pathogen is encountered again. The capacity of the adaptive immune system to protect against different pathogens is truly astounding. It has been estimated that B cells can produce 10^{14} different immunoglobulin molecules, and that T cells can have up to 10^{18} different T-cell receptors (TCRs) for specific antigens.

B Lymphocytes

Antibodies are glycoproteins produced by B cells that recognize specific structural motifs (i.e., epitopes) on microbial pathogens. In antimicrobial defense, binding of an antibody to a pathogen may inhibit the ability of the pathogen to infect a cell or the ability of a toxin to be effective (i.e., neutralization); prompt phagocytosis by phagocytic cells such as neutrophils and macrophages (i.e., opsonization); activate the complement cascade; or kill an infected cell through the process of antibody-dependent cellular cytotoxicity (ADCC).

Antibody-mediated host defense occurs mainly in the extracellular space. T cell–mediated host defenses act primarily on intracellular organisms (i.e., those that enter cells and survive intracellularly). The five major classes (i.e., isotypes) of antibodies are summarized in Table 86-4. Complement fixation is accomplished by IgM and IgG molecules, whereas opsonization is effected by IgG and IgA molecules. IgG antibodies cross the placenta, providing protective immunity to newborns for months. IgA molecules are secretory antibodies that act at mucosal surfaces and are the predominant antibody in external secretions such as mucus. IgE is responsible for allergic responses and host defenses against parasites. IgD acts as an immunomodulatory molecule with the capacity to trigger innate immune responses.

Structurally, antibodies are composed of two large heavy chains and two small light chains (Fig. 86-2). Each heavy and light chain has a constant and a variable region. Each of the five isotypes of heavy chains designates a specific antibody class (i.e., IgM, IgG, IgA, IgE, and IgD) and two types of light chains (i.e., κ and λ). The antigen-binding site of each molecule is composed of the variable region of a heavy chain and the variable region of a light chain. There are two such binding sites for each molecule. The B-cell receptor is composed of the specific immunoglobulin associated with that B cell. Unstimulated B cells express single IgM molecules on their cell surfaces. When stimulated, B cells may initially produce IgM antibodies. Later, a B cell may switch the type of immunoglobulin produced (e.g., from IgM to IgG) and become a plasma cell producing large amounts of antibody or become a long-term memory cell. B cells do not change their antigen specificity.

The constant region of the two heavy chains comprises the Fc portion, which after immunoglobulin has bound to antigen, can then bind to Fc receptors on the cell surface of neutrophils, macrophages, and dendritic cells. This interaction binds antigen-antibody complexes to phagocytic cells and allows opsonization and phagocytosis or activation of the classic complement pathway, depending on the isotype.

Humans can generate billions of different antibodies, and this diversity results from organization of the genes that encode the variable regions of antibodies. The two major genetic strategies that allow humans to produce antibody specific to virtually any microorganism are somatic hypermutation and recombination of the variable (V), diversity (D), and joining (J) gene segments of the immunoglobulin light and heavy chains. The variable region of the heavy chain is encoded by V, D, and J genes. The variable region of the light chain is encoded by V and J genes.

There are more than 1000 different V, D, and J genes. During B-cell differentiation, somatic translocations randomly select the V, D, and J heavy chain genes and the V and J light chain genes. In this manner, an enormously diverse set of variable chains is assembled. Further genetic variation arises from somatic mutations in B cells as they encounter antigen in lymphoid tissues. B cells have specific Ig antibodies on their surface, with specificity produced by V(D)J recombinations that recognize three-dimensional structures. These molecular structures are on the surface of pathogens or are toxins produced by pathogens.

The adaptive immune cell response begins with recognition of antigen by specific B cells in lymph node follicles. IgM antibodies are produced by B cells whose Ig surface receptors have affinity for the antigen. Interaction with complementary T cells in lymph nodes may result in class switching (e.g., from IgM to IgG classes or others). The switch is called an *isotype switch* and is driven by specific cytokines, such as IL-4, IL-10, IL-5, and others produced by T cells. The isotype switch allows the host to take advantage of the different functions of different isotypes specific for the same antigen (e.g., complement fixation for IgM, opsonic activity for IgG). T-cell interaction through surface coreceptors and stimulatory soluble molecules results in B-cell division and increased

TABLE 86-4 PROPERTIES OF HUMAN IMMUNOGLOBULINS

PROPERTY	IgG	IgA	IgM	IgD	IgE
H chain class	γ	α	μ	δ	ε
Molecular weight (approx.)	150,000	170,000	900,000	180,000	190,000
Complement fixation (classic)	++	0	++++	0	0
Opsonic activity (for binding)	++++	++	0	0	0
Reaginic activity	0	0	0	0	++++
Serum concentration (approx.)	1500 mg/dL	150-350 mg/dL	100-150 mg/dL	2 mg/dL	2 mg/dL
Serum half-life	23 days	6 days	5 days	3 days	2.5 days
Major functions	Recall response; opsonization; transplacental immunity	Secretory immunity	Primary response; complement fixation	Immune modulation of inflammation	Allergy; anthelmintic immunity

Ig, Immunoglobulin; +, minimal; ++++, maximal.