The adaptive immune system is characterized by its ability to distinguish self from nonself; responds specifically to encounters with foreign antigens (e.g., pathogens); and develops immunologic memory allowing for a more vigorous response to subsequent challenges with the same antigen. T lymphocytes play several roles in adaptive immunity, autoimmune disease, and allergy; new T-helper cell subsets continue to be described, promising to better explain autoimmunity and primary immunodeficiency diseases.1–6

**T CELL DEVELOPMENT**

Bone marrow pluripotent hematopoietic stem cells first give rise to multipotent, then to common, lymphoid progenitor cells; some of the latter further traffic to the thymus for T-cell lymphocyte differentiation.1–3 T cells are marked by the presence of the surface-expressed heterodimeric T-cell receptor (TCR) that consists of combinations of either the α and β, or the γ and δ chains. The germline TCR genes contain multiple variable (V), diversity (D) (in αβ TCR), and joining (J) segments. The V(D)J recombinase enzyme complex (including enzymes encoded by the RAG1, RAG2, and Artemis genes, among others) mediates cleavage and repair of DNA near the V, D, and J segments in a series of coordinated steps. If the gene recombination is productive and the RNA message has no abnormal stop codons present, the subsequently translated protein chains pair to form the TCR, which is expressed on the cell surface. Similar to immunoglobulin gene rearrangement, tremendous TCR-binding site diversity results from this process—the large number of possible recombinations of V, D, and J segments provide combinatorial diversity, and additional diversity is conferred by imprecision in the DNA-joining reaction.2,3,7

The maturing T cells can be divided into 2 groups depending on the cluster of differentiation, or CD, surface markers expressed. If an αβ TCR is expressed at the cell surface, the cell first transitions to a “double positive” T cell, expressing both the CD4 and CD8 surface markers. The T cell then undergoes the 2 thymic processes of positive and negative selection (Fig. 1). Positive selection occurs when the TCR binds, with low avidity, to a major histocompatibility (MHC) molecule presenting a self-peptide. T cells that are not able to bind strongly enough to these self-peptide-MHC complexes are eliminated by apoptosis (“death by neglect”). Cells positively selected by an MHC class I molecule become CD8 single-positive, while cells selected through MHC class II molecules become CD4 single-positive. Negative selection occurs when a TCR binds with too great avidity to the self-peptide-MHC; these cells are eliminated to ensure that potentially autoreactive T cells do not persist.2,3 Negative selection is carried out under the control of the AIRE (autoimmune regulator) transcription factor of thymic medullary epithelial cells.3,9

**ANTIGEN RECOGNITION BY T LYMPHOCYTES**

T cells respond to peptide antigens bound to MHC molecules; the peptide antigens are either produced in or taken up by the body’s own cells. CD8+ T cells are the cytotoxic T cells of the adaptive immune system. They respond to peptides that are 8 to 10 amino acids in length bound specifically to the peptide-binding groove of MHC class I molecules. The MHC class I molecule is expressed on all nucleated cells in the body. In contrast, CD4+ T cells respond to peptides presented by MHC class II molecules, which are only expressed on a limited subset of host cells—the “professional” antigen-presenting cells (APCs, including B cells, macrophages, and dendritic cells). CD4+ T cells perform many accessory functions within the immune system; hence, they are generally referred to as “helper” T cells.1

MHC molecules exhibit a vast amount of polymorphism in their peptide-binding pockets, and in addition, up to 6 unique MHC class I and 12 unique MHC class II molecules are able to be expressed simultaneously. Together with the diversity of TCRs, this allows for the binding of the tremendous array of pathogen and tumor cell epitopes which the immune system may encounter.1,2,7 Although peptides presented on MHC class I molecules typically are derived from intracellular and nuclear proteins (e.g., from intracellular viral infection), certain dendritic cells have the ability to “cross-present” antigens derived from extracellular...
T LYMPHOCYTE EFFECTOR 
FUNCTIONS

