Auto-imunidade

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

Mas qual o conceito de auto-imunidade mesmo ?

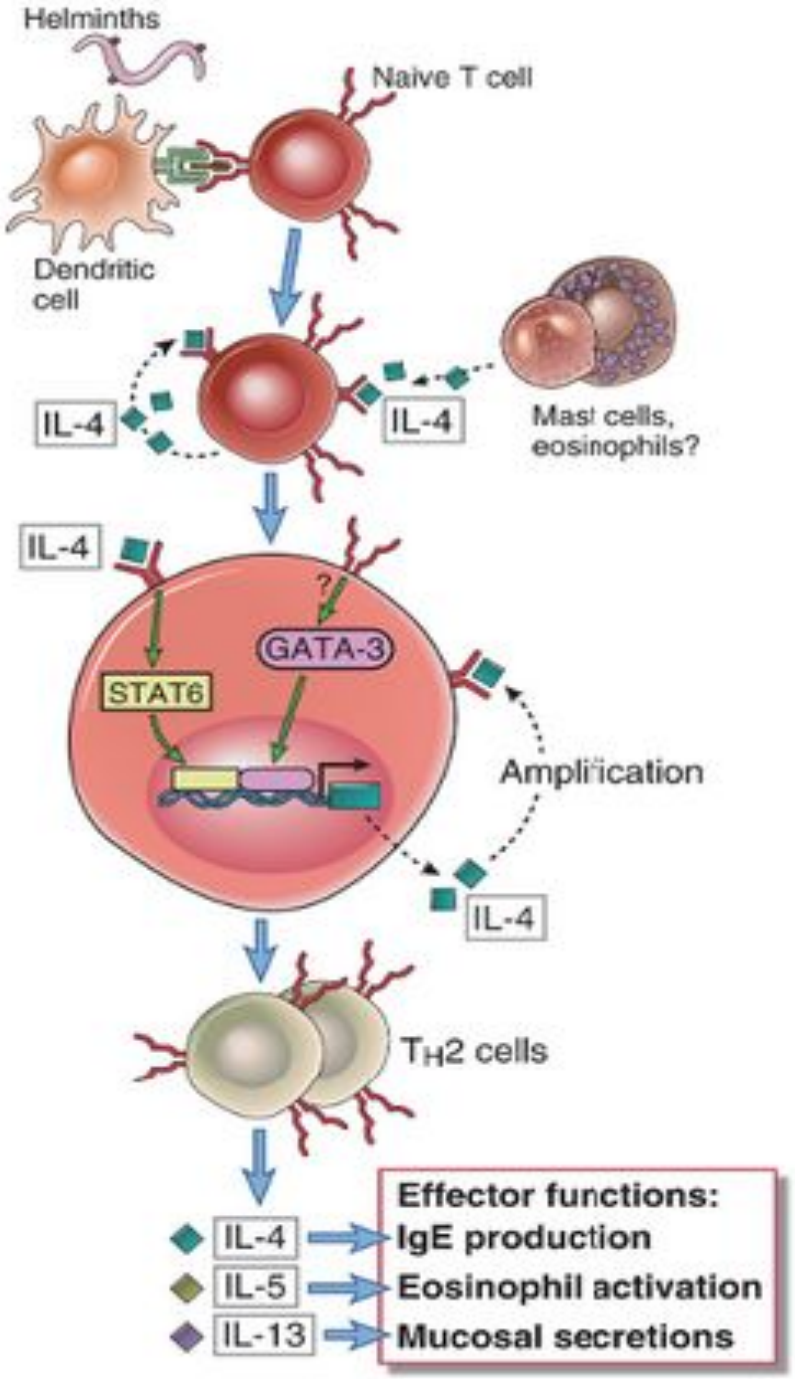
...sistema imune reconhece antígenos próprios e monta respostas inflamatórias contra estes, got it ?

Doença Autoimunes

- Humoral (Th2)
- Linfócitos B auto-reativos.
  - Ativação complemento
  - Fagócitos receptores Fc:
    - Neutrófilos
    - Macrófagos

- Celular (Th1-Th17)
- Linfócitos T auto-reativos.
  - T CD4
  - T CD8

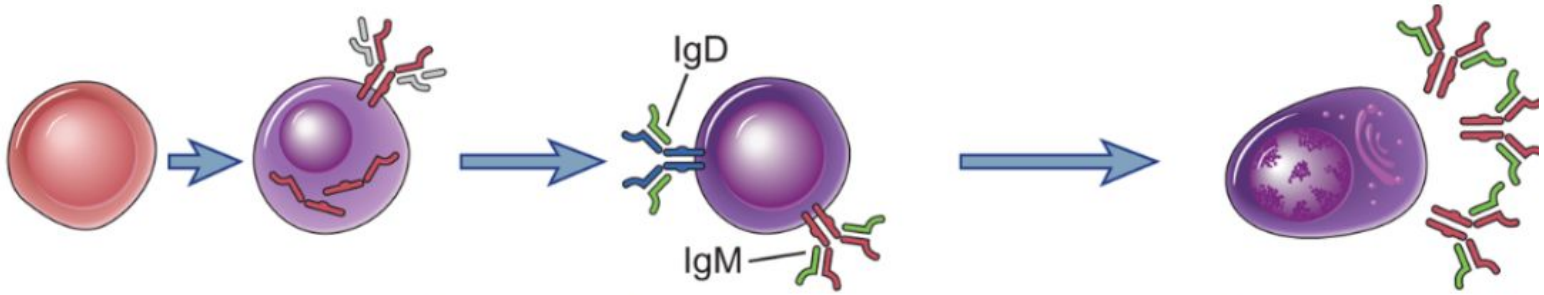
Morte Celular e Destruição Tecidual



Resposta Th2

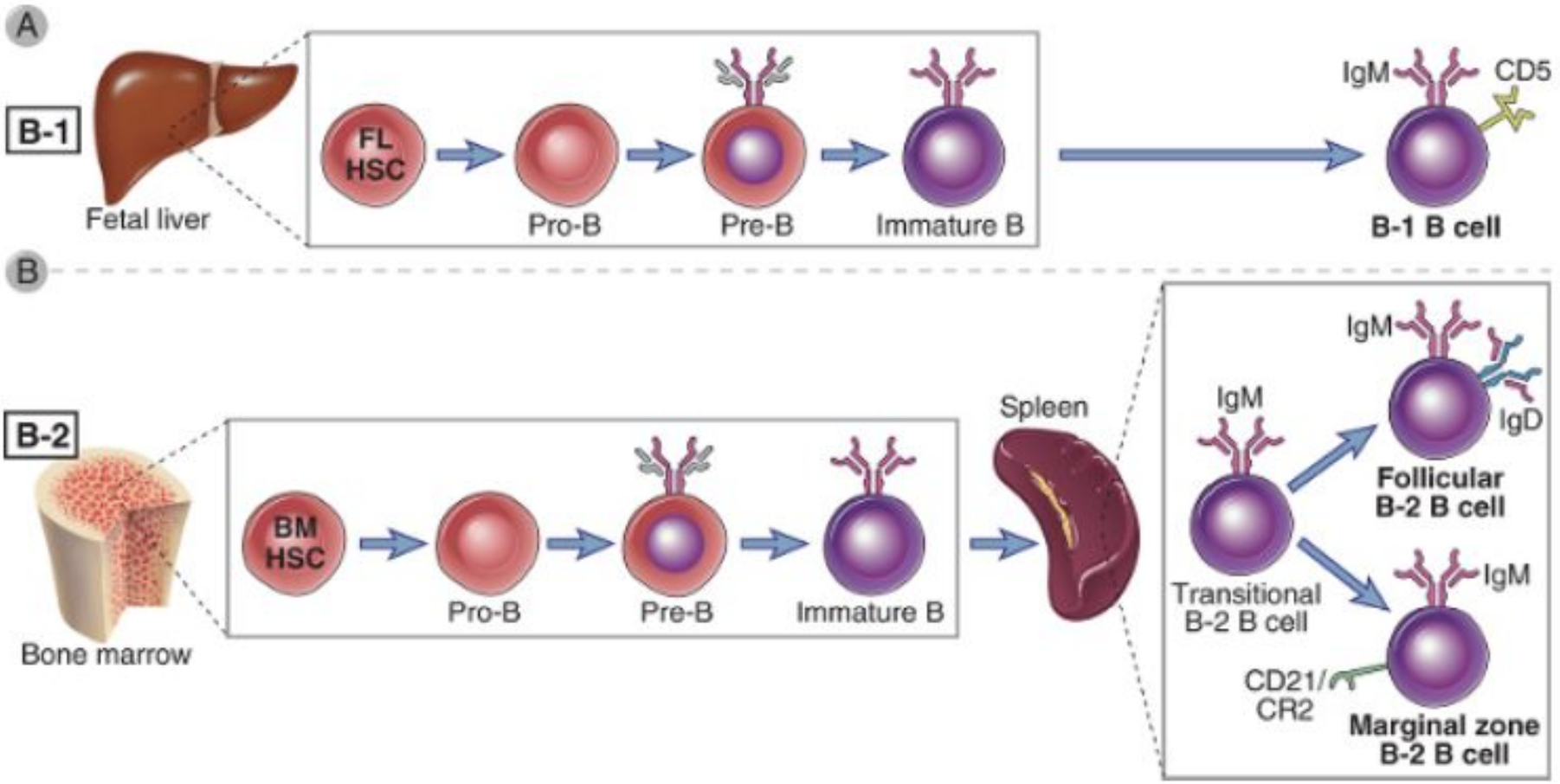
- Agentes Extra-celulares ou Vermes
- Anticorpos OPSONISANTES
- Ativação de vias do Complemento
- Desgranulação Granulócitos
- Ativação Monócitos
- Citocinas principais
- IL-4, IL-5, IL-13
- Fator de Transcrição
- STAT-6, GATA-3

Ontogenia Linfócitos B

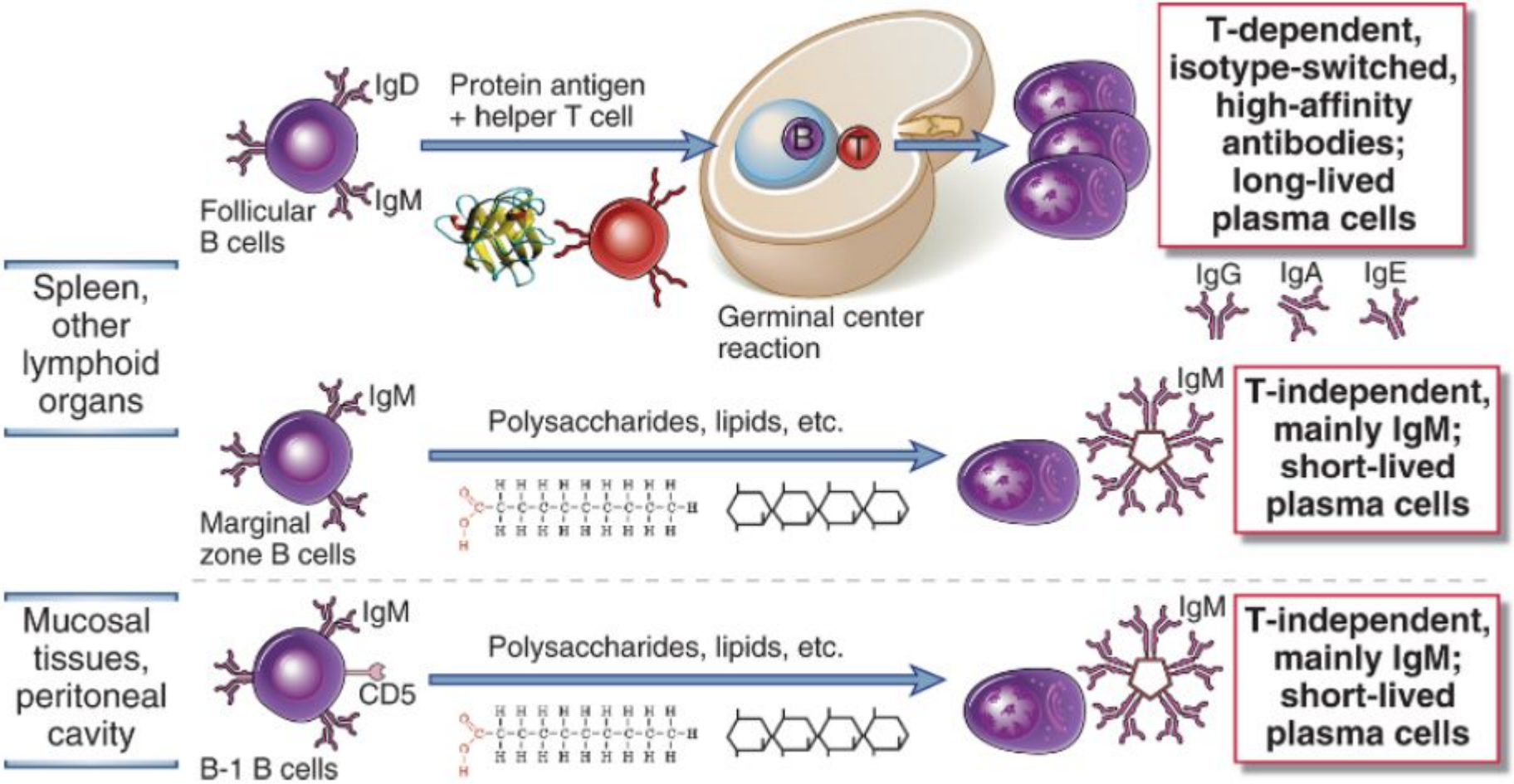


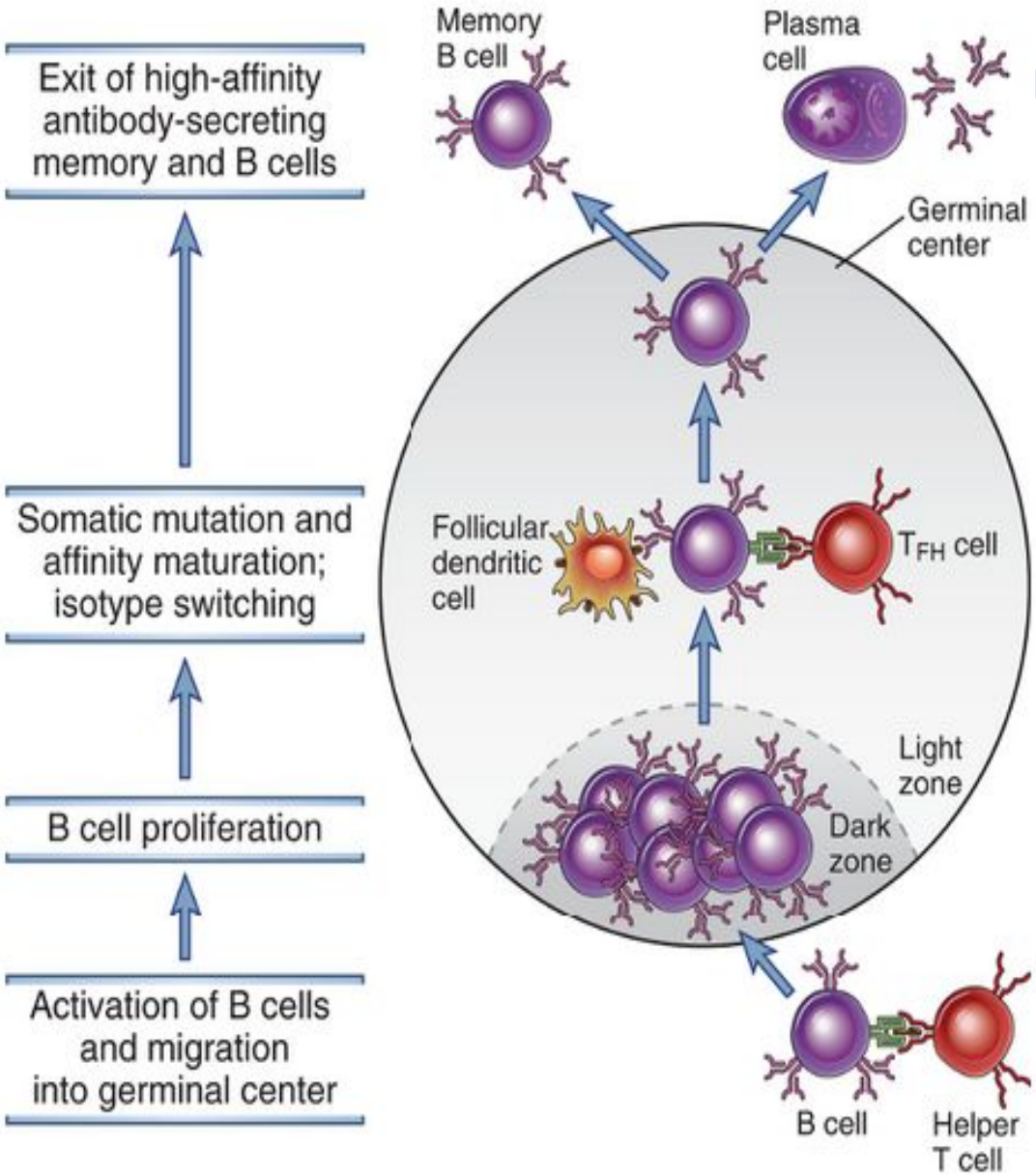
Stage of maturation	Stem cell	Pre-B cell	Immature B cell	Mature B cell	Activated B cell	Antibody-secreting cell
Pattern of immunoglobulin production	None	Cytoplasmic μ heavy chain and pre-B receptor	Membrane IgM	Membrane IgM, IgD	Low rate Ig secretion; heavy chain isotype switching; affinity maturation	High rate Ig secretion; reduced membrane Ig

Subtipos de Linfócitos B



Antígenos T Dependentes e Independentes





Auto-anticorpos

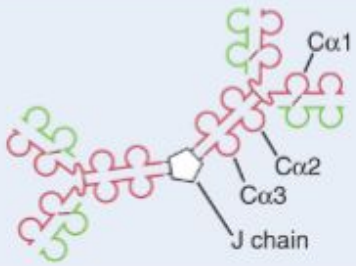
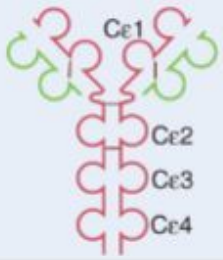
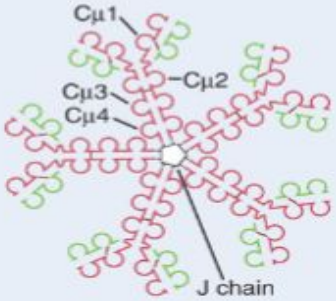
Membrana celular

Solúveis
(imunocomplexos)

Ativação dos
Mecanismos
Efetores da Resposta
Imune
Humoral

Ativação do
Complemento
Ativação de Fagócitos
Por Receptores Fc

TABLE 5–2 Human Antibody Isotypes

Isotope of Antibody	Subtypes (H Chain)	Serum Concentration (mg/mL)	Serum Half-life (days)	Secreted Form		Functions
IgA	IgA1,2 (α1 or α2)	3.5	6	IgA (dimer) Monomer, dimer, trimer		Mucosal immunity
IgD	None (δ)	Trace	3	None		Naive B cell antigen receptor
IgE	None (ε)	0.05	2	IgE Monomer		Defense against helminthic parasites, immediate hypersensitivity
IgG	IgG1-4 (γ1, γ2, γ3, or γ4)	13.5	23	IgG1 Monomer		Opsonization, complement activation, antibody-dependent cell-mediated cytotoxicity, neonatal immunity, feedback inhibition of B cells
IgM	None (μ)	1.5	5	IgM Pentamer		Naive B cell antigen receptor, complement activation

Tudo bem, já entendi essa história de Ag na membrana + Auto-anticorpo...

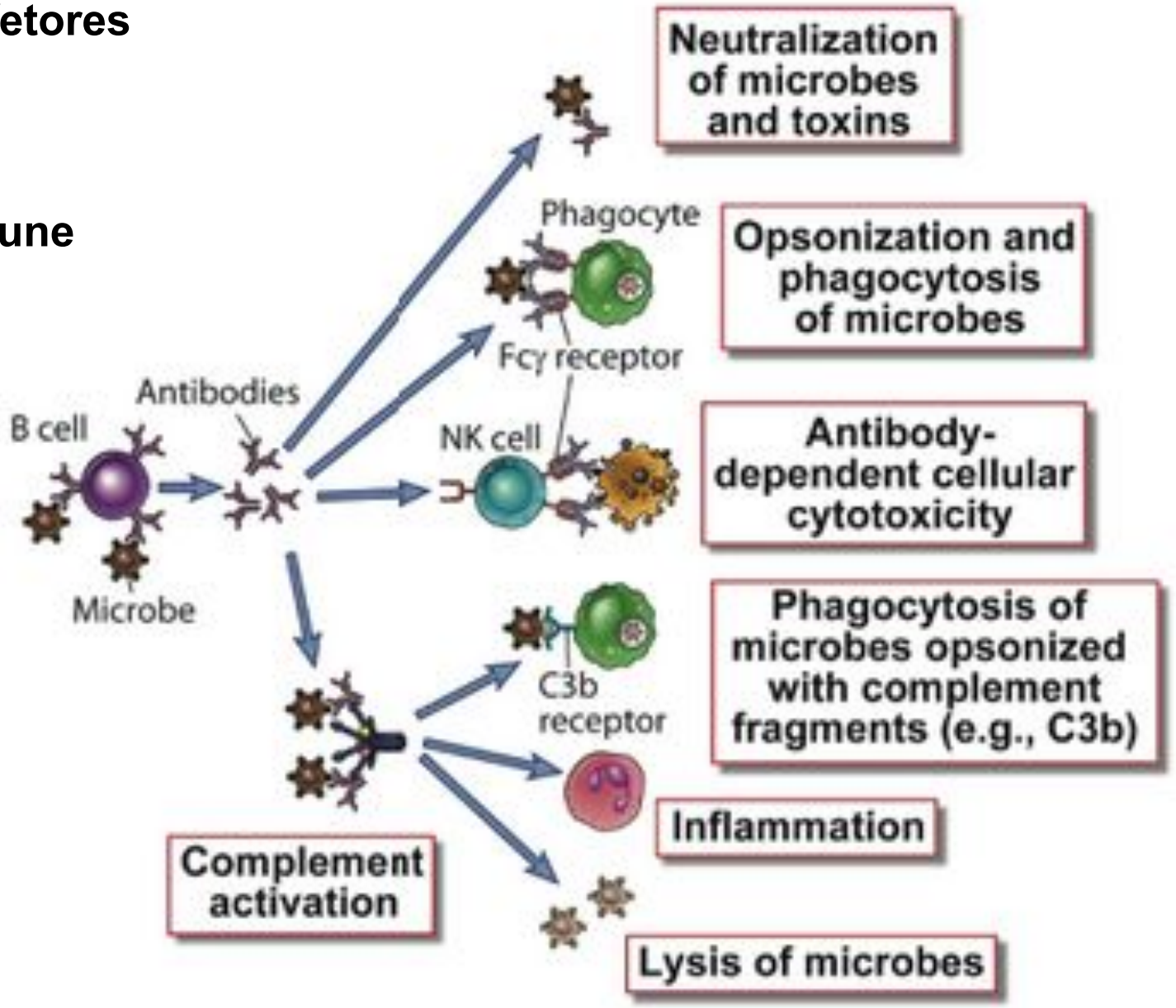
E os mecanismos, são os mesmos da resposta imune humoral ?

