Hipersensibilidades

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Laboratório de Interações Neuroimunes
ICB IV - USP

Reações de Hipersensibilidades



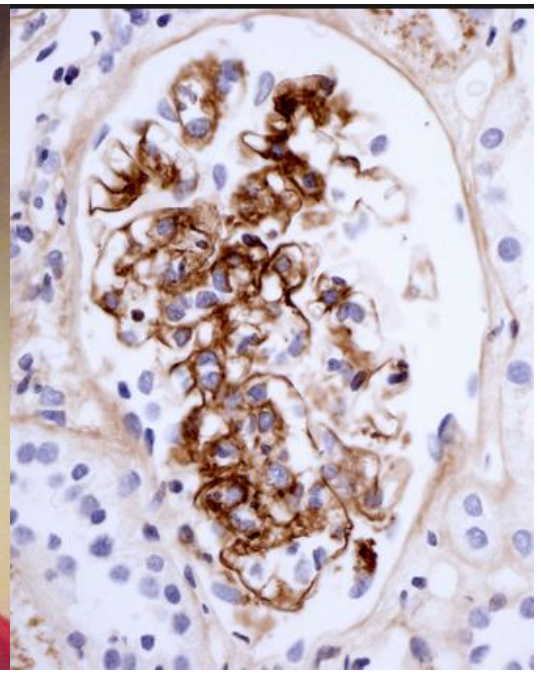
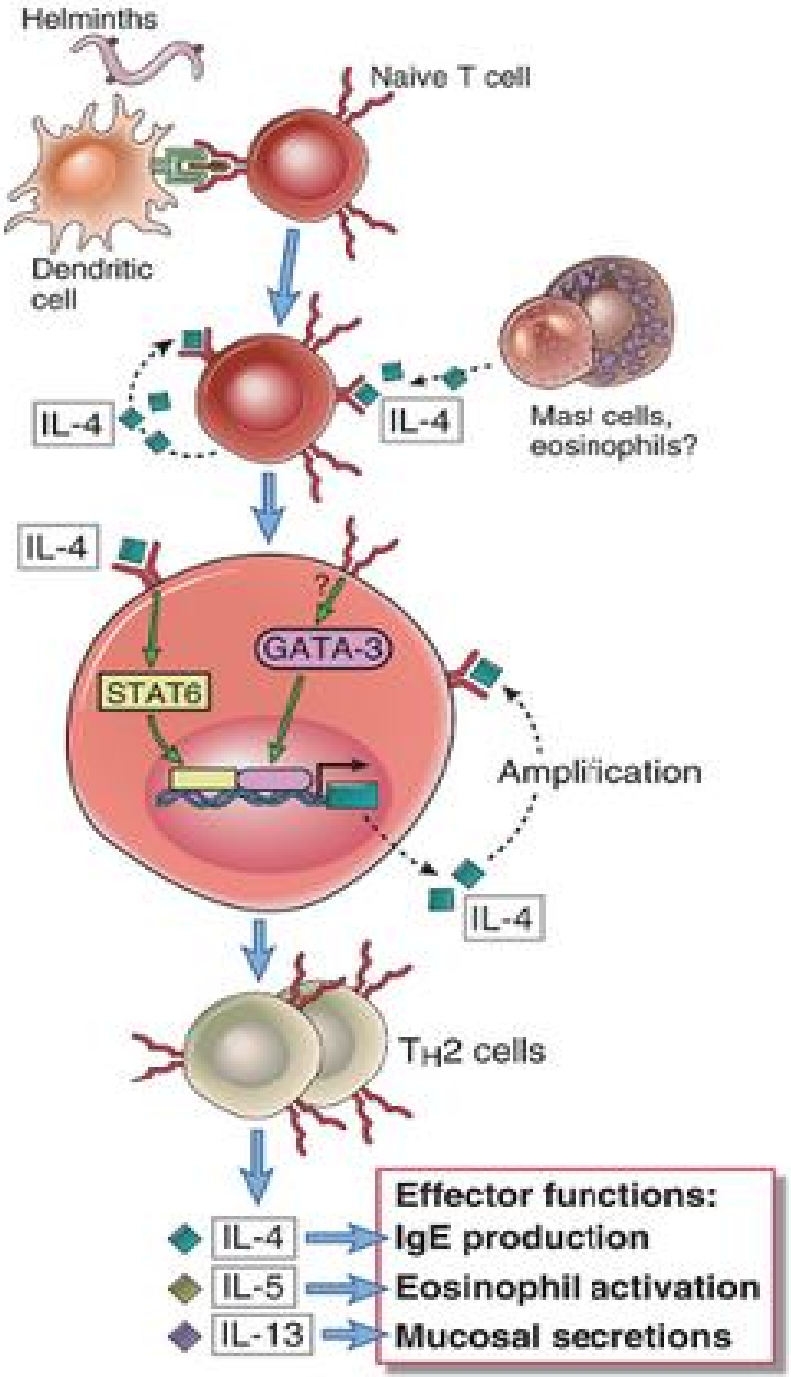


TABLE 18–1 Classification of Immunologic Diseases

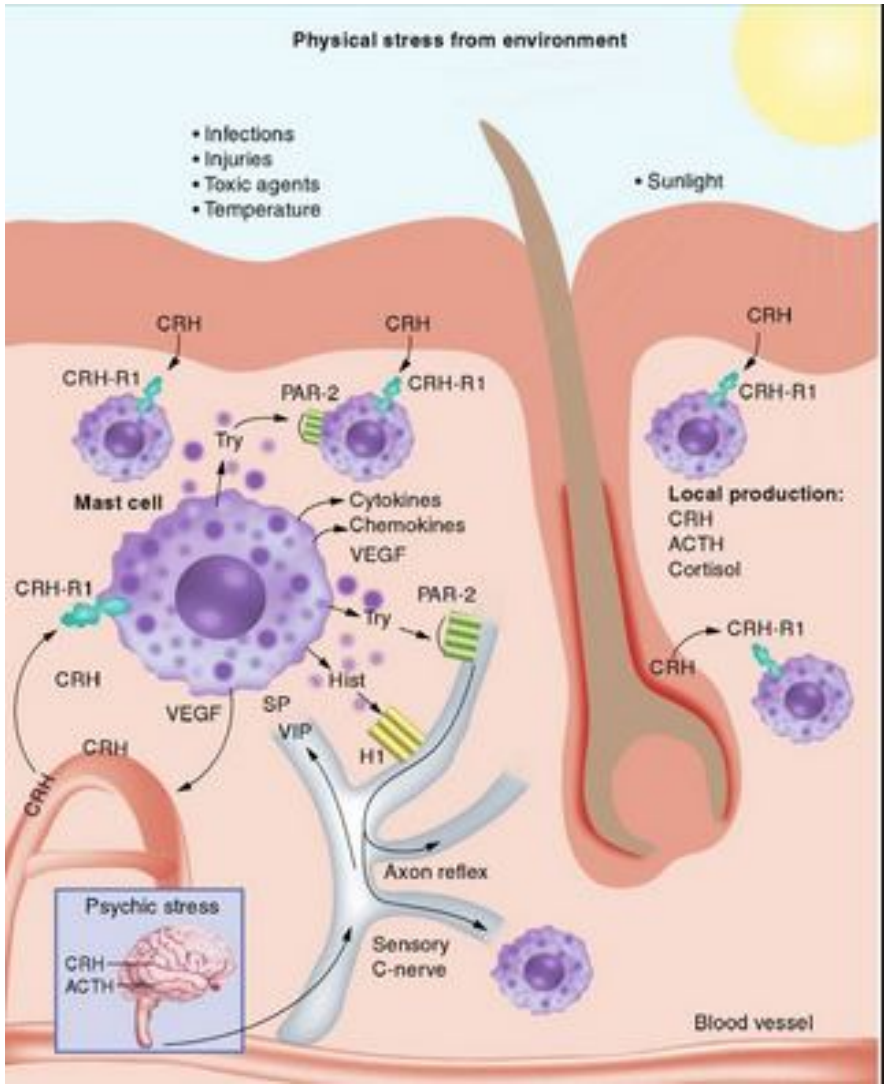
Type of Hypersensitivity	Pathologic Immune Mechanisms	Mechanisms of Tissue Injury and Disease
Immediate hypersensitivity: type I	IgE antibody	Mast cells and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody mediated: type II	IgM, IgG antibodies against cell surface or extracellular 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

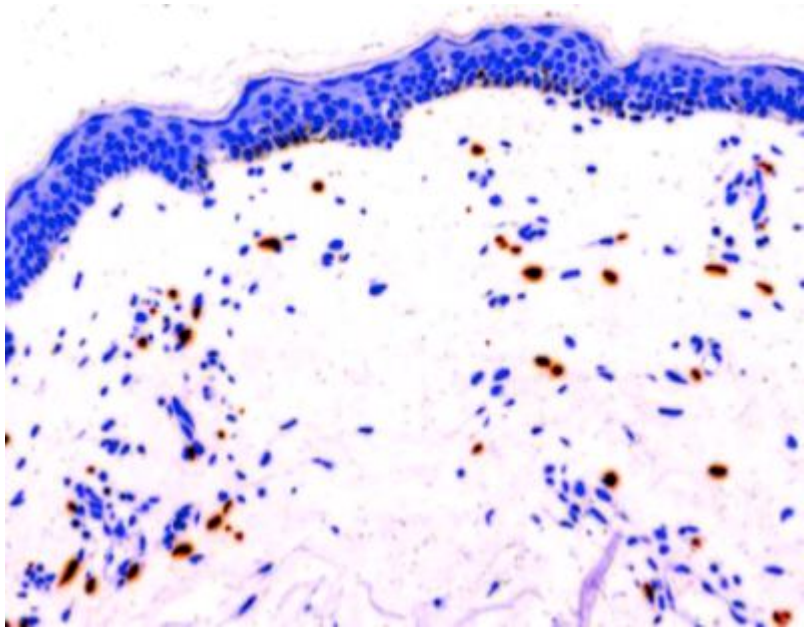


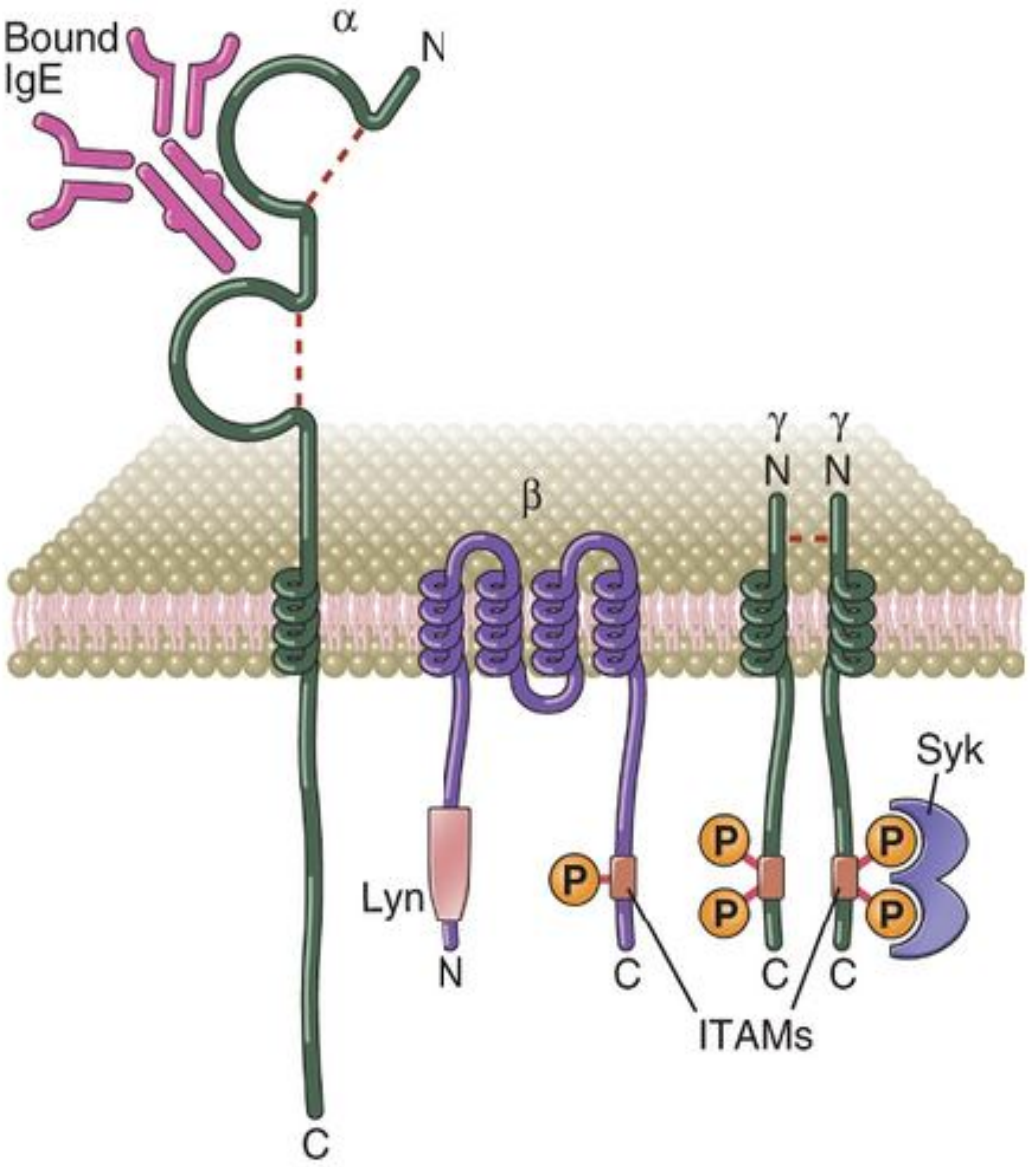
Resposta Th2

- **Agentes Extra-celulares ou Vermes**
- **Ativação de fatores eliminadores**
- **Anticorpos OPSONISANTES ou IgE anafilática**
- **Ativação de vias do Complemento**
- **Desgranulação de Eosinófilos e Granulócitos**
- **Citocinas principais**
- **IL-4, IL-5 e IL-13**

