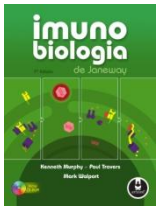
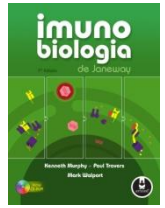
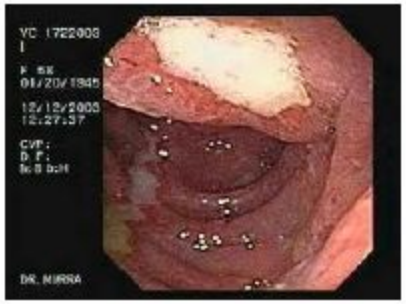


Imunodeficiências Primárias

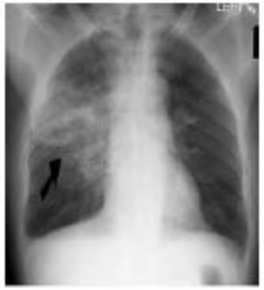
Prof. Dr. Jean Pierre Schatzmann Peron
Laboratório de Interações Neuroimunes
ICB IV - USP



Imunodeficiências – Infecções de Repetição

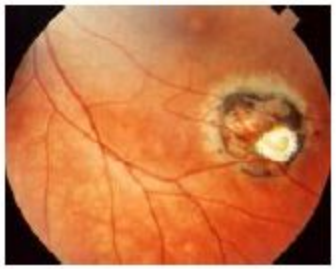


Colite

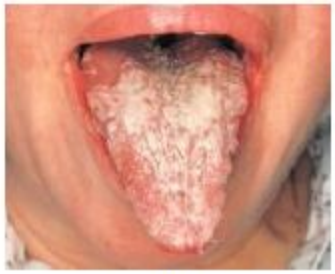


Pneumonia

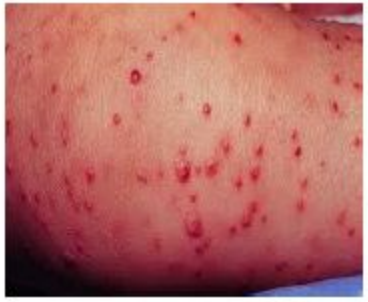
AIDS



Toxoplamose Ocular

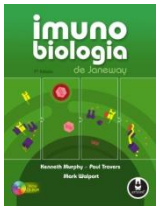


Candida



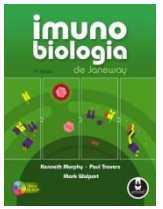
Staphilococcus

Infecções Múltiplas



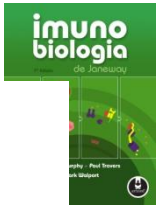
Valores de Referência para Leucócitos no Sangue

	Linfócitos B	Linfócitos T	Fagócitos	
X 10^9 por L de sangue	0,3	Total – 1-2,5 CD4 – 0,5-1,6 CD8 – 0,3-0,9	Monócitos 0,15-,06 Neutrófilos 3-5,5 Eosinófilos 0,05-0,25 Basófilos 0,02	
Análise da Função (in vivo)	Anticorpos	DTH		
Análise da função (in vitro)	Anticorpos	Linfoproliferação e secreção de citocinas	Fagocitose Killing	



Valores de Referência para Imunoglobulinas no Plasma

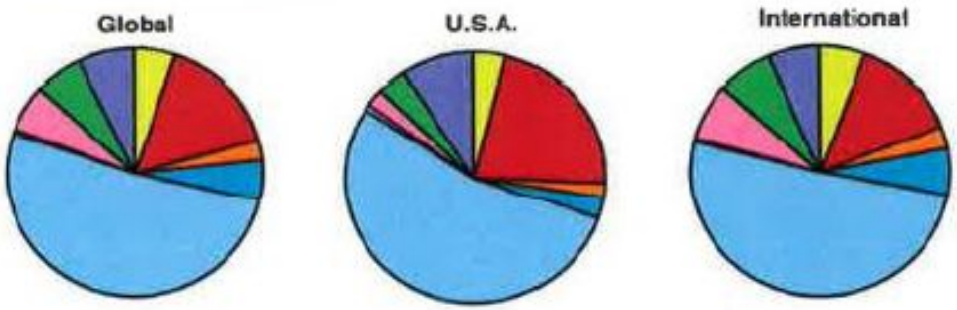
IgM	IgG	IgA	IgE	Complemento	
600-1400 mg/ dL	40-345 mg/dL	60-380 mg/dL	0-200 IU/mL	CH50 125-300 IU/mL	



Prevalência USA vs Mundo

Major Categories of PI

Categories	Global		U.S.A.		International	
Combined T and B–cell Immunodeficiencies	3,163	5.24%	608	3.90%	2,555	5.71%
Other Well Defined Immunodeficiency Syndromes	9,427	15.62%	3,413	21.88%	6,014	13.44%
Diseases of Immune Dysregulaton	1,553	2.57%	282	1.81%	1,271	2.84%
Congenital Defects of Phagocyte Numbers and Function	3,189	5.28%	461	2.95%	2,728	6.09%
Predominantly Antibody Deficiencies	31,162	51.62%	8,388	53.76%	22,774	50.88%
Defects in Innate Immunity	328	0.54%	118	0.76%	210	0.47%
Autoinflammatory Disorders	3,600	5.96%	352	2.26%	3,248	7.26%
Complement Deficiencies	3,652	6.05%	564	3.61%	3,088	6.90%
Other Immunodeficiencies	4,290	7.11%	1,416	9.08%	2,874	6.42%
Total	**60,364**		**15,602**		**44,762**	



Immunol Res (2011) 51:61–70
DOI 10.1007/s12026-011-8241-y

Global study of primary immunodeficiency diseases (PI)—diagnosis, treatment, and economic impact: an updated report from the Jeffrey Modell Foundation

Vicki Modell · Bonnie Gee · David B. Lewis · Jordan S. Orange · Chaim M. Roifman · John M. Routes · Ricardo U. Sorensen · Luigi D. Notarangelo · Fred Modell

Tipos de Imunodeficiências Encontradas

TABLE I. Combined T and B–cell immunodeficiencies	
ADA Deficiency	298
Artemis Deficiency (DCLRE1C)	101
CD3 δ / CD3 ε / CD3 ζ Deficiency	25
Cernunnos Deficiency	10
DNA Ligase IV Deficiency	14
γc Deficiency	454
IL-2Ralpha Deficiency (CD25 Deficiency)	34
IL-7R α Deficiency	98
JAK3 Deficiency	116
MHC Class I or II Deficiency	226
Omenn Syndrome	237
PNP Deficiency	38
RAG 1/2 Deficiency	312
Reticular Dysgenesis (AK2 Deficiency)	15
ZAP-70 Deficiency	51
Other SCID:	1,134
Total	3,163

TABLE II. Other well defined immunodeficiency syndromes	
Ataxia-Telangiectasia (A-T)	2,190
Ataxia-Telangiectasia like Disease (ATLD)	22
Bloom Syndrome	26
Cartilage Hair Hypoplasia	135
Chronic Mucocutaneous Candidiasis	456
Comel-Netherton Syndrome	59
DiGeorge Syndrome (DGS)	4,310
Dyskeratosis Congenita	37
Hyper IgE, AD (STAT3, Job Syndrome)	760
Hyper-IgE, AR (DOCK8, TYK2 Deficiency)	156
ICF-ID Centromeric Instability and Facial Anomalies	15
Nijmegen Breakage Syndrome	227
PMS2 Deficiency	4
Schimke Syndrome	30
Wiskott Aldrich Syndrome (WAS)	1,000
Total	9,427

TABLE III. Diseases of immune dysregulaton	
ALPS Type 1a, CD95 (fas) Defects	242
ALPS, other types	210
APECED	165
Chediak-Higashi Syndrome	174
Griscelli Syndrome Type 2	96
Hermansky Pudlak Syndrome (Type 2; AP3 deficiency)	11
HLH (other types, Munc13-4, Munc 18-2, STX11)	183
HLH Perforin Deficiency	101
IPEX (X-Linked)	80
IPEX-Like Syndrome	77
XLP1, SH2D1A Deficiency	189
XLP2, XIAP Deficiency	25
Total	1,553

TABLE IV. Congenital defects of phagocyte #s and function	
CGD, AR	964
CGD, XL	1,029
Glycogen Storage Disease Type 1b	31
Leukocyte Adhesion Deficiency I	168
Leukocyte Adhesion Deficiency II, III, and others	26
MSMD (IL-12p40, IL12RB, IFN-γR1/2, STAT1 Deficiency)	150
Neutropenia w/ Cardiac + Urogenital Malformations	12
Neutropenia, Cyclical	269
Neutropenia, Severe Congenital (ELA2, HAX1)	505
Neutropenia, XL (WASP mutation)	21
Papillon-Lefèvre Syndrome	14
Total	3,189

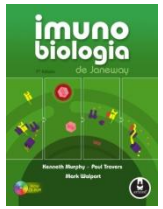


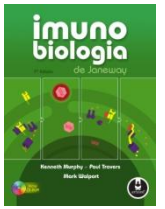
TABLE 20–1 Features of Immunodeficiencies Affecting T or B Lymphocytes

Feature	B Cell Deficiency	T Cell Deficiency
Susceptibility to infection	Pyogenic bacteria (otitis, pneumonia, meningitis, osteomyelitis), enteric bacteria and viruses, some parasites	*Pneumocystis jiroveci*, many viruses, atypical mycobacteria, fungi
Diagnosis		
Serum Ig levels	Reduced	Normal or reduced
DTH reactions to common antigens	Normal	Reduced
Morphology of lymphoid tissues	Absent or reduced follicles and germinal centers (B cell zones)	Usually normal follicles, may be reduced parafollicular cortical regions (T cell zones)

DTH, delayed-type hypersensitivity.

Consistem em Defeitos

- Nos mecanismos de reconhecimento
  - Inata: TLRs, NLRs, entre outros
  - Adaptativa: TCR, Complexo CD3,Igs
- Na sinalização
  - Fatores de Transcrição: MyD88, STATs...
- Defeitos nos mecanismos efetores da resposta imune
  - Inata: ROS (NADPH oxidase), NO (iNOS)...
  - Adaptativa: IFN-γ.



Imunodeficiências

- Imunidade Humoral:
  - Bactérias encapsuladas, bactérias formadoras de pus, viroses.
- Imunidade Celular:
  - patógenos intracelulares e viroses.
- Tumores
  - Imunovigilância
- Autoimunidade - ?

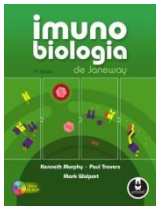
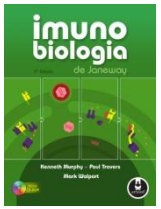
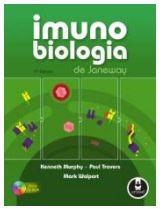


TABLE 20–3 Severe Combined Immunodeficiencies

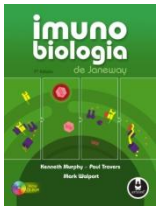
Disease	Functional Deficiencies	Mechanism of Defect
Defects in cytokine signaling		
X-linked SCID	Marked decrease in T cells; normal or increased B cells; reduced serum Ig	Cytokine receptor common γ chain mutations; defective T cell development in the absence of IL-7–derived signals
Autosomal recessive forms	Marked decrease in T cells; normal or increased B cells; reduced serum Ig	Mutations in *IL2RA, IL7RA, JAK3*
Defects in nucleotide salvage pathways		
ADA deficiency	Progressive decrease in T, B, and NK cells; reduced serum Ig	ADA deficiency caused by mutations in the gene, leading to accumulation of toxic metabolites in lymphocytes
PNP deficiency	Progressive decrease in T, B, and NK cells; reduced serum Ig	PNP deficiency caused by mutations in the gene, leading to accumulation of toxic metabolites in lymphocytes
Defects in V(D)J recombination		
RAG1 or RAG2 deficiency recombination*	Decreased T and B cells; reduced serum Ig; absence or deficiency of T and B cells	Cleavage defect during V(D)J recombination; mutations in *RAG1* or *RAG2*
Double-stranded break repair and checkpoint	Decreased T and B cells; reduced serum Ig; absence or deficiency of T and B cells	Failure to resolve hairpins during V(D)J recombination; mutations in *ARTEMIS,* DNA-PKcs, *CERNUNNOS, LIG4, NBS1, MRE11, ATM*
Defective thymus development		
Defective pre-TCR checkpoint	Decreased T cells; normal or reduced B cells; reduced serum Ig	Mutations in *CD45, CD3D, CD3E, ORAI1* (CRAC channel component), *STIM1*
DiGeorge syndrome	Decreased T cells; normal B cells; normal or reduced serum Ig	22q11 deletion; T-box 1 (*TBX1*) transcription factor mutations
FoxN1 deficiency	Thymic aplasia with defective thymic cell development	Recessive mutation in *FOXN1*



Nome da síndrome de deficiência	Anormalidade específica	Defeito imune	Suscetibilidade
Imunodeficiência combinada severa	Ver Figura 12.14		Geral
Síndrome de DiGeorge	Aplasia tímica	Números variáveis de células T e B	Geral
Deficiência do MHC de classe I	Mutações TAP	Ausência de célulasT CD8	Inflamação crônica dos pulmões e da pele
Deficiência do MHC de classe II	Ausência de expressão do MHC de classe II	Ausência de células T CDA	Geral
Síndrome de Wiskott–Aldrich	Ligada ao X; gene WASP defeitoso	Respostas humorais a polissacarídeos defeituosas e incapacidade de respostas decorrentes de ativação das células T e disfunção das células T_{reg}	Bactérias encapsuladas extracelulares
Agamaglobulinemia ligada ao X	Perda da tirosina quinase Btk	Ausência de células B	Bactérias extracelulares, vírus
Síndrome Hiper IgM	Deficiência de AID Deficiência de ligante CD40 Deficiência do CD40 Deficiência de NEMO (IKK)	Sem mudança de isotipo e/ou tripermutação somática	Bactérias extracelulares *Pneumocystis carinii* *Cryptosporidium parvum*

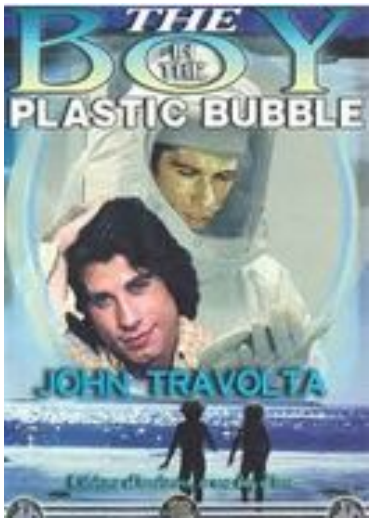


Nome da síndrome de deficiência	Anormalidade específica	Defeito imune	Suscetibilidade
Imunodeficiência variável comum	Deficiência de ICOS Outras	Defeito na produção de IgA e IgG	Bactérias extracelulares
Seletiva de IgA	Desconhecida ligada ao MHC	Nenhuma síntese de IgA	Infecções respiratórias
Deficiência de fagócitos	Muitas diferentes	Perda de função fagocitária	Bactérias e fungos extracelulares
Deficiências do complemento	Muitas diferentes	Perda de componentes específicos do complemento	Bactérias extracelulares, especialmente espécies de *Neisseria* spp.
Síndrome linfoproliferativa ligada ao X	Mutante SAP (SH2D1A)	Incapacidade de controlar o crescimento das células B	Tumores de células B induzidos pelo EBV
Ataxia telangiectasia	Mutação no domínio da quinase do ATM	Células T reduzidas	Infecções respiratórias
Síndrome de Bloom	DNA-helicase defeituosa	Células T reduzidas Níveis reduzidos de anticorpos	Infecções respiratórias



Imunodeficiência Combinada Severa (SCID)

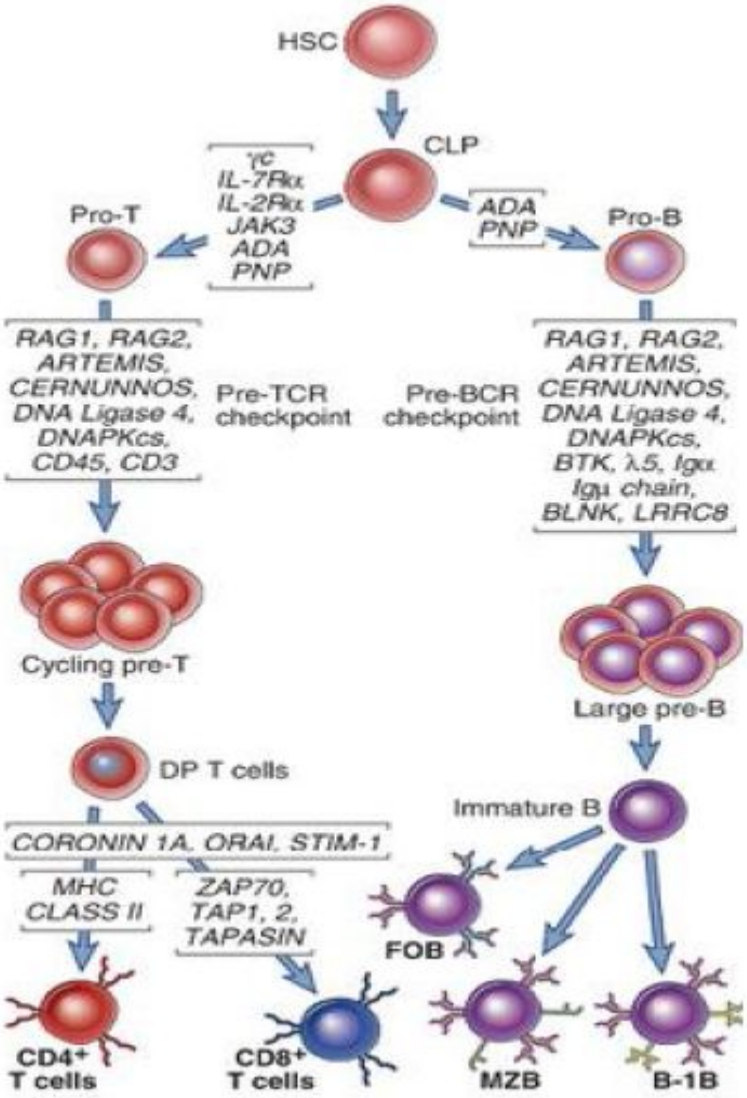
- Autossômica – Mutação nos genes RAG
  - Susceptibilidade múltiplos patógenos
- Síndrome de Omenn –
  - Mutação em RAG porém com alguns linfócitos T com função residual – Repertório muito restrito. Ausência de linfócitos B.
  - Rash cutâneo, eosinofilia, aumento dos linfonodos e diarreia.
- Adenosina deaminase (ADA) e Purine nucleotide phosphorilase (maior prevalência)
  - degradação de purina e resulta no acúmulo de metabólitos tóxicos de nucleotídeos
- Mutação na cadeia γcomum (Compartilhado pelas citocinas IL-2, IL-4, IL-7, IL-15, IL-21 e TSLP.
  - Deficiência na maturação de linfócitos T e consequentemente pouco help para linfócitos B



David Vetter (September 21, 1971 -- February 22, 1984)

https://www.youtube.com/watch?v=4CFPdUAj41Y

1971 – Houston Hospital – Primeiro transplante de coração e a primeira separação de gêmeos xifópagos.