Exatamente ! Ativação do Complemento e Fagócitos !!!

Mecanismos Efetores

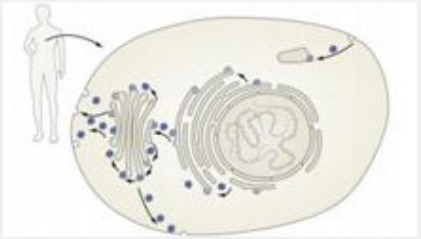
Da

Resposta Imune Humoral



Como se dá então, a destruição tecidual em cada tipo De doença auto-imune ?

2013 Medicine Prize



Transport of Molecular Cargo

The Nobel Prize in Physiology or Medicine 2013 was awarded jointly to James E. Rothman, Randy W. Schekman and Thomas C. Südhof.

"We Like People that Fail"

For James Rothman, science is a very emotional and social thing.

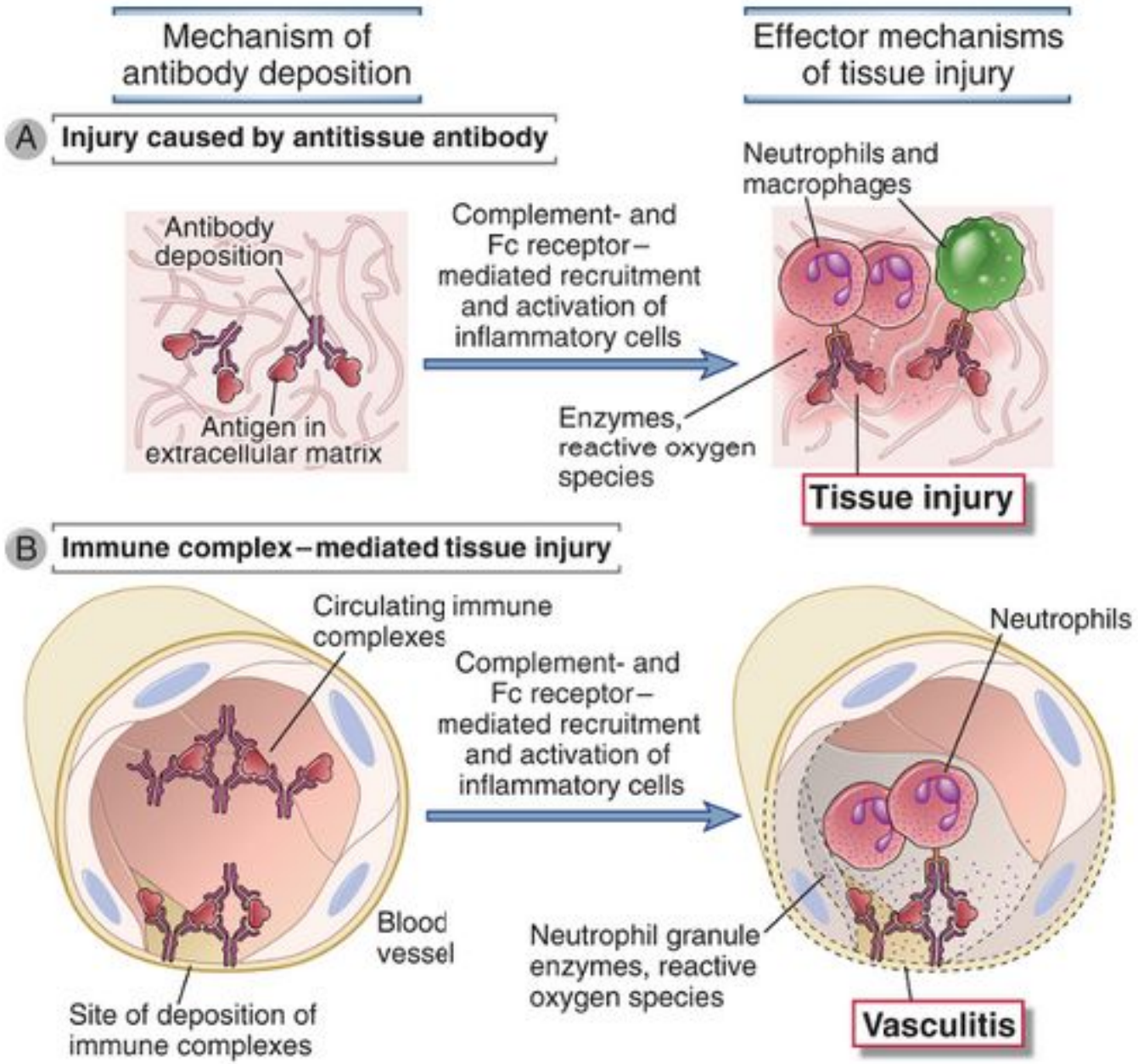
→ Listen to James E. Rothman

Randy W. Schekman in Interview

→ Watch Randy W. Schekman explain his Nobel Prize awarded work to young students

"Billions of Nerve Cells that Constantly Talk to Each Other"

→ Thomas C. Südhof explains his work in this video



Auto-anticorpos

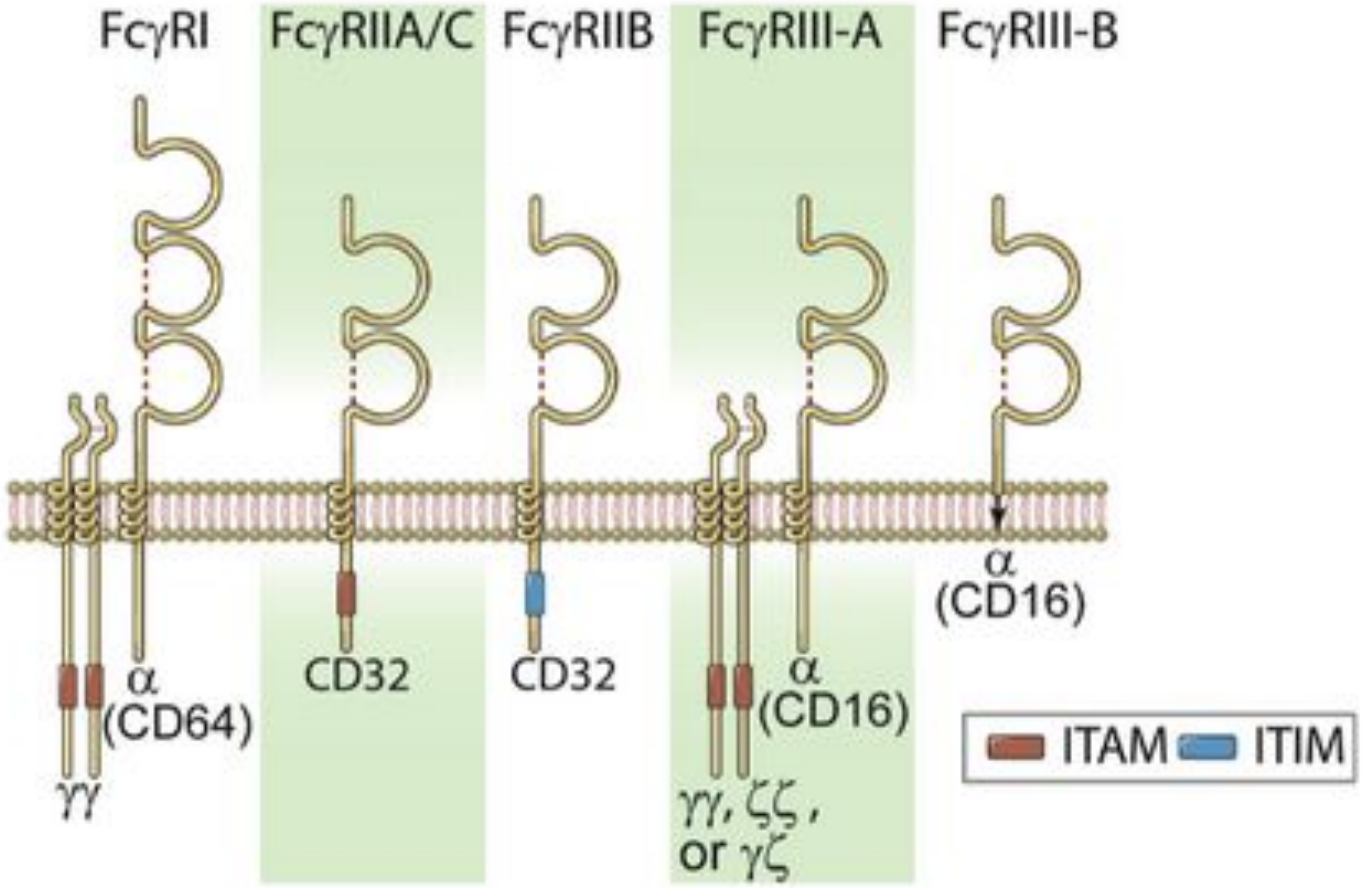
Contra Antígenos Presentes Na Membrana Celular

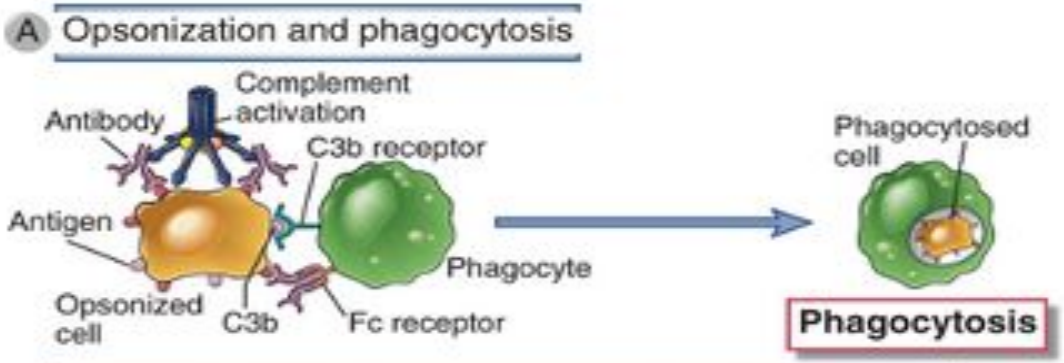
Ou

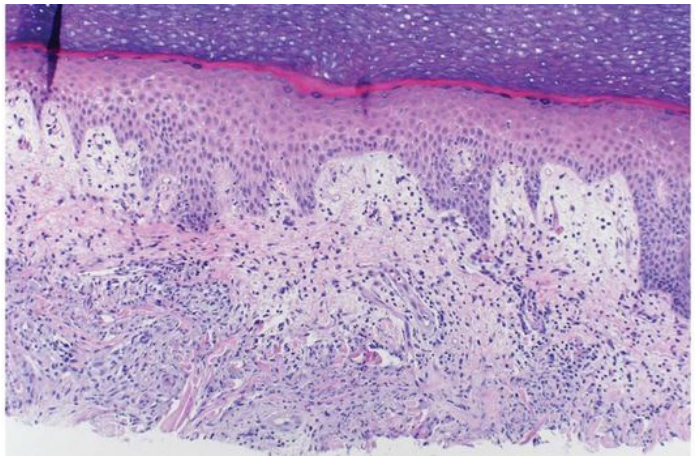
Solúveis

Gravidade da doença se relaciona:
Abundância Ag
Disponibilidade Ag
Tecido Acometido

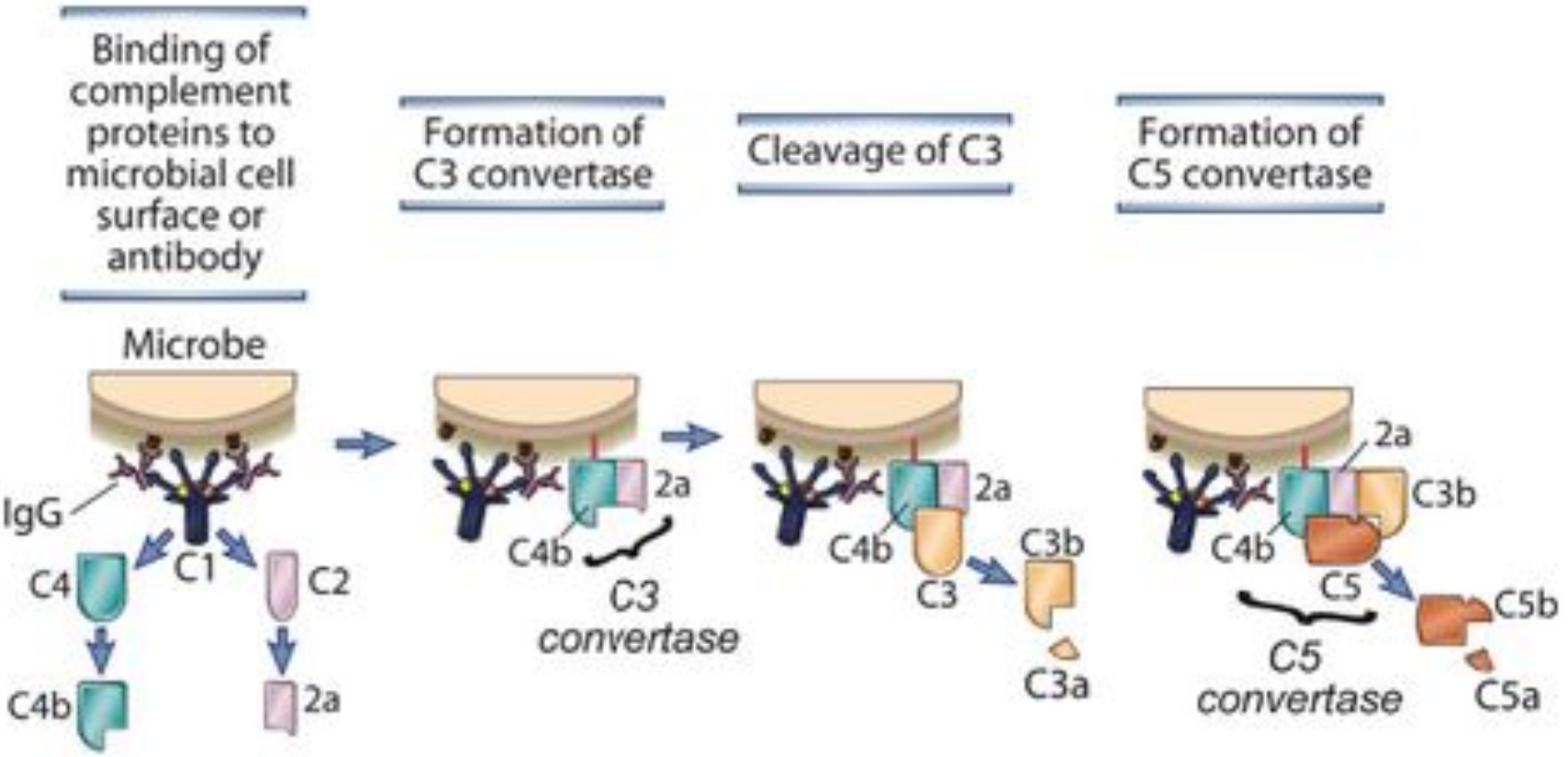
Subunit Composition of Fcγ receptors

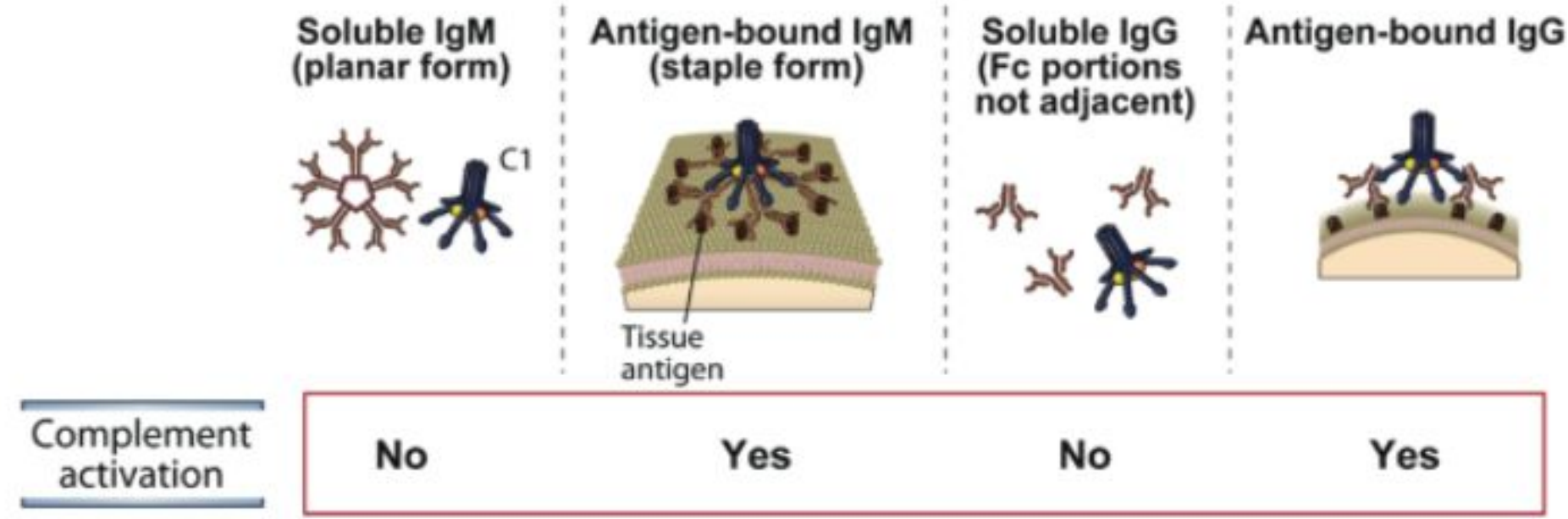


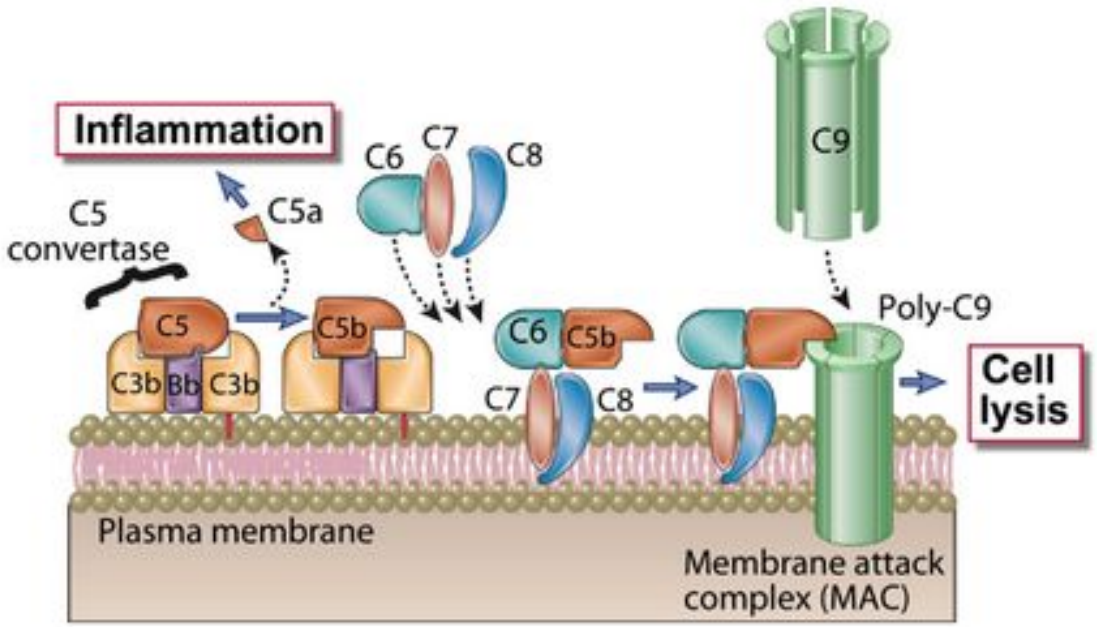

A Opsonization and phagocytosis
Complement activation
Antibody
C3b receptor
Antigen
Phagocyte
Opsonized cell
C3b
Fc receptor
Phagocytosed cell
Phagocytosis



Classical Pathway







Inflamação Local

Inicia-se

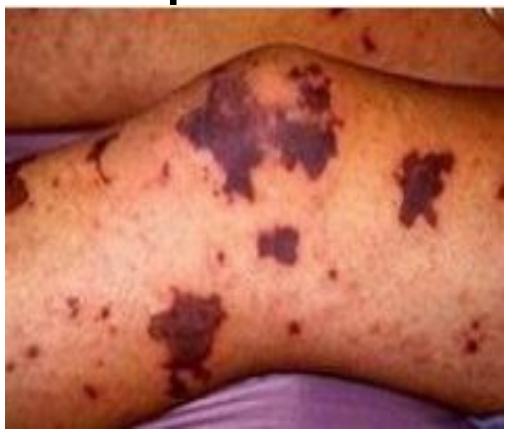
Lise Celular
Extravazamento
De Conteúdo

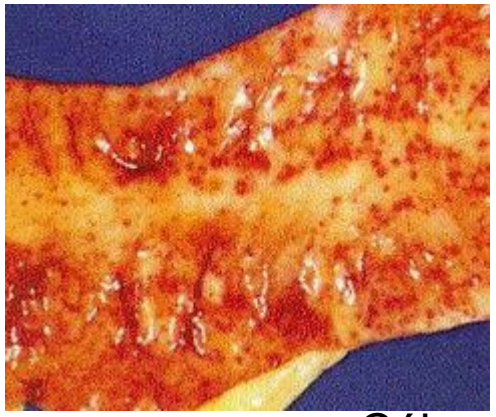
TABLE 18–2 Examples of Diseases Caused by Cell- or Tissue-Specific Antibodies

Disease	Target Antigen	Mechanisms of Disease	Clinicopathologic Manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes, complement-mediated lysis	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (gpIIb-IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (desmoglein)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation	Vasculitis
Goodpasture's syndrome	Non-collagenous NC1 protein of basement membrane in glomeruli and lung	Complement- and Fc receptor–mediated inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, downmodulates receptors	Muscle weakness, paralysis
Graves' disease (hyperthyroidism)	TSH receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Insulin-resistant diabetes	Insulin receptor	Antibody inhibits binding of insulin	Hyperglycemia, ketoacidosis
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor; decreased absorption of vitamin B_{12}	Abnormal erythropoiesis, anemia

ANCA, antineutrophil cytoplasmic antibodies; TSH, thyroid-stimulating hormone.