Mastócitos da Pele



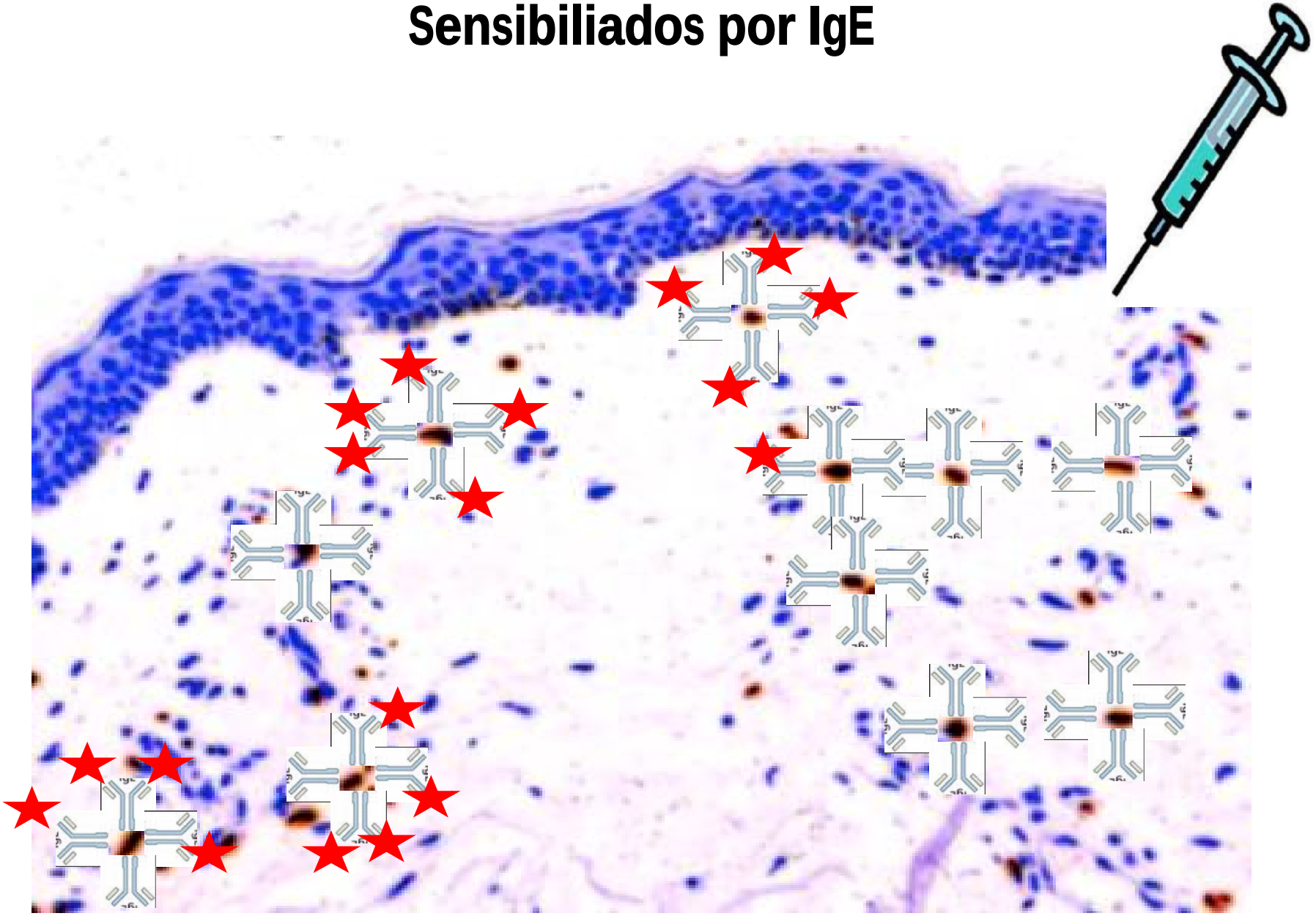




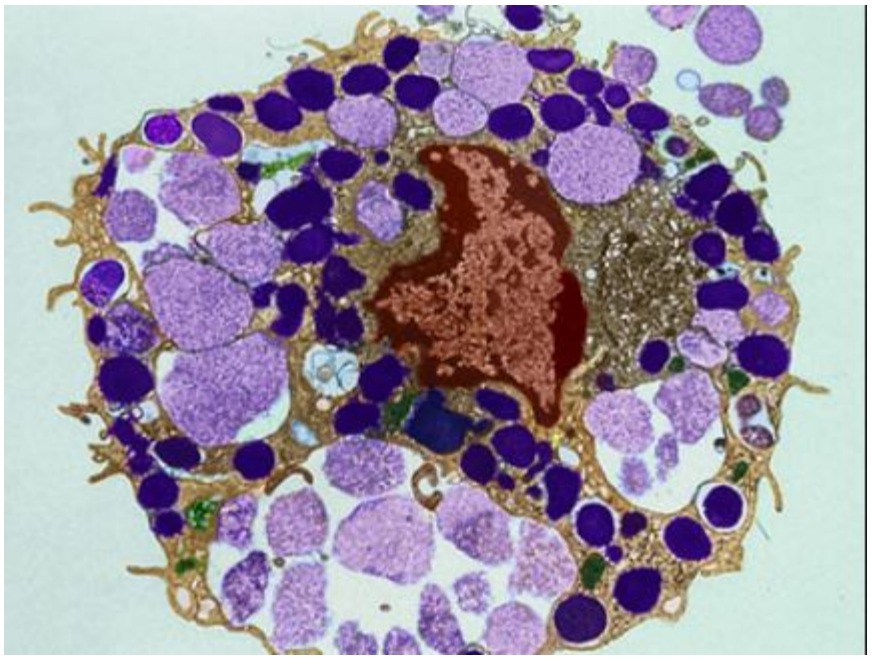
FcεRI

São Os Ùnicos
Capazes
De Ligar Igs
Não
Complexadas
Ao Antígeno

Em Indivíduos Atópicos os Mastócitos Estão Sensibiliados por IgE



Mastócitos Desgranulados



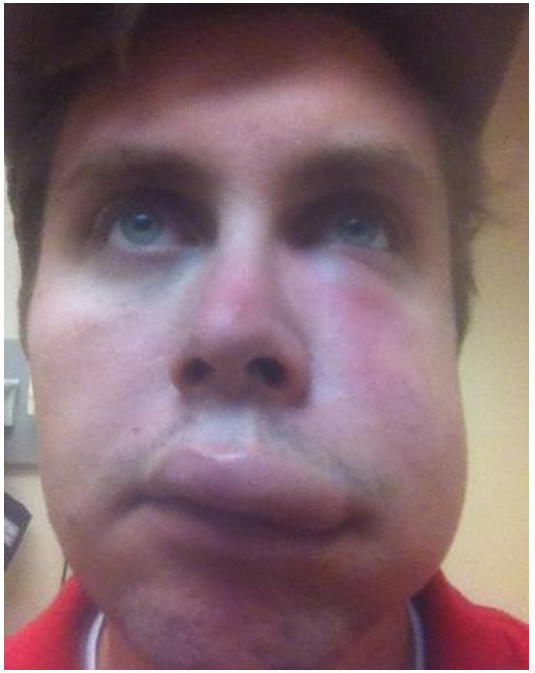
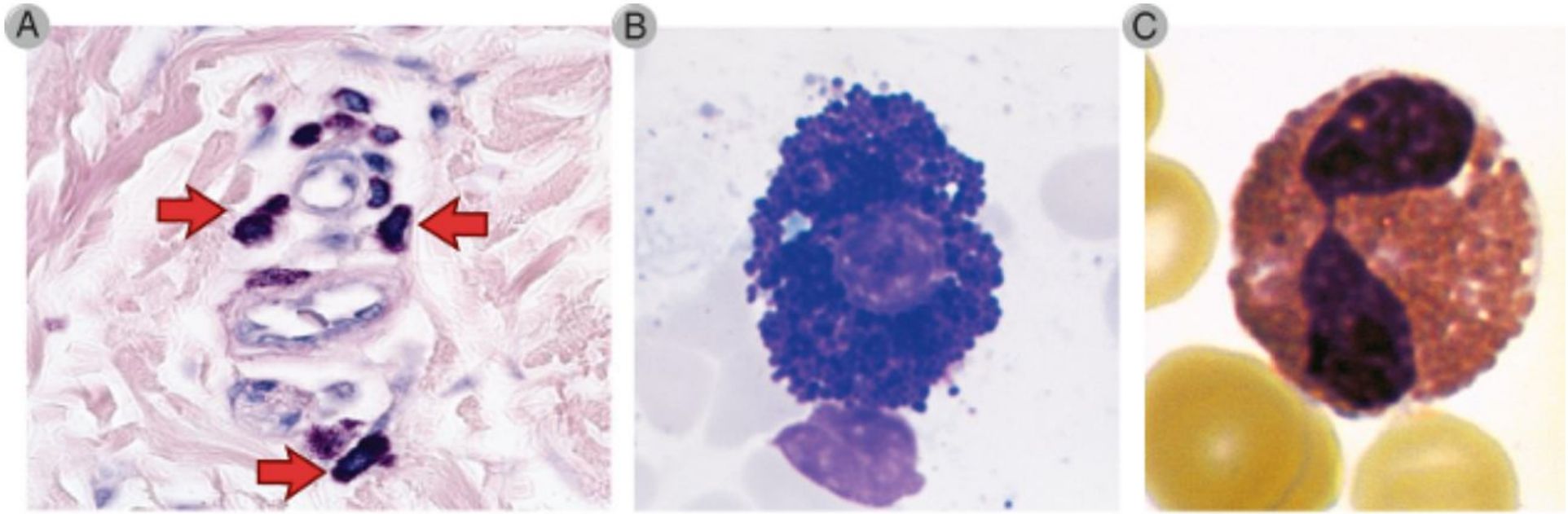
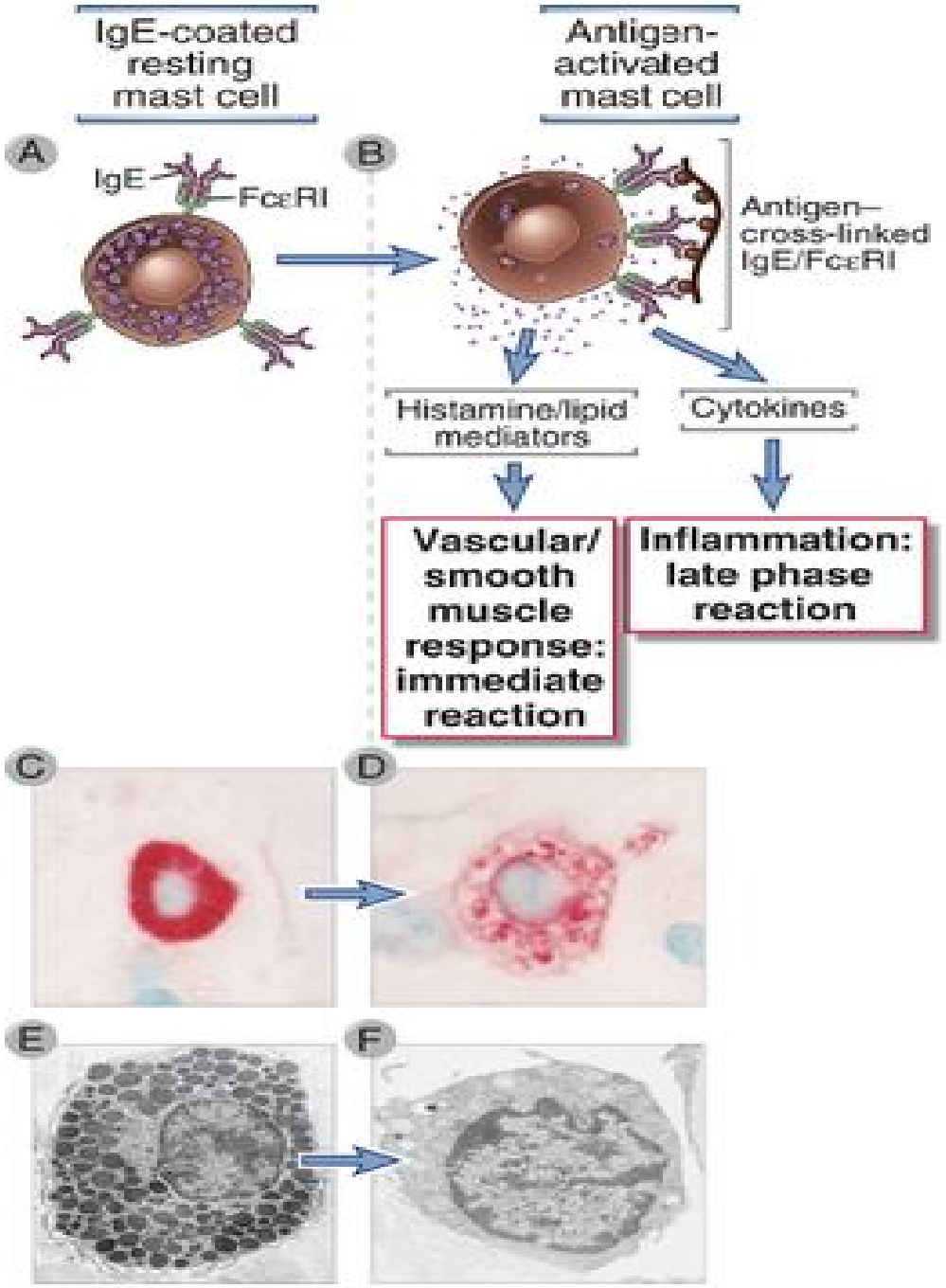


TABLE 19–1 Properties of Mast Cells, Basophils, and Eosinophils

Characteristic	Mast Cells	Basophils	Eosinophils
Major site of maturation	Connective tissue	Bone marrow	Bone marrow
Major cells in circulation	No	Yes (0.5% of blood leukocytes)	Yes (~2% of blood leukocytes)
Mature cells recruited into tissues from circulation	No	Yes	Yes
Mature cells residing in connective tissue	Yes	No	Yes
Proliferative ability of mature cells	Yes	No	No
Life span	Weeks to months	Days	Days to weeks
Major development factor (cytokine)	Stem cell factor, IL-3	IL-3	IL-5
Expression of FcεRI	High levels	High levels	Low levels (function unclear)
Major granule contents	Histamine, heparin and/or chondroitin sulfate, proteases	Histamine, chondroitin sulfate, protease	Major basic protein, eosinophil cationic protein, peroxidases, hydrolases, lysophospholipase

FcεRI, Fcε receptor type I; IL, interleukin.


A
B
C



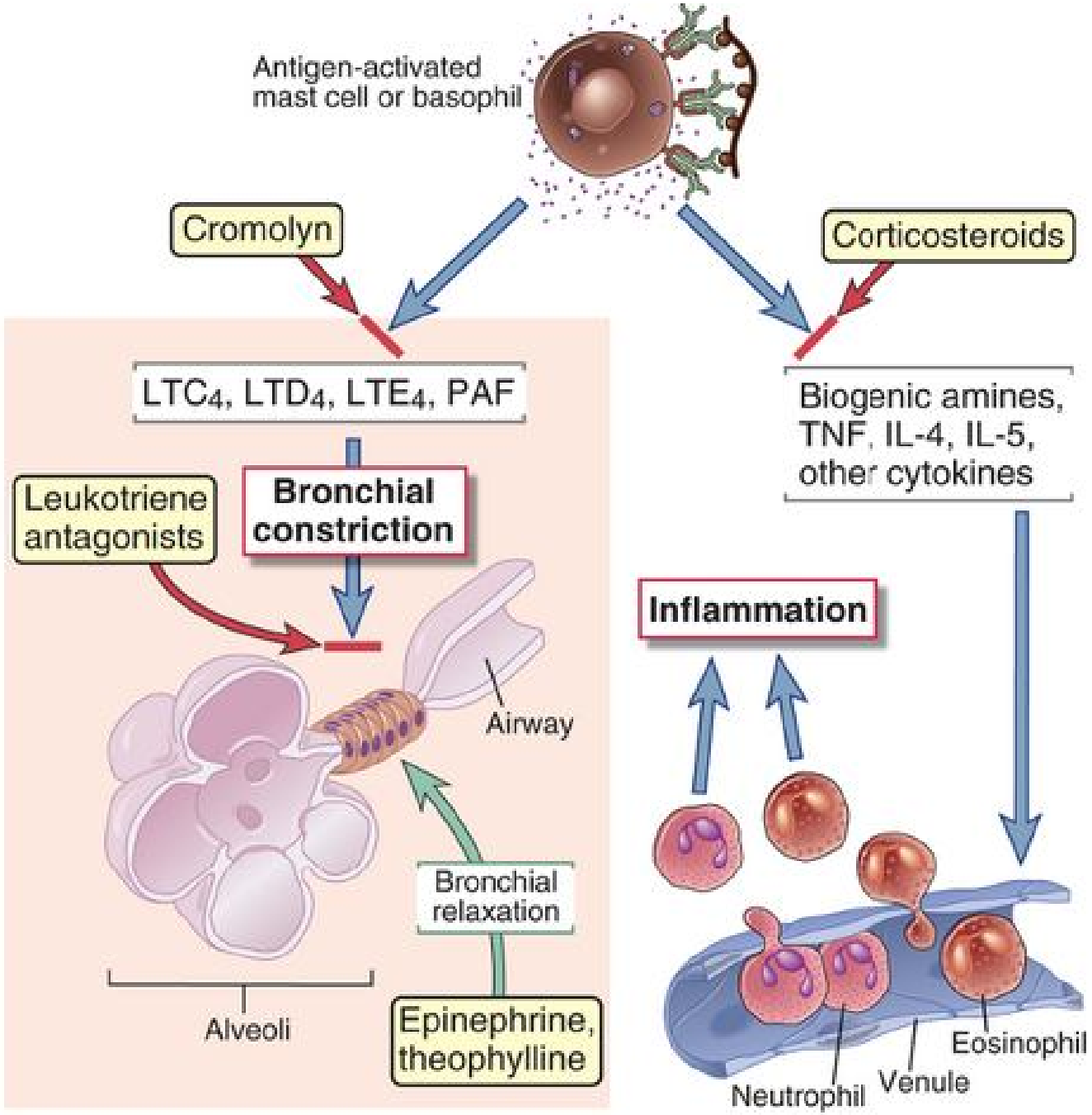
Desgranulação

Liberação de Mediadores Vasoativos Presentes nos Grânulos

Histamina
Serotonina
TNF-α

Mediadores Lipídicos
Leucotrienos
Prostaglandinas
Tromboxanas

Síntese de Citocinas
Transcrição Gênica



Fisiopatologia da

ASMA

Mastócitos Pulmonares

Mucocosa Nasal (Rinite)

