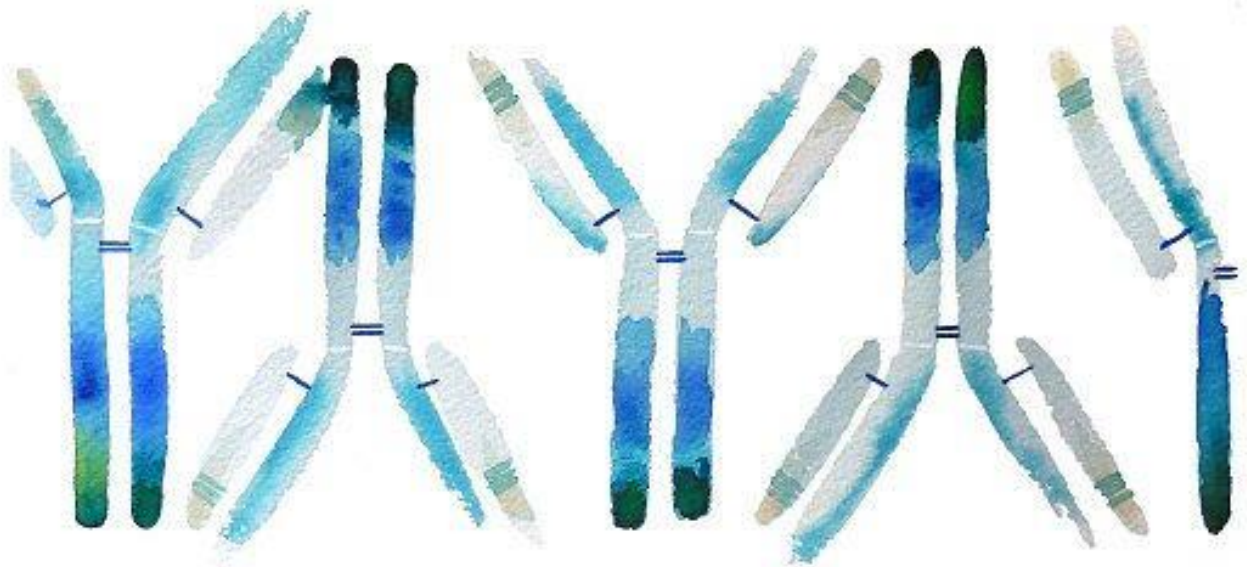
Medical Immunology



Anas Abu-Humaidan
M.D. Ph.D.

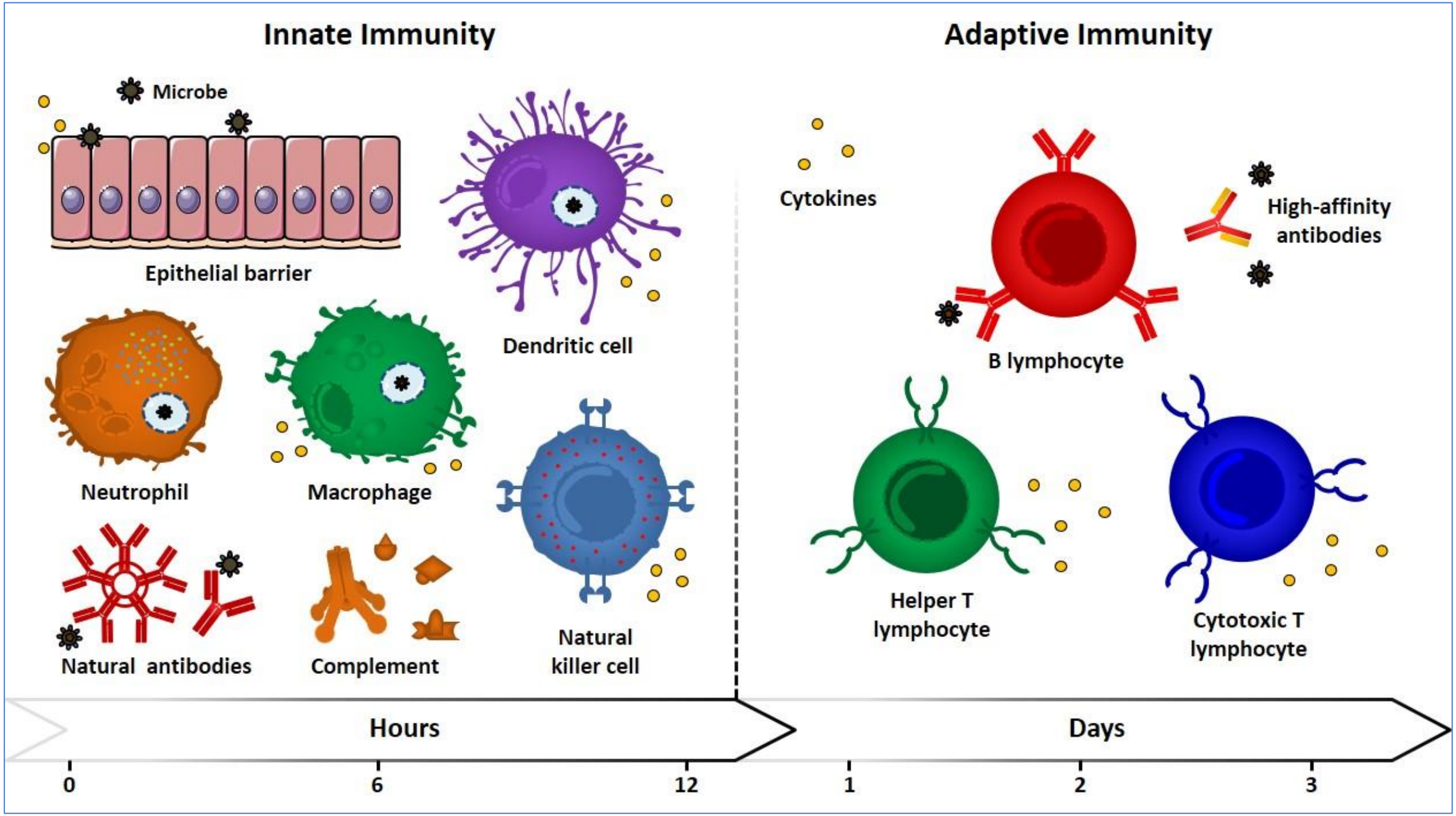
Lecture 8

- In this lecture we will discuss

- Main topics:

