Mecanismos de lesión tisular mediados por la respuesta inmune

Masyelly Rojas, 2011

IDIC-ULA

- Inflamación: consecuencias de la respuesta inmune
- Eventos inespecíficos en la respuesta inflamatoria
- Hipersensibilidad
- Mecanismos de lesión: Gell y Coombs

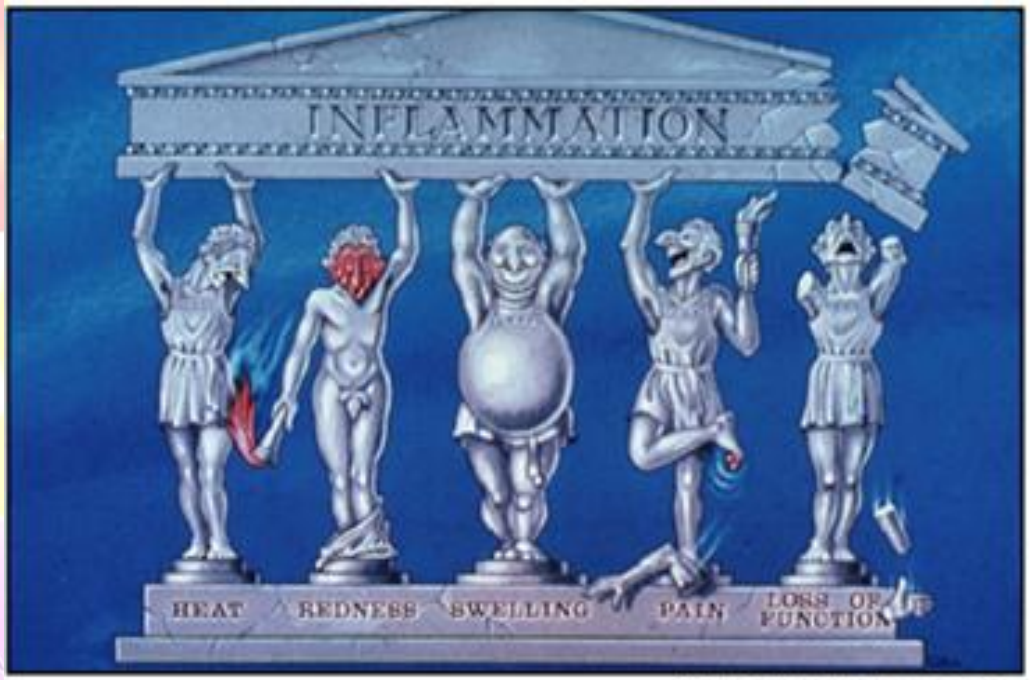
Alergía-Atopía

Enfermedades pseudoalérgicas: mecanismos patogénicos

- Enfermedades autoinflamatorias

La inflamación es un conjunto complejo de interacciones entre los factores solubles y células que puede surgir en cualquier tejido en respuesta a traumatismos, infecciones, daño post-isquémico, tóxico o autoinmune

