of inflammation in the infected tissue.

The induced production and flow of lymph will carry some of the pathogens into the regional (draining) lymph nodes. Activated dendritic cells also reach the lymph nodes through the lymph, where they present processed phagocytosed antigens to the T lymphocytes. Thus B and T lymphocytes, which recognize the pathogen-specific antigens, get activated, proliferate and differentiate into effector or memory cells. Depending on the amount and the growth rate of the invading pathogen we can distinguish between three potential courses of the immune response. Small amounts of pathogens are immediately recognized at the site of infection and eliminated by macrophages found almost everywhere in our body.

If this mechanism is insufficient for clearing the pathogen more participants of the innate immune system will be recruited to help macrophages. If the pathogen survives for an extended period, the adaptive immune system will also be activated, which finally eliminates the pathogens either by its own mechanisms, or more often by enhancing the innate response. If the organism has already met the pathogen, the effector mechanisms of the adaptive immune response can provide immediate protection. Pathogen-specific antibodies produced by the long-lived plasma cells neutralize the pathogens and the effector T cells eliminate the infected cells in a few days

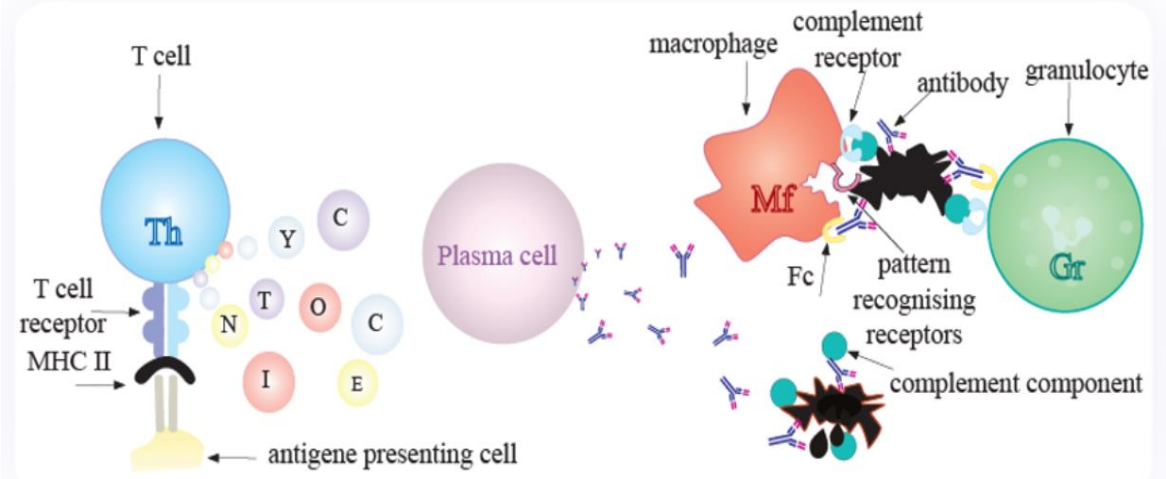
or produce cytokines to enhance the efficiency of the other participants of the immune system. In parallel, memory cells in the lymph nodes get activated and begin to proliferate rapidly.

Bacteria, viruses and parasites

Pathogens use diverse strategies for infection and to escape immune surveillance. Accordingly, the immune system uses different strategies to override these mechanisms.

