AIDS and Other Immunodeficiencies

Immunodeficiencies

A condition resulting from a genetic or developmental defect in the immune system is called a primary immunodeficiency.

A primary immunodeficiency may affect either adaptive or innate immune functions.

Secondary immunodeficiency, or acquired immunodeficiency, is the loss of immune function and results from exposure to various agents.

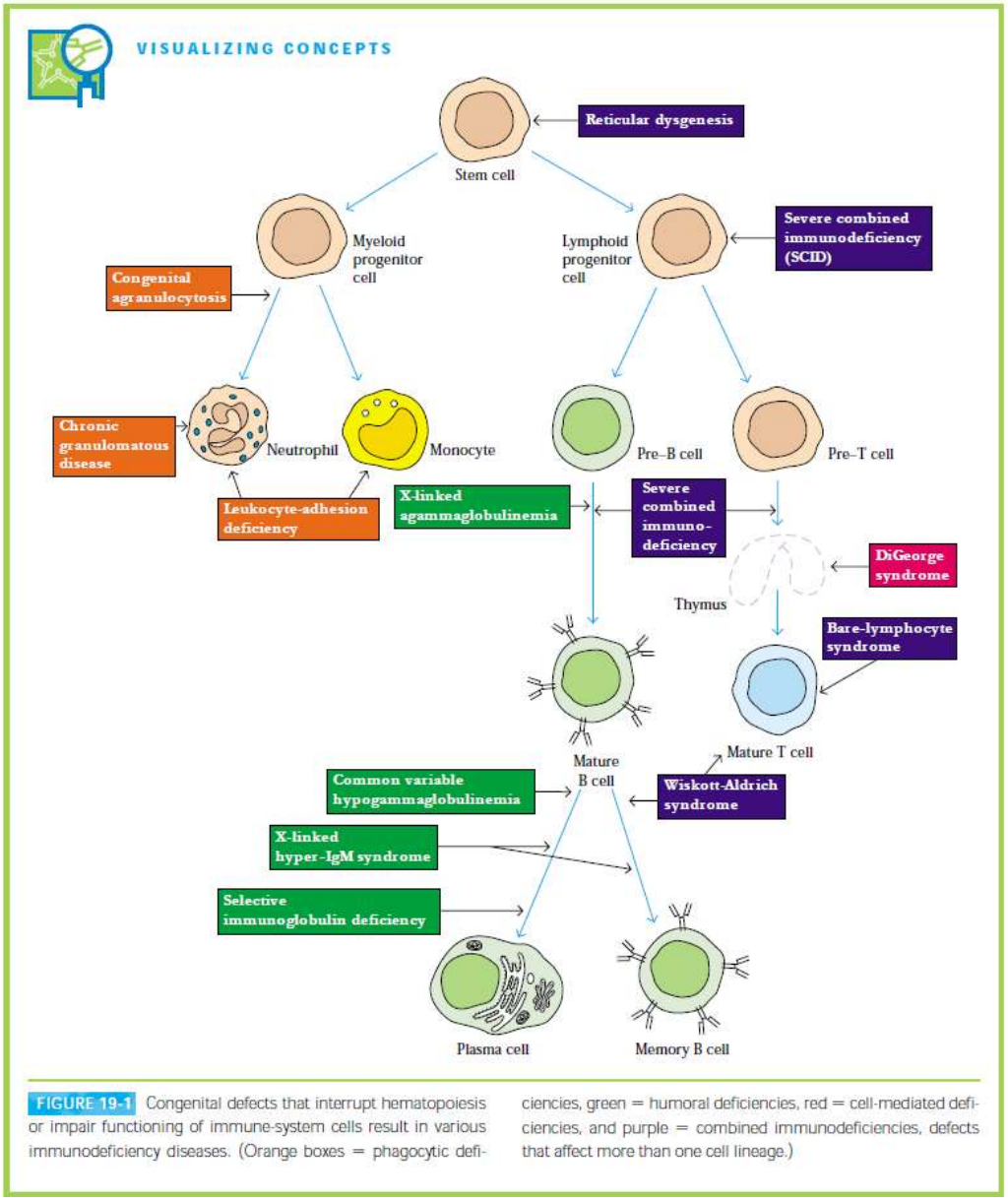

FIGURE 19-1 Congenital defects that interrupt hematopoiesis or impair functioning of immune-system cells result in various immunodeficiency diseases. (Orange boxes = phagocytic deficiencies, green = humoral deficiencies, red = cell-mediated deficiencies, and purple = combined immunodeficiencies, defects that affect more than one cell lineage.)

Congenital defects that interrupt hematopoiesis or impair functioning of immune-system cells result in various mmunodeficiency diseases.

TABLE 19-1 Some primary human immunodeficiency diseases and underlying genetic defects

Immunodeficiency disease	Specific defect	Impaired function	Inheritance mode*	Chromosomal defect
Severe combined immunodeficiency (SCID)	RAG-1/RAG-2 deficiency	No TCR or Ig gene rearrangement	AR	11p13
	ADA deficiency	Toxic metabolite in T and B cells	AR	20q13
	PNP deficiency		AR	14q13
	JAK-3 deficiency	Defective signals from IL-2, 4, 7, 9, 15,	AR	19p13