Anemia Hemolítica - Trombocitopenia





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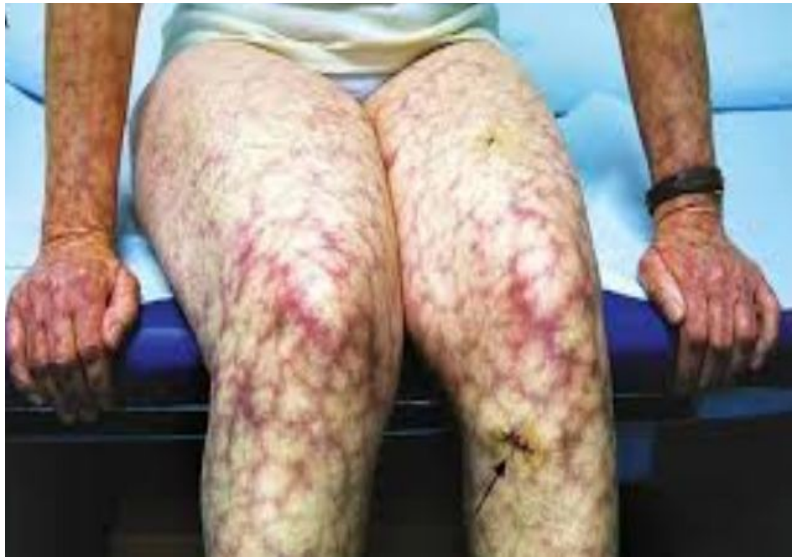
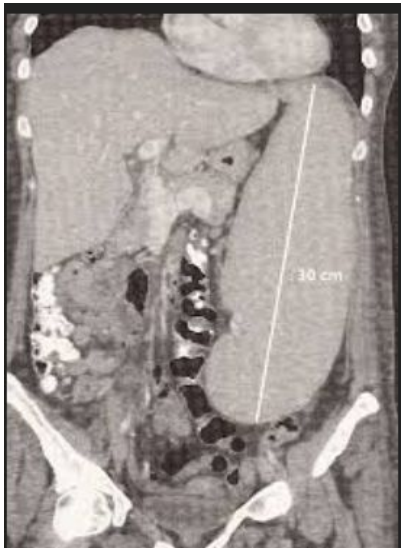
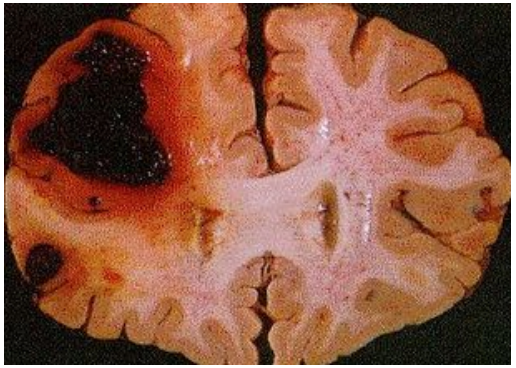


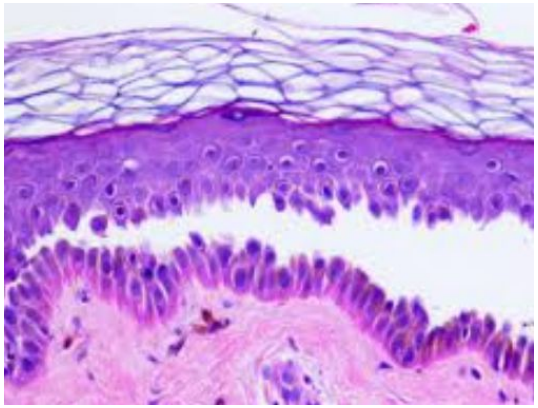
Anemia Hemolítica Trombocitopenia

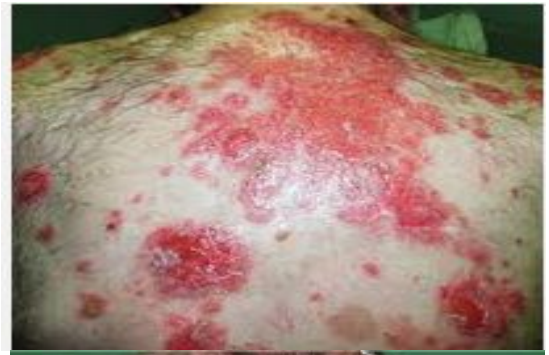


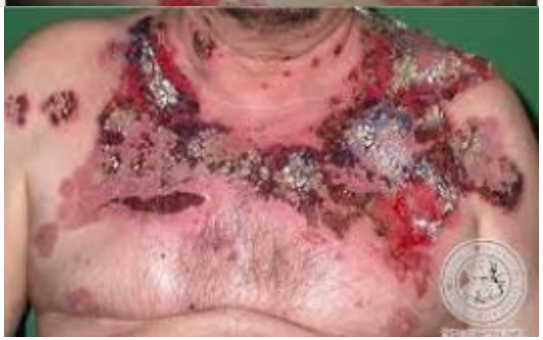


Esplenomegalia

Pemphigus vulgaris







Doença Auto-imune contra antígenos Da pele

Desmogleína é uma proteína importante Na adesão intercelular

Anticorpos anti-desdmogleína quebram a Estabilidade do tecido, resultando no descolamento
E formação de bolhas

Pode ser desencadeada por medicamentos

-Penicilamina
Inibidores da ECA
– Captopril, Enalapril...

J Invest Dermatol. 1996 Feb;106(2):351-5.

Pemphigus vulgaris antigen (desmoglein 3) is localized in the lower epidermis, the site of blister formation in patients.

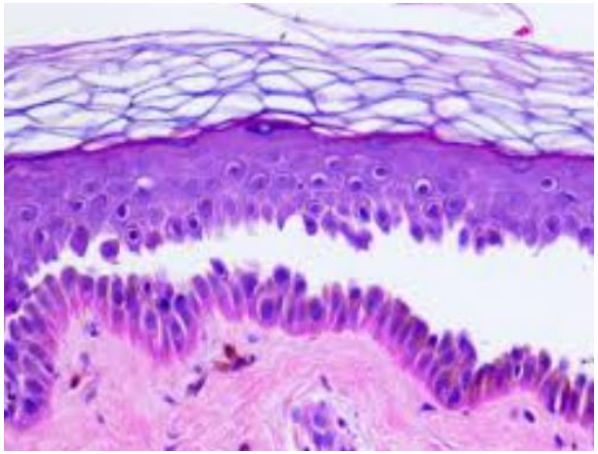
Amagai M[1], Koch PJ, Nishikawa T, Stanley JR.

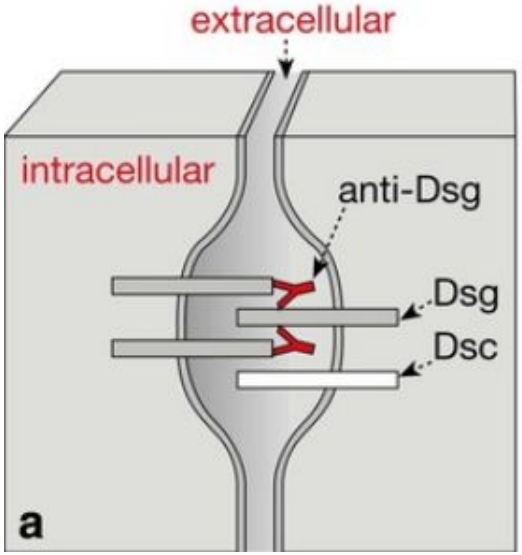
Author information

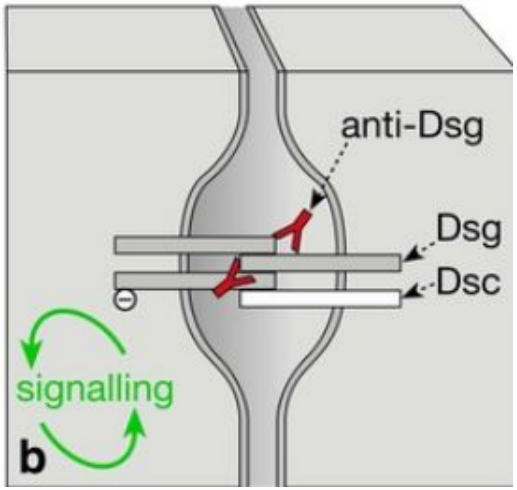
Abstract

In Patients with pemphigus vulgaris, autoantibodies against the desmosomal glycoprotein desmoglein 3 (Dsg3) cause blisters due to loss of keratinocyte cell-cell adhesion in the basal and immediate suprabasal layer of the deeper epidermis, leaving the superficial epidermis intact. Autoantibodies from these patients, however, usually bind to the cell surface of keratinocytes throughout the entire epidermis, as determined by indirect immunofluorescence. To explain this apparent paradox, we immunoadsorbed pemphigus vulgaris sera with the extracellular domains of Dsg3 and desmoglein 1 (Dsg1) produced by insect cells infected with recombinant baculovirus. When adsorbed with extracellular domains of both Dsg3 and Dsg1, these sera no longer stained epidermis, demonstrating that most, if not all, of their cell surface reactivity can be attributed to antibodies against the extracellular domains of these desmogleins. Adsorption with only the Dsg1 extracellular domain left antibodies that stained only the basal and immediate suprabasal layers of the epidermis and immunoprecipitated only Dsg3, not Dsg1, from extracts of cultured cells synthesizing these molecules. In contrast, adsorption with only the Dsg3 extracellular domain left antibodies that stained only the more superficial epidermis and immunoprecipitated only Dsg1. These data localize Dsg3 exactly to the area in the epidermis where blisters occur in pemphigus vulgaris.

PMID: 8601740 [PubMed - indexed for MEDLINE]







ANCA-Positive Vasculitis

Lavanya Kamesh†, Lorraine Harper*† and Caroline O. S. Savage*†

[+] Author Affiliations

Correspondence to Professor Caroline O. S. Savage, Renal Immunobiology, Division of Medical Sciences, The Medical School, University of Birmingham, Birmingham, UK, B15 277. Phone: 0-121-414-6841; Fax: 0-121-414-6840; E-mail: C.O.S.Savage@bham.ac.uk

Inflammation and necrosis of blood vessel wall occurs in a dozen or so primary vasculitic disorders. An attempt to classify these diverse forms of vasculitis resulted in the Chapel Hill international consensus definitions, which used the vessel size as the determinant of classification (1). Wegener granulomatosis, microscopic polyangiitis, and Churg Strauss syndrome are described as small-vessel vasculitides and are acknowledged to be commonly associated with antineutrophil cytoplasm antibodies (ANCA). These diseases share a common pathology with focal necrotizing lesions, which affect many different vessels and organs; in the lungs, a capillaritis may cause alveolar hemorrhage; within the glomerulus of the kidney, a crescentic glomerulonephritis may cause acute renal failure; in the dermis, a purpuric rash or vasculitic ulceration may occur. Wegener granulomatosis and Churg Strauss syndrome have additional granulomatous lesions (for further review, see reference 2). The incidence of these diseases is increasing, with more than 20 per million affected and occurring more often in an elderly population (peak age, 55 to 70 yr) (3).

« Previous | Next Article »
Table of Contents

This Article

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JASN July 1, 2002 vol. 13 no. 7 1953-1960

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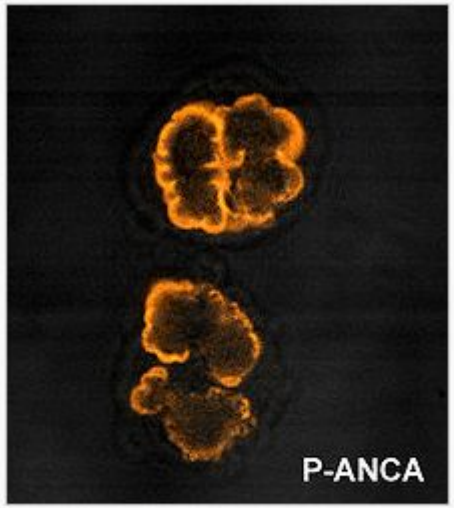
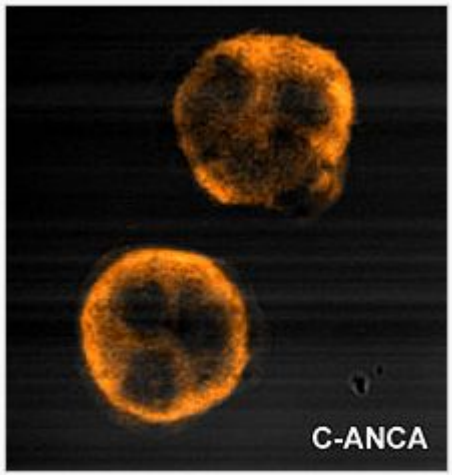
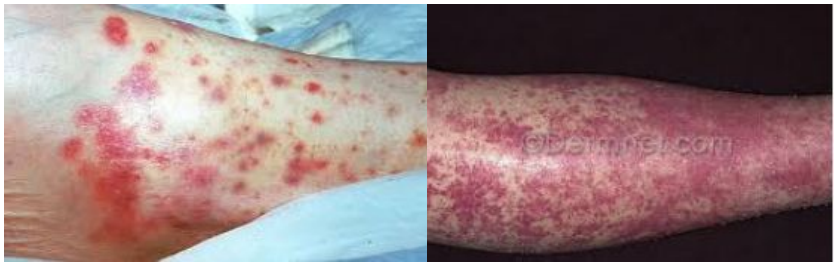
Anti-Neutrophil Cytoplasm Antibody



Perinuclear staining typical of p-ANCA



The granular, cytoplasmic staining pattern of c-ANCA



Mimetismo Molecular

98% dos pacientes são Portadores crônicos de *Staphylococcus aureus*

Depuração de Células em Apoptose De forma defeituosa

Geração de auto-anticorpos

Antígenos – Proteinase -3 Mieloperoxidase

frontiers in IMMUNOLOGY
http://www.frontiersin.org/Immunology

REVIEW ARTICLE
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Rheumatic heart disease: molecules involved in valve tissue inflammation leading to the autoimmune process and anti-*S. pyogenes* vaccine

***Luiza Guilherme*[1,2]* and *Jorge Kalil*[1,2,3]**

[1] *Heart Institute (InCor), School of Medicine, University of São Paulo, São Paulo, Brazil*
[2] *Immunology Investigation Institute, National Institute for Science and Technology, University of São Paulo, São Paulo, Brazil*
[3] *Clinical Immunology and Allergy Division, School of Medicine, University of São Paulo, São Paulo, Brazil*

Table 1 | Genes of genetic susceptibility of RF and RHD.

Genetic markers	Role
MBL; TLR2; FCN2; FCγRIIa	Innate immunity Inadequate immune response against *S. pyogenes*
HLA class II genes (DR and DQ, several alleles)	Adaptive immune response T cell antigen presentation and immune response
TNF-α, ILRA, TGF-β, IL-10	Both innate immunity/adaptive immune response Mediators of inflammatory reactions

INTRODUCTION

Rheumatic fever (RF) and its major sequelae rheumatic heart disease (RHD) are autoimmune diseases that arise following infection of the throat by *S. pyogenes* in children and young individuals (3–19 years old) who present genetic components that confer susceptibility to the disease.

The disease still remains a major cause of cardiovascular disability in school children and young individuals, and it represents a high burden for public health in the developing world. The incidence of this disease in the so-called "hotspots" ranges from 20 to 51 per 100,000 habitants, causing ~500,000 deaths each year (1). In Brazil, the number of beta hemolytic streptococcus throat infections is ~10 million cases/year, leading to 30,000 new cases of RF, of which ~15,000 cases develop RHD (2).

The aim of this review is to explore the role of several genes in the control of *S. pyogenes* infection and the associated autoimmune reactions, as well as to depict the molecular mechanisms leading to these autoimmune reactions.

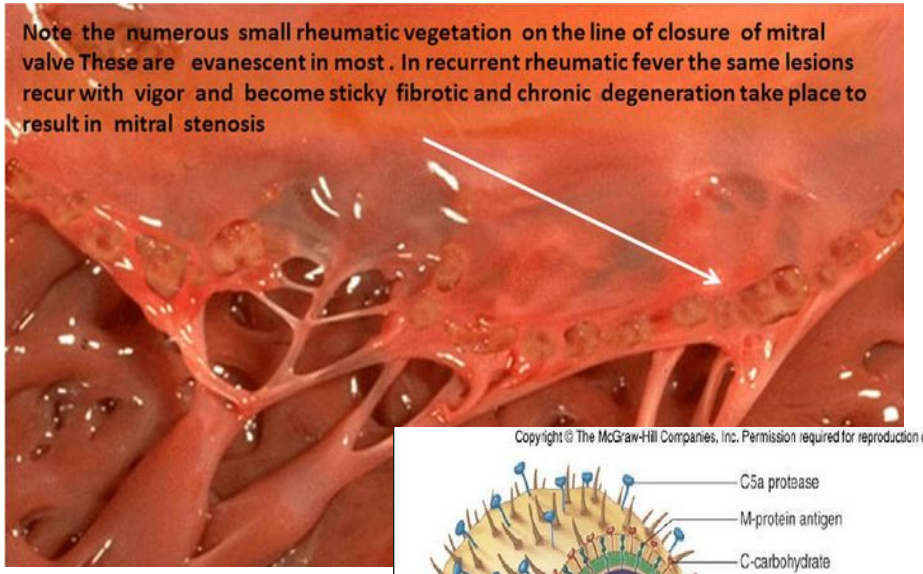
Febre Reumática – pós Streptococcus pyogenes A

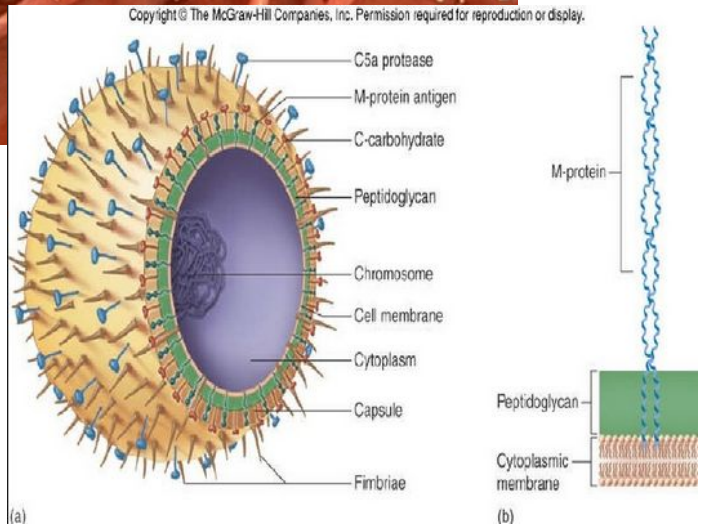
Afeta frequentemento
Crianças de 5 -15 anos
Ocorre aproximadamente
14-28 dias depois da infecção.