TODA RESPUESTA INMUNOLÓGICA LLEVA CONSIGO UNA RESPUESTA INFLAMATORIA DE INTENSIDAD Y DURACIÓN VARIABLES



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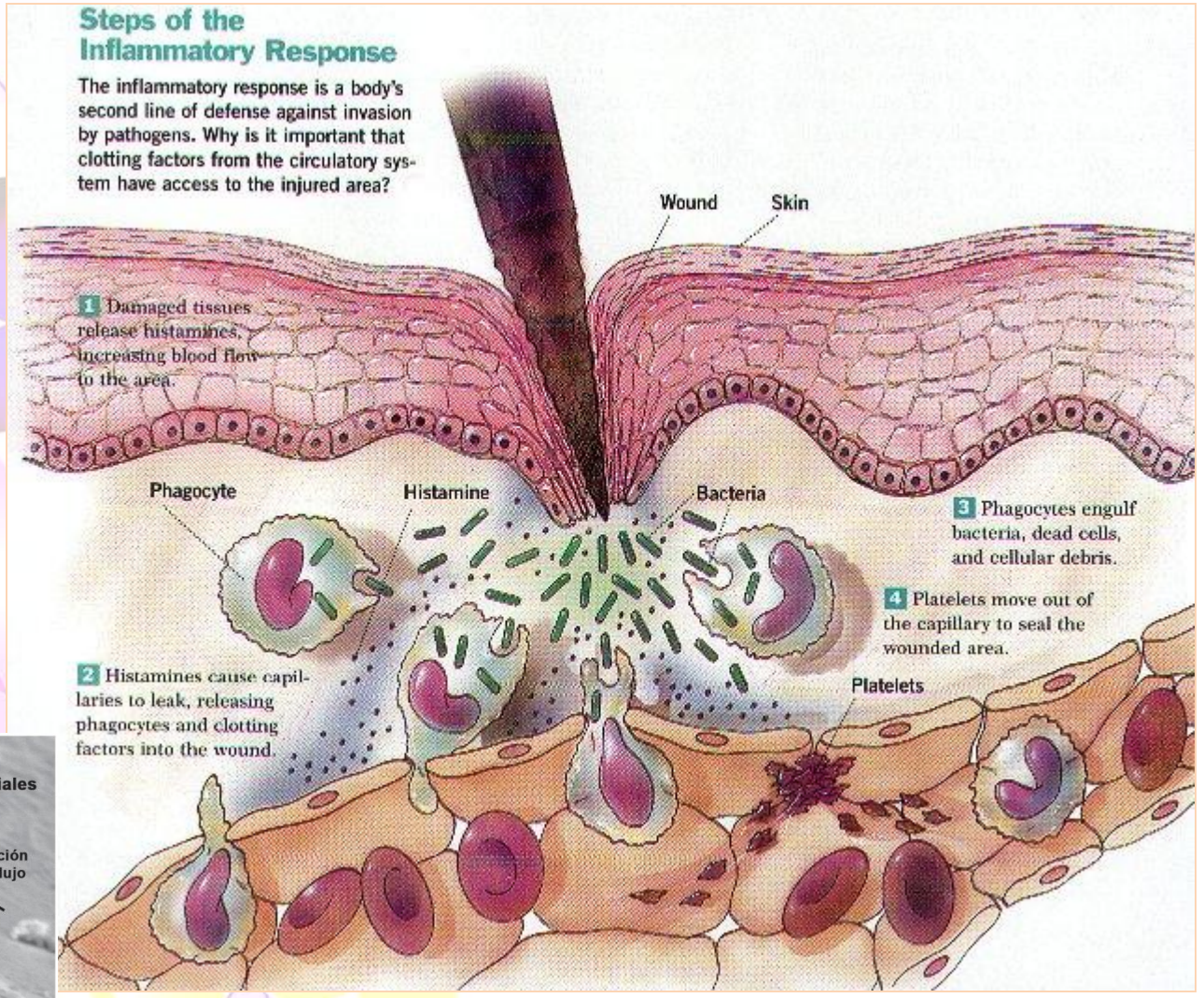
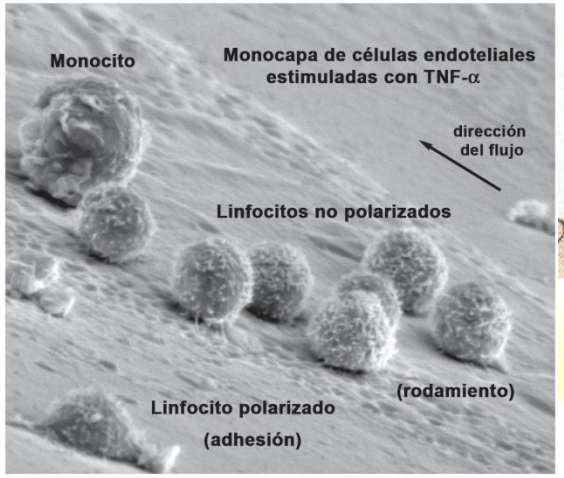
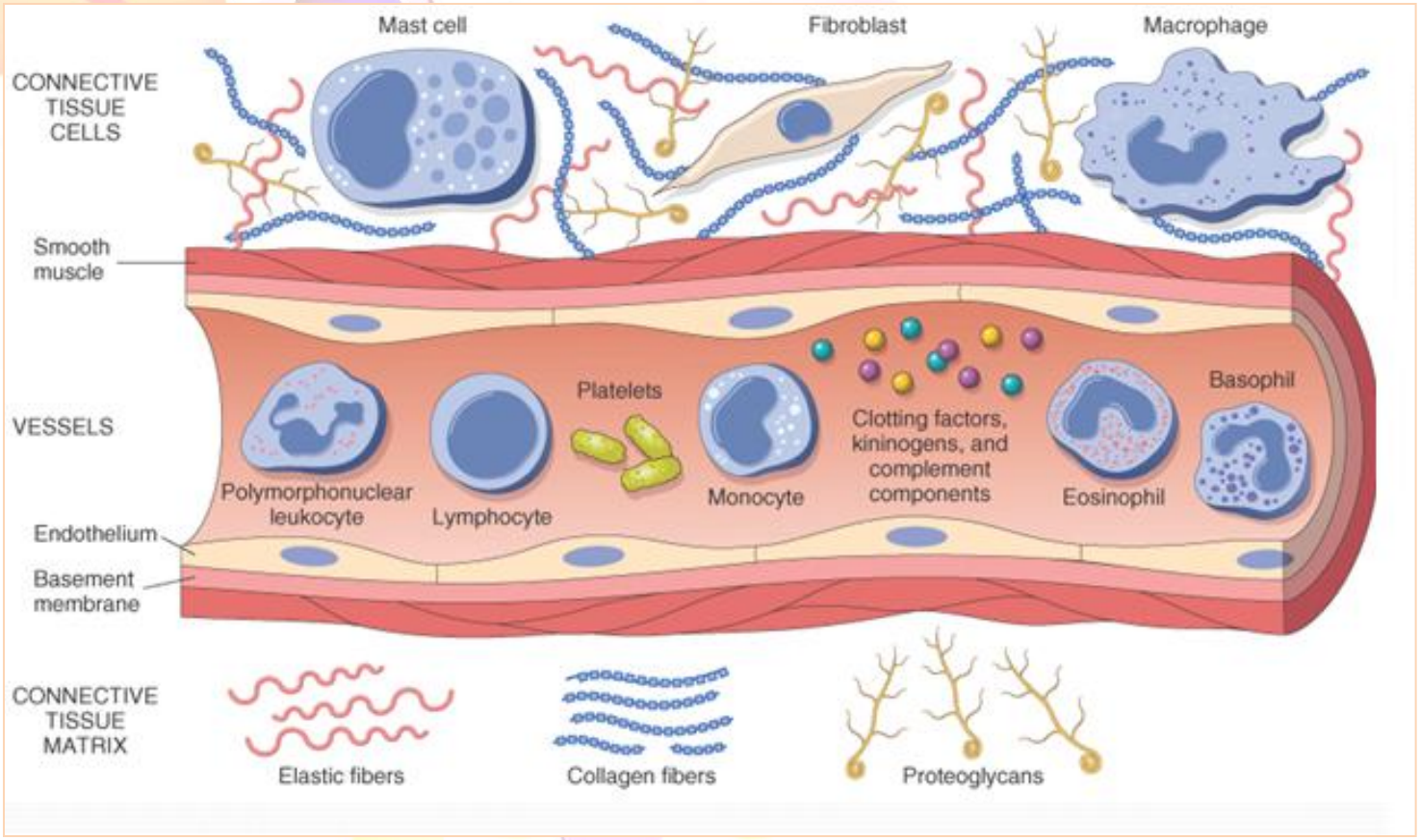
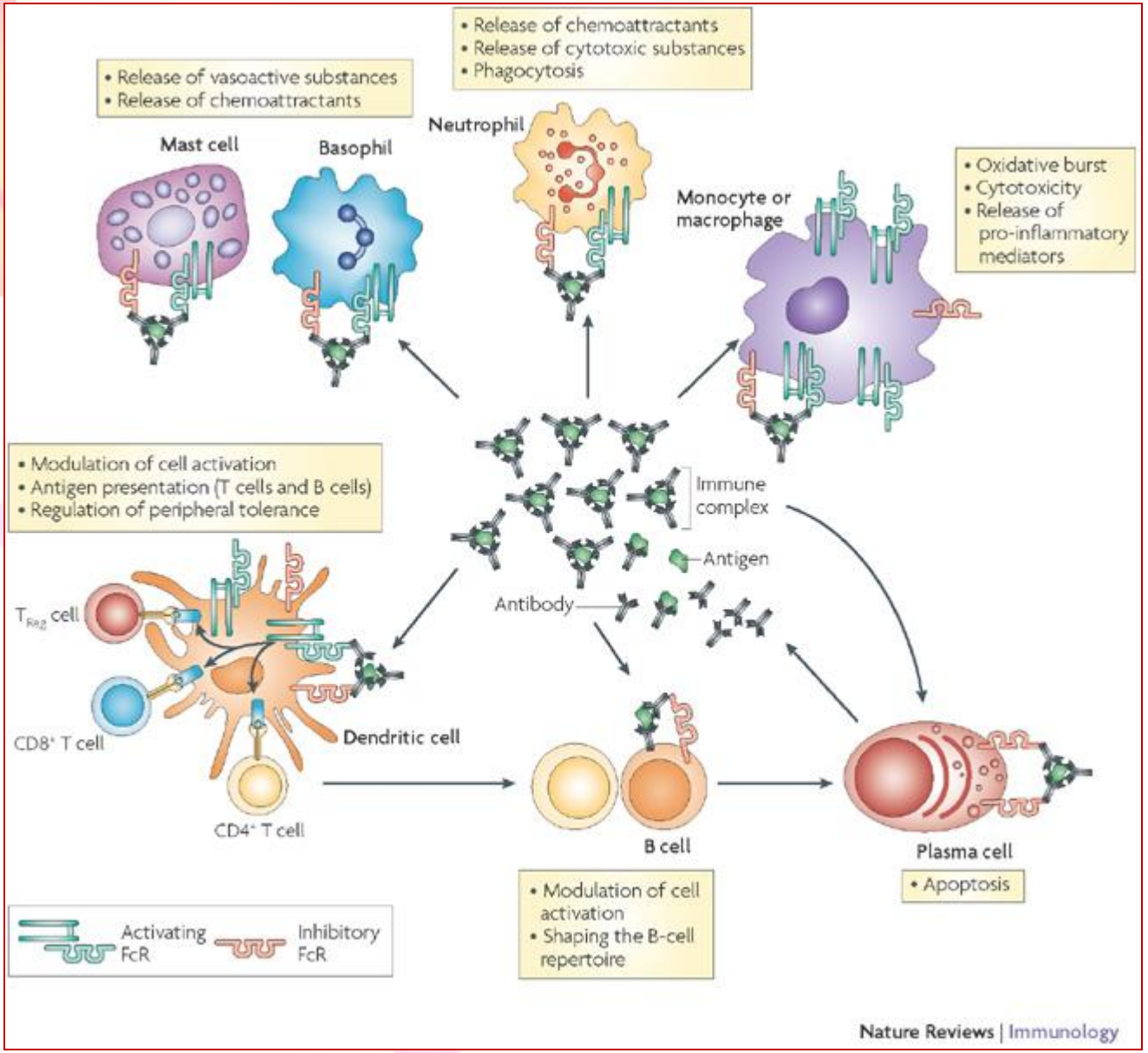
Eventos inespecíficos en la respuesta inflamatoria





