

MICR2209

Introduction to the Immune System

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Synopsis: In this lecture we will review basic concepts in immunology, including the cells of the immune system, the innate and adaptive immune responses, and the basis of vaccination

Outcomes: You should be able to describe the fundamental concepts of immunity including an overview of innate immunity, adaptive immunity, and the cells involved in these responses

Origin of immunology attributed to Edward Jenner

Jenner tested folk tradition that infection with cowpox protected against infection with smallpox

Variolation was common practice at that time

Exudate from milkmaid Sarah Nemes placed into scratches on arm of James Phipps, May 14 1796; challenge with smallpox did not induce disease



‘An Inquiry into the Causes and Effects of the Variolae Vaccinae, a Disease by the Name of Cowpox’ published 1798
Variolation banned in England in 1840

Smallpox is first virus to be eradicated

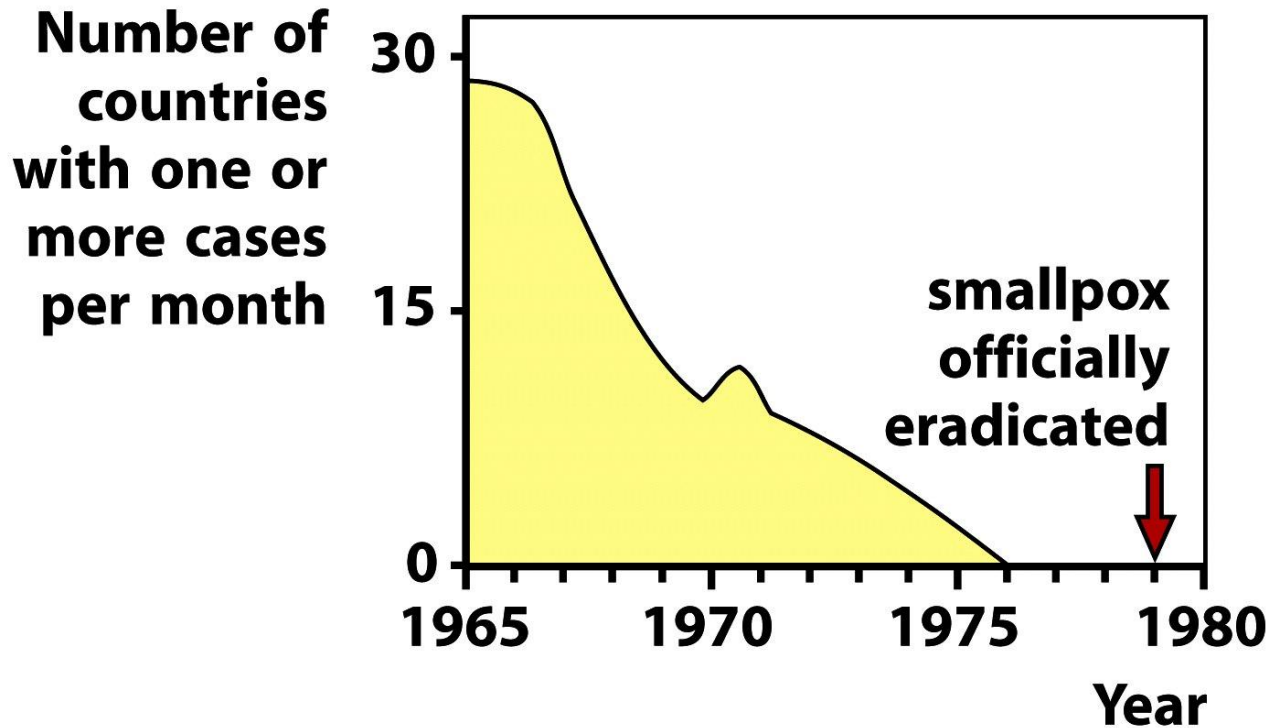


Figure 1-2 Immunobiology, 7ed. (© Garland Science 2008)

The immune system must be highly discriminatory

- English word 'immunity' refers to all mechanisms used by the body as protection against environmental agents (microorganisms or their products; foods; chemicals; drugs; pollen; animal hair) that are foreign to the body. Arose from the Latin 'immunis' meaning 'exempt'
- Immune system must differentiate between individual's own cells and those of harmful invading organisms
- Must not attack commensal flora that inhabit the gut, skin, and other tissues to the host's benefit

Functions of the immune response

The immune system recognizes and responds to antigens. In order to protect the individual effectively against disease, the following tasks need to be fulfilled:

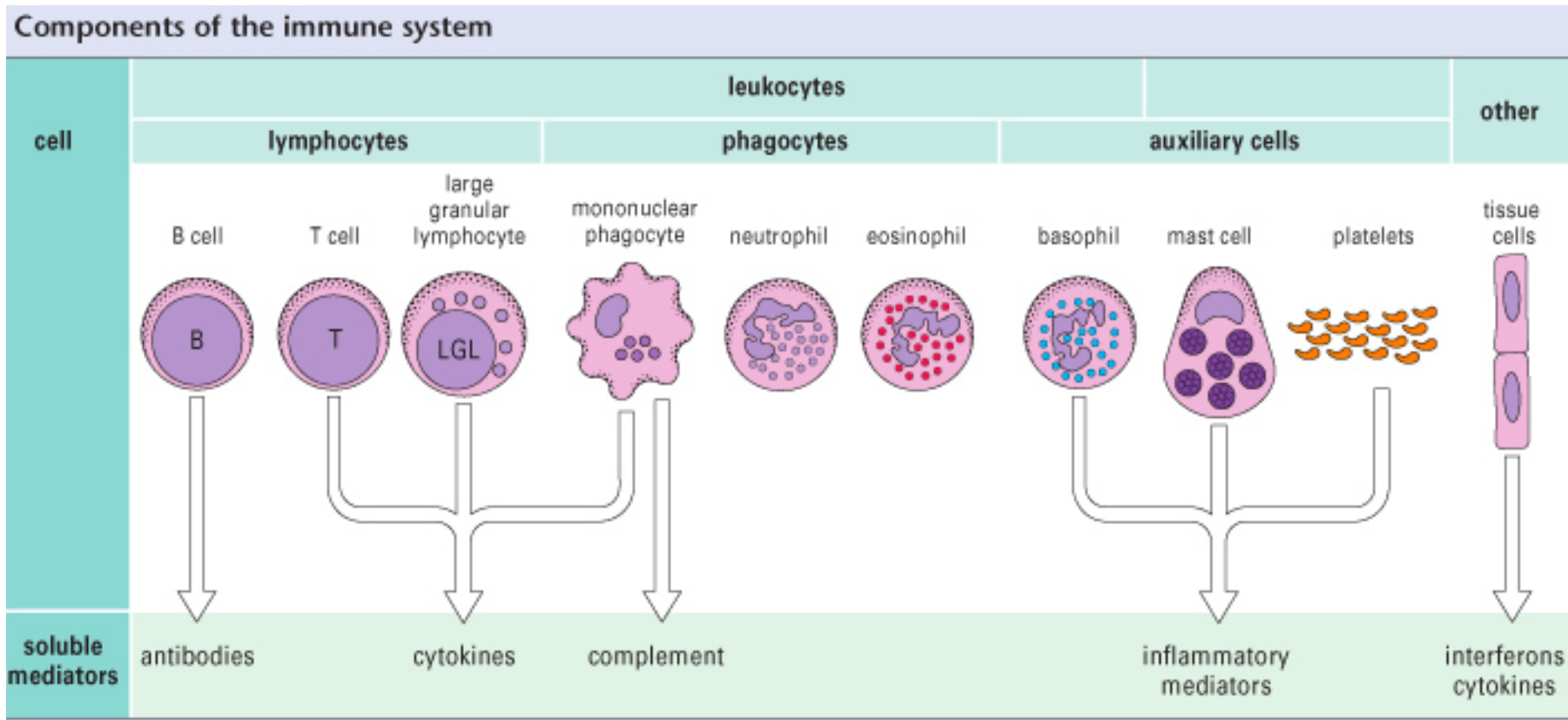
- **Immunological recognition:** presence of an infection must be detected (by the innate and adaptive immune systems)
- Contain the infection and if possible eliminate it, via various **immune effector functions** (eg. antibodies, complement)
- **Immune regulation** limits damage to the host by the immune response to antigen. Failure of this regulation contributes to disease states including allergy and autoimmune disease
- The adaptive immune system generates **immunological memory** – exposure to an infectious agent produces an immune response that can persist, and protect the host in a subsequent exposure