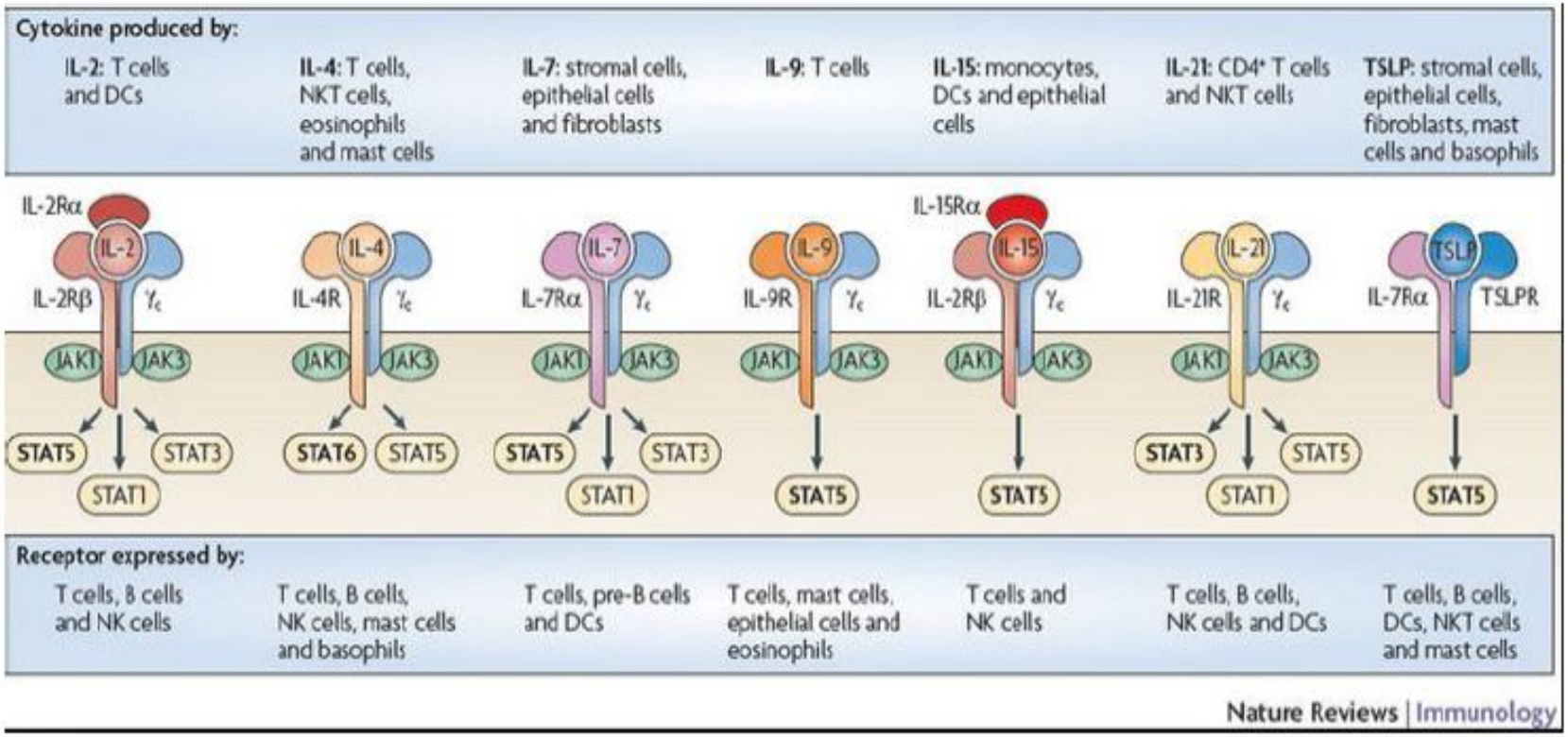
Imunodeficiência

Combinada

Severa
(SCID)

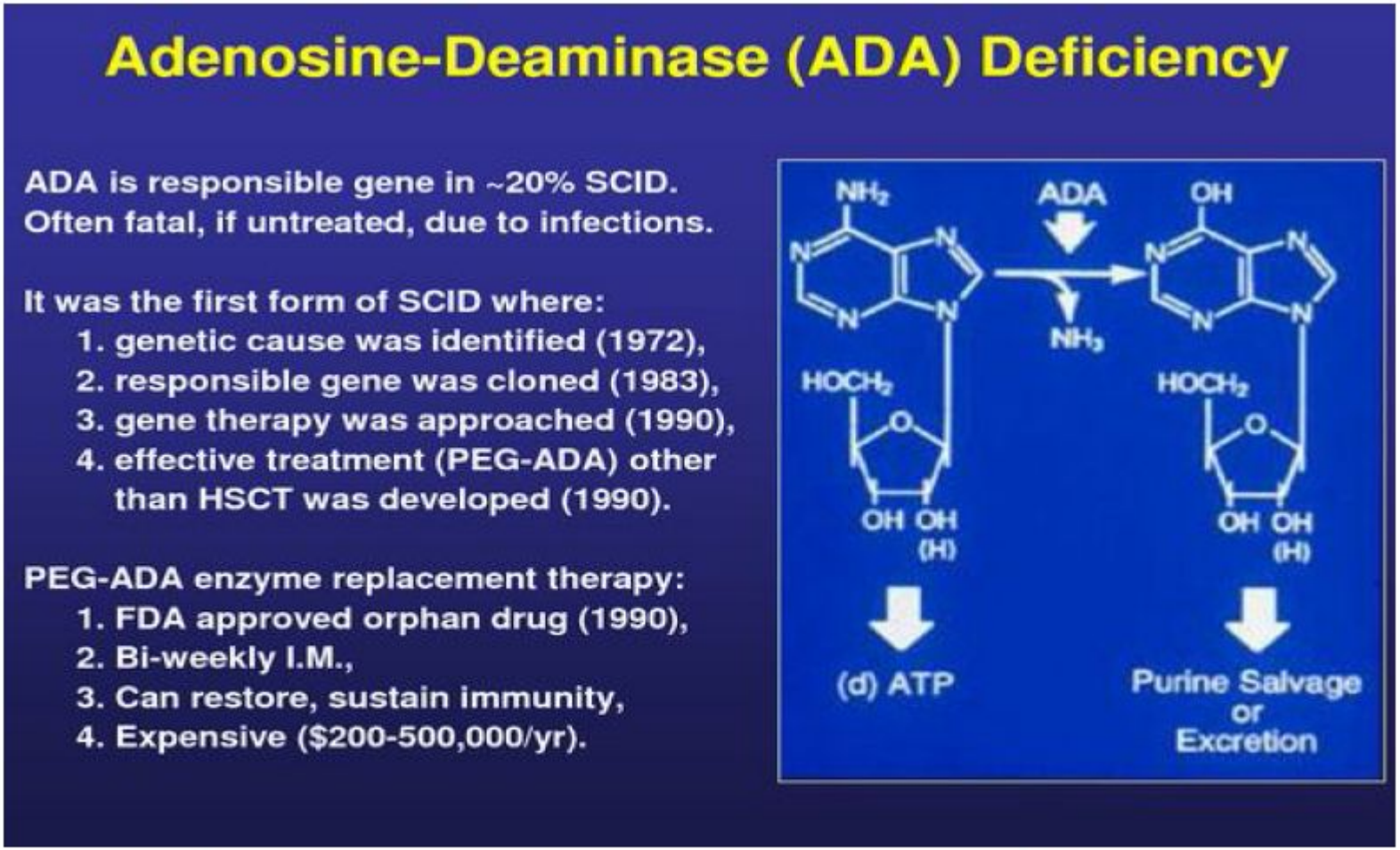
Defeitos na Geração
De Linfócitos T e B

SCID Ligada ao X



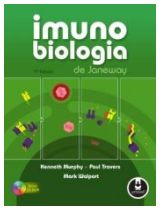
Deficiência na maturação de linfócitos T

Linfócitos ligeiramente reduzidos



ADA – Desaminação da adenosina – desoxiadenosina em inosina e desoxiadenosina.

Tóxico por inibir a síntese de DNA – Linfócitos são mais susceptíveis.



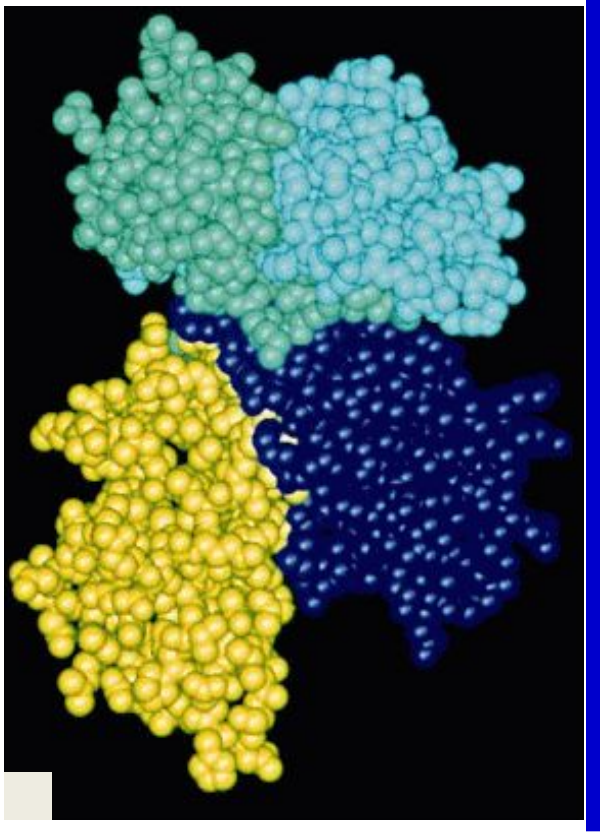
Síndrome do linfócitos nu

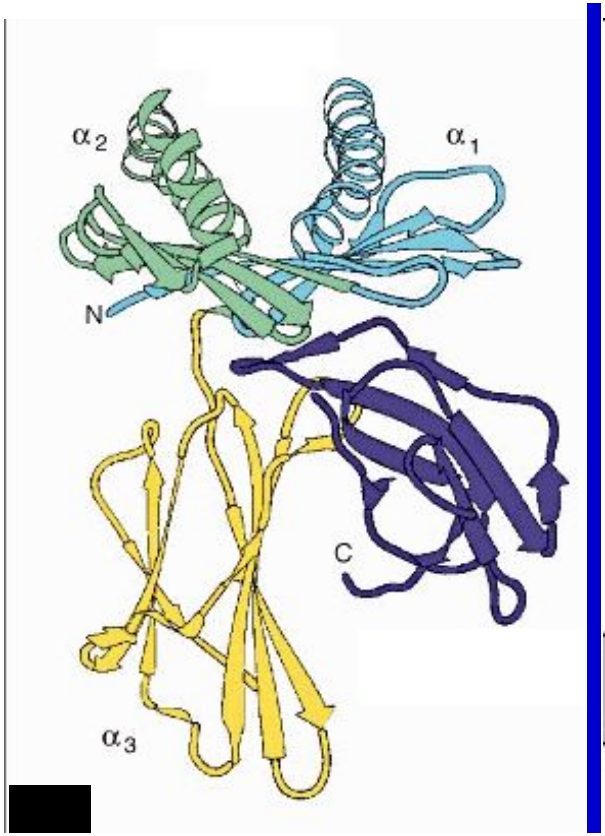
Defeitos na síntese de moléculas do MHC

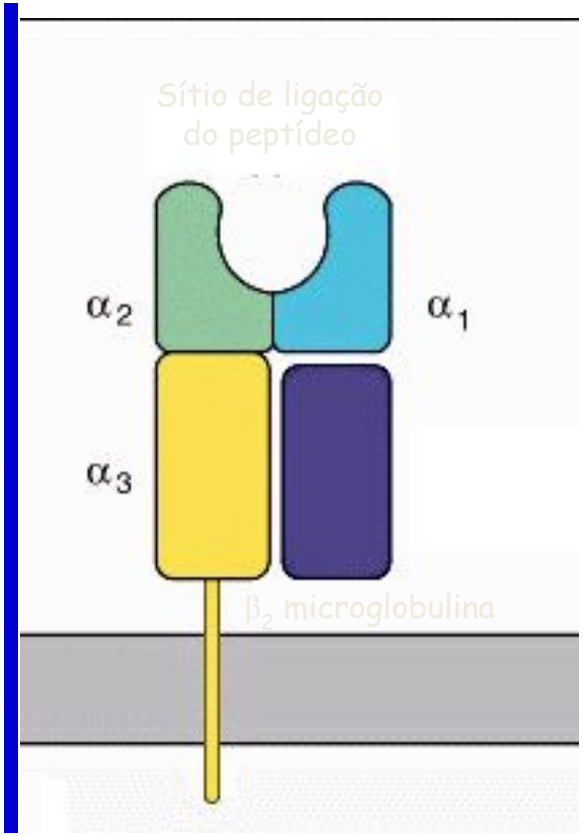
- MHC I – Comprometimento na maturação e ativação de linfócitos T CD8 – TAP ou Tapasina