Sensibilizados Com IgE

Mediadores
PGE
LTs
Histamina
Serotonina
ATP

Controle

Asma

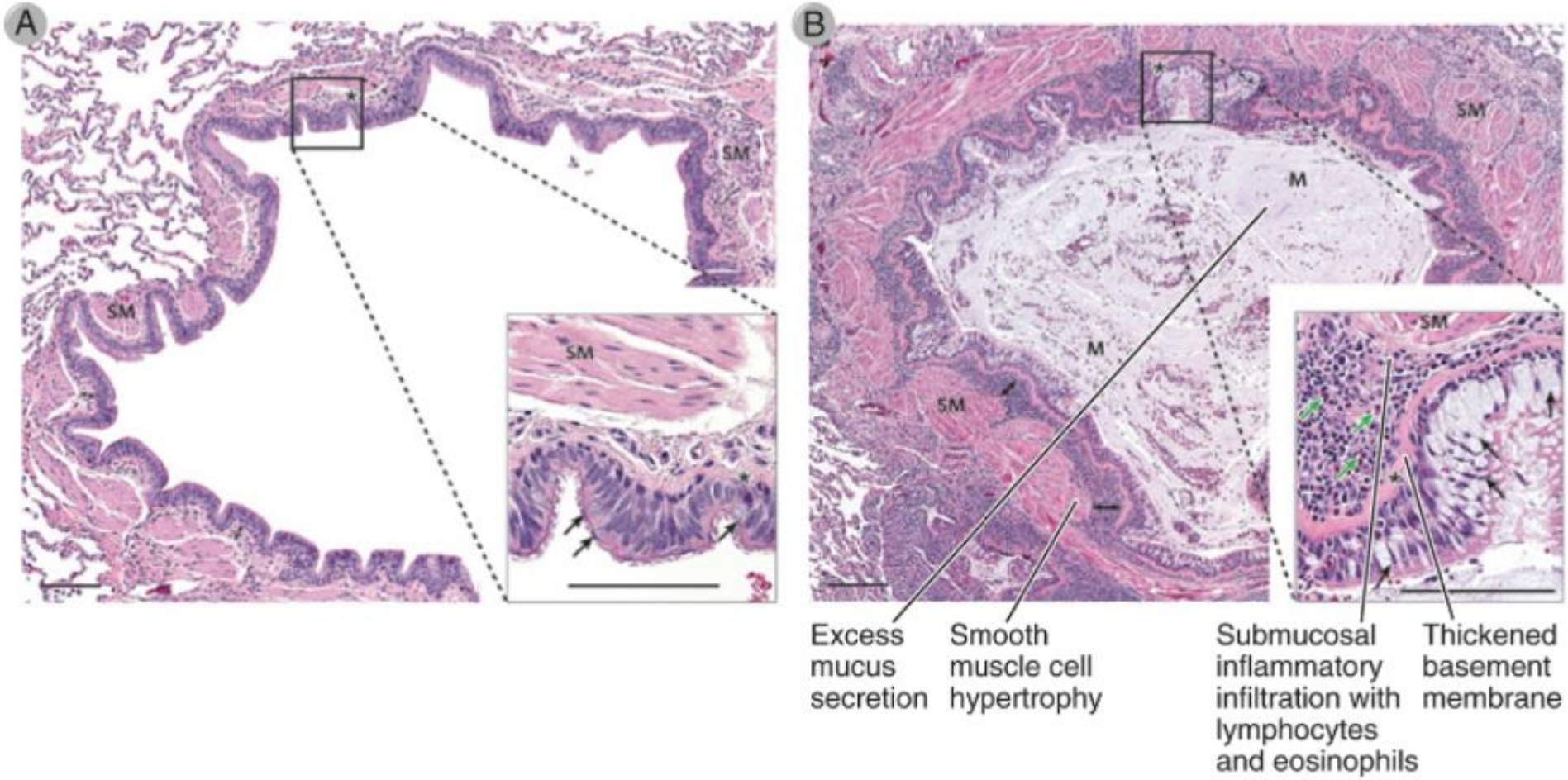


TABLE 19–2 Mediators Produced by Mast Cells, Basophils, and Eosinophils

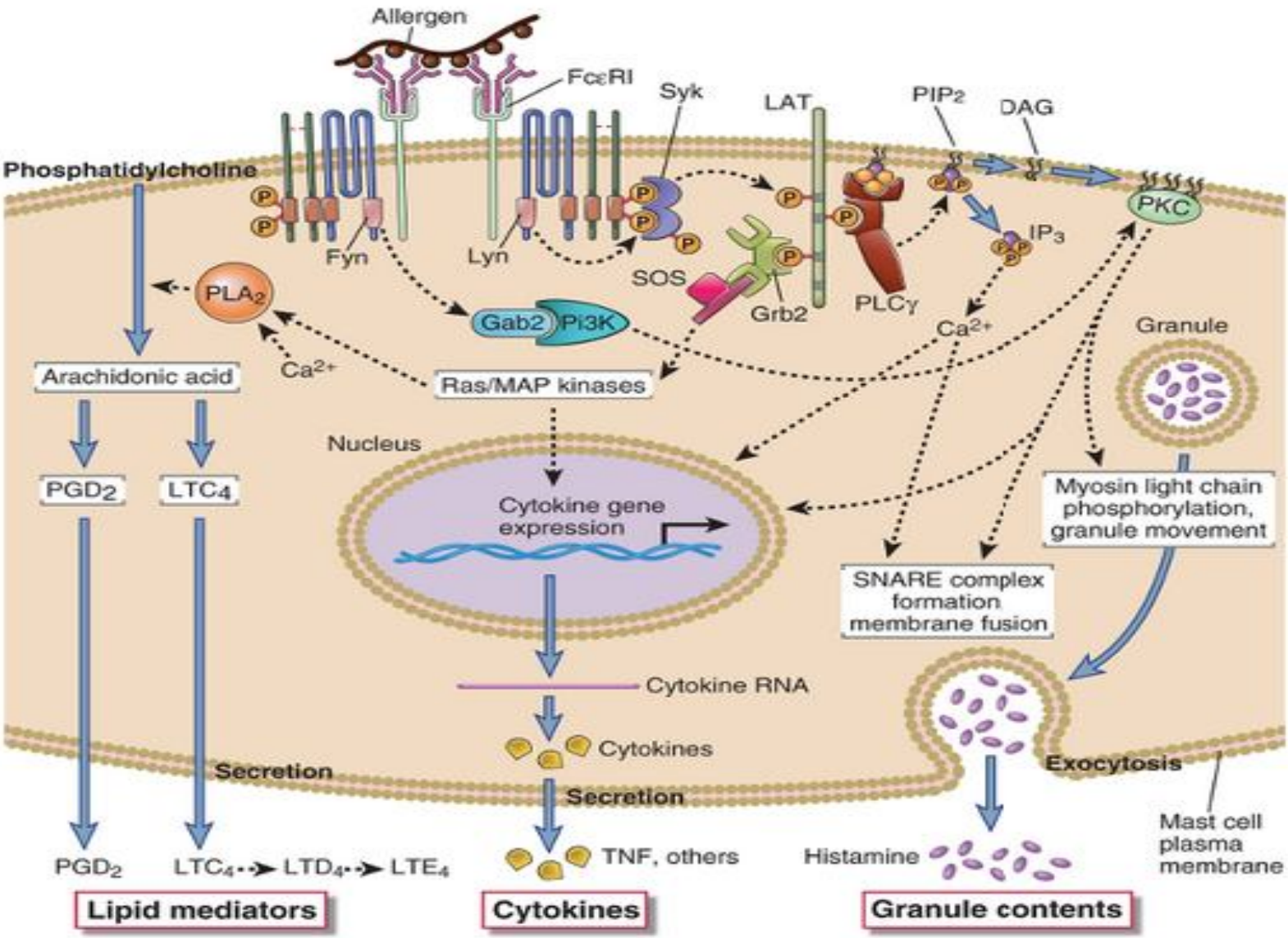
Cell Type	Mediator Category	Mediator	Function/Pathologic Effects
Mast cells and basophils			
	Stored preformed in cytoplasmic granules	Histamine	Increases vascular permeability; stimulates smooth muscle cell contraction
		Enzymes: neutral proteases (tryptase and/or chymase), acid hydrolases, cathepsin G, carboxypeptidase	Degrade microbial structures; tissue damage/remodeling
	Major lipid mediators produced on activation	Prostaglandin D_2	Vasodilation, bronchoconstriction, neutrophil chemotaxis
		Leukotrienes C_4, D_4, E_4	Prolonged bronchoconstriction, mucus secretion, increased vascular permeability
		Platelet-activating factor	Chemotaxis and activation of leukocytes, bronchoconstriction, increased vascular permeability
	Cytokines produced on activation	IL-3	Mast cell proliferation
		TNF, MIP-1α	Inflammation/late-phase reaction
		IL-4, IL-13	IgE production, mucus secretion
		IL-5	Eosinophil production and activation
Eosinophils			
	Stored preformed in cytoplasmic granules	Major basic protein, eosinophil cationic protein	Toxic to helminths, bacteria, host cells
		Eosinophil peroxidase, lysosomal hydrolases, lysophospholipase	Degrades helminthic and protozoan cell walls; tissue damage/remodeling
	Major lipid mediators produced on activation	Leukotrienes C_4, D_4, E_4	Prolonged bronchoconstriction, mucus secretion, increased vascular permeability
	Cytokines produced on activation	IL-3, IL-5, GM-CSF	Eosinophil production and activation
		IL-8, IL-10, RANTES, MIP-1α, eotaxin	Chemotaxis of leukocytes

GM-CSF, granulocyte-monocyte colony-stimulating factor; IL, interleukin, MIP-1α, monocyte inflammatory protein 1α; RANTES, regulated by activation, normal T cell expressed and secreted; TNF, tumor necrosis factor.

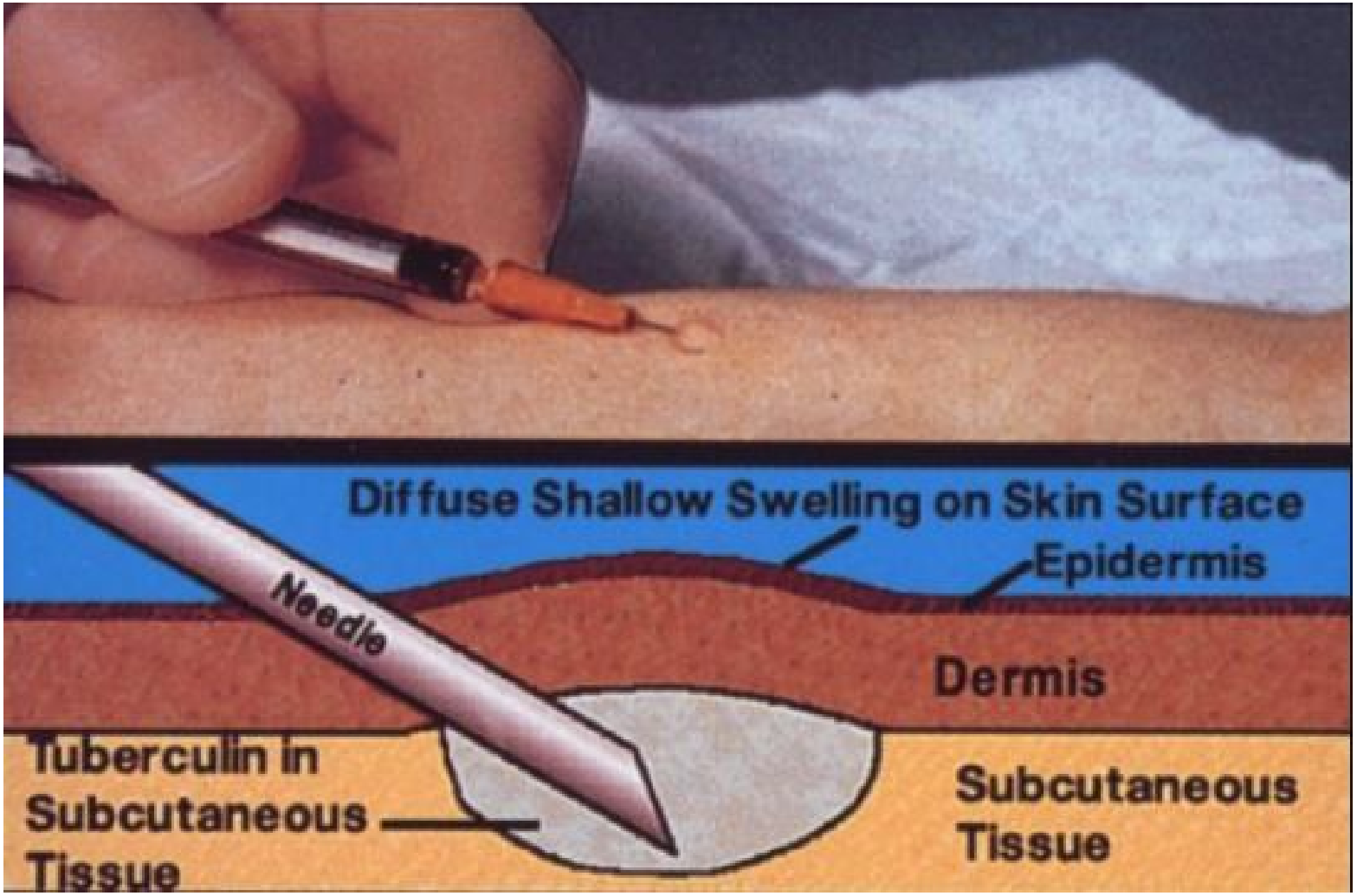
TABLE 19–3 Mast Cell Subsets

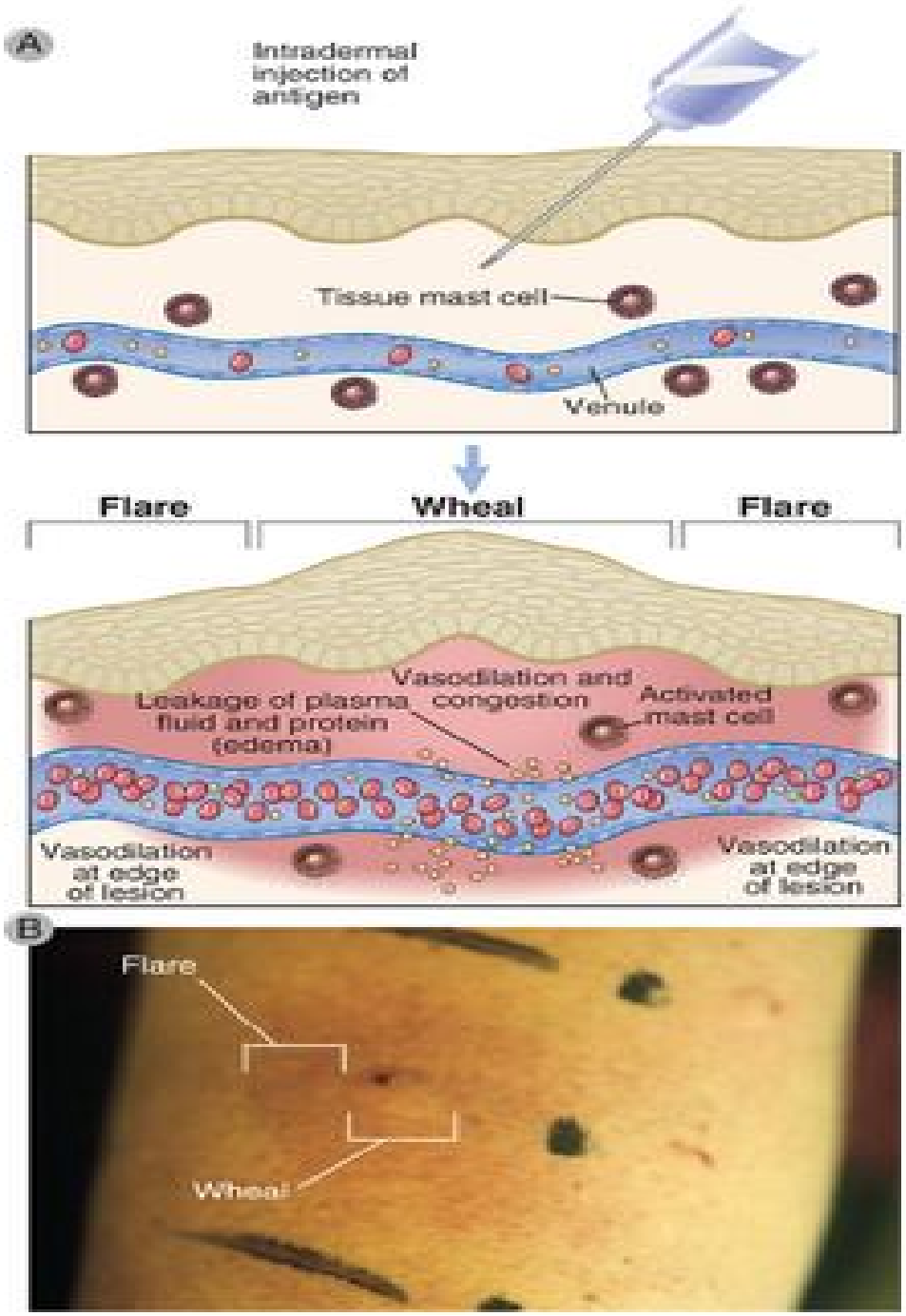
	Connective Tissue Mast Cells		Mucosal Mast Cells	
Characteristic	**Rodent**	**Human**	**Rodent**	**Human**
Location	Peritoneal cavity	Skin, intestinal submucosa	Intestinal mucosa	Alveoli, intestinal mucosa
T cell dependence for development of phenotype in tissues	No	No	Yes	Yes
Granule contents	High levels of histamine, heparin	Major neutral proteases: tryptase, chymase, carboxypeptidase, cathepsin G	Low levels of histamine; high levels of chondroitin sulfate	Major neutral protease: tryptase

Vias de Sinalização na Desgranulação de Mastócitos



Teste Intra-dérmico





IMPORTANTE

A REAÇÃO DE DESGRANULAÇÃO

DE MASTÓCITOS É UMA REAÇÃO

IMEDIATA

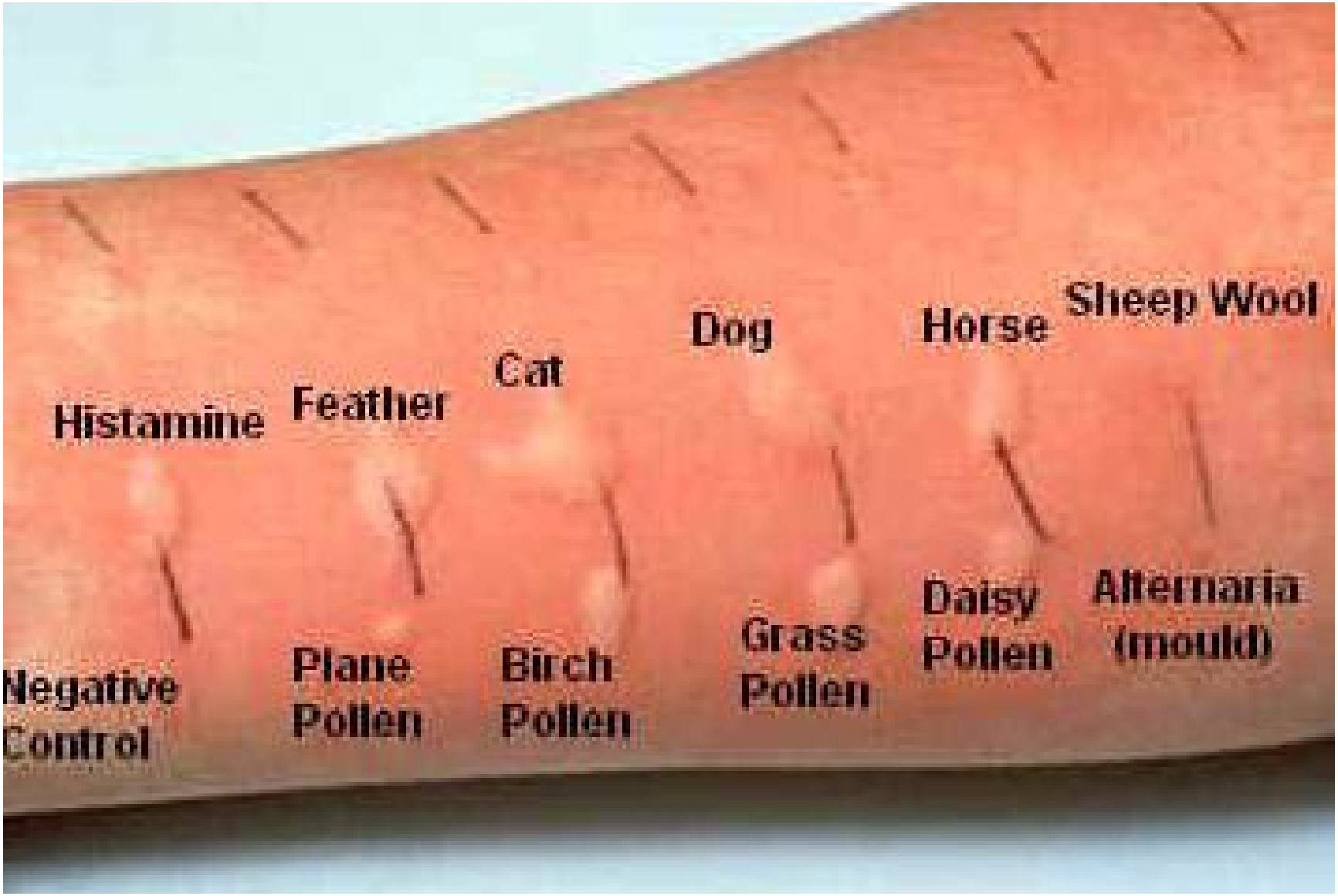
DIFERENTE DO PPD (hipersensibilidade tipo IV)