Innate immune response to extracellular and intracellular pathogens

Innate immunity



Innate immunity

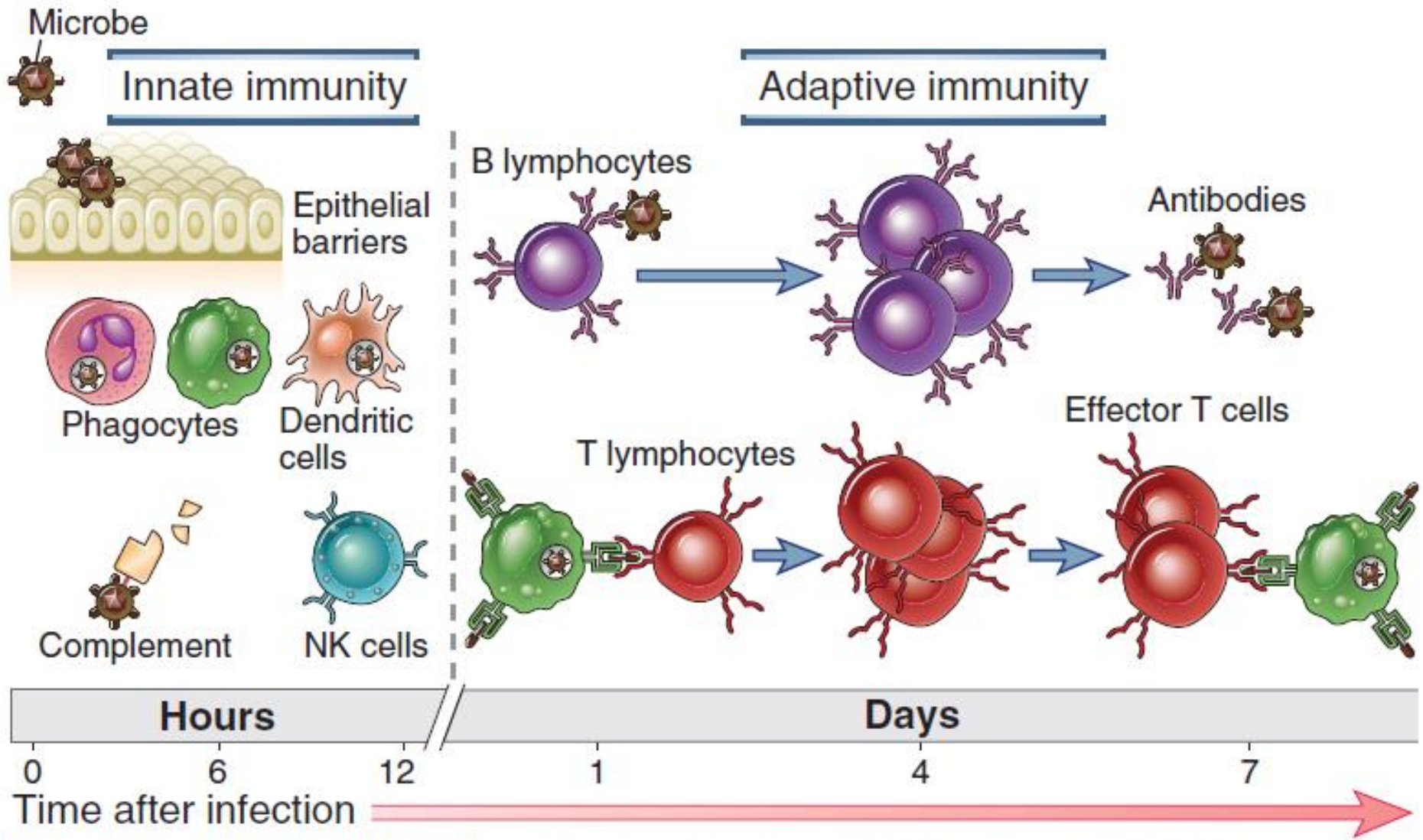


FIGURE 1–1 Innate and adaptive immunity. The mechanisms of innate immunity provide the initial defense against infections. Adaptive immune responses develop later and consist of activation of lymphocytes. The kinetics of the innate and adaptive immune responses are approximations and may vary in different infections.

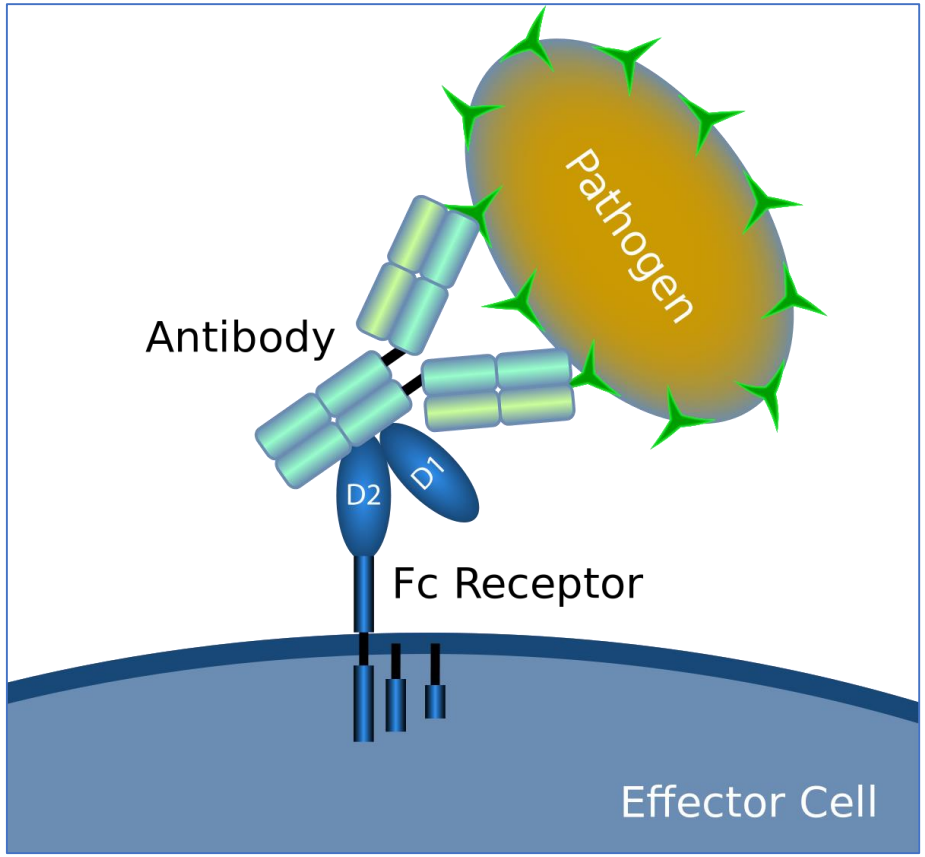
Innate Immunity to Extracellular Bacteria

- The principal mechanisms of innate immunity to extracellular bacteria are :

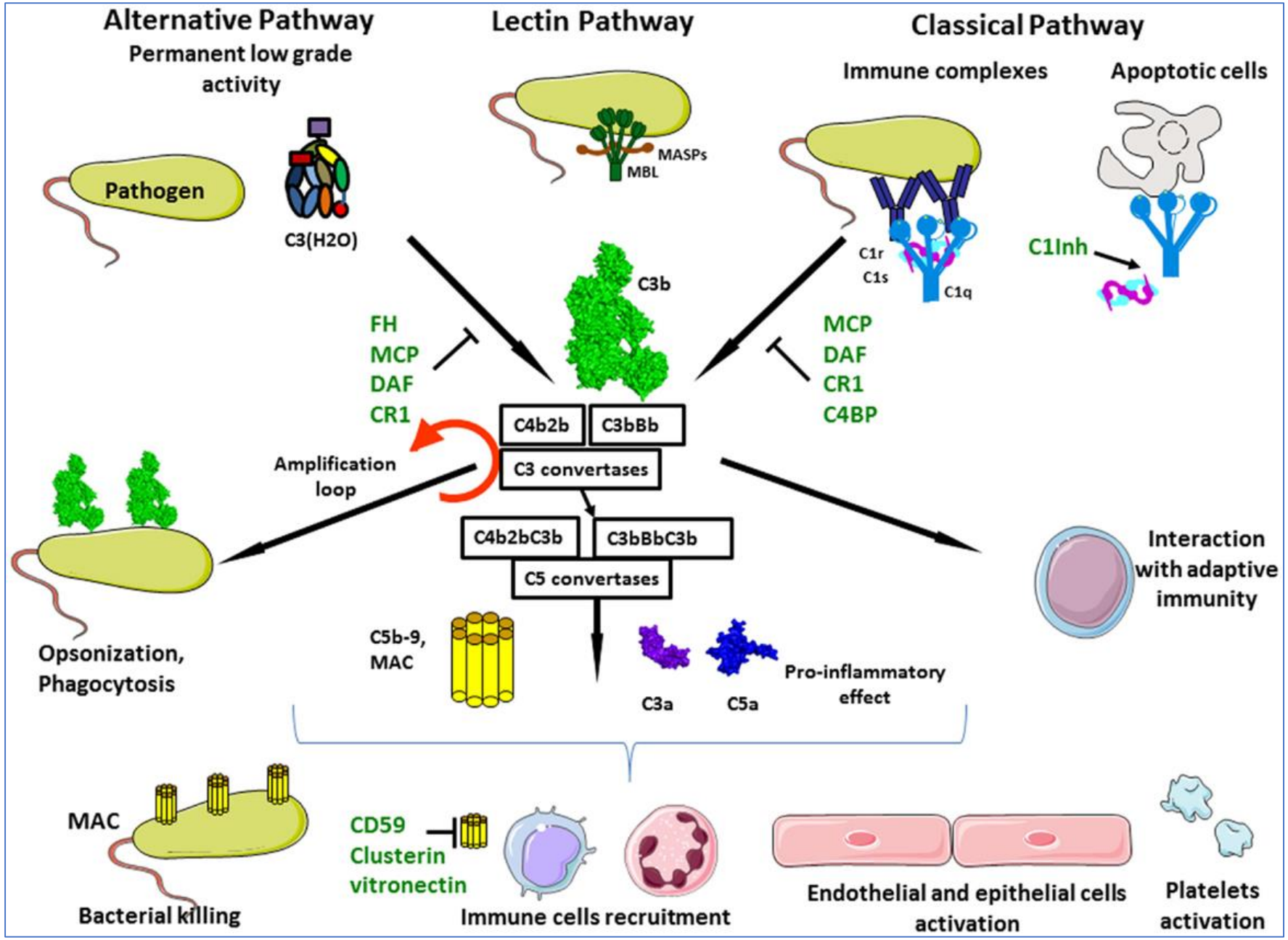
- **complement activation**.