The major types of pathogens confronting the immune system, and some of the diseases they cause

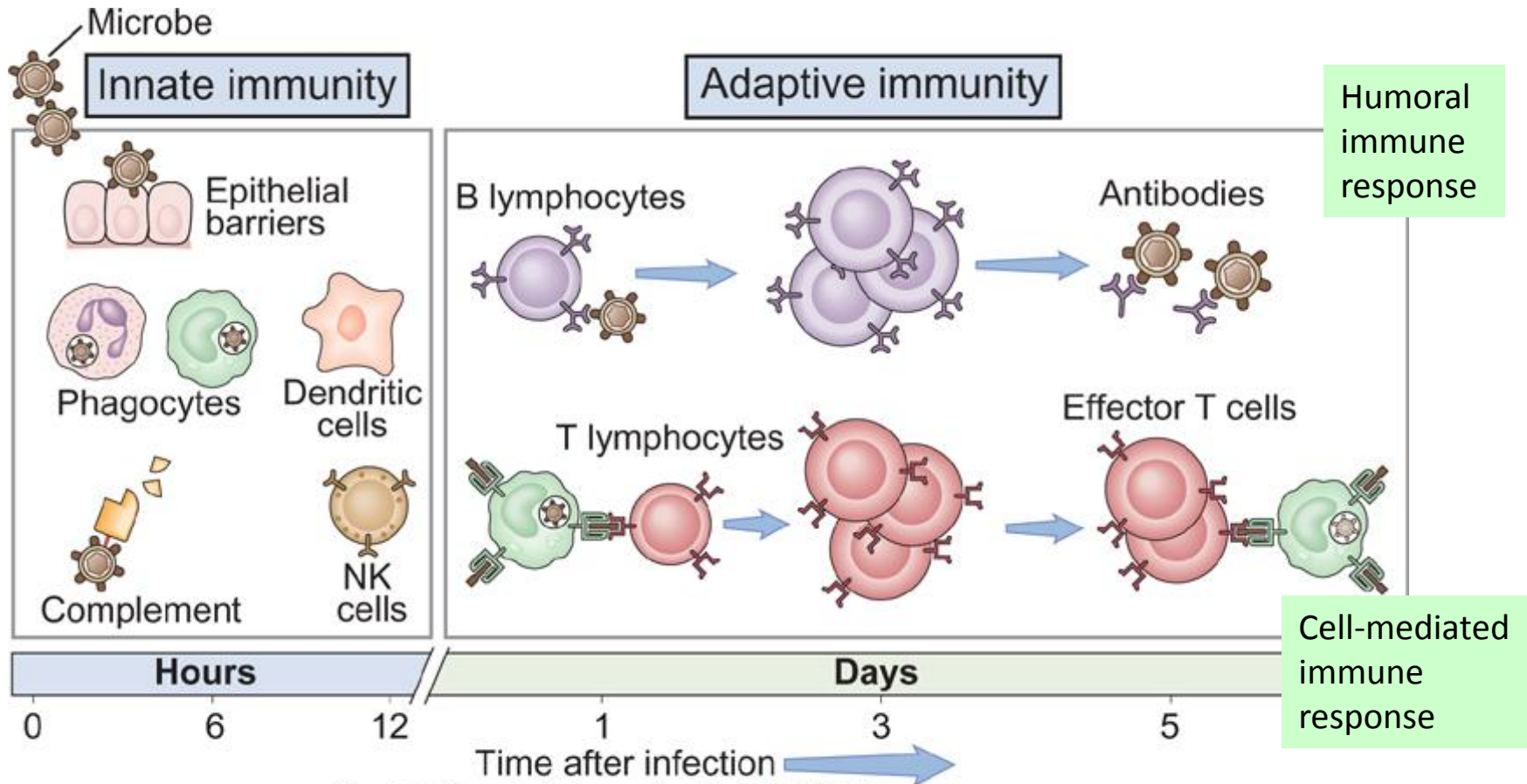
The immune system protects against four classes of pathogens		
Type of pathogen	Examples	Diseases
Extracellular bacteria, parasites, fungi	<i>Streptococcus pneumoniae</i> <i>Clostridium tetani</i> <i>Trypanosoma brucei</i> <i>Pneumocystis carinii</i>	Pneumonia Tetanus Sleeping sickness <i>Pneumocystis pneumonia</i>
Intracellular bacteria, parasites	<i>Mycobacterium leprae</i> <i>Leishmania donovani</i> <i>Plasmodium falciparum</i>	Leprosy Leishmaniasis Malaria
Viruses (intracellular)	Variola Influenza Varicella	Smallpox Flu Chickenpox
Parasitic worms (extracellular)	<i>Ascaris</i> <i>Schistosoma</i>	Ascariasis Schistosomiasis

Figure 1-25 Immunobiology, 7ed. (© Garland Science 2008)

Immune responses are mediated by a variety of cells and by the soluble molecules these cells secrete



Host defenses can be divided into Innate and Adaptive Immunity



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Timeline of an Immune Response

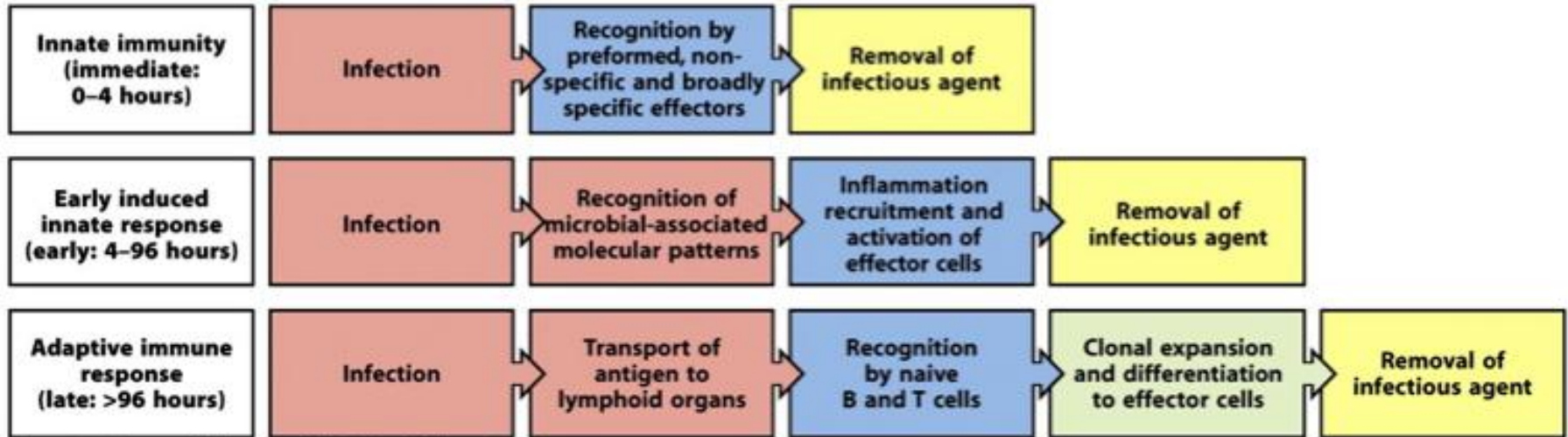


Figure 2-1 Immunobiology, 7ed. (© Garland Science 2008)