Células inflamatorias




• Release of chemoattractants
• Release of cytotoxic substances
• Phagocytosis
• Release of vasoactive substances
• Release of chemoattractants
Mast cell
Basophil
Neutrophil
Monocyte or macrophage
• Oxidative burst
• Cytotoxicity
• Release of pro-inflammatory mediators
• Modulation of cell activation
• Antigen presentation (T cells and B cells)
• Regulation of peripheral tolerance
Immune complex
Antigen
Antibody
T_{Reg} cell
CD8⁺ T cell
Dendritic cell
CD4⁺ T cell
B cell
Plasma cell
• Apoptosis
• Modulation of cell activation
• Shaping the B-cell repertoire
Activating FcR
Inhibitory FcR
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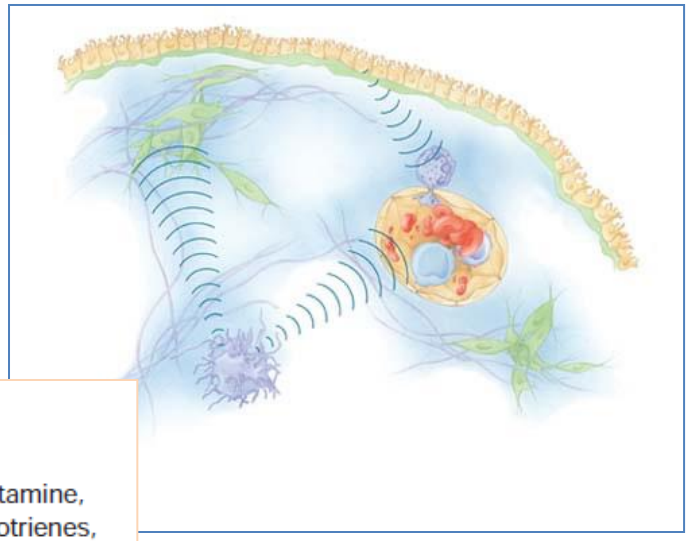
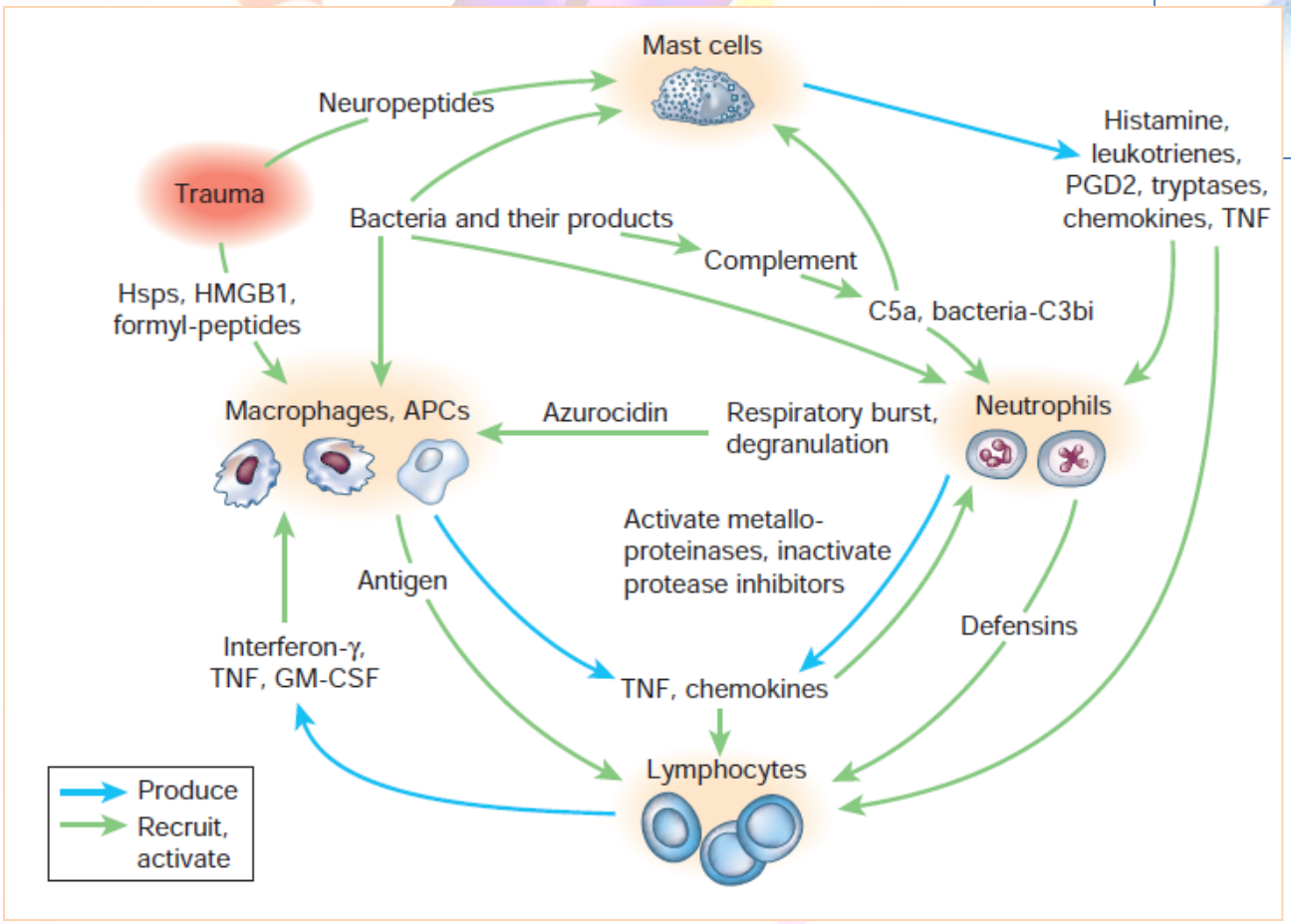
Flujo de información en las primeras etapas siguientes a un trauma débil con infección