LEITURA

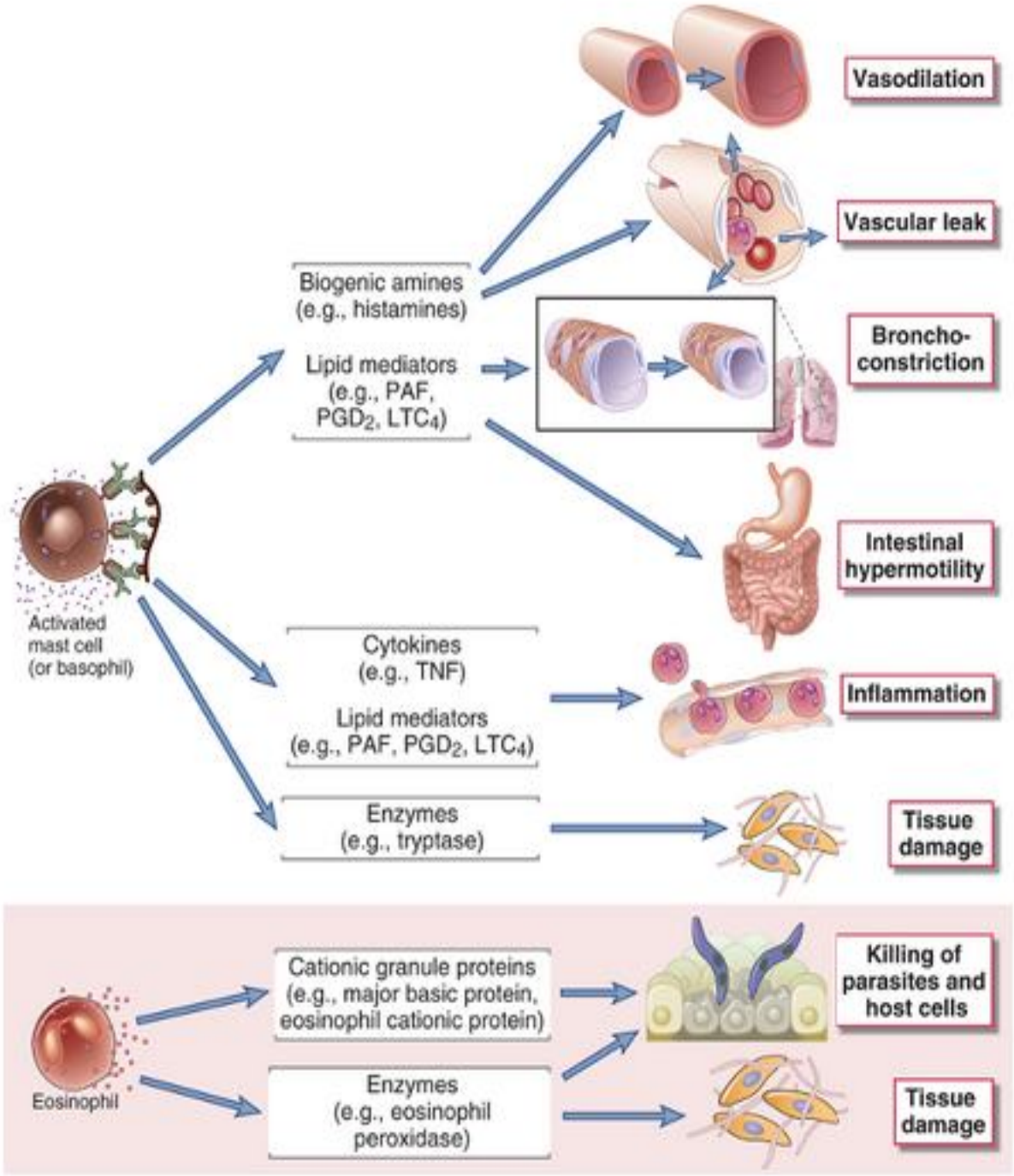
48-72 HORAS

Natureza Ag Importa Alérgenos

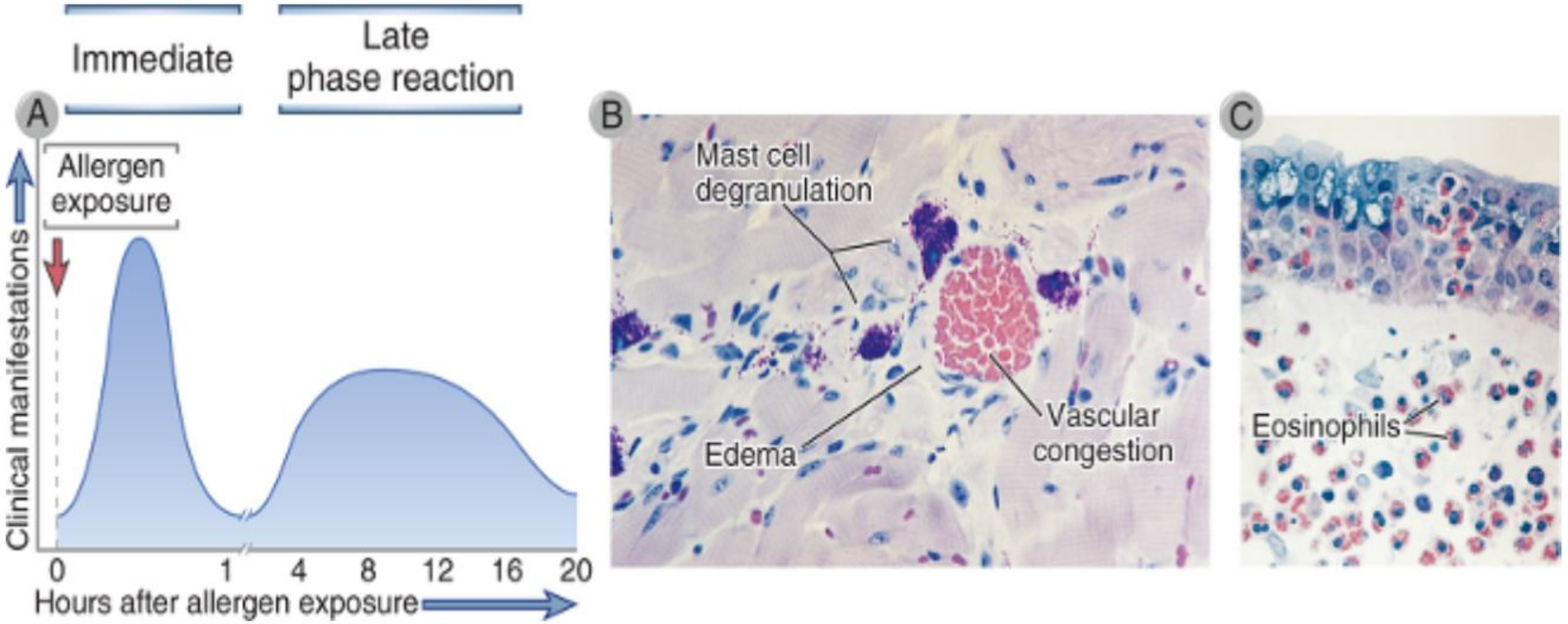
Prick Test


Histamine
Feather
Cat
Dog
Horse
Sheep Wool
Negative Control
Plane Pollen
Birch Pollen
Grass Pollen
Daisy Pollen
Alternaria (mould)

Resposta Biológica



Fase Tardia


A
Immediate
Late
phase reaction
Allergen
exposure
Clinical manifestations
0
1
4
8
12
16
20
Hours after allergen exposure
B
Mast cell
degranulation
Edema
Vascular
congestion
C
Eosinophils

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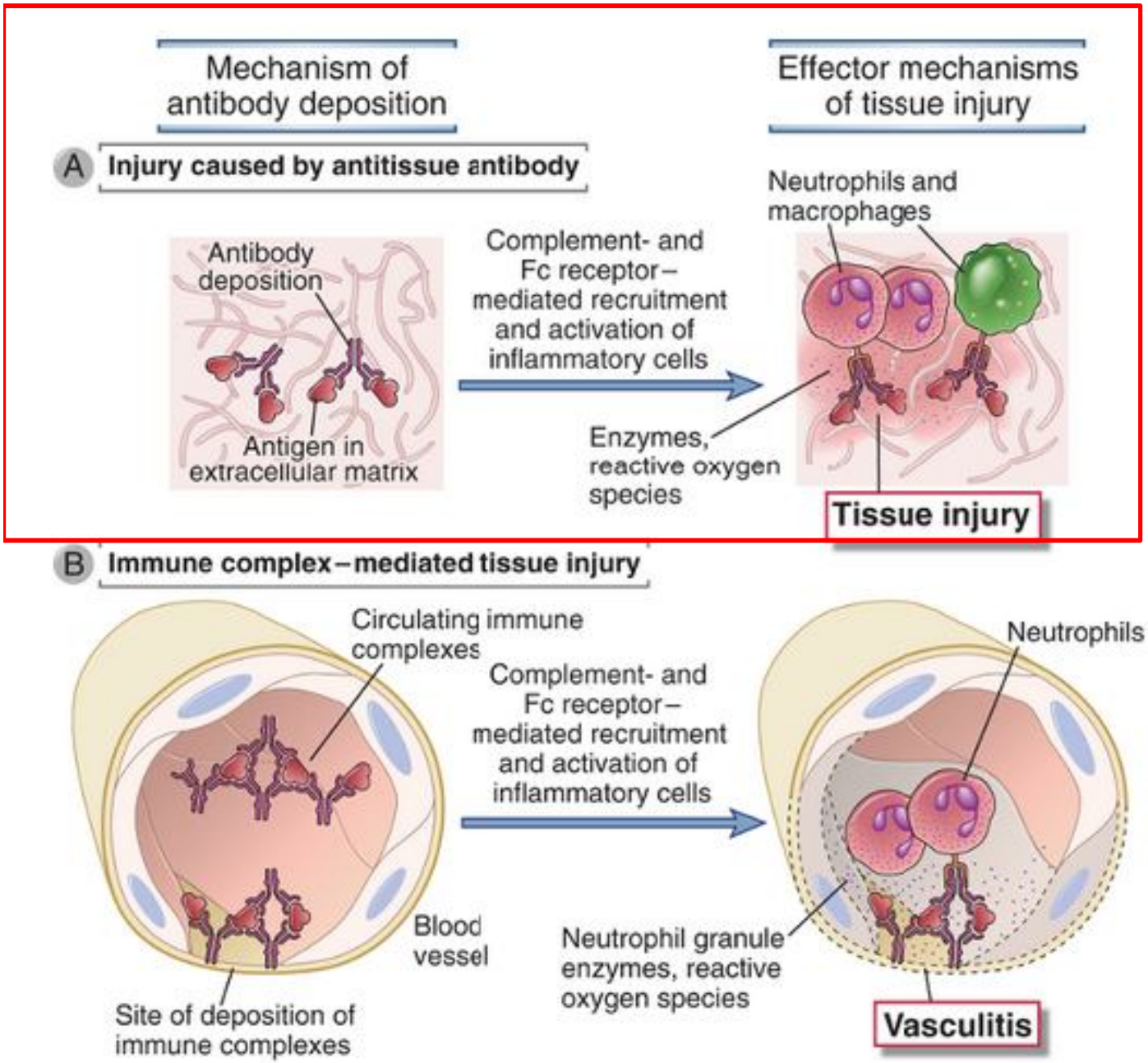


Anticorpos

Contra Antígenos Presentes Na Membrana Celular

Auto-anticorpos

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

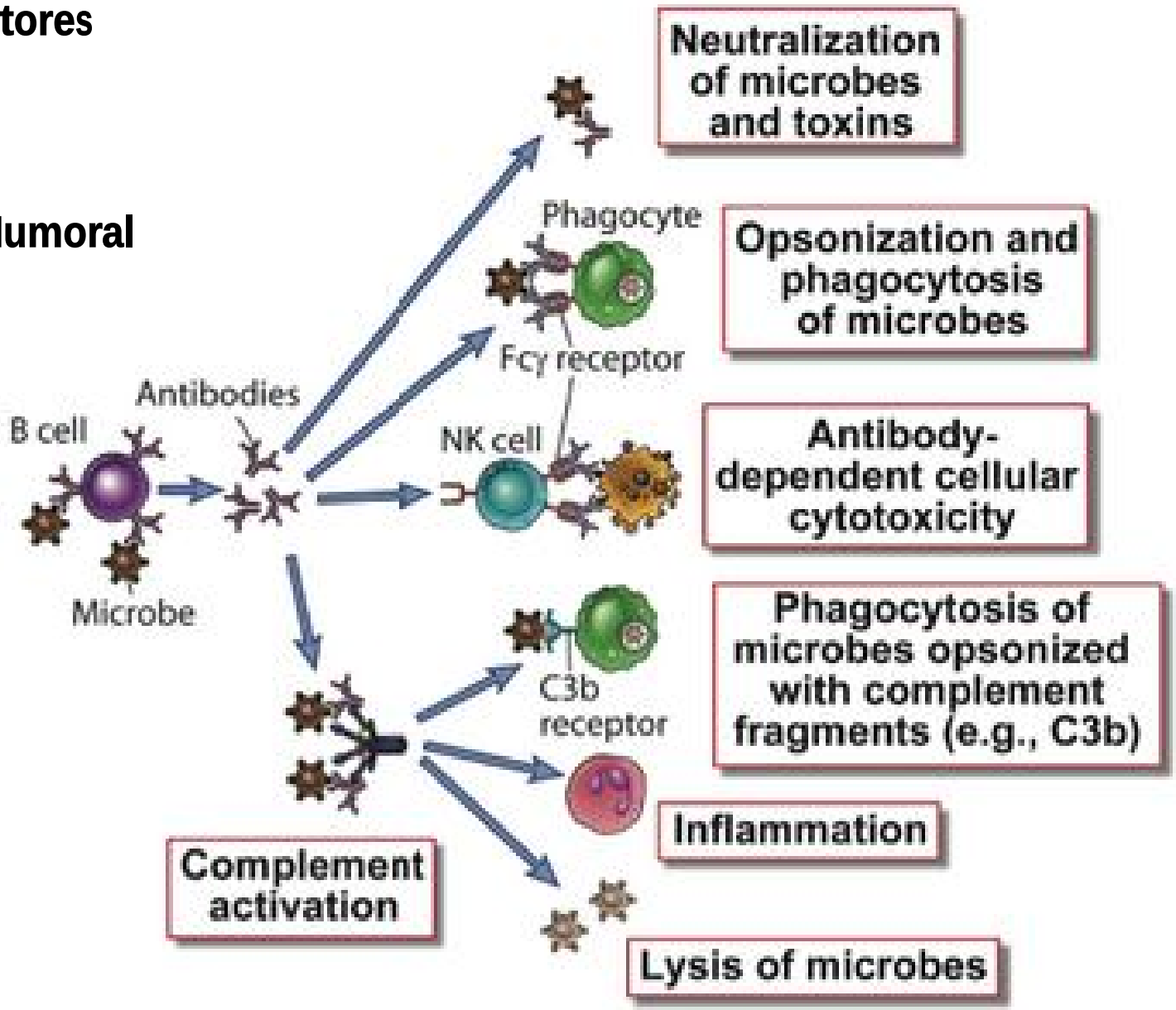
Mas quais os mecanismos imunes
Envolvidos no estabelecimento
Das lesões?

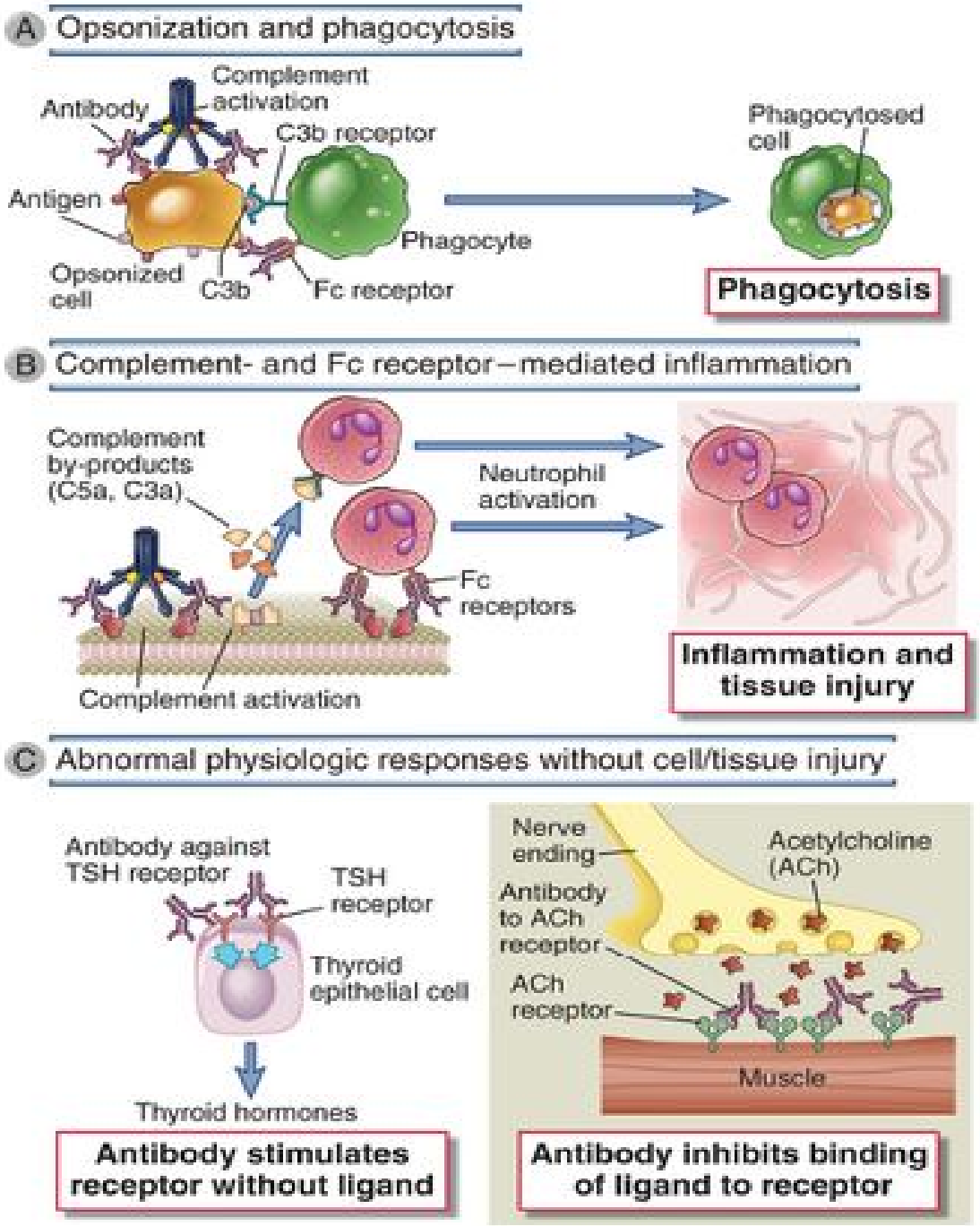
Efetores os Mecanismos São !

