Chapter 33
T-Cell Lymphomas

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Molecular Basis of Disease

There are two broad genetic changes that can be studied in T-cell lymphomas, namely, T-cell receptor (TCR) gene rearrangements and chromosomal translocations, deletions, or additions.

TCR Gene Rearrangements

Pluripotent bone marrow stem cells give rise to progenitor T cells, which migrate to the thymus for primary ontogeny. There, TCR genes undergo somatic rearrangement of germline gene sequences, similar to the process that occurs in immunoglobulin heavy (IGH) and light-chain (IGLK and IGLL) genes. The four TCR genes are rearranged in the following order: TCRD (on chromosome 14q11), TCRG (7p15), TCRB (7q34), and TCRA (14q11). These rearrangements occur early in T-cell development and are unique to each cell, ensuring great receptor diversity (Figure 33-1). The genetic recombination occurs when the variable (V) segments are joined with a diversity (D) region (present only in the TCRB and TCRD genes) or with a joining (J) region by deletion of the intervening coding and noncoding DNA sequences. Thus, the TCRB and TCRD gene rearrangements result in V-D-J juxtaposition similar to the IGH gene, whereas the TCRA and TCRG genes contain only V-J rearrangements. In all cases, the TCR genes are translated into two types of receptors, which exist as heterodimers (αβ or γδ). Approximately 95% of mature, circulating T cells express the αβ receptor because the initial δ or γ rearrangements failed to produce a functional receptor. In the skin, spleen, gastrointestinal tract, and other extranodal sites, γδ T cells are more commonly identified. T-cell neoplasms ensue after maturation arrest at one of the stages of T-cell development (Figure 33-1). They can originate from immature T cells as in lymphoblastic T-cell lymphoma, or from more mature T cells, as seen in peripheral T-cell lymphoma and mycosis fungoides. Related neoplasms of natural killer (NK) cells also occur, but because these are not true T-cell-derived tumors, they do not usually demonstrate T-cell receptor gene rearrangements. The T- and NK-cell neoplasms of the World Health Organization (WHO) classification are listed in Table 33-1.

Translocations and Deletions

Clonal T-cell abnormalities can originate from a variety of molecular genetic events. Translocations can result in a fusion of (parts of) different genes if the breakpoint is within the affected genes. Upregulation of gene expression also can result, if the breakpoint is located outside the coding region. This can expose a gene to the enhancing effects of other genes and regulatory sequences that are in close proximity due to the translocation. Anaplastic large cell lymphoma, which is a T-cell or null-cell lymphoma, is associated with translocation t(2;5) (p23;q35). This translocation is characterized by a fusion between the nucleophosmin (NPM) gene on chromosome 5 and the anaplastic lymphoma kinase (ALK) gene on chromosome 2. It is the most common cytogenetic abnormality in noncutaneous forms of anaplastic large cell lymphoma and the only recurring translocation that is routinely tested for in mature T-cell lymphomas. ALK can fuse with other genes as well, including TPM3 at 1p21, TFG at 3q21, ATIC at 2q35, CTLC at 17q23, and MSN at Xq11-12. In addition to gene translocations, allelic loss of a tumor suppressor gene can contribute to the development of lymphoma. An example is loss of function of the P15 and P16 genes on the short arm of chromosome 9. Allelic loss and gene silencing due to promoter methylation were identified in both early and advanced stages of Sézary syndrome and mycosis fungoides. Cytogenetic anomalies, including deletions and inversions on the long arms of chromosomes 8, 11, and 14, are associated with T-cell prolymphocytic leukemia. However, due to the variation in gene fusion
sites, none of these translocations is currently analyzed routinely at the molecular level.

**Indications for Testing**

The diagnosis of a T-cell malignancy is best made in the context of clinical information, tissue morphology, immunohistochemical stains, and immunophenotypic analysis. In contrast to the restricted IGL protein expression in mature B-cell lymphomas, however, T cells do not have a definitive immunophenotypic marker of clonality. Therefore, TCR gene rearrangement studies can be essential to complement a diagnostic evaluation and to distinguish polyclonal from monoclonal lymphoproliferations. When clonality is assessed by TCR polymerase chain reaction (PCR), a visible band with products of exactly the same size is indicative of the presence of a clone, whereas polyclonal amplification generates a smear of nondistinct products of various sizes. A result is considered oligoclonal if more than two distinct bands are visible. The number of bands that would lead to a determination of oligoclonality varies by method, but the band size often will vary between duplicate PCR reactions in oligoclonal proliferations. In addition to the differentiation of reactive and neoplastic proliferations, molecular methods can be applied to identify disease-related findings, such as an associated virus or a specific gene fusion product, that enable subclassification of the malignancy.

Anaplastic large cell lymphoma, characterized by translocation t(2;5)(p23;q35), is the only translocation for which testing is widely available. Diagnostic testing is complicated by the variety of ALK fusion partners and inconsistency of genetic anomalies seen during tumor progression.

Adult T-cell leukemia/lymphoma (ATLL) is strongly associated with HTLV-1 infections. The provirus is clonally integrated in the host DNA in virtually all ATLL patients, but in situ hybridization studies for this virus are difficult to perform and are not routinely offered. Serologic studies or PCR analysis are better suited to detect the virus.

![Figure 33-1. Various stages of T-cell development and an overview of the order of TCR gene rearrangements. (TdT, terminal deoxynucleotidyl transferase.)](image)

![Figure 33-2. The TCRB locus on chromosome region 7q34 is used as an example to demonstrate the rearrangement of the variable (V), diversity (D), joining (J), and constant (C) regions. N, nucleotides added by the enzyme TdT.](image)