Los mensajes son transmitidos entre las células a través de mediadores solubles

Gene product(s)	Human (H) or mouse (M)	Inflammatory phenotype	Predominant sites
Factors directly involved in regulation of apoptosis			
Fas (CD95)	H	Urticarial rash, glomerulonephritis, oral ulceration, lymphocyte infiltration	Skin, kidney, mouth, liver
Fas (CD95) (lpr)	M	Glomerulonephritis, necrotizing vasculitis, erosive synovitis, interstitial pneumonitis, dermatitis	Kidney, mesentery, joints, lung, skin, vessels
Factors thought to be involved in clearance of immune complexes and material from apoptotic cells			
C1q (*A*, *B* and *C* genes)	H	Rash, glomerulonephritis, oral ulceration	Skin, kidney, mouth
C1q (*a* gene)	M	Glomerulonephritis	Kidney
C2	H	Rash, vasculitis, arthritis, glomerulonephritis, asthma	Skin, joints, lung
C4	H	Rash	Skin
C4	M	Glomerulonephritis	Kidney
C3	H	Glomerulonephritis	Kidney
C4-binding protein	H	Ulcerations	Mouth
Factor H	H	Glomerulonephritis, rash	Kidney, skin
Crry	M	Neutrophil infiltration	Placenta
Serum amyloid P component	M	Glomerulonephritis	Kidney
DNAse I	M	Glomerulonephritis	Kidney
FcγRIIB	M	Glomerulonephritis	Kidney
WASP (Wiskott–Aldrich syndrome protein)	H	Eczema, vasculitis, renal disease, arthritis, inflammatory bowel disease	Skin, kidney, joints, bowels
WASP	M	Lymphocyte and neutrophil infiltration	Colon
Cytokines, cytokine receptors and other cell surface receptors			
TNF-R1 (tumour-necrosis factor receptor 1)	H	Familial Hibernian fever (periodic fever, conjunctivitis, periorbital edema, arthralgia)	Systemic, eyes, joints
TGF-β1 (transforming growth factor-β1)	M	Macrophage, lymphocyte and neutrophil infiltration in blood vessels and parenchyma; gastric ulceration	Lung, heart, stomach, liver spleen, lymph nodes, pancreas, colon, salivary glands, striated muscle
IL-2Rα (interleukin-2 receptor-α)	M	Lymphocyte and neutrophil infiltration; ulceration	Colon
IL-2	M	Granulocyte, lymphocyte and plasma cell infiltration; ulceration	Colon
IL-10	M	Lymphocyte and neutrophil infiltration	Duodenum, jejunum, ileum, colon
GM-CSF (granulocyte–macrophage colony-stimulating factor)	M	Lymphocyte infiltration around airways and veins	Lung
IL-1Ra (IL-1 receptor antagonist)	M	Neutrophil, macrophage and $CD4^+$ lymphocyte infiltration	Aorta, coronaries, iliac and popliteal arteries
IL-1Ra	M	Erosive arthritis	Joints
T-cell receptor-α	M	γδ T-cell, B-cell, plasma cell and neutrophil infiltration	Colon
T-cell receptor-β	M	γδ T-cell, B-cell, plasma cell and neutrophil infiltration	Colon
Major histocompatibility complex class II	M	Lymphocyte and neutrophil infiltration	Colon
CTLA4 (cytotoxic T-lymphocyte antigen 4)	M	Lymphocyte, macrophage and granulocyte infiltration	Heart, pancreas, lung, bone marrow, liver, salivary glands, joints, blood vessels
PD-1 (immunoreceptor tyrosine-based inhibitory motif (ITIM)-bearing Ig superfamily member; orphan receptor)	M	Arthritis, glomerulonephritis, carditis	Joints, kidneys, heart
Intracellular factors in lymphocytes, leukocytes and epithelial cells affecting their activation			
LAT (linker for activation of T cells)	M	$CD4^+$ T-cell, eosinophil, B-cell and macrophage infiltration	Multiple organs
SOCS1 (suppressor of cytokine signalling)	M	Macrophage infiltration	Liver, lungs, pancreas, heart, skin
Phosphatidylinositol 3-phosphate kinase p110δ	M	Leukocyte infiltration	Caecum, rectum

PRODUCTOS CODIFICADOS POR GENES CUYA INTERRUPCIÓN O MUTACIÓN CONDUCE A INFLAMACIÓN ESPONTÁNEA

NATURE | VOL 420 | 19/26 DECEMBER 2002 | www.nature.com/nature

Hipersensibilidad:

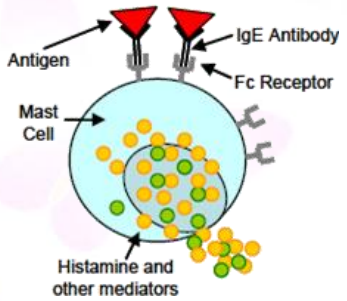
- Se refiere a un estado de reactividad alterada en el cual el cuerpo monta una respuesta inmune a una sustancia
- Pueden manifestarse solamente seguido de un segundo contacto con un antígeno particular
- Existe un fracaso de la autotolerancia
- Se manifiesta como enfermedades heterogéneas y están determinadas por

Tipo de respuesta inmune

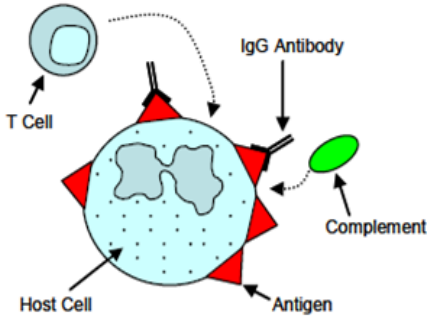
Naturaleza y localización del antígeno

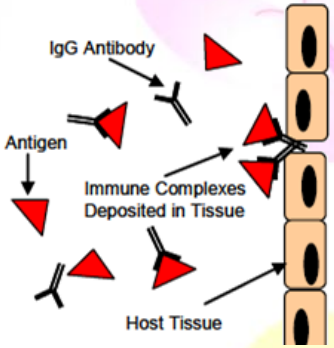
Mecanismos de lesión: (Gell y Coombs)

- Hipersensibilidad inmediata mediada por IgE

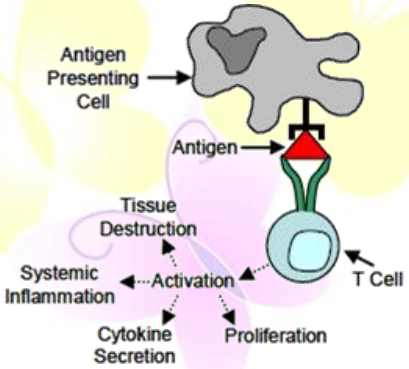


- Hipersensibilidad dependiente de anticuerpos citotóxicos





- Hipersensibilidad secundaria al depósito de complejos inmunológicos (CI)



- Hipersensibilidad retardada mediada por células

Validez de la Clasificación de Gell y Coombs

- Solo un número reducido de alergia inducida por drogas entra en esta clasificación