- **Phagocytosis**: Phagocytes use various surface receptors, including **mannose receptors** and **scavenger receptors**, to recognize extracellular bacteria, and they use **Fc receptors** and **complement receptors** to recognize bacteria **opsonized** with antibodies and complement proteins, respectively. As well as TLRs and other PRR.

- **The inflammatory response**: dendritic cells and phagocytes that are activated by the microbes secrete cytokines, which induce leukocyte infiltration.



Innate immunity/ complement activation



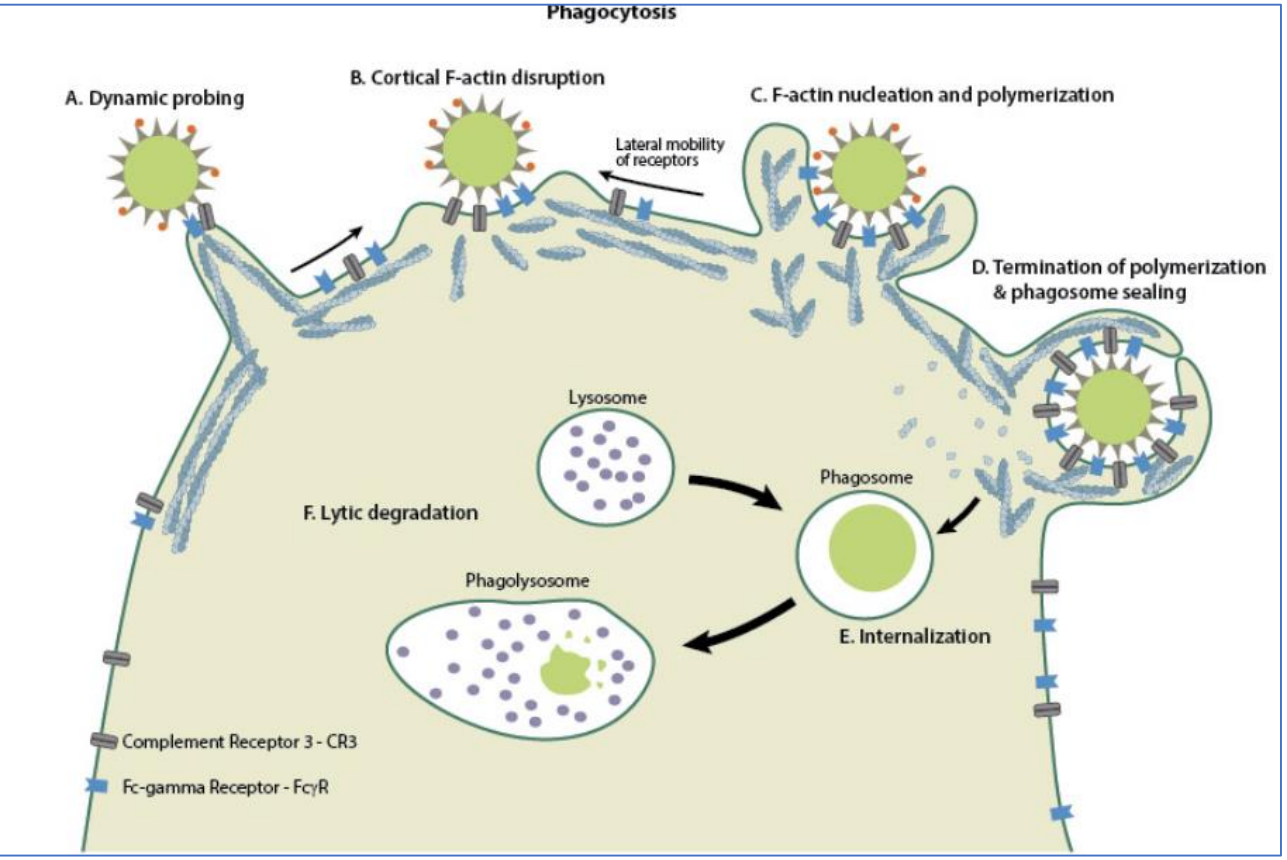
Innate immunity/ professional phagocytes

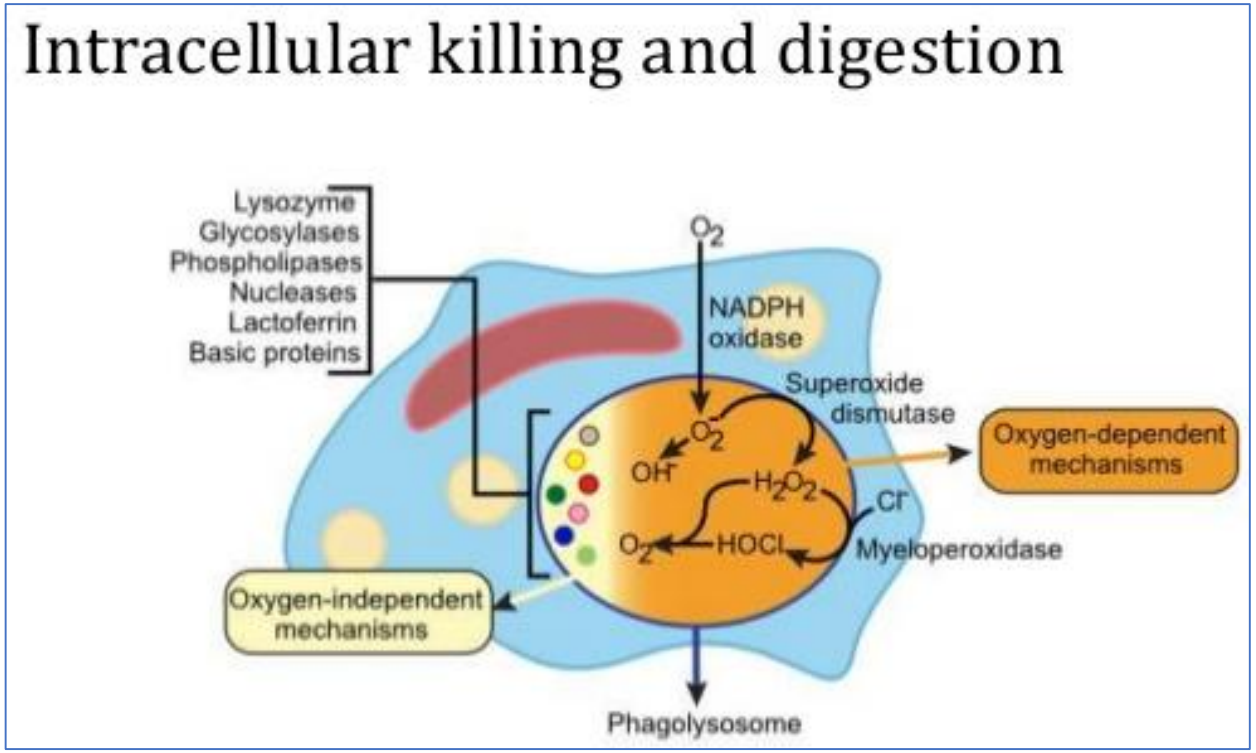
- Cells that have specialized phagocytic functions, primarily macrophages and neutrophils, are the **first line of defense against microbes** that breach epithelial barriers.

- They serve several functions: 1) **Internalize and kill microbes**. Neutrophils macrophages are particularly good at this function. 2) Phagocytes respond to microbes by **producing various cytokines** that promote inflammation. Macrophages are particularly good at this.

- The essential role that phagocytes play in innate immune defense against microbes is demonstrated by the **high rate of lethal bacterial and fungal infections** in patients with **low blood neutrophil counts** caused by bone marrow cancers or cancer therapy, or inherited deficiencies.

