Primary Immunodeficiency Disorders

- Chapter 23
- Molecular basis of congenital immunodeficiencies
- Immune consequences of defects in hematopoesis
- Consequences of defects in the function of immune cell types
- Types of infection that are likely in various immunodeficient states
- Clinical features of various immunodeficient states

Primary Immune Deficiency

Table 23.2 Common clinical manifestations of primary immune deficiency

Bacterial infections
Invasive bacterial disease
Recurrent or prolonged respiratory tract illness including recurrent otitis and/or sinusitis
Bronchiectasis
Lung, hepatic, or splenic abscess
Gingivitis
Recurrent cutaneous abscesses
Viral infections
Disseminated varicella
Recurrent herpes zoster
Paralytic polio due to vaccine strain (oral polio vaccine)
Chronic enteroviral meningoencephalitis
Giant cell pneumonia secondary to measles or measles vaccine virus
Severe Epstein-Barr virus disease
Fungal infections
Mucocutaneous candidiasis
PCP

Molecular basis of congenital immunodeficiencies

Table 23.1 Molecular defects associated with immunodeficiency

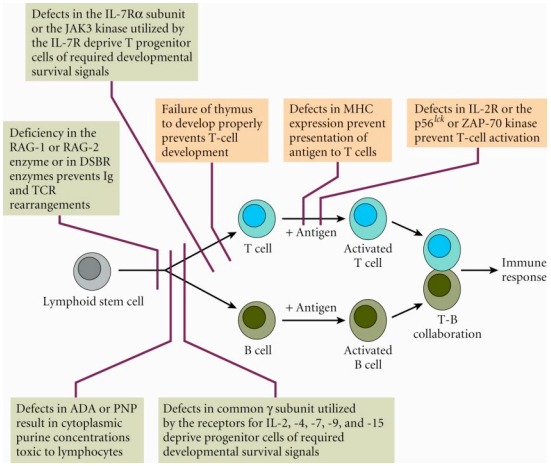
Defective protein	Name of deficiency	Phenotype
Growth factors and receptors		
IL-2	SCID	T-cell activation not possible
IL-7, IL-7R[a]	SCID	No T-cell maturation
γc	SCID	No T-cell or B-cell maturation
Regulatory/activational receptors		
CD40, CD40L	Hyper-IgM syndrome	No T-cell-dependent humoral responses, no class switching
Cellular metabolism		
PNP, ADA	SCID	No T-cell or B-cell maturation
phox, MPO	CGD	Inefficient phagocytic killing
Cell adhesion molecules		
CD18 (β2 integrin)	LAD	Leukocytes cannot extravasate
Antigen presentation machinery		
TAP-1/2	Bare lymphocyte syndrome	Low expression of MHC class I
Transcription factors		
CIITA, RFX	Bare lymphocyte syndrome	No expression of MHC class II
DNA recombination and repair		
RAG-1/2, DNA-PK, XRCC4, ligase-IV	SCID	No V(D)J recombination
Complement proteins		
C3		Susceptibility to infection by all bacteria
C4, C2		Immune complex disorders owing to poor clearance of complexes
C5, C6, C7, C8, C9		Susceptibility to infection by gram-negative bacteria

[a]IL-R, interleukin receptor; γc, common gamma subunit of IL-2 cytokine receptor subfamily; phox, phagocyte oxidase; MPO, myeloperoxidase; DNA-PK, DNA-dependent protein kinase.

Defects in Lymphocyte Development and Function

- Immunodeficiencies due to lack of T and B cells or lack of T and B cell function
- Severe Combined Immunodeficiency (SCID)
  - Deficiency in T cells only result in SCID due to a lack of T helper cell help to B cells
- Omenn syndrome: RAG-1 and/or RAG-2 mutations
  - Graft vs host-like disease
- Ataxia Telangiectasia: autosomal recessive defective ATM gene
  - Compromised T cell function
- X-linked SCID: common gamma subunit defects
  - "boy in the bubble" disease
- DiGeorge syndrome: loss of thymus and T cell development
- Bare Lymphocyte Syndrome: autosomal recessive
  - Loss of expression of MHC I or MHC II

Defects in Lymphocyte Development and Function



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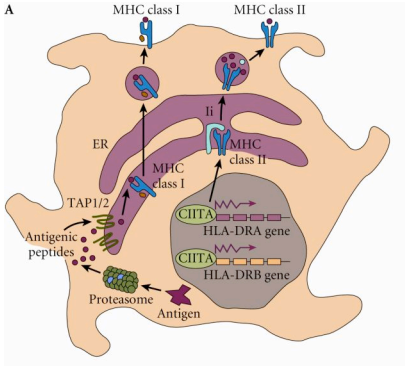
Bare Lymphocyte Syndrome



Trafficking and peptide loading by MHC I and MHC II in a normal antigen presenting cell

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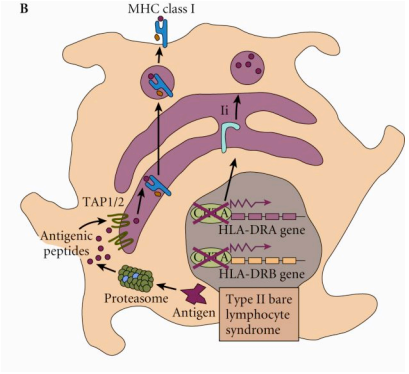
Bare Lymphocyte Syndrome



- Loss of MHC II expression
- Defect in transcription factor CIITA
- Or Defect in transcription factor RFX