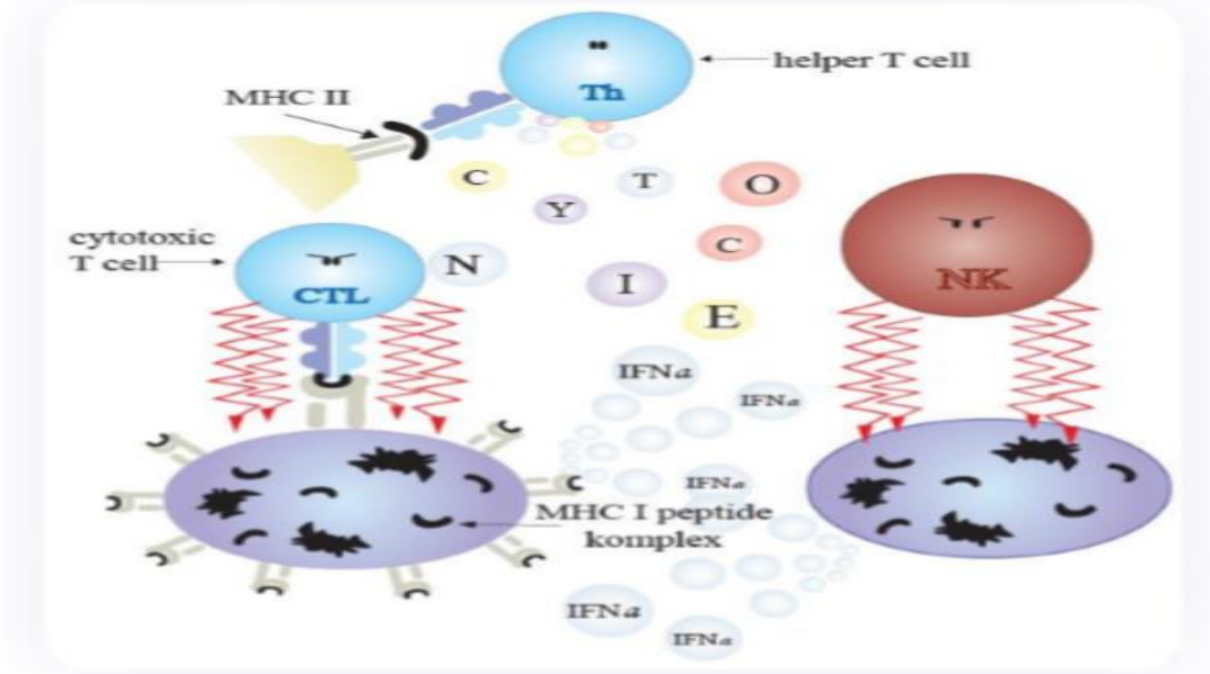
Most pathogenic bacteria and fungi entering the body live in the interstitial space between cells. These pathogens are called extracellular pathogens. These are the main targets of antibodies and complement proteins diffusing out of the plasma during inflammation. Pathogens opsonized by antibodies are efficiently recognised by phagocytes, mainly by macrophages and neutrophil granulocytes, and the complement system. The complement system can itself lyse some microbes. In addition, via complement receptors and Fc-receptors phagocytes are induced to ingest and kill opsonized pathogens.

Dendritic cells activated by microbes start expressing costimulatory molecules at high levels and migrate to draining lymph nodes, where they activate naive T lymphocytes. The pathogens phagocytosed by macrophages are usually destroyed in the phagolysosomes. If this for some reason does not occur, microbial antigens can be presented on MHC II to the helper T-cells. In turn, T-helper cells activated by macrophages using cell-cell contact and secretion of cytokines (e.g. IFNγ) will help macrophages to kill the ingested pathogens.



Elimination of extracellular pathogens Phagocytes (Mf) recognize pathogens via PRR or pathogens opsonised with antibodies and/or complement via Fc- and/or complement-receptors. Pathogens bound by these receptors get ingested and killed in the phagolysosomes by multiple mechanisms (right). Antibodies produced by plasma cells may neutralize the pathogen and/or activate antibody-mediated effector functions (middle). (Complement components may directly eliminate pathogens) Type 2 cytokine-producing T

helper cells augment immune response against extracellular pathogens primarily (left).



