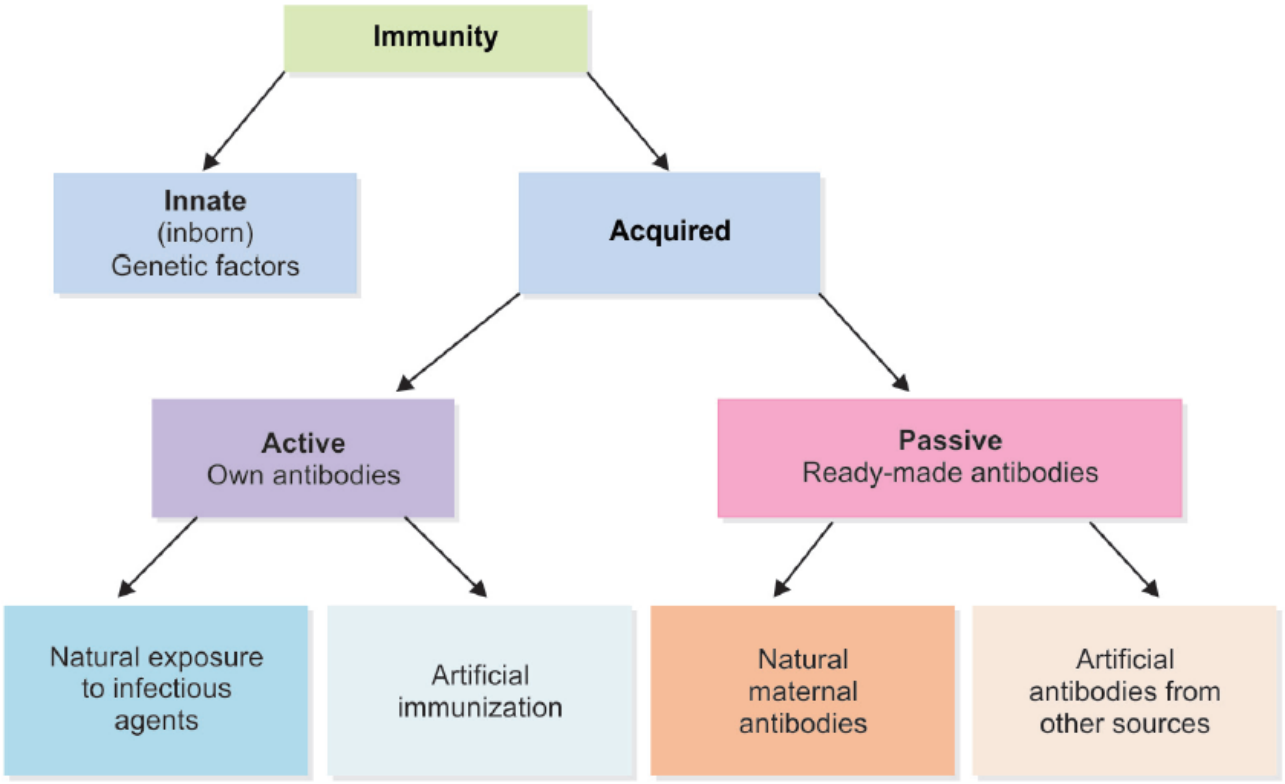
Immunity

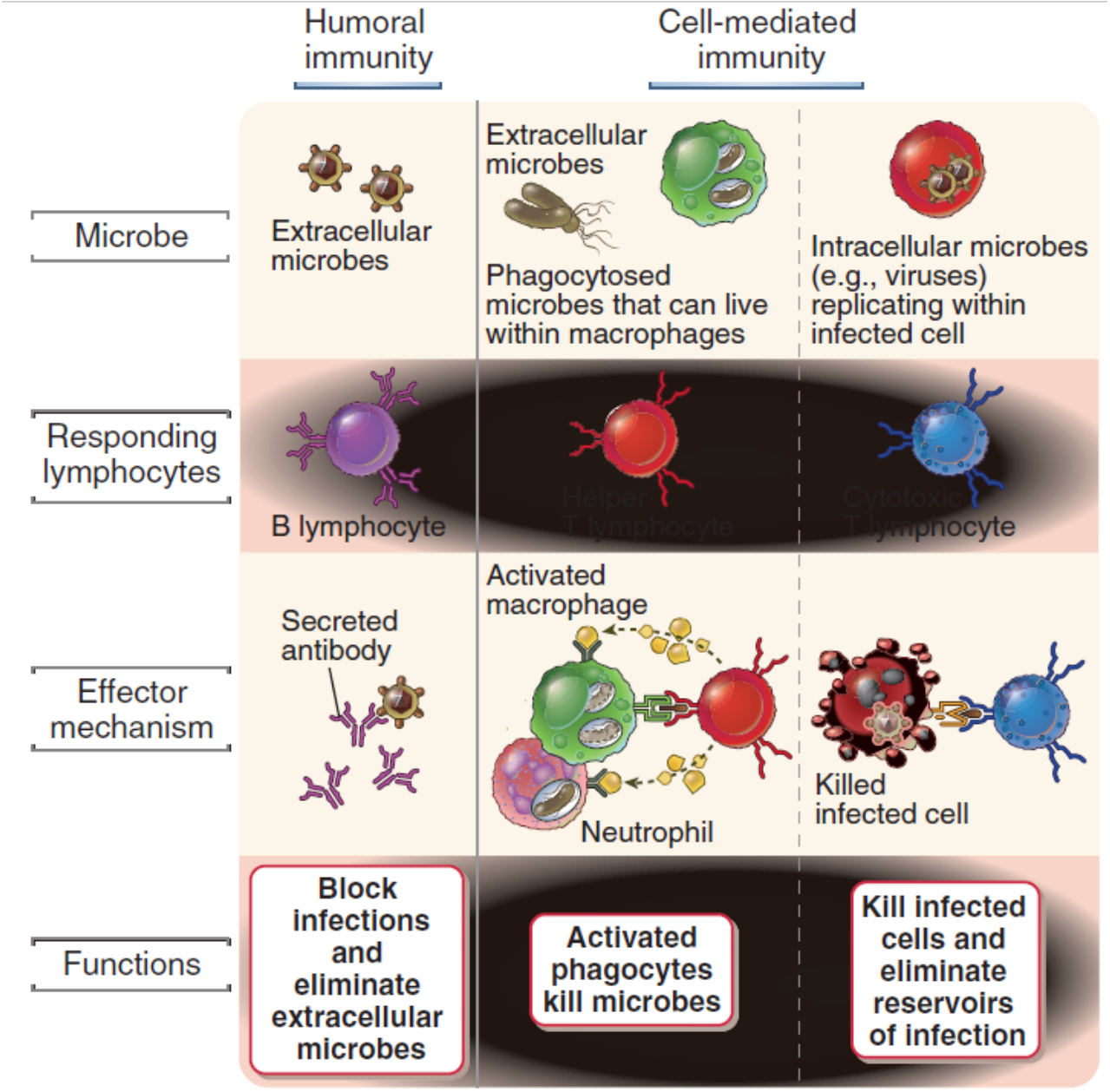


Adaptive immunity

The adaptive immune response is mediated by cells called lymphocytes and their products. Lymphocytes express highly diverse receptors that can recognize a vast number of antigens. There are two major populations of lymphocytes, called **B lymphocytes** and **T lymphocytes**, which mediate different types of adaptive immune responses.

The adaptive immune responses take some days and weeks to be finished. However, they are more effective in eliminating invading pathogens than the innate immunity. Furthermore, they develop the immune memory to the invading pathogens. There are two types of adaptive immunity, called humoral immunity and cell-mediated immunity, which are induced by

different types of lymphocytes and function to eliminate different types of microbes (Figs. below).



