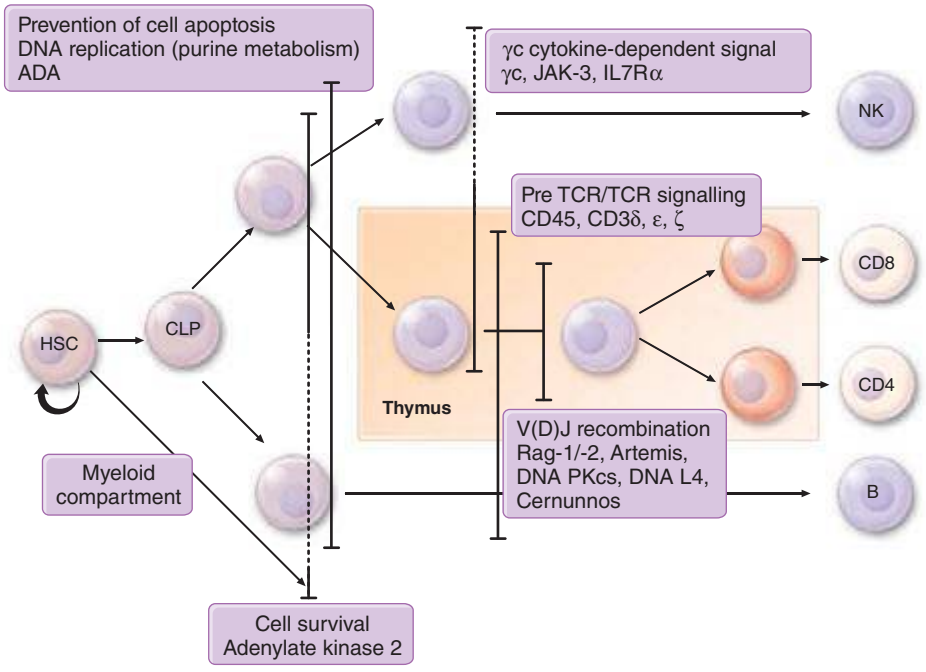

FIGURE 374-3 T cell differentiation and severe combined immunodeficiencies (SCIDs). The vertical bars indicate the five mechanisms currently known to lead to SCID. The names of deficient proteins are indicated in the boxes adjacent to the vertical bars. A broken line means that deficiency is partial or involves only some of the indicated immunodeficiencies. ADA, adenosine deaminase deficiency; CLPs, common lymphoid progenitors; DNAL4, DNA ligase 4; HSCs, hematopoietic stem cells; NKs, natural killer cells; TCR, T cell receptor.

(derived from maternal-fetal blood transfers) that cannot be eliminated. Although counts are usually low (<500/μL of blood), higher maternal T cell counts may, under some circumstances, initially mask the presence of SCID. Thus, screening for maternal cells by using adequate genetic markers should be performed whenever necessary. Inheritance pattern analysis and lymphocyte phenotyping can discriminate between various forms of SCID and provide guidance in the choice of accurate molecular diagnostic tests (see below). To date, five distinct causative mechanisms for SCID (Fig. 374-3) have been identified:

SEVERE COMBINED IMMUNODEFICIENCY CAUSED BY A CYTOKINE-SIGNALING DEFICIENCY The most frequent SCID phenotype (accounting for 40–50% of all cases) is the absence of both T and NK cells. This outcome results from a deficiency in either the common γ chain (γc) receptor that is shared by several cytokine receptors (the IL-2, -4, -7, -9, -15, and -21 receptors) or Jak-associated kinase (JAK) 3 that binds to the cytoplasmic portion of the γc chain receptor and induces signal transduction following cytokine binding. The former form of SCID (γc deficiency) has an X-linked inheritance mode, while the second is autosomal recessive. A lack of the IL-7Rα chain (which, together with γc, forms the IL-7 receptor) induces a selective T cell deficiency.