Reacciones pseudoalérgicas

Reacciones mediadas por anticuerpos

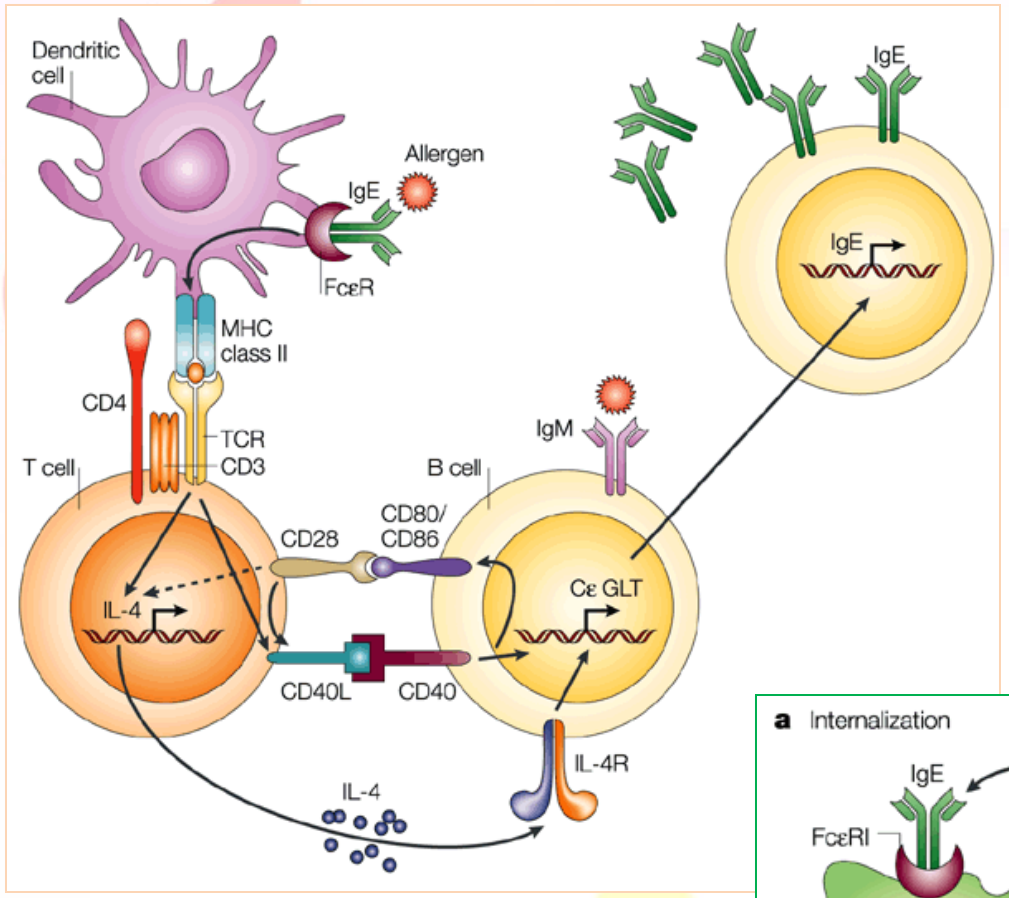
Reacciones mediadas por células

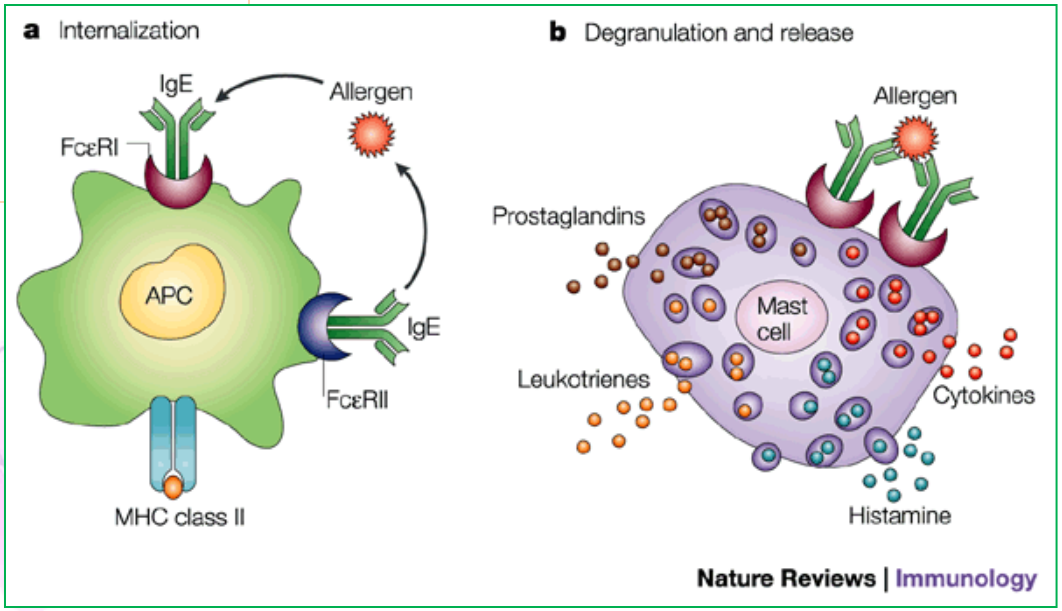
TABLE 16-5 Penicillin-induced hypersensitive reactions

Type of reaction	Antibody or lymphocytes induced	Clinical manifestations
I	IgE	Urticaria, systemic anaphylaxis
II	IgM, IgG	Hemolytic anemia
III	IgG	Serum sickness, glomerulonephritis
IV	T_{DTH} cells	Contact dermatitis

- No existe un mecanismo único de producción de las reacciones de hipersensibilidad