- MHC II - Comprometimento na maturação e ativação de linfócitos T CD4 - CIITA

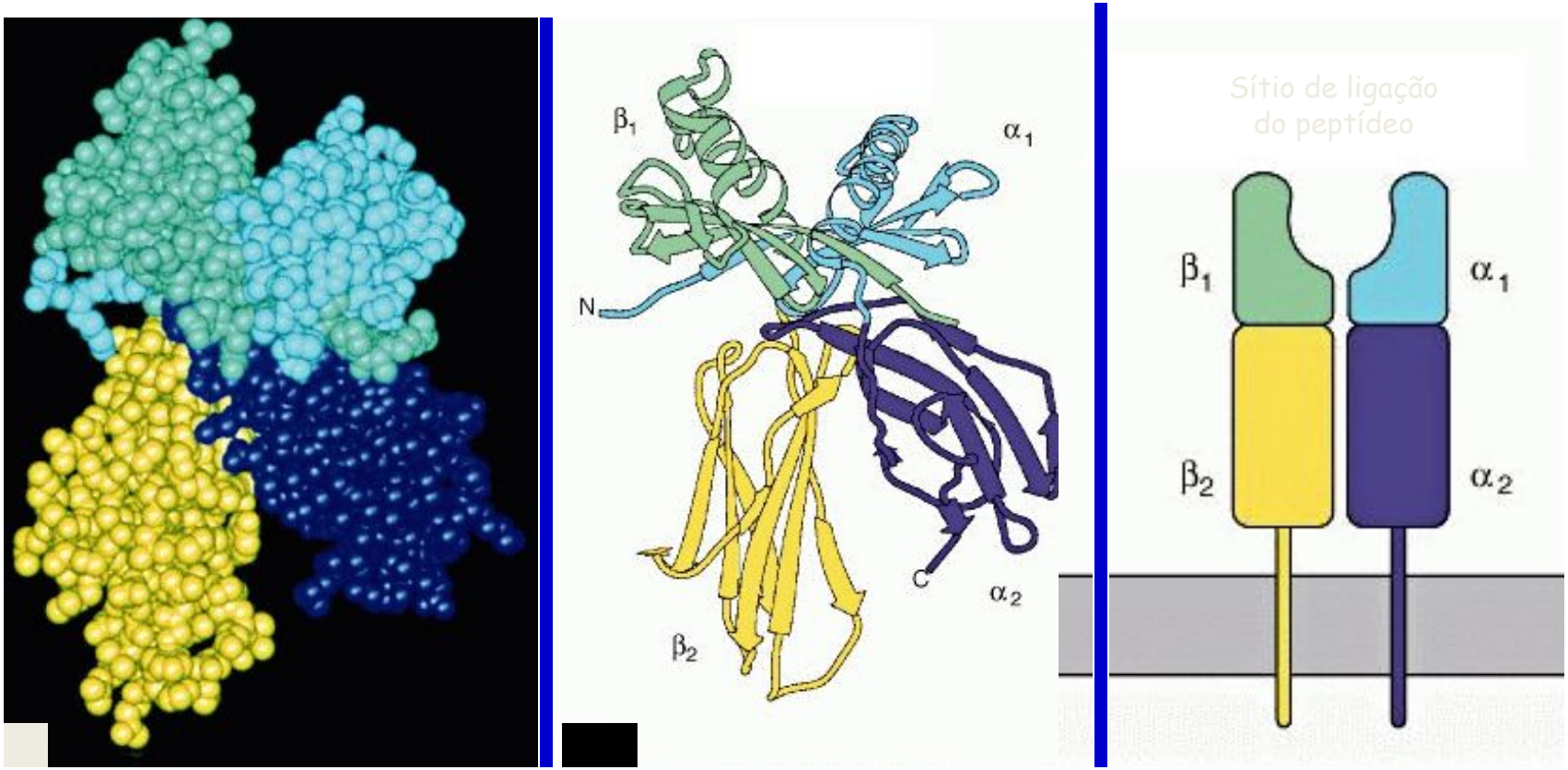
Estrutura da molécula de MHC classe I

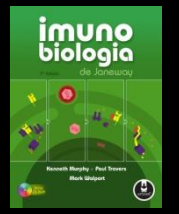




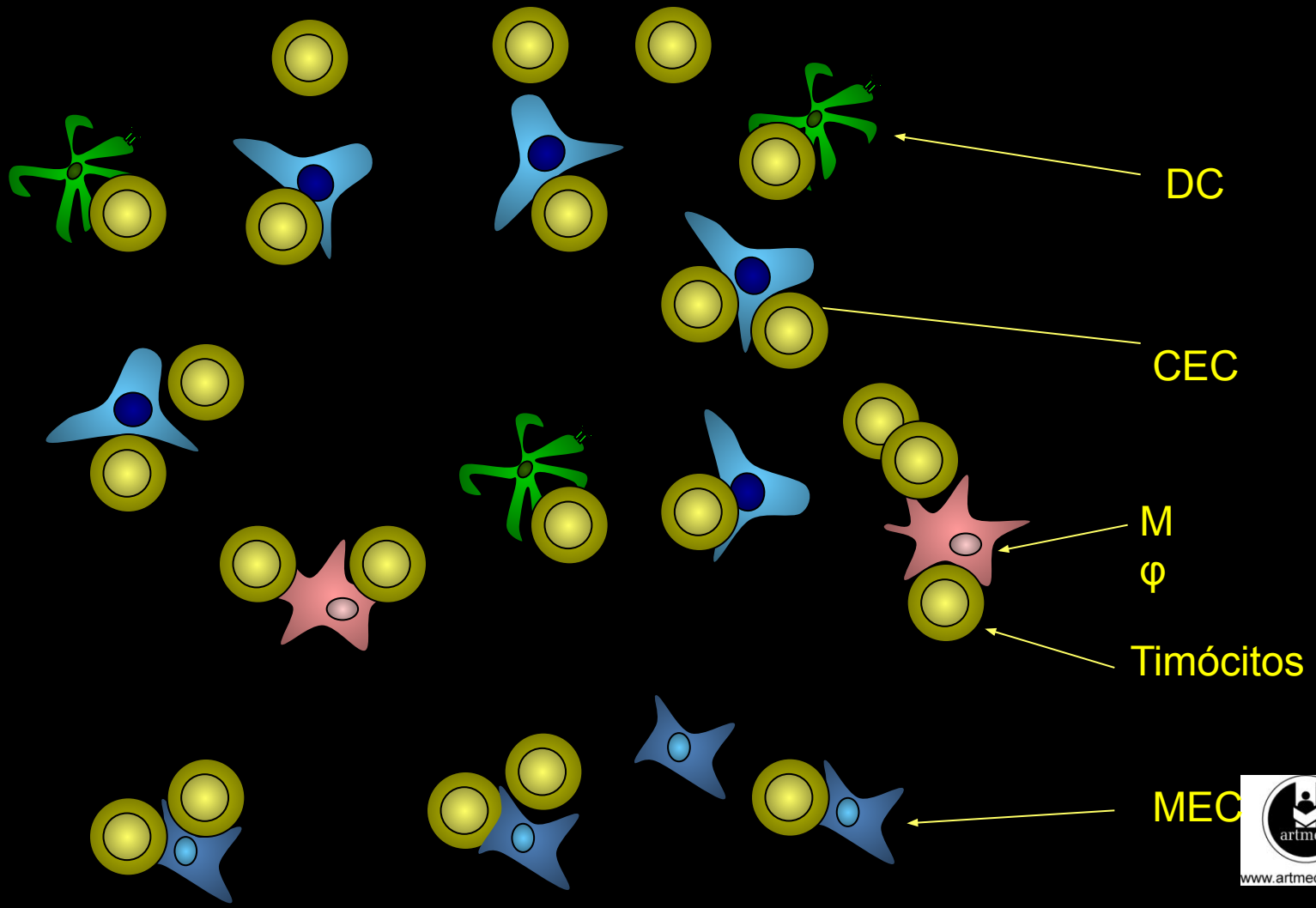


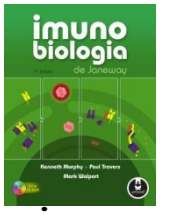
Estrutura da molécula de MHC classe II

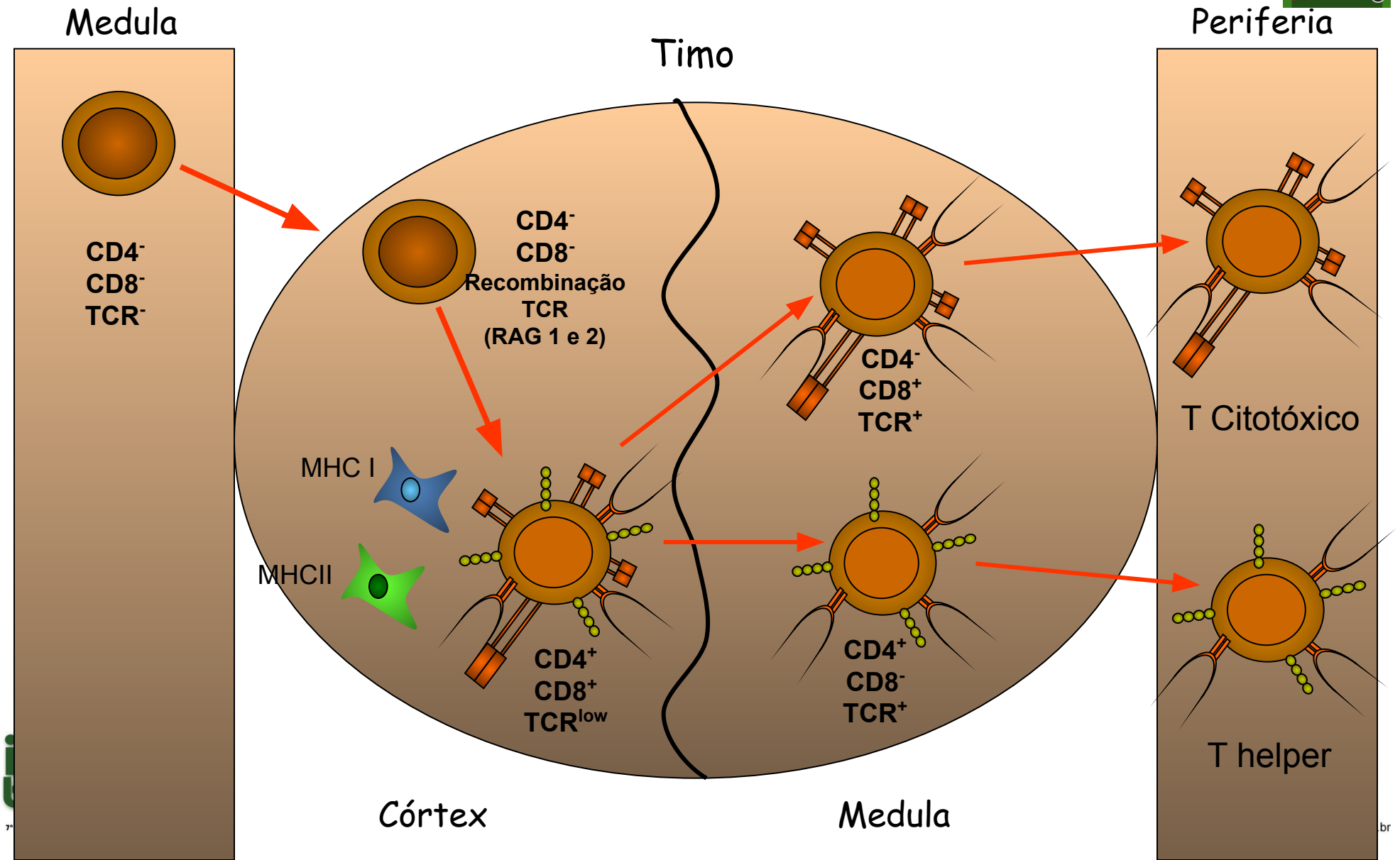


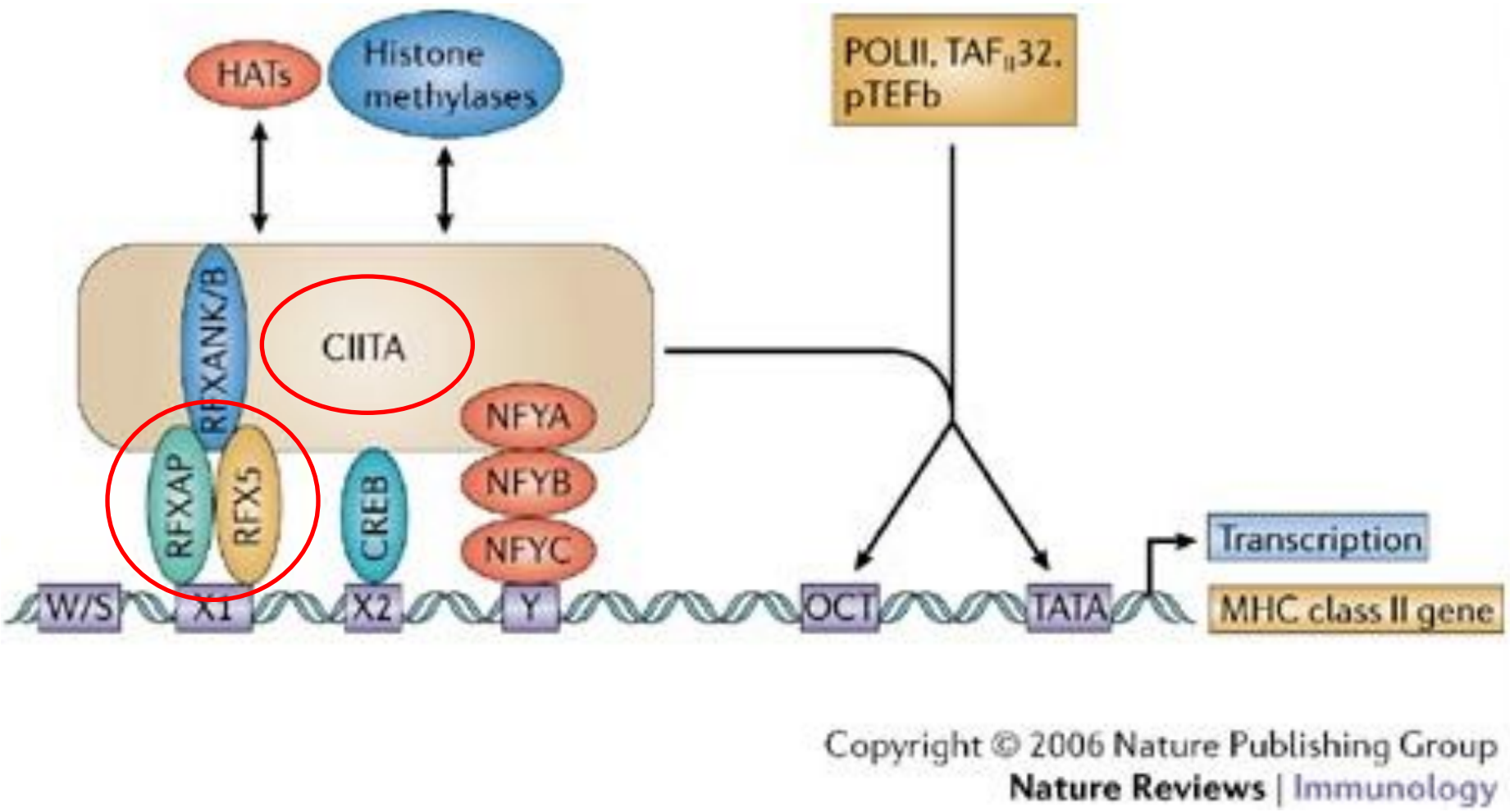


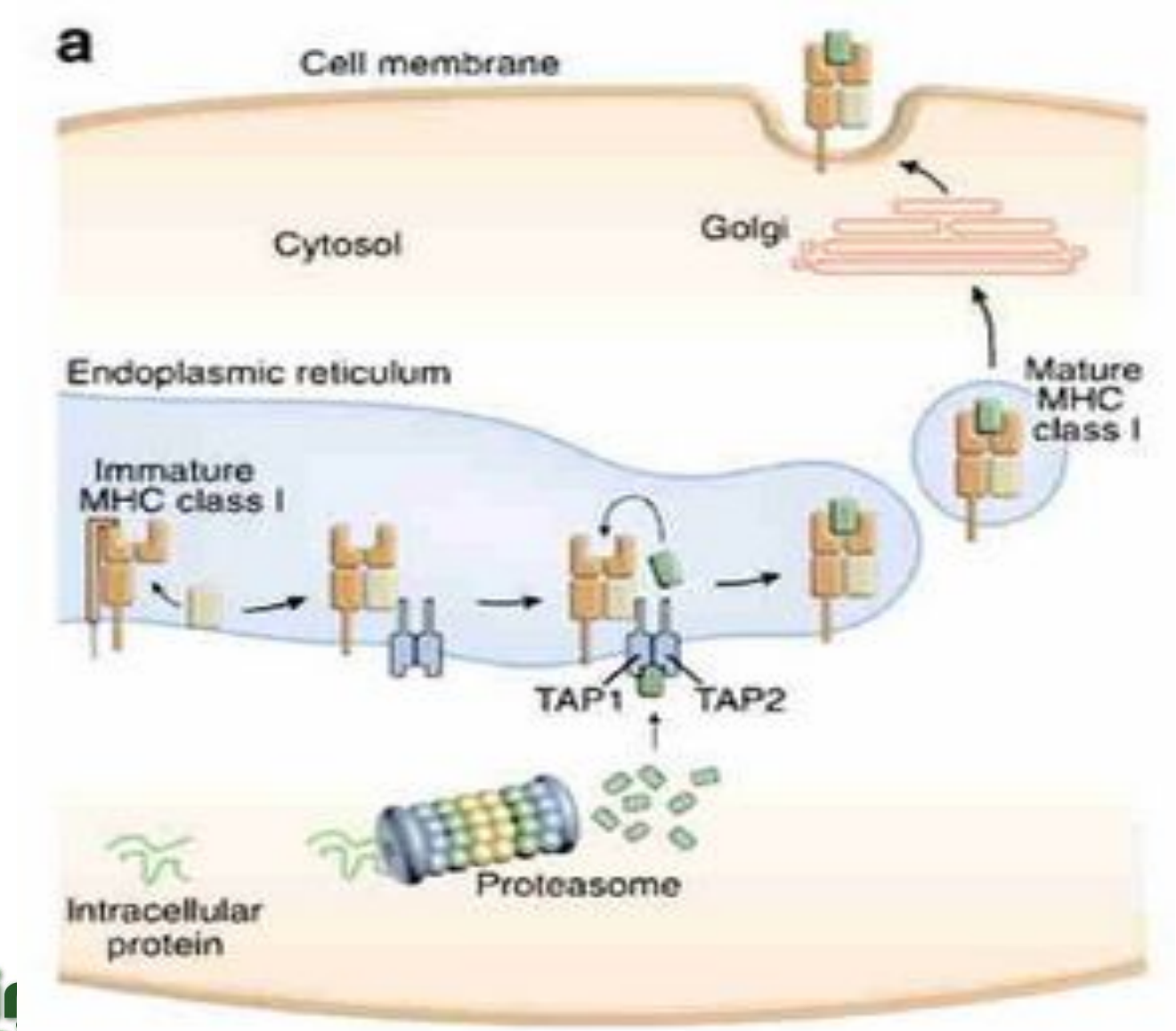
Maturação




imuno
biologia


Medula
Timo
Periferia
CD4-
CD8-
TCR-
CD4-
CD8-
Recombinação
TCR
(RAG 1 e 2)
MHC I
MHCII
CD4+
CD8+
TCRlow
CD4-
CD8+
TCR+
CD4+
CD8-
TCR+
T Citotóxico
T helper
Córtex
Medula

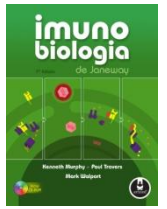




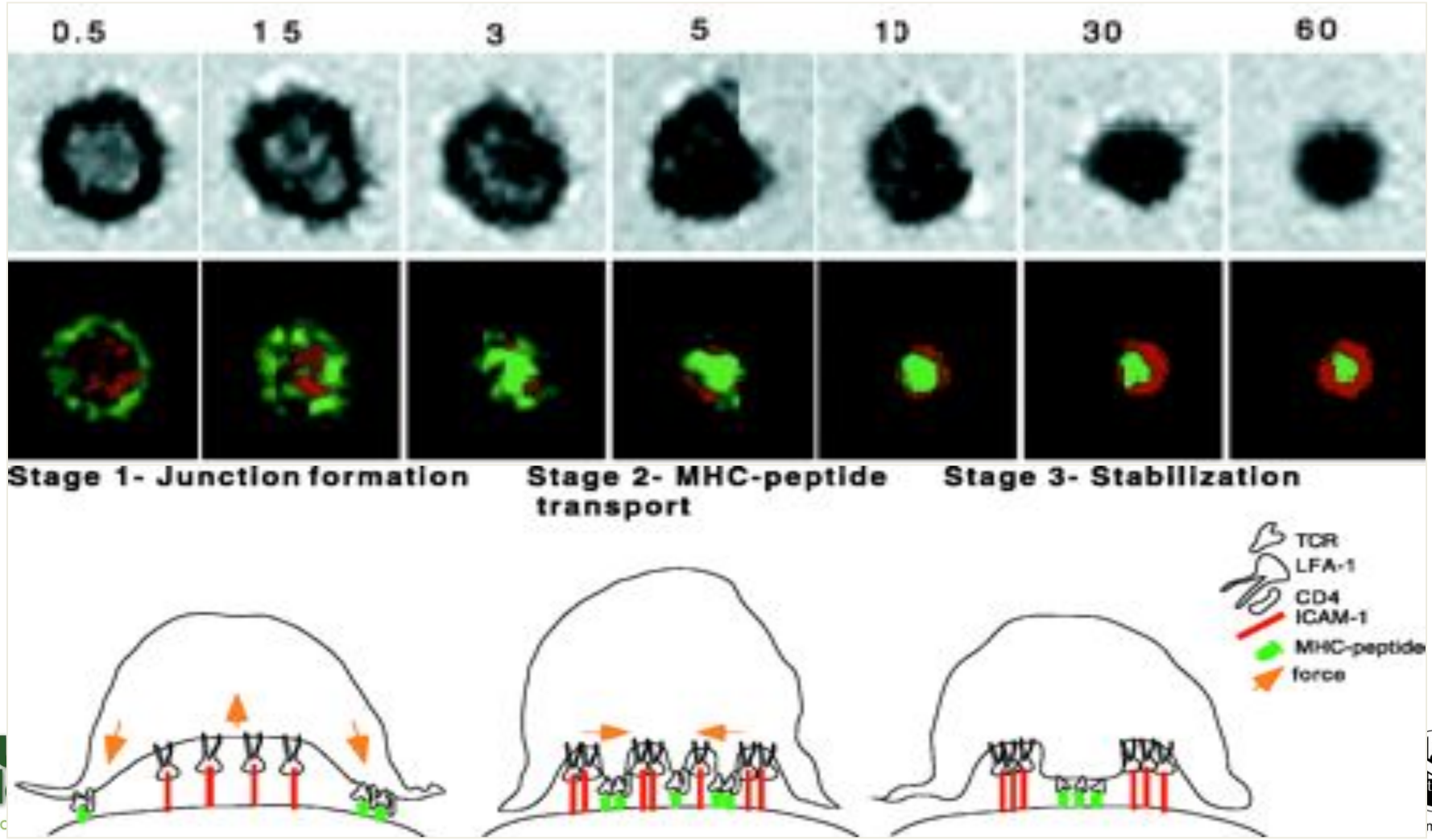
Deficiências no TAP ou Tapasina Impedem que a Molécula de MHC I seja expressa Na membrana celular