Mecanismos Efetores

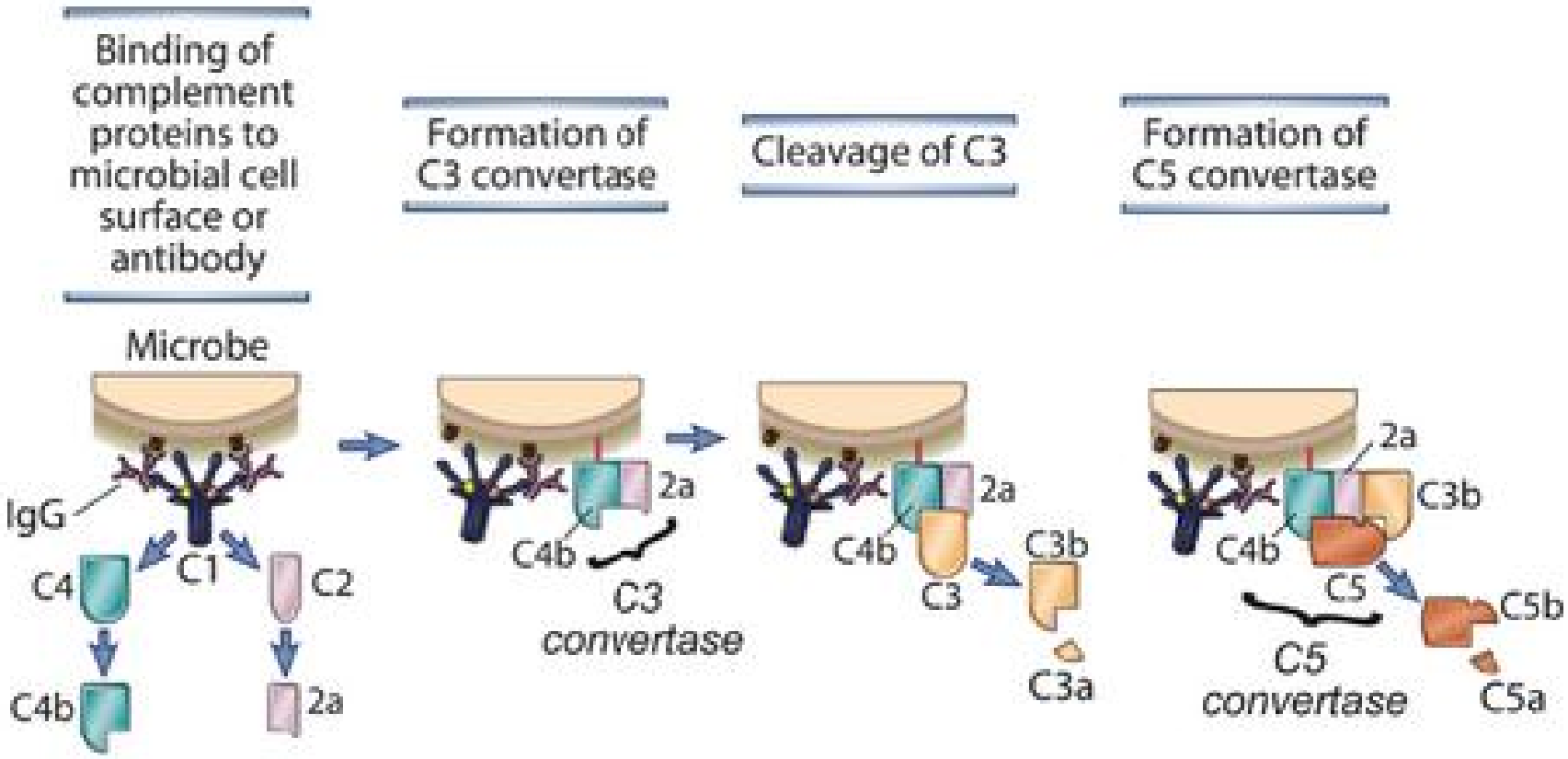
Da

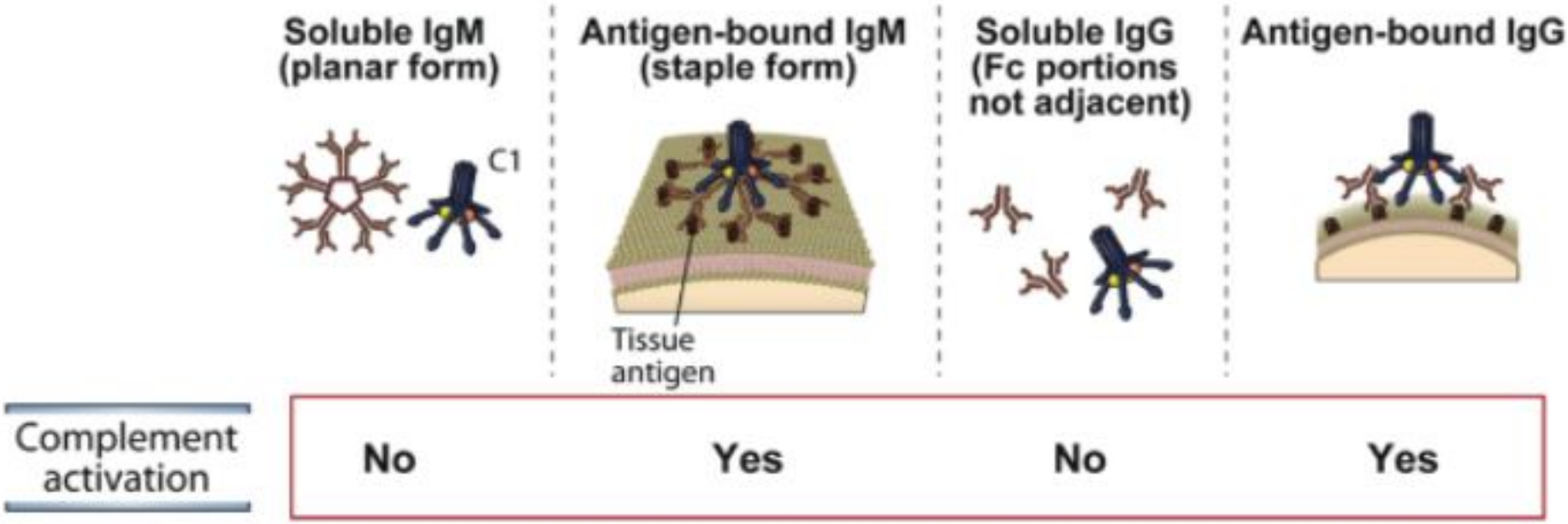
Resposta Imune Humoral

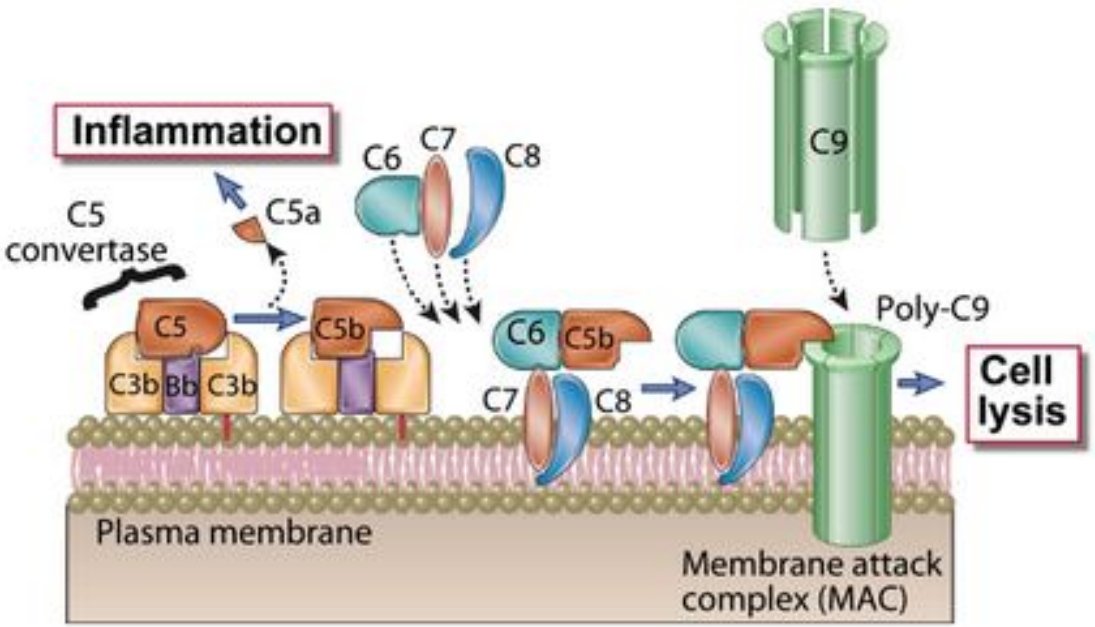



A Opsonization and phagocytosis
Complement activation
Antibody
C3b receptor
Antigen
Phagocyte
Opsonized cell
C3b
Fc receptor
Phagocytosed cell
Phagocytosis
B Complement- and Fc receptor–mediated inflammation
Complement by-products (C5a, C3a)
Neutrophil activation
Fc receptors
Complement activation
Inflammation and tissue injury
C Abnormal physiologic responses without cell/tissue injury
Antibody against TSH receptor
TSH receptor
Thyroid epithelial cell
Thyroid hormones
Antibody stimulates receptor without ligand
Nerve ending
Acetylcholine (ACh)
Antibody to ACh receptor
ACh receptor
Muscle
Antibody inhibits binding of ligand to receptor

Classical Pathway







Inflamação Local

Inicia-se

Lise Celular
Extravazamento
De Conteúdo
Citoplasmático

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.

TABLE 19–4 Examples of Genes Associated with Atopy and Asthma

Candidate Genes or Encoded Protein	Chromosomal Location	Disease Association	Putative Role of Gene Products in Disease
Cytokine gene cluster (IL-4, IL-5, IL-13), CD14, β_2-adrenergic receptor	5q	Asthma	IL-4 and IL-13 promote IgE switching, IL-5 promotes eosinophil growth and activation; CD14 is a component of the LPS receptor that, through interaction with TLR4, may influence the balance between T_H1 and T_H2 responses to antigens; β_2-adrenergic receptor regulates bronchial smooth muscle contraction
Class II MHC	6p	Asthma	Some alleles may regulate T cell responses to allergens
FcεRI β chain	11q	Asthma	Mediates mast cell activation
Stem cell factor, interferon-γ, STAT6	12q	Asthma	Stem cell factor regulates mast cell growth and differentiation; interferon-γ opposes actions of IL-4; STAT6 mediates IL-4 signal transduction
IL-4 receptor α chain	16	Asthma	Subunit of both IL-4 and IL-13 receptors
ADAM33	20p	Asthma	Metalloproteinase involved in airway remodeling
DPP10		Asthma	Peptidase that may regulate chemokine and cytokine activity
PHF11	13q	Asthma	Transcriptional regulator involved in B cell clonal expansion and Ig expression
ORMDL3	17q	Asthma	Unknown
IL-1 receptor–like 1	2q	Asthma	Membrane receptor that mediates effects of IL-1 on T cells
Phosphodiesterase 4D	5q	Asthma	Degrades cAMP and regulates airway smooth muscle contractility
Filaggrin		Atopic dermatitis	Component of terminally differentiated keratinocytes

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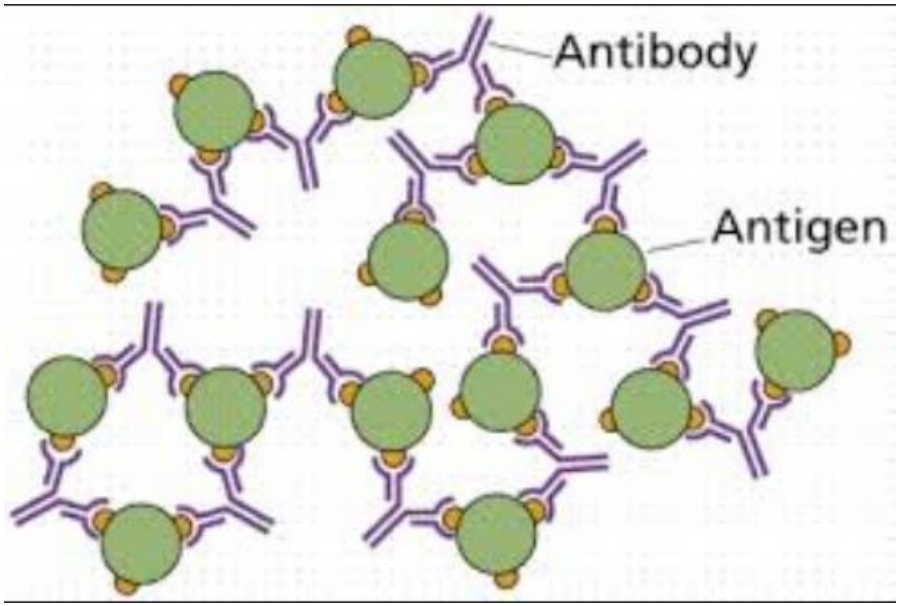
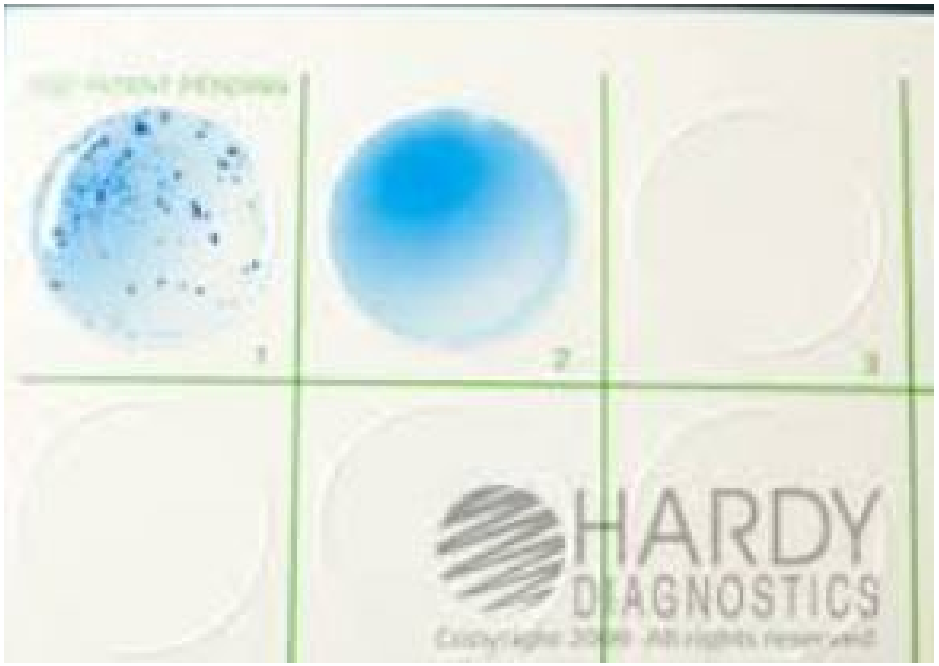
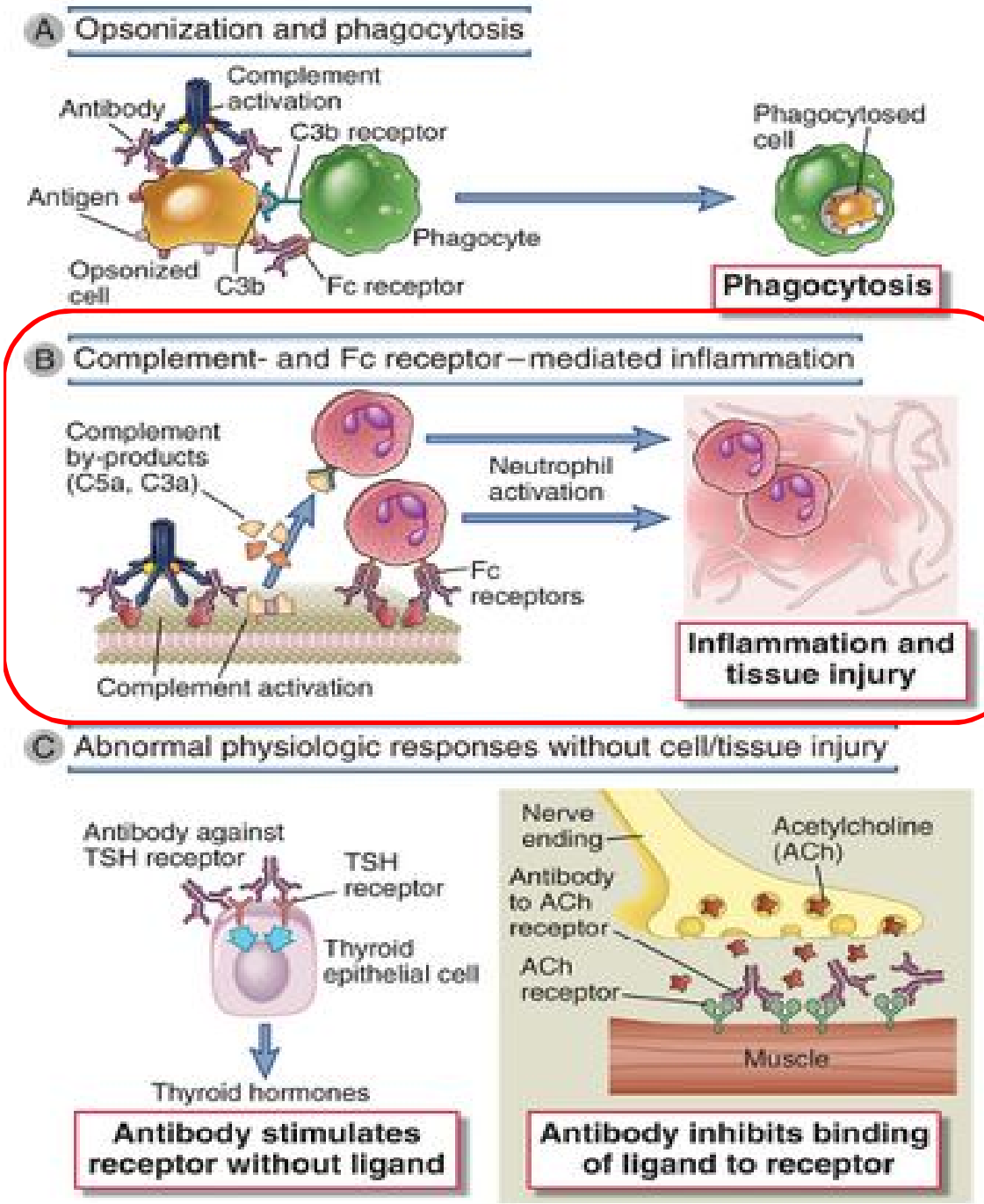
Imunocomplexo



Detecção de E coli





Anticorpos

Contra Antígenos Solúveis

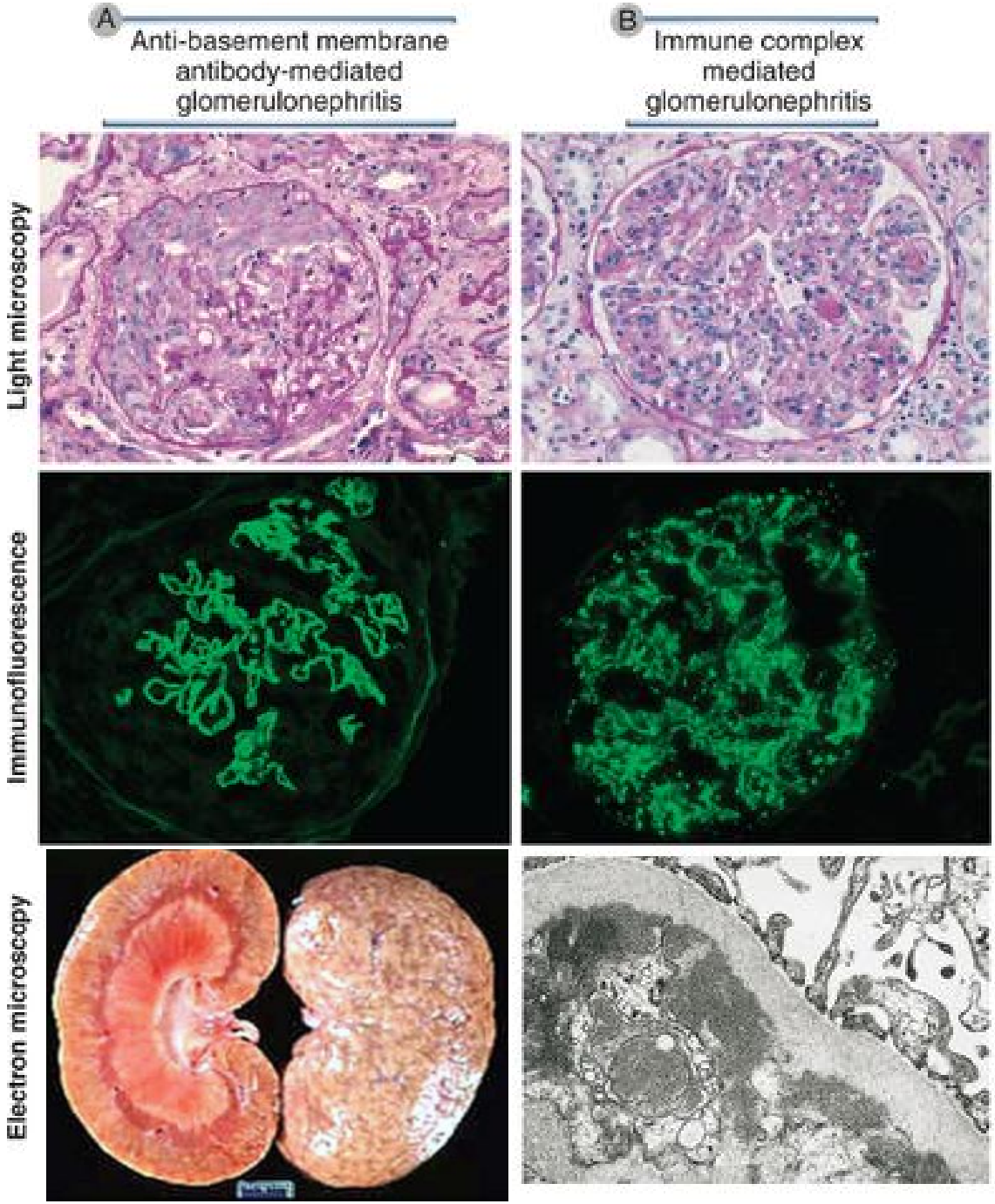
Auto-anticorpos

Mioglobina
DNA
Histonas
Ags exógenos

Medicamentos

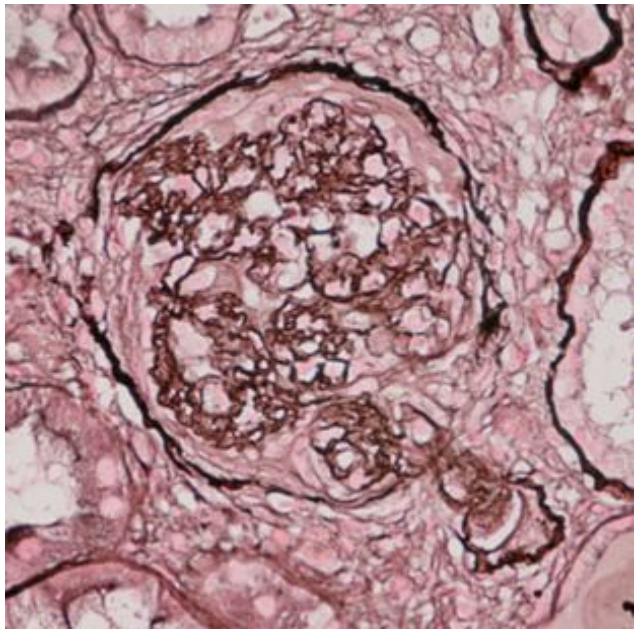
Gravidade da doença se relaciona:
Abundância Ag