	IL-2Rγ-deficiency		XL	Xq13
	ZAP-70 deficiency	Defective signal from TCR	AR	2q12
Bare lymphocyte syndrome	Defect in MHC class II gene promoter	No class II MHC molecules	AR	16p13
Wiskott-Aldrich syndrome (WAS)	Cytoskeletal protein (CD43)	Defective T cells and platelets	XL	Xp11
Interferon gamma receptor	IFN-γ–receptor defect	Impaired immunity to mycobacteria	AR	6q23
DiGeorge syndrome	Thymic aplasia	T- and B-cell development	AD	22q11
Ataxia telangiectasia	Defective cell-cycle kinase	Low IgA, IgE	AR	11q22
Gammaglobulinemias	X-linked agammaglobulinemia	Bruton's tyrosine kinase (Btk); no mature B cells	XL	Xq21
	X-linked hyper-IgM syndrome	Defective CD40 ligand	XL	Xq26
	Common variable immunodeficiency	Low IgG, IgA; variable IgM	Complex	
	Selective IgA deficiency	Low or no IgA	Complex	
Chronic granulomatous disease	Cyt $p91^{phox}$	No oxidative burst for bacterial killing	XL	Xp21
	Cyt $p67^{phox}$		AR	1q25
	Cyt $p22^{phox}$		AR	16q24
Chediak-Higashi syndrome	Defective intracellular transport protein (LYST)	Inability to lyse bacteria	AR	1q42
Leukocyte-adhesion defect	Defective integrin β2 (CD18)	Leukocyte extravasation	AR	21q22

*AR = autosomal recessive; AD = autosomal dominant; XL = X linked; "Complex" indicates conditions for which precise genetic data are not available and that may involve several interacting loci.