Innate immunity/ professional phagocytes





Binding of **Fc receptors** causes an increase in **oxygen uptake** by the phagocyte called the **respiratory burst**. This influx of oxygen is used in a variety of mechanisms to cause damage to microbes inside the phagolysosome, but the common theme is the creation of **highly reactive small molecules** that damage the biomolecules of the pathogen.

Innate immunity/ Macrophages

- Macrophages the most plastic cells of the hematopoietic system are found in all tissues and exhibit great functional diversity.

- They have roles in development, homeostasis, tissue repair, and immunity.

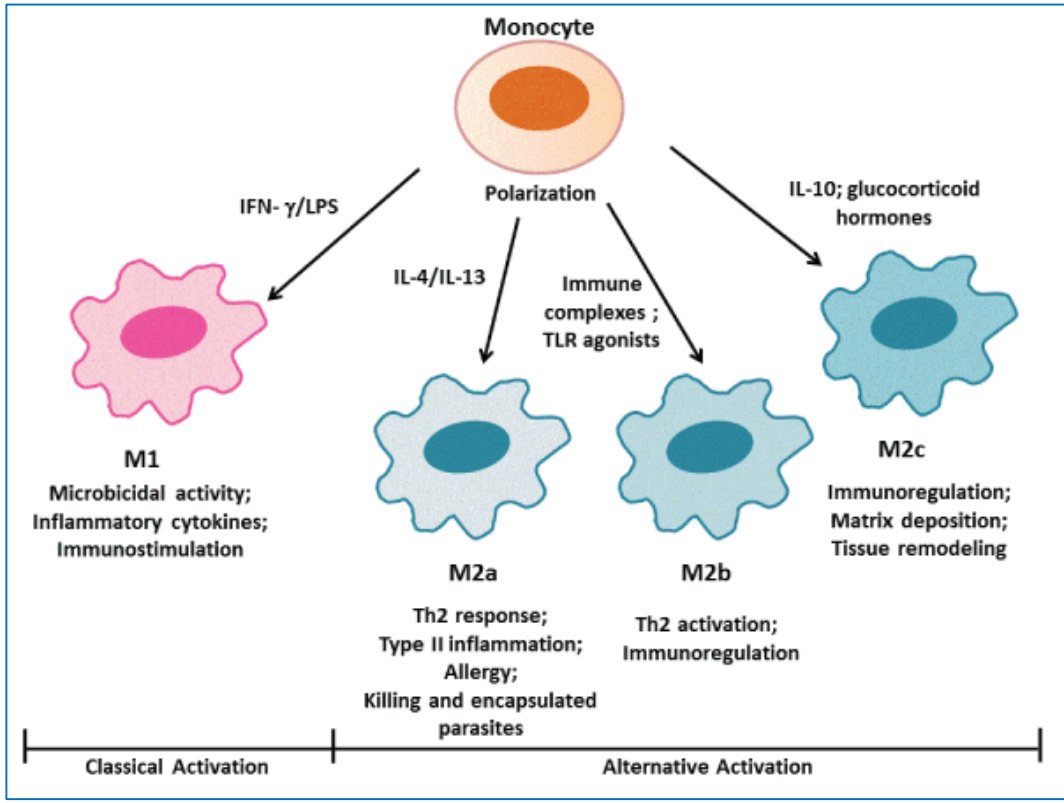
- Macrophages exist in **all vertebrate tissues**, and **different stimuli** will affect **macrophage phenotypes differently.**

- Generally, it is considered that **embryonic-derived macrophages** play a strong role in the maintenance of **tissue homeostasis** and that **macrophages derived from bone marrow monocytes** are related to **host defense** reactions and **inflammatory diseases**.

- Unlike neutrophils, macrophages are not terminally differentiated and **can undergo cell division** at **an inflammatory site**. Therefore, macrophages are the **dominant effector cells** of the **later stages of the innate immune response**, several days after infection.

- Macrophages **activated by the invasion of pathogens to destroy them are categorized as M1** macrophages, and macrophages causing chronic inflammation because of allergic reactions, fat metabolism, wound healing, and cancer invasion and metastasis are categorized as M2 macrophages.

- Generally, **PAMPs, DAMPs**, and inflammatory cytokines such as **TNF-α and IFN-γ** induce the **M1 phenotype**. Conversely, **anti-inflammatory cytokines such as IL-10, and IL-13** induce the **M2 phenotype**.



Innate immunity/ professional phagocytes

- Macrophages and dendritic cells function as antigen-presenting cells (APCs). They present peptide antigens derived from digested bacteria on the major histocompatibility complex class II and activate acquired immunity by activating helper T cells. While macrophages present antigens within tissues, dendritic cells present antigens in the lymph node. **Only dendritic cells can activate naïve T cells to become effector T cells, and are the most powerful APCs**

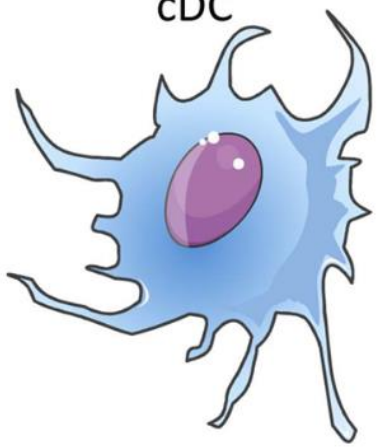
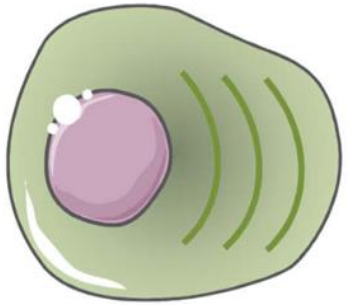
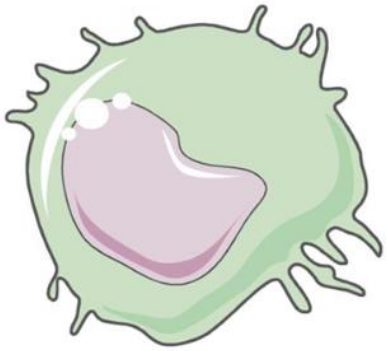
Innate immunity/ Dendritic cells

- Heterogeneous family of bone marrow–derived cells with long dendrite-like cytoplasmic processes are constitutively present in epithelia and most tissues of the body.

- Most versatile sensors of PAMPs and DAMPs among all cell types in the body.

- TLR signaling induces dendritic cell expression of molecules, including **costimulatory molecules and cytokines**, that are needed, in addition to antigen, **for the activation of the naive T cells.** Activation into **effector T cell** subtypes depends on the nature of the pathogen.

Innate immunity/ Dendritic cells

APC type	cDC	pDC	Monocyte / Macrophage
			
Primary functions	T cell priming and functional polarization, Induction of Immunity vs Tolerance	Interferon-α/β production Innate defenses against viruses	Tissue homeostasis Trophic and scavenger functions Microbicidal compound production

DC include two main cell types, the **plasmacytoid DC (pDC**) that are **expert in type I interferon synthesis** upon viral stimulation and the **conventional DC (cDC)** that are specialized in **antigen capture**, **processing**, and **presentation for T-cell priming.**

Innate immunity/ Dendritic cells

Eur J Immunol. 1998 Dec;28(12):4114-22.

Dendritic cell chemotaxis and transendothelial migration are induced by distinct chemokines and are regulated on maturation.

Lin CL[1], Suri RM, Rahdon RA, Austyn JM, Roake JA.

Author information

1 Nuffield Department of Surgery, University of Oxford, John Radcliffe Hospital, GB.

Abstract

The capacity of dendritic cells (DC) to initiate immune responses is dependent on their specialized migratory and tissue homing properties. Chemotaxis and transendothelial migration (TEM) of DC were studied in vitro. Immature DC were generated by culture of human monocytes in granulocyte-macrophage colony-stimulating factor and IL-4. These cells exhibited potent chemotaxis and TEM responses to the CC chemokines macrophage inflammatory protein (MIP)-1alpha, MIP-1beta, RANTES, and monocyte chemotactic protein-3, and weak responses to the CC chemokine MIP-3beta and the CXC chemokine stromal cell-derived factor (SDF)-1alpha. Maturation of DC induced by culture in lipopolysaccharide, TNF-alpha or IL-1beta reduced or abolished responses to the former CC chemokines but markedly enhanced responses to MIP-3beta and SDF-1alpha. This correlated with changes in chemokine receptor expression: CCR5 expression was reduced while CXCR4 expression was enhanced. These findings suggest two stages for regulation of DC migration in which one set of chemokines may regulate recruitment into or within tissues, and another egress from the tissues.

