Adaptive immunity

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The innate immune system provides critical mechanisms for the rapid sensing and elimination of pathogens. Adaptive immunity has evolved to provide a broader and more finely tuned repertoire of recognition for both self- and nonself-antigens. Adaptive immunity involves a tightly regulated interplay between antigen-presenting cells and T and B lymphocytes, which facilitate pathogen-specific immunologic effector pathways, generation of immunologic memory, and regulation of host immune homeostasis. Lymphocytes develop and are activated within a series of lymphoid organs comprising the lymphatic system. During development, sets of gene segments are rearranged and assembled to create genes encoding the specific antigen receptors of T and B lymphocytes. The rearrangement mechanism generates a tremendously diverse repertoire of receptor specificities capable of recognizing components of all potential pathogens. In addition to specificity, another principal feature of adaptive immunity is the generation of immunologic memory. During the first encounter with an antigen (pathogen), sets of long-lived memory T and B cells are established. In subsequent encounters with the same pathogen, the memory cells are quickly activated to yield a more rapid and robust protective response. (J Allergy Clin Immunol 2010;125:S33-40.)

Key words: *Adaptive immunity, antibody, B cell, lymphocytes, T cell*

Abbreviations used

APC:	Antigen-presenting cell
CTL:	Cytolytic T lymphocyte
NK:	Natural killer
NKT:	Natural killer T
PLCγ1:	Phospholipase Cγ1
RAG:	Recombinase activating gene
SCID:	Severe combined immunodeficiency
SHM:	Somatic hypermutation
TACI:	Transmembrane activator and CamL interactor
TCR:	T-cell receptor
TI:	T independent
TLR:	Toll-like receptor
TREC:	T-cell receptor excision circle
ZAP-70:	ζ-Associated protein, 70 kd

Although the innate immune system has evolved to rapidly sense and effect the elimination of a wide range of pathogens, the range of common pathogenic molecular patterns it can recognize is limited. The overwhelming variability of antigenic structures, as well as the ability of pathogens to mutate to avoid host detection, has driven the evolution of the adaptive immune system.[1] In contrast to the recognition receptors of the innate immune system, which are all encoded in their fully functional form in the germline genome, adaptive immune responses depend on receptors that are custom tailored and selected through a process of somatic recombination of a large array of gene segments. These arose by means of gene duplication early in the evolution of vertebrates to generate highly specific and flexible immune responses. After initial pathogen encounters, cells expressing these immune receptors can persist in the host for life, providing immunologic memory and the capacity for rapid response in the event of re-exposure.

Cells of the adaptive immune system include the effectors of cellular immune responses, the T lymphocytes, which mature in the thymus, and antibody-producing cells, the B lymphocytes, which arise in the bone marrow. Lymphocytes are highly mobile. After developing in the primary lymphoid organs (thymus and bone marrow), they traffic to secondary lymphoid organs, including lymph nodes and the spleen, which serve to capture circulating antigens from lymph and blood, respectively. Adaptive immune responses originate in these areas, often under the influence of innate immune system signals provided either directly by circulating pathogens or indirectly by pathogen-activated cutaneous or mucosal antigen-presenting cells (APCs) migrating to the secondary lymphoid organs. Lymphocytes emigrating from the spleen and lymph nodes can then travel to many sites in the body to exert effector functions. This trafficking is regulated by an array of adhesion molecules and chemokine receptors; CLA-1^+ CCR4-bearing lymphocytes traffic to skin, whereas cells bearing the $\alpha4\beta7$ integrin which binds to mucosal addressin cellular adhesion molecule-1 (MadCAM-1) on gut endothelial cells preferentially home to the gastrointestinal tract.