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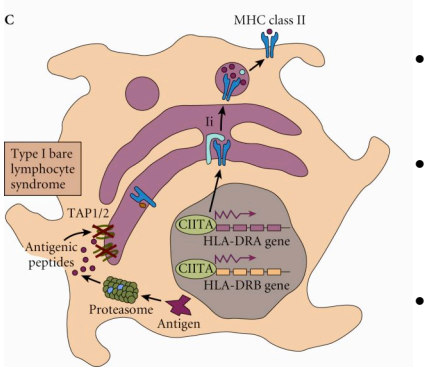
Bare Lymphocyte Syndrome



- Normal expression of MHC I protein
- No plasma membrane expression of MHC I
- Defect in TAP1/2 genes so that no peptides are loaded onto MHC I
- MHC I retained in the ER

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Table 23.4 Clinical manifestations of B-cell defects

Immune defect	Clinical manifestations
Reduced IgG (<200 mg/dl)	Invasive bacterial disease Recurrent respiratory tract disease (upper and lower) Paralytic polio secondary to vaccine strain (oral poliovirus vaccine) Chronic enteroviral meningoencephalitis Autoimmune disease
Diminished IgA and/or IgG subclass concentrations	Recurrent otitis and/or sinusitis Bronchiectasis

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Table 23.6 Clinical manifestations of T-cell deficiency or dysfunction

Defect	Clinical manifestation
Decrease in T-cell number or function	PCP Mucocutaneous candidiasis Disseminated varicella Recurrent herpes zoster Measles pneumonia Disseminated BCG infection Disseminated *Mycobacterium avium-M. intracellulare* infection

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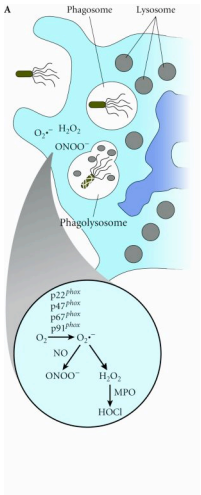

Defects in Phagocytic Killing

- Normal Phagocytosis:
- Engulf bacterium into phagosome
- Fusion of phagosome with lysosome
- Hydrolytic enzymes damage ingested bacteria
- NADPH oxidase and myeloperoxidase enzymes become activated and Oxidative burst occurs to kill bacteria

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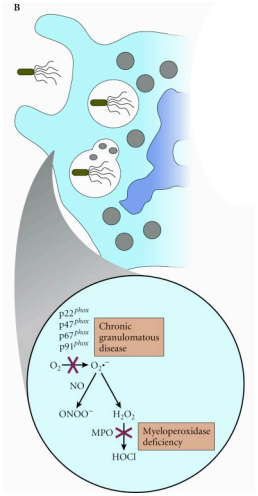

Defects in Phagocytic Killing

- Defects in the enzymes needed for oxidative burst
- NADPH oxidase and myeloperoxidase enzymes
- Hydrolytic enzymes alone cannot kill ingested microbe

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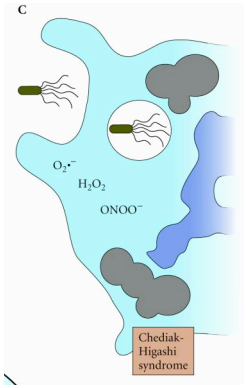
Defects in Phagocytic Killing



- Chediak-Higashi syndrome
- Defect in regulation of lysosome trafficking and fusion
- Most lysosomes fuse with each other rather than the phagosome
- Results in giant nonfunctional lysosomes
- Oxidative burst occurs normally, but cannot kill microbe without phagolysosome

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Table 23.3 Clinical manifestation of granulocyte defects

Defect	Clinical symptoms
Granulocytopenia	Omphalitis Perianal abscess Hepatic abscess Invasive bacterial disease
Granulocyte killing defect	Lung, splenic, or hepatic abscess Suppurative lymphadenitis Fungal or commensal pathogens (usually lung) Recurrent cutaneous abscesses Gingivitis

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Leukocyte Adhesion Deficiency

- LAD syndrome is caused by lack of the integrin common beta2 subunit
- LAD syndrome patients lack high affinity integrins causing
- Altered chemotaxis of cells
- Defects in cell spreading
- Random migration patterns
- Defect in diapedesis
- Failure to produce complement receptors
- No CR-mediated pathogen killing

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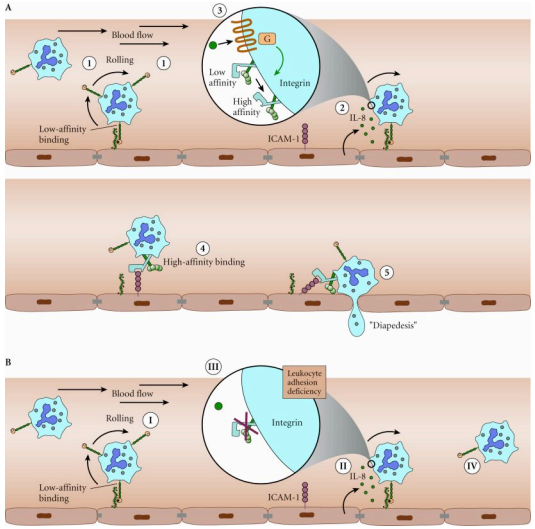

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Table 23.5 Clinical illness in association with complement deficiency

Immune defect	Clinical syndrome
C5, C6, C7, or C8 deficiency	Meningococcal sepsis or meningitis Disseminated gonococcal syndromes
C3 deficiency	Invasive bacterial disease due to encapsulated pathogens

Reticular Dysgenesis

- Most severe form of SCID
- Rare defect in bone marrow stem cells
- Unknown gene defect
- Autosomal recessive inheritance
- Defieciency of all lineages of red and white blood cells
- Severe immunodeficiency resulting in early death without bone marrow transplant

Leukopoiesis