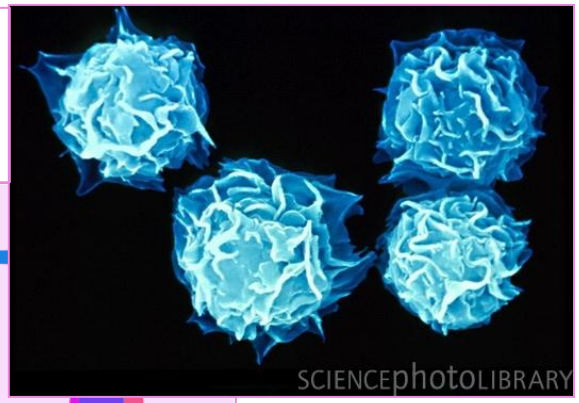
Hipersensibilidad inmediata

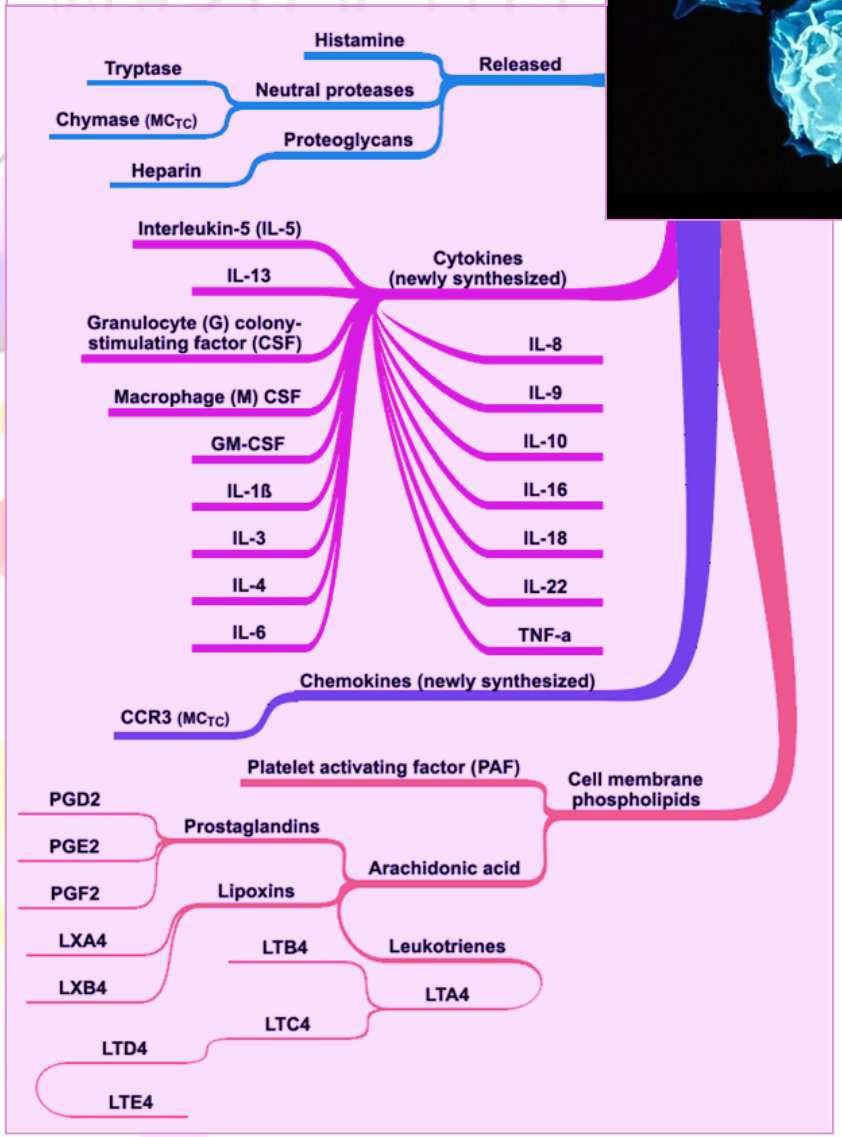




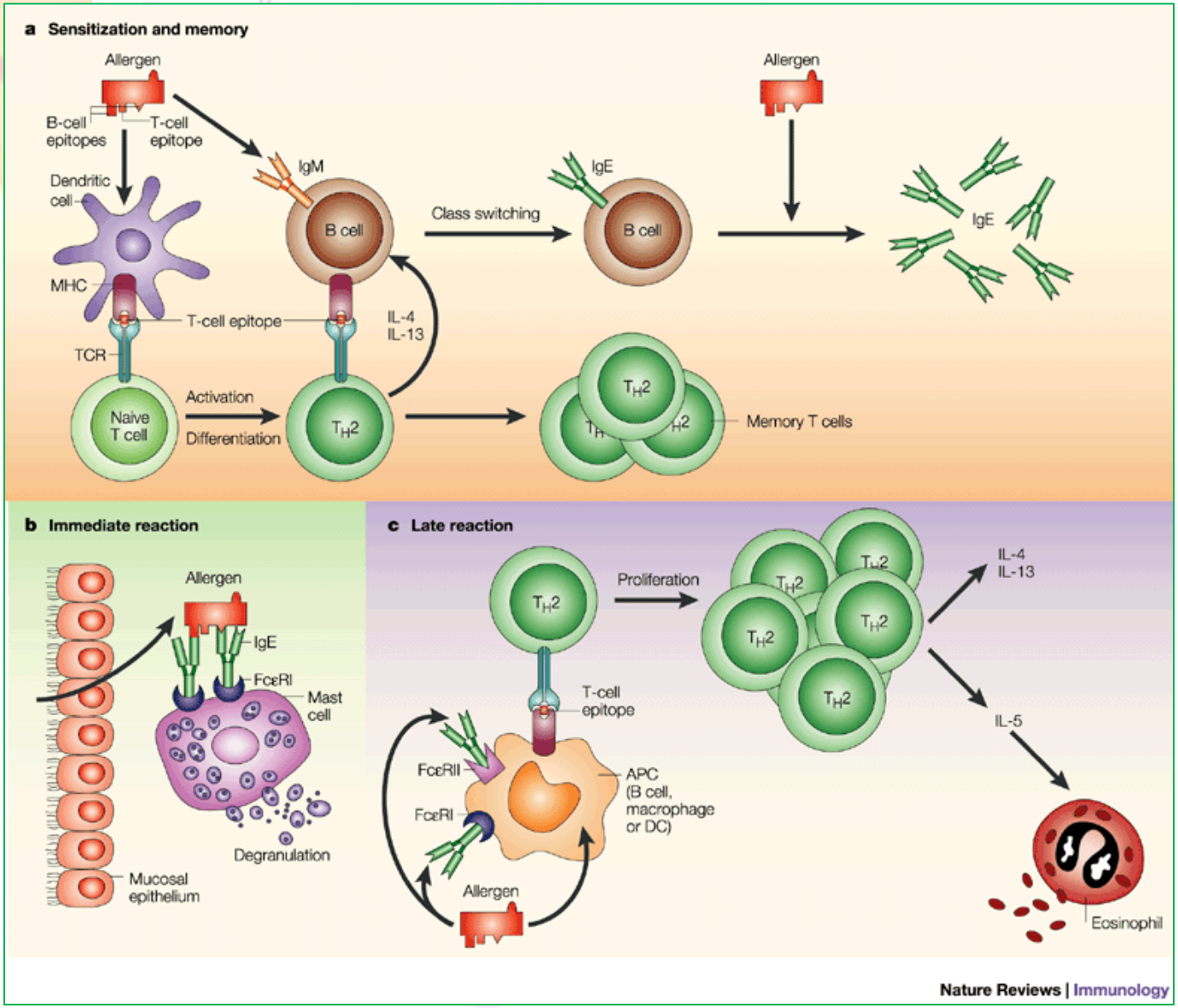
Mecanismos efectores en las reacciones alérgica

