125 T-Cell Immune Defects

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T-cell immunodeficiency comprises a heterogeneous group of disorders with impaired development and/or function of T lymphocytes (◉ *Fig. 125.1*). The thymus is the primary lymphoid organs where development of T lymphocytes takes place, starting from a common lymphoid progenitor that originates from a bone-marow-derived hematopoietic stem cell. Within the thymus, several differentiation steps mark progressive maturation of thymocytes, and ultimately lead to generation of mature naïve T lymphocytes. The earliest stages of T-cell development are characterized by lack of CD4 and CD8 expression (double negative T cells). This is followed by co-expression of CD4 and CD8 molecules, along with expression of the T-cell receptor (TCR), at the double-positive (DP) stage of T-cell differentiation. Expression of the TCR enables positive selection of thymocytes in the thymic cortex, followed by further differentiation into single positive (SP) CD4 or CD8 thymocytes that migrate to the thymic medulla, where negative selection of self-reactive T cells takes place. Eventually, mature naïve T lymphocytes leave the thymus and reach the periphery, where they colonize the lymph nodes, the spleen, and patrol the skin, the mucosa, and peripheral tissues.

Development of T lymphocytes is under strict genetic control. Sigle-gene disorders that affect the early stages in T-cell development (up to DP stage of differentiation) are associated with Severe Combined Immune Deficiency (SCID), with lack of circulating T lymphocytes. Some of these genetic disorders may also compromise development of B and/or NK lymphocytes. Defects that affect later stages in T-cell development and/or function are also known as Combined Immune Deficiencies (CID), and are characterized by the presence of a variable number of circulating T lymphocytes. Finally, defects in the ontogeny of the thymus also compromise development of T lymphocytes. DiGeorge syndrome represents the prototype of such conditions. In this chapter, we will review the clinical features, pathophysiology, diagnostic approach, and treatment to human T-cell immunodeficiencies.

Severe Combined Immunodeficiencies (SCID)

Clinical Presentation

SCID include a heterogeneous group of genetic disorders characterized by inability to generate mature T lymphocytes. While some of these defects also affect development of B and/or NK lymphocytes, all forms of SCID are characterized by impaired humoral immunity, due to the lack of helper T-cell activity. Hence, the clinical presentation of SCID is marked by early onset and severe infections of bacterial, viral, or fungal origin. Opportunistic infections are very common. Interstitial pneumonia is very frequent and may be due to *P. jiroveci*, cytomegalovirus (CMV), adenovirus, parainfluenza 3, and respiratory syncitial virus (RSV). Chronic diarrhea typically leads to failure to thrive. Persistent candidiasis is also common. Typically, infections develop already in the first months of life, reflecting the essential role of T lymphocytes in mediating and orchestrating pathogen-specific immune responses. The early onset and the severity of infections in infants with SCID mark a clear difference vs. pure antibody deficiencies, whose clinical manifestations most often consist of recurrent bacterial infections, that tend to become more prominent when maternally derived immunoglobulins have disappeared. Skin manifestations (maculopapular rash, erythroderma, alopecia) may also be observed in patients with SCID, and often represent manifestations of immune dysregulation due to infiltration by maternal T lymphocytes that have engrafted into the fetus, or the presence of a residual number of autologous and activated T lymphocytes. Infants with SCID typically have hypoplastic lymphoid tissue (tonsils, lymph nodes), and absence of a thymic shadow can be demonstrated on chest X-ray. Additional features are characteristically associated with specific forms of SCID. For instance, microcephaly is present in most infants with SCID due to defects in DNA repair. Sensorineural deafness is observed in infants with reticular dysgenesis, but may also be present in patients with adenosine deaminase