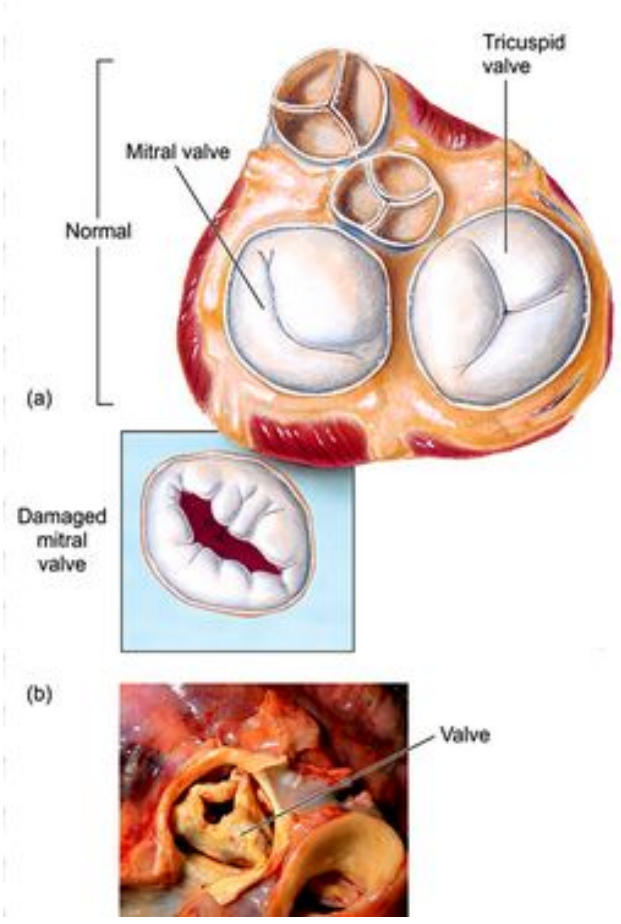
Mimetismo Molecular

Anticorpos Anti-proteína M
Pericardite – Miocardite – Valvulite
Miosina Cardíaca (miocpardio pericárdio)
Vimentina (vávulas)

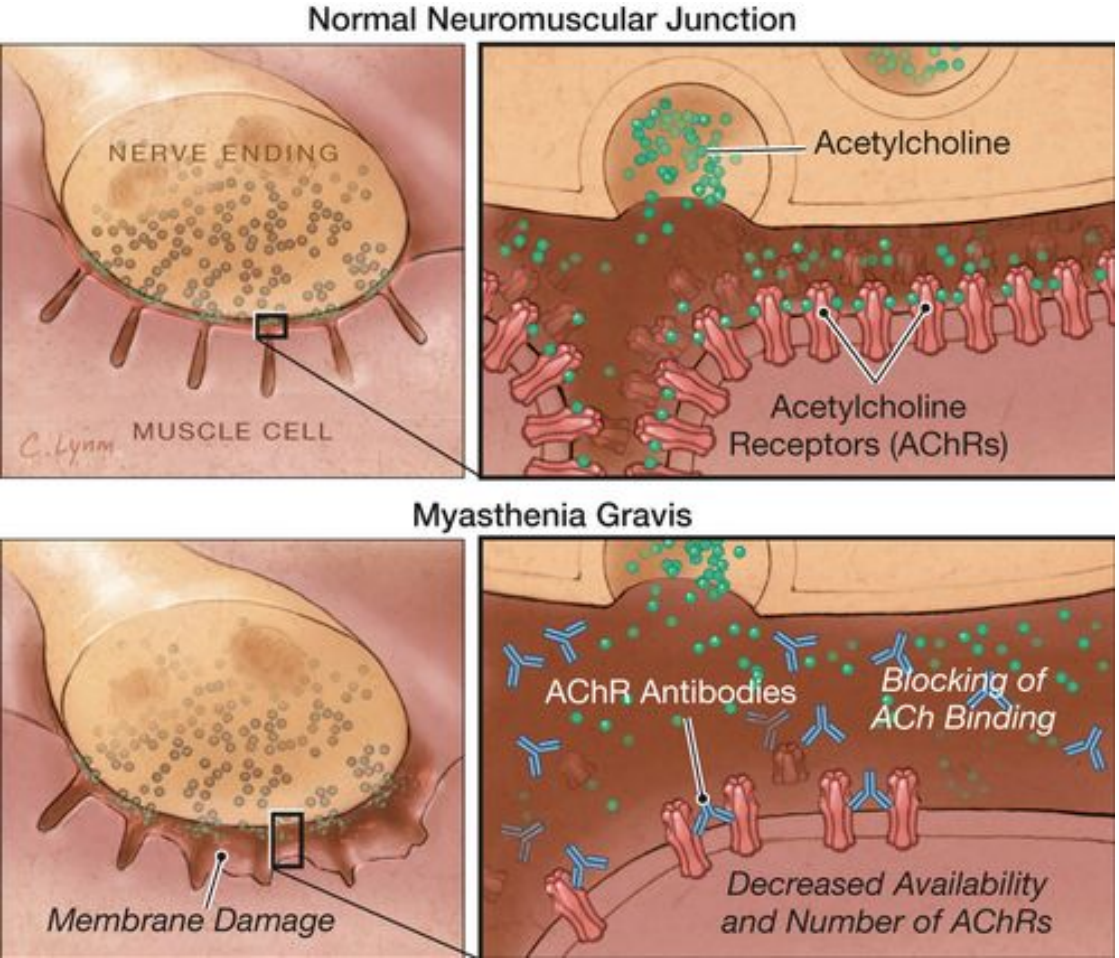
Lysoganglioside GM1 - *N-acetyl-b-d-glucosamine*
*(*Sydenham Chorea (SC) - acomete SNC







Myasthenia gravis



Antibody Dependent

Bloqueio dos Receptores Colinérgicos

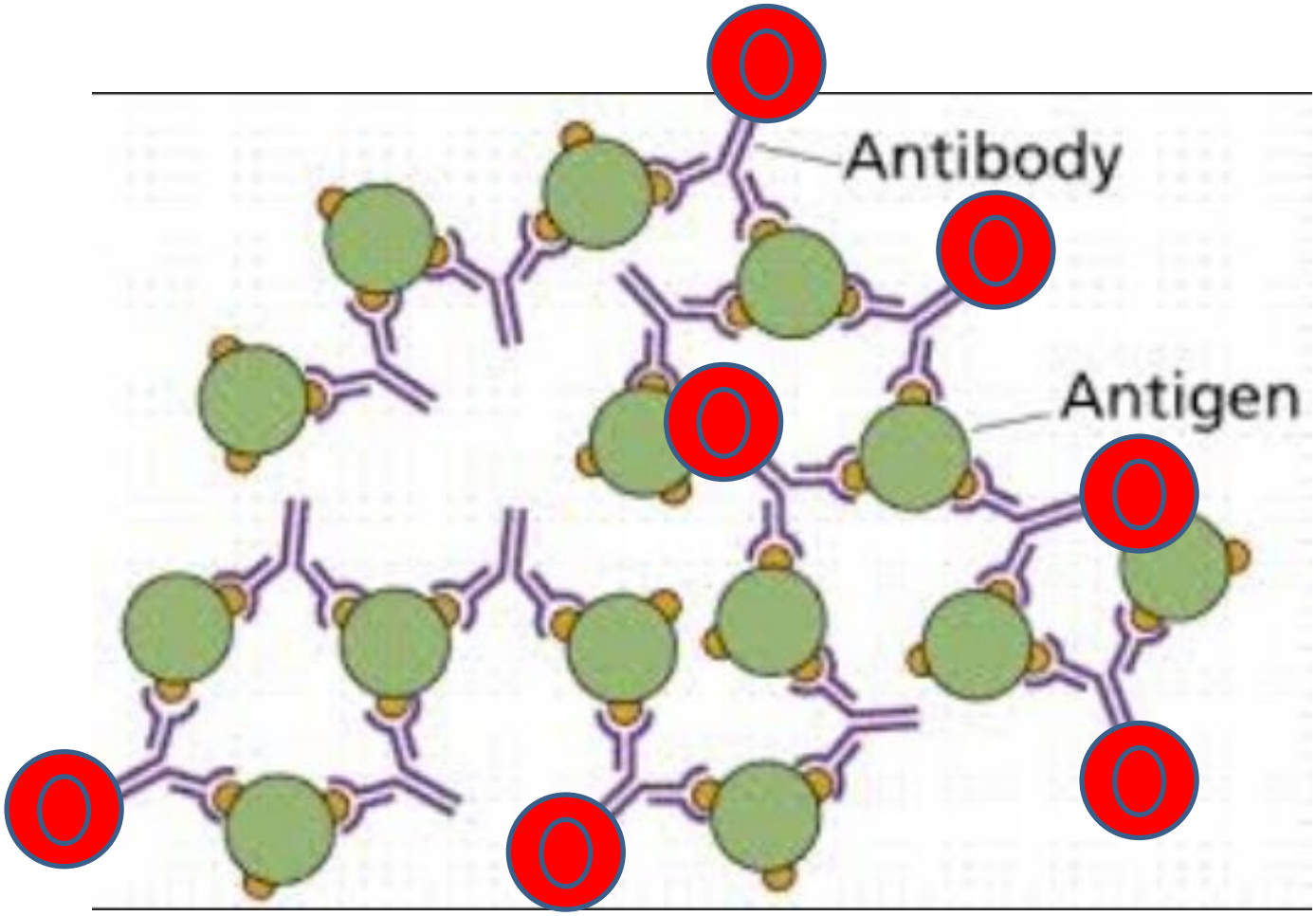
Flacidez – Espasmos

Paralisia

TABLE 18–1 Classification of Immunologic Diseases

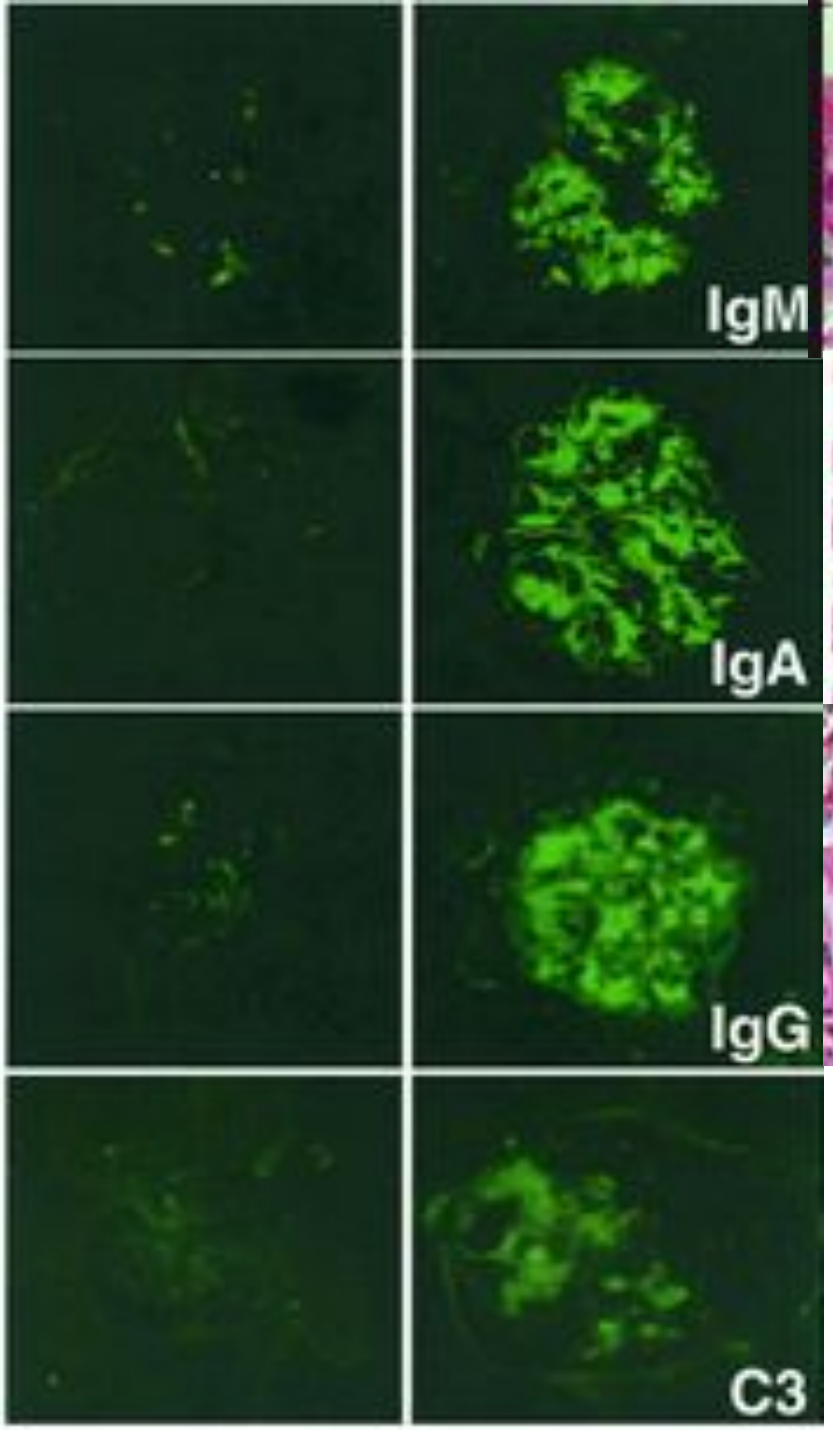
Type of Hypersensitivity	Pathologic Immune Mechanisms	Mechanisms of Tissue Injury and Disease
Immediate hypersensitivity: type I	IgE antibody	Mast cells and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody mediated: type II	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular functions, e.g., hormone receptor signaling
Immune complex mediated: type III	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement- and Fc receptor–mediated recruitment and activation of leukocytes
T cell mediated: type IV	$CD4^+$ T cells (cytokine-mediated inflammation) $CD8^+$ CTLs (T cell–mediated cytolysis)	Recruitment and activation of leukocytes Direct target cell killing, cytokine-mediated inflammation

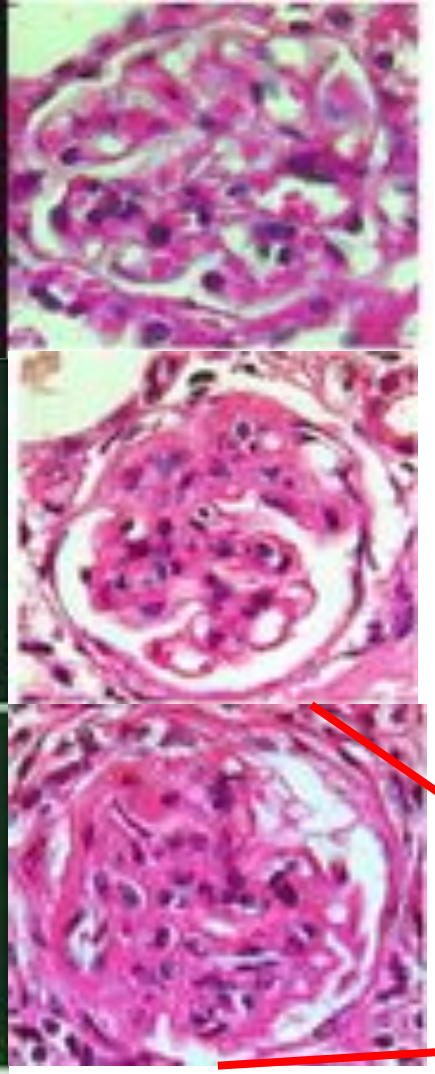
Imunocomplexo
Hipersensibilidade Tipo III



Receptores

CR1



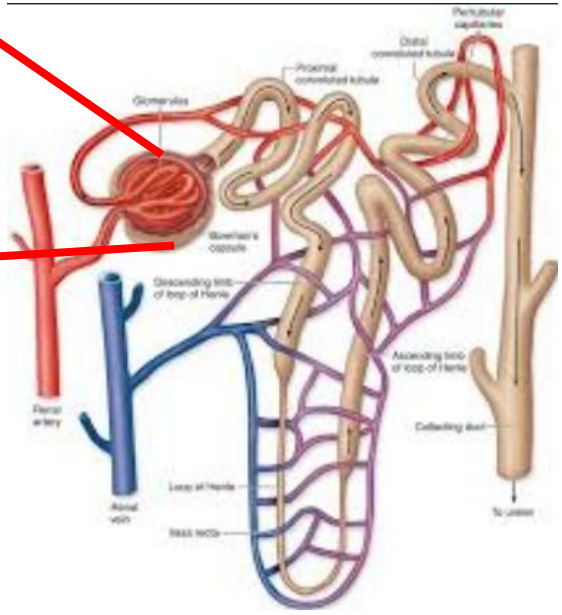


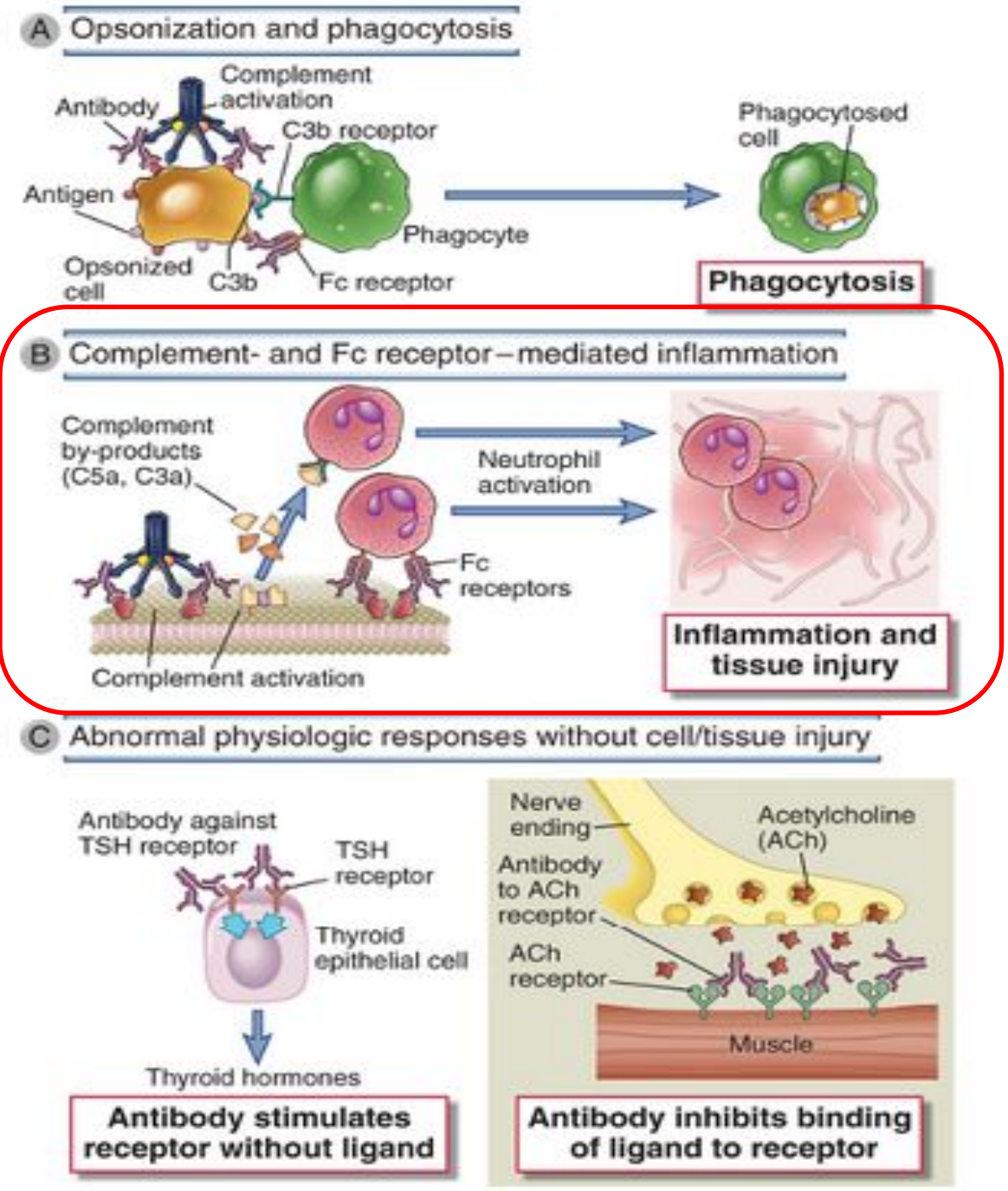
Imunocomplexos Depositados nos Rins

IgM

IgA

IgG





Hipersensibilidade Tipo II

Contra Antígenos Celulares (Geralmente Menbrana)

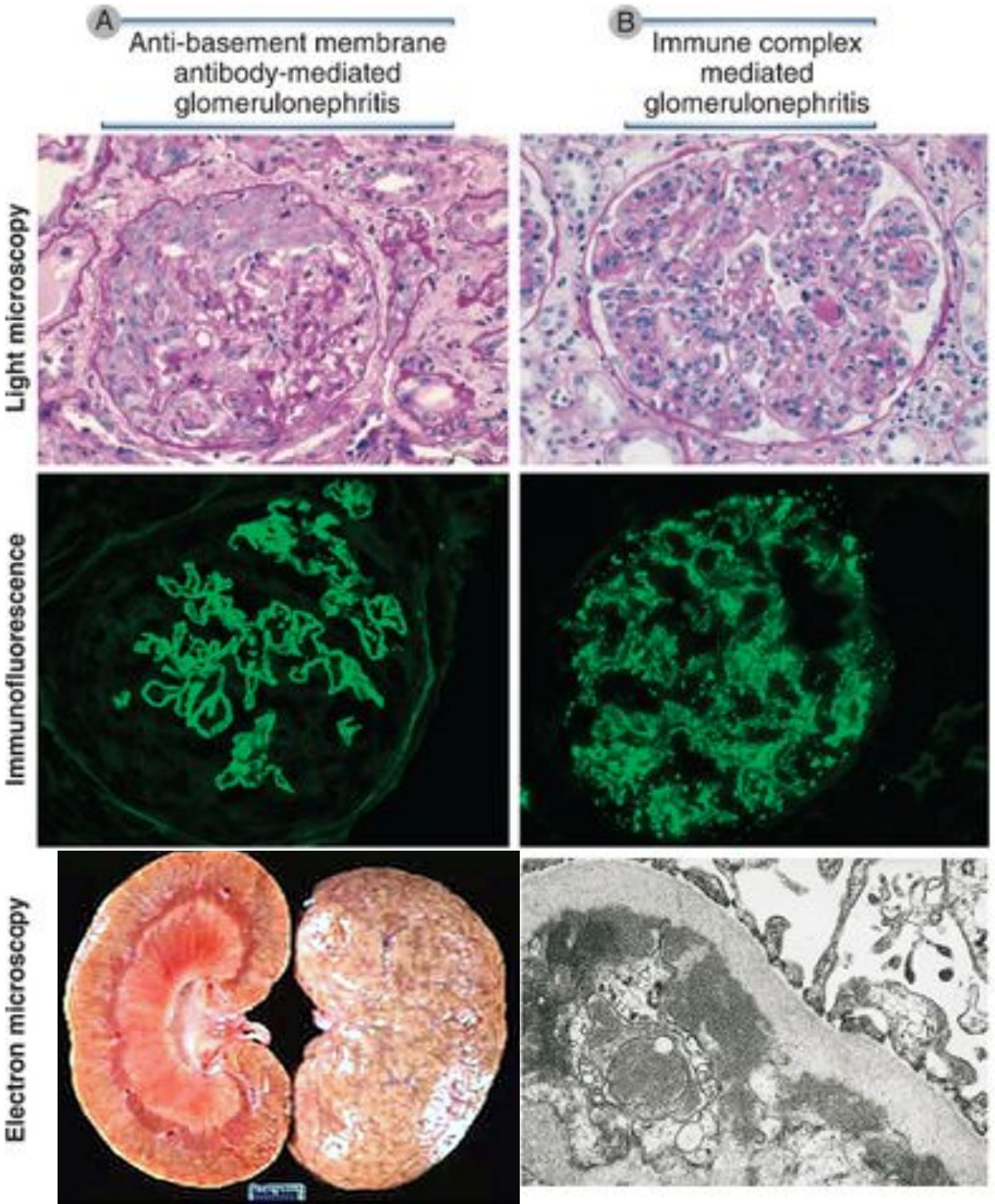
Auto-anticorpos

Mioglobina
DNA
Histonas
Ags exógenos

Medicamentos

Gravidade da doença se relaciona:
Abundância Ag

Tecido Acometido
Rins
Articulações



Anticorpo anti-membrana basal
Tipo II

Vs.