PURINE METABOLISM DEFICIENCY Ten to 20% of SCID patients exhibit a deficiency in adenosine deaminase (ADA), an enzyme of purine metabolism that deaminates adenosine (ado) and deoxyadenosine (dAdo). An ADA deficiency results in the accumulation of ado and dAdo metabolites that induce premature cell death of lymphocyte progenitors. The condition results in the absence of B and NK lymphocytes as well as T cells. The clinical expression of complete ADA deficiency typically occurs very early in life. Since ADA is a ubiquitous enzyme, its deficiency can also cause bone dysplasia with abnormal costochondral junctions and metaphyses (found in 50% of cases) and neurologic defects. The very rare purine nucleoside phosphorylase (PNP) deficiency causes a profound although incomplete T cell deficiency that is often associated with severe neurologic impairments.

DEFECTIVE REARRANGEMENTS OF T AND B CELL RECEPTORS A series of SCID conditions are characterized by a selective deficiency in T and B lymphocytes with autosomal recessive inheritance. These conditions account for 20–30% of SCID cases and result from mutations in genes encoding proteins that mediate the recombination of V(D)J gene elements in T and B cell antigen receptor genes (required for the generation of diversity in antigen recognition). The main deficiencies involve RAG-1, RAG-2, DNA-dependent protein kinase, and Artemis. A less severe (albeit variable) immunologic phenotype can result from other deficiencies in the same pathway, i.e., DNA ligase 4 and Cernunnos deficiencies. Given that these latter factors are involved in DNA repair, these deficiencies also cause developmental defects.

DEFECTIVE (PRE-)T CELL RECEPTOR SIGNALING IN THE THYMUS A selective T cell defect can be caused by a series of rare deficiencies in molecules involved in signaling via the pre-TCR or the TCR. These include deficiencies in CD3 subunits associated with the (pre-)TCR (i.e., CD3δ, ε, and ζ) and CD45.

RETICULAR DYSGENESIS Reticular dysgenesis is an extremely rare form of SCID that causes T and NK deficiencies with severe neutropenia and sensorineural deafness. It results from an adenylate kinase 2 deficiency.

Patients with SCID require appropriate care with aggressive anti-infective therapies, immunoglobulin replacement, and (when necessary) parenteral nutrition support. In most cases, curative treatment relies on HSCT. Today, HSCT provides a very high curative potential for SCID patients who are otherwise in reasonably good condition. In this regard, neonatal screening, based on quantification of T cell receptor excision circles (TRECs) on a Guthrie card sample, is being developed. Gene therapy has been found to be successful for cases of X-linked SCID (γc deficiency) and SCID caused by an ADA deficiency, although toxicity has become an issue in the treatment of the former disease that may now be overcome by use of newly generated vectors. Lastly, a third option for the treatment of ADA deficiency consists of enzyme substitution with a pegylated enzyme.

Thymic Defects A profound T cell defect can also result from faulty development of the thymus, as is most often observed in rare cases of DiGeorge syndrome—a relatively common condition leading to a constellation of developmental defects. In approximately 1% of such cases, the thymus is completely absent, leading to virtually no mature T cells. However, expansion of oligoclonal T cells can occur and is associated with skin lesions. Diagnosis (using immunofluorescence in situ hybridization) is based on the identification of a hemizygous deletion in the long arm of chromosome 22. To recover the capability for T cell differentiation, these cases require a thymic graft. CHARGE (*c*oloboma of the eye, *h*eart anomaly, choanal *a*tresia, *r*etardation, *g*enital and *e*ar anomalies) syndrome (CHD7 deficiency) is a less frequent cause of impaired thymus development. Lastly, the very rare "nude" defect is characterized by the absence of both hair and the thymus.

Omenn Syndrome *Omenn syndrome* consists of a subset of T cell deficiencies that present with a unique phenotype, including early-onset erythrodermia, alopecia, hepatosplenomegaly, and failure to thrive. These patients usually display T cell lymphocytosis, eosinophilia, and low B cell counts. It has been found that the T cells of these patients exhibit a low TCR heterogeneity. This peculiar syndrome is the consequence of hypomorphic mutations in genes usually associated with SCID, i.e., *RAG-1*, *RAG-2*, or (less frequently) *Artemis* or *IL-7Rα*. The impaired homeostasis of differentiating T cells thus causes this immune system–associated disease. These patients are very fragile,