In both innate and adaptive immunity, there are distinct phases:

RECOGNITION (of PAMPS and host breakdown products)

ACTIVATION (inflammation and recruitment of immune cells)

EFFECTOR (removal of infectious agent) phases

Innate Immunity

- Innate immune responses can start acting immediately on encounter with infectious agents
- Does not generate long-term protective immunological memory
- Receptors on responding cells are not unique to that cell but are expressed on all cells of that type. For example, Toll-like receptors (TLRs) on sentinel cells of the innate immune system, such as macrophages, recognize structural motifs (pathogen associated molecular patterns, PAMPs) on microbes, via the pattern recognition receptor (PRR). PRRs are germline encoded proteins evolutionarily selected to recognize PAMPs carried by potential invaders

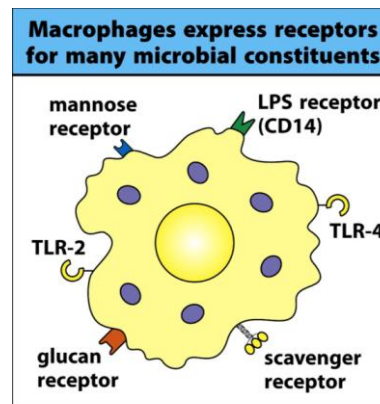
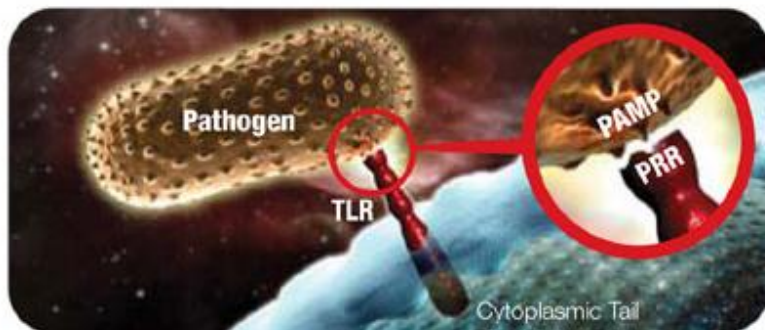
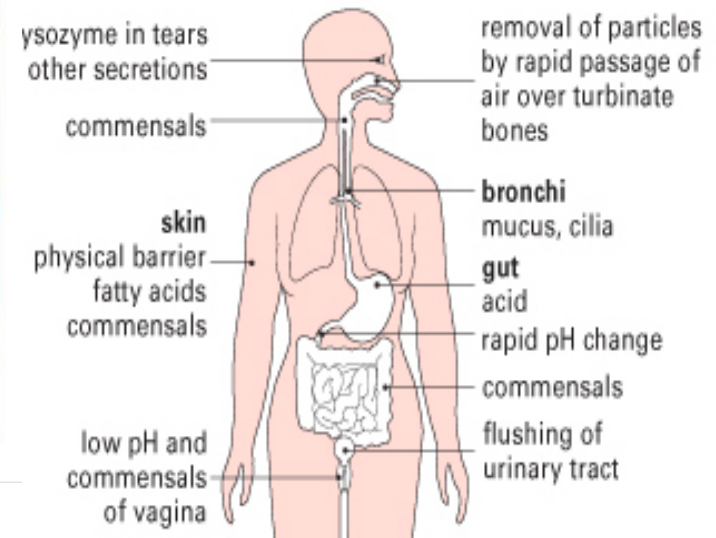


Figure 1-10 Immunobiology, 7ed. (© Garland Science 2008)

Exterior defenses are part of the innate immune response. Most infectious agents prevented from entering body by physical and biochemical barriers

	Skin	Gut	Lungs	Eyes/nose
Mechanical	Epithelial cells joined by tight junctions			
	Longitudinal flow of air or fluid		Movement of mucus by cilia	Tears Nasal cilia
Chemical	Fatty acids	Low pH Enzymes (pepsin)		Enzymes in tears (lysozyme)
	Antibacterial peptides			
Microbiological	Normal flora			

Figure 2-7 Immunobiology, 7ed. (© Garland Science 2008)



In the absence of wounding or disruption, pathogens normally cross epithelial barriers by binding to molecules on internal epithelial surfaces, or establish an infection by adhering to and colonizing these surfaces. This specific attachment allows the pathogen to infect the epithelial cell or to damage it so that the epithelium can be crossed, or to avoid being dislodged by the flow of air or fluid across the epithelial surface.

After entering tissues, many pathogens are recognized, ingested, and killed by phagocytes, as part of the innate immune response

Macrophages express receptors for many bacterial components, including bacterial carbohydrate (mannose and glucan), lipids (LPS) and other pathogen-derived components (Pathogen Associated Molecular Patterns, PAMPs)

Binding of bacteria to macrophage receptors stimulates phagocytosis and uptake of pathogens into intracellular vesicles, where they are destroyed

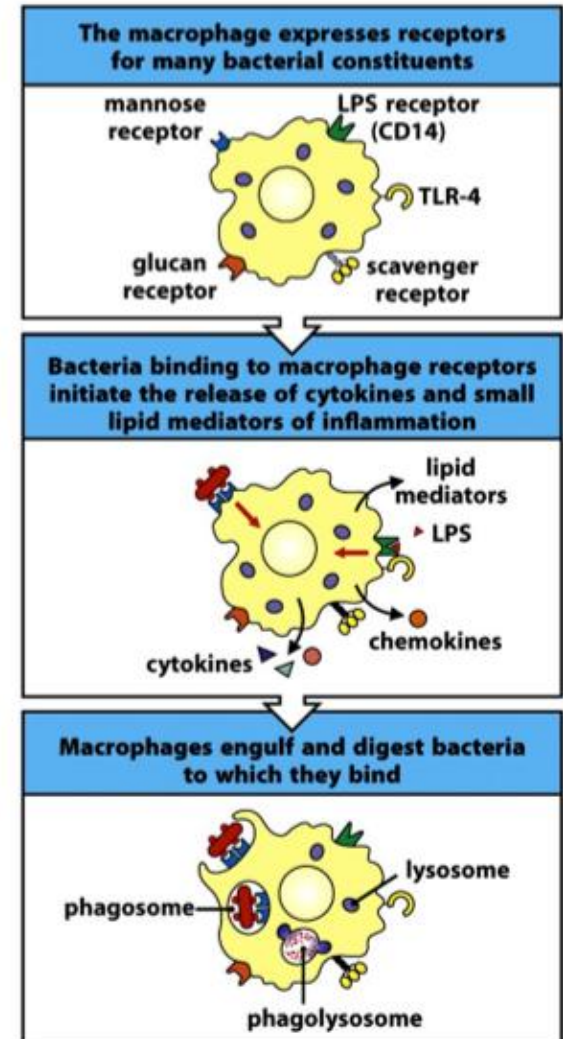


Figure 2-8 Immunobiology, 7ed. (© Garland Science 2008)