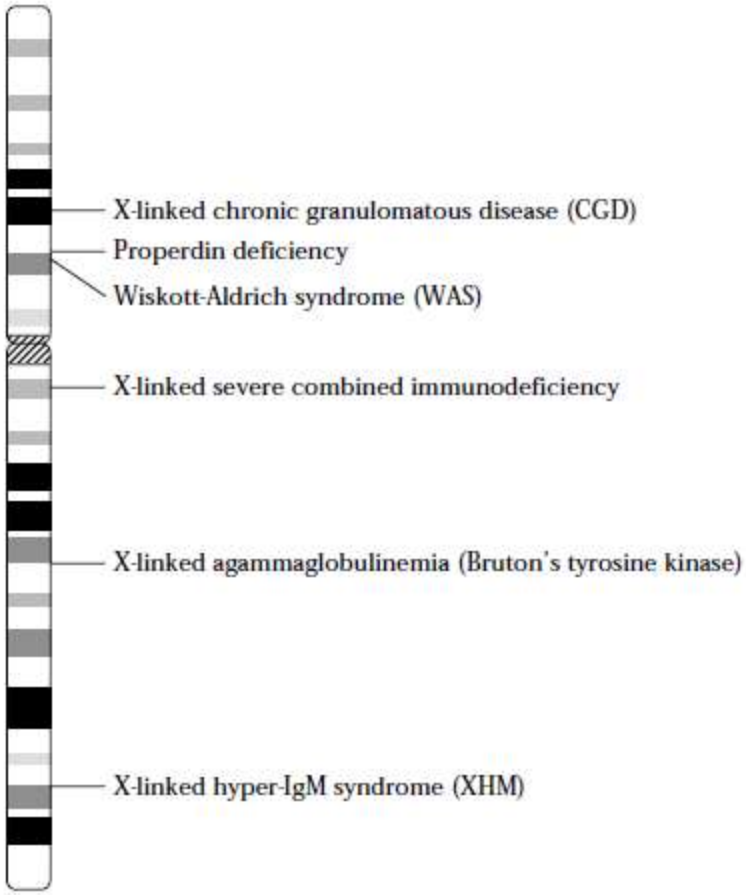

FIGURE 19-2 Several X-linked immunodeficiency diseases result from defects in loci on the X chromosome. *[Data from the Natl. Center for Biotechnology Information Web site.]*

SEVERE COMBINED IMMUNODEFICIENCY (SCID)

The family of disorders termed SCID stems from defects in lymphoid development that affect either T cells or both T and B cells.

Clinically, SCID is characterized by a very low number of circulating lymphocytes.

The thymus does not develop, and the few circulating T cells in the SCID patient do not respond to stimulation by mitogens, indicating that they cannot proliferate in response to antigens.

SCID results in severe recurrent infections and is usually fatal in the early years of life

Defects in cell interaction and signaling can lead to severe immunodeficiency.