Deposição de Imunocomplexo
Tipo III

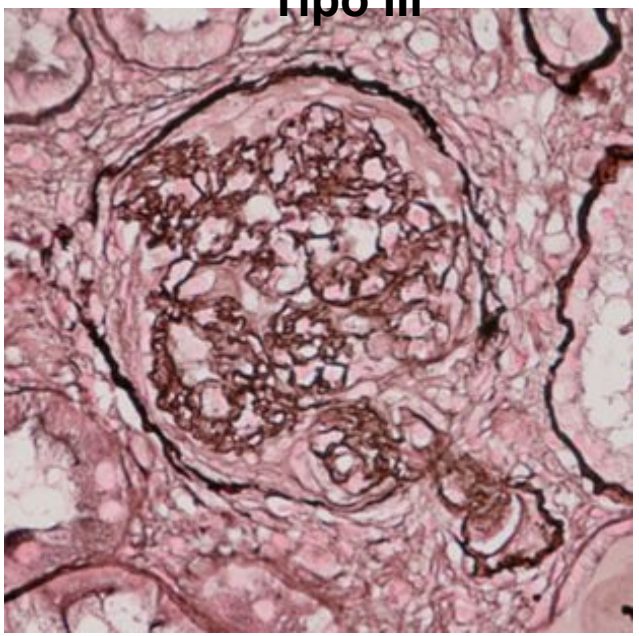
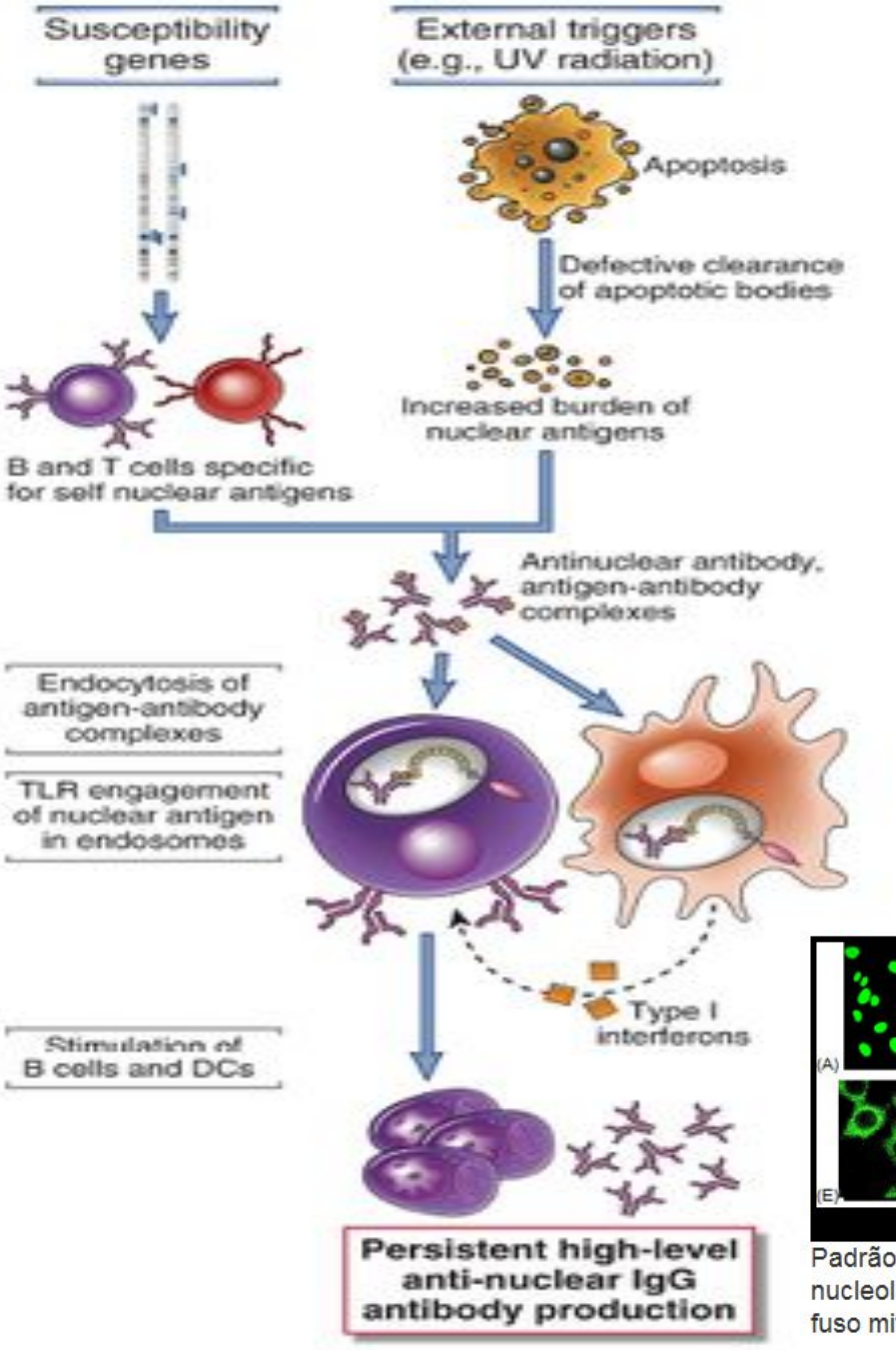
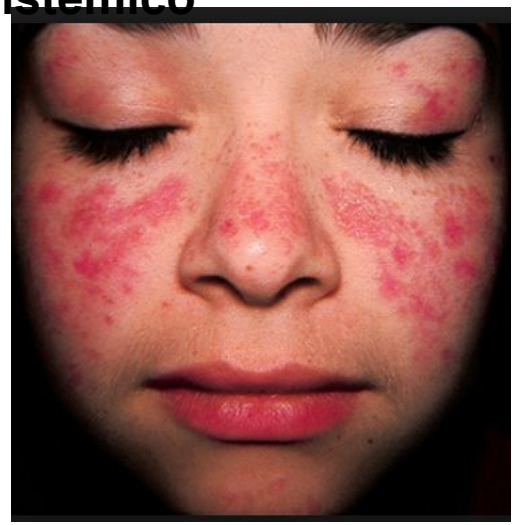


TABLE 18–3 Examples of Human Immune Complex–Mediated Diseases

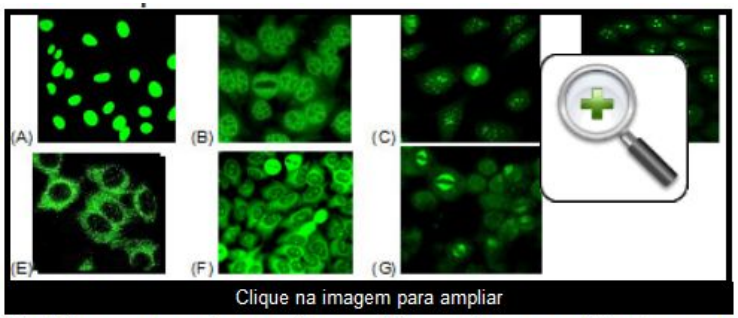
Disease	Antigen Involved	Clinicopathologic Manifestations
Systemic lupus erythematosus	DNA, nucleoproteins, others	Nephritis, arthritis, vasculitis
Polyarteritis nodosa	Hepatitis B virus surface antigen	Vasculitis
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigens; may be "planted" in glomerular basement membrane	Nephritis
Serum sickness	Various proteins	Arthritis, vasculitis, nephritis



Lupus Eritematoso Sistêmico



Rash cutâneos



Clique na imagem para ampliar

Padrão nuclear homogêneo (A), nuclear pontilhado grosso (B), centromérico (C), nucleolar (D), citoplasmático (E), misto citoplasmático pontilhado fino e nucleolar (F), fuso mitótico (G).

Anticorpos Anti-DNA, Anti-Histona Fatores Anti-núcleo

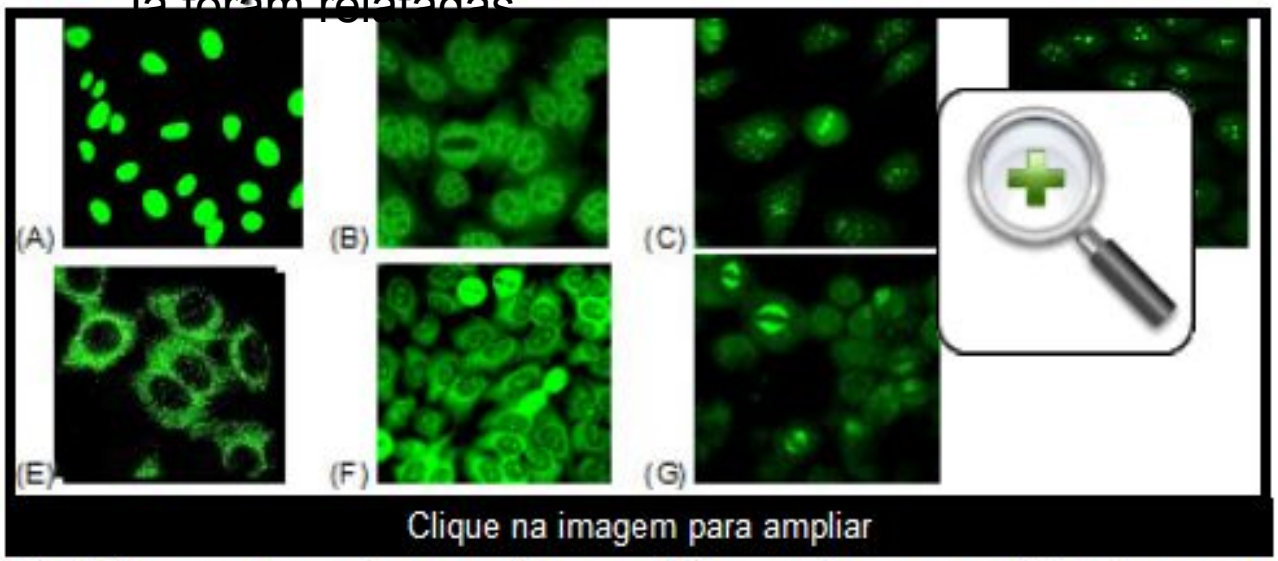
Agentes Infecciosos

Ainfecções por HTLV
Já foram relatadas

Radiação UV

Rash cutâneos
Ativam a doença

Químicos
Hidralazine, Procainamid e Isoniazid



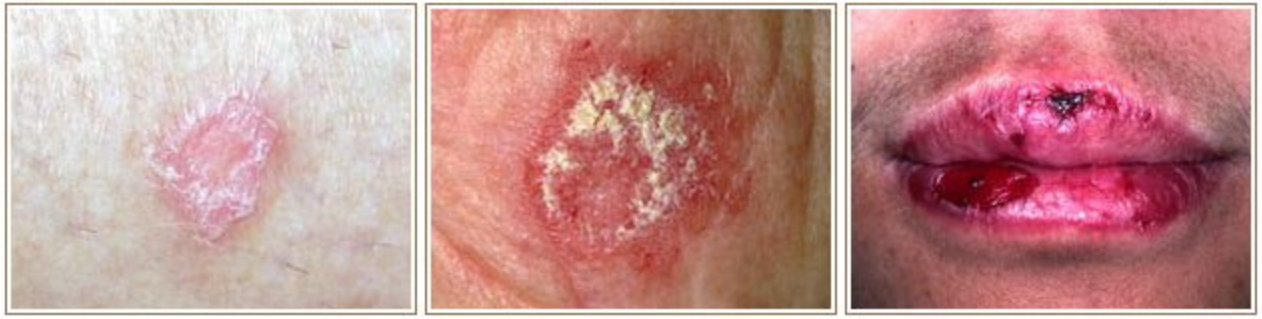
Padrão nuclear homogêneo (A), nuclear pontilhado grosso (B), centromérico (C), nucleolar (D), citoplasmático (E), misto citoplasmático pontilhado fino e nucleolar (F), fuso mitótico (G).

Discoid lupus erythematosus

In the most common form, discoid LE, unsightly red scaly patches develop which leave postinflammatory pigmentation and white scars. It may be localised or widespread.

- Discoid LE predominantly affects the cheeks, nose and ears, but sometimes involves the upper back, V of neck, and backs of hands.
- Hypertrophic LE results in thickened and warty skin resembling viral warts or skin cancers.
- Rarely, discoid LE occurs on the palms and/or soles (palmoplantar LE).
- If the hair follicles are involved, they are first plugged with adherent scale and then bald areas can develop. If the follicles are destroyed, the bald patches are permanent (scarring alopecia).
- Discoid LE may affect the lips and inside the mouth, causing ulcers and scaling. These lesions may predispose to squamous cell carcinoma.

Discoid lupus erythematosus

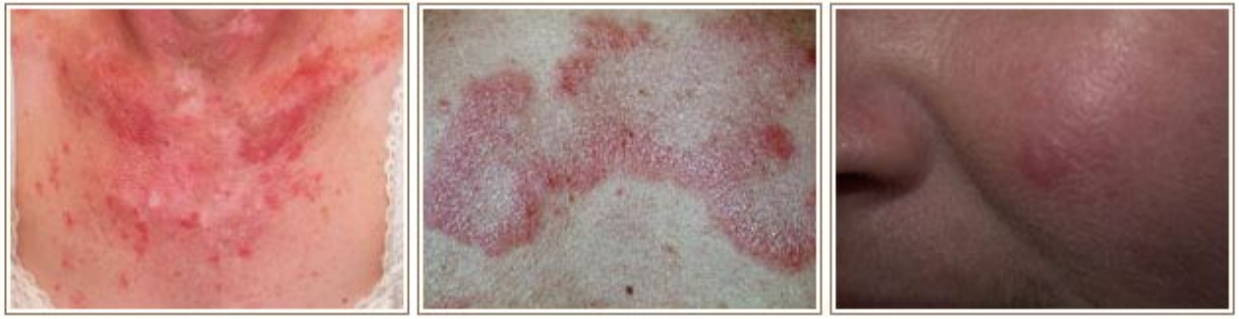


Lupus tumidus

Lupus erythematosus tumidus is a dermal form of lupus. The rash is characteristically photosensitive, so it affects sun-exposed sites. It presents with red, swollen, urticaria-like bumps and patches, some of which are ring-shaped (annular). It tends to clear during the winter months and does not leave any marks or scars.

Lupus tumidus is similar to Jessner lymphocytic infiltrate, in which diagnostic criteria for lupus are absent.

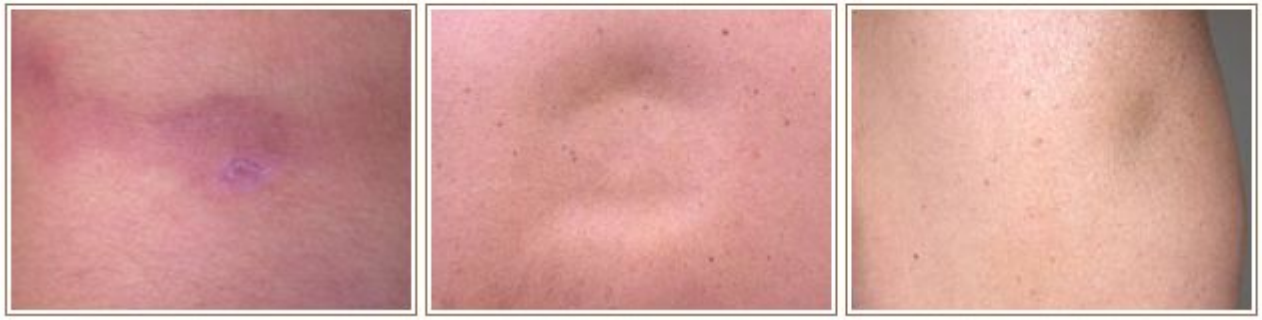
Lupus tumidus



Lupus profundus

Lupus profundus is the name given to lupus affecting the fat underlying skin and may also be called 'lupus panniculitis'. it may develop at any age, including children. The face is the most common area to be affected. Inflammation of the fat results in firm deep nodules for some months. The end result is unsightly dented scars (lipodystrophy) as the fat cells are completely destroyed by the lupus.

Lupus profundus

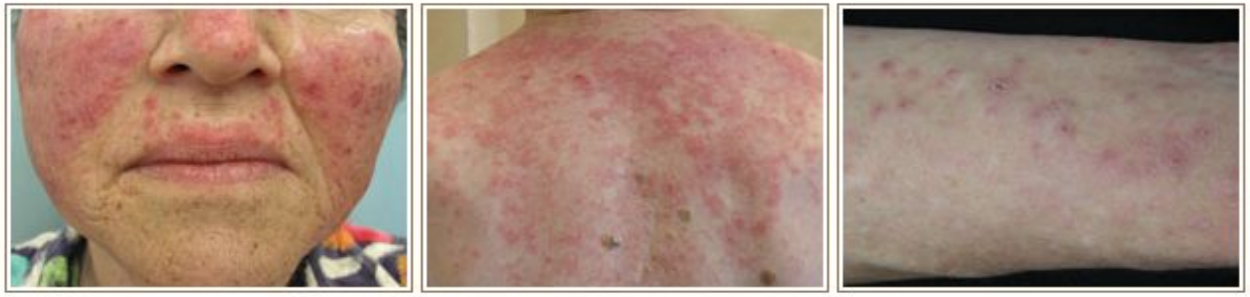


Drug-induced lupus erythematosus

Certain medications may rarely precipitate lupus in predisposed individuals. Generally symptoms take some months to develop. Drug-induced lupus does not usually affect the skin. The most frequent drugs to be implicated are:

- Hydralazine
- Carbamazepine
- Lithium
- Phenytoin
- Sulphonamides
- Minocycline

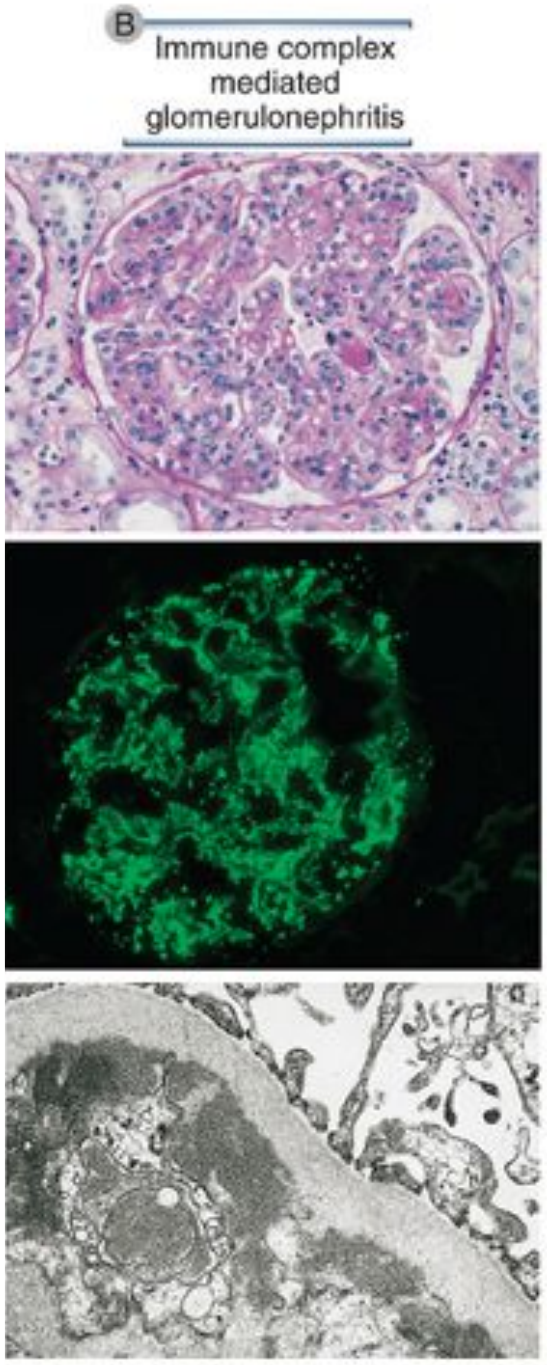
Drug-induced lupus



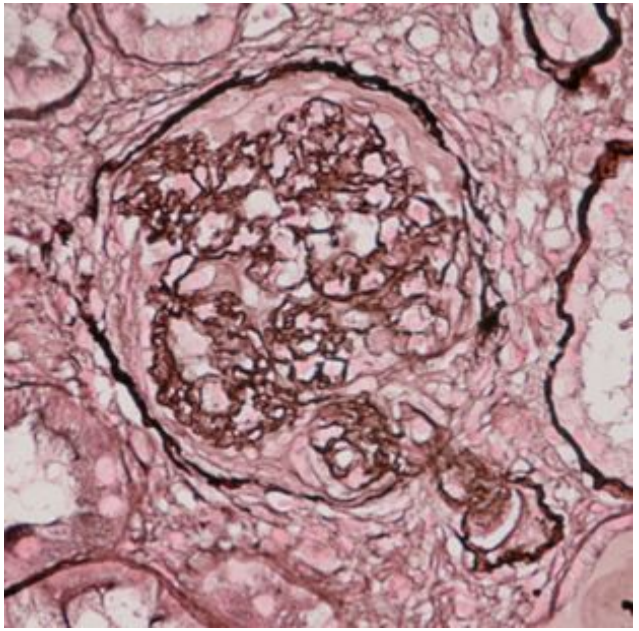
Auto-anticorpos
Já detectados no
LUPUS

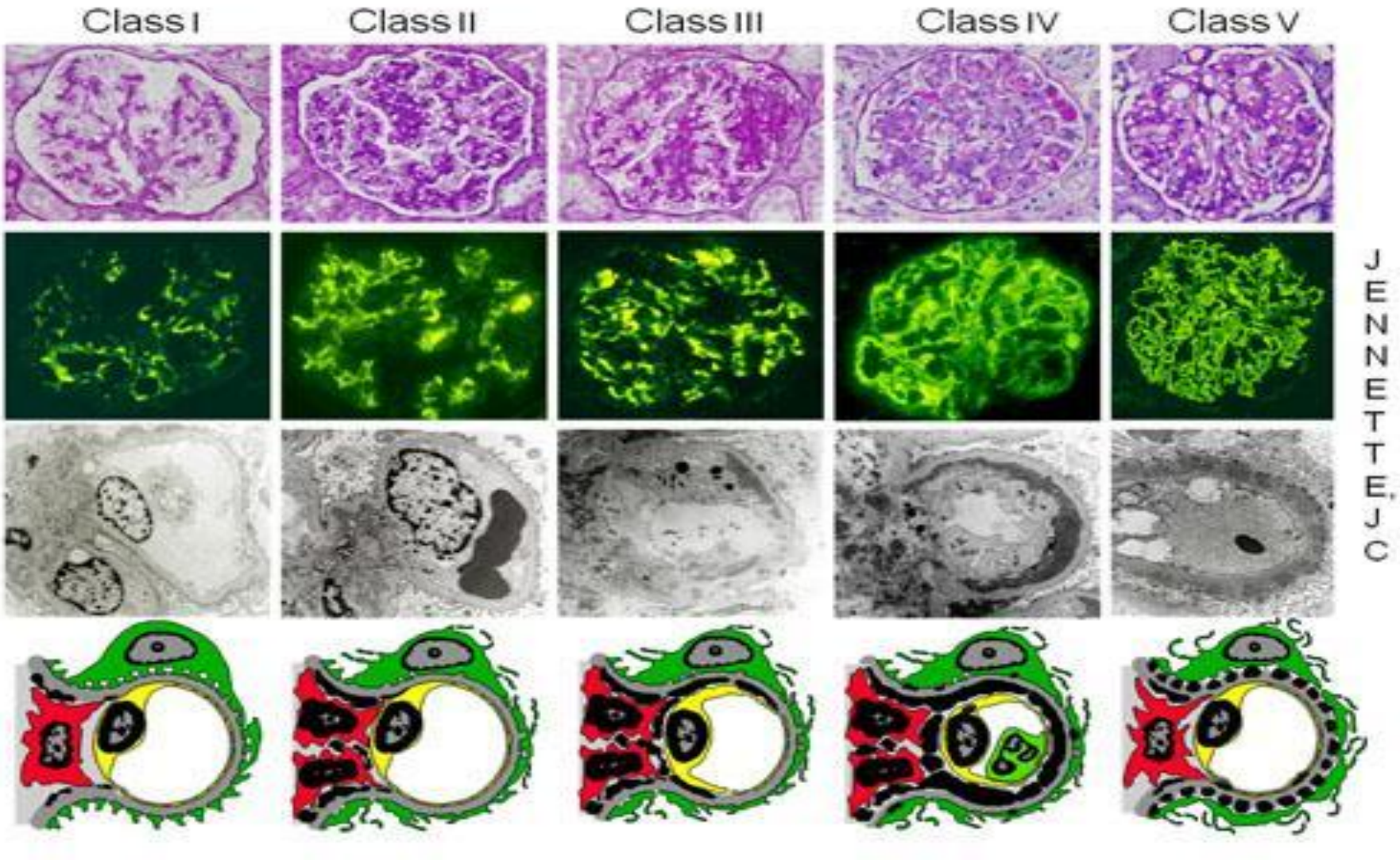
Anti-dsDNA
Antifosfolípides
Antineuronal
Anti-Ro
Anti-eritrócitos
Anti-linfócitos
Anti-plaquetas

Participam
diretamente
Das lesões..