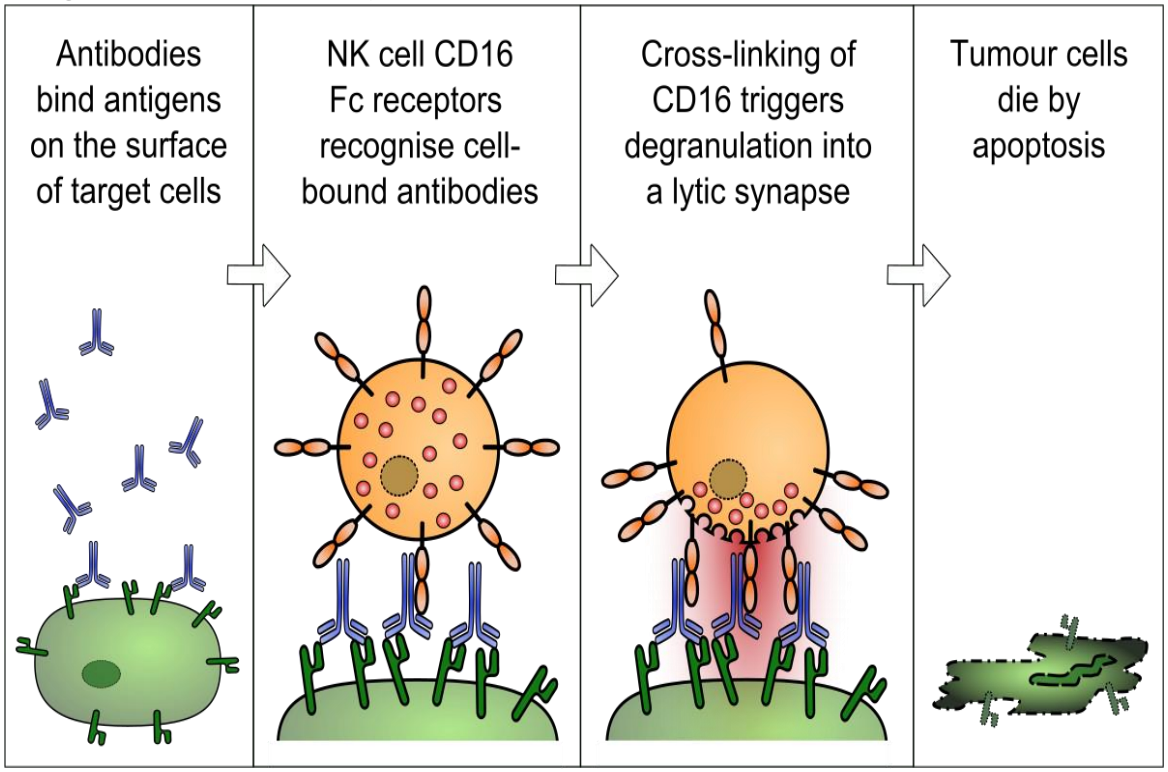
Elimination of intracellular pathogens Virus-infected cells are recognized via intracellular pattern recognition receptors followed by production of type I interferons. Concomitantly, MHC class I molecules present antigens of intracellular pathogens on the cell surface and activate cytotoxic T lymphocytes, which kill the infected cells (bottom left). In the absence of cell surface MHC I (indicating an aberrant cellular function) cells become targets for NK cells, which again leads to the elimination of the cell (right).

Interferons play a key role in anti-viral immunity. IFN-γ is produced mainly by T helper cells and cytotoxic cells (NK, Tc), and besides their direct antiviral effect, their main function is to it promote macrophage functions. Due to its effect macrophages kill engulfed microorganisms more efficiently.

In addition, IFN-γ enhances the expression of MHC class I and II molecules on the surface of professional antigen-presenting cells. IFN-α, IFN-β can be produced by almost any cell types, infected with a virus. They often have autocrine or paracrine. They interfere with viral replication by various mechanisms eg. inhibition of protein synthesis, increased expression of MHC class I molecules etc.

Antibodies may also partake in the defence against viruses. The neutralizing effect of antibodies prevents adherence of viruses on host cells and thereby infection. Viral proteins may also be displayed on the membrane of infected cells. Antibodies recognizing these antigens will bind them, therefore mark the cell for (antibody-dependent cellular cytotoxicity (ADCC) is an immune mechanism through which Fc receptor-bearing effector cells can recognize

and kill antibody-coated target cells expressing tumour- or pathogen-derived antigens on their surface).