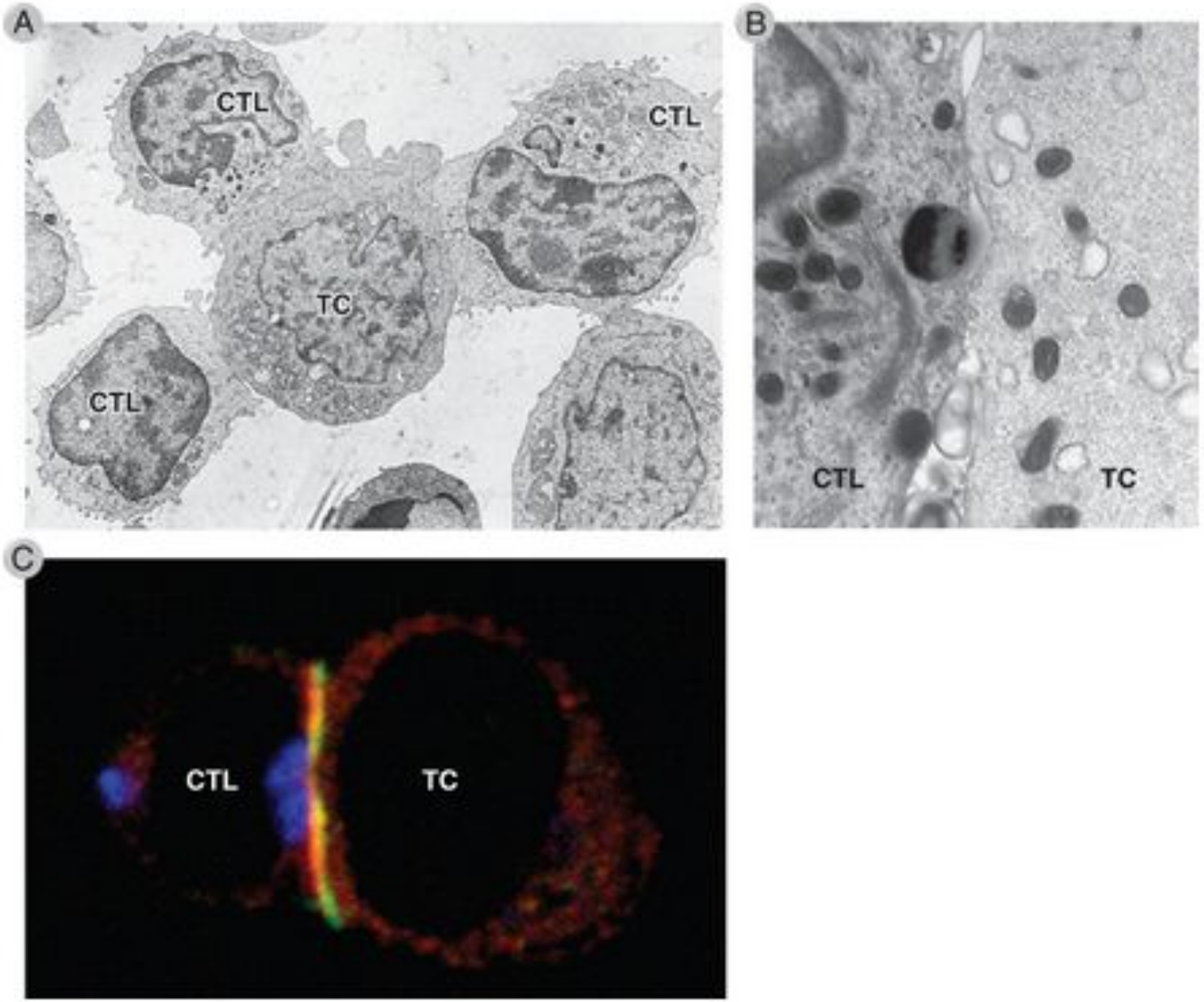
Comprometimento

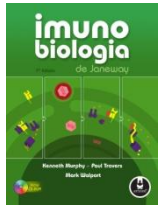
CD8



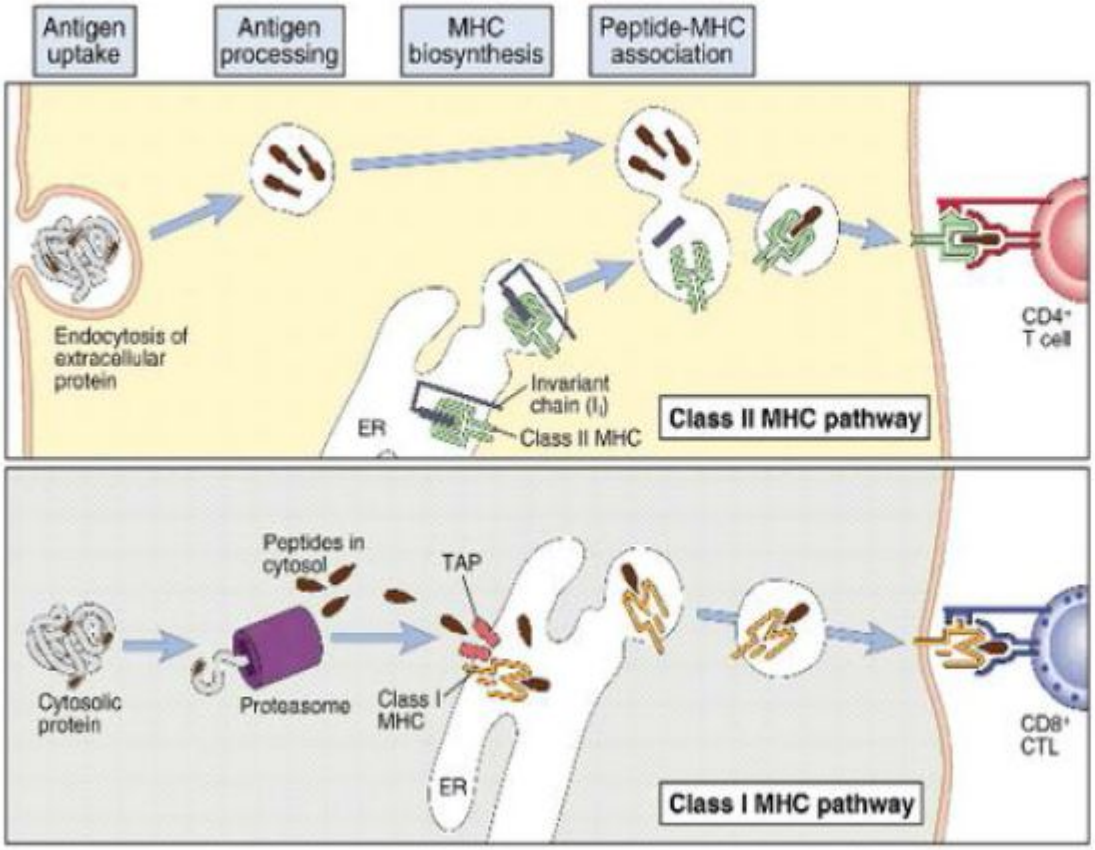
A ligação com o complexo MHC-peptídeo promove a formação de sinapses




A
CTL
CTL
TC
CTL
B
CTL
TC
C
CTL
TC



Síndrome do Linfócito Nu



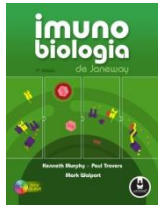
Deficiência de TAP

Transportador de Peptídeos para O retículo.

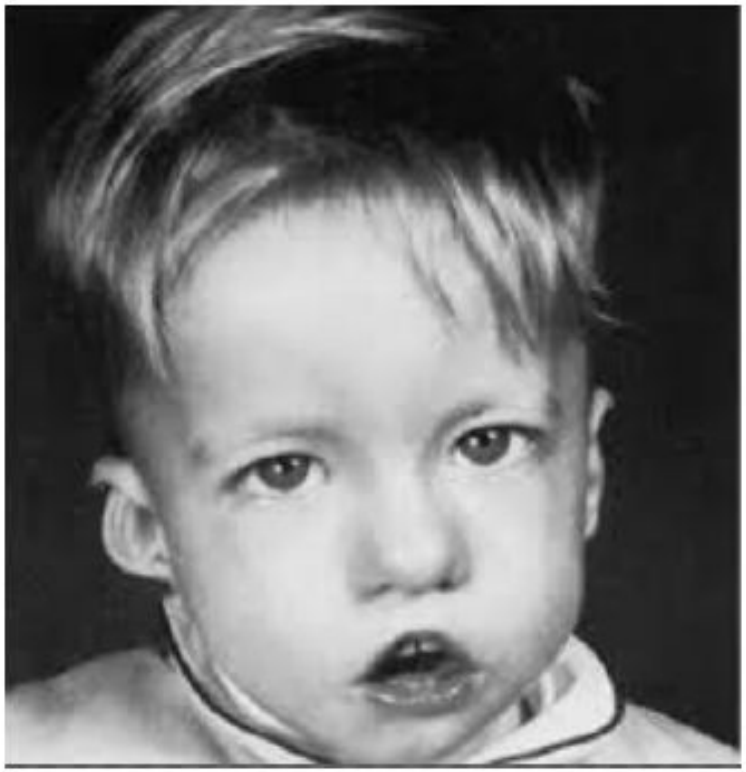
Ausência ou pouco MHC I

Lesões granuloma tosas de Pele

Infecções Bacterianas Pulmonares



Síndrome de Di George

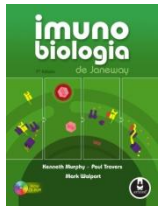


Deleções 22q11

Gene Tbox1

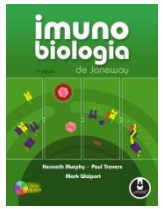
Agenesia Tímica

Foxn1



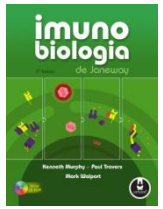
Deficiências em Linfócitos B e Anticorpos

- Agamaglobulinemia ligada ao X
- Deficiência em BTK – Bruton tirosina Kinase
- Impede a maturação de linfócitos B
- Igs Indetectáveis
- 20% dos pacientes desenvolvem autoimunidade
- Tratamento com gama-globulinas intra-venosa.



Hypogammaglobulinemias/isotype defects		
Selective IgA deficiency	Decreased IgA; may be associated with increased susceptibility to bacterial infections and protozoa such as *Giardia lamblia*	Mutations in *TACI* in some patients
Selective IgG2 deficiency	Increased susceptibility to bacterial infections	Small subset have deletion in IgH γ2 locus
Common variable immunodeficiency	Hypogammaglobulinemia; normal or decreased B cell numbers	Mutations in *ICOS* and *TACI* in some patients
ICF syndrome	Hypogammaglobulinemia, occasional mild T cell defects	Mutations in *DNMT3B*
Hyper-IgM syndromes		
X-linked	Defects in T helper cell–mediated B cell, macrophage, and dendritic cell activation; defects in somatic mutation, class switching, and germinal center formation; defective cell-mediated immunity	Mutation in *CD40L*
Autosomal recessive with cell-mediated immune defects	Defects in T helper cell–mediated B cell, macrophage, and dendritic cell activation; defects in somatic mutation, class switching, and germinal center formation; defective cell-mediated immunity	Mutations in *CD40, NEMO*
Autosomal recessive with antibody defect only	Defects in somatic mutation and isotype switching	Mutations in *AID, UNG*

AID, activation-induced cytidine deaminase; DNMT3B, DNA methyltransferase 3B; ICF, immunodeficiencies-centromeric instability-facial anomalies; ICOS, inducible costimulator; NEMO, NF-κB essential modulator; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor; UNG, uracil N-glycosylase.



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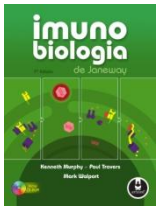
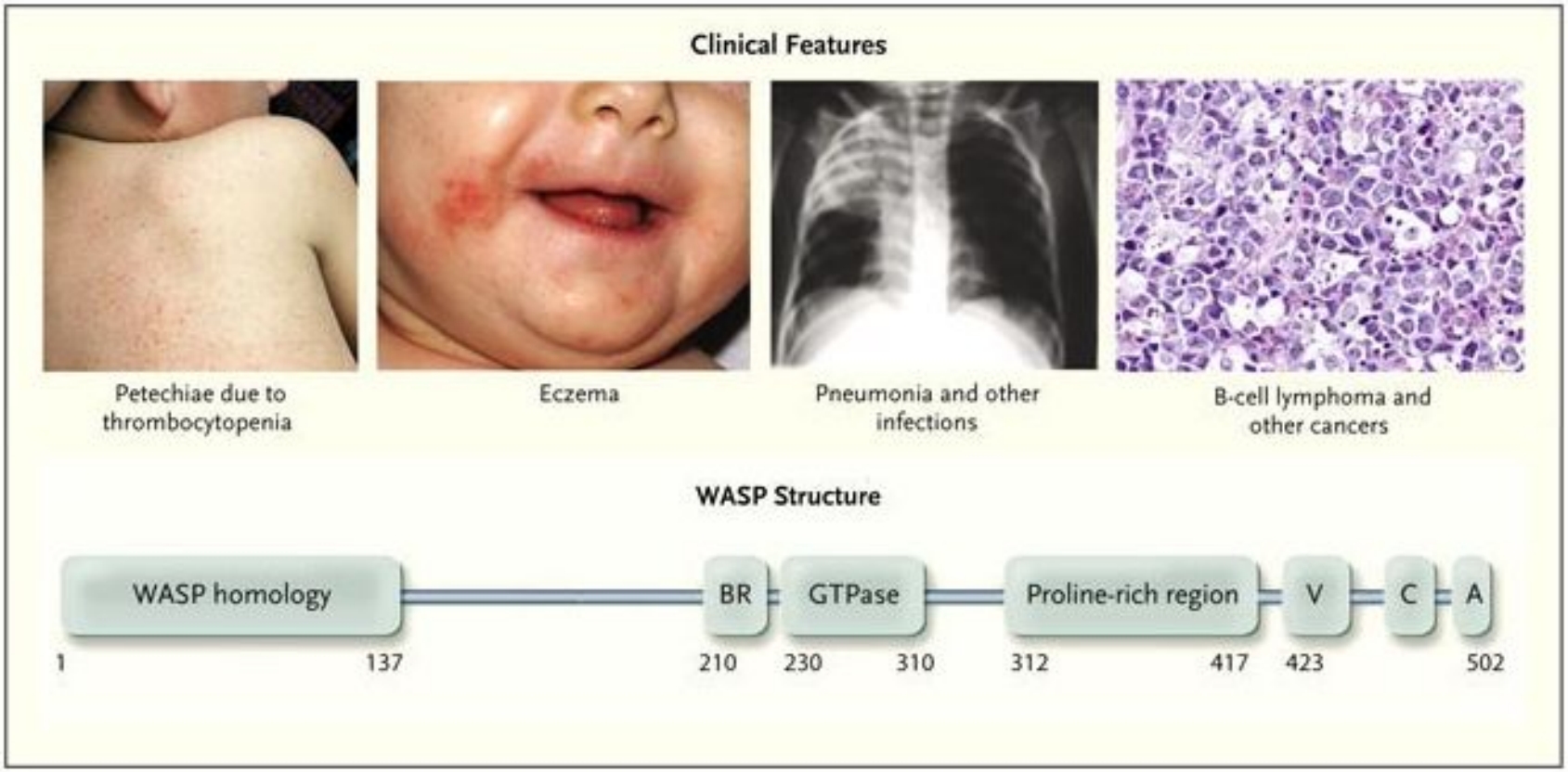
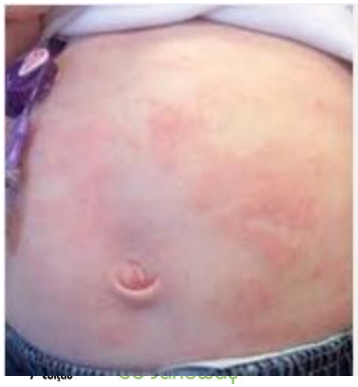
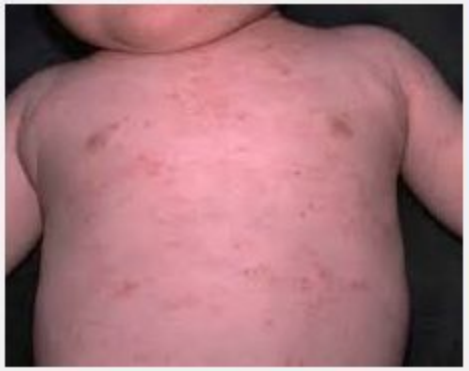
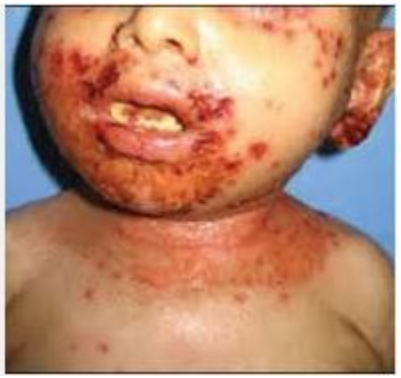


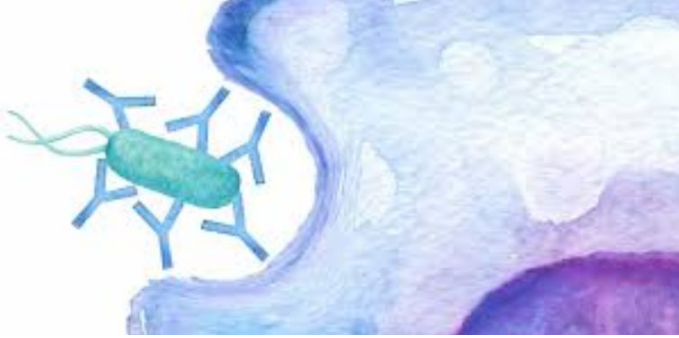
- Wiskott-Aldrich Syndrome (WAS) – Deficiências na proteína WAS ligada ao cromossomo X, responsável por mudanças do citoesqueleto importantes na ativação de linfócitos T e na colaboração com linfócitos B
- Linfócitos hiporresponssivos à mitógenos
- Resposta citotóxica também esta comprometida
- Proteína WAS também é expressa em plaquetas, as quais também estão alteradas e reduzidas - trombocitopenia