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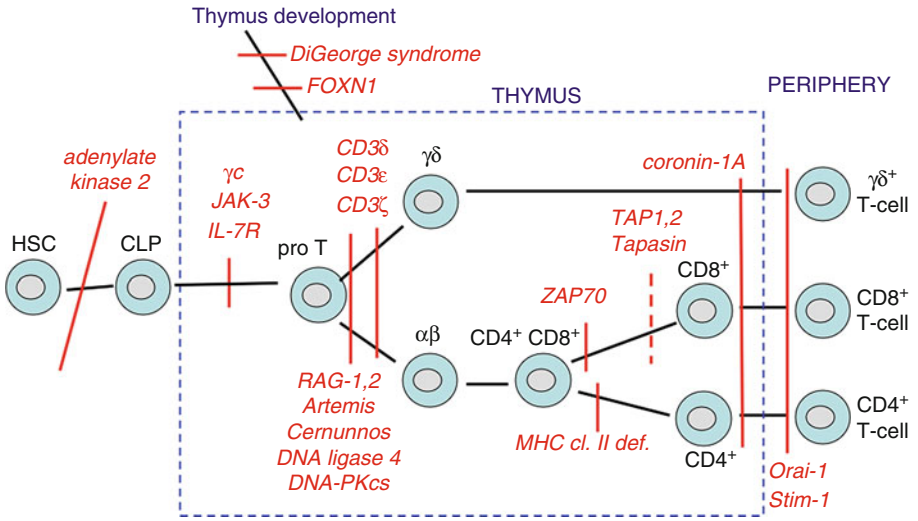

Figure 125.1

Schematic representation of defects along human T-cell development that cause SCID or other severe T-cell immunodeficiencies. Red lines identify specific blocks in development, and the genes involved are annotated. HSE: hematopoietic stem cell; CLP: common lymphoid progenitor

(ADA) deficiency. Progressive neurological deterioration is often seen in patients with purine nucleoside phosphorylase (PNP) deficiency, and neurobehavioral problems are common also in ADA deficiency. ADA-deficient patients also often have flaring of the ribs at chest X-ray.

Pathogenesis and Genetics

SCID comprise a heterogeneous group of mendelian disorders, and their overall prevalence is estimated to be 1:50,000 to 1:100,000 births, with significant geographic variability. In Western countries, the most common form of SCID is inherited as an X-linked trait; however, a variety of autosomal recessive (AR) forms are also known. AR-SCID are more common in countries with higher consanguinity rate or among restricted ethnic groups.

The pathophysiology of the various forms of SCID reflects distinct defects in critical steps along T-cell development. In some cases, these defects may also involve additional blood lineages, including B and/or NK lymphocytes or myeloid cells, or may affect non-hematopoietic cells as well.

Increased apoptosis of lymphoid precursors is observed in reticular dysgenesis (RD), ADA deficiency, and PNP deficiency, three autosomal recessive forms of SCID. RD is due to mutations of the *AK2* gene, encoding for adenylate kinase 2. This defect is associated with perturbed homeostasis of ADP and ATP levels in mitochondria, resulting in increased cell death. The defect is not restricted to T lymphocytes, but also involves myeloid neutrophil progenitors and the inner ear, accounting for severe neutropenia and sensorineural deafness.

ADA and PNP are two enzymes of the purine salvage pathway. ADA converts adenosine (Ado) and deoxy-adenosine (dAdo) into inosine and deoxy-inosine, respectively. In the absence of ADA, high intracellular levels of Ado, dAdo, and their toxic phosphorylated metabolites cause apoptosis of lymphoid precursors, and hence result in the virtual absence of T lymphocytes that is usually associated with marked reduction of B and NK lymphocytes ($T^-B^-NK^-$ SCID). PNP catalyzes the phosphorylation of inosine, guanosine, and deoxyguanosine. In the absence of PNP, high intracellular levels of dGTP cause lymphoid and neuronal toxicity. Immature thymocytes are particularly susceptible to PNP deficiency. Accordingly, the immunological phenotype of PNP deficiency is characterized by decreased T-cell counts, whereas B and NK lymphocytes are often unaffected. Both ADA and PNP deficiency have extraimmune manifestations, reflecting the ubiquitous expression of these genes.