Innate immunity/ adaptive Immunity to Extracellular Bacteria

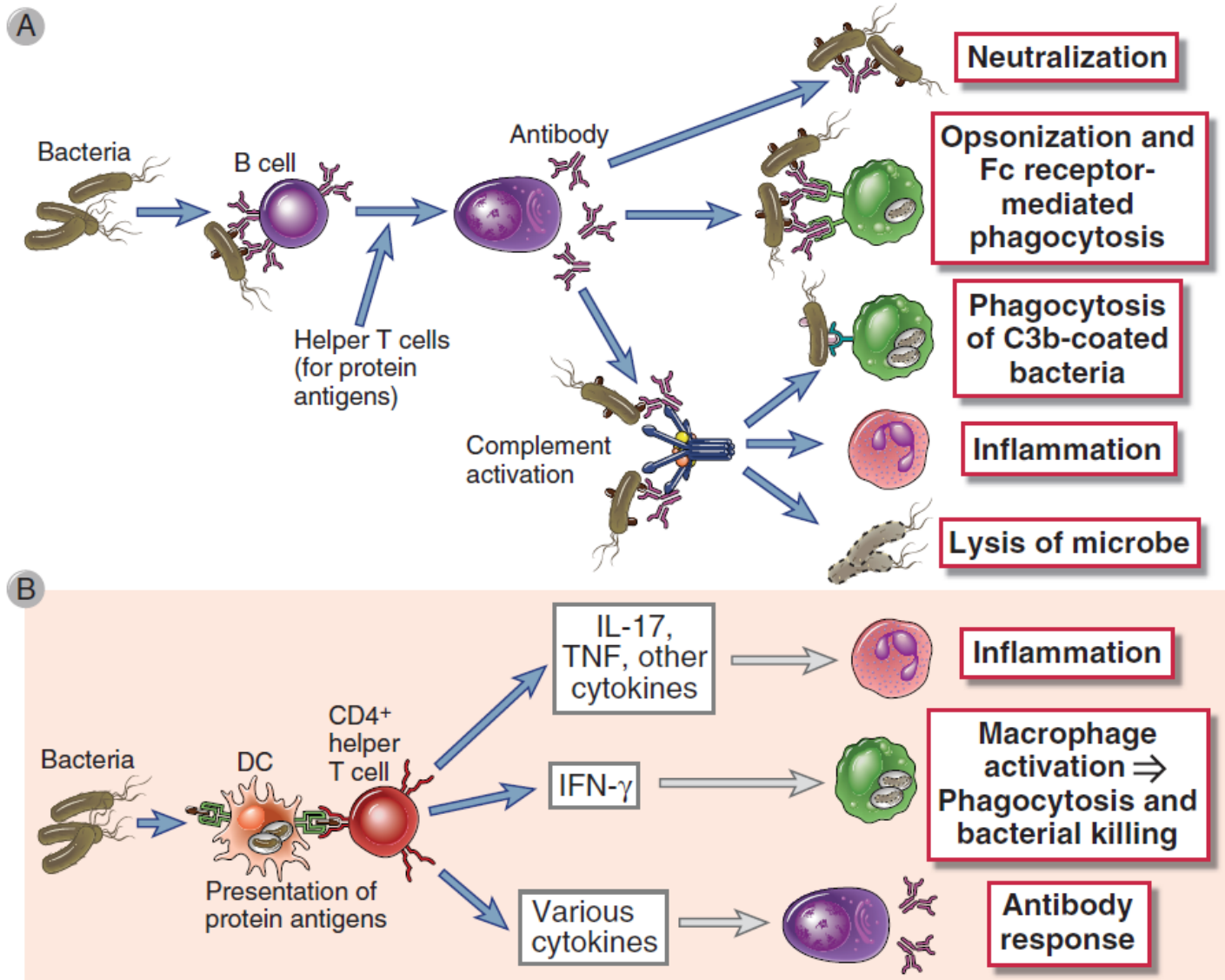


FIGURE 15–1 Adaptive immune responses to extracellular microbes. Adaptive immune responses to extracellular microbes such as bacteria and their toxins consist of antibody production **(A)** and the activation of $CD4^+$ helper T cells **(B)**. Antibodies neutralize and eliminate microbes and toxins by several mechanisms. Helper T cells produce cytokines that stimulate inflammation, macrophage activation, and B cell responses. DC, dendritic cell.

Innate immunity / Innate Immunity to Intracellular Pathogens

- The innate immune response to intracellular bacteria is mediated mainly by phagocytes and natural killer (NK) cells

- Phagocytes, initially neutrophils and later macrophages, ingest and attempt to destroy these microbes, but pathogenic intracellular bacteria are resistant to degradation within phagocytes.

- Products of these bacteria are recognized by TLRs and cytoplasmic proteins of the NOD like receptor (NLR) family, resulting in activation of the phagocytes.

- Intracellular bacteria activate NK cells by inducing expression of NK cell–activating ligands on infected cells and by stimulating dendritic cell and macrophage production of IL-12 and IL-15, both of which are NK cell–activating cytokines.

- The major protective immune response against intracellular bacteria is T cell–mediated immunity.

Innate immunity/ Natural killer (NK) cells

- NK are lymphocytes important in innate immunity. The term natural killer derives from the fact that these cells are capable of performing their killing function without a need for clonal expansion and differentiation.

- NK cells distinguish infected and stressed cells from healthy cells, and NK cell activation is regulated **by a balance between signals** that are generated from activating receptors and inhibitory receptors.

- In general, the **activating receptors** recognize ligands on **infected and injured cells**, and the inhibitory receptors recognize healthy normal cells. Most NK cells express **inhibitory receptors** that recognize **class I major histocompatibility complex** (MHC) molecules .

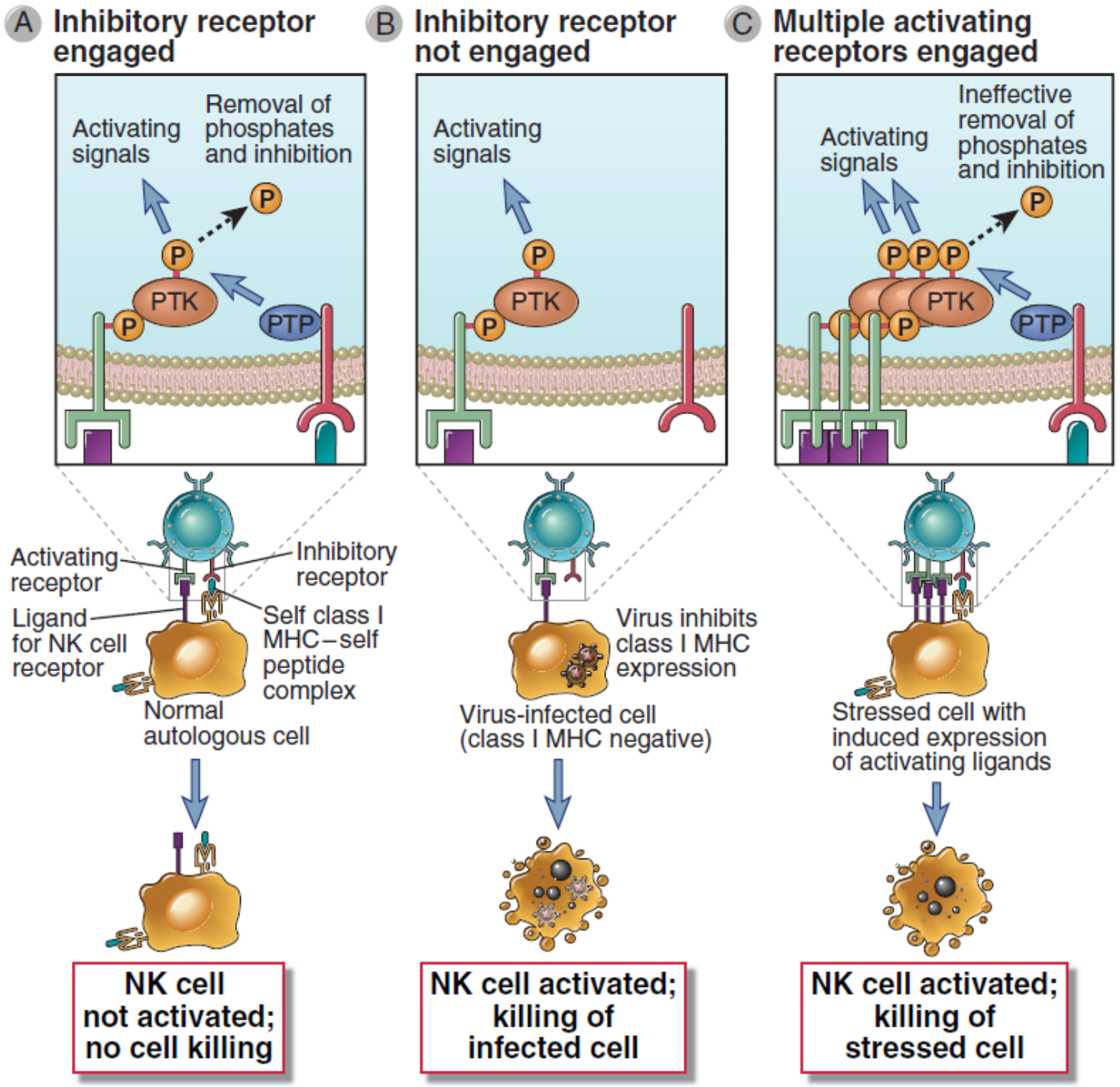
- This ability of NK cells to become activated by host cells that lack class I MHC has been called recognition of missing self.