Clinical Features
Petechiae due to thrombocytopenia
Eczema
Pneumonia and other infections
B-cell lymphoma and other cancers
WASP Structure
WASP homology
BR
GTPase
Proline-rich region
V
C
A
1
137
210
230
310
312
417
423
502





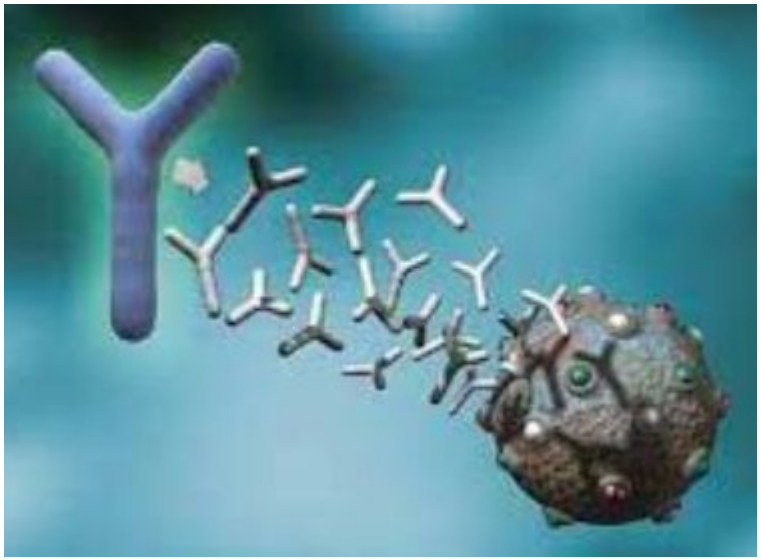




Deficiências de Linfócitos B

Redução na síntese total de anticorpos

Ou na mudança de isotipo



Agamaglobulinemia Ligada ao X

Hiper IgM

CVID

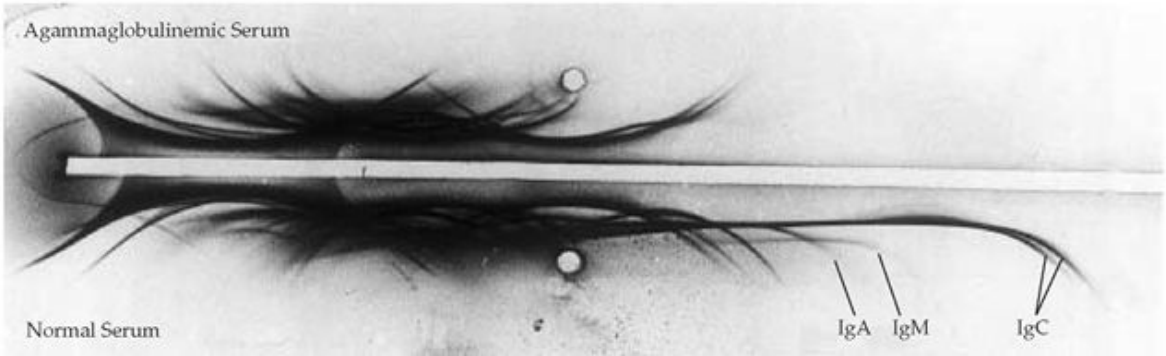
Susceptibilidade à infecções por bactérias Encapsuladas, pois necessitam do Reconhecimento por anticorpos para a opsonização.

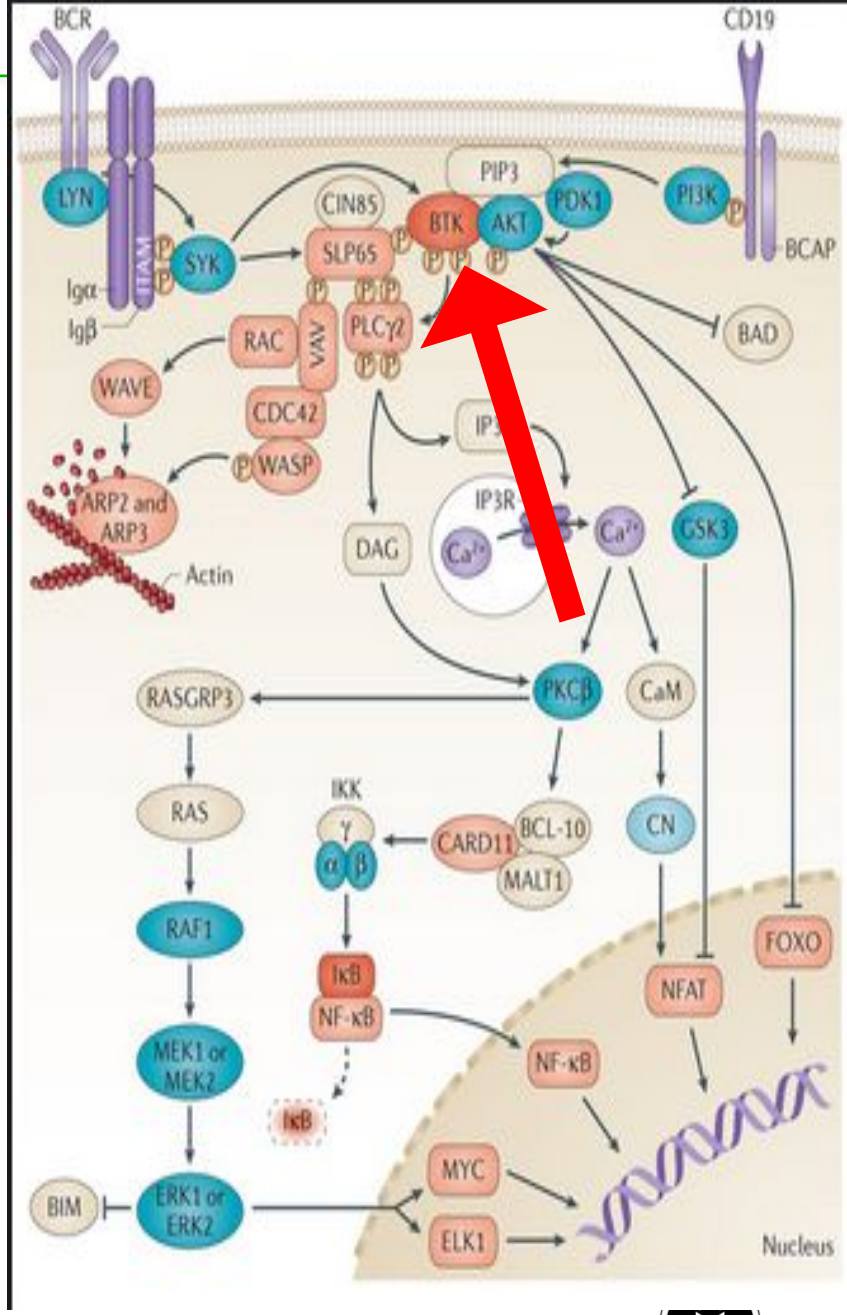
Primeira Imunodeficiência descrita – 1952 por Ogden C Bruton

Mais tarde caracterizada a deficiência de uma proteína batizada de Btk – Bruton
Tirosina
Kinase

Importante na maturação de linfócitos B – pré-B cell receptor.

Linfócitos





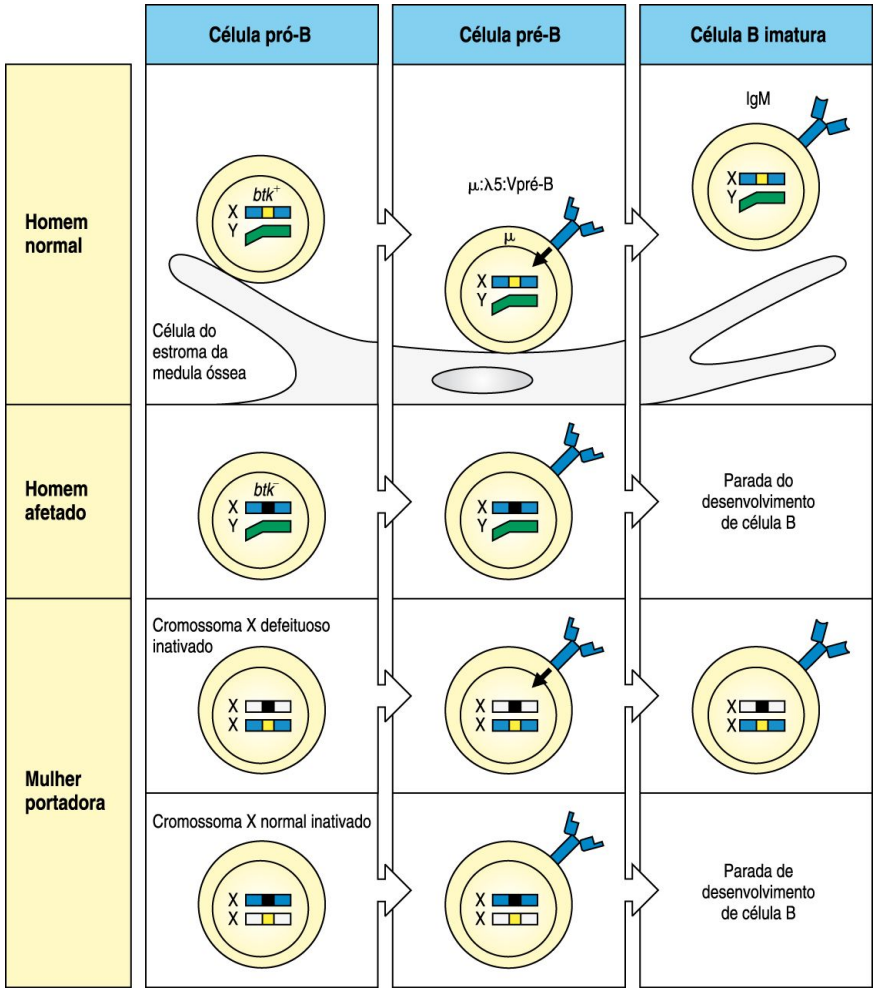
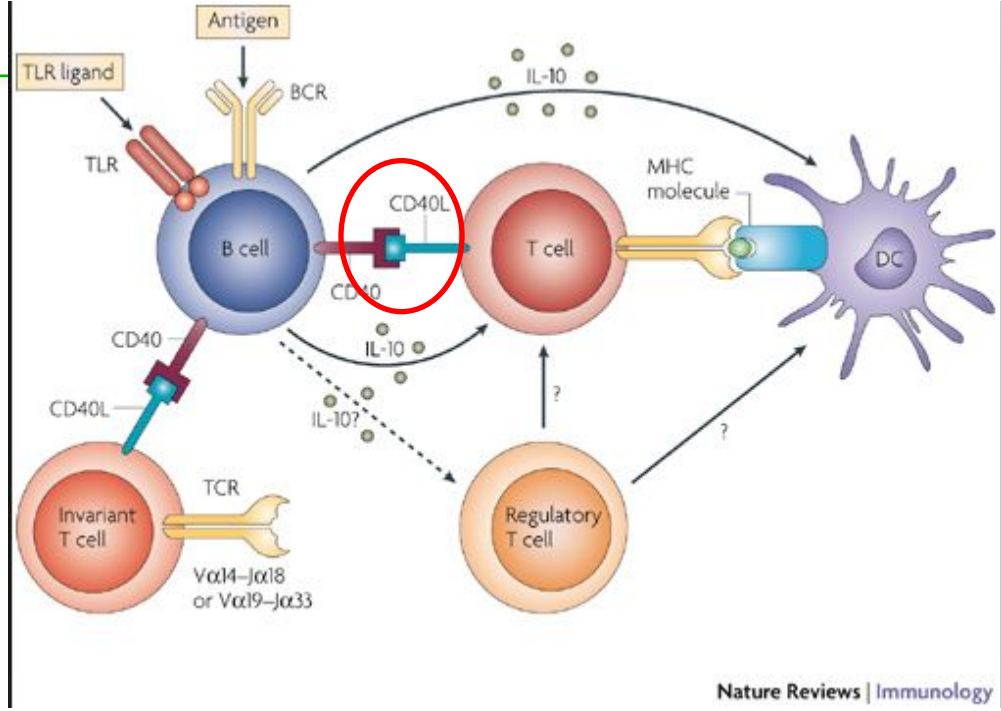
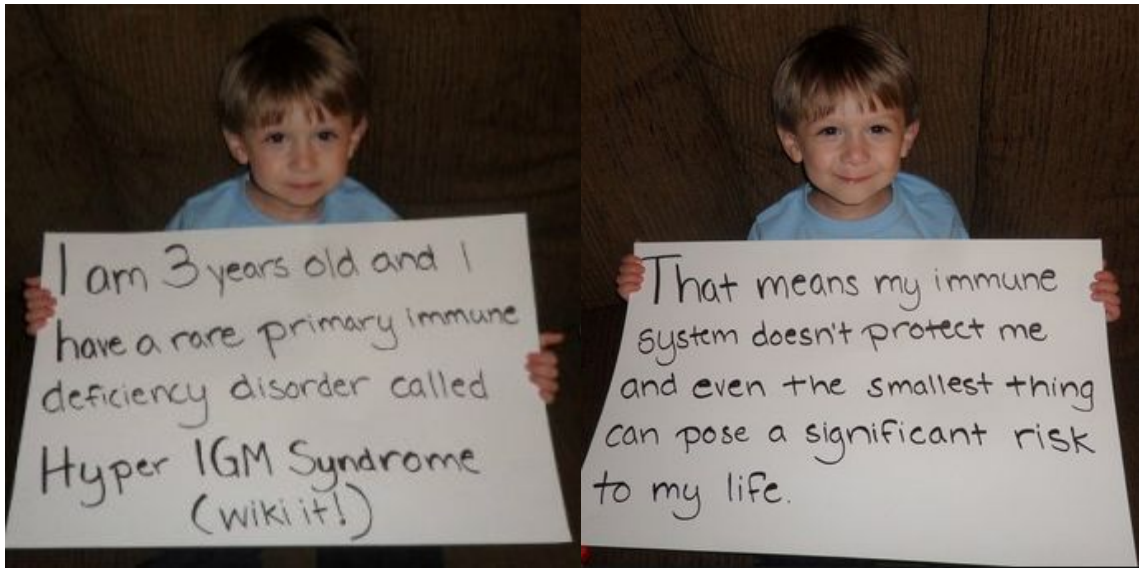


Figura 12.9 O produto do gene btk é importante para o desenvolvimento da célula B.

Hiper IgM

- Mutações no CD40
- Não há mudança de isotipo
- Ausência de IgG e IgA





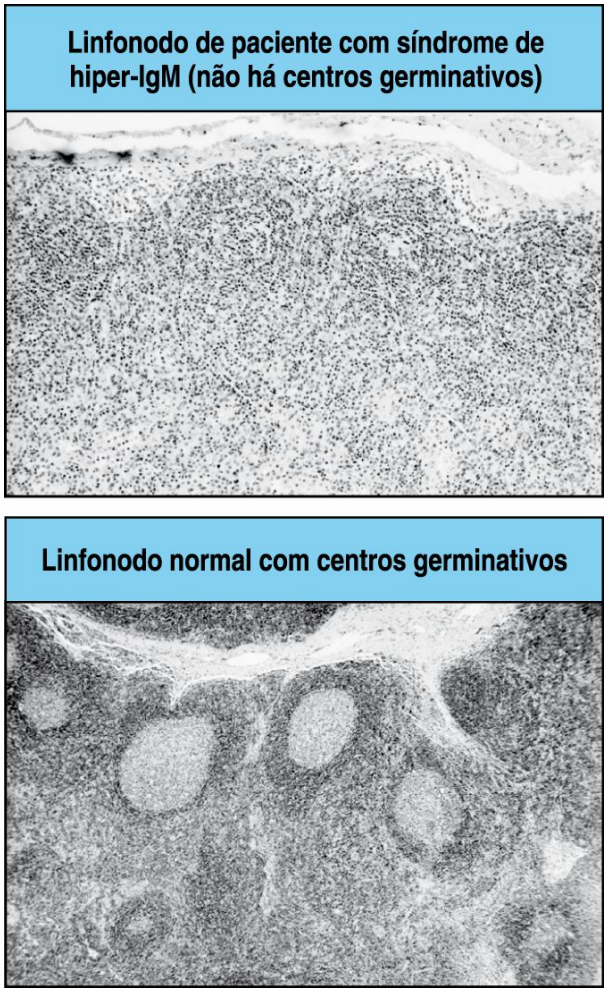
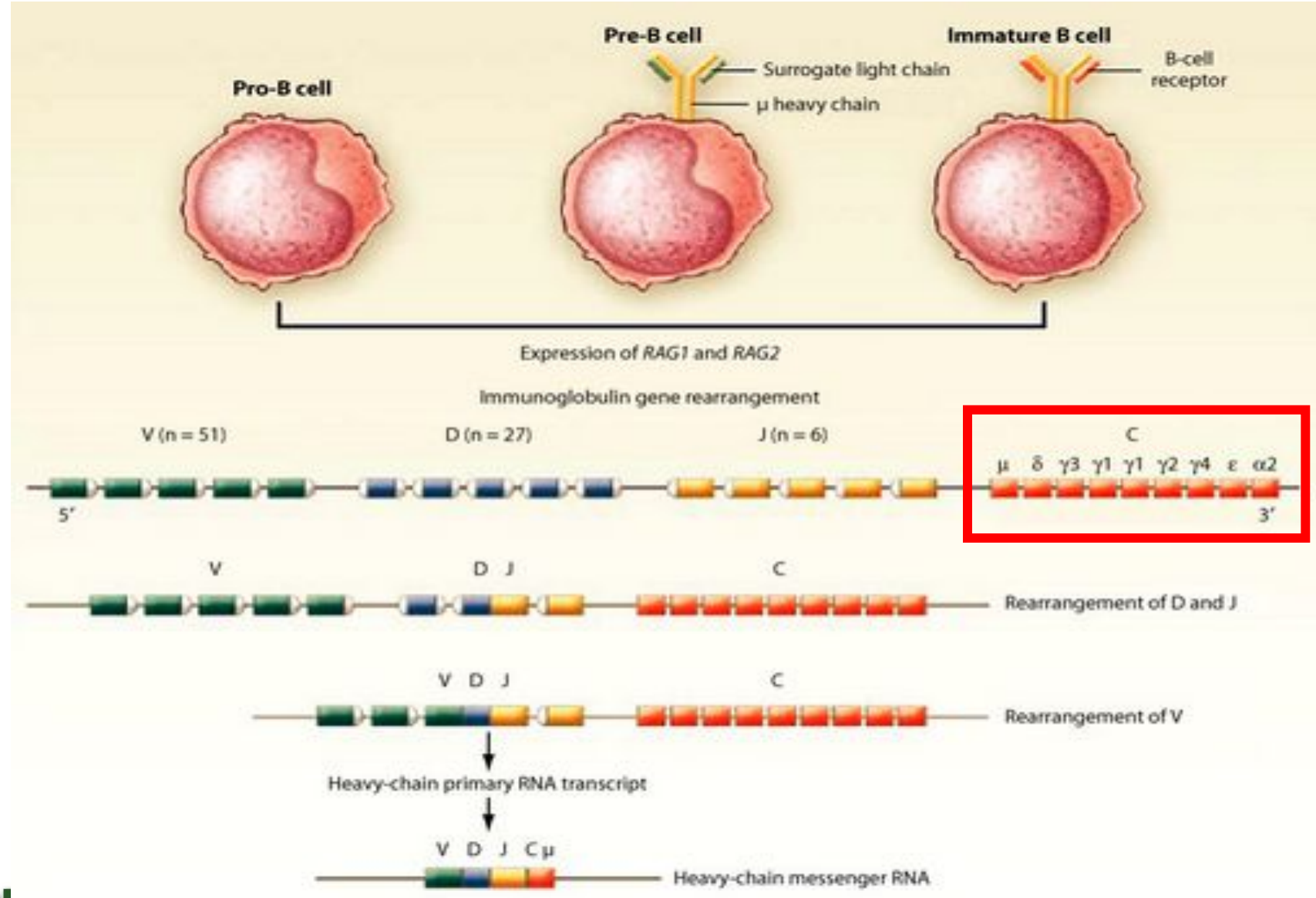
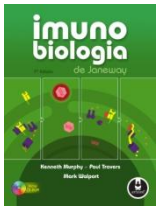


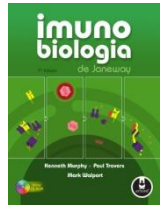
Figura 12.11 Pacientes com a síndrome de hiper-IgM ligada ao X são incapazes de ativar completamente suas células B.