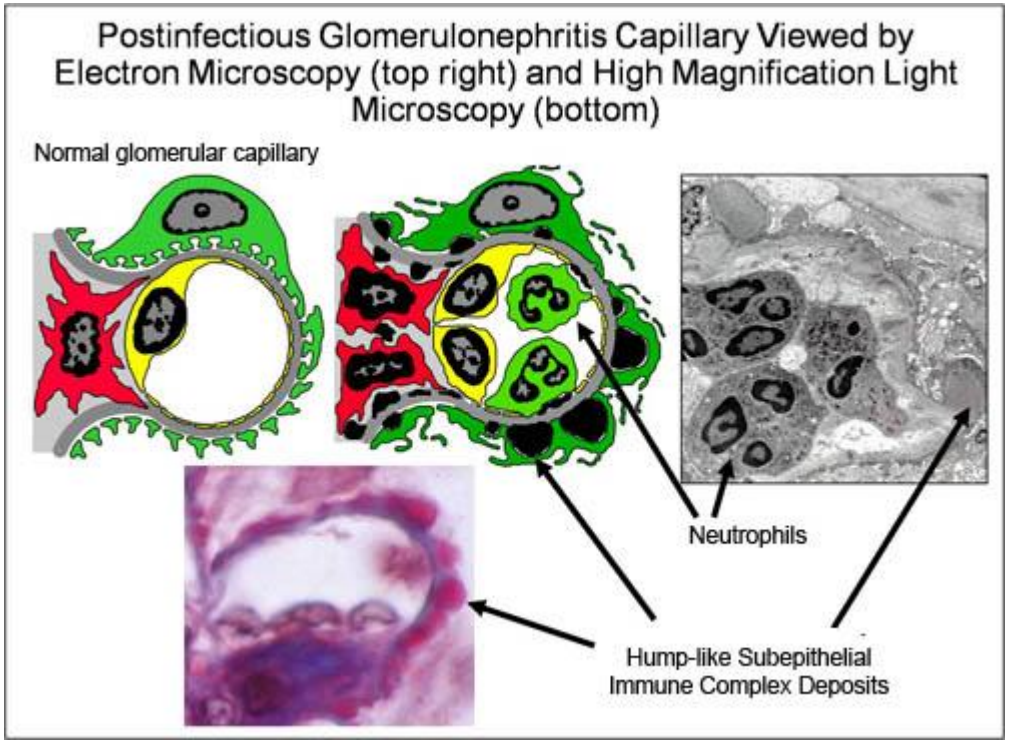
Deposição de
Imunocomplexo

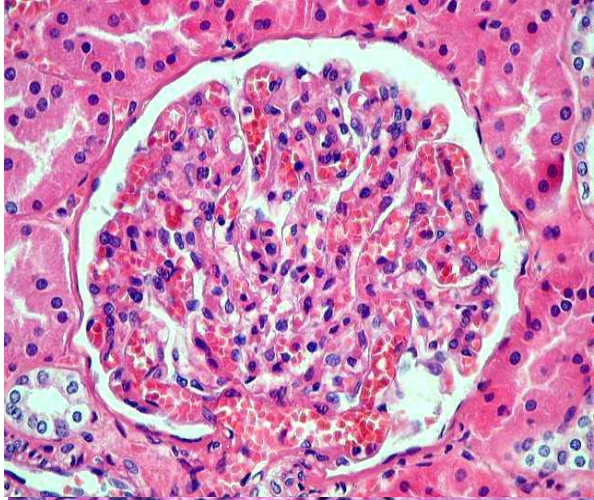


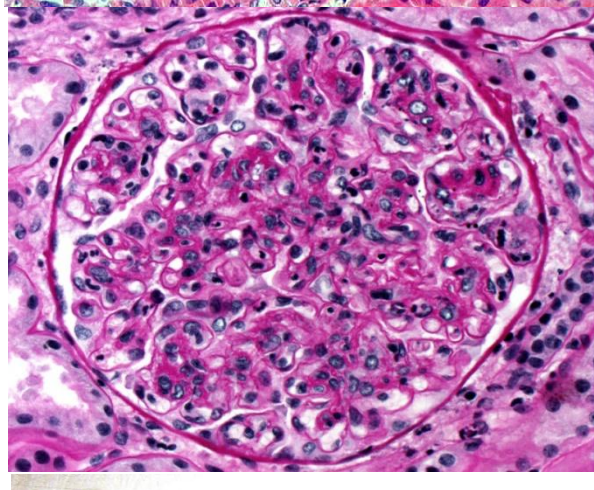


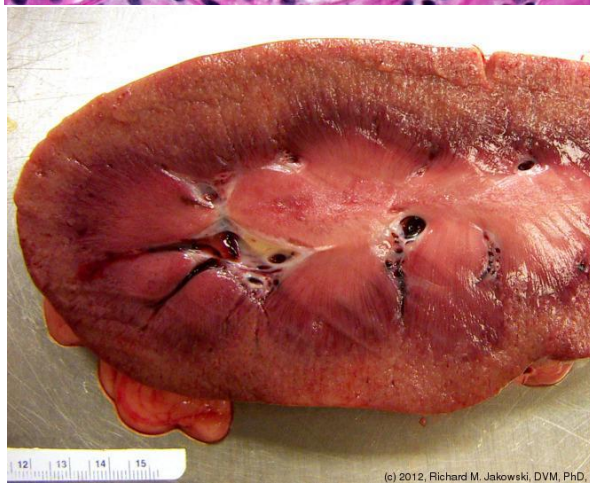
Class I: Mild disease with small amount of swelling
Class II: Still fairly mild disease but more swelling than Class I
Class III : Moderate degree of swelling with less than 50% of the filtering units (glomeruli) affected
Class IV : Severe degree of swelling with greater than 50% filtering units affected
Class IV-S: Of the affected filtering unit, less than ½ of it is affected by swelling
Class IV-G: Of the affected filtering unit, most of it is affected by inflammation
Class V: Most of the swelling is confined to the outer layer surrounding the filter unit
Class VI : Most of the filter units show scarring

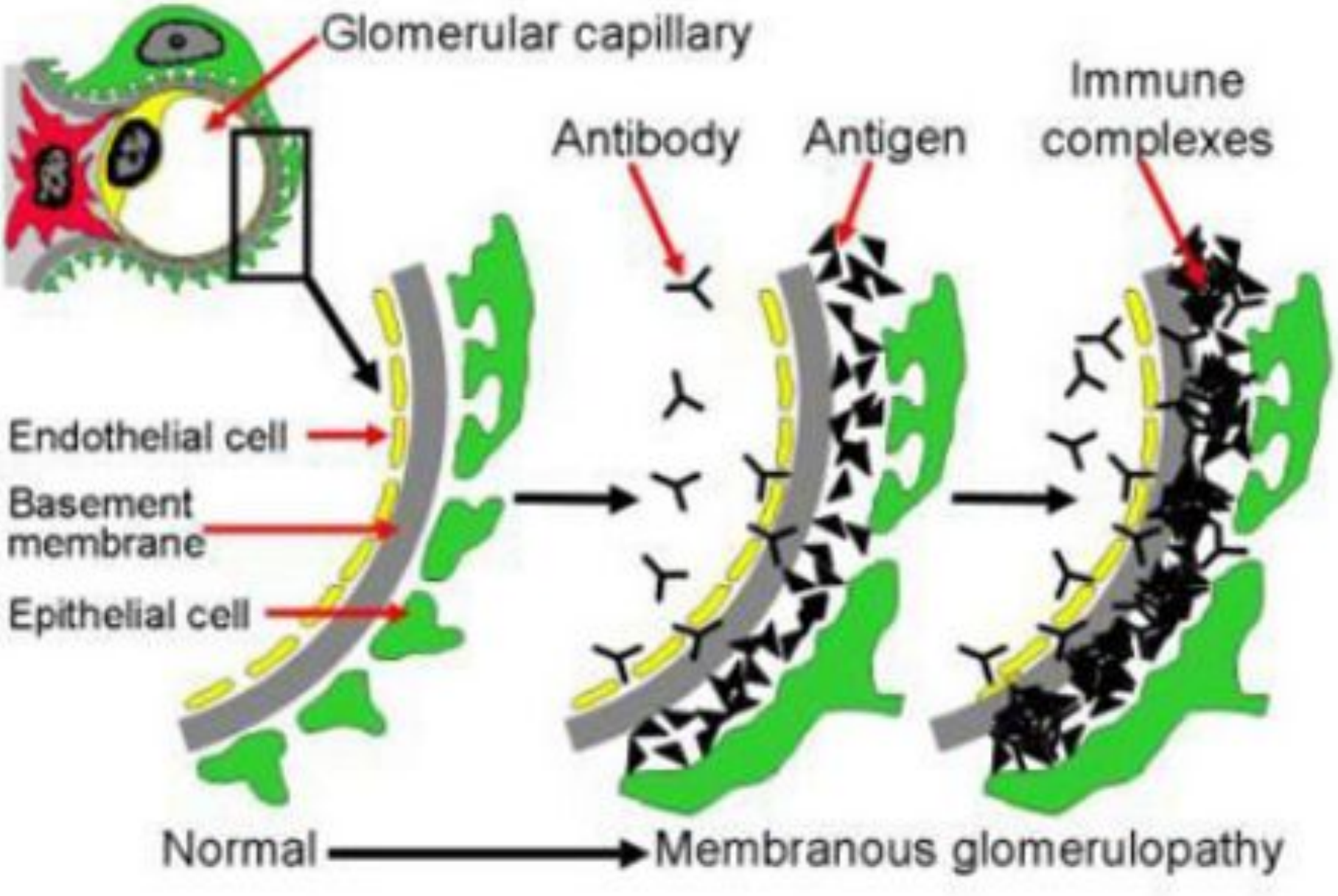
Glomerulonefrite Pós-streptocóccica










Glomerular capillary
Antibody
Antigen
Immune complexes
Endothelial cell
Basement membrane
Epithelial cell
Normal
Membranous glomerulopathy

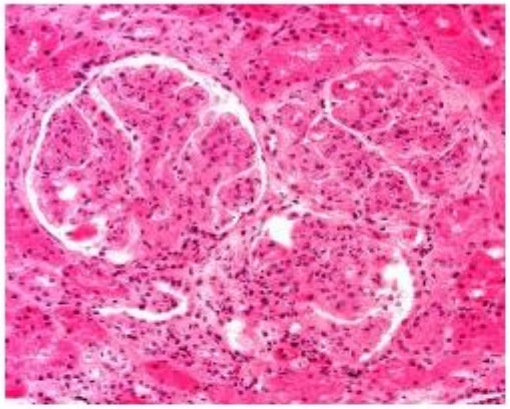


Fig. 1. Light micrograph of three glomeruli showing prominent hypersegmentation (lobulation) and hypercellularity (H&E stain, original magnification 200x).

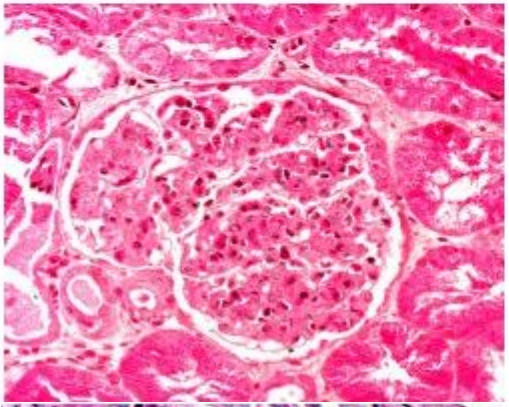


Fig. 2. Light micrograph of a glomerulus showing prominent hypersegmentation (lobulation), hypercellularity, and segmented neutrophils within capillary lumens (H&E stain, original magnification 400x).

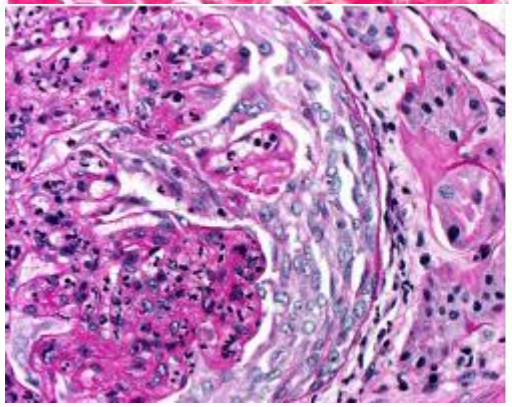
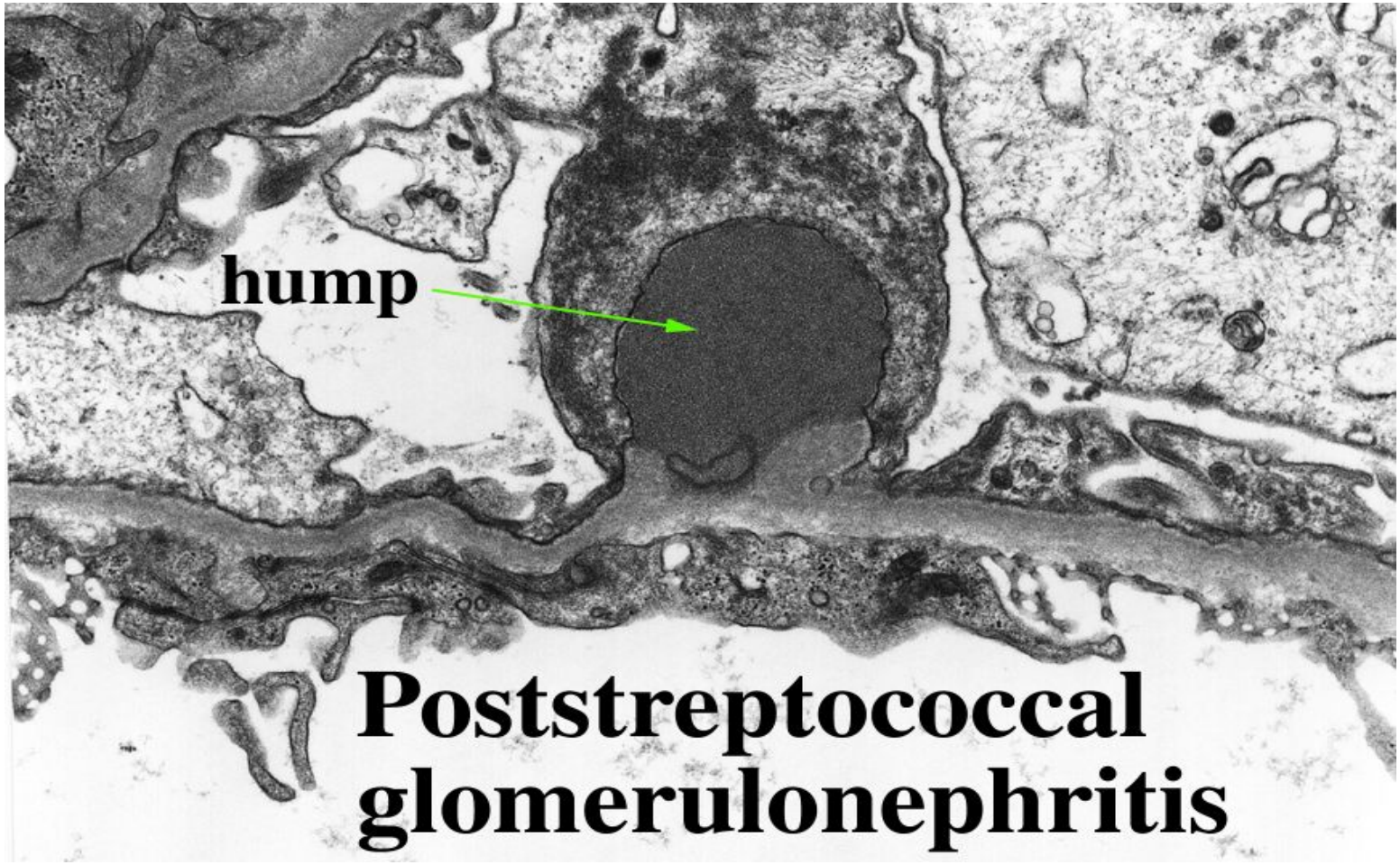


Fig. 9. Light micrograph of a glomerulus showing crescent formation with hyperlobularity, hypercellularity, and segmented neutrophils within capillary lumens (PAS stain, original magnification 400x).

Depósitos de Imunocomplexos subendoteliais



Pathophysiology

Poststreptococcal glomerulonephritis follows infection with only certain strains of streptococci, designated as nephritogenic. The offending organisms are virtually always group A streptococci. Acute poststreptococcal glomerulonephritis (APSGN) follows pyodermatitis with streptococci M types 47, 49, 55, 2, 60, and 57 and throat infection with streptococci M types 1, 2, 4, 3, 25, 49, and 12.

Although many morphologic, clinical, and serologic features suggest that APSGN is an immune complex disorder, the precise nature of the antigen-antibody interaction is undefined. APSGN is believed to be an immune-mediated disease, in which an immune complex containing a streptococcal antigen is deposited in the affected glomeruli. The size of glomerular basement membrane (GBM) pores and the molecular size of the streptococcus-Ig complex are also important determinants. The molecular size of the streptococcus-Ig complex is about 15 nm (10 nm for streptococcus group A and 5 nm for immunoglobulin). The GBM pore sizes in children and adults are 2-3 nm and 4-4.5 nm, respectively. Therefore, the immune complex molecule can be more easily rodded into the glomerulus in children than in adults and, thus, may explain the increased frequency of APSGN in children compared to that in adults.

The 2 antigens isolated from nephritogenic streptococci are under investigation in APSGN. These include the cationic cysteine protease streptococcal pyrogenic exotoxin B and nephritis-associated streptococcal plasmin receptor, which is a plasmin-binding protein with glyceraldehyde phosphate dehydrogenase (also known as presorbing antigen or PA-Ag).[5] These fractions have an affinity for glomeruli and have been shown to induce specific, long-lasting antibody responses in biopsy specimens from patients with APSGN. The relevance of exotoxin B and glyceraldehyde phosphate dehydrogenase was evaluated in the same renal biopsy and serum samples of patients with well-defined APSGN.