MASTOCITO

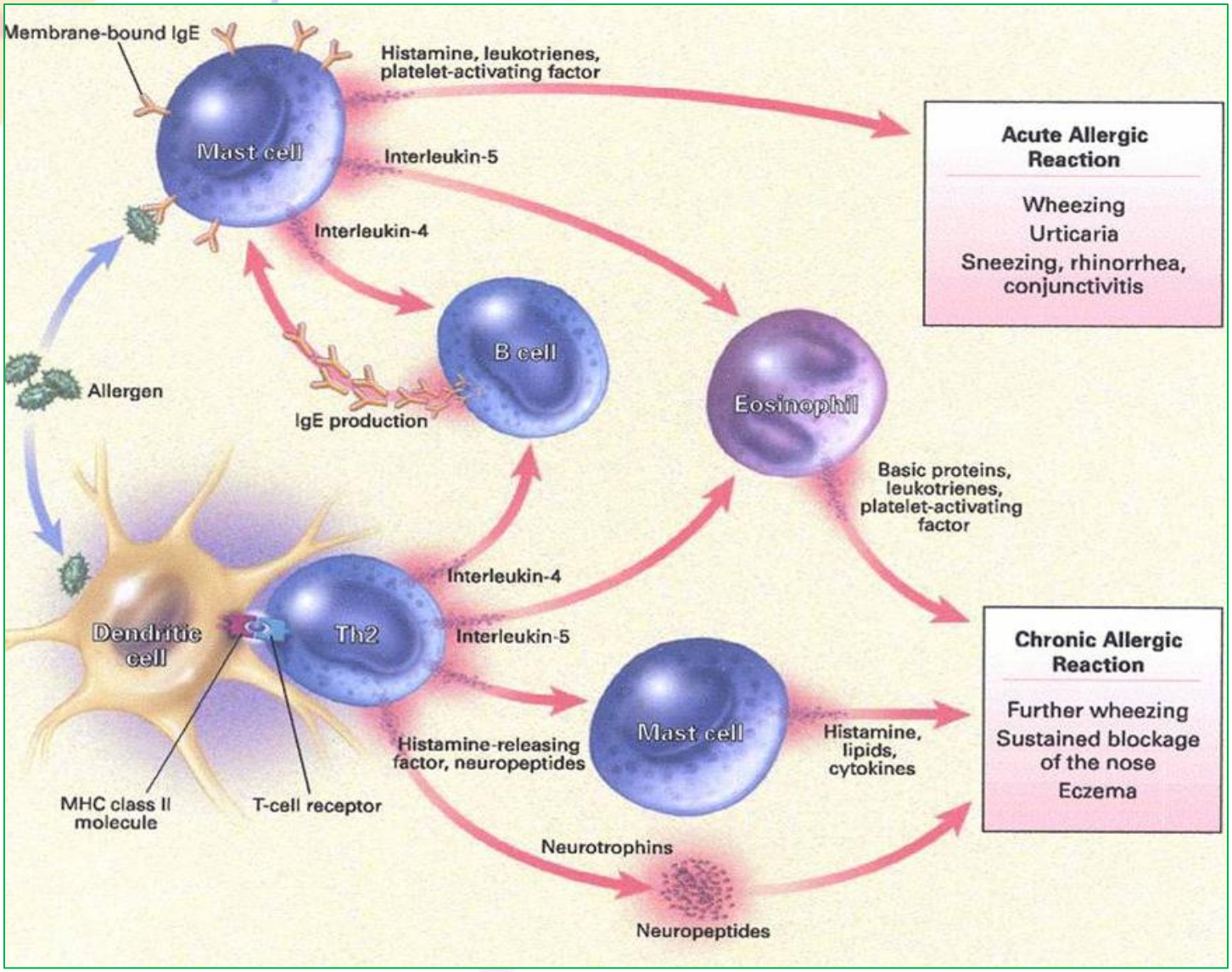




Mecanismos efectores en las reacciones alérgica

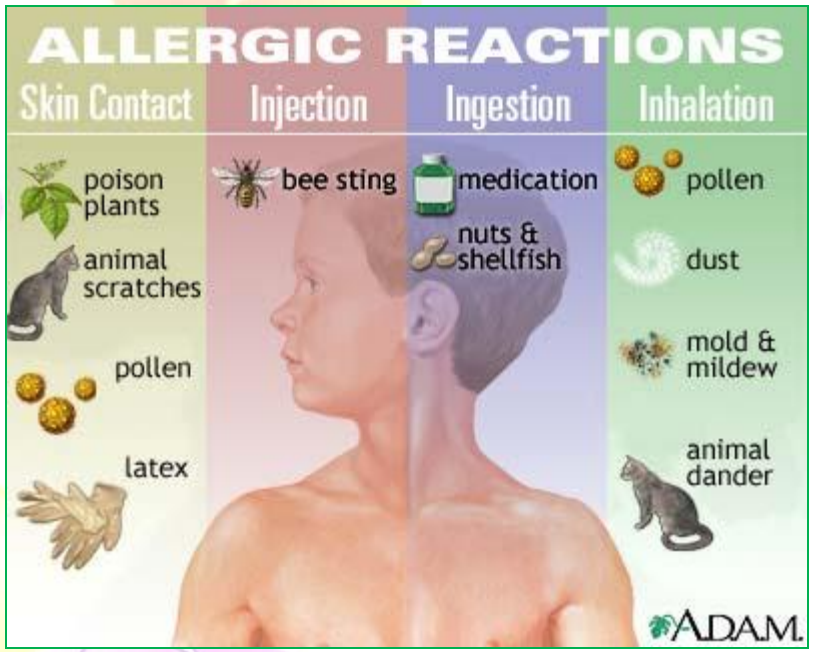


Vías que conducen a reacciones alérgicas crónicas y agudas

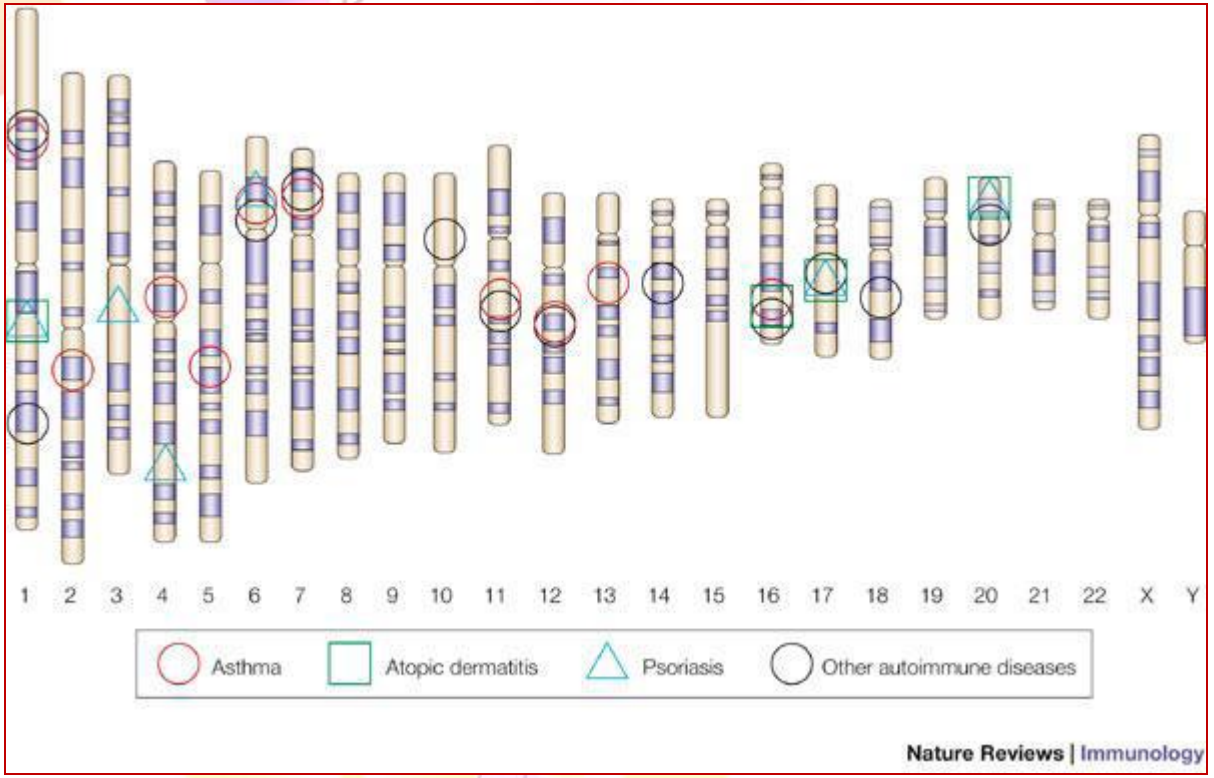


ALERGIA-ATOPÍA:

Predisposición genética para responder ante el antígeno o alérgeno con la producción de IgE



Predisposición genética



Enfermedades pseudoalérgicas: mecanismos patogénicos

- Enfermedades de hipersensibilidad inmediata inducidas por drogas
- No mediadas por IgE. Producen degranulación directa de los mastocitos y activan el complemento, exceso de anafilotoxinas en sangre

1-Agentes de contraste y preparados endovenosos en liposomas

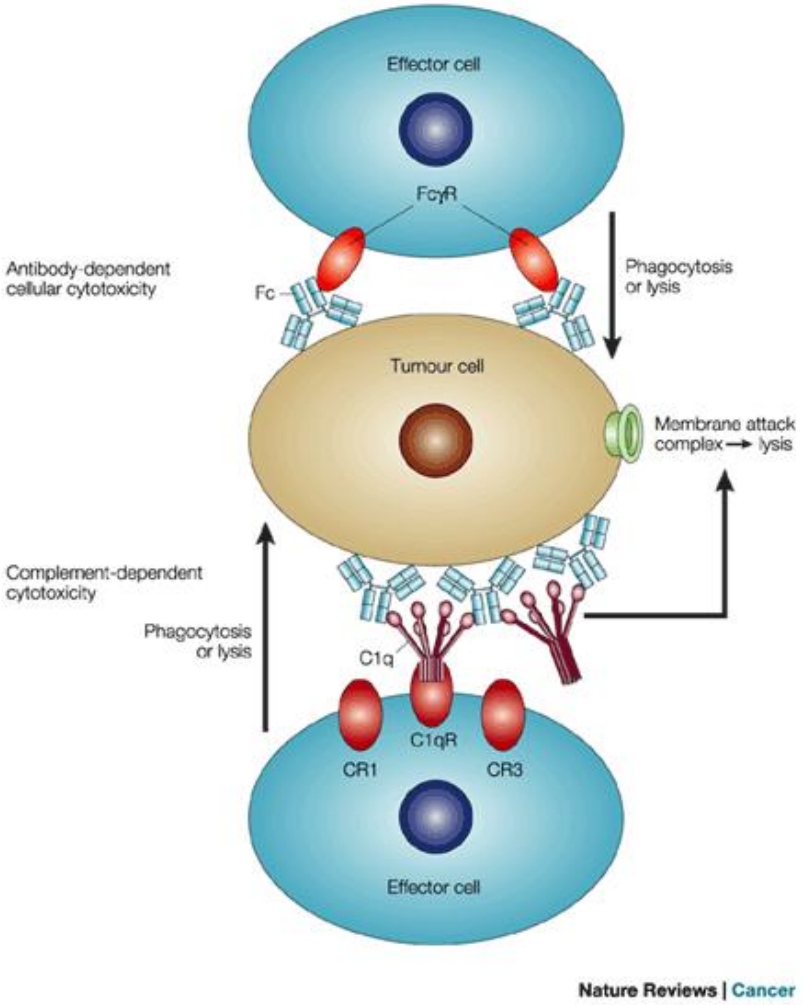
2-Infusiones líquidas que contienen lípidos anfifílicos formadores de miscelas