Pro-B cell
Pre-B cell
Surrogate light chain
μ heavy chain
Immature B cell
B-cell receptor
Expression of RAG1 and RAG2
Immunoglobulin gene rearrangement
V (n = 51)
D (n = 27)
J (n = 6)
C
μ δ γ3 γ1 γ1 γ2 γ4 ε α2
5′
3′
V
D J
C
Rearrangement of D and J
V D J
C
Rearrangement of V
Heavy-chain primary RNA transcript
V D J Cμ
Heavy-chain messenger RNA

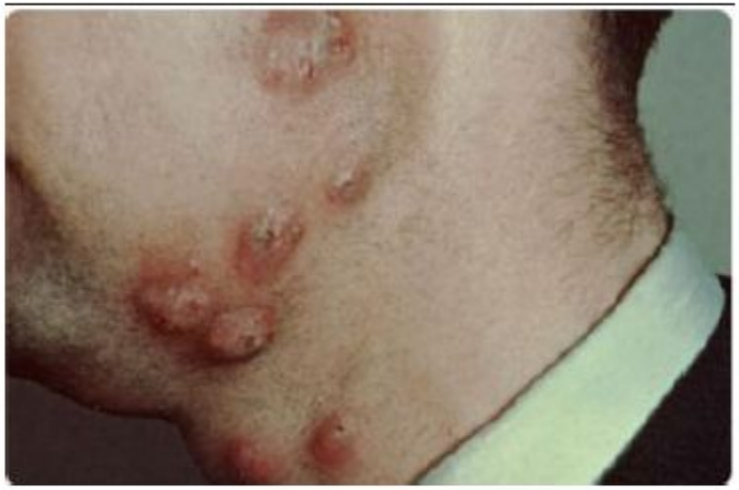


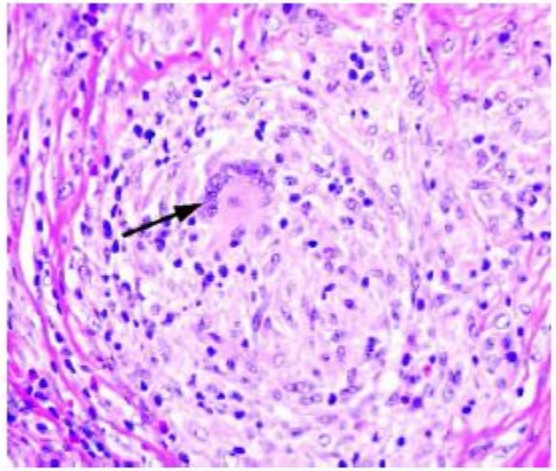
CVID – Imunodeficiência Comum Variável

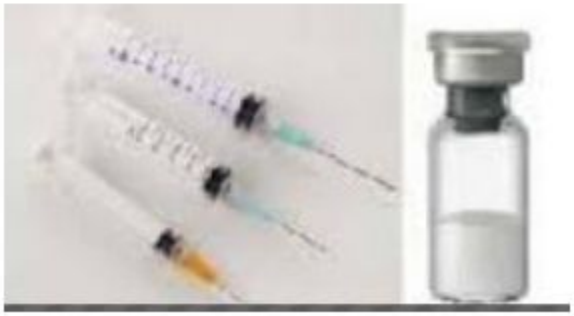
- Multifatorial
- XBP-1 – IRE-1
- Deficiência da secreção de IgG
- Pode ser desencadeada por vários fatores
  - Medicamentos, infecções, etc...



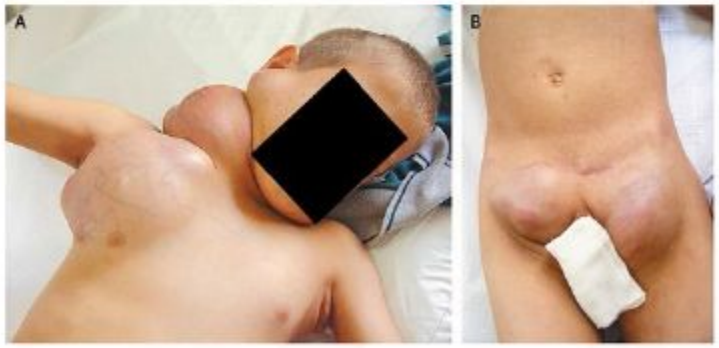
Doença Granulomatosa Crônica

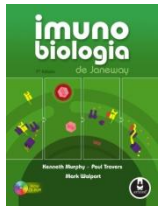




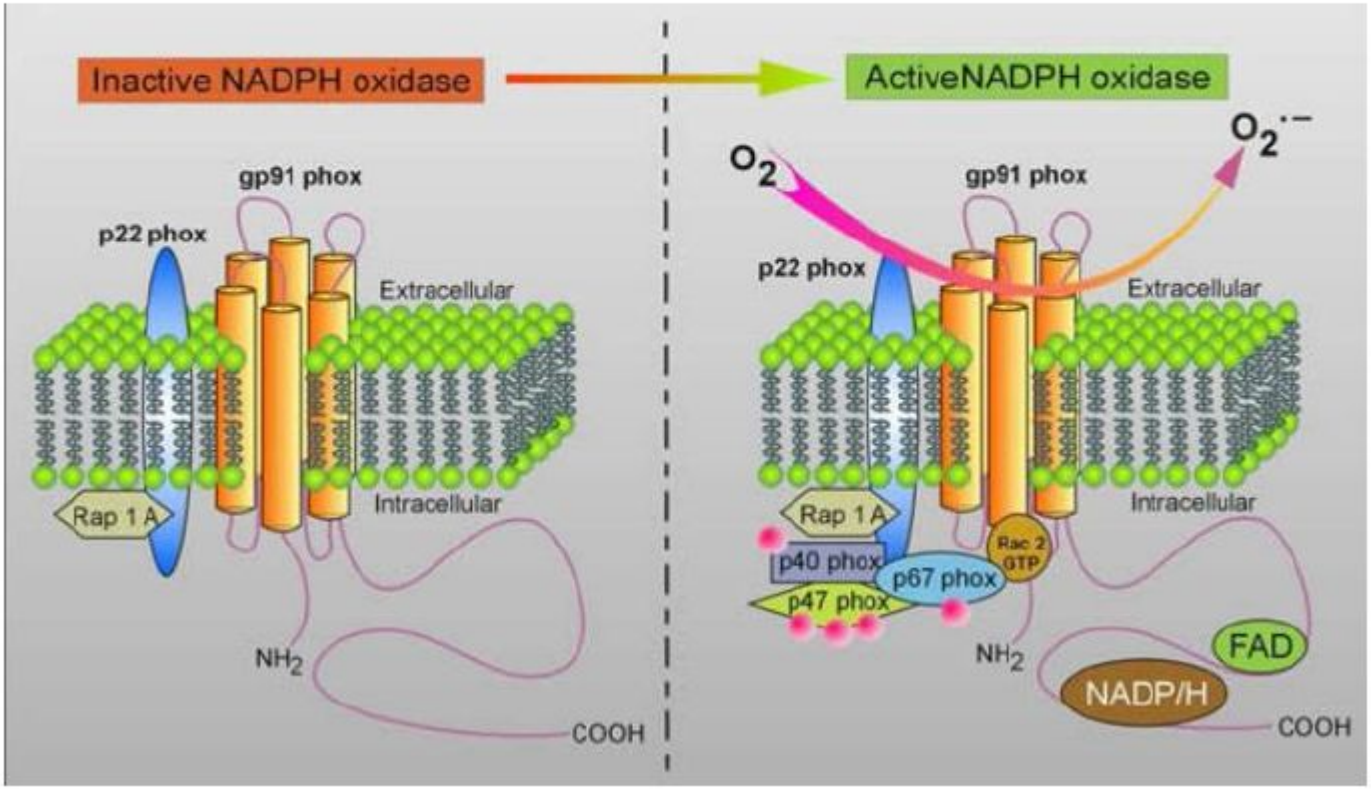


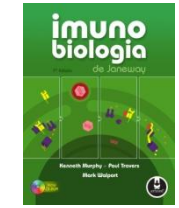
rhIFN-γ



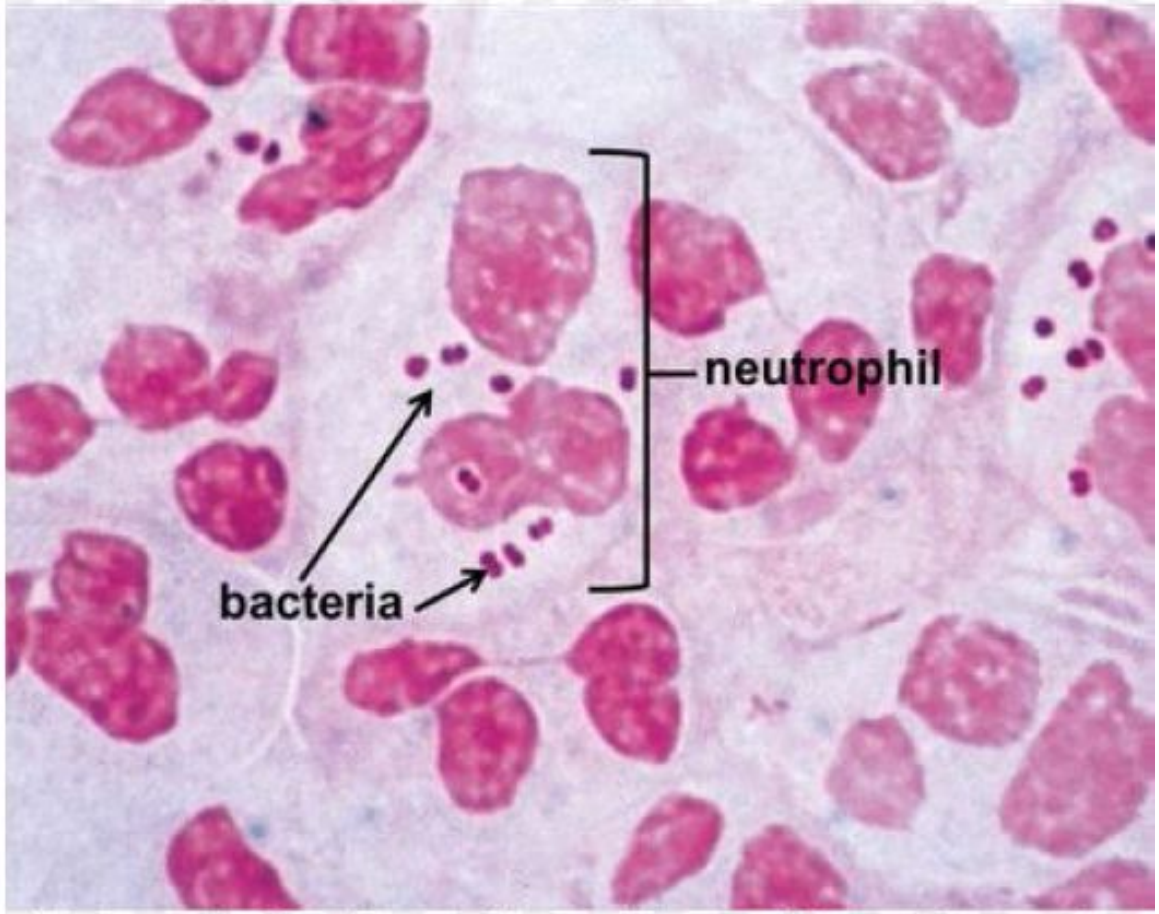


Deficiências em Fagócitos
NADPH Oxidase



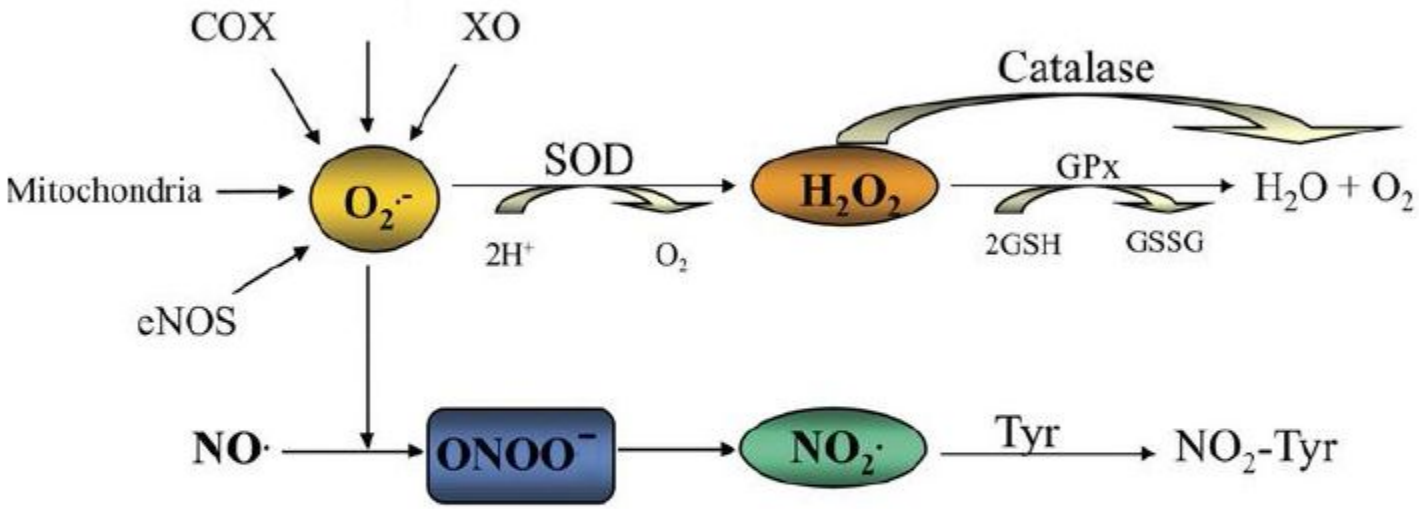


Phagocytosis by Neutrophils



Gram stain of pus from the urethra of a male patient with gonorrhea. Note the intracellular (phagocytosed) bacteria within neutrophils.