B-Cell-Mediated (Humoral) Responses

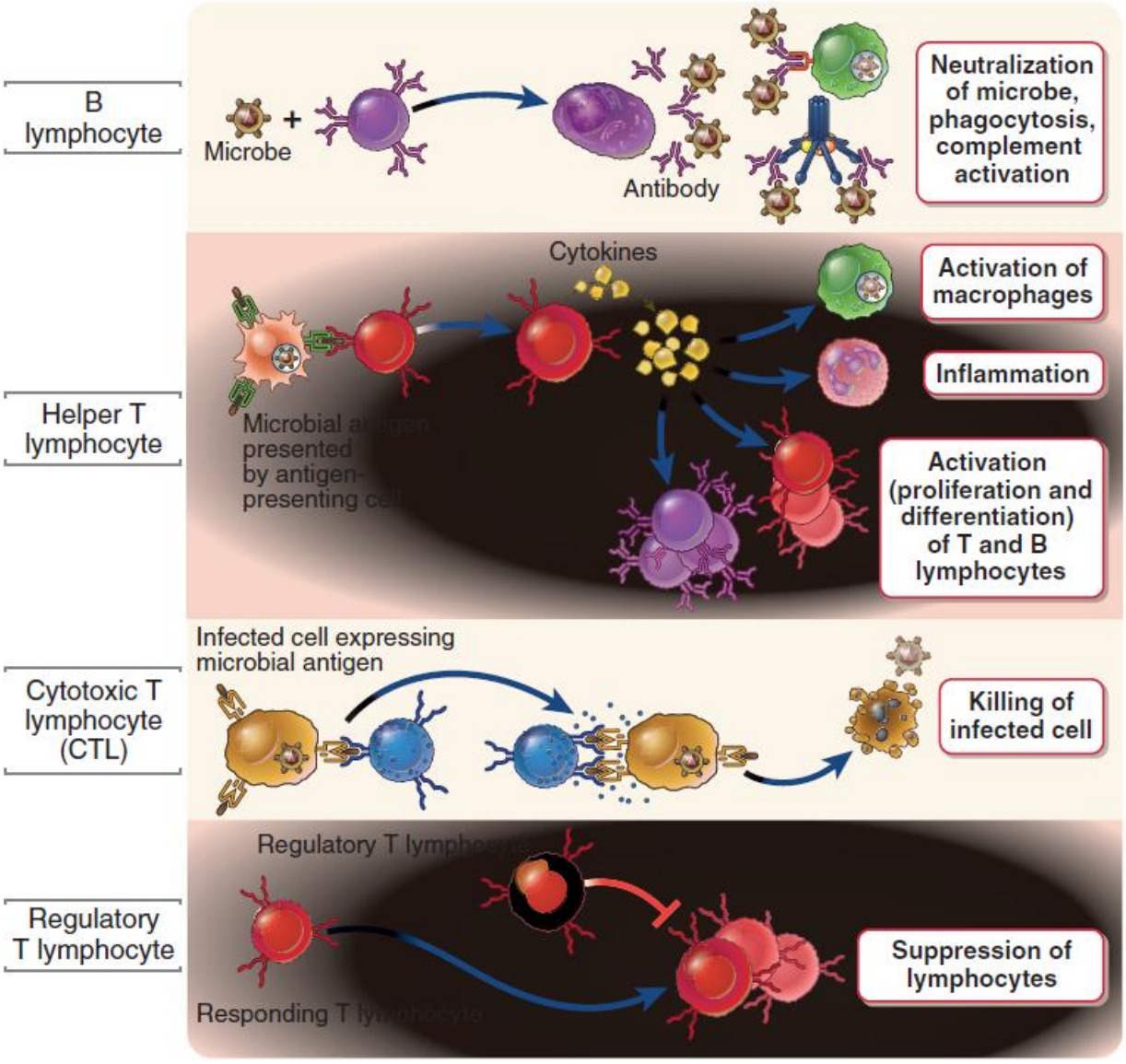
1. Simple B-cell response formation of only one class of immunoglobulins, IgM, but no long-term memory. This type of response may be triggered by “patterns” too.

2. Advanced B-cell response – switching antibodies after each other: IgM, IgG, IgA, and even IgE, and inducing the formation of long-lived memory plasma cells and lifelong memory B cells.