CD8+ T Cells

During an immune response, naive cytotoxic CD8+ T cells responding to antigen undergo rapid clonal expansion within the draining lymph node, with the resulting generation of a large number of antigen-specific T cells. These cells can express chemokine receptors that allow them to travel to sites of inflammation or infection. There they bring about pathogen clearance by secreting effector cytokines such as IFNγ and TNFα, and by producing molecules that result in direct cell contact-dependent cytolytic action of target cells, including perforin and granzyme B. After the peak of the effector phase of the immune response, the antigen-specific CD8+ T-cell population contracts by apoptosis, with only about 5% to 10% of the original cells surviving as long-lived memory cells.4,12,13 Especially in settings with only a low level of inflammation, CD4+ T cells help support the development of CD8+ T-cell effector function by multiple mechanisms, including through the maturation of APCs and the production of IL-2.12,13 CD4+ T cells also play an important role in the development of long-lived, functional CD8+ memory T cells.12,13 This memory has been broadly divided into central and effector memory. Central memory cells reside in lymphoid organs, where they proliferate rapidly in response to antigen re-exposure, but do not have immediate lytic function. Effector memory cells are found in nonlymphoid tissues and are able to express immediate lytic activity on recall. These cells can be rapidly recalled on re-exposure to antigen, resulting in rapid pathogen clearance.12,13 Therefore, activation of CD8+ T cells through antigen encounter elicits both robust effector function capable of selective pathogen elimination at the site of infection, and the development of specific memory cells that are able to be rapidly mobilized upon future encounter with the original or a related pathogen. Such immunologic memory plays an important role in the immune response to vaccination.

CD4+ T Cells

CD4+ T cells provide help to B cells, enabling both class switching and production of high-affinity antibodies, initiate and maintain CD8+ T-cell responses, regulate macrophage function, and also directly mediate pathogen clearance. CD4+ T cells may also suppress the immune response to autoantigens and adjust the magnitude and persistence of immunity. Two decades ago, seminal research divided CD4+ T-cell responses into 2 main T helper subsets (Th1 and Th2) that could be distinguished by the secretion of particular effector cytokines. Subsequent work has defined Th17 cells, regulatory T cells (Tregs), and follicular helper T cells (Tfh), each distinguished by unique cytokine profiles and transcription factor expression. T-helper cell lineage commitment was once thought to be irreversible, but newer evidence suggests that some degree of interconversion may occur in vivo. Th1 cells are important in cell-mediated immune responses, and are able to make IFNγ, TNFα, and IL-2. Th1 cells activate macrophages, assist in the clearance of intracellular pathogens, and mediate delayed-type hypersensitivity responses. Cytokine production by Th1 cells is also important in B cell class switching to immunoglobulin isotypes that are useful for neutralization of toxins and viruses.

Th2 cells play a central role in mediating immunity to parasitic infections. Inappropriate activation of this CD4+ T-cell differentiation pathway has also been strongly implicated in the development of asthma and allergy. Cytokines produced by Th2 cells include IL-4, IL-5, IL-9, and IL-13. These cytokines play an important part in the recruitment of eosinophils (IL-5) and mast cells (IL-9). Th2 cells are also able to regulate B cell class switching to IgE; in turn, IgE immune complexes activate basophils and mast cells, resulting in their degranulation and the release of cytokines, chemokines, histamine, heparin, serotonin, and proteases.

Th17 cells are important in clearance of extracellular pathogens, including Candida albicans and Staphylococcus aureus, especially from the skin and lungs. However, Th17 cells have also been implicated in the development of autoimmune diseases, including inflammatory bowel disease, psoriasis, multiple sclerosis and systemic lupus erythematosus, as well as in chronic allergic inflammatory processes such as asthma. Th17 cells are able to produce multiple cytokines, including IL-17 (important in the recruitment of neutrophils) and IL-22 (important in the production of antimicrobial defensins).5,6,18

Tregs are critical for the maintenance of self-tolerance and immune homeostasis, promoting the contraction of the immune response after pathogen clearance. They function not only to prevent autoimmunity, immune-mediated damage, and allergy, but can also suppress antitumor immune responses and favor tumor progression. Generally, these cells can be classified as either naturally occurring regulatory cells, derived from the thymus, or inducible Tregs, formed in the periphery under the influence of TGFβ. Although both naturally occurring and inducible Tregs exert suppressor functions in mice, to date only the naturally occurring Tregs have been shown to have this function in human beings. These cells are characterized by the expression of the CD25 surface marker and can produce TGFβ and IL-10.