NADPH Oxidase



XO: xanthine oxidase

SOD: superoxide dismutase

GSH: reduced gluthatione

ONOO⁻ : peroxynitrite

Nox: NADPH oxidase

H_2O_2: hydrogen peroxide

GSSG: oxidized gluthatione

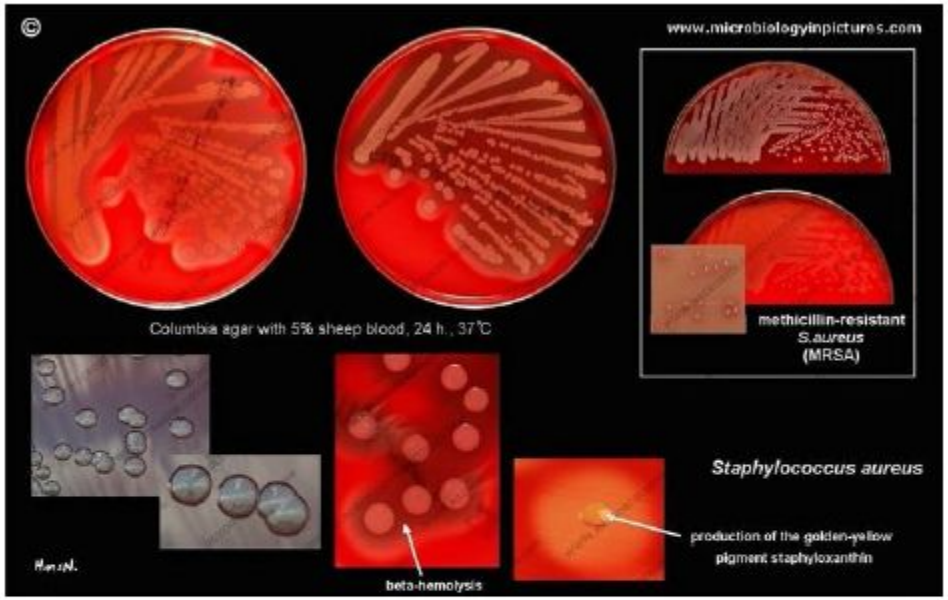
$NO_2^{\cdot}$: nitrogen dioxide

$O_2^{\cdot -}$: superoxide anion

GPx: gluthatione peroxidase

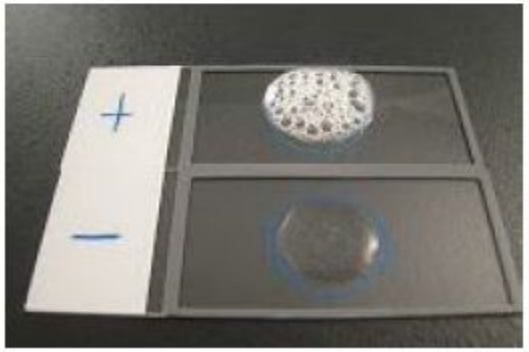
NO·: nitric oxide

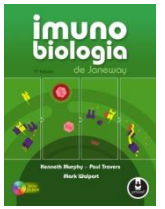
NO_2-Tyr: nitrotyrosine



S aureus

Catalase (+)

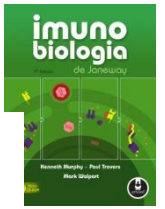




Deficiências de Adesão Leucocitária

- Redução na infiltração de leucócitos, principalmente neutrófilos ao sítio de infecção (ausência de pus)

- Rolling e transmigração leucocitária está amplamente comprometida



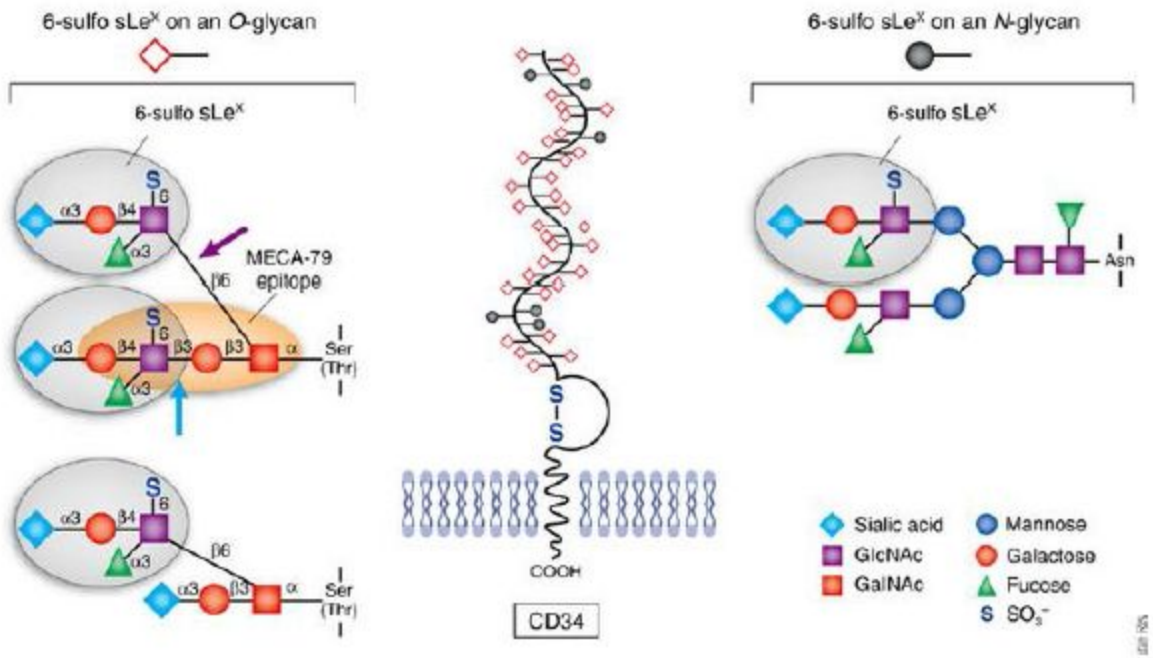
LAD1 – Mutação em CD18

TABLE 3–1 Major Leukocyte-Endothelial Adhesion Molecules

Family	Molecule	Distribution	Ligand (molecule; cell type)
Selectin	P-selectin (CD62P)	Endothelium activated by cytokines (TNF, IL-1), histamine, or thrombin	Sialyl Lewis X on PSGL-1 and other glycoproteins; neutrophils, monocytes, T cells (effector, memory)
	E-selectin (CD62E)	Endothelium activated by cytokines (TNF, IL-1)	Sialyl Lewis X (e.g., CLA-1) on glycoproteins; neutrophils, monocytes, T cells (effector, memory)
	L-selectin (CD62L)	Neutrophils, monocytes, T cells (naive and central memory), B cells (naive)	Sialyl Lewis X/PNAd on GlyCAM-1, CD34, MadCAM-1, others; endothelium (HEV)
Integrin	LFA-1 (CD11aCD18)	Neutrophils, monocytes, T cells (naive, effector, memory)	ICAM-1 (CD54), ICAM-2 (CD102); endothelium (upregulated when cytokine activated)
	Mac-1 (CD11bCD18)	Monocytes, dendritic cells	ICAM-1 (CD54), ICAM-2 (CD102); endothelium (upregulated when cytokine activated)
	VLA-4 (CD49aCD29)	Monocytes, T cells (naive, effector, memory)	VCAM-1 (CD106); endothelium (upregulated when cytokine activated)
	$\alpha_4\beta_7$ (CD49dCD29)	Monocytes, T cells (gut homing, naive, effector, memory)	VCAM-1 (CD106), MadCAM-1; endothelium in gut and gut-associated lymphoid tissues

CLA-1, cutaneous lymphocyte antigen 1; GlyCAM-1, glycan-bearing cell adhesion molecule 1; HEV, high endothelial venule; ICAM-1, intracellular adhesion molecule 1; IL-1, interleukin-1; LFA-1, leukocyte function-associated antigen 1; MadCAM-1, mucosal addressin cell adhesion molecule 1; PNAd, peripheral node addressin; PSGL-1, P-selectin glycoprotein ligand 1; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule 1; VLA-4, very late antigen 4.

Infecções bacterianas e fúngicas recorrentes e reduzida capacidade de reparo.



LAD -2

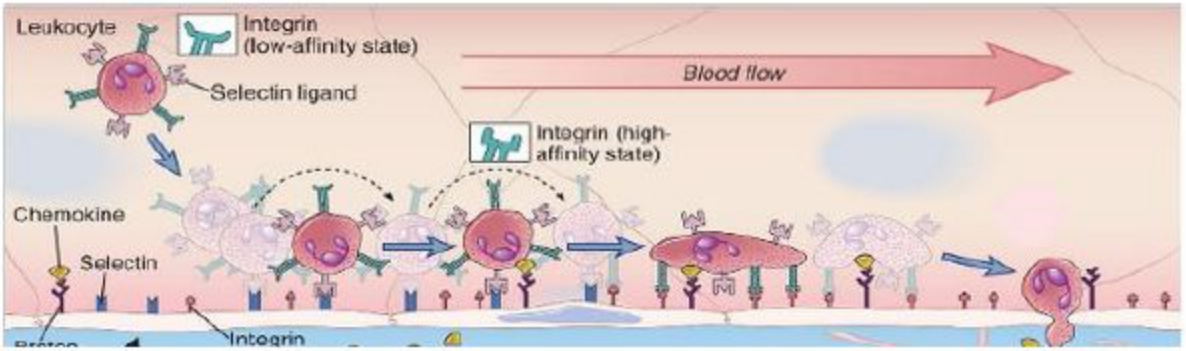
Defeitos

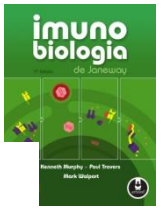
No

Rolling

E

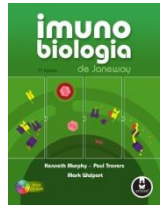
Migração



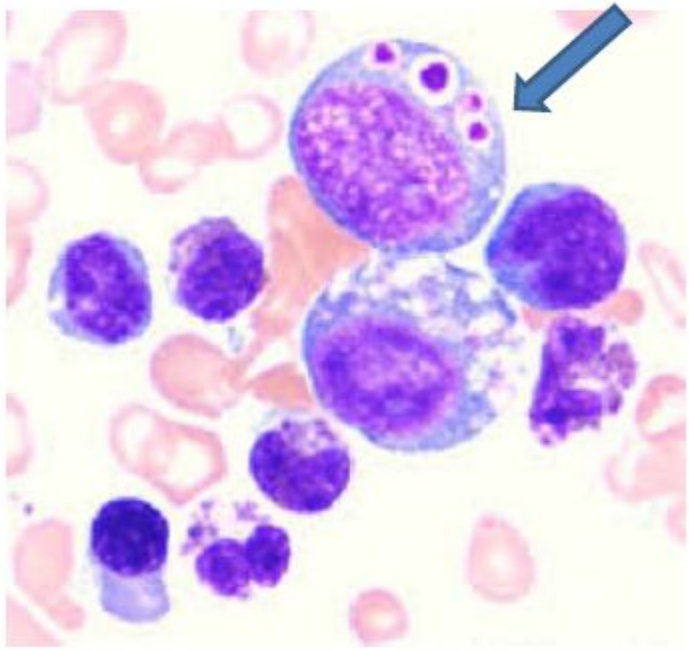


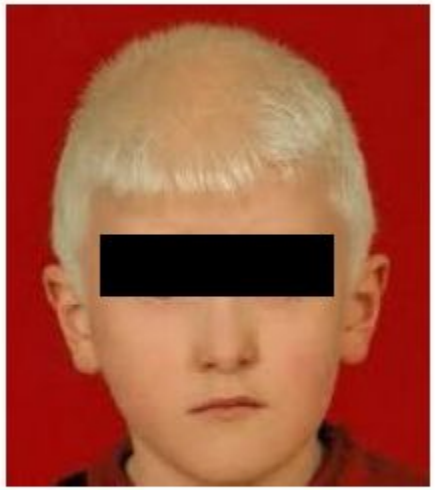
Defeitos em Fagócitos

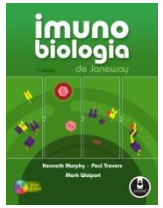
- **Chediak-Higashi:**
  - autossômica recessiva caracteriada por infecções recorrentes com bactérias piogênicas, albinismo oculocutâneo e infiltrado de linfócitos.
- Fagócitos contém lisossomos gigantes
- Mutação no gene *lyst*
  - Lysossomal traficking regulator. Dificuldade de fusão entre o fagosomo e o lisossmo.



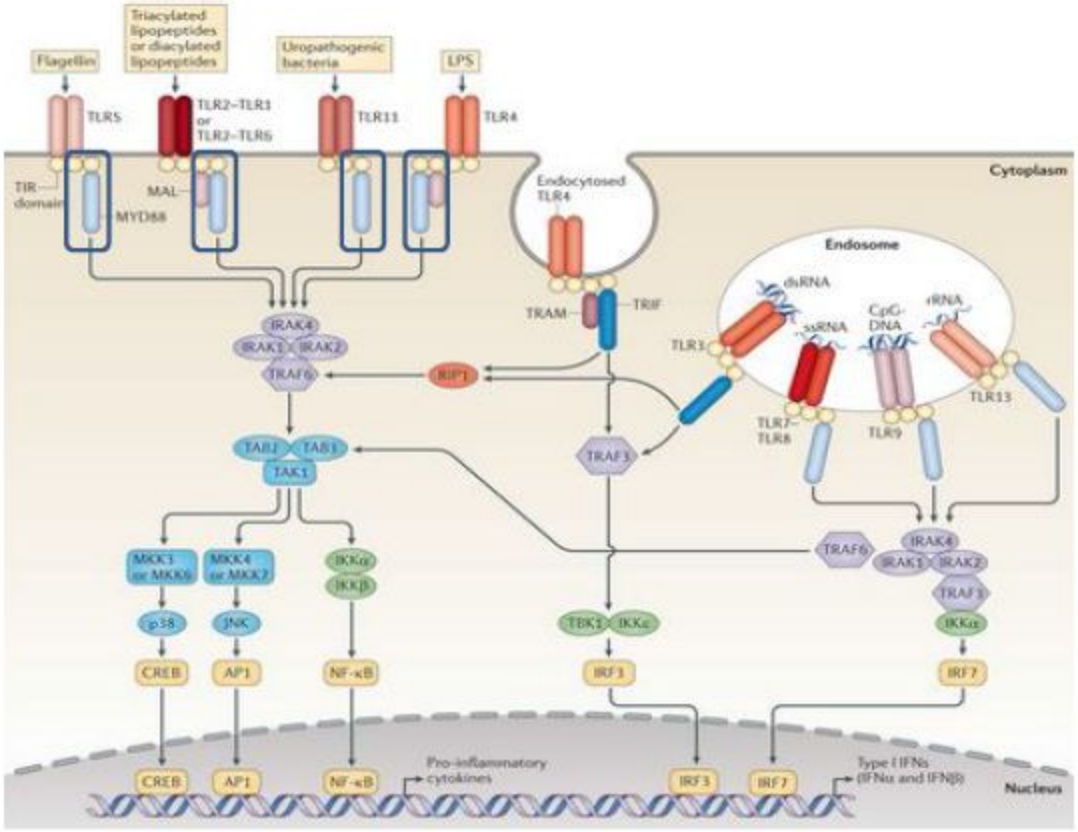
Chediak - Higashi







Toll-Like Receptors



MyD88

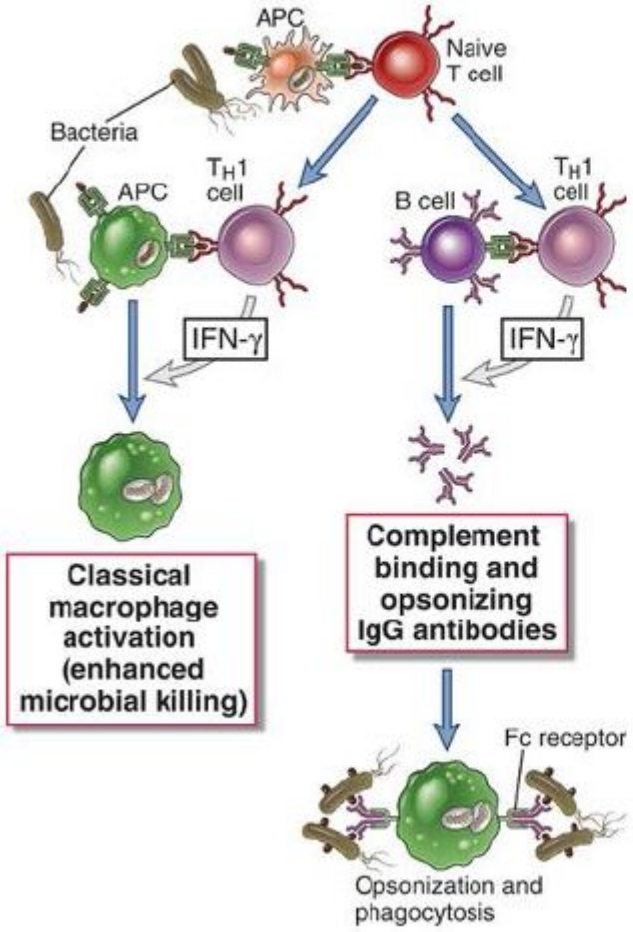
IRAK

Deficiência

No

reconhecimento

Eixo IFN-γ / IL-12



Susceptibilidade

À

Infecções por Bactérias Intracelulares

Mycobacterium tuberculosis

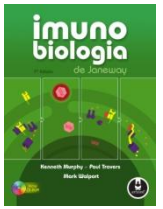
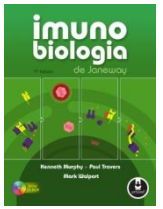


TABLE 20–5 Defects in T Cell Activation

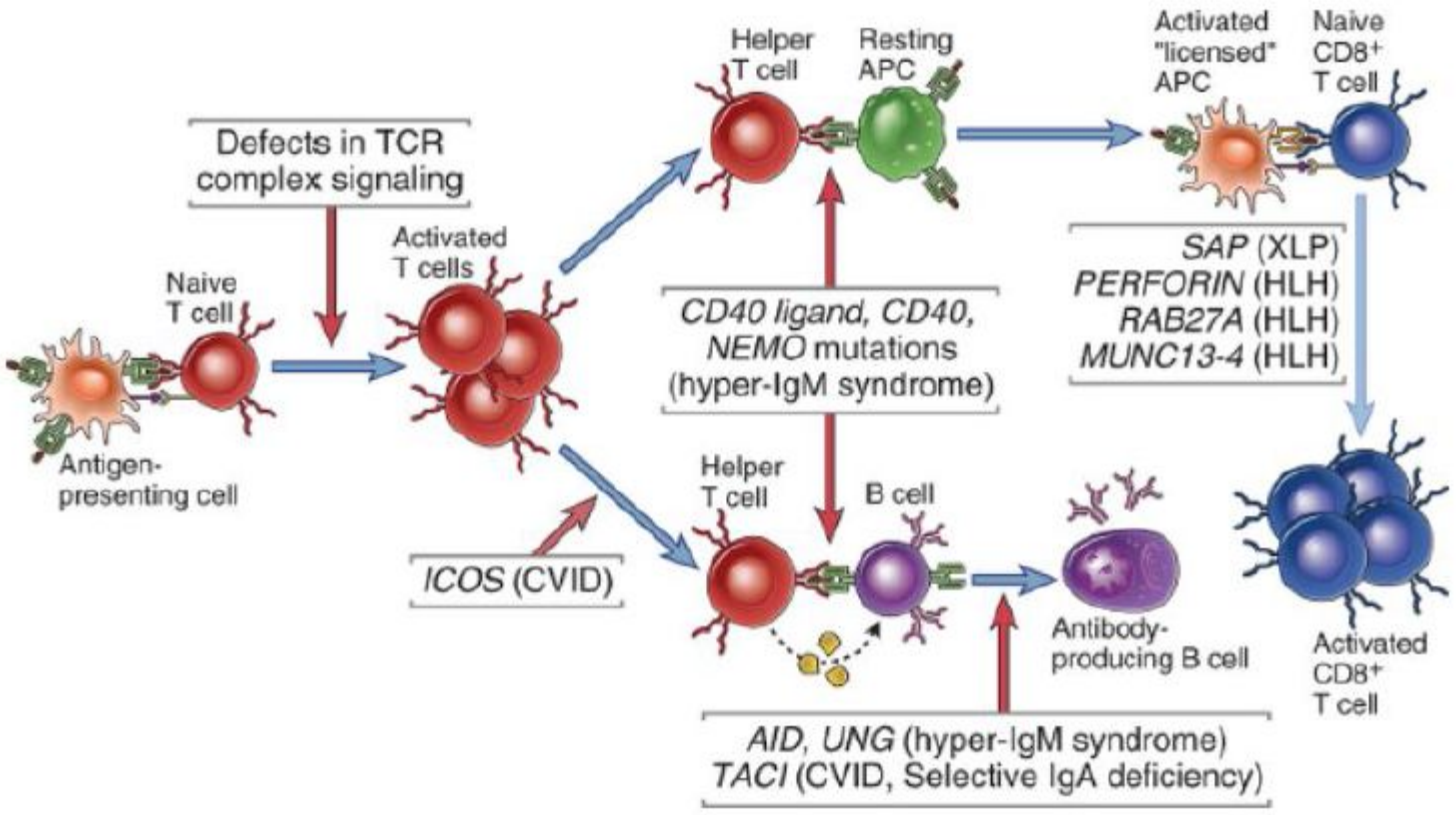
Disease	Functional Deficiencies	Mechanism of Defect
Defects in MHC expression		
Bare lymphocyte syndrome	Defective MHC class II expression and deficiency in $CD4^+$ T cells; defective cell-mediated immunity and T-dependent humoral immune responses	Defects in transcription factors regulating MHC class II gene expression, including *CIITA*, *RFXANK*, *RFX5*, and *RFXAP*
MHC class I deficiency	Decreased MHC class I levels; reduced $CD8^+$ T cells	Mutations in *TAP1*, *TAP2*, and *TAPASIN*
Defective T cell signaling		
Proximal TCR signaling defects	Defects in cell-mediated immunity and T-dependent humoral immunity	Mutations in *CD3* genes, *CD45*, *STIM1*, *ORAI1*
Wiskott-Aldrich syndrome	Defective T cell activation, leukocyte mobility	TCR-dependent actin-cytoskeletal rearrangements are defective because of mutations in *WASP*