- **T-Cell-Mediated Responses**

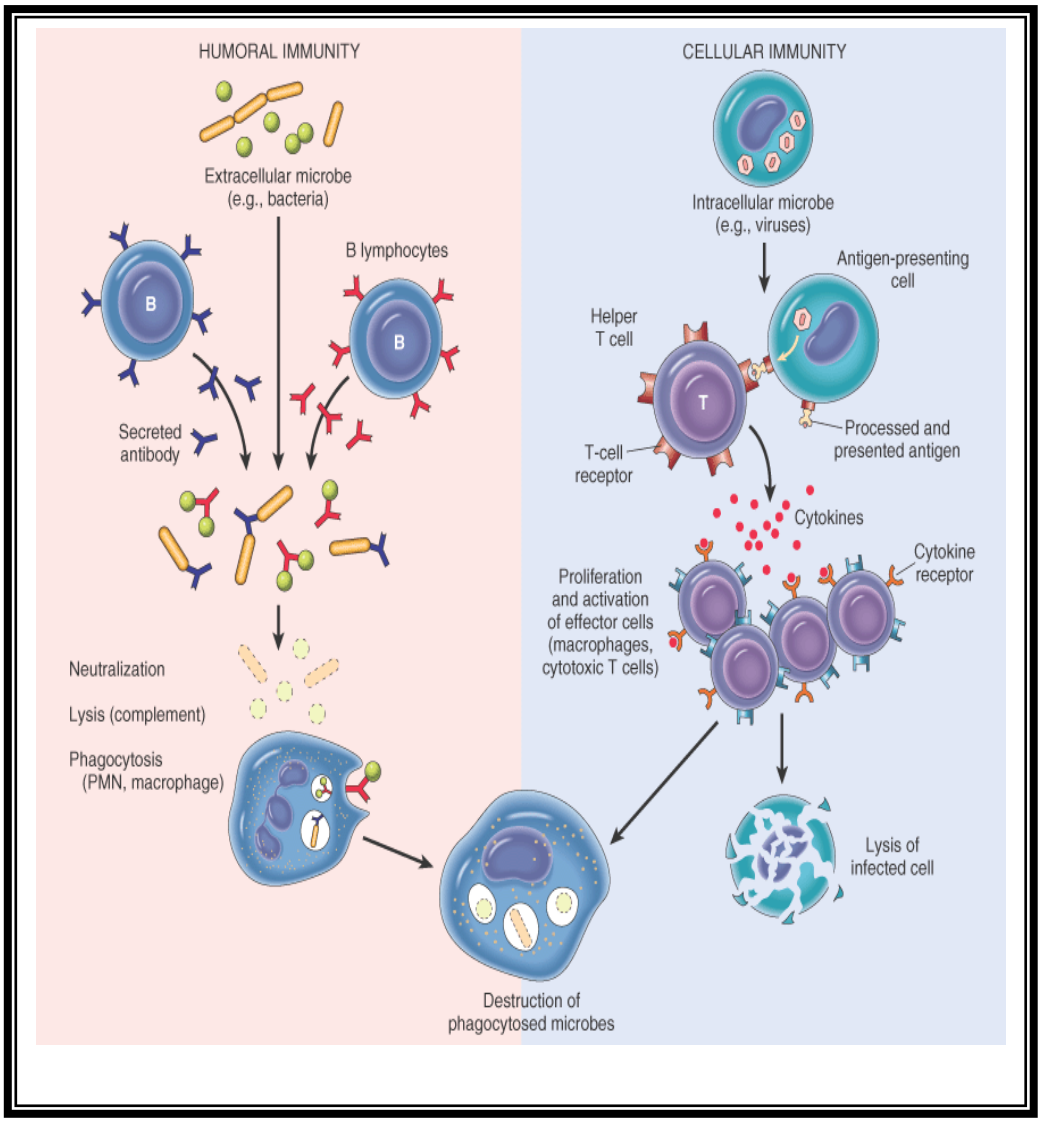
3. Inflammatory CD4+T-cell response that leads to the production of effector CD4+T cells and the lifelong memory CD4+T cells.