Interleukin-7 (IL-7)-mediated signaling plays a critical role in the expansion of early thymocyte progenitors, which express IL-7 receptor (IL-7R), composed of an IL-7R α chain and a common γ chain (γc), also shared by

receptors for IL-2, IL-4, IL-9, IL-15, and IL-21. In all of these receptors, the γc is coupled to the intracellular tyrosine kinase JAK3. In humans, defects of IL-7-mediated signaling abrogate T-cell development, whereas impaired signaling through IL-15R affects development of NK cells. X-linked SCID, due to *IL2RG* mutations, represents approximately 40% of all cases of SCID, and is characterized by lack of T and NK lymphocytes but normal development of B cells ($T^-B^+NK^-$ SCID). B lymphocyte function, however, is severely compromised by both the lack of T-cell help and γc. JAK3 deficiency is inherited as an autosomal recessive trait, and its phenotype is identical to that of X-linked SCID ($T^-B^+NK^-$ SCID). In contrast, autosomal recessive IL7R deficiency due to mutation of the α chain is characterized by the selective lack of T cells ($T^-B^+NK^+$ SCID).

Expression of the pre-T-cell receptor (pre-TCR), which is composed of a pre-Tα chain, a TCR β chain, and the CD3 γ,δ,ε, and ζ chains, marks the next step in T-cell development. Signaling through the pre-TCR permits rearrangement of the TCRα chain and expression of a mature TCRαβ. Alternatively, thymocytes may express the γδ chains of the TCR. Signaling through the TCR is essential for positive selection of cortical thymocytes. Defects in the mechanisms of assembly and signaling of the pre-TCR and TCR complexes result in SCID in humans. Rearrangement of the TCR loci is accomplished by means of the V(D)J recombination, whereby the lymphoid specific RAG1 and RAG2 proteins mediate DNA cleavage at the Variable (V), Diversity (D), and Joining (J) elements of the TCR loci. DNA Double Strand Breaks (DSB) at the coding ends are initially sealed as a hairpin, which are then resolved by Artemis (encoded by the *DCLRE1C* gene). Eventually, sealing of coding and signal joins is mediated by the Ku70/80 heterodimer, XRCC4, DNA ligase IV (LIG4), DNA-Protein Kinase catalystic subunit (DNA-PKcs), and Cernunnos/XLF. The V(D)J recombination process is essential not only in T cell development, but also for B cell development, where it mediates rearrangement at the immunoglobulin heavy and light chain loci. Hence, defects in any of the steps of the V(D)J recombination process cause $T^-B^-NK^+$ SCID. RAG1 or RAG2 deficiencies are the most common V(D)J recombination defect and account for about 10% of all forms of SCID. Defects in Artemis, DNA-PKcs, LIG4, and Cernunnos/XLF are less frequent. Importantly, while expression of the *RAG1* and *RAG2* genes is restricted to lymphocytes, Artemis, DNA-PJcs, LIG4, and Cernunnos/XLF are ubiquitously expressed and mediate nonhomologous end joining (NHEJ) DNA repair. Accordingly, deficiency in any of these proteins is associated with increased cellular radiosensitivity and extraimmune clinical manifestations (microcephaly, growth and developmental defects, increased risk of malignancies).

The CD3 δ,ε, or ζ chains represent the signaling elements of the pre-TCR and of the TCR. Defects in these molecules cause autosomal recessive $T^-B^+NK^+$ SCID. In contrast, CD3γ deficiency is associated with mild T-cell lymphopenia and a variable clinical phenotype.

CD45 is a tyrosine phosphatase that is also involved in signaling through the TCR and the B-cell receptor (BCR). CD45 deficiency has been reported in few patients with $T^-B^+NK^+$ SCID.