Innate immunity/ Natural killer (NK) cells

A, Activating receptors of NK cells recognize ligands on target cells and activate protein tyrosine kinase (PTK), whose activity is inhibited by inhibitory receptors that recognize class I MHC molecules and activate protein tyrosine phosphatases (PTP). NK cells do not efficiently kill class I MHC–expressing healthy cells.

B, If a virus infection or other stress inhibits class I MHC expression on infected cells and induces expression of additional activating ligands, the NK cell inhibitory receptor is not engaged and the activating receptor functions unopposed to trigger responses of NK cells, such as killing of target cells and cytokine secretion.

C. Cells stressed by infection or neoplastic transformation may express increased amounts of activating ligands, which bind NK cell activating receptors and induce more tyrosine phosphorylation than can be removed by inhibitory receptor associated phosphatases, resulting in killing of the stressed cells



Innate immunity/ Natural killer (NK) cells

- Antibodies that bind to antigens can be recognised by **FcϒRIII** (CD16) receptors expressed on NK cells, resulting in NK activation, release of cytolytic granules and consequent cell apoptosis. This allows NK cells to **target cells against which a humoral response** has been gone through and to lyse cells through antibody-dependant cytotoxicity (**ADCC**).

- NK cells work to **control viral infections** by secreting **IFNγ and TNFα**. IFNγ activates macrophages for phagocytosis and lysis, and TNFα acts to promote direct NK tumor cell killing.

Innate immunity/ Innate Immunity to Intracellular Pathogens

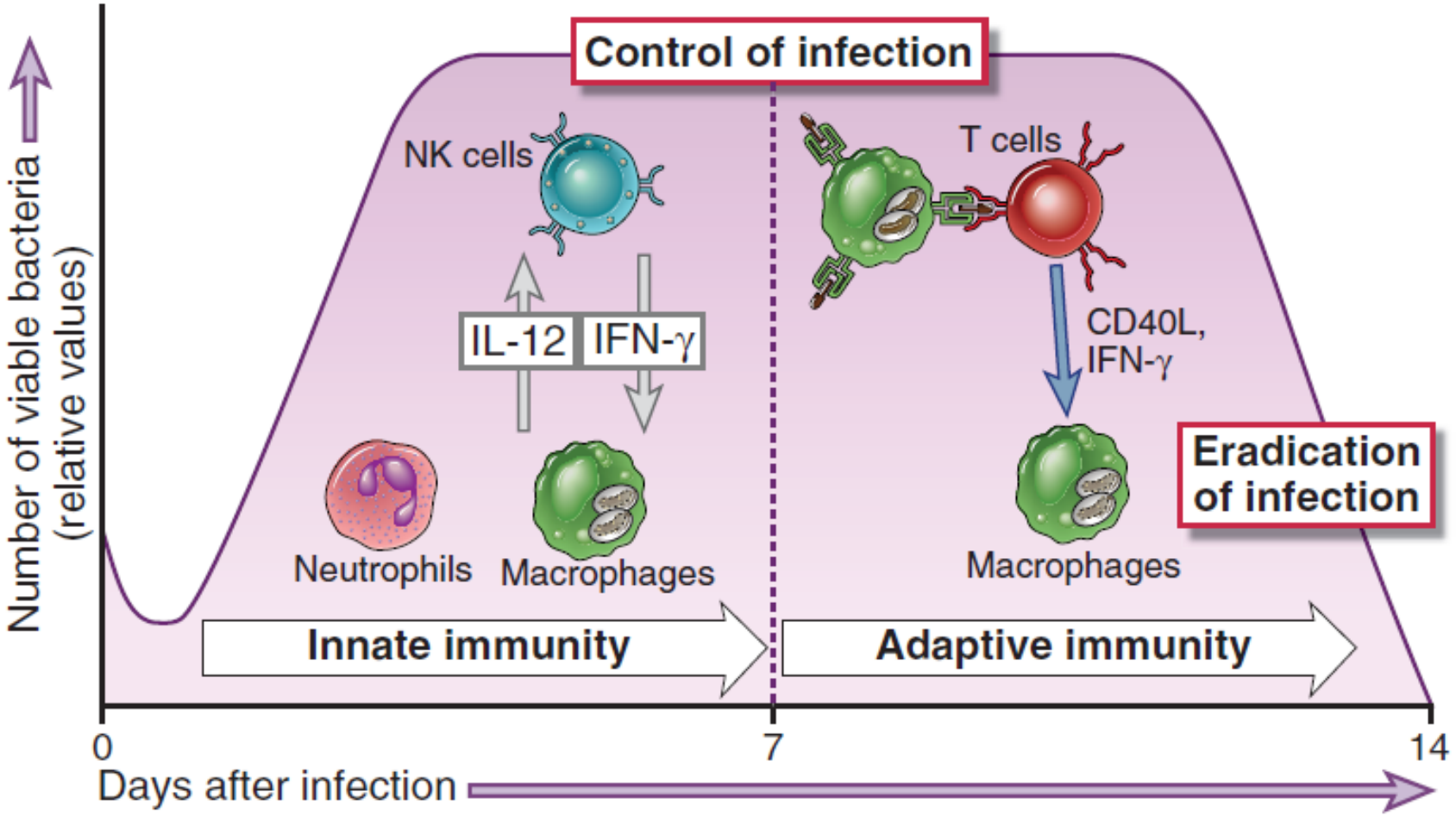


FIGURE 15–3 Innate and adaptive immunity to intracellular bacteria. The innate immune response to intracellular bacteria consists of phagocytes and NK cells, interactions among which are mediated by cytokines (IL-12 and IFN-γ). The typical adaptive immune response to these microbes is cell-mediated immunity, in which T cells activate phagocytes to eliminate the microbes. Innate immunity may control bacterial growth, but elimination of the bacteria requires adaptive immunity. These principles are based largely on analysis of *Listeria monocytogenes* infection in mice; the numbers of viable bacteria shown on the y-axis are relative values of bacterial colonies that can be grown from the tissues of infected mice. *(Data from Unanue ER. Studies in listeriosis show the strong symbiosis between the innate cellular system and the T-cell response. Immunological Reviews 158: 11-25, 1997.)*