4. Cytotoxic CD8+T-cell response, which results in the formation of cytotoxic CD8+T cells capable of apoptosis in target cells and lifelong memory CD8+T cells.



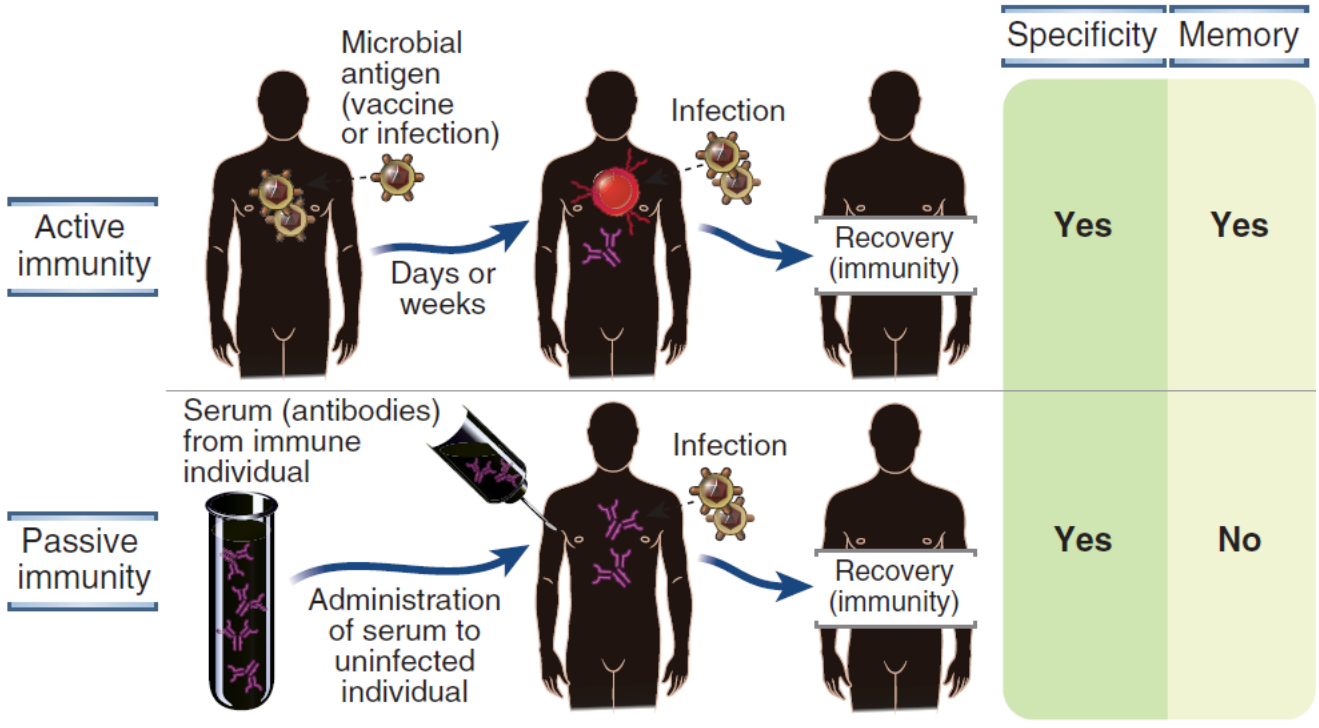
Humoral immunity is mediated by molecules in the blood and mucosal secretions, called antibodies, which are produced by B lymphocytes. Antibodies recognize microbial antigens, neutralize the infectivity of the microbes, and target microbes for elimination by phagocytes and the complement system. Humoral immunity is the principal defense mechanism against microbes and their toxins located outside cells (e.g. in the lumens of the gastrointestinal and respiratory tracts and in the blood) because secreted antibodies can bind to these microbes and toxins, neutralize them, and assist in their elimination.