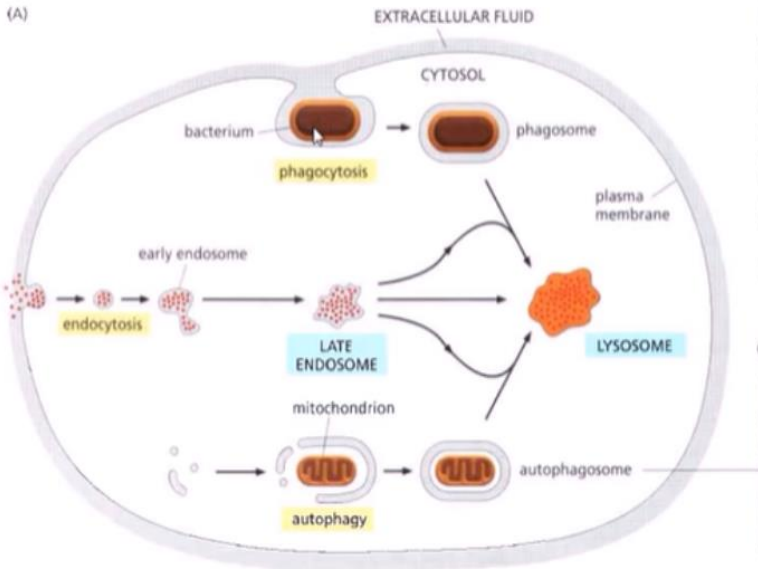


NK cells may also kill infected cells by ADCC via activation by their Fc receptors. Some small, single-cell intracellular parasites such as Plasmodium species eukaryotic parasites induce similar T cell responses.
Nevertheless, antibodies still recognize the extracellular form of the parasite during their life cycle. Elimination of large multicellular extracellular parasites (e.g. flat- and roundworms) often requires a much broader spectrum of immune response delivered by specialized cells.

Eosinophil and basophil granulocytes or mast cells are involved in inflammation triggered by parasites. These cells release special toxic agents and degrading enzymes from their vacuoles to destroy the parasites at the area of infection. Besides toxic agents, many pro-inflammatory cytokines are secreted. Some of these increase peristaltic activity in case of intestinal infection or trigger coughing, sneezing and induce mucus production in case of a respiratory infection to help to remove the parasites from the body. The parasite-specific IgE antibodies bound to high-affinity Fc receptors of mast cells and basophil granulocytes play important role in the activation of these cells and thereby in the immune response against parasites.

Cross-presentation of particulate antigen is time-dependent, whereas cross-presentation of soluble antigens is localization-dependent.
Extracellular antigens are internalized into specialized organelles, which are termed phagosomes in case of cell-associated antigens, and endosomes for soluble antigens. Both compartments subsequently mature and undergo a

series of molecular changes, such as acidification and fusion with organelles containing degrading enzymes, in particular lysosomes.



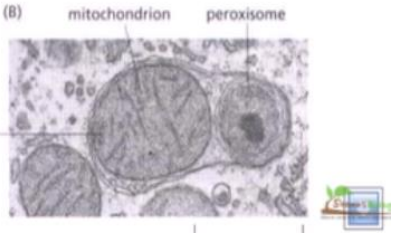


Figure 13–42 **Three pathways to degradation in lysosomes.** (A) Materials in each pathway are derived from a different source. Note that the autophagosome has a double membrane. (B) An electron micrograph of an autophagosome containing a mitochondrion and a peroxisome. (B, courtesy of Daniel S. Friend, from D.W. Fawcett, A Textbook of Histology, 12th ed. New York: Chapman and Hall, 1994. With permission from Kluwer.)

In late endosomes/lysosomes, antigenic peptides can be generated and loaded onto MHC II molecules, followed by transport of these complexes to the cell surface for presentation to CD4+ T cells.