Innate immunity/ Innate Immunity to Intracellular Pathogens

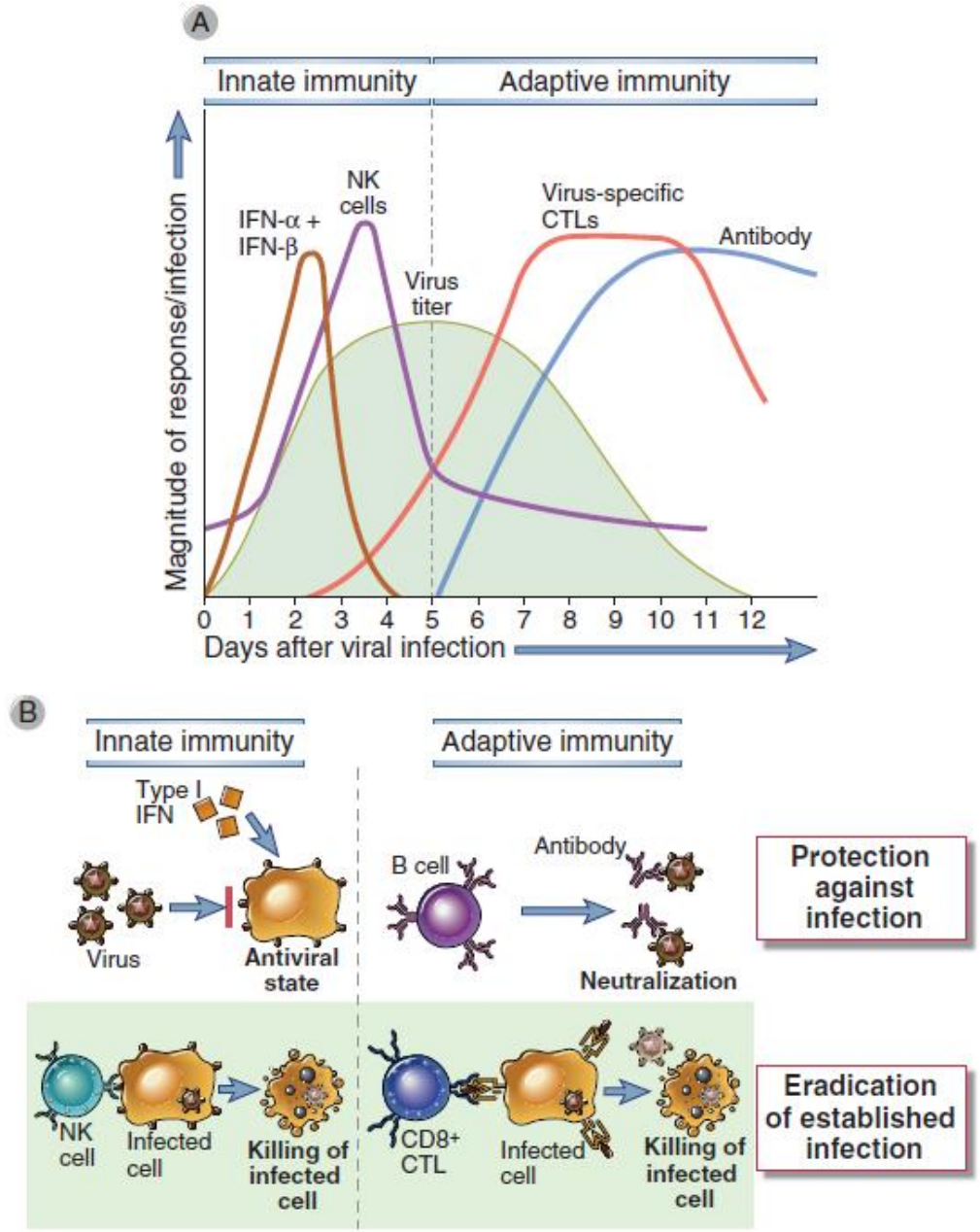
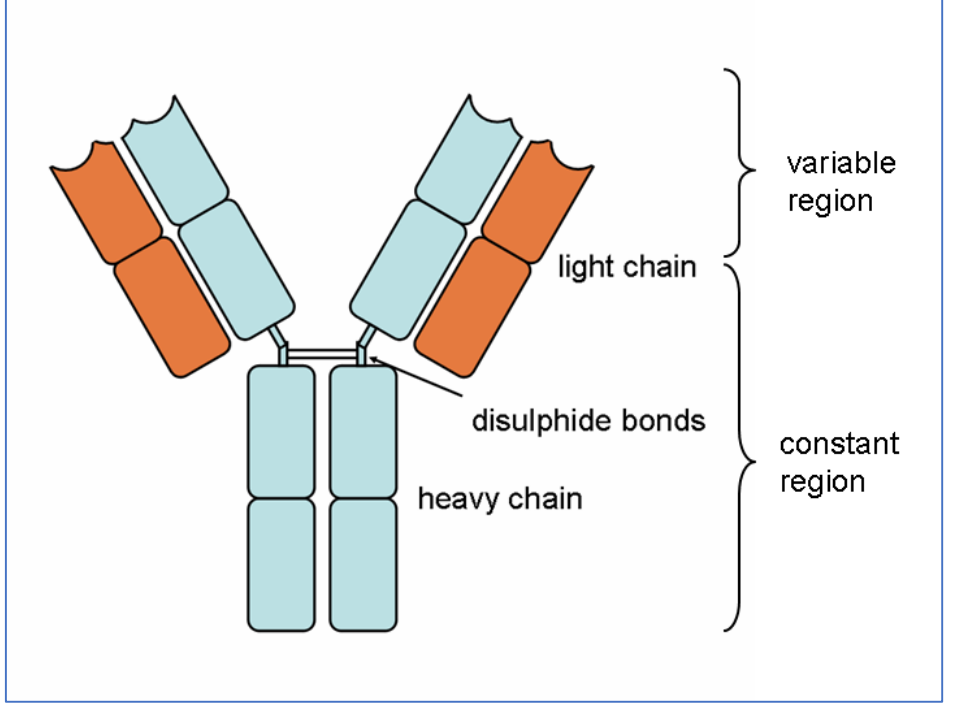


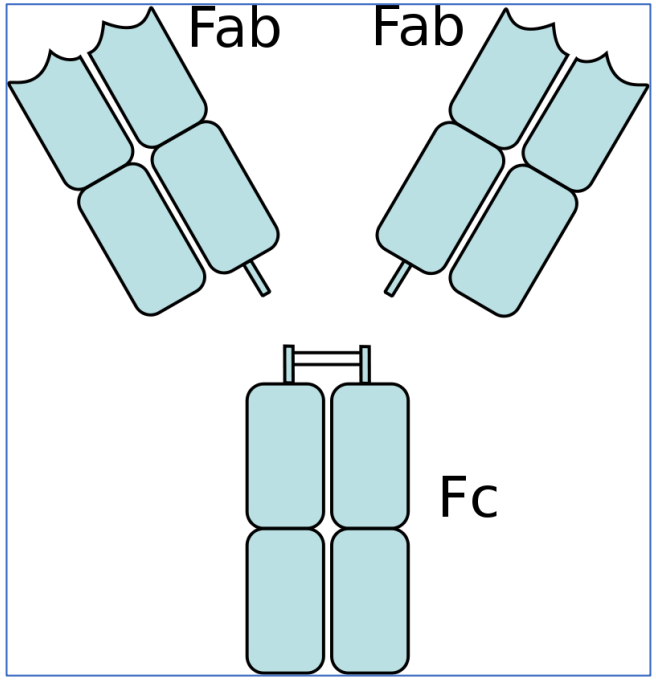
FIGURE 15–6 Innate and adaptive immune responses against viruses. A, Kinetics of innate and adaptive immune responses to a virus infection. **B,** Mechanisms by which innate and adaptive immunity prevent and eradicate virus infections. Innate immunity is mediated by type I interferons, which prevent infection, and NK cells, which eliminate infected cells. Adaptive immunity is mediated by antibodies and CTLs, which also block infection and kill infected cells, respectively.

Antibodies

- Antibodies (immunoglobulins) are made of 2 heavy chains and 2 light chains, those chains combined give us an antibody binding region **(Fab)** and the fragment crystallizable region (**Fc region**) which is the tail region of an antibody that interacts with **cell surface receptors** called **Fc receptors** and some proteins of the **complement** system.

- Immunoglobulins are divided into different classes (isotypes).