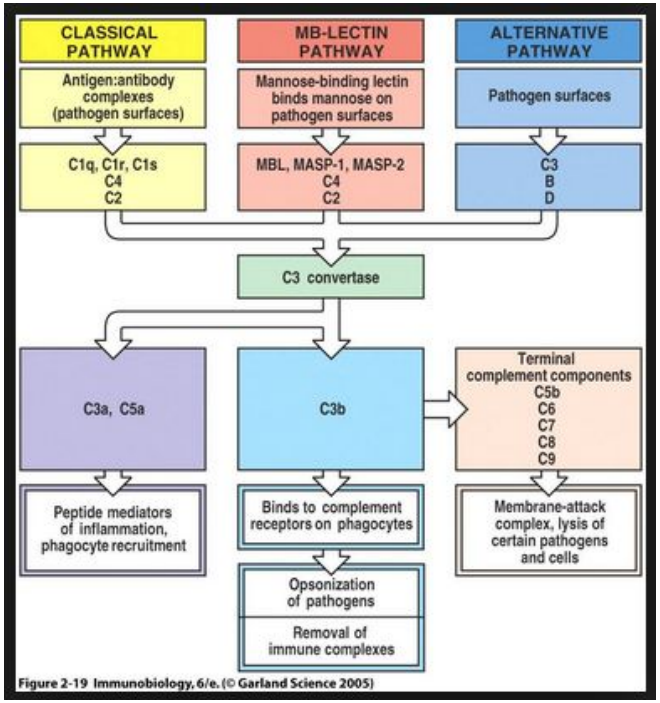
Familial hemophagocytic lymphohistiocytoses		
X-linked lymphoproliferative syndrome	Uncontrolled EBV-induced B cell proliferation, uncontrolled macrophage and CTL activation, defective NK cell and CTL function	Mutations in *SAP*
Perforin deficiencies	Uncontrolled macrophage and CTL activation, defective NK cell and CTL function	Mutations in *PERFORIN*
Granule fusion	Uncontrolled macrophage and CTL activation, defective NK cell and CTL function	Defective cytotoxic granule exocytosis; mutations in *RAB27A, MUNC13-4, SYNTAXIN, AP3* (and in *LYST* in Chédiak-Higashi syndrome—see Table 20-2)

AP3, adaptor-related protein complex 3; LYST, lysosomal trafficking regulator protein; SAP, SLAM-associated protein; TAP, transporter associated with antigen processing; WASP, Wiskott-Aldrich syndrome protein.

Defeitos na Sinalização de Linfócitos



Disease	Functional Deficiencies	Mechanism of Defect
Chronic granulomatous disease	Defective production of reactive oxygen species by phagocytes; recurrent intracellular bacterial and fungal infections	Mutation in genes of phagocyte oxidase complex: phox-91 (cytochrome b_{558} α subunit) is mutated in X-linked form
Leukocyte adhesion deficiency type 1	Defective leukocyte adhesion and migration linked to decreased or absent expression of β_2 integrins; recurrent bacterial and fungal infections	Mutations in gene encoding the β chain (CD18) of β_2 integrins
Leukocyte adhesion deficiency type 2	Defective leukocyte rolling and migration linked to decreased or absent expression of leukocyte ligands for endothelial E- and P- selectins, causing failure of leukocyte migration into tissues; recurrent bacterial and fungal infections	Mutations in gene encoding a GDP-fucose transporter required for the synthesis of the sialyl Lewis X component of E- and P- selectin ligands
Leukocyte adhesion deficiency type 3	Defective leukocyte adhesion and migration linked to defective inside-out signaling and therefore defective integrin activation	Mutations in gene encoding KINDLIN-3
Chédiak-Higashi syndrome	Defective vesicle fusion and lysosomal function in neutrophils, macrophages, dendritic cells, natural killer cells, cytotoxic T cells, and many other cell types; recurrent infections by pyogenic bacteria	Mutation in LYST leading to defect in secretory granule exocytosis and lysosomal function
Toll-like receptor signaling defects	Recurrent infections because of defects in TLR and CD40 signaling and defective type I interferon production	Mutations in NEMO, UNC93B, MyD88, IκBα, and IRAK-4 compromise NF-κB activation downstream of Toll-like receptors

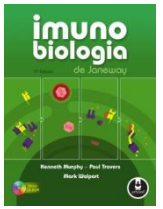


VIA CLÁSSICA		VIA DA MBL		VIA ALTERNATIVA	
C1 C2 C4	Deficiência leva à doença do complexo imune	MBL MASP-1 MASP-2 C2 C4	Deficiência de MBL leva a infecções bacterianas, principalmente na infância	Fator D Fator P	Deficiência leva à infecção por bactérias piogênicas e *Neisseria* spp., mas não à doença do complexo imune

Convertase C3

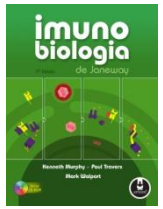
Deposição de C3b	
C3	Deficiência leva à infecção por bactérias piogênicas e *Neisseria* spp.; algumas vezes, à doença do complexo imune

Componentes do ataque à membrana	
C5 C6 C7 C8 C9	Deficiência leva à infecção somente por *Neisseria* spp.



Tipo do defeito/nome da síndrome	Infecções associadas ou outras doenças
Deficiência de adesão de leucócitos	Infecções bacterianas piogênicas generalizadas
Doença granulomatosa crônica	Infecção intra e extracelular, granulomas
Deficiência de G6PD	Queima respiratória defeituosa, infecção crônica
Deficiência de mieloperoxidase	Morte celular defeituosa, infecção crônica
Síndrome de Chediak-Higashi	Infecção intra e extracelular, granulomas

Figura 12.13 Os defeitos nas células fagocíticas estão associados à persistência da infecção bacteriana.



Doença	Defeito gênico	Mecanismo afetado	Fenótipo	
			Humano	Camundongo
XSCID	Cadeia γ do receptor da IL-2	Sinalização de citocinas	$T^-B^+NK^-$	$T^-B^-NK^-$
	JAK3	Sinalização de citocinas	$T^-B^+NK^-$	$T^-B^-NK^-$
	Receptor de IL-7	Sinalização de citocinas	$T^-B^+NK^+$	$T^-B^-NK^+$
Deficiência de RAG Síndrome de Omenn	*RAG1*	Recombinação do receptor do antígeno	$T^-B^-NK^+$	$T^-B^-NK^+$
	RAG2	Recombinação do receptor do antígeno	$T^-B^-NK^+$	$T^-B^-NK^+$
	Artemis	Recombinação do receptor do antígeno	$T^-B^-NK^+$	$T^-B^-NK^+$
Deficiência ADA	*ADA*	Metabolismo	$T^-B^-NK^-$	$T^-B^-NK^+$

Figura 12.14 Síndromes de imunodeficiência severa combinada.

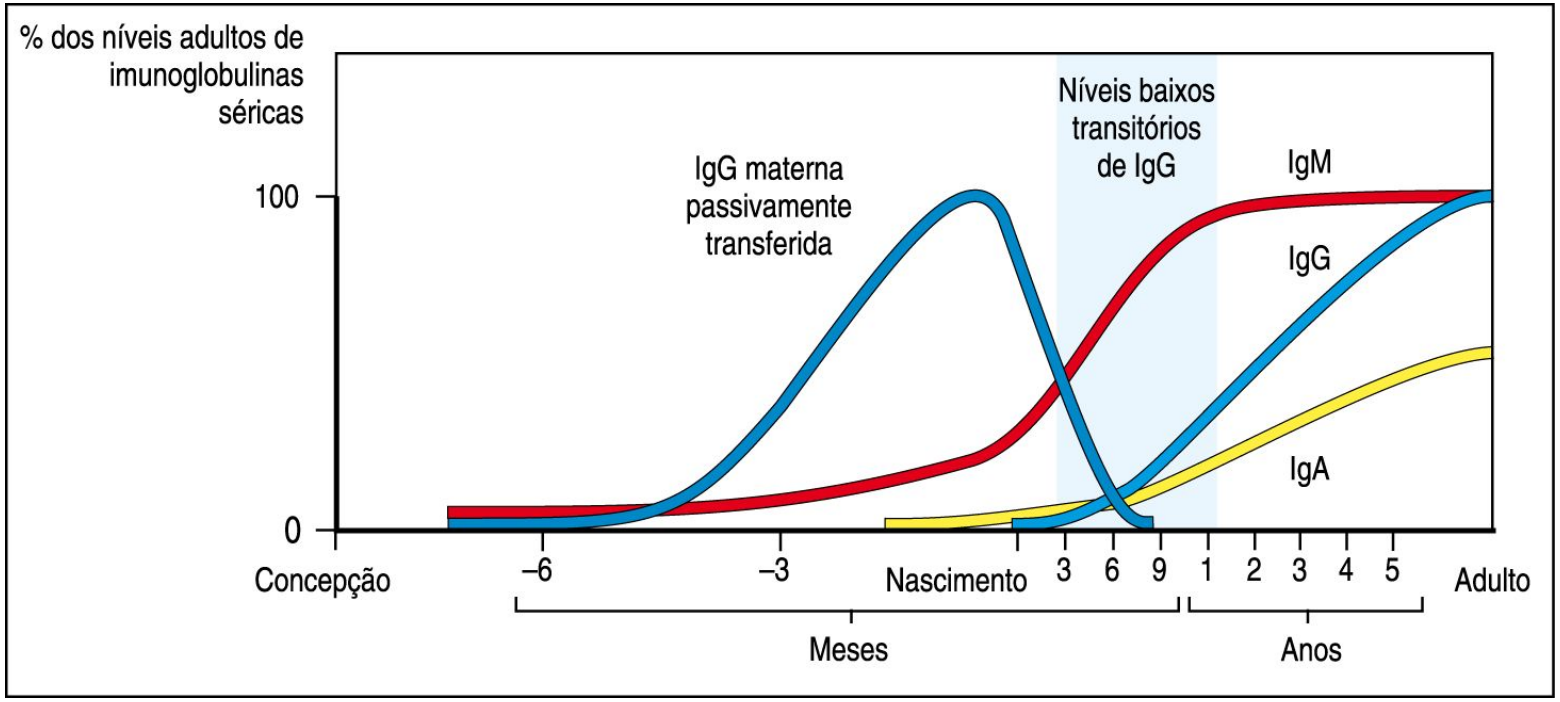


Figura 12.10 Os níveis de imunoglobulina, em recém-nascidos, caem a baixos níveis em torno dos seis meses de vida.

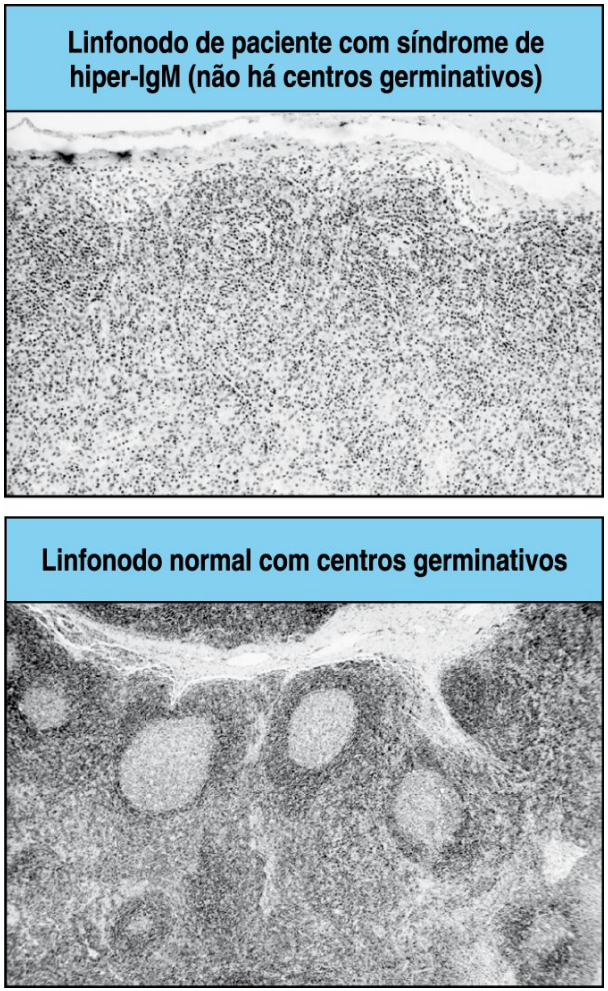
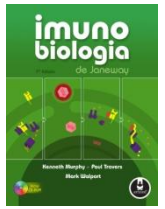


Figura 12.11 Pacientes com a síndrome de hiper-IgM ligada ao X são incapazes de ativar completamente suas células B.



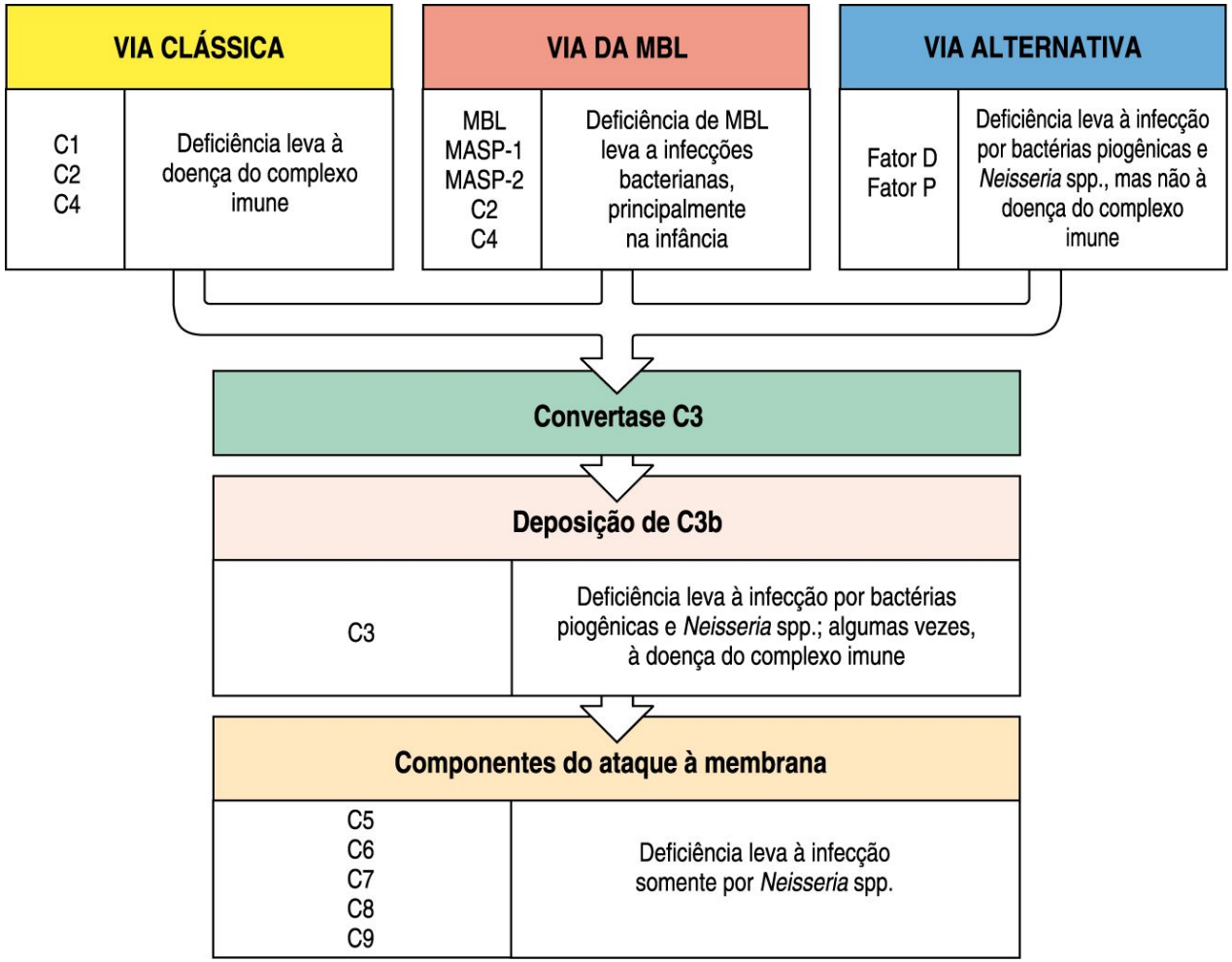
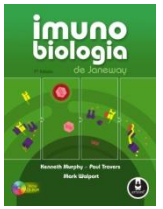


Figura 12.12 Defeitos nos componentes do complemento estão associados à suscetibilidade a certas infecções e ao acúmulo de complexos imunes.



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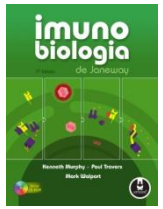
Síndrome de Chediak-Higashi	Infecção intra e extracelular, granulomas

Figura 12.13 Os defeitos nas células fagocíticas estão associados à persistência da infecção bacteriana.



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	Artemis	Recombinação do receptor do antígeno	$T^-B^-NK^+$	$T^-B^-NK^+$
Deficiência ADA	*ADA*	Metabolismo	$T^-B^-NK^-$	$T^-B^-NK^+$

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