Diagnostic Approach

Diagnosis of SCID is based on clinical and family history and on typical laboratory features. Presentation early in life with severe infections, especially if sustained by opportunistic pathogens, should always prompt to consider SCID as a possible diagnosis. Family history should be addressed to document other male subjects on the maternal side who presented and/or died with severe infections early in life (suggestive of a possible X-linked form of the disease) or the presence of parental consanguinity (indicative of possible autosomal recessive inheritance). Laboratory investigation should be primarily based on careful evaluation of the absolute lymphocyte count (ALC), and values should be compared with age-matched controls. The vast majority of infants with SCID present with severe lymphopenia. If the ALC is $<2{,}000/mm^3$, analysis of lymphocyte subsets should be immediately performed. Typically, infants with SCID have markedly reduced or absent circulating T cells. Depending on whether the development of B and/or NK lymphocytes is also affected, SCID can be classified into distinct immunological phenotypes: (a) $T^-B^+NK^-$ SCID (the most common variant), (b) $T^-B^+NK^+$ SCID, (c) $T^-B^-NK^+$ SCID, or (d) $T^-B^-NK^-$ SCID. These different immunological phenotypes reflect distinct genetic defects (*Table 125.1*) and thus may guide in the molecular diagnosis. However, a normal ALC does not rule out SCID, if suggestive clinical features are present. In particular, subnormal or even normal ALC in SCID may reflect maternal T-cell engraftment, a phenomenon observed in more than 50% of infants with SCID. Most often asymptomatic, it may cause skin rash or, less frequently, typical graft-versus-host disease (GvHD) with generalized rash, liver disease, profuse diarrhea, jaundice, and cytopenias (thrombocytopenia, anemia, leukopenia) due to bone

Table 125.1
Molecular basis of SCID, divided by immunological phenotype

Immunological phenotype	Underlying molecular defect	Inheritance
$T^- B^+ NK^-$	IL2RG (γc)	XL
	JAK3	AR
$T^- B^+ NK^+$	IL7R	AR
	CD3D	AR
	CD3E	AR
	CD3Z	AR
	CD45	AR
$T^- B^- NK^+$	RAG1	AR
	RAG2	AR
	Artemis	AR
	LIG4	AR
	DNA-PKcs	AR
	XLF	AR
$T^- B^- NK^-$	ADA	AR
	AK2	AR

XL: X-linked; AR: autosomal recessive

marrow damage. The presence of detectable T lymphocytes in peripheral blood in infants with SCID may also reflect hypomorphic mutations or somatic reversions in SCID-causing genes, which allow for residual development of autologous T cells, resulting in a "leaky" SCID phenotype. Characteristically, maternally engrafted T lymphocytes in patients with SCID, and autologous T cells in patients with leaky SCID, express the CD45R0 memory/activation antigen on their membrane, whereas most T cells in normal infants have a naive $CD45RA^+$ phenotype. Furthermore, autologous activated T cells in infants with leaky SCID have a restricted TCR repertoire, as indicated by expression of a limited set of TCR Vβ families with a restricted diversity of CDR3 length. Lymphocytes from SCID infants fail to proliferate in vitro to mitogens and specific antigens. Patients with PNP deficiency often show progressive decline of T lymphocyte number and function, and are at increased risk for autoimmune hemolytic anemia. Ineffective thymopoiesis in patients with SCID is also marked by very low or undetectable levels of T-cell receptor excision circles (TRECs) in circulating lymphocytes. TRECs are a by-product of V(D)J recombination that consist of circularized signal joins and are maintained in newly generated mature T lymphocytes that leave the thymus. Because TRECs cannot be detected in infants with SCID, assessment of TREC levels by polymerase chain reaction has been proposed for newborn screening for SCID.

Regardless of the presence or absence of circulating B lymphocytes, patients with SCID show hypogammaglobulinemia. However, normal IgG levels may be observed early in life, reflecting transplacental passage of maternal immunoglobulins. Specific antibody responses to immunization antigens are abolished. However, humoral immunity may be spared in patients with PNP deficiency.

Eosinophilia and elevated IgE levels are common, especially in patients with leaky SCID, whereas infections may associate with anemia, thrombocytopenia, and/or neutropenia. Bone marrow dysplastic changes may be observed, especially in patients with Cernunnos/XLF or with LIG4 deficiencies.

Differential diagnosis of SCID includes secondary forms of immunodeficiencies, especially HIV infection. Congenital rubella or CMV infections, severe malnutrition, and defects of vitamin B12 and folate metabolism may also mimic the SCID phenotype.