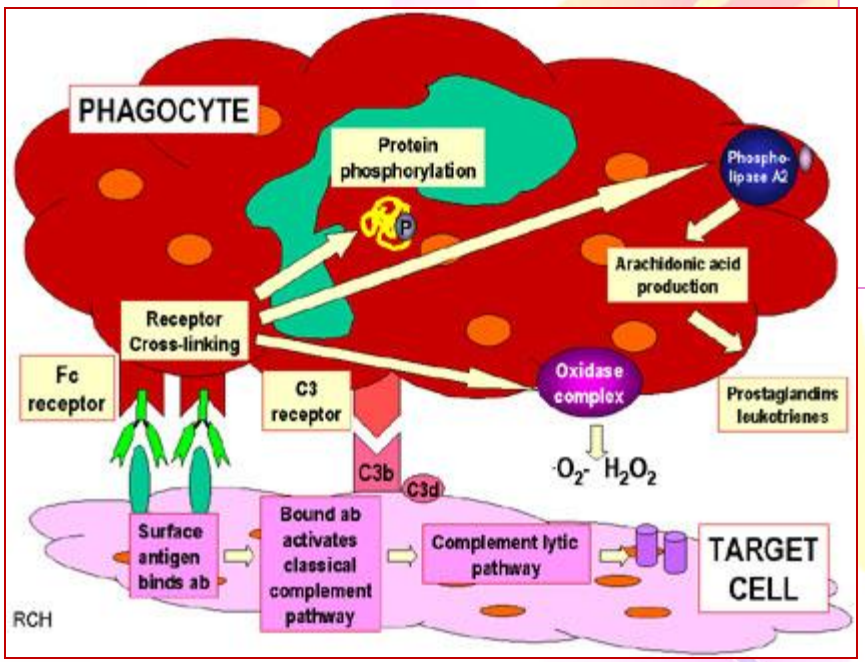
3-Agentes de contraste basados en Iodo con escasa solubilidad en agua

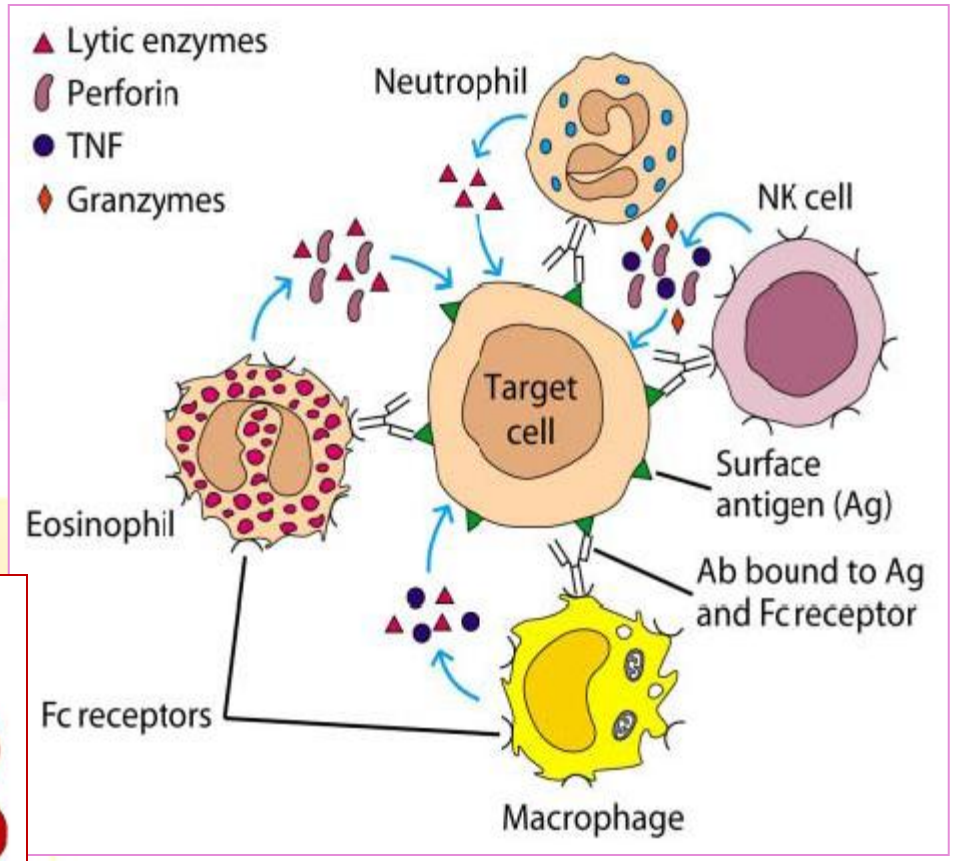
Hipersensibilidad tipo II.

Mecanismos efectores de las enfermedades mediadas por anticuerpos

- Anticuerpos que opsonizan células y activan el complemento, fagocitosis
- Reclutamiento de leucocitos como respuesta de amplificación: mediado por Fc o por complemento
- Anticuerpos específicos contra receptores en la membrana: activadores (receptor para hormona tiroidea: hipertiroidismo) o inhibidores (receptor para acetilcolina: miastenia gravis)



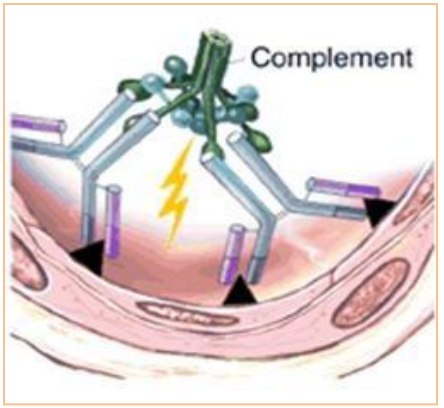

PHAGOCYTE
Protein phosphorylation
P
Phospho-lipase A2
Arachidonic acid production
Receptor Cross-linking
Fc receptor
C3 receptor
Oxidase complex
Prostaglandins leukotrienes
O_2^- H_2O_2
C3b
C3d
Surface antigen binds ab
Bound ab activates classical complement pathway
Complement lytic pathway
TARGET CELL
RCH


Lytic enzymes
Perforin
TNF
Granzymes
Neutrophil
NK cell
Target cell
Surface antigen (Ag)
Eosinophil
Ab bound to Ag and Fc receptor
Fc receptors
Macrophage

Enfermedades mediadas por anticuerpos citotóxicos

- Anemia hemolítica autoinmune

Proteínas de la membrana del eritrocito



- Púrpura trombocitopénica

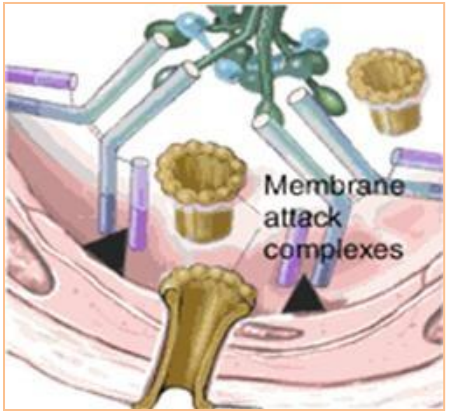
Proteínas de membrana plaquetaria

- Fiebre reumática aguda

Reactividad cruzada entre pared celular de streptococo y miocardio

- Miastenia gravis

Receptor de acetilcolina



- Enfermedad de Graves