Cell-mediated immunity, also called cellular immunity, is mediated by T lymphocytes. Many microbes are ingested by but survive within phagocytes, and some microbes, notably viruses, infect and replicate in various host cells. In these locations the microbes are inaccessible to circulating antibodies. Defense against such infections is a function of cell-mediated immunity, which promotes the destruction of microbes inside phagocytes and the killing of infected cells to eliminate reservoirs of infection.



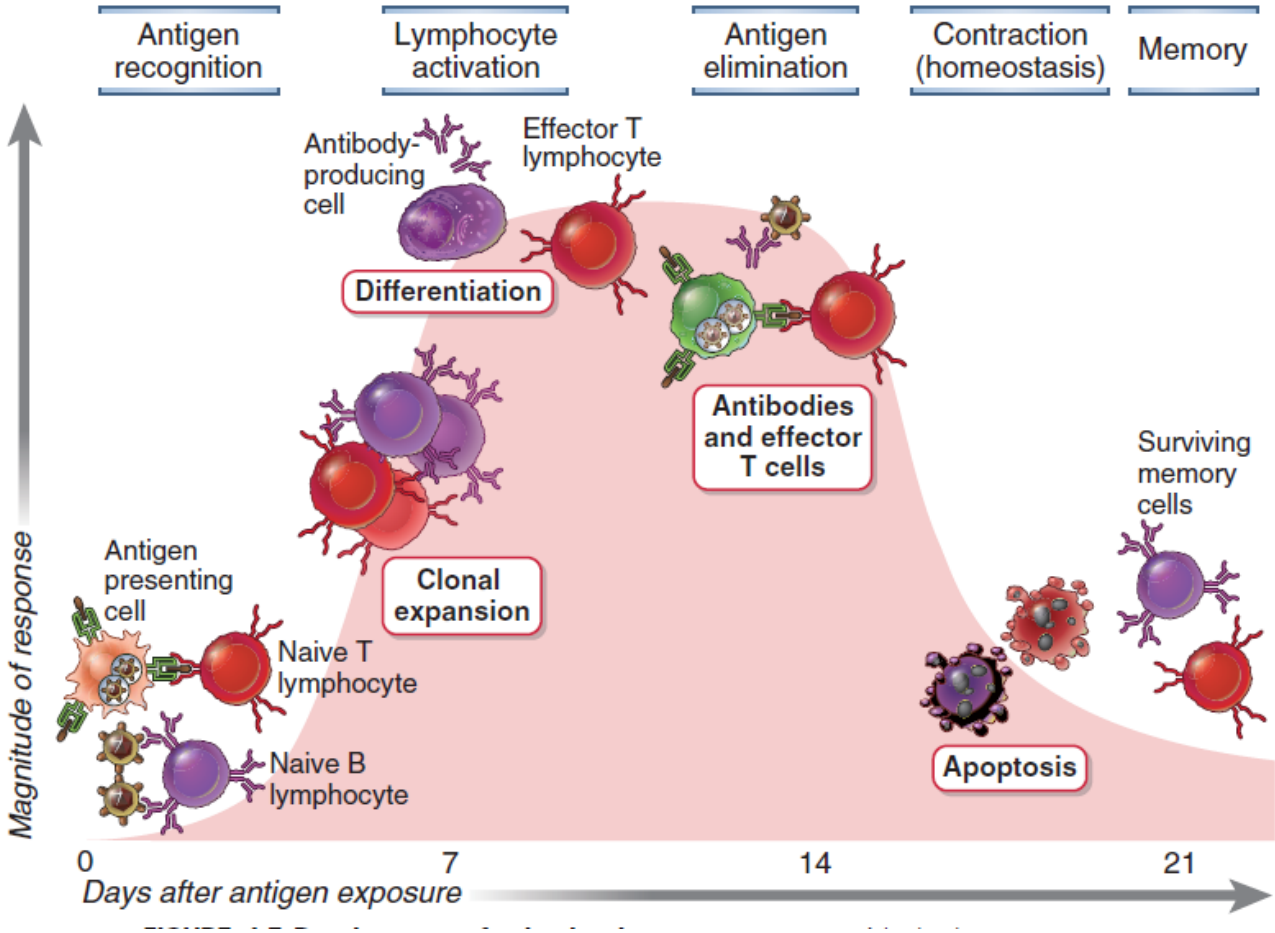
Protective immunity against a microbe may be provided either by the host's response to the microbe or by the transfer of antibodies that defend against the microbe. The form of immunity that is induced by exposure to a foreign antigen is called **Active immunity** because the immunized individual plays an active role in responding to the antigen. Individuals and lymphocytes that have not encountered a particular antigen are said to be naive, implying that they are immunologically inexperienced. Individuals who have responded to a microbial antigen and are protected from subsequent exposures to that microbe are said to be immune.