Treatment

SCID are inevitably and rapidly fatal unless immune reconstitution is attained by means of treatment. Treatment of active infections and initiation of appropriate laboratory testing should be immediately performed in infants with possible SCID. *P. jiroveci* pneumonia is usually treated with high-dose intravenous sulfamethoxazol/trimethoprim (20 mg/kg). CMV or adenoviral infections must be treated with gancyclovir or cidofovir, respectively. Administration of antitubercular Bacillus Calmette-Guerin (BCG) immunization at birth carries risk of BCGosis, and should prompt treatment with isoniazid and rifampicin, regardless of the presence of clinical signs of infection. Regular use of intravenous immunoglobulins and antimicrobial prophylaxis are part of the mainstay of therapy. Enteral or parenteral nutrition may be required in infants with chronic diarrhea and malnourishment.

Live-attenuated vaccines should not be administered to infants with SCID because of the risk of disseminated infection due to vaccine strain (59–61). All blood products should be irradiated to avoid fatal transfusional graft-versus-host disease (GvHD):

Ultimately, survival of SCID infants depends on attainment of robust immune reconstitution. Hematopoietic cell transplantation is the treatment of choice, and was successfully used for the first time in humans in a patient

with X-linked SCID. Excellent results, with >90% long-term survival, have been obtained with HCT from HLA-identical family donors, with no need of pre-transplant chemotherapy. However, this option is available only to 15–20% of patients. Excellent results without chemotherapy have been reported also after haploidentical transplantation, if performed in the neonatal period or in the first 3.5 months of life; however, survival is only 50–65% if haploidentical HCT is performed at a later age. Promising results have been reported with HCT from matched unrelated donors (MUD) and unrelated cord blood (UCB). Although graft rejection should not be possible in infants with SCID (making the use of pre-transplant chemotherapy not necessary), engraftment and immune reconstitution are problematic in recipients of haploidentical HCT, especially for $T^-B^-NK^+$ SCID, ADA deficiency, and reticular dysgenesis. Furthermore, B-cell reconstitution may not be achieved, unless pre-transplant conditioning that favors engraftment of donor stem cells is used.

Most patients with SCID enjoy good quality of life after transplant, however infections, autoimmune/inflammatory complications, and GvHD are observed in a significant fraction of patients. ADA or PNP deficiency and SCID with increased cellular radiosensitivity are at particularly higher risk for these complications, and for neurological and developmental problems, even if successful T-cell reconstitution is achieved.

For patients with ADA deficiency, an alternative form of treatment is represented by enzyme replacement therapy with weekly intramuscular injections of pegylated bovine ADA, although T-cell counts often remain low, in spite of successful detoxication.

Gene therapy has led to immune reconstitution in infants with X-linked SCID or with ADA deficiency; however, 5 out of 20 patients with X-linked SCID treated by gene therapy have developed leukemic proliferation due to insertional mutagenesis.

Other Combined Immunodeficiencies

Combined immune deficiencies (CID) include disorders with residual ability to support T-cell development and/or function. They may be due to either: (a) hypomorphic mutations in SCID-causing genes that allow for some T-cell development or (b) genetic defects that affect late stages in T-cell development or peripheral T-cell function. The clinical features of CID overlap with SCID, but also include autoimmunity and/or inflammatory manifestations reflecting unbalanced immune homeostasis.

Omenn Syndrome

Omenn syndrome (OS) is characterized by severe infections associated with early-onset generalized skin rash/erythroderma, alopecia, lymphadenopathy, hepatosplenomegaly, eosinophilia, and oligoclonal expansion of anergic, activated autologous T lymphocytes that infiltrate and damage target tissues. Serum immunoglobulins are usually very low, but IgE levels are increased. Hypoproteinemia is common, leading to edema. OS is associated with hypomorphic mutations in SCID-causing genes that allow for residual T-cell development. The few T cells that are generated in the thymus undergo extensive homeostatic proliferation in the periphery. Poor thymopoiesis in OS causes abnormalities of thymic stroma, with impairment in the mechanisms of negative selection of autoreactive T cells and of generation of regulatory T cells. These abnormalities contribute to the immunopathology of OS. Mutations in *RAG1* and *RAG2* are the most common genetic defect in OS; however, mutations in *DCLRE1C* (Artemis), *IL7R*, *LIG4*, *RMRP*, *IL-2RG*, *ADA*, and *ZAP70* have been also reported.