The cells of the innate immune system initiate adaptive immune responses

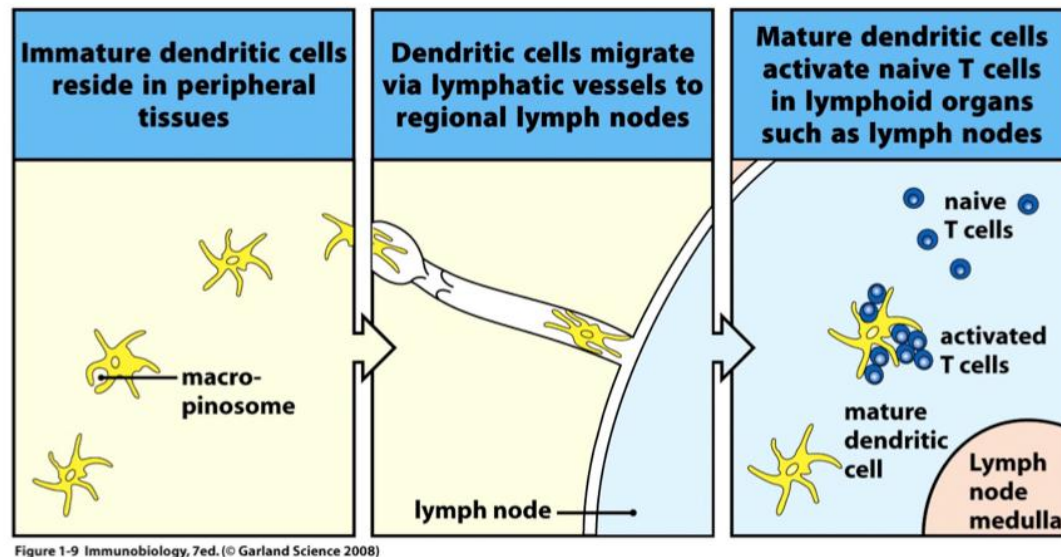


Figure 1-9 Immunobiology, 7ed. (© Garland Science 2008)

Recognition of PAMPs by TLRs on immature dendritic cells (DC) is followed by ingestion of the pathogen

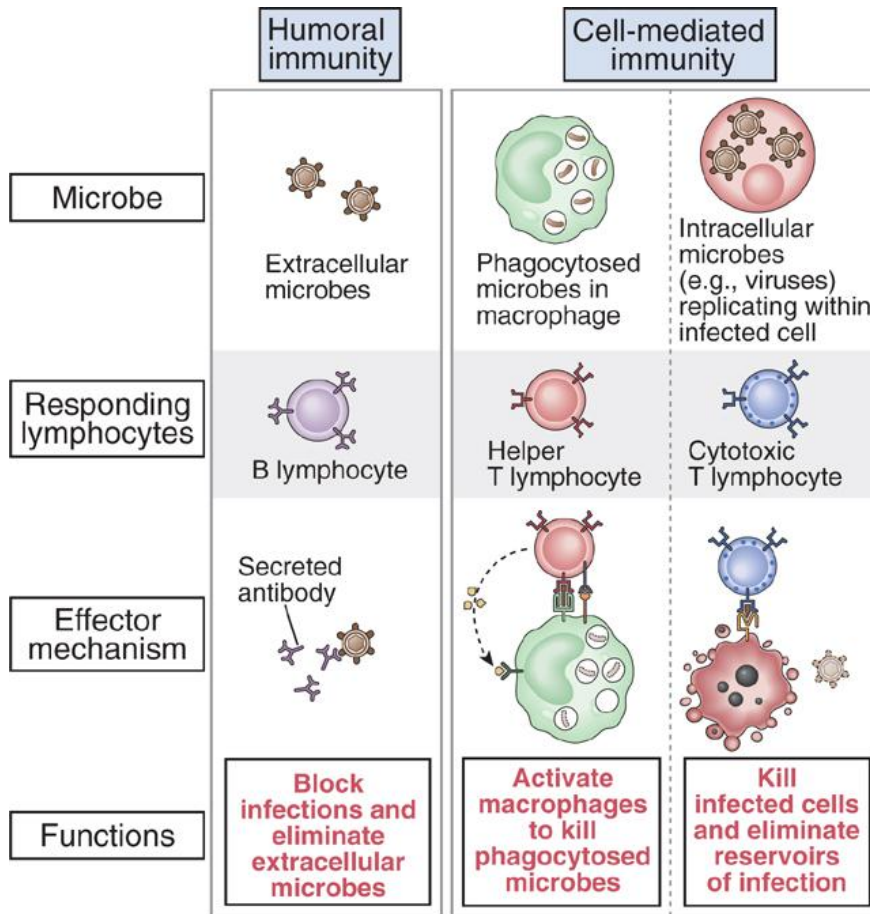
DC migrate through the lymphatic system towards lymph nodes, where they present pathogen antigens to T cells and in so doing stimulate the adaptive immune response

Types of Adaptive Immunity

In **HUMORAL** immunity, B lymphocytes secrete antibodies that eliminate extracellular microbes

In **CELL MEDIATED** immunity, T lymphocytes either activate macrophages to destroy phagocytosed microbes, or kill infected cells.

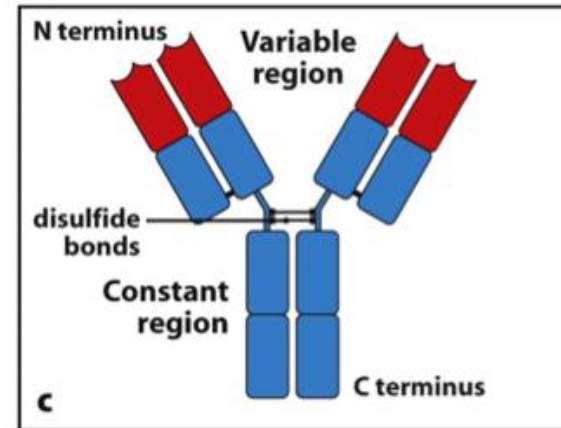
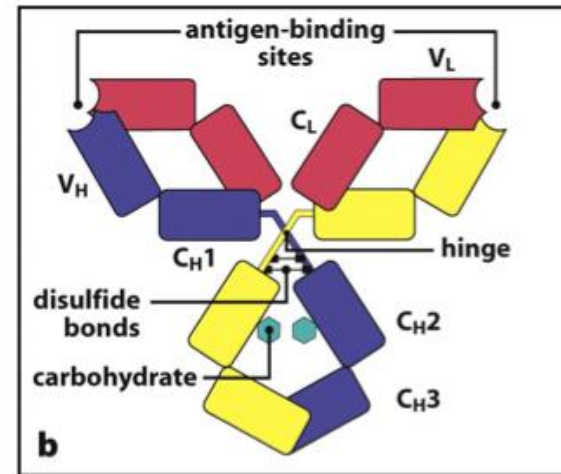
T lymphocytes also provide a helper function for B cells.