Acceleration of phagosome maturation enhances pathogen killing, while a delay in phagosome maturation preserves antigenic peptides for presentation to T cells and to initiate adaptive immune responses.

Besides its functions in pathogen killing and antigen presentation, the phagosome also functions as a signalling platform and interacts with other cell organelles.

Some pathogens are able to arrest phagosome maturation to enhance their intraphagosomal survival and replication or to promote phagosomal escape.

1- Transient alkalization of the phagosome prevents lysosomal antigen degradation and allows cross-presentation.

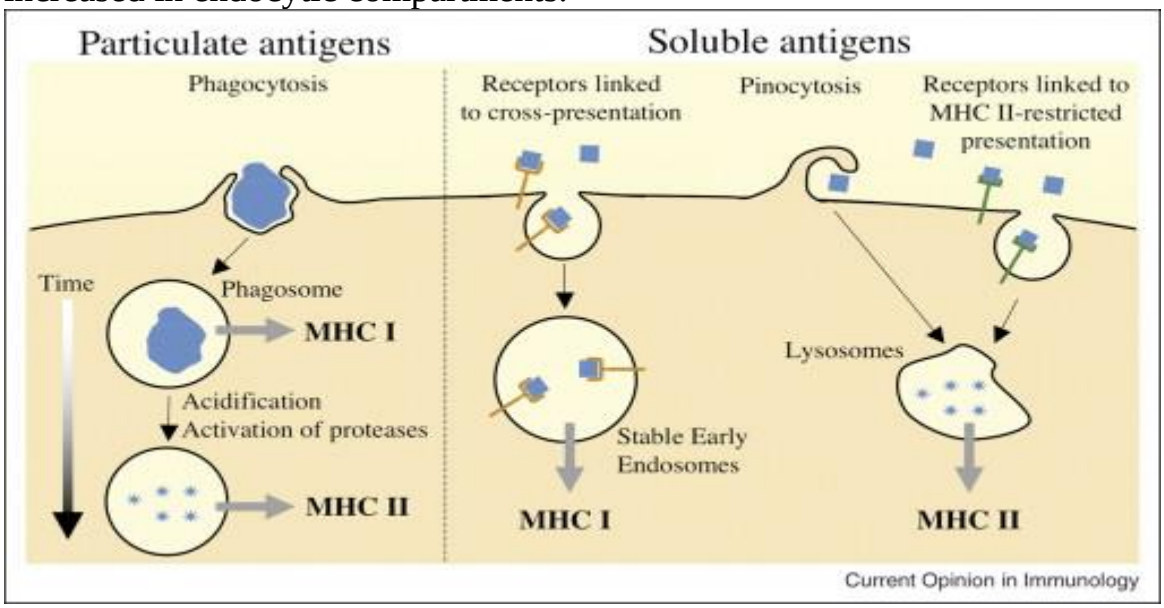
The alkalization of the phagosome by the NADPH oxidase NOX2 prevented activation of lysosomal proteases so that internalized particulate antigens were rescued from rapid degradation and remained available for loading onto MHC I.

and TAP-dependent import of resulting peptides into the compartment where they are loaded onto MHC I molecules, which has been proposed to be the same phagosome.