Patients with OS have a variable number of circulating T lymphocytes that carry a characteristic activated/memory ($CD45R0^+$) phenotype and have a restricted repertoire. The distribution of CD4 and CD8 subsets is generally skewed. The in vitro lymphocyte response to antigens is abolished; responses to mitogens are variable, but are often reduced. Depending on the nature of the underlying genetic defect, B and NK lymphocytes may be absent or present.

Differential diagnosis includes maternal T-cell engraftment and complete atypical DiGeorge syndrome. HCT represents the mainstay of treatment. In preparation for HCT, aggressive treatment of infection, nutritional support, correction of hypoproteinemia, and immune suppression with steroids and/or cyclosporine A to control extensive T-cell-mediated tissue damage are necessary.

ZAP-70 Deficiency

The Zeta-associated protein of 70 kDa (ZAP-70) is an intracellular kinase that is involved in TCR-mediated signaling. In humans, mutations of the *ZAP70* gene result in autosomal recessive CID with selective deficiency of CD8+ T cells. $CD4^+$ lymphocytes are present, but are functionally impaired. Variable defects have been reported in immunoglobulin levels and antibody responses. Clinical features do not differ from what observed in

SCID, however lymph nodes are palpable, and the thymus can be visualized by chest X-ray.

Differential diagnosis includes MHC class I deficiency and CD8α deficiency, two conditions also characterized by a severe reduction of $CD8^+$ lymphocytes (110, 111). The only curative treatment of ZAP-70 deficiency is HCT.

MHC Class I Deficiency

MHC class I deficiency is an autosomal recessive disorder, characterized by reduced expression of MHC class I molecules at the cell surface. It is caused by defects in the *TAP1* (112), *TAP2* (113), or Tapasin (114) genes, which encode for molecules involved in intracellular loading of peptide antigens MHC class I molecules, and cell surface expression of the complex.

Patients with MHC class I deficiency suffer from recurrent respiratory infections, chronic inflammatory lung disease, and skin lesions that resemble Wegener's granulomatosis. The number of circulating $CD8^+$ T cells is reduced because positive selection of $CD8^+$ lymphocytes in the thymus depends on the recognition of MHC class I molecules. In vitro lymphocyte proliferation is normal, facilitating differential diagnosis with ZAP-70 deficiency, and accounting for a less severe clinical phenotype. Levels of serum immunoglobulin may be variable.

Antibiotic prophylaxis to prevent recurrent respiratory infections, and topical treatment of the cutaneous granulomatous lesions, are the mainstay of treatment.

MHC Class II Deficiency

MHC class II molecules are constitutively expressed by B lymphocytes, monocytes, and dendritic cells, but may also be expressed by other cells (T lymphocytes, endothelial and certain epithelial cells) upon activation. Recognition of MHC class II molecules in the thymus promotes positive selection of $CD4^+$ thymocytes. In the periphery, recognition of antigens in the context of MHC class II molecules is essential to elicit $CD4^+$ T-cell-mediated responses.

MHC class II deficiency is inherited as an autosomal recessive trait and is caused by mutations in any of four different genes (*CIITA*, *RFXANK*, *RFX5*, and *RFXAP*) that encode for transcription factors that control MHC class II genes expression.

The clinical phenotype is marked by increased susceptibility to bacterial, viral, and opportunistic respiratory tract infections; chronic diarrhea; and sclerosing cholangitis, often secondary to *Cryptosporidium* or CMV infection. However, less severe presentations and survival into adulthood have been also reported.

The number of circulating $CD4^+$ T cells is markedly reduced, reflecting an impairment of positive selection in the thymus. Delayed-type hypersensitivity responses are absent, but in vitro proliferative responses to mitogens are preserved. Hypogammaglobulinemia and poor antibody response to immunization are also present. Differential diagnoses include HIV infection and idiopathic CD4 lymphopenia. Both these conditions are characterized by a reduced number of circulating $CD4^+$ lymphocytes; however, expression of MHC class II molecules is preserved.