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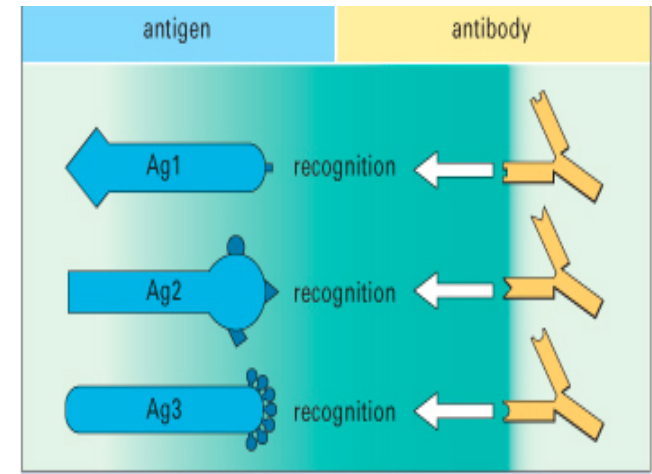
Humoral Immunity

- Antibody: Y-shaped structure with variable Fab regions at tips that bind antigen
- Stem of Y (Fc) is constant region, not involved in antigen recognition
- 5 classes of antibodies in mammals – IgG, IgA, IgM, IgD, and IgE

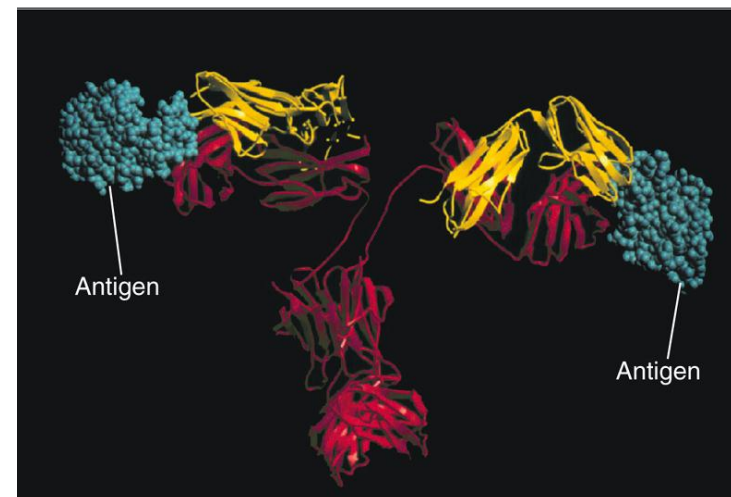


Humoral Immunity

- Antibodies recognize epitopes on the surface of antigens
- Antigens may be recognized by more than one antibody when more than one epitope exists
- The antigen-binding site can accommodate soluble macromolecules in their native state

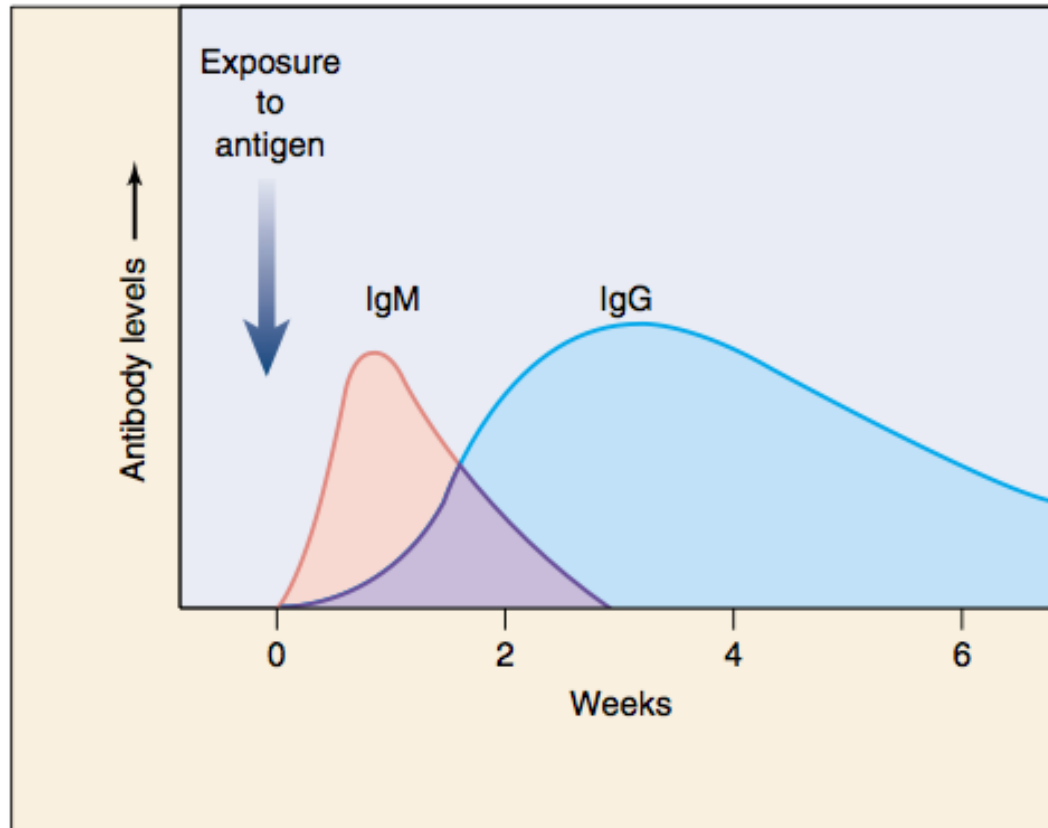


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Primary humoral response



The first antibodies produced in the humoral immune response are IgM antibodies. IgM is very effective at activating the complement system. IgM production peaks after about one week and is followed by a more extended production of IgG antibodies.

Cell Mediated Immunity

- T cells recognize antigen as peptide presented by MHC molecules
- Antigenic peptides are processed intracellularly from pathogen and tumour proteins and transported to the cell surface bound to MHC/HLA molecules

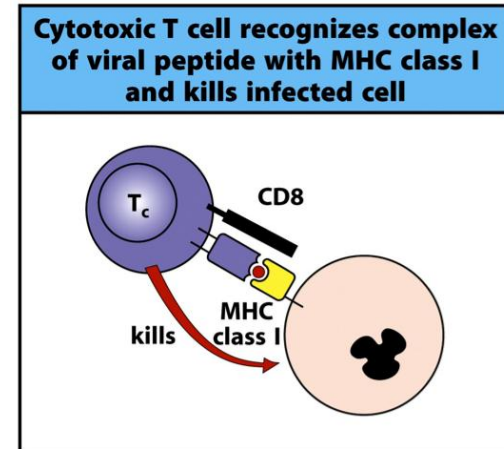


Figure 1-32 Immunobiology, 7ed, (© Garland Science 2008)

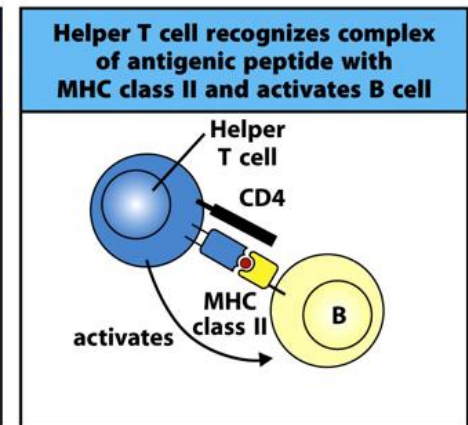
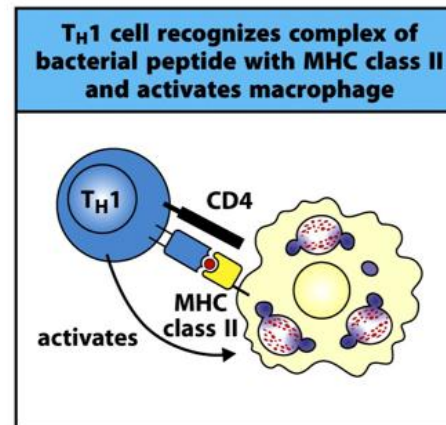
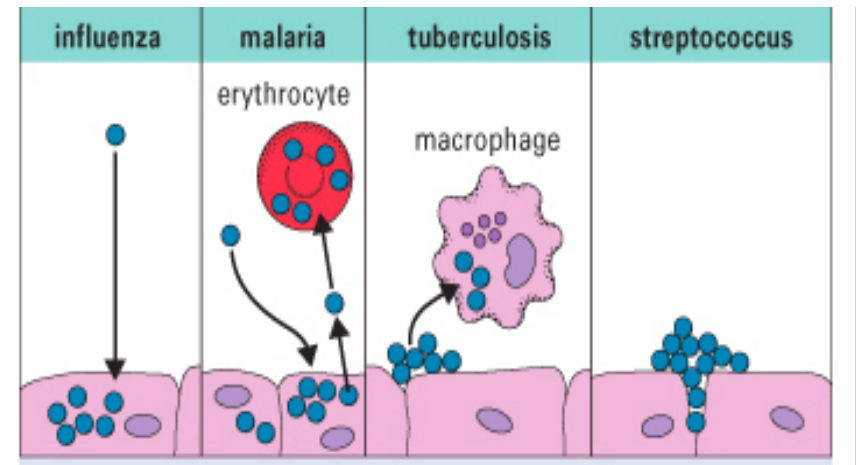