T CELLS AND CELLULAR IMMUNITY

T-cell development

T cells develop in the thymus from common lymphoid progenitors coming from the bone marrow or fetal liver.[2-4] Seeding of the thymus is promoted by the interaction of platelet selectin glycoprotein 1 on the progenitors with the adhesion molecule P-selectin on thymic epithelium. Recently arrived cells rapidly expand under the influence of IL-7, the receptor of which signals through the common γ chain, which is encoded on the X-chromosome, and is shared by a number of other cytokine receptors (IL-2, IL-4, IL-9, IL-15, and IL-21). Mutations in this polypeptide underlie X-linked severe combined immunodeficiency (SCID), which is characterized by absent T cells. This early thymocyte expansion is accompanied by induction of Notch-1 and other

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transcription factors, which commit precursors to the T-cell lineage and induce the expression of genes important in T-cell receptor (TCR) assembly. Subsequent differentiation of the expanded pool of T-cell progenitors or pro-T cells in the thymus involves an antigen-independent process in which a coordinated series of genomic rearrangements leads to the creation of functional genes encoding the α and β or γ and δ chains of the TCR.

In their germline configuration the TCR loci contain arrays of V (variable), D (diversity) and J (joining) segments. V and J segments are present at all TCR loci, whereas only the β and δ TCR loci contain D segments. In a spatially and sequentially ordered process, one V, one D (for β and δ) and one J segment are randomly spliced together (Fig 1). This is mediated by an enzymatic complex, the V(D)J recombinase composed of 2 proteins encoded by the recombinase-activating genes 1 and 2 (*RAG1* and *RAG2*). RAG1 and RAG2 bind to recombinase signal sequences flanking the borders of V-D-J segments. Recombination signal sequence accessibility is regulated by chromatin structure.[5] The V(D)J recombinase cleaves the DNA at these sites to give rise to hairpin structures. These, in turn, are substrates for cleavage by the nuclear enzyme Artemis, which is activated by DNA-dependent protein kinase catalytic subunit and exerts endonuclease activity on 5′ and 3′ overhangs and hairpins. Repair of the DNA breaks with resultant genomic juxtaposition of V, D, and J segments is effected by ubiquitous DNA repair enzymes including XRCC4 (X-ray repair cross-complementing protein 4) and Ligase IV in a process called nonhomologous end-joining. As would be predicted, null mutations in *RAG*, Artemis (DCLRE1C), DNA Ligase IV, and other enzymes involved in V(D)J recombination (including the XRCC4-like enzyme Cernunnos) give rise to SCID.

Each assembled V-D-J cassette represents one of a huge number of possible permutations of recombinations of the component V, D, and J segments, and the resulting structure dictates the amino acid sequence and binding specificity of the TCR. This is referred to as combinatorial diversity. Additional diversity, known as junctional diversity, is conferred by some inherent imprecision in the DNA-joining reactions involved in ligation of double-strand DNA breaks, resulting in some addition or removal of bases. Furthermore, the enzyme terminal deoxyribonucleotidyl transferase catalyzes the template-independent addition of several (generally 1-5) nucleotides at the joints. These junctional areas encode the third complementarity determining region of the antigen-binding pocket of the TCR, and this is the site of greatest variability.

In their germline configuration the component gene segments of the TCR are separated by large amounts of DNA. These intervening stretches of DNA are excised in the process of recombination but remain in the nucleus, where they circularize and are stable in an episomal form known as T-cell receptor excision circles (TRECs). TRECs are not duplicated during cell division, and therefore they dilute as newly formed T-cell clones expand. Measurement of TRECs in peripheral blood by means of PCR can be used to examine T-cell emigration from the thymus, and this approach is now in used in several states to analyze newborn blood spots in pilot screening programs for SCID.[6]

Gene-segment rearrangements are termed productive if they do not introduce stop codons and give rise to a gene encoding a full-length TCR protein. Sequential productive rearrangements of 2 TCR genes leading to surface expression of an αβ or γδ TCR marks the transition from a pre-T to a double-positive T cell; these