Most patients with MHC class II deficiency die in their first years of life of severe infections. Antibiotic prophylaxis, immunoglobulin replacement therapy, and adequate nutritional support are an important part of treatment, but definitive cure can be only achieved with HCT. However, the results of HCT for this disease are far less satisfactory than in other forms of severe T-cell immunodeficiency.

Defects of Thymocyte Egress and of Lymphocyte Activation

Once they have completed their intrathymic maturation, T lymphocytes are exported to the periphery. This process requires active cytoskeleton reorganization. Coronin 1A is an actin regulator that plays a key role in regulating thymocytes egress and trafficking of naïve T lymphocytes to secondary lymphoid organs. Coronin 1A mutations have been shown to cause peripheral T-cell lymphopenia and severe and recurrent infections. The disease can be cured by HCT.

In the periphery, activation of T lymphocytes requires mobilization of intracellular calcium stores and influx of extracellular calcium across calcium-release activation channels (CRACs). Mutations of Orai1 (a component of CRAC channels) and of Stim1 (a sensor of Ca^{2+} concentration in the endoplasmic reticulum) have been identified in patients whose clinical features resembled SCID, associated with non progressive myopathy autoimmune cytopenias. In these patients, the number of circulating T lymphocytes is normal, but in vitro proliferation to mitogens is drastically decreased. The disease is fatal, unless immune reconstitution is achieved following HCT. However, myopathy persists.

Defects of Thymic Development

DiGeorge Syndrome

The DiGeorge Syndrome (DGS) is a disorder caused by impaired migration of neural crest cells of the third and fourth pharyngeal arches during early embryonic development. This abnormality causes impaired formation of the thymus and of the parathyroid glands, defects of the aortic arch, and facial dysmorphisms. However, significant variability of the clinical phenotype, and especially of the immunological phenotype, can be observed. Neonatal hypocalcemia is characteristic and reflects hypoparathyroidism. Approximately 80% of infants with DGS require calcium supplementation and/or treatment with calcitriol; however, hypoparathyroidism often resolves during the first year of life due to hypertrophy of residual parathyroid tissue. Cardiac malformations affect the outflow tract in particular. Interrupted aortic arch, Fallot's tetralogy, and truncus arteriosus are particularly common. Facial dysmorphisms include low-set ears with abnormal folding of the pinna, short nasal philtrum, and micrognathia. Velopharyngeal insufficiency is also very common. Feeding difficulties, mostly due to esophageal dysmotility and gastroesophageal reflux, may represent a significant concern. Laryngomalacia and aspiration pneumonia are common. During adult life, psychiatric and behavioral problems have been frequently diagnosed.

The immunodeficiency is an important component of DGS, but its severity is variable. Most patients present with *partial DiGeorge syndrome*, characterized by mild to moderate immune deficiency, with a low but detectable number of circulating T lymphocytes. The *complete DiGeorge syndrome* phenotype consists of congenital cardiac defects, hypocalcemia due to parathyroid insufficiency, and profound T-cell immune deficiency as a consequence of thymic aplasia. Finally, a few patients with DGS may present with an atypical phenotype characterized by a pronounced erythematous rash and lymphadenopathy, associated with oligoclonal, activated, and anergic T cells. This phenotype, which mimics Omenn syndrome, is also known as *complete atypical DiGeorge syndrome*. The different degrees of immunological impairment in patients with DGS dictate the spectrum of clinical manifestations related to immune dysfunction. Oral thrush and recurrent infections are common; however, patients with complete and atypical complete DGS suffer from early onset and severe infections (*P. jiroveci* pneumonia, interstitial pneumonia, or disseminated infections of viral origin) and warrant immediate attention. Autoimmune manifestations are also relatively common in patients with DGS.