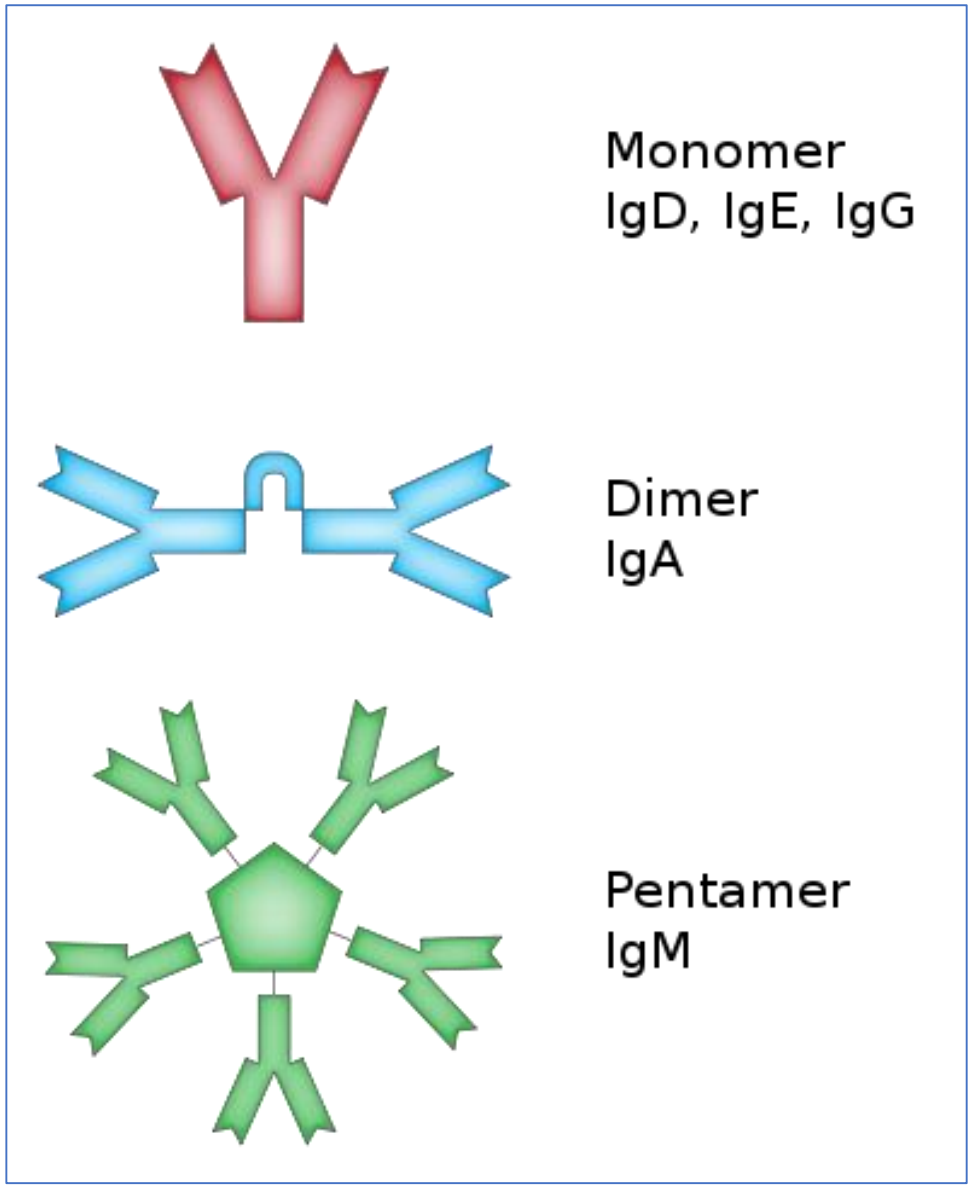




Antibodies

- Antibodies of different classes **differ** in their **location** around the body, appear at **different stages of an adaptive immune response**.

- IgM is the first immunoglobulin expressed during B cell development as a monomer on the surface of B naive cells.



Antibodies/ Functions

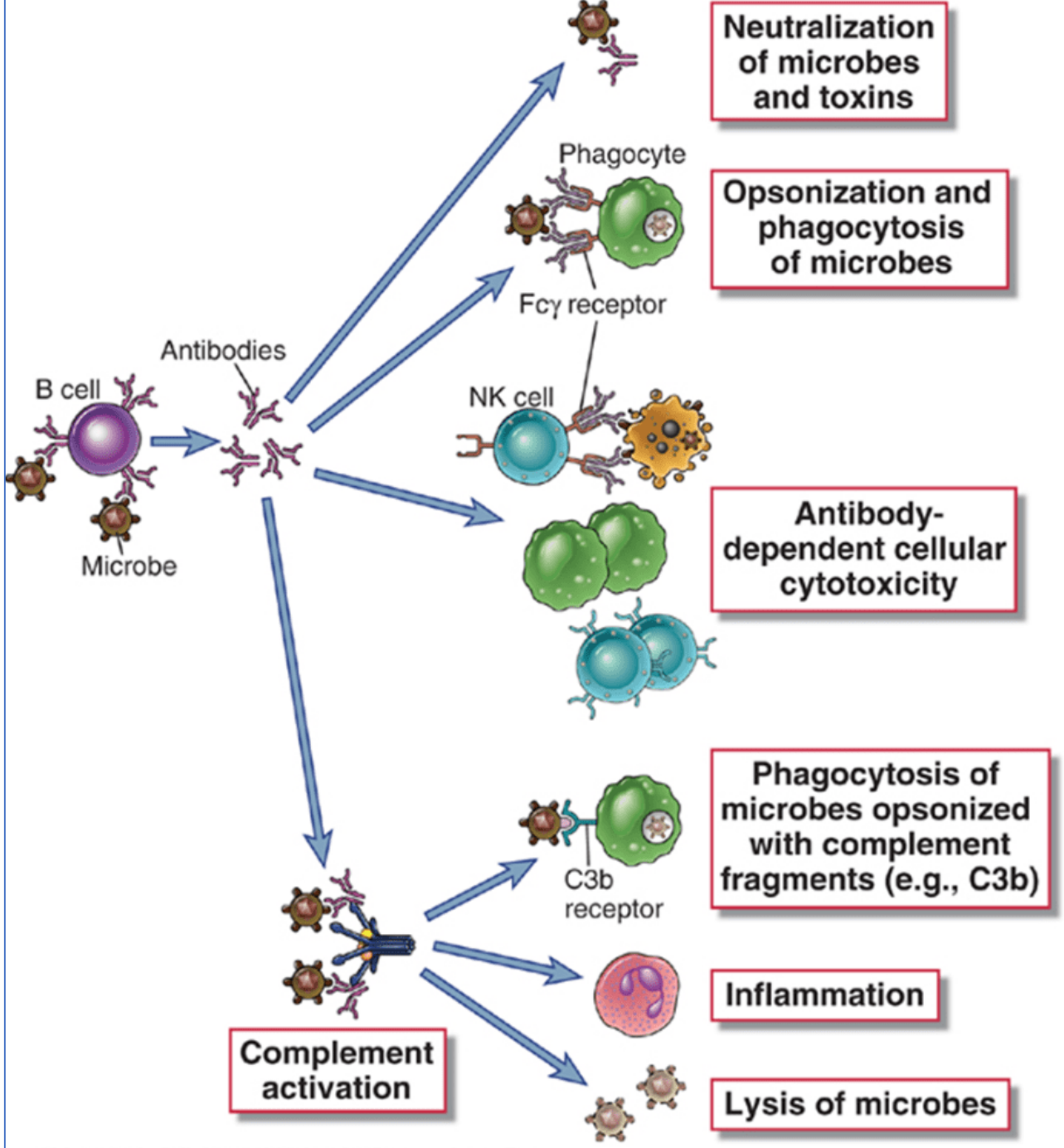
1.Neutralization of infectivity,

2.Phagocytosis,

3.Antibody-dependent cellular cytotoxicity (ADCC),

4.Complement-mediated lysis of pathogens or of infected cells:

5.Transcytosis, mucosal immunity & neonatal immunity



Further reading:

- Cellular and Molecular Immunology. 7th Edition..

Chapter 4. Innate immunity

Chapter 15. Immunity to microbes