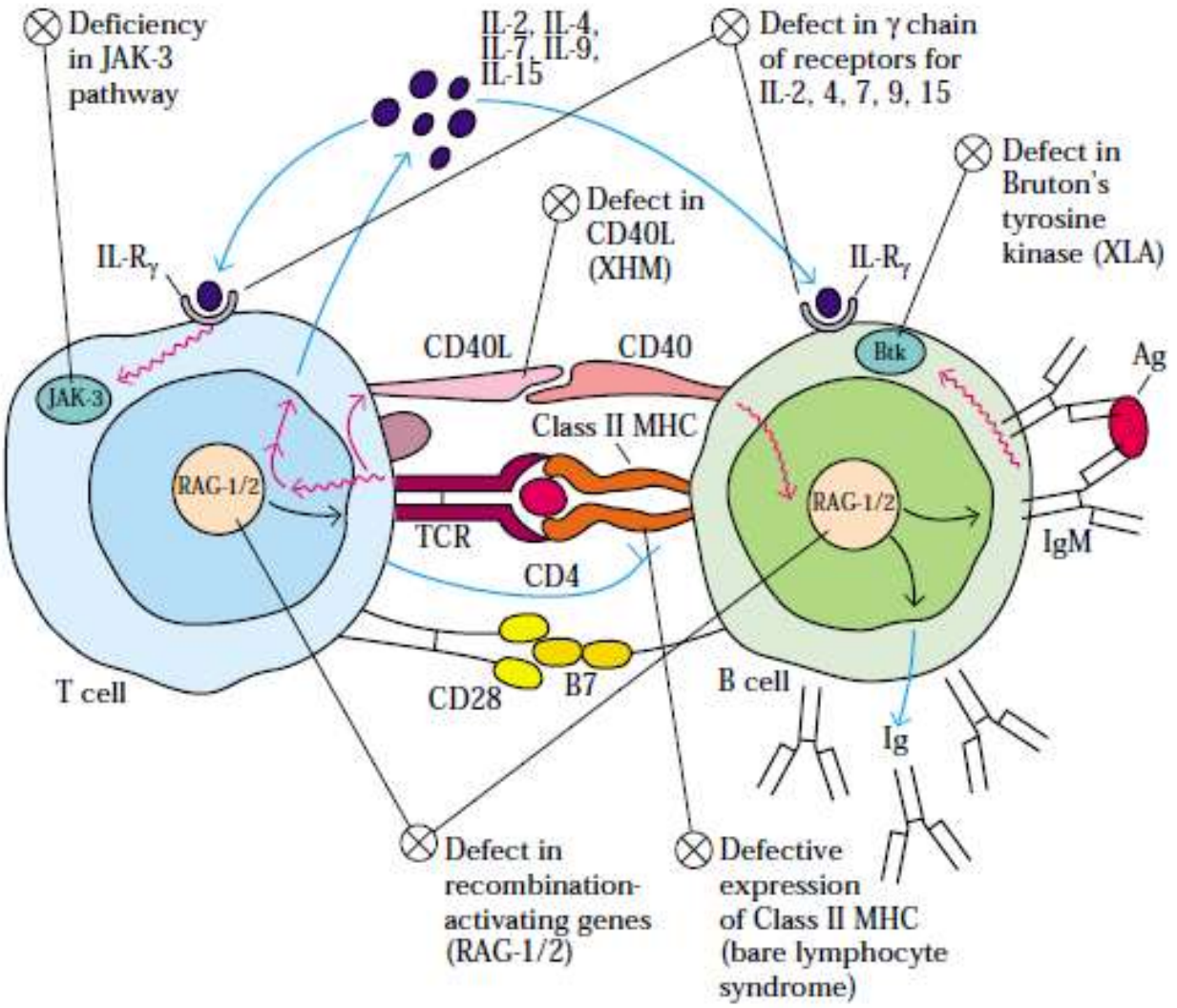

FIGURE 19-3 Defects in cell interaction and signaling can lead to severe immunodeficiency. The interaction of T cell and B cell is shown here with a number of the components important to the intra- and extracellular signaling pathways. A number of primary immunodeficiencies are rooted in defects in these interactions. SCID may result from defects in (1) the recombination-activating genes (*RAG-1* and *-2*) required for synthesis of the functional immunoglobulins and T-cell receptors that characterize mature B and T cells; (2) the γ chain of receptors for IL-2, 4, 7, 9, and 15 (IL-Rγ); (3) JAK-3, which transduces signals from the gamma chain of the cytokine receptor; or (4) expression of the class II MHC molecule (bare lymphocyte syndrome). XLA results from defective transduction of activating signals from the cell-surface IgM by Bruton's tyrosine kinase (Btk). XHM results from defects in CD40L that preclude normal maturation of B cells. *[Adapted from B. A. Smart and H. D. Ochs, 1997,* Curr. Opin. Pediatr. ***9:****570.]*

Immunodeficiencies of the Myeloid Lineage Affect Innate Immunity

REDUCTION IN NEUTROPHIL COUNT

Congenital neutropenia is often due to a genetic defect that affects the myeloid progenitor stem cell; it results in reduced production of neutrophils during hematopoiesis

CHRONIC GRANULOMATOUS DISEASE (CGD)

This disease is rooted in a defect in the oxidative pathway by which phagocytes generate hydrogen peroxide and the resulting reactive products, such as hypochlorous acid, that kill phagocytosedbacteria. CGD sufferers undergo excessive inflammatory reactions

CHEDIAK-HIGASHI SYNDROME

Phagocytes from patients with this immune defect contain giant granules but do not have the ability to kill bacteria.The molecular basis of the defect is a mutation in a protein (LYST) involved in the regulation of intracellular trafficking.

LEUKOCYTE ADHESION DEFICIENCY (LAD)

cell-surface molecules belonging to the integrin family of proteins function as adhesion molecules. An immunodeficiency related to dysfunction of the adhesion molecules