DGS may be sustained by different mechanisms. Hemizygous deletion of chromosome 22q11.2 accounts for DGS in 55–65% of the patients. CHARGE association is responsible for about 25% of the cases of DGS, whereas diabetic embryopathy and monosomy of chromosome 10p have been documented in 15% and 2% of the patients, respectively. The 22q11.2 region contains the TBX1 gene that encodes for a transcription factor; isolated mutations of this gene have been identified in a few patients with DGS.

Diagnosis of DGS is based on typical clinical features, and should not be restricted to patients with 22q11 deletion, that can be demonstrated by FISH. ALC and enumeration of CD3 count is important to define the degree of immunological impairment. In most cases, variable CD3 lymphopenia is documented; however, a severe deficiency of circulating T cells is typical of complete DGS. The total CD3 count can be normal in patients with atypical complete DGS, but in these cases the circulating CD3+ T cells co-express activation (CD45R0, DR, CD25) antigens, there are very few if any recent thymic emigrants ($CD4^+$ $CD45RA^+$ $CD31^+$) in the peripheray, and the TCR repertoire of circulating T cells is severely restricted. In vitro proliferative responses are most often normal in patients with partial DGS, but are significantly reduced in the most severe cases. Most patients with DGS have normal immunoglobulin levels and antibody responses; however, impairment of humoral immunity can be also observed. Treatment of DGS consists of correction of congenital heart defects, when present, and of hypocalcemia. Depending on the severity of the immune deficiency, patients may require antibiotic prophylaxis; IVIG replacement therapy may be needed in selected cases. However, complete DGS (including atypical presentation) is associated with a very high mortality rate early in life. In such cases, survival strictly depends on immune reconstitution. Thymic transplantation is the treatment of choice. The thymus, usually obtained from infants undergoing partial thymectomy at the time of heart surgery, is sliced, cultured, and then implanted in the quadriceps muscle. T cells develop approximately 4–5 months after thymic transplantation in patients with complete DGS, and 1-year survival is close to 75%. Patients with complete atypical DGS often require immune suppression prior to thymic transplantation, to control the effects of activated and oligoclonal T cells. Unmanipulated bone marrow transpplantation from HLA-identical related donors has been also used with success in infants with complete DGS; in these cases, long-term immune reconstitution has been

provided by mature T cells contained in the graft, which have expanded and persisted for up to 20 years.

FOXN1 Deficiency

The transcription factor FOXN1 is essential to promote differentiation of thymic epithelial cells. In mice, Foxn1 mutations are associated with the nude/scid phenotype, with lack of circulating T cells and of hair. Mutations of the FOXN1 gene have been identified in Italian siblings who presented with severe infections, alopecia, and nail dystrophy. One of the affected siblings also showed features of Omenn syndrome. The immunological phenotype consisted of T-cell lymphopenia that involved predominantly the $CD4^+$ subset. Immune reconstitution was obtained in one of the siblings following unmanipulated bone marrow transplantation from her healthy HLA-matched brother.

Conclusions

Irrespective of the specific diagnosis, all forms of T-cell immunodeficiencies are characterized by significant morbidity and some of them also by high early-onset mortality rates, thus emphasizing the critical role played by T lymphocytes in ensuring effective immune defense mechanisms and in maintaining homeostasis. Therefore, accurate clinical and laboratory evaluation are critically important in patients with a putative T-cell immunodeficiency. Whereas the clinical and family history and physical examination may disclose the diagnosis in some forms of T-cell immunodeficiency, laboratory evaluation is most often required to provide a definitive diagnosis. Simple laboratory assays (total lymphocyte count and subsets distribution, in vitro proliferative responses) are usually sufficient to confirm the suspicion. Some forms of T-cell immunodeficiencies, and SCID in particular, represent true medical emergencies that warrant prompt and accurate evaluation and early treatment by HCT.

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On-Line Resources for Parents

For SCID: http://www.info4pi.org/aboutPI/index.cfm?section=aboutPI&content=syndromes&area=6&CFID=2813523&CFTOKEN=3

For DiGeorge Syndrome

http://www.info4pi.org/aboutPI/index.cfm?section=aboutPI&content=syndromes&area=3&CFID=2813523&CFTOKEN=3

On-Line Resources for Professionals

http://www.usidnet.org/

http://www.esid.org