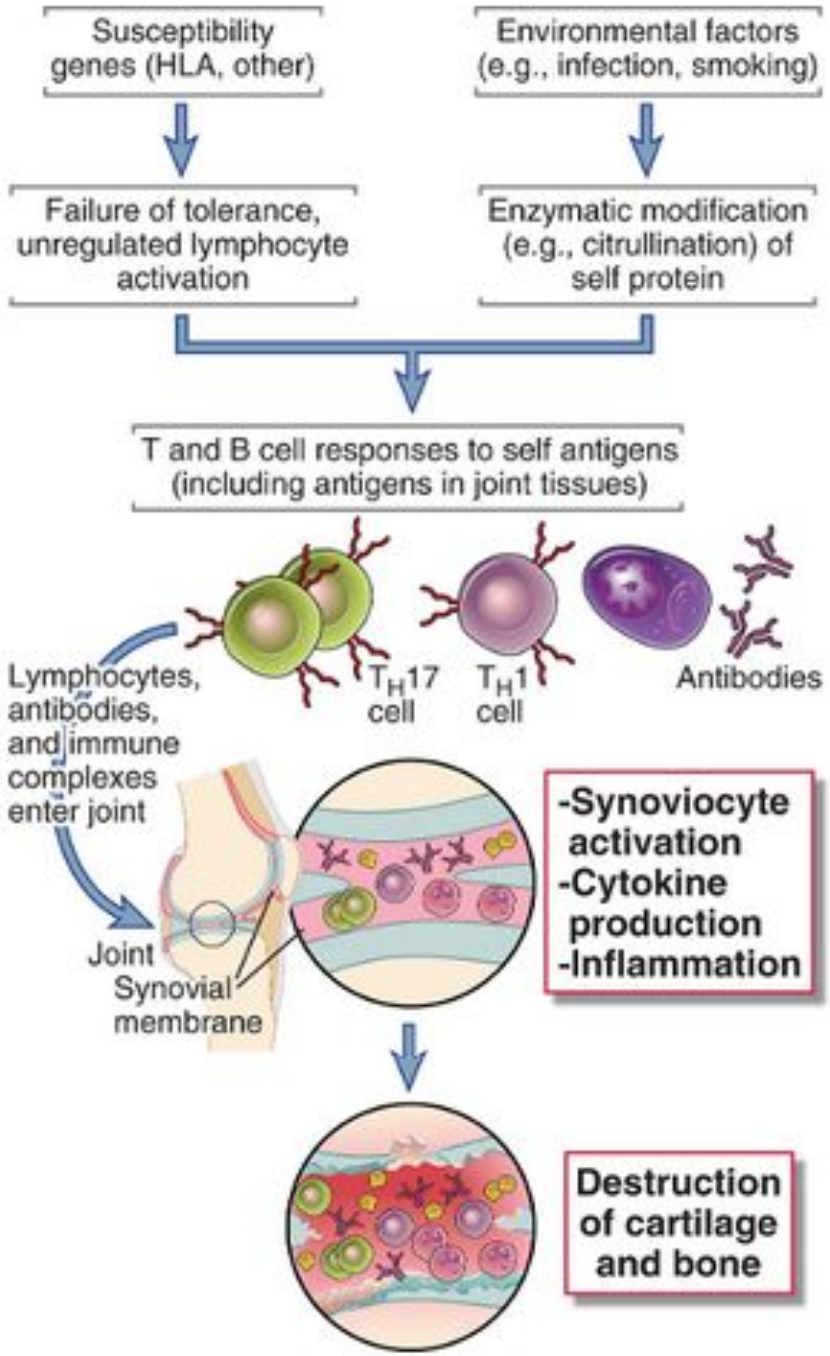
Table 1 Genes associated with predisposition to develop spontaneous lupus disease

Gene loci	*Species*	*Immunological effects*	*Reference*
Complement components and receptors: C1q, C2, C4, CR1, CR2	Human	Inadequate removal of immune complexes and apoptotic bodies	9
Cytokines: IL-10, IL-6, TNF-α	Human and mouse	Perturbed lymphocyte functions and lack of regulatory T cells	10
Cytokine receptors: TNFα-RII, IL-4R, IFN-γ RI and II	Human	Perturbed lymphocyte functions	11–13
MHC class II: DR, DQ (human), I-A, I-E (mouse)	Human and mouse	Abnormal T-lymphocyte repertoire and autoantibody production	14,15
TCR: α, β, γ gene loci	Human	Distorted T-cell repertoire and autoantibody production	16,17
Ig heavy and light chain gene loci	Human	Skewing of the B-lymphocyte repertoire	18
IgG Fc receptors: FcγIIa, IIIa, IIIb	Human	Binding of immune complexes to macrophages and lymphocytes	19–21
TCR associated signalling molecules: TCRζ chain, SHP-1	Human and mouse	Defective TC-mediated signalling and function, lymphoproliferation, autoantibody production	22–24
BCR associated signalling molecules: SHP-1, FcγRIIb, Yaa	Mouse	Enhanced B-lymphocyte proliferative responses, autoantibody production	24,25
Apoptosis: Fas, FasL	Mouse	Defect in clonal deletion of T and B lymphocytes, lymphoproliferation, autoantibody production	26,27
Membrane accessory molecules on lymphocytes: CD40L, CD22, FcγRIIIb	Human and mouse	Excessive lymphocyte proliferative responses	28–31
Cell cycle gene: p21	Human and mouse	Accumulation of T-lymphocytes in the G1 phase of the cell cycle, defective apoptosis	32,33
Nuclease enzymes: Dnase 1	Human and mouse	Accumulation of DNA leading to loss of immune tolerance	34,35
Genes regulating B- and T-lymphocyte responses and tolerance to chromatin: sle1, sle2, sle3	Mouse	Breakdown of tolerance to chromatin, B-lymphocyte hyper responsiveness, T-lymphocyte hyper responsiveness and defective apoptosis	36

The table includes only loci with known linkages with spontaneous lupus in human and murine models of the disease. Genes in knockout and transgenic mice which result in lupus-like phenotype in mice are not included since the relevance of these to idiopathic lupus is not known.

TABLE 18–1 Classification of Immunologic Diseases

Type of Hypersensitivity	Pathologic Immune Mechanisms	Mechanisms of Tissue Injury and Disease
Immediate hypersensitivity: type I	IgE antibody	Mast cells and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody mediated: type II	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular functions, e.g., hormone receptor signaling
Immune complex mediated: type III	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement- and Fc receptor–mediated recruitment and activation of leukocytes
T cell mediated: type IV	$CD4^+$ T cells (cytokine-mediated inflammation) $CD8^+$ CTLs (T cell–mediated cytolysis)	Recruitment and activation of leukocytes Direct target cell killing, cytokine-mediated inflammation



Tipo IV

Antígenos Protéicos

Apresentados

aos Linfócitos T

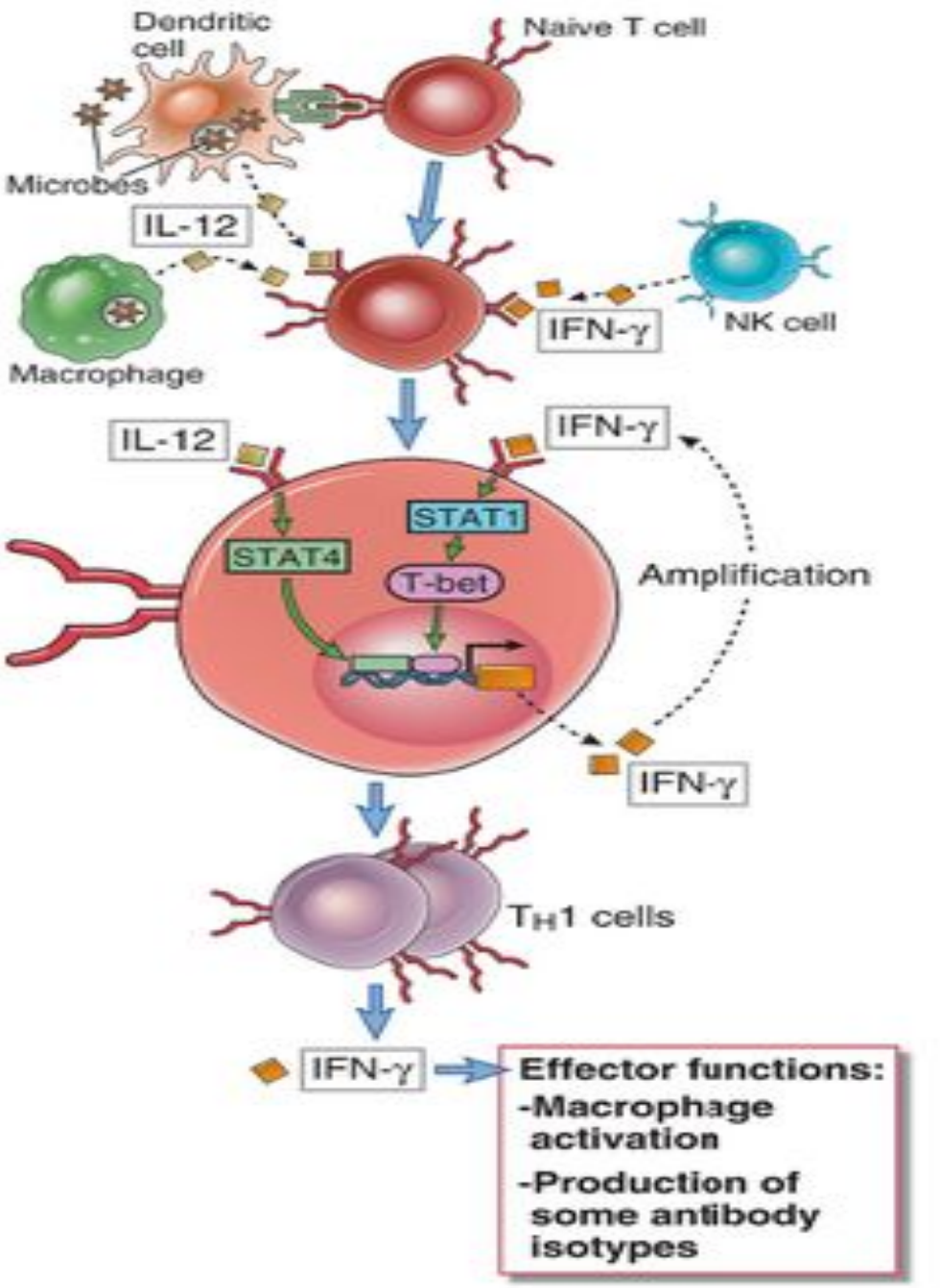
Th1

Th17

TABLE 18–4 T Cell–Mediated Diseases

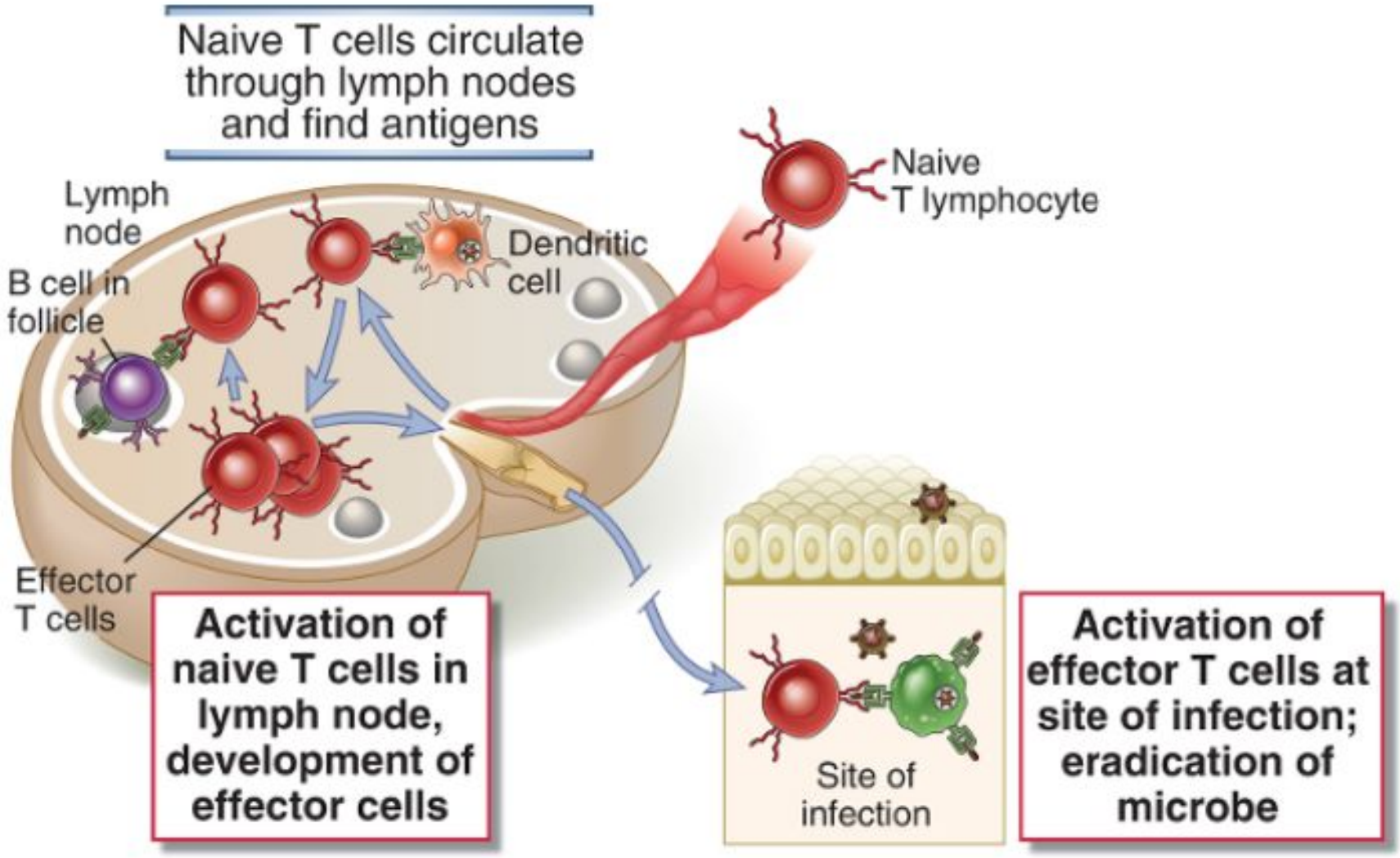
Disease	Specificity of Pathogenic T Cells	Principal Mechanisms of Tissue Injury
Rheumatoid arthritis	Collagen? Citrullinated self proteins?	Inflammation mediated by T_H17 (and T_H1?) cytokines Role of antibodies and immune complexes?
Multiple sclerosis	Protein antigens in myelin (e.g., myelin basic protein)	Inflammation mediated by T_H1 and T_H17 cytokines Myelin destruction by activated macrophages
Type 1 diabetes mellitus	Antigens of pancreatic islet β cells (insulin, glutamic acid decarboxylase, others)	T cell–mediated inflammation Destruction of islet cells by CTLs
Inflammatory bowel disease	Enteric bacteria Self antigens?	Inflammation mediated by T_H17 and T_H1 cytokines
Autoimmune myocarditis	Myosin heavy chain protein	CTL-mediated killing of myocardial cells Inflammation mediated by T_H1 cytokines

Examples of human T cell–mediated diseases are listed. In many cases, the specificity of the T cells and the mechanisms of tissue injury are inferred on the basis of the similarity with experimental animal models of the diseases.

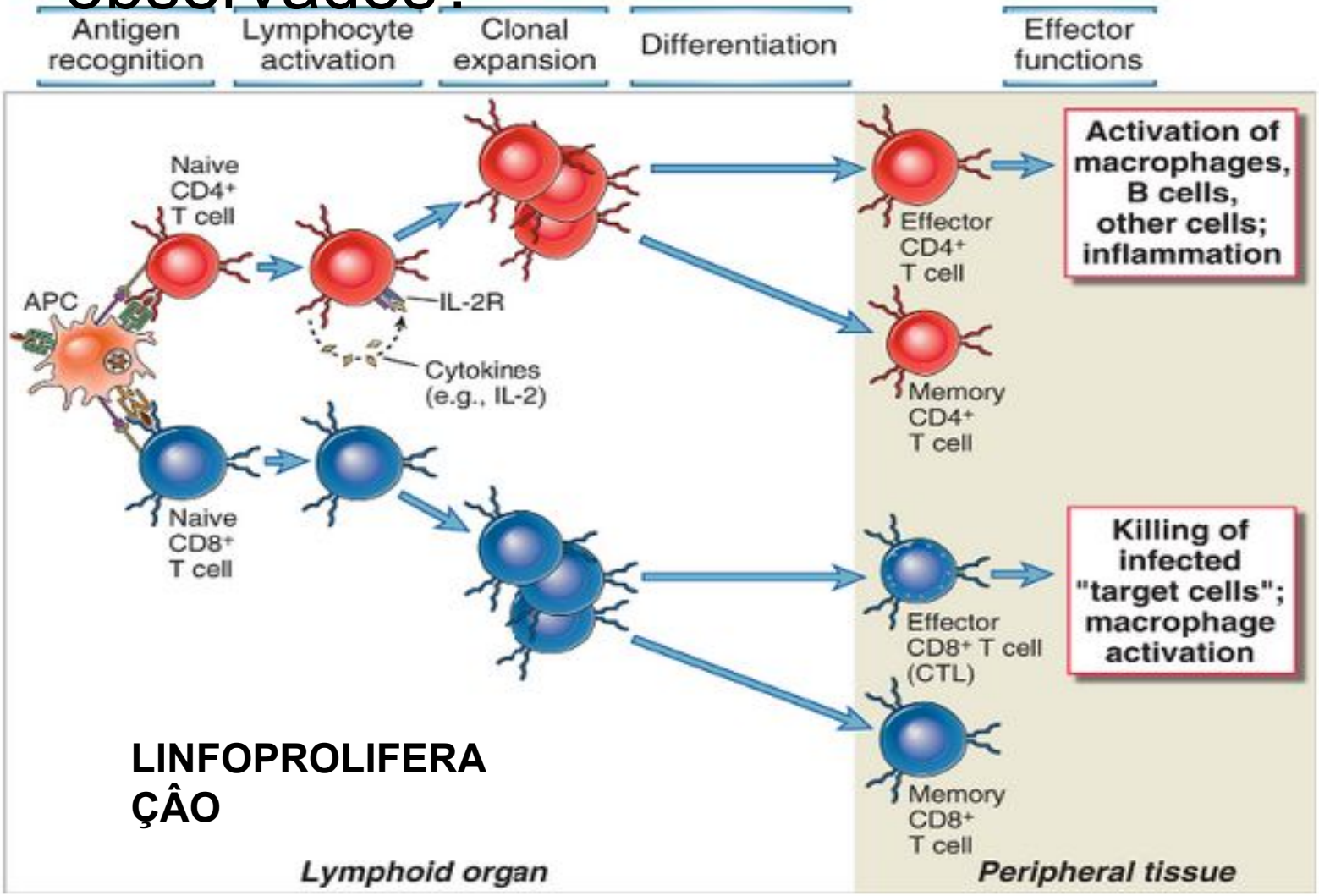


Resposta Th1

- Agentes Intra-celulares
- Ativação da Capacidade Fagocítica e de Degradação Intracelular
- Macrófagos Inflamatórios M1
- Anticorpos Neutralizantes
- Células NK
- Citocinas principais
- IL-1, IL-8, IL-18

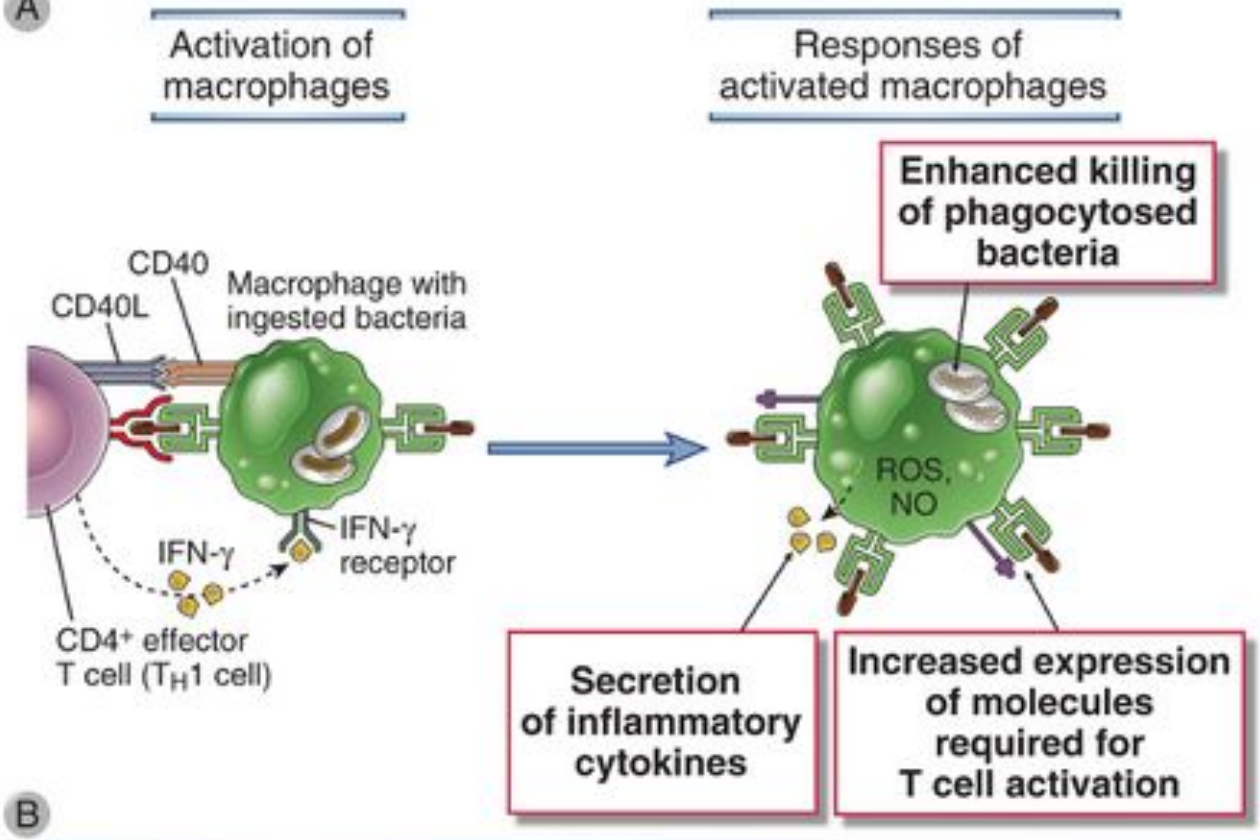

Naive T cells circulate through lymph nodes and find antigens
Lymph node
B cell in follicle
Dendritic cell
Naive T lymphocyte
Effector T cells
Activation of naive T cells in lymph node, development of effector cells
Site of infection
Activation of effector T cells at site of infection; eradication of microbe

Quais eventos celulares são observados?