Immunity can also be conferred on an individual by transferring antibodies from an immunized individual into an individual who has not encountered the antigen (see Fig. below). The recipient of such a transfer becomes immune to the particular antigen without ever having been exposed to or having responded to that antigen. Therefore, this form of immunity is called **Passive immunity**. A physiologically important example of passive immunity is the transfer of maternal antibodies through the placenta to the fetus, which enables newborns to combat infections for several months before they develop the ability to produce antibodies themselves. Passive immunization is also a medically useful method for conferring resistance rapidly, without having to wait for an active immune response to develop. Passive immunization against potentially lethal toxins by the administration of antibodies from immunized animals or people is a lifesaving treatment for rabies infection and snake bites. Patients with some genetic immunodeficiency diseases are passively immunized by transfer of pooled antibodies from healthy donors.



Initiation and Development of Adaptive Immune Responses

Adaptive immune responses develop in several steps, starting with the capture of antigen, followed by the activation of specific lymphocytes (Fig. below). Most microbes and other antigens enter through epithelial barriers and adaptive immune responses to these antigens develop in peripheral (secondary) lymphoid organs. The initiation of adaptive immune responses requires that antigens be captured and displayed to specific lymphocytes. The cells that serve this role are called **antigen-presenting cells (APCs)**. The most specialized APCs are **dendritic cells**, which capture microbial antigens that enter from the external environment, transport these antigens to lymphoid organs, and present the antigens to naive T lymphocytes to initiate immune responses. Other cell types function as APCs at different stages of cell-mediated and humoral immune responses.



The activation of these lymphocytes by antigen leads to the proliferation of these cells, resulting in an increase in the size of the antigen-specific clones, called clonal expansion. This is followed by differentiation of the activated lymphocytes into cells capable of eliminating the antigen, called effector cells because they mediate the ultimate effect of the immune response, and memory cells that survive for long periods and mount strong

responses to repeat antigen encounter. Antigen elimination often requires the participation of other, nonlymphoid cells, such as macrophages and neutrophils, which are also sometimes called effector cells. These steps in lymphocyte activation typically take a few days, which explains why the adaptive response is slow to develop and innate immunity has to provide protection initially.

After the adaptive immune response has eradicated the infection, the stimuli for lymphocyte activation dissipate and most of the effector cells die, resulting in the decline of the response. Memory cells remain, ready to respond vigorously if the same infection recurs. The cells of the immune system interact with one another and with other host cells during the initiation and effector stages of innate and adaptive immune responses. Many of these interactions are mediated by cytokines. Cytokines are a large group of secreted proteins with diverse structures and functions, which regulate and coordinate many activities of the cells of innate and adaptive immunity. All cells of the immune system secrete at least some cytokines and express specific signaling receptors for several cytokines.

Humoral Immunity (Whole Story)

B lymphocytes that recognize antigens proliferate and differentiate into plasma cells that secrete different classes of antibodies with distinct functions. Each clone of B cells expresses a cell surface antigen receptor, which is a membrane-bound form of antibody, with a unique antigen specificity. Many different types of antigens, including proteins, polysaccharides, lipids, and small molecules, are capable of eliciting antibody responses.