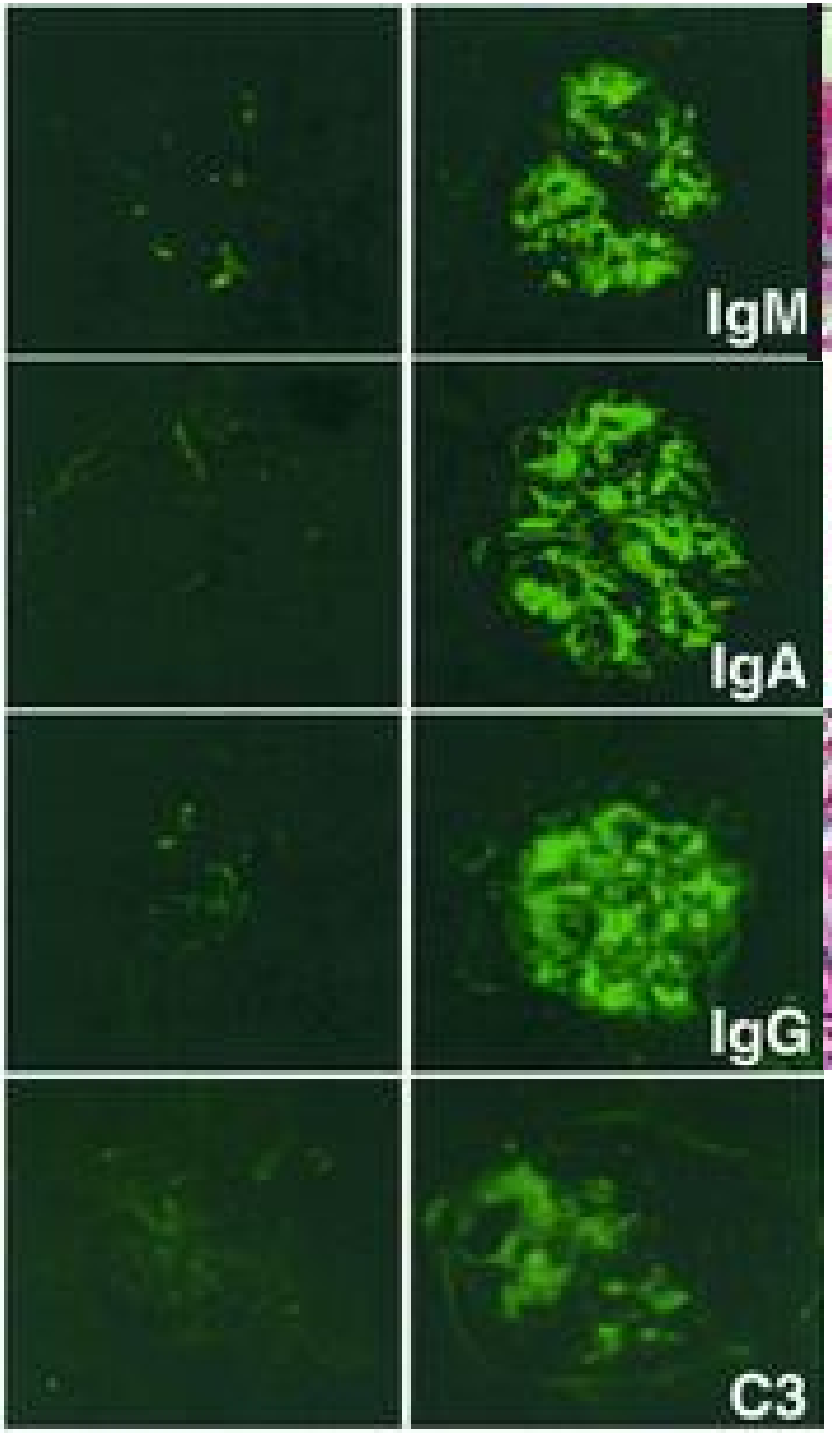
Tecido Acometido
Rins
Articulações



Deposição de Imunocomplexo

Nos Rins





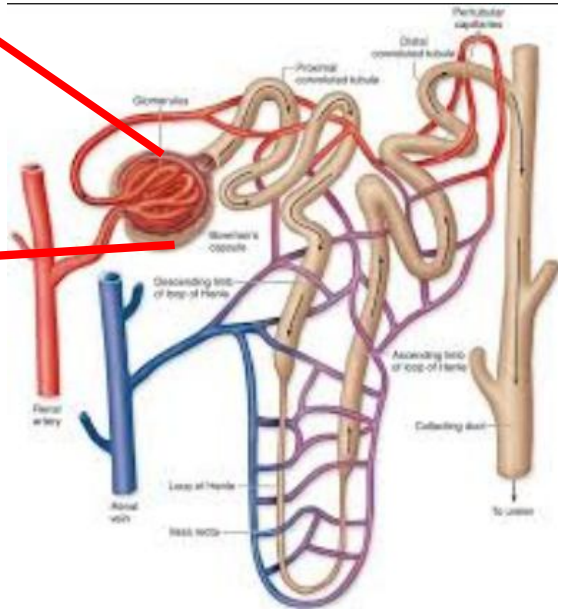
Imunocomplexo

IgM

IgA

IgG

Complemento



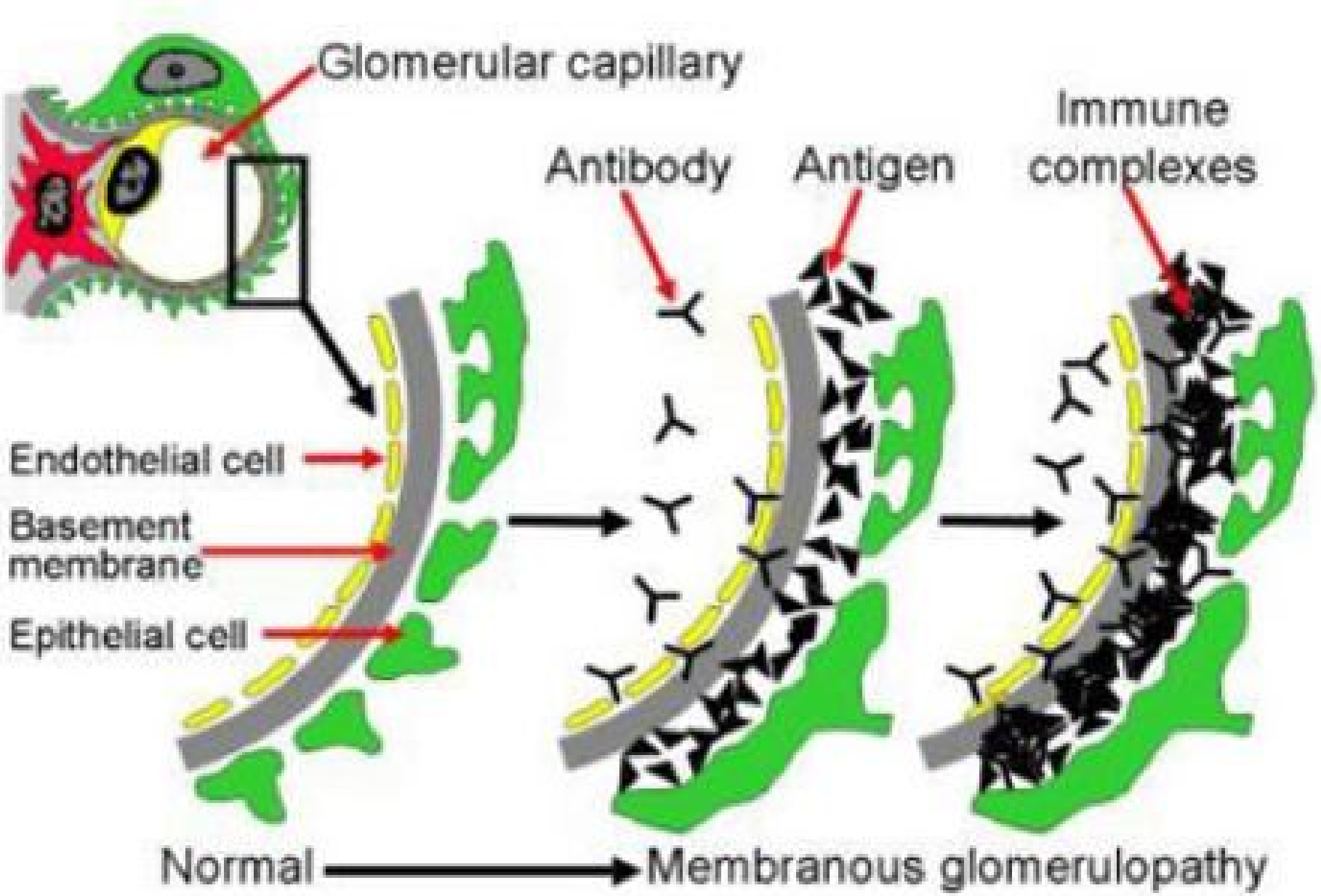
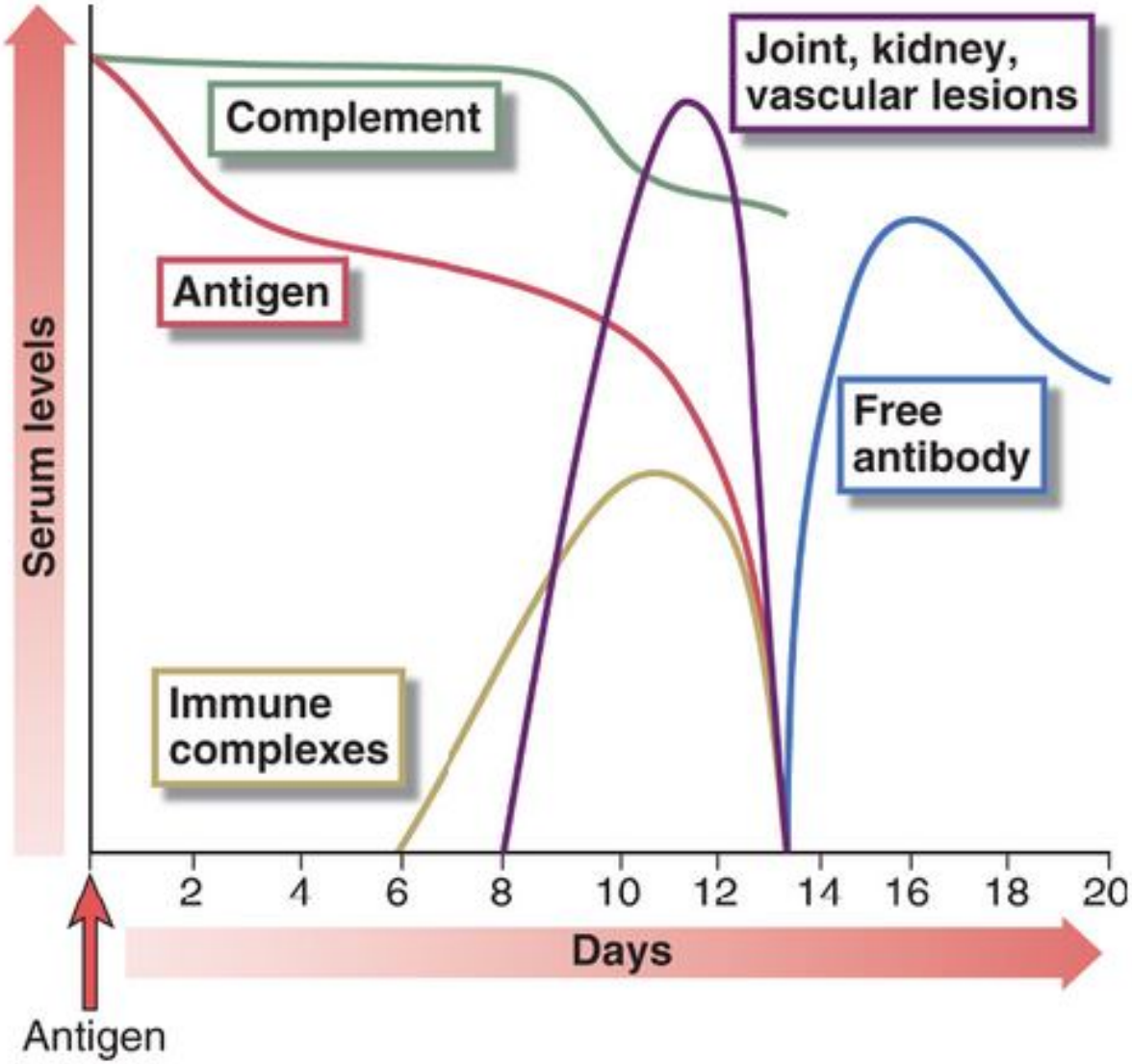
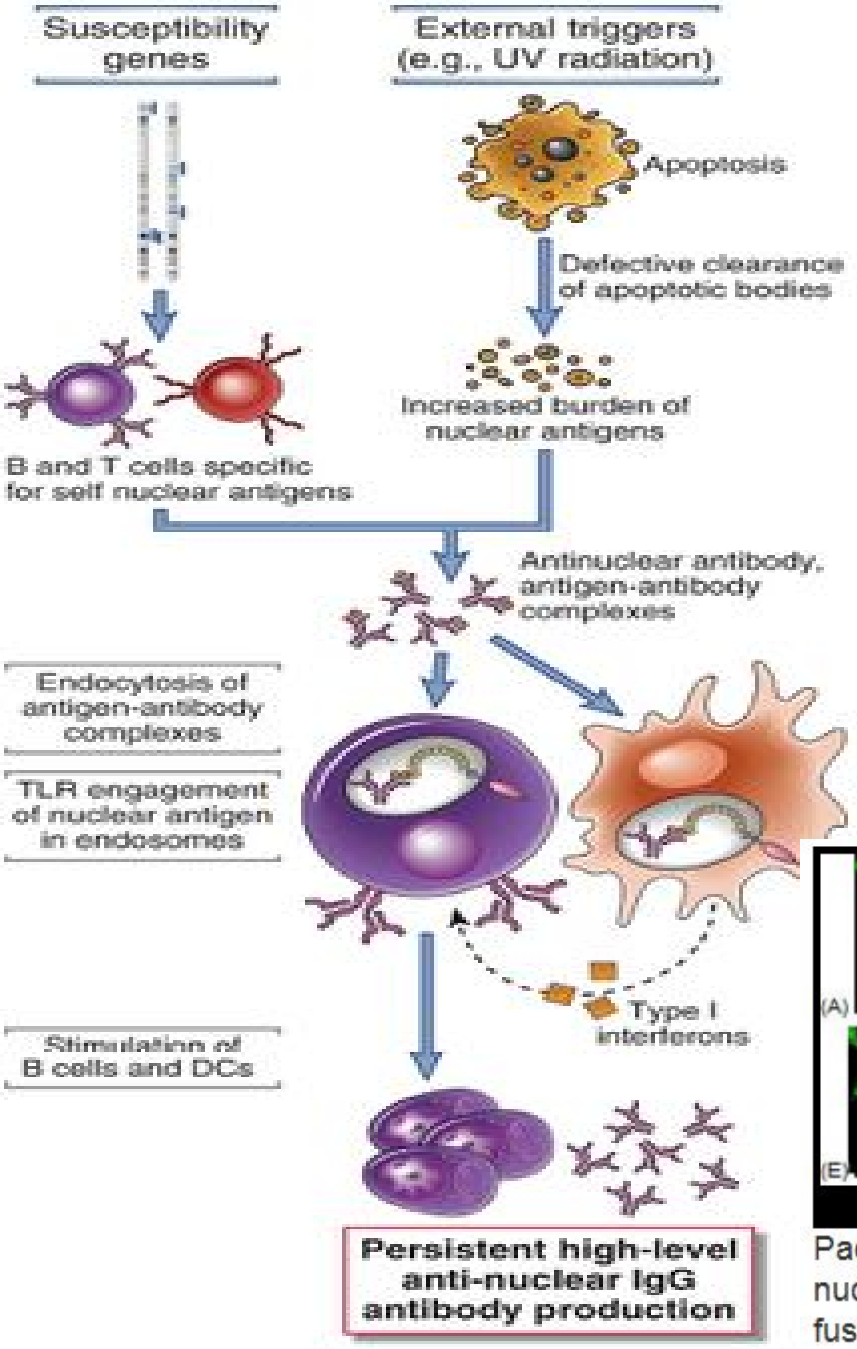

Glomerular capillary
Antibody
Antigen
Immune complexes
Endothelial cell
Basement membrane
Epithelial cell
Normal
Membranous glomerulopathy

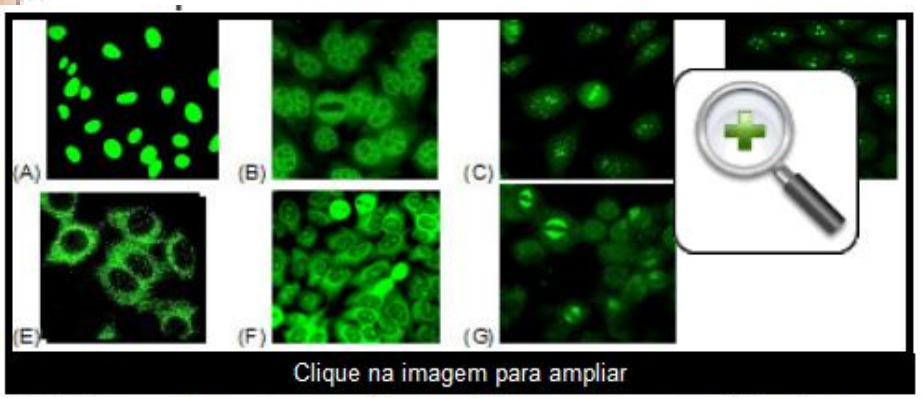
TABLE 18–3 Examples of Human Immune Complex–Mediated Diseases

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


Joint, kidney, vascular lesions
Complement
Antigen
Free antibody
Immune complexes
Serum levels
2
4
6
8
10
12
14
16
18
20
Days
Antigen