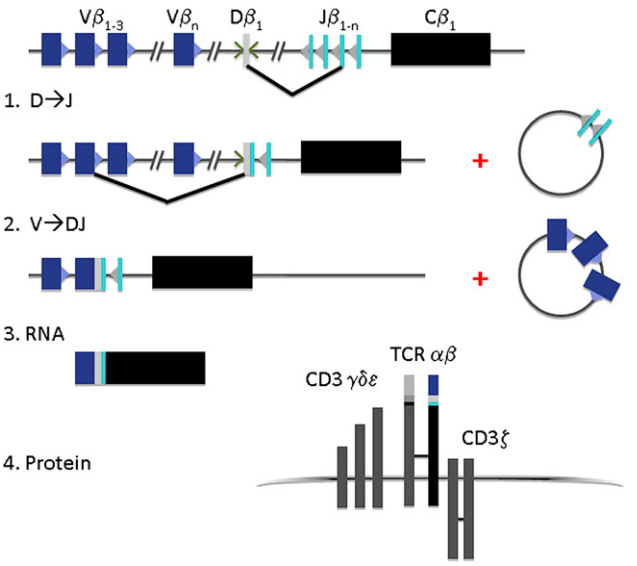

FIG 1. Sequential recombination of a random assortment of gene fragments dictates TCR structure and specificity. This schematic depiction of the TCR $V\beta_1$ locus indicates the relative locations of the Vβ, Dβ, and Jβ segments upstream of $C\beta_1$. *1,* The V(D)J recombinase recognizes signal sequences *(triangles)* upstream of one of many possible Jβ segments and introduces DNA breaks. The same process occurs at an upstream Dβ segment. Double-stranded DNA breaks are generated, and the 2 broken DNA ends are brought together and ligated by means of cellular DNA repair mechanisms (nonhomologous end-joining). The excised intervening DNA (the stretch between Dβ and $J\beta_n$) circularizes and remains in the nucleus as an episome known as a TREC. Such DNA circles are stable but are not replicated during cell division and dilute out during clonal expansion after T cells exit the thymus. *2,* By using the same mechanism, one of approximately 70 possible Vβ segments is brought into juxtaposition with the DJβ segment. A second excision product is generated. *3,* Transcripts of the rearranged TCRβ locus contain Vβ, Dβ, Jβ, and C cassettes. *4,* If this series of events has not introduced any stop codons, the rearrangement is termed productive, and a full functional TCRβ protein is translated. This event is permissive for subsequent TCRα rearrangement followed by expression of the complete TCR complex, including TCRαβ and CD3γδϵζ chains at the T-cell surface. Rearrangement of α genes is the same as for β genes, except that the α gene is assembled only from Vα, Jα, and Cα. The γ chain of the TCR is similar to α and is also assembled from V, J, and C segments. The TCR δ chain is similar to the β chain and is comprised of V, D, J, and C segments. The α and δ gene loci are on chromosome 14. The β and γ loci are on chromosome 7.

cells express both CD4 and CD8. The TCR chains are assembled at the cell surface as a complex with the proteins constituting CD3, including the γ, δ, ϵ and ζ chains.

Further differentiation of these double-positive cells, which reside in the thymic cortex, to single-positive T cells, which are found in the medulla, is regulated by both positive and negative selection events involving antigens and molecules of the MHC. Positive selection occurs when the TCR of double-positive T cells binds with low avidity to self-MHC (complexed with self-peptides) on thymic epithelium. Double-positive cells bearing a TCR, which does not bind to self-MHC, are eliminated. Conversely, negative selection is exerted on double-positive T cells, the TCR of which binds with very high avidity to self-MHC/peptide, ensuring that autoreactive T-cell precursors are not permitted to mature (central tolerance). Deletion of T-cell clones interacting with peptides normally expressed in distant organs is facilitated by the function of the gene *AIRE* (autoimmune regulator), which stimulates expression of genes with wide tissue

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