The response of B cells to protein antigens requires activating signals (help) from CD4+ T cells (which is the historical reason for calling these T cells helper cells). B cells can respond to many nonprotein antigens without the participation of helper T cells. Each plasma cell secretes antibodies that have the same antigen-binding site as the cell surface antigen receptor that first recognized the antigen. Polysaccharides and lipids stimulate secretion mainly of the antibody class called immunoglobulin M (IgM). Protein antigens induce the production of antibodies of different classes (IgG, IgA, IgE) from a single clone of B cells. These different antibody classes serve distinct functions, mentioned later. Helper T cells also stimulate the production of antibodies with increased affinity for the antigen. This process, called affinity maturation, improves the quality of the humoral immune response. The humoral immune response combats microbes in many ways. Antibodies bind to microbes and prevent them from infecting cells, thus neutralizing the

microbes. In fact, antibody-mediated neutralization is the only mechanism of adaptive immunity that stops an infection before it is established; this is why eliciting the production of potent antibodies is a key goal of vaccination. IgG antibodies coat microbes and target them for phagocytosis because phagocytes (neutrophils and macrophages) express receptors for parts of IgG molecules. IgG and IgM activate the complement system, and complement products promote phagocytosis and destruction of microbes. IgA is secreted from mucosal epithelia and neutralizes microbes in the lumens of mucosal tissues, such as the respiratory and gastrointestinal tracts, thus preventing inhaled and ingested microbes from infecting the host. Maternal IgG is actively transported across the placenta and protects the newborn until the baby's immune system becomes mature. Most IgG antibodies have half-lives in the circulation of approximately 3 weeks, whereas other classes of antibodies have half-lives of just a few days. Some antibody-secreting plasma cells migrate to the bone marrow or mucosal tissues and live for years, continuing to produce low levels of antibodies. The antibodies that are secreted by these long-lived plasma cells provide immediate protection if the microbe return to infect the individual. More effective protection is provided by memory cells that are activated by the microbe and rapidly differentiate to generate large numbers of plasma cells.

Cell-Mediated Immunity (Whole Story)

T lymphocytes, the cells of cell-mediated immunity, recognize the antigens of cell-associated microbes, and different types of T cells help phagocytes to destroy these microbes or kill the infected cells. T cells do not produce antibody molecules. Their antigen receptors are membrane molecules distinct from but structurally related to antibodies (**see Lec8**). T lymphocytes have a restricted specificity for antigens; they recognize peptides derived from foreign proteins that are bound to host proteins called major histocompatibility complex (MHC) molecules, which are expressed on the surfaces of other cells. As a result, these T cells recognize and respond to cell surface associated but not soluble antigens. T lymphocytes consist of functionally distinct populations, the best defined of which are helper T cells and cytotoxic (or cytolytic) T lymphocytes (CTLs). The functions of helper T cells are mediated mainly by secreted cytokines, whereas CTLs produce molecules that kill other cells. Some T lymphocytes, which are called regulatory T cells, function mainly to inhibit immune responses. Different classes of lymphocytes can be distinguished by the expression of cell surface proteins, many of which are designated by a unique "CD" number, such as CD4 or CD8. Upon activation in secondary lymphoid organs, naïve T lymphocytes differentiate into effector cells, and many of them leave and migrate to sites

of infection. When these effector T cells again encounter cell-associated microbes, they are activated to perform the functions that are responsible for elimination of the microbes. Some CD4+ helper T cells secrete cytokines that recruit leukocytes and stimulate production of microbicidal substances in phagocytes. Thus, these T cells help phagocytes to kill the infectious pathogens. Other CD4+ helper T cells secrete cytokines that help B cells to produce a type of antibody called IgE and activate leukocytes called eosinophils, which are able to kill parasites that may be too large to be phagocytosed. Some CD4+ helper T cells stay in the lymphoid organs and stimulate B cell responses. CD8+ CTLs kill cells harboring microbes in the cytoplasm. These microbes may be viruses that infect many cell types or bacteria that are ingested by macrophages but escape from phagocytic vesicles into the cytoplasm (where they are inaccessible to the killing machinery of phagocytes, which is largely confined to vesicles). By destroying the infected cells, CTLs eliminate the reservoirs of infection. CTLs also kill tumor cells that express antigens that are recognized as foreign.