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Site of infection determines nature of the immune response

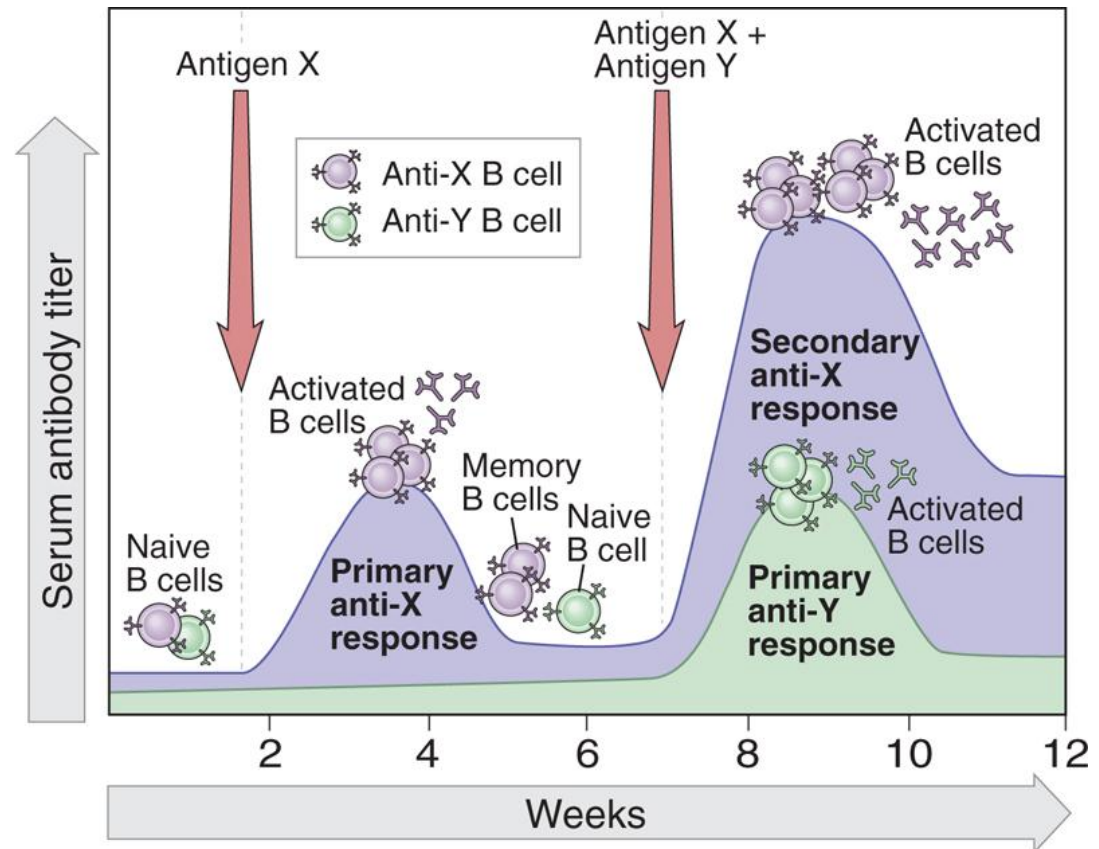
- Extracellular pathogens do not invade host cells: humoral (antibody mediated) immunity
- Intracellular pathogens invade host cells to divide and reproduce: cell mediated immunity



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Primary and Secondary Immune Responses

- Antigen X and Y induce the production of different antibodies (a reflection of specificity)
- The secondary response to antigen X is more rapid and larger than the primary response (illustrating memory) and is different from the primary response to antigen Y (again reflecting specificity)
- Antibody levels decline with time after each immunization



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Properties of Adaptive Immune Responses

Feature	Functional significance
Specificity	Ensures that distinct antigens elicit specific responses
Diversity	Enables immune system to respond to a large variety of antigens
Memory	Leads to enhanced responses to repeated exposures to the same antigens
Clonal expansion	Increases number of antigen-specific lymphocytes to keep pace with microbes
Specialization	Generates responses that are optimal for defense against different types of microbes
Contraction and homeostasis	Allows immune system to respond to newly encountered antigens
Nonreactivity to self	Prevents injury to the host during responses to foreign antigens

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- T and B cells use very large repertoire of specific antigen receptors
- Responses are highly specific for any given pathogen
- Specificity of response allows generation of immunological memory; this can be artificially induced by vaccines

Clonal Selection

Each lymphoid progenitor gives rise to a large number of lymphocytes, each bearing a distinct antigen receptor

Lymphocytes with receptors that bind ubiquitous self antigens are eliminated before they become fully mature, ensuring tolerance to such antigens

When a foreign antigen interacts with the receptor on a mature naïve lymphocyte, that cell is activated and starts to divide

It gives rise to a clone of identical progeny, all of whose receptors bind the same antigen

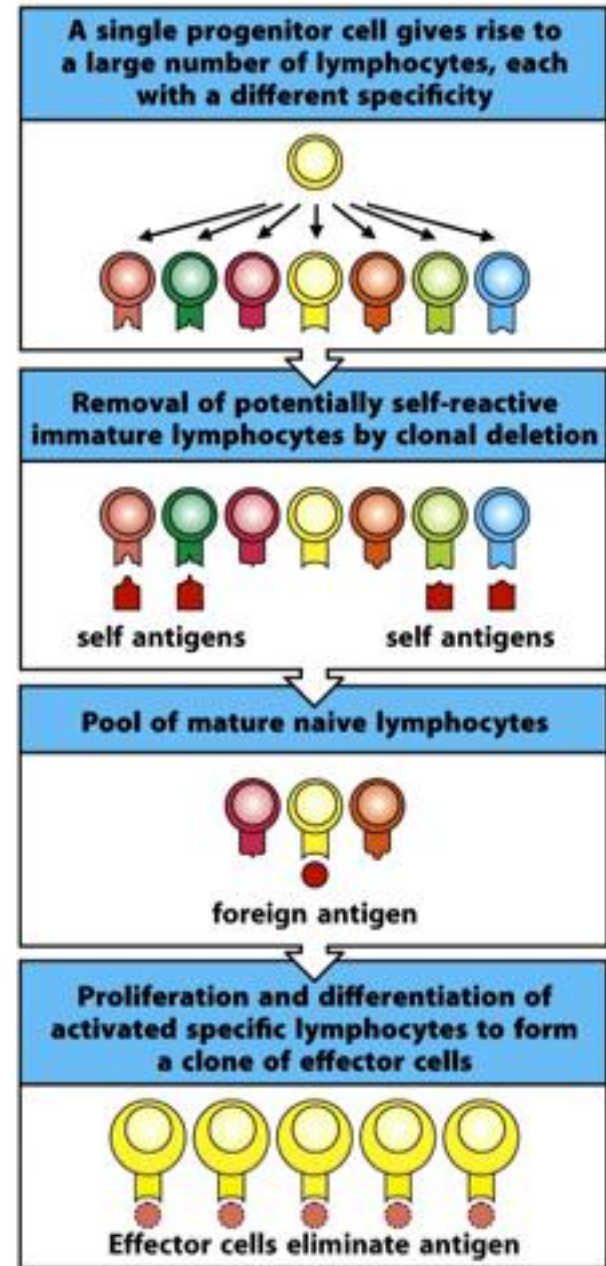


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Postulates of the clonal selection hypothesis