Lupus Eritematoso Sistêmico

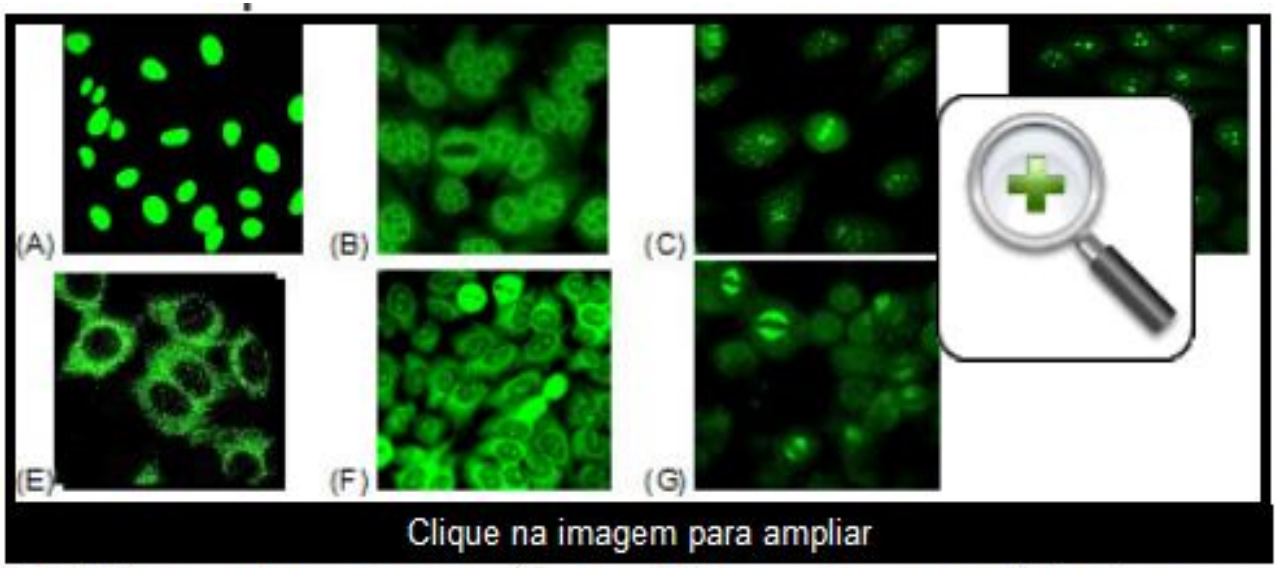




Clique na imagem para ampliar

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

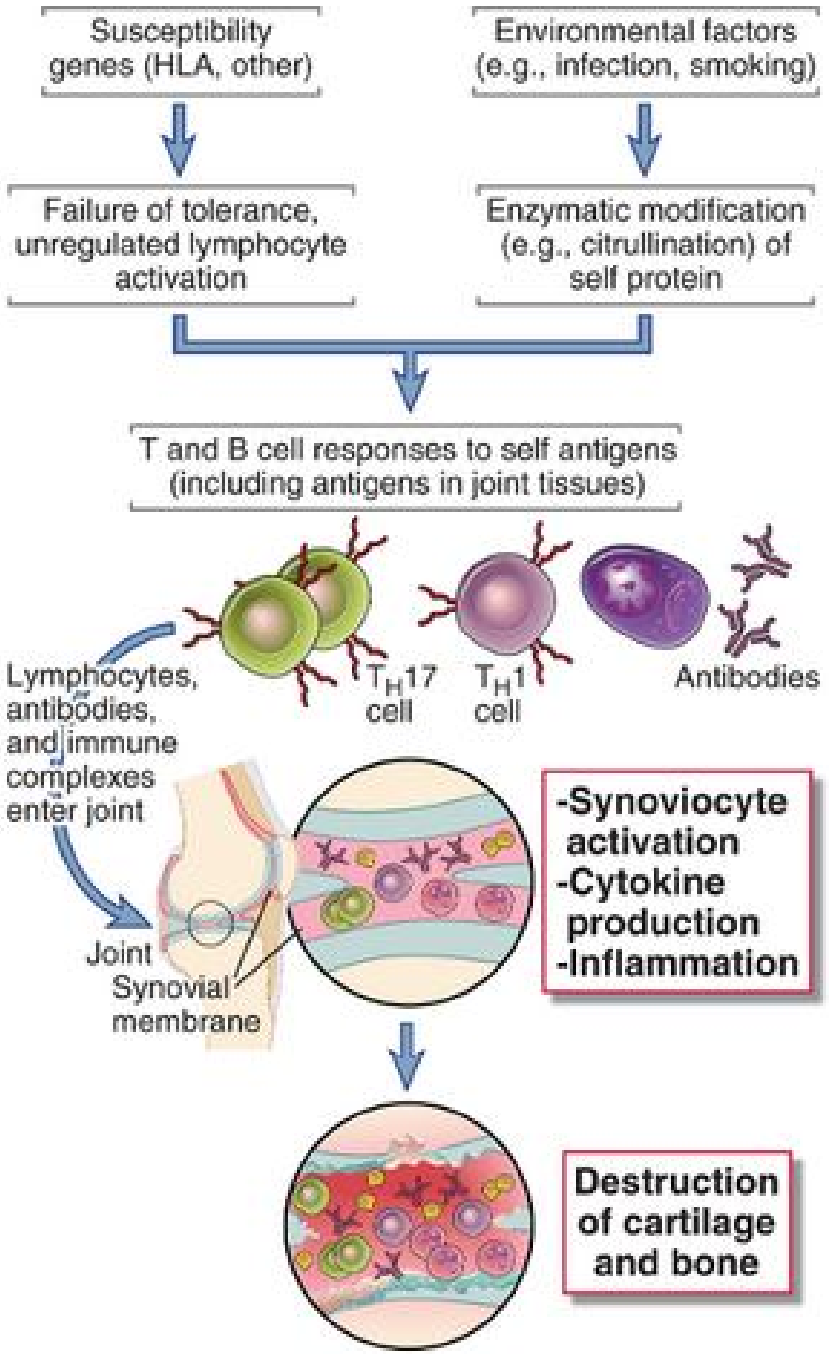
Anticorpos Anti-DNA, Anti-Histona
Fatores Anti-núcleo



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

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

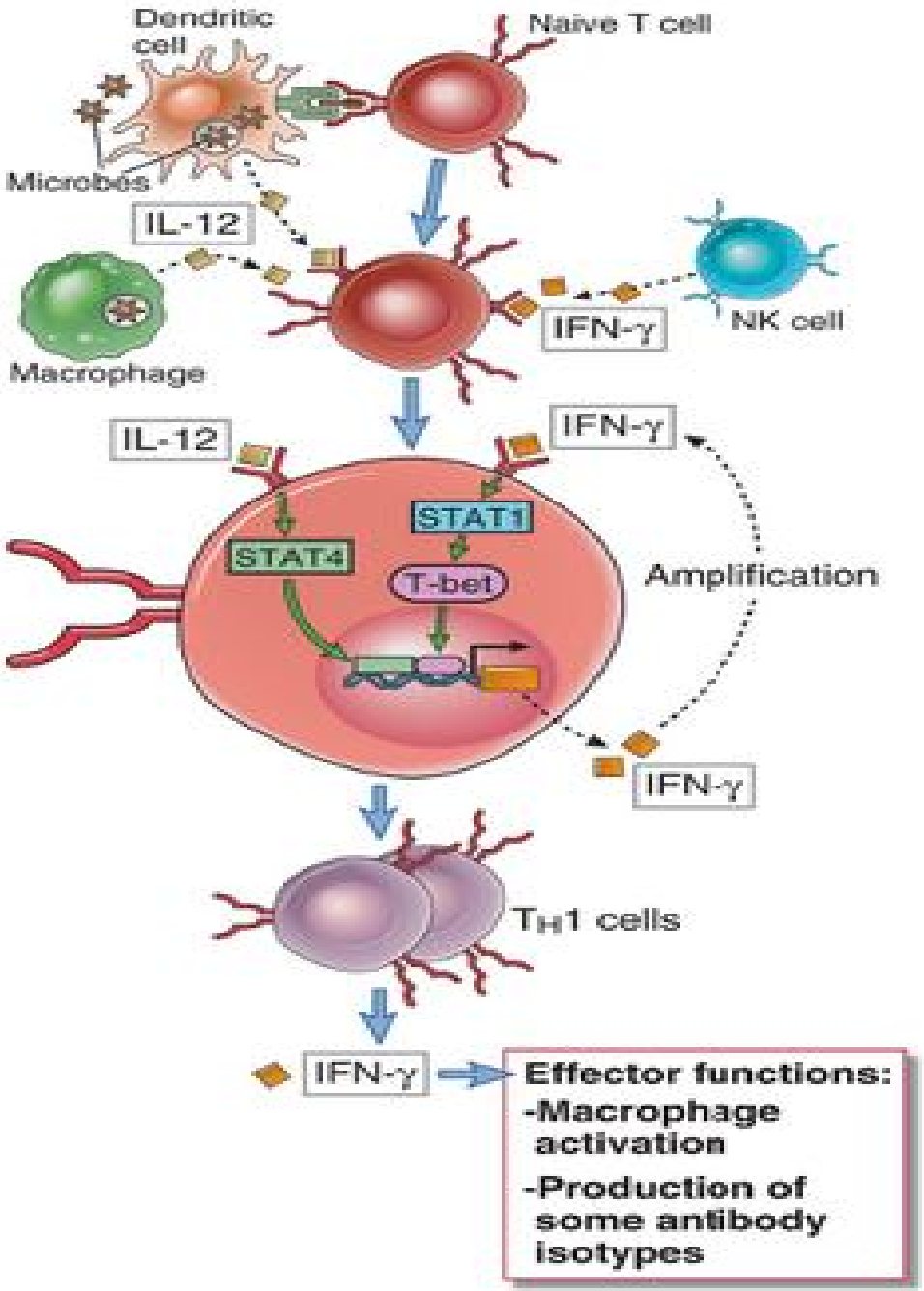
Th1

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**

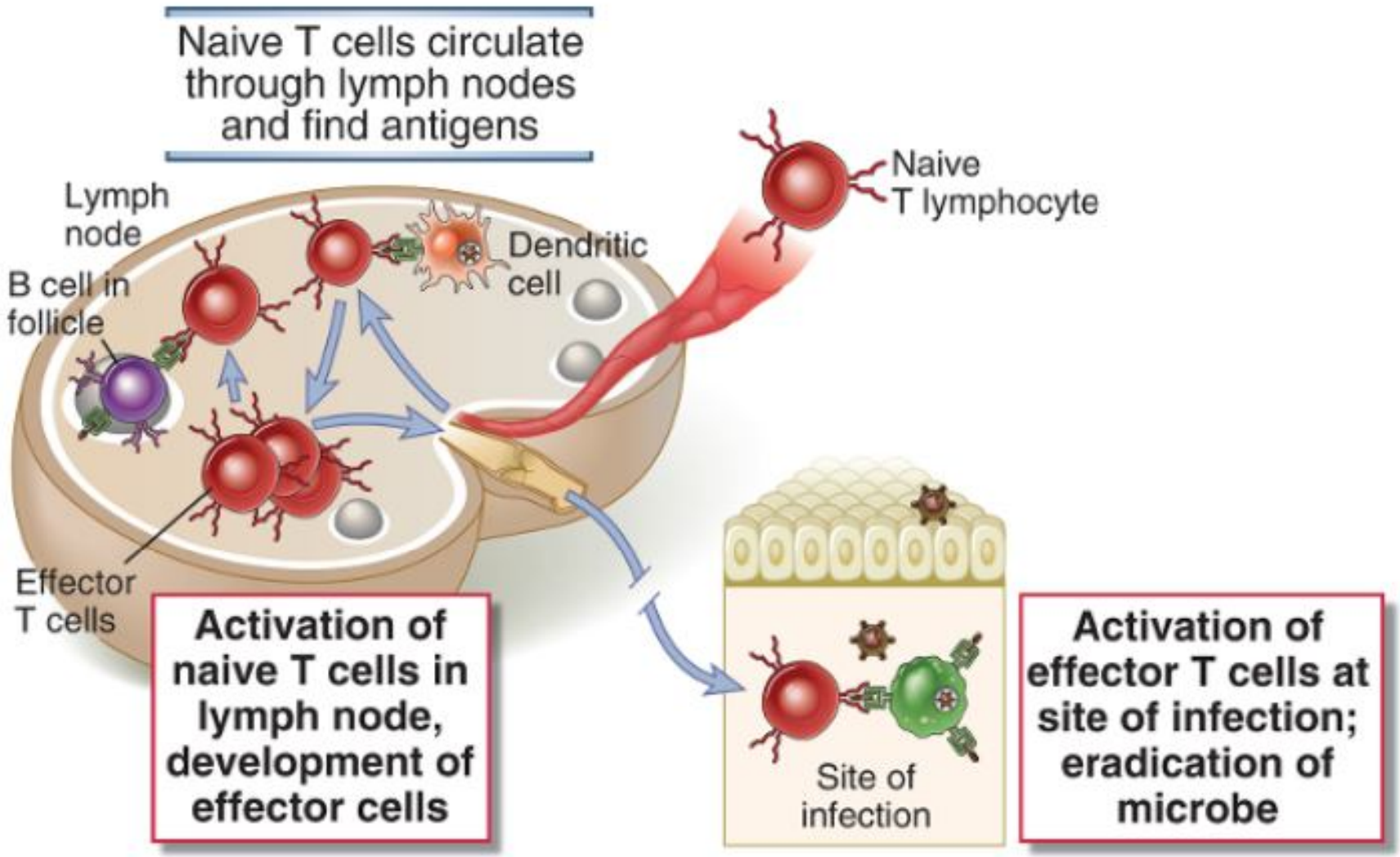
IL-12, TNF-α, IFN-γ

Então estarão presentes todos os mecanismos da resposta Imune celular ?

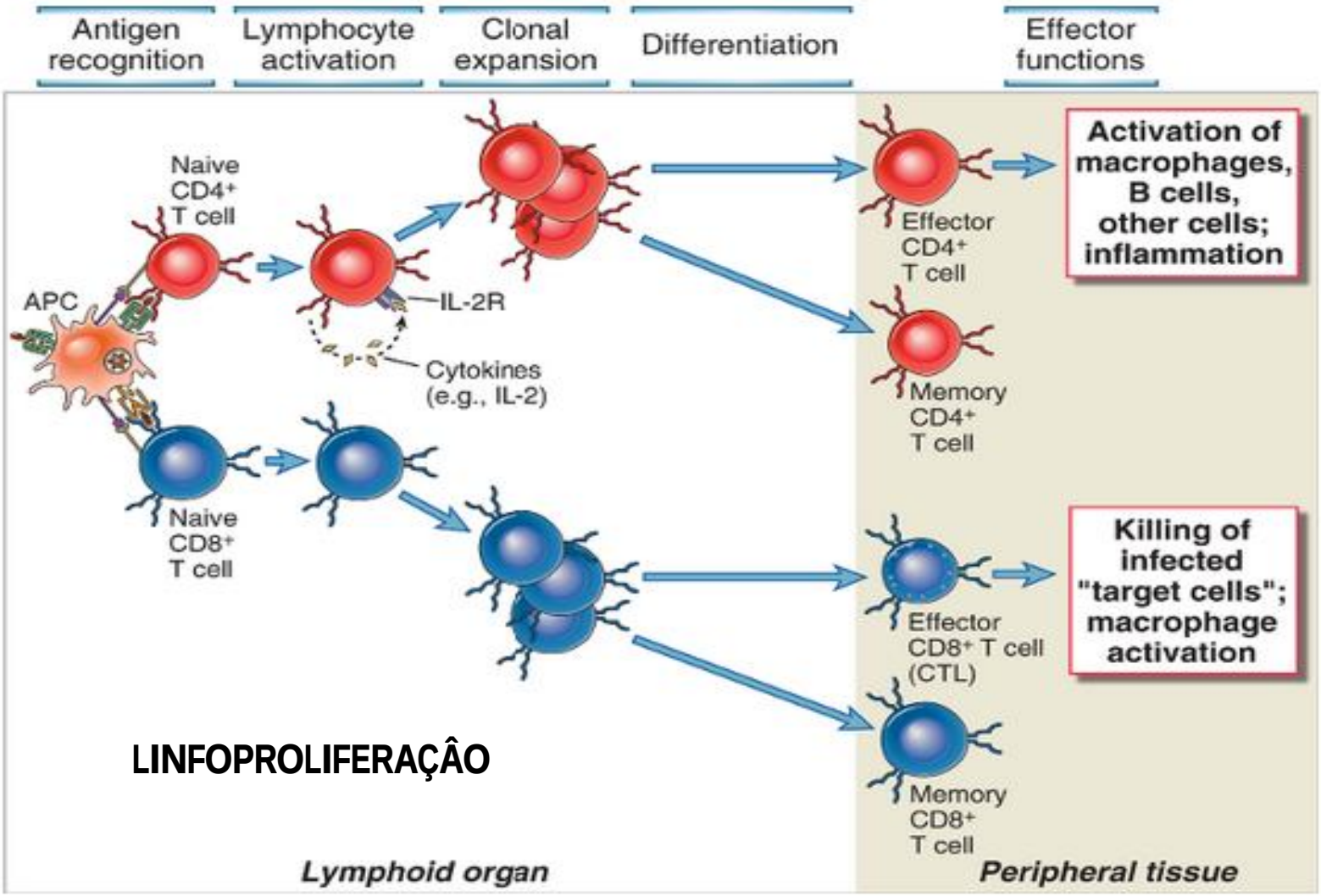
Correto vc está !

Contato Prévio
Imunizações!

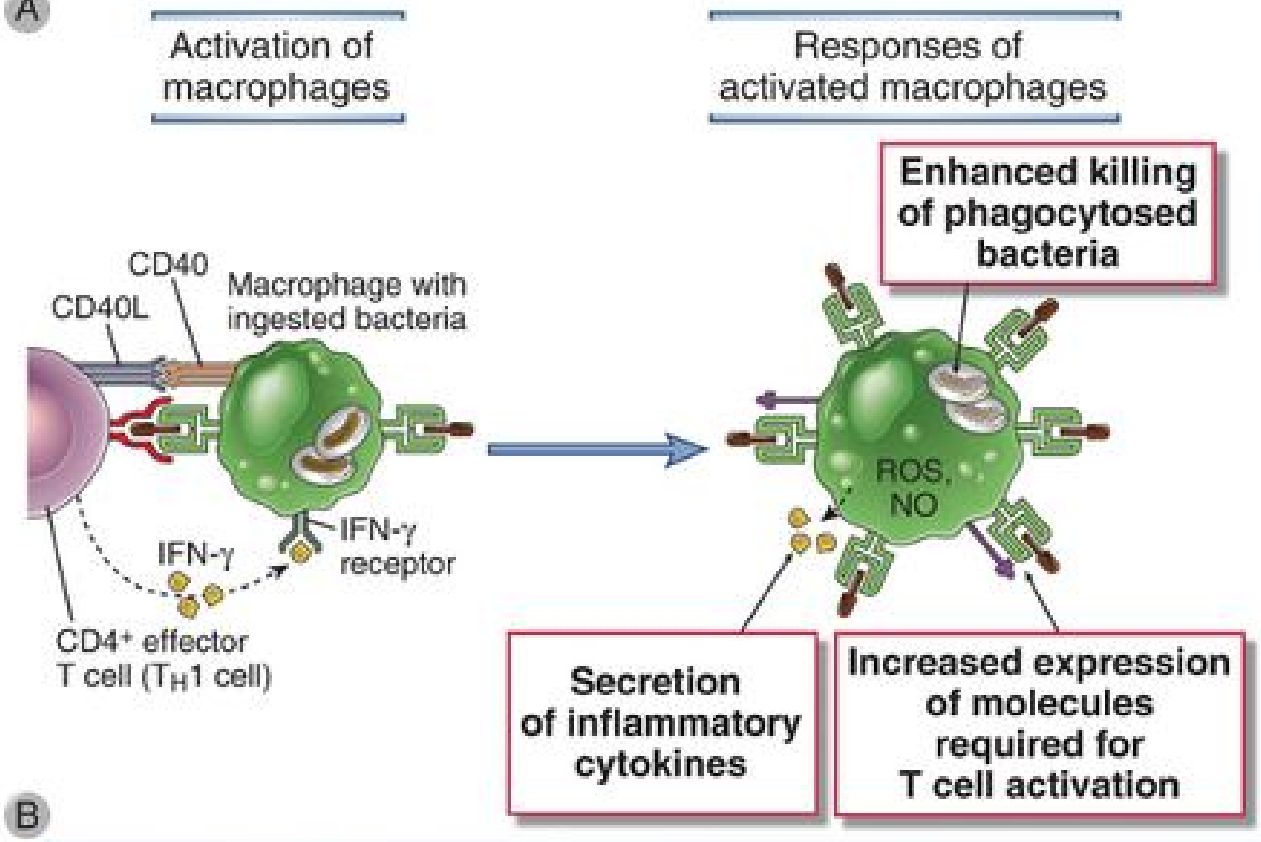
Memória Imunológica


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?