Tfh travel to the B-cell areas of the lymph nodes, where they facilitate the germinal center reaction of B cells as well as...
immunoglobulin affinity maturation and class switching. These cells can be distinguished from other effector cells by their expression of the chemokine receptor CXCR5 (allowing positioning within the follicular area of the lymphoid tissue), downregulation of the CCR7 receptor (a chemokine receptor that retains cells in the T-cell zones of the lymph nodes), and production of IL-21. However, some authorities do not consider Tfh cells to be a separate T-helper cell subset, as opposed to simply a differentiated stage.16,19

T LYMPHOCYTES AND DISEASE

Defects in development T cell can result in either immunodeficiency or autoimmunity. Many T-cell immunodeficiency syndromes are now known to be associated with specific problems in T cell development; others are part of combined immunodeficiencies also affecting B cells and/or NK cells; the pathogenesis of still others is not yet clear.20 Most are rare autosomal recessive disorders, occurring in 1 per 100,000 live births or fewer.

The chromosome 22q11.2 deletion syndrome (DiGeorge syndrome) causes a developmental defect of the thymus, and is an unusually common T-cell defect, found in approximately 1 per 5000 live births.20,21 A large amount of phenotypic variability is found in the disorder; individuals with complete DiGeorge syndrome have cardiac outflow tract anomalies, hypoparathyroidism, facial dysmorphism, and profound T-cell hypolymphopenia due to thymic aplasia. More commonly, partial DiGeorge syndrome is observed, with a much milder level of immunodeficiency consisting of only a slight decline in T-cell numbers and normal T-cell function.20,21

Mutations within the AIRE transcription factor gene are responsible for the multiorgan disease known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome. This autosomal recessive disorder appears to be caused by interruption of the negative selection of T cells reactive to self-peptides, preventing apoptosis of self-reactive T cells. It is characterized by chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency along with other variable autoimmune manifestations such as thyroiditis, type 1 diabetes, ovarian failure, alopecia, or hepatitis.8,9,20

Some defects in the development of T cell affect only selected subsets of T cells. Although no isolated defects in the TH1 pathway have been discovered, defects in the IFNγ and IL-12 pathways, key mediators of TH1 differentiation, have been reported, including deficiencies in the genes encoding the IFNγ or IL-12 receptors, the STAT1 transcription factor, or IL-12 itself. These disorders are all uniquely characterized by an increased susceptibility to intracellular pathogens, especially mycobacterial infections, and sometimes Salmonella and certain viral infections.22 Loss of Treg cell function from FOXP3 gene mutations leads to the immunodeficiency, polyendocrinopathy, enteropathy, X-linked syndrome, characterized by severe diarrhea, insulin-dependent diabetes mellitus, eczema, and often hypothyroidism, hemolytic anemia, thrombocytopenia, and neutropenia. This immunodeficiency syndrome, along with animal models of FOXP3 deletion, provides clear evidence of the importance of Tregs in maintaining the homeostasis of the immune system.23 Recently, a majority of the cases of the autosomal dominant form of hyper-IgE recurrent infection syndrome (formerly known as Job syndrome), characterized by recurrent staphylococcal infections of the skin and lung, chronic eczema, elevated serum IgE, joint hyperextensibility, and dental abnormalities, were found to be caused by mutations in the STAT3 gene important in TH17 cell differentiation; patients with this disorder were subsequently found to have defects in TH17 cells.24-25 Dysregulation of the Tfh cell type has been proposed to play a role in autoimmune/immunity mediated antibody production in antibody-mediated autoimmune diseases such as SLE. This has been suggested in both mouse and human studies and is thought to occur by Tfh cells providing inappropriate helper signals to self-reactive B cells.17,18 Additionally, ineffective T cell help to B cells is thought to underlie several immunodeficiencies, including X-linked lymphoproliferative disease and common variable immunodeficiency.19,26

Finally, severe combined immunodeficiency syndromes (SCIDS) affect T cells, either alone or in combination with B or NK cells (eg, T+B+NK− cell phenotype of ADA deficiency, T+B+NK+ X-linked SCIDS from defects in the IL2 receptor, or T+B+NK+ SCIDS from defects in the IL7 receptor).29 One form of SCIDS, Omenn syndrome, is characterized by low-to-normal levels of T cells along with low B cells but normal NK cells (T+B+NK+). Children with Omenn syndrome have erythoderma, chronic diarrhea, hepatosplenomegaly, lymphadenopathy, eosinophilia, and elevated serum IgE; mutations in the RAG genes impair development of T cell in the thymus, with a resulting limited repertoire of low-affinity T cells skewed toward a Th2 phenotype (overproduction of IL-4 and IL-5, eosinophilia, and elevated serum IgE).3,20

REFERENCES