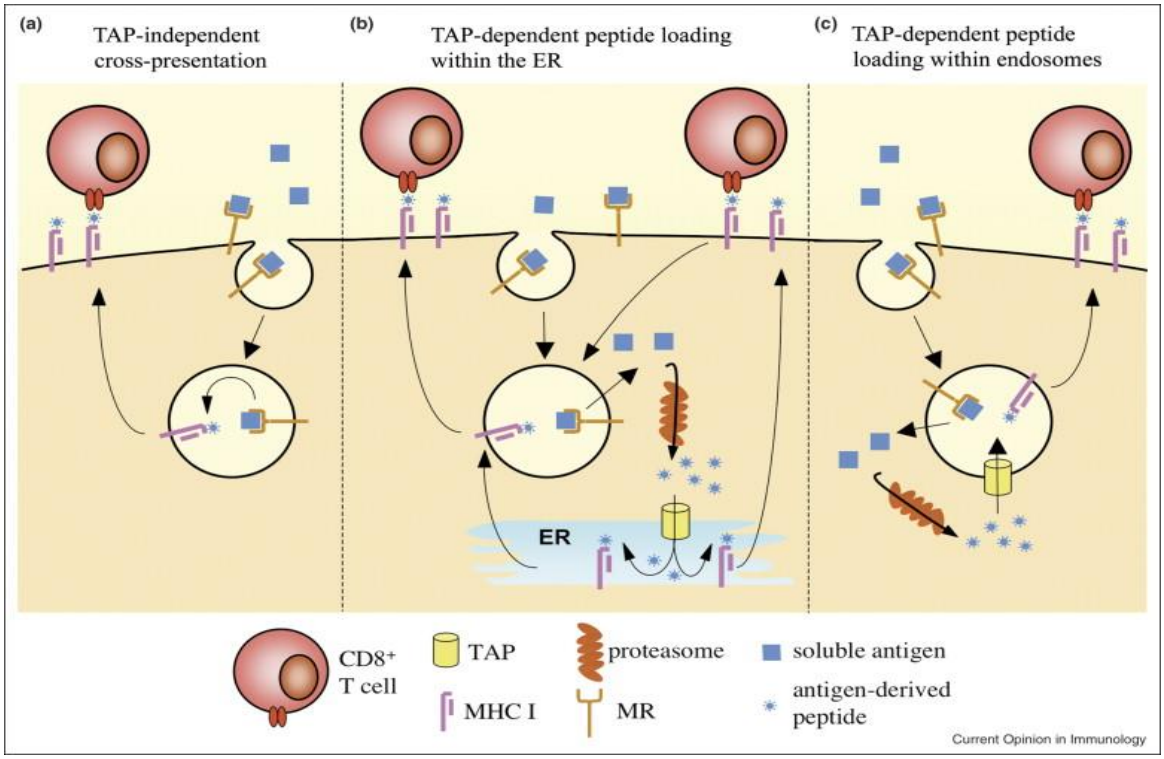
2- Antigens could escape endocytic compartments through membrane rupture, termed “indigestion model,” due to large particles are more efficiently cross-presented than small ones, and could thus be responsible for phagosomal overload, leading to membrane disruption and efficient antigen leakage to the cytosol.

3- The alteration of lipid structure (by ROS, Lipid Peroxidation) disrupts endosomal membrane integrity, leading to antigen escape to the cytosol and cross-presentation.

4- Changes in Endolysosomal Membrane Lipid Composition of sphingolipids conversion into membrane-disrupting sphingosine could be increased in endocytic compartments.



Cross-presentation of particulate antigen is time-dependent, whereas cross-presentation of soluble antigens is localization-dependent. Particulate antigens are taken up by phagocytosis. Transient alkalization of the phagosome prevents lysosomal antigen degradation and allows cross-presentation. After acidification, lysosomal proteases are activated and process antigens for presentation on MHC II molecules. Soluble antigens intended for cross-presentation are internalized into stable early endosomes, whereas those aimed at classical MHC-II-restricted presentation are taken up by distinct endocytosis mechanisms and are routed into lysosomes.



Putative intracellular mechanisms of cross-presentation. (a) Antigens are degraded by endosomal proteases and loaded within endosomes on MHC I molecules. (b) Antigens are exported from endosomes into the cytoplasm and degraded by the proteasome. Antigen-derived peptides are transported by TAP into the ER, where they are loaded onto MHC I molecules. These complexes can then be transported either toward early endosomes and onto the cell membrane, or directly from the ER toward the cell membrane. From there they might reach early endosomes by recycling. (c) Antigens are degraded by the cytosolic proteasome, and resulting peptides are transported by TAP into the endosomes for MHC I loading.