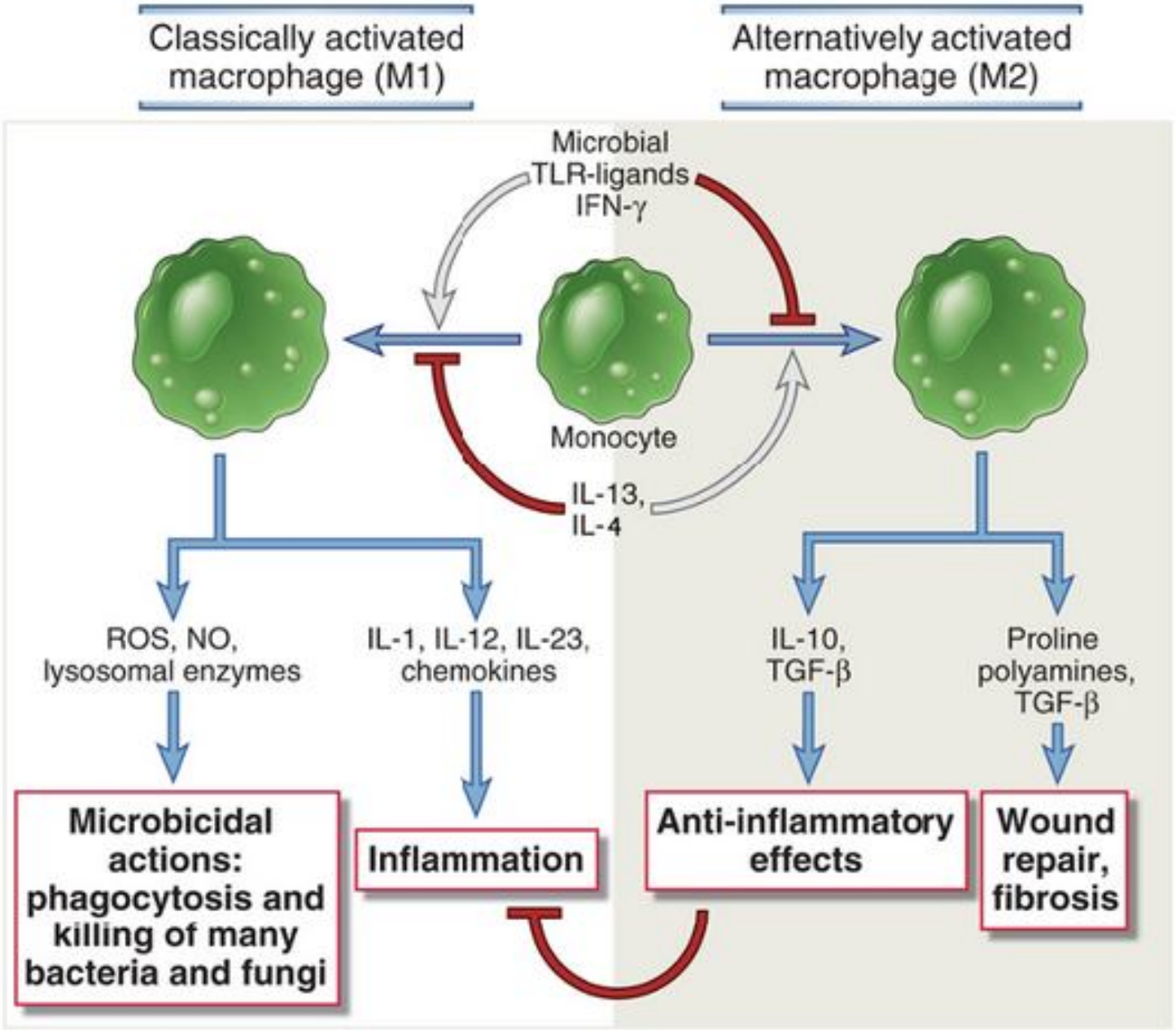


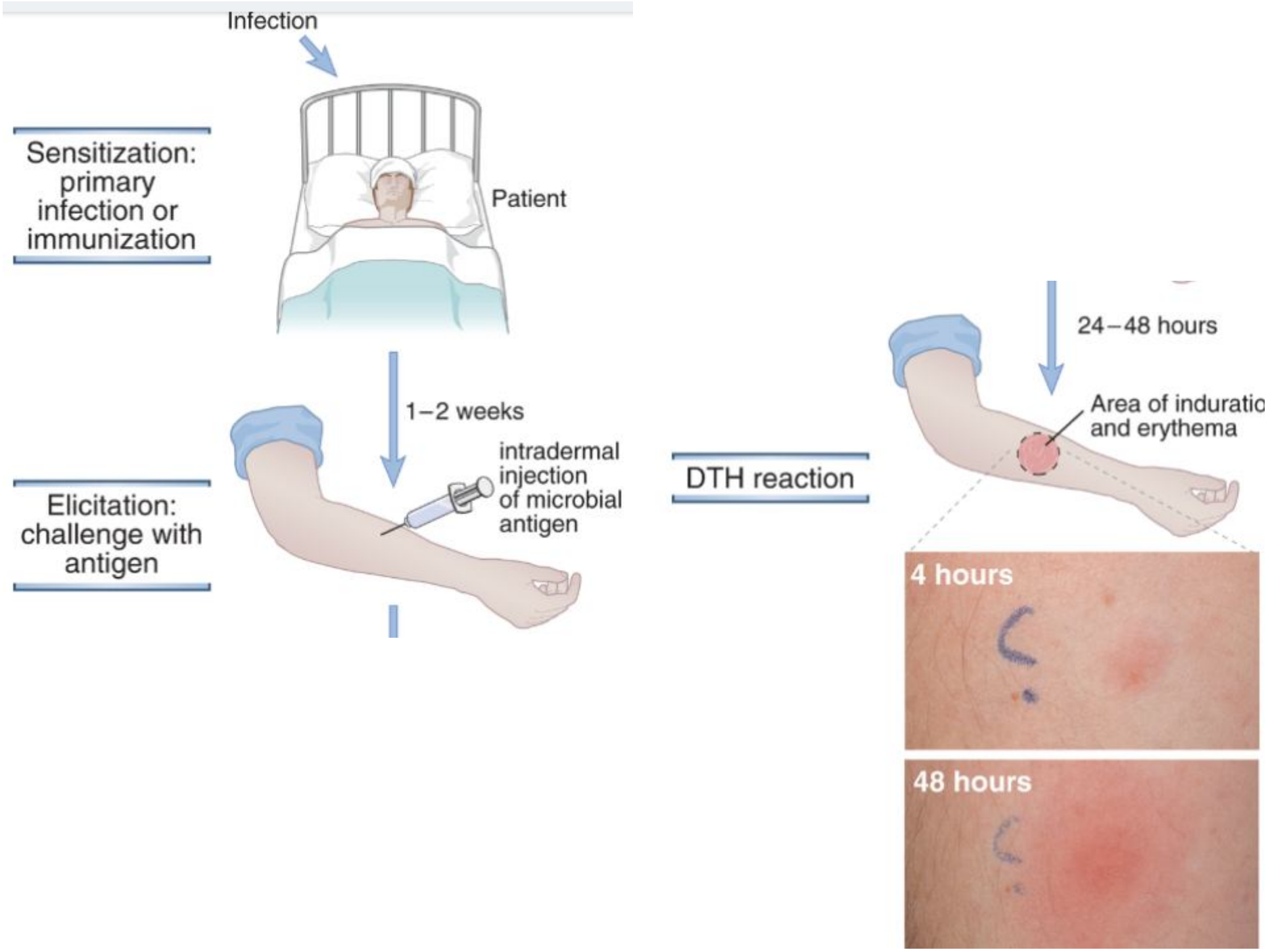
A

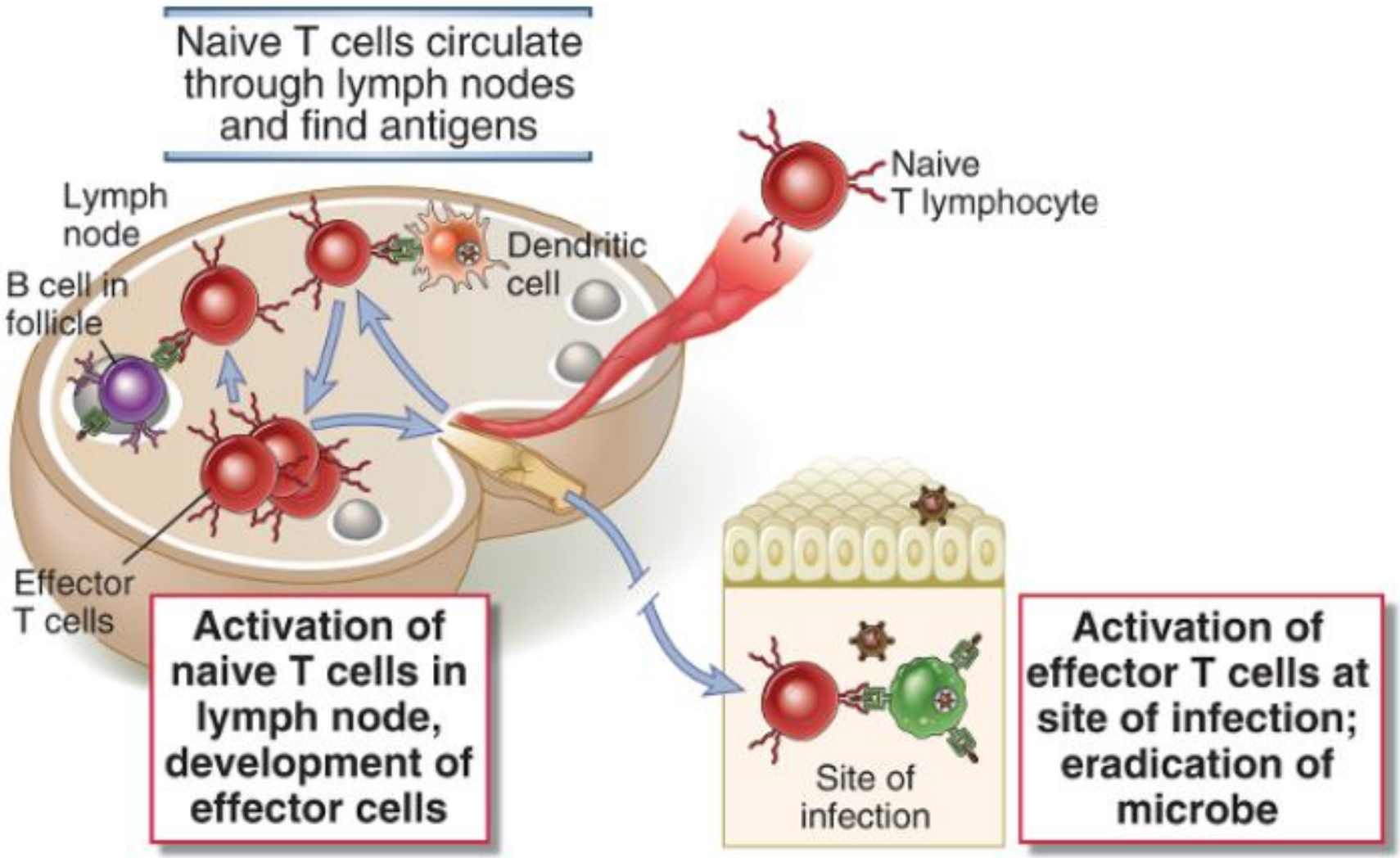


B

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)

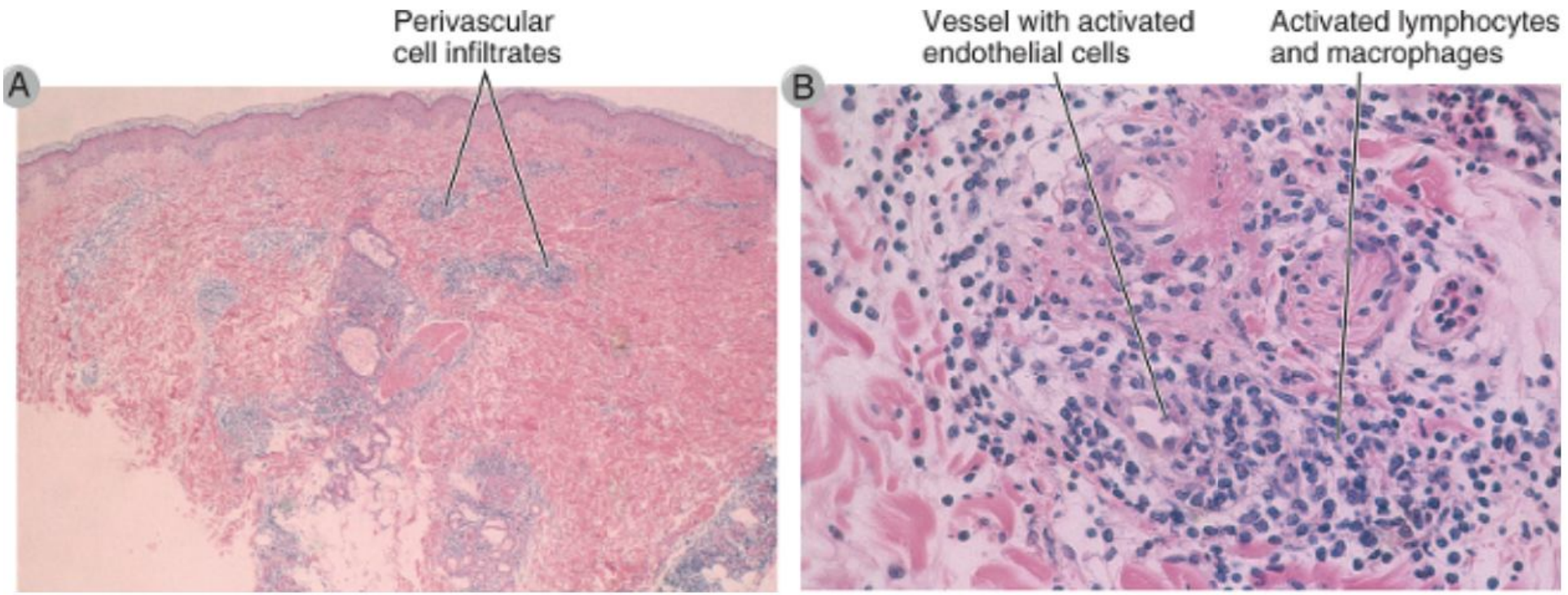

Classically activated macrophage (M1)
Alternatively activated macrophage (M2)
Microbial
TLR-ligands
IFN-γ
Monocyte
IL-13,
IL-4
ROS, NO,
lysosomal enzymes
IL-1, IL-12, IL-23,
chemokines
IL-10,
TGF-β
Proline
polyamines,
TGF-β
Microbicidal actions: phagocytosis and killing of many bacteria and fungi
Inflammation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


Infection
Sensitization: primary infection or immunization
Patient
1–2 weeks
intradermal injection of microbial antigen
Elicitation: challenge with antigen
DTH reaction
24–48 hours
Area of induratio and erythema
4 hours
48 hours



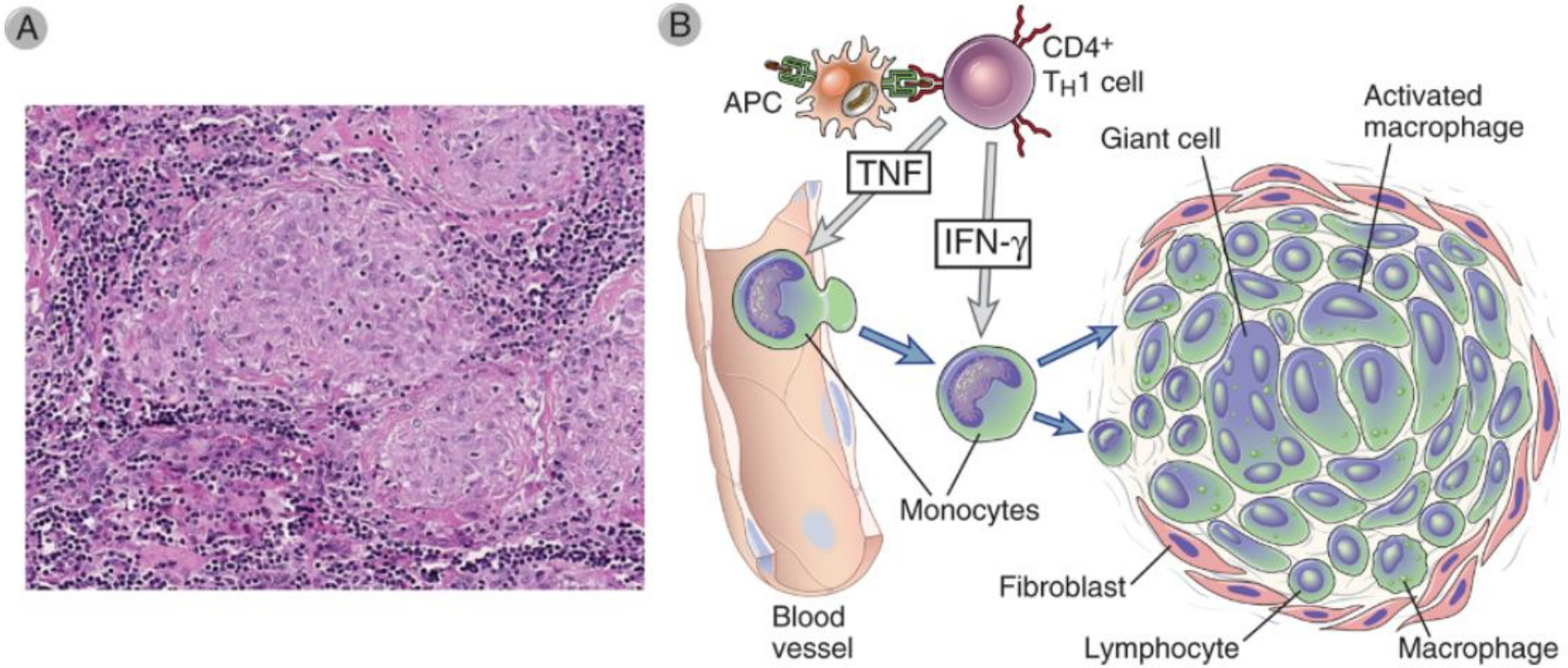
Sítio de Desafio
Ag

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.