Each lymphocyte bears a single type of receptor with a unique specificity

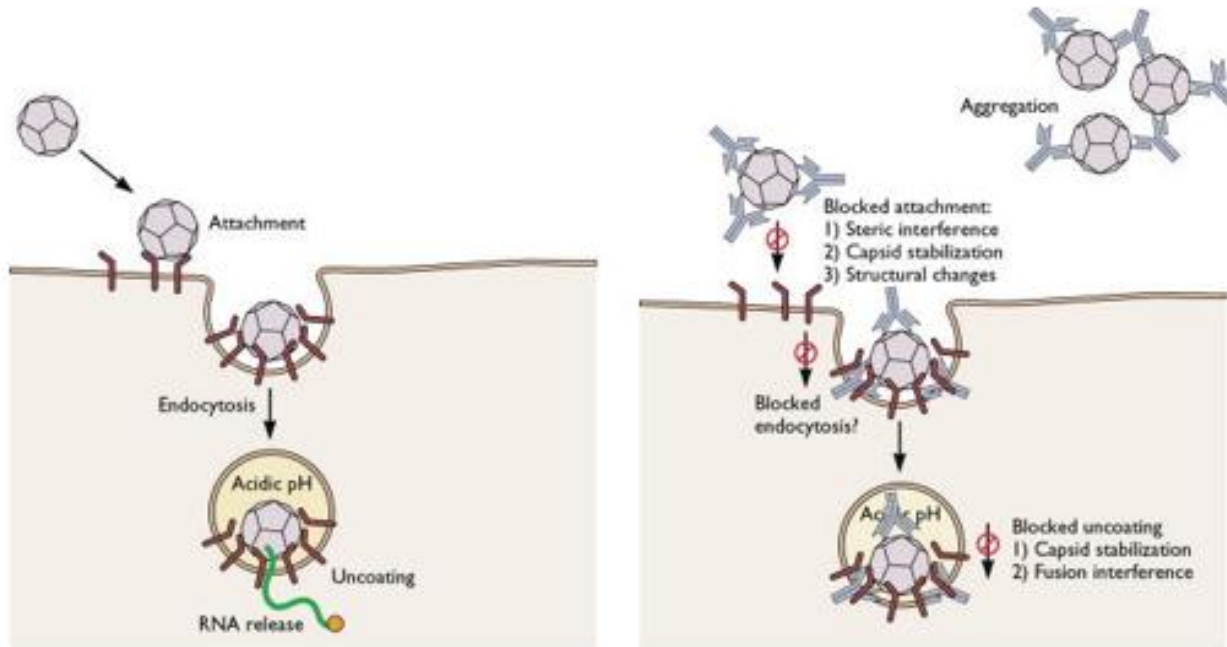
Interaction between a foreign molecule and a lymphocyte receptor capable of binding that molecule with high affinity leads to lymphocyte activation

The differentiated effector cells derived from an activated lymphocyte will bear receptors of identical specificity to those of the parental cell from which that lymphocyte was derived

Lymphocytes bearing receptors specific for ubiquitous self molecules are deleted at an early stage in lymphoid cell development and are therefore absent from the repertoire of mature lymphocytes

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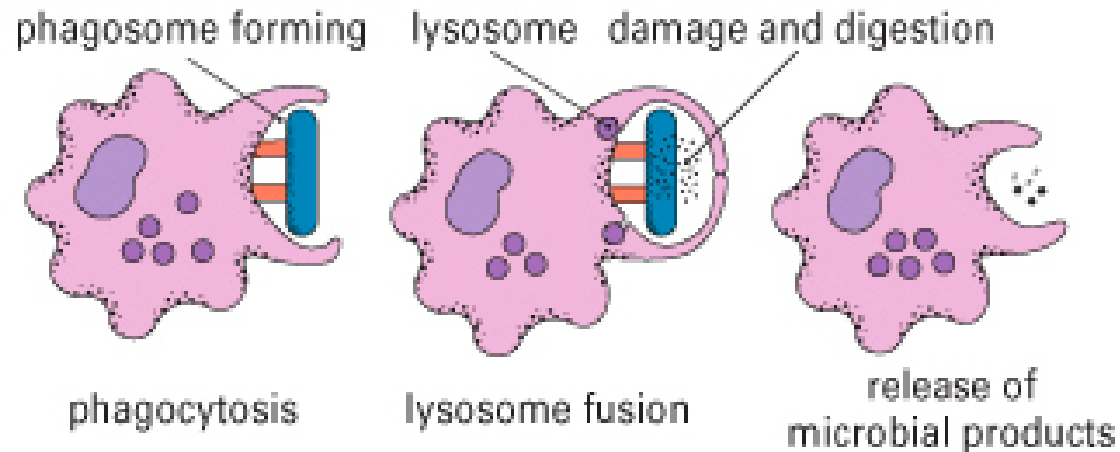
Antigen Eradication



Racaniello www.virology.ws

Antibodies can bind to virus particles and prevent infection of host cells

Antigen Eradication

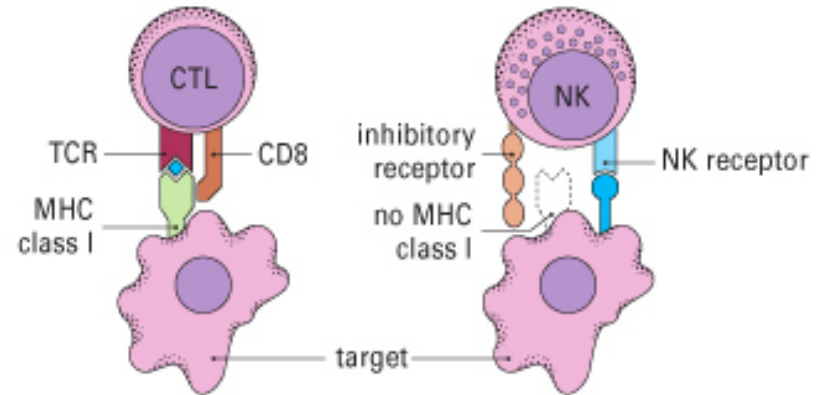
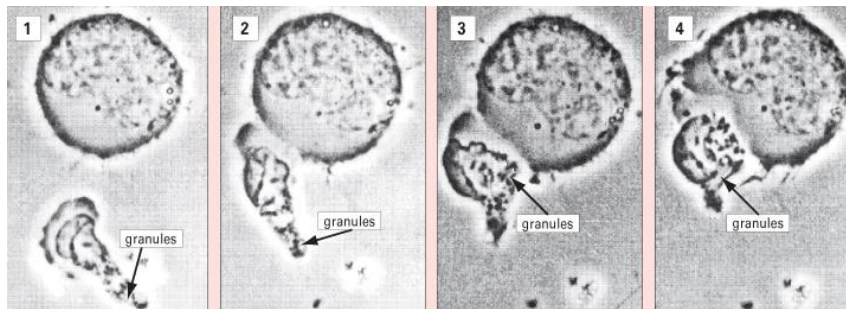


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Phagocytes (macrophages, neutrophils) internalize opsonized microbes into phagosomes where they are digested