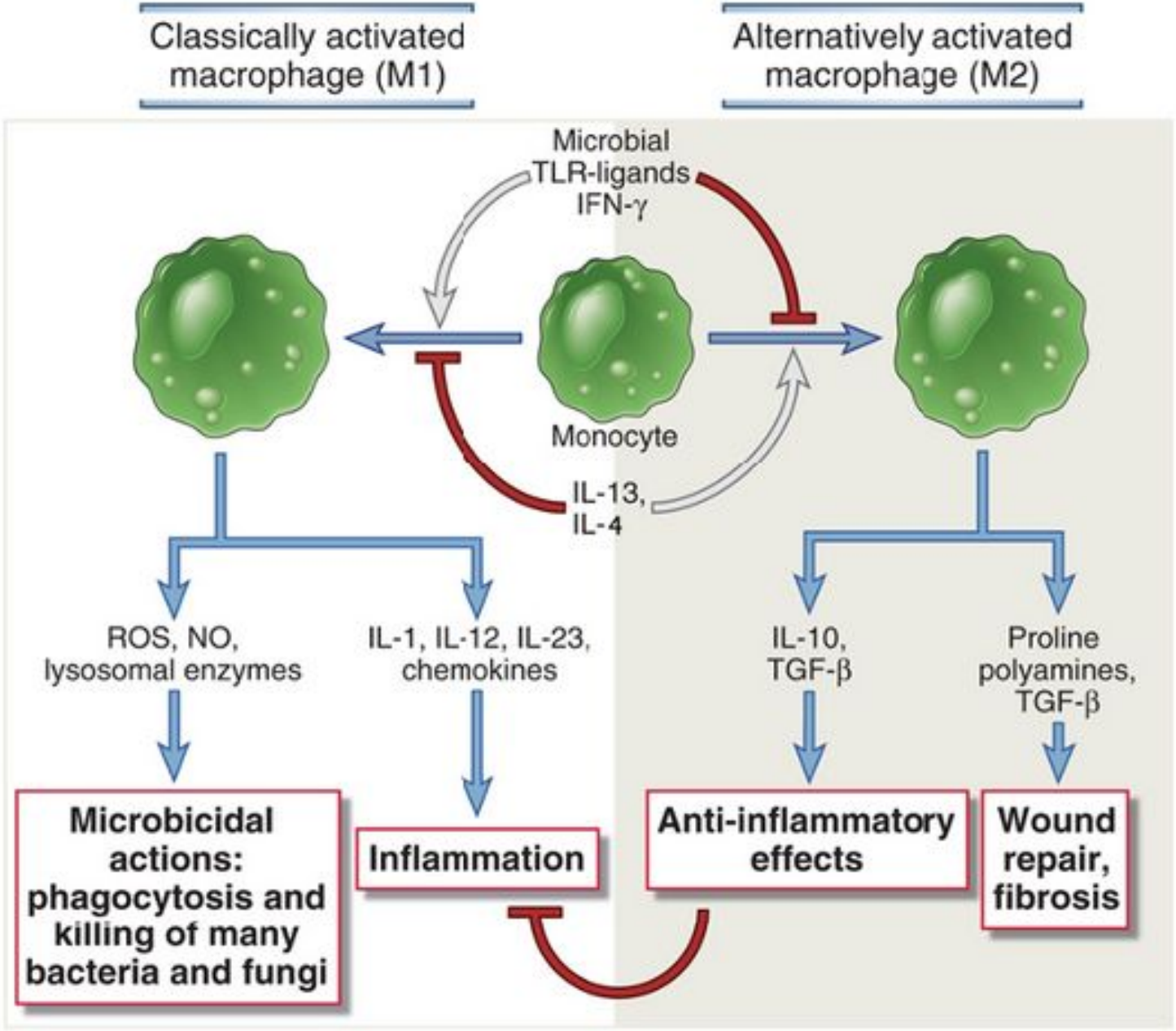
LINFOPROLIFERAÇÃO

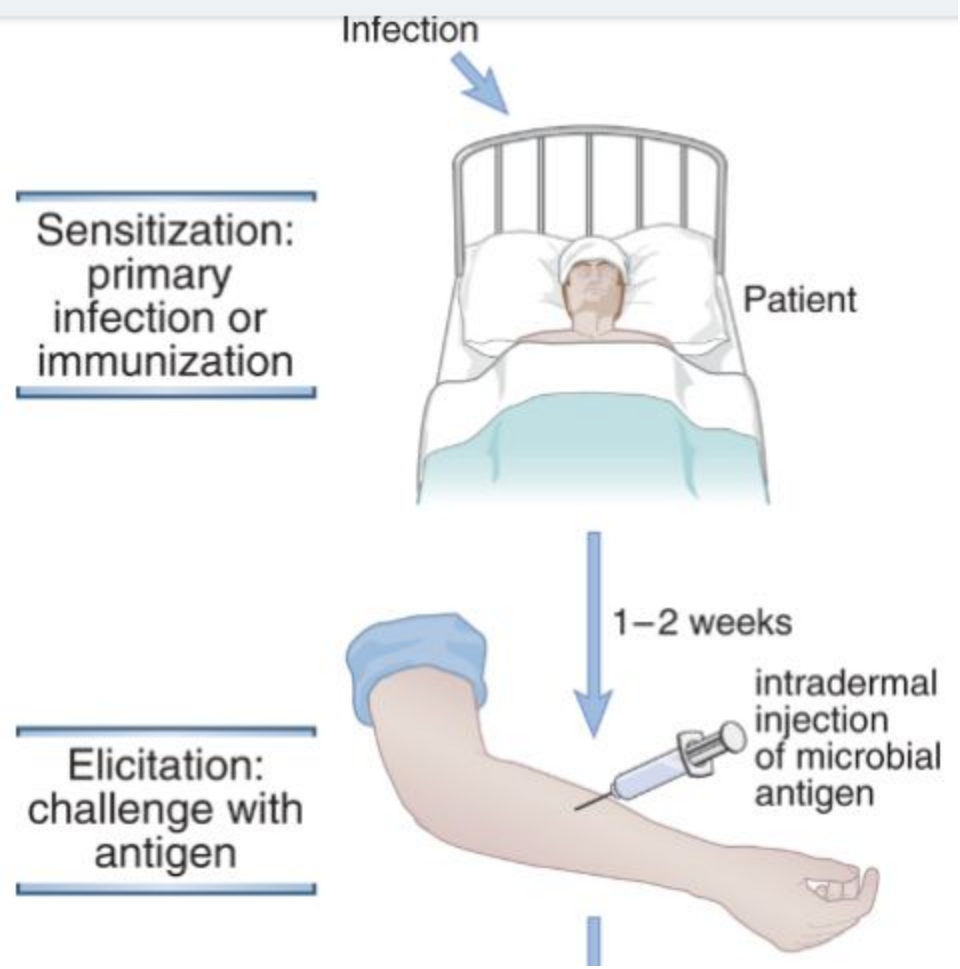
A

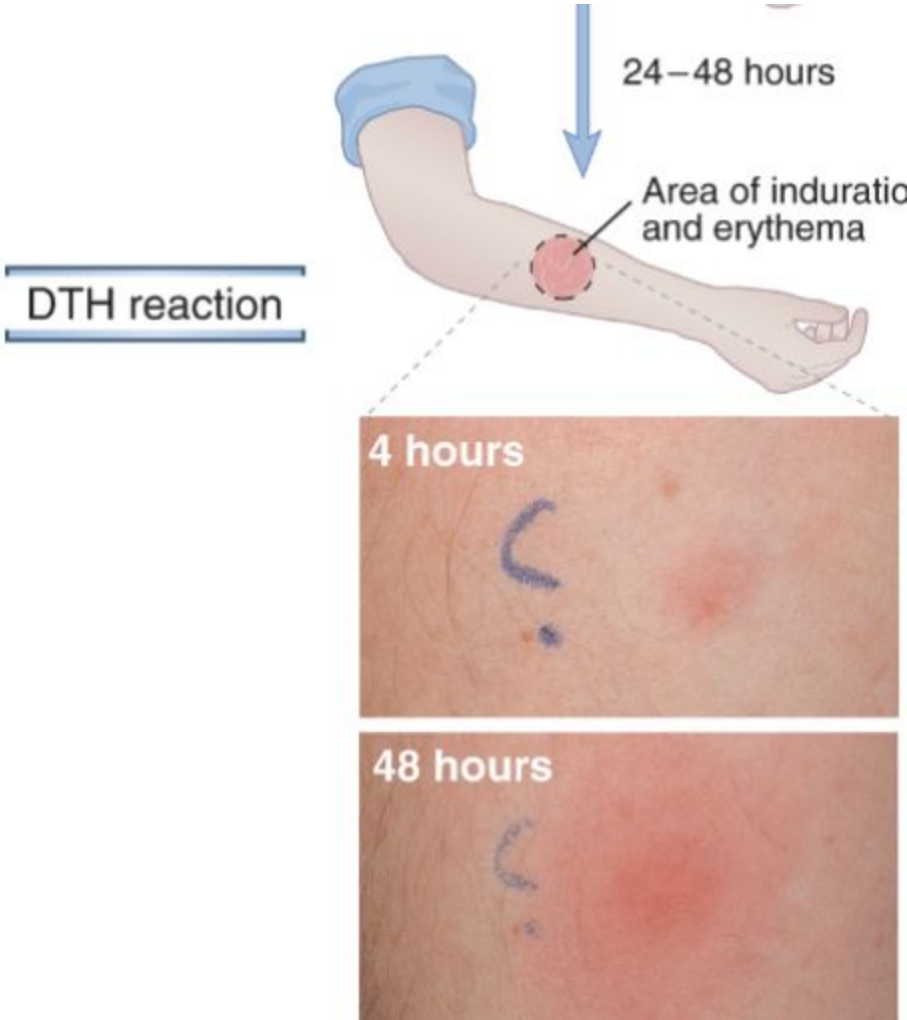


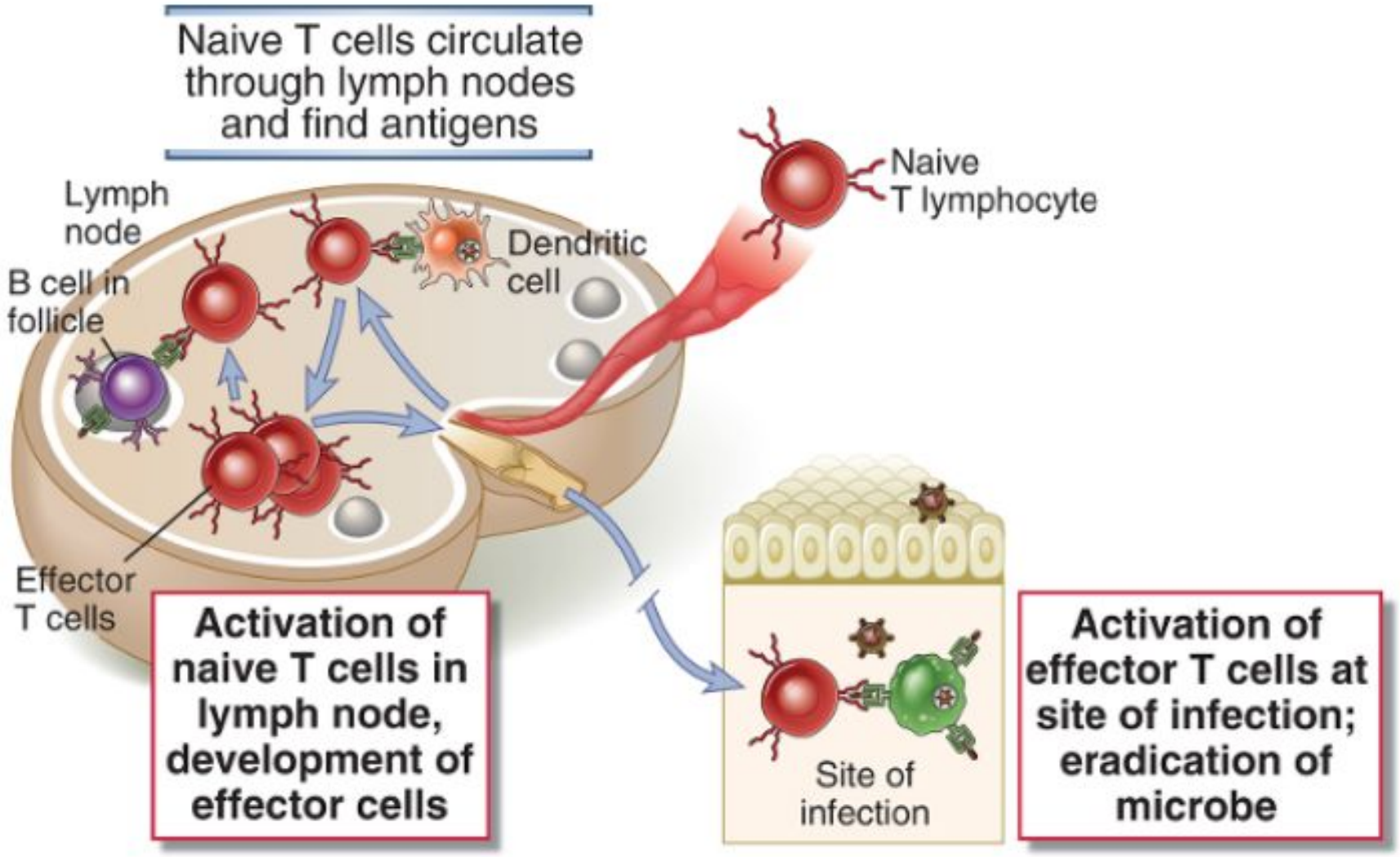
B

Macrophage response	Role in cell-mediated immunity
Production of reactive oxygen species, nitric oxide, increased lysosomal enzymes	Killing of microbes in phagolysosomes (effector function of macrophages)
Secretion of cytokines (TNF, IL-1, IL-12) and chemokines	TNF, IL-1, chemokines: leukocyte recruitment (inflammation) IL-12: T_H1 differentiation, IFN-γ production
Increased expression of B7 costimulators, MHC molecules	Increased T cell activation (amplification of T cell response)


Classically activated macrophage (M1)
Alternatively activated macrophage (M2)
Microbial
TLR-ligands
IFN-γ
Monocyte
IL-13,
IL-4
ROS, NO,
lysosomal enzymes
IL-1, IL-12, IL-23,
chemokines
IL-10,
TGF-β
Proline
polyamines,
TGF-β
Microbicidal actions: phagocytosis and killing of many bacteria and fungi
Inflammation
Anti-inflammatory effects
Wound repair, fibrosis

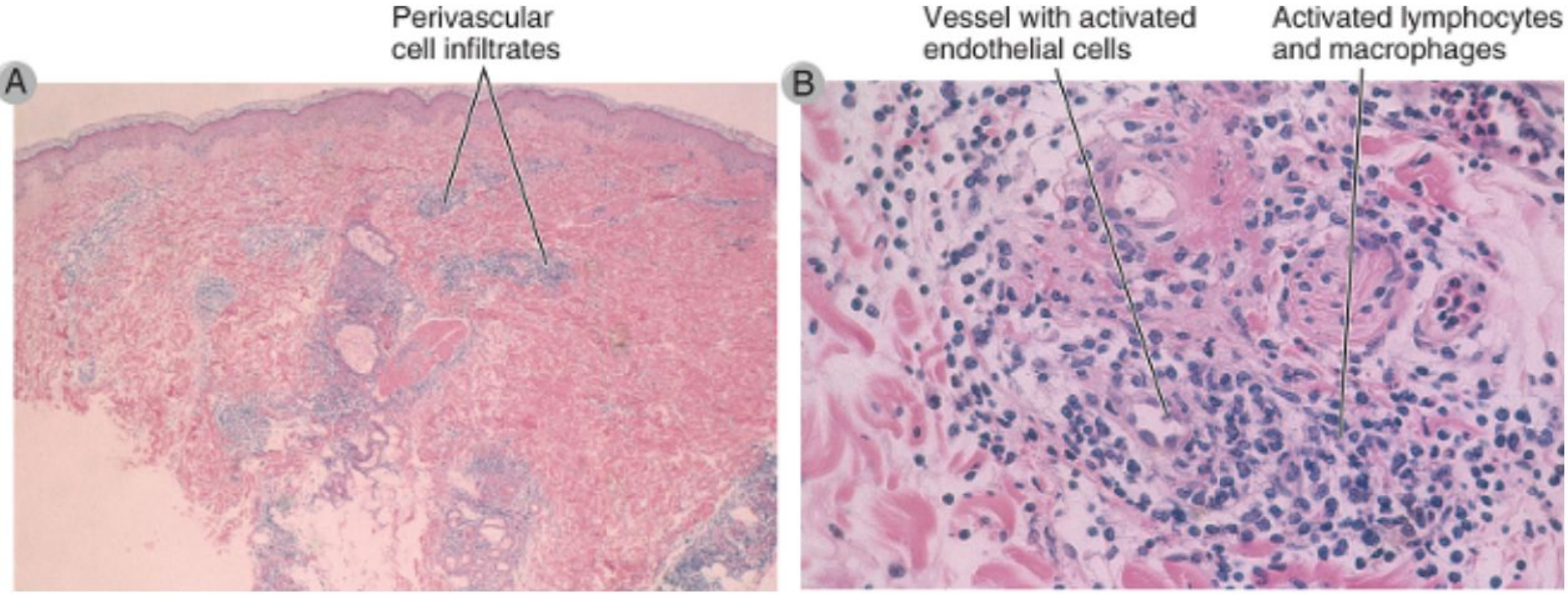

Infection
Sensitization: primary infection or immunization
Patient
1–2 weeks
Elicitation: challenge with antigen
intradermal injection of microbial antigen


DTH reaction
24–48 hours
Area of indurati
and erythema
4 hours
48 hours



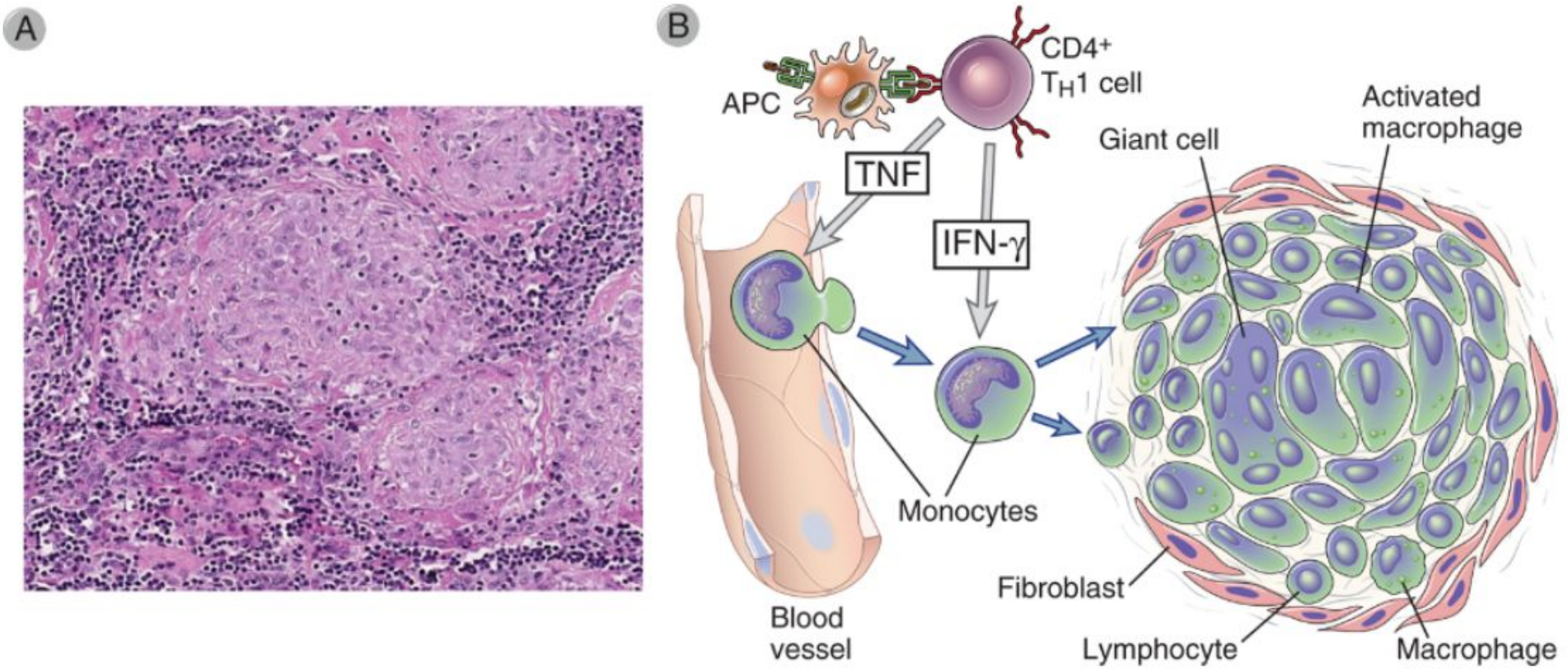
Sítio de Desafio Ag

Infiltrado Linfomonocítico



Citocinas Quimiocinas Mediadores Lipídicos Metaloproteinases

Formação de Granuloma



Abordagens Terapêuticas

TABLE 18–5 Examples of Cytokine Antagonists in Clinical Use or Trials

Cytokine or Receptor Targeted	Predicted Biologic Effects Of Antagonist	Clinical Indications
TNF	Inhibits leukocyte migration into sites of inflammation	Rheumatoid arthritis, psoriasis, inflammatory bowel disease
IL-1	Inhibits leukocyte migration into sites of inflammation	Rare autoinflammatory syndromes, severe gout, rheumatoid arthritis
IL-6 and IL-6 receptor	Inhibits synthesis of acute-phase proteins, antibody responses?	Juvenile idiopathic arthritis, rheumatoid arthritis
IL-17	Inhibits leukocyte recruitment into sites of inflammation	Rheumatoid arthritis, psoriasis
p40 chain of IL-12 and IL-23	Inhibits T_H1 and T_H17 responses	Inflammatory bowel disease, psoriasis
IL-2 receptor (CD25)	Inhibits IL-2–mediated T cell proliferation	Acute graft rejection
IFN-α	May be multiple effects on T_H1 differentiation, antibody production	Systemic lupus erythematosus
IL-4	Inhibits T_H2 differentiation, IgE production	Asthma
IL-5	Inhibits eosinophil activation	Asthma

The table lists examples of antagonists against cytokines (antibodies or soluble receptors) that are approved for clinical use or in trials. IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.