Antigen Eradication

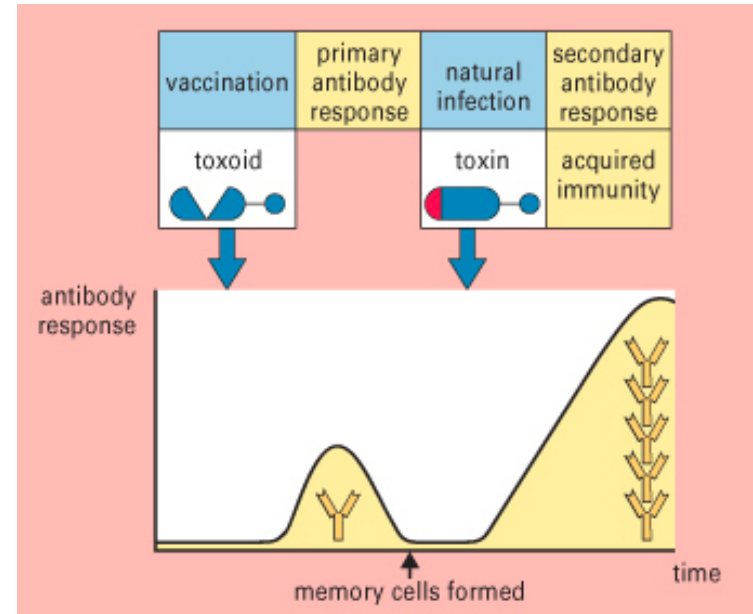
NK and CTL cells kill targets, without killing themselves, by releasing lytic granules containing perforin and granzymes



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Vaccination

- Pathogens are altered so that they maintain their antigenicity while losing their virulence
- Vaccination induces primary antibody and cellular immune responses



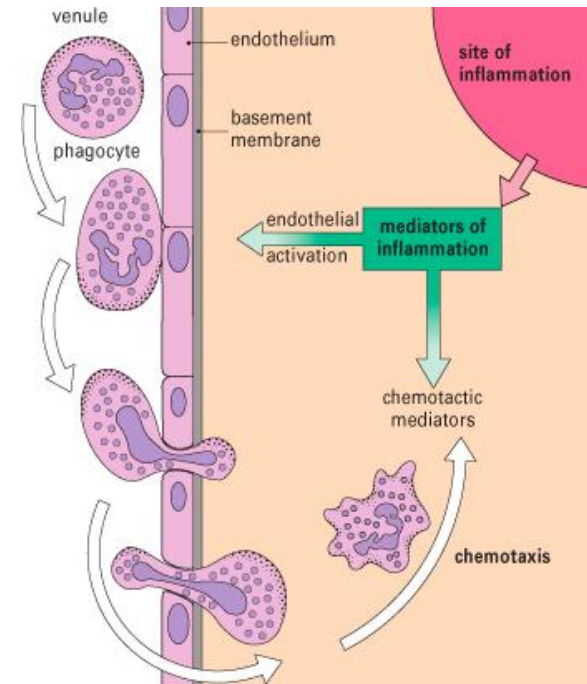
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- Memory cells proliferate rapidly in secondary immune responses induced in natural infection

Inflammation is a response to tissue damage

At site of inflammation: tissue damage and complement activation cause release of chemotactic molecules

Activated phagocytes migrate across vessel walls and along concentration gradient to inflammatory site

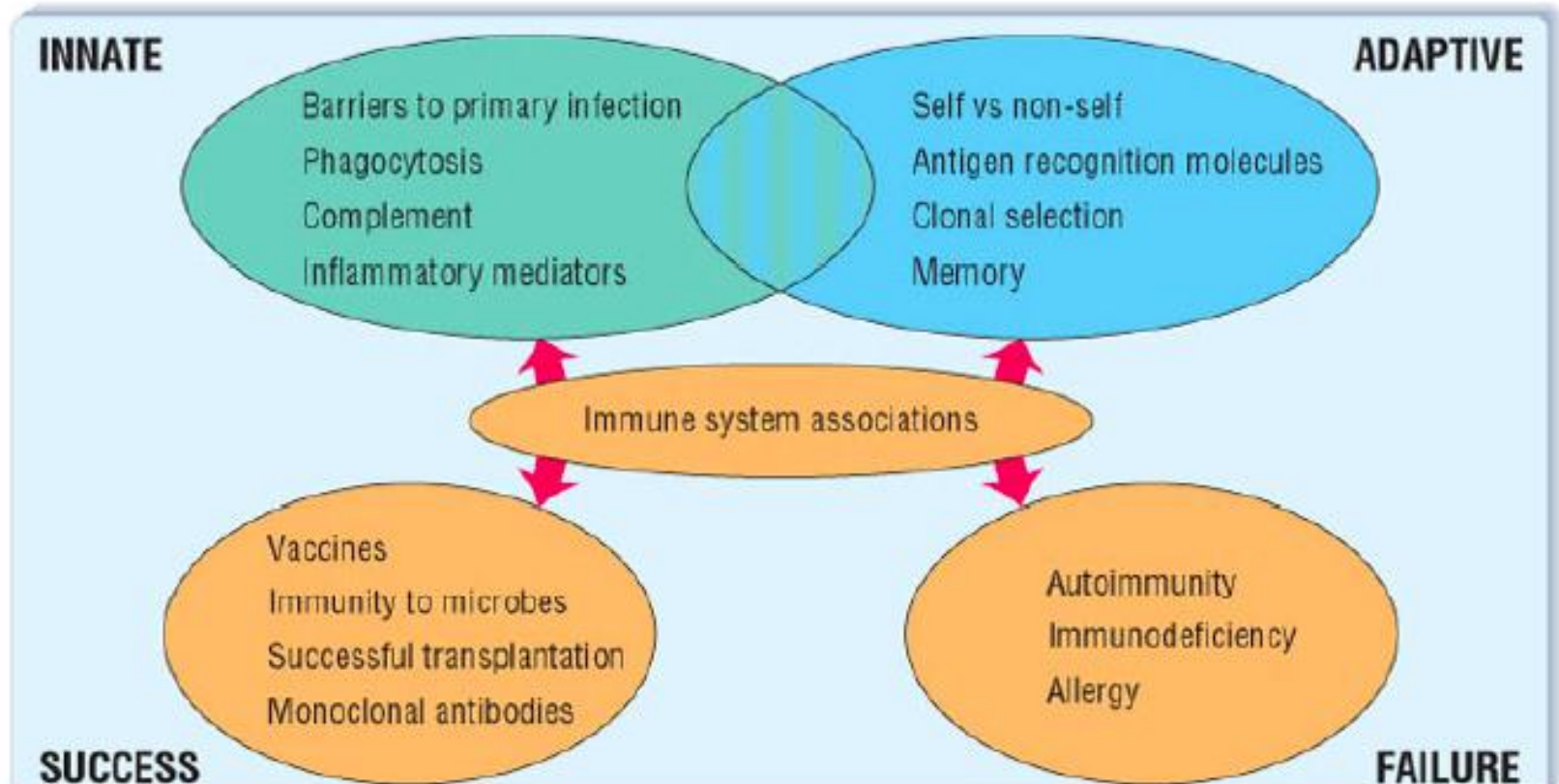


Immunopathology

Immune systems may become dysregulated and induce disease. Examples of such diseases are rheumatoid arthritis; Netherton's syndrome; allergy; systemic lupus erythematosus; celiac disease



SUMMARY



Feature

Response time

Pathogen (non-self) recognition mechanisms

Memory

Improvements to pathogen-recognition molecules made during response

Innate

Rapid (minutes/hours)

Few

No

No

Adaptive

Slow (days/weeks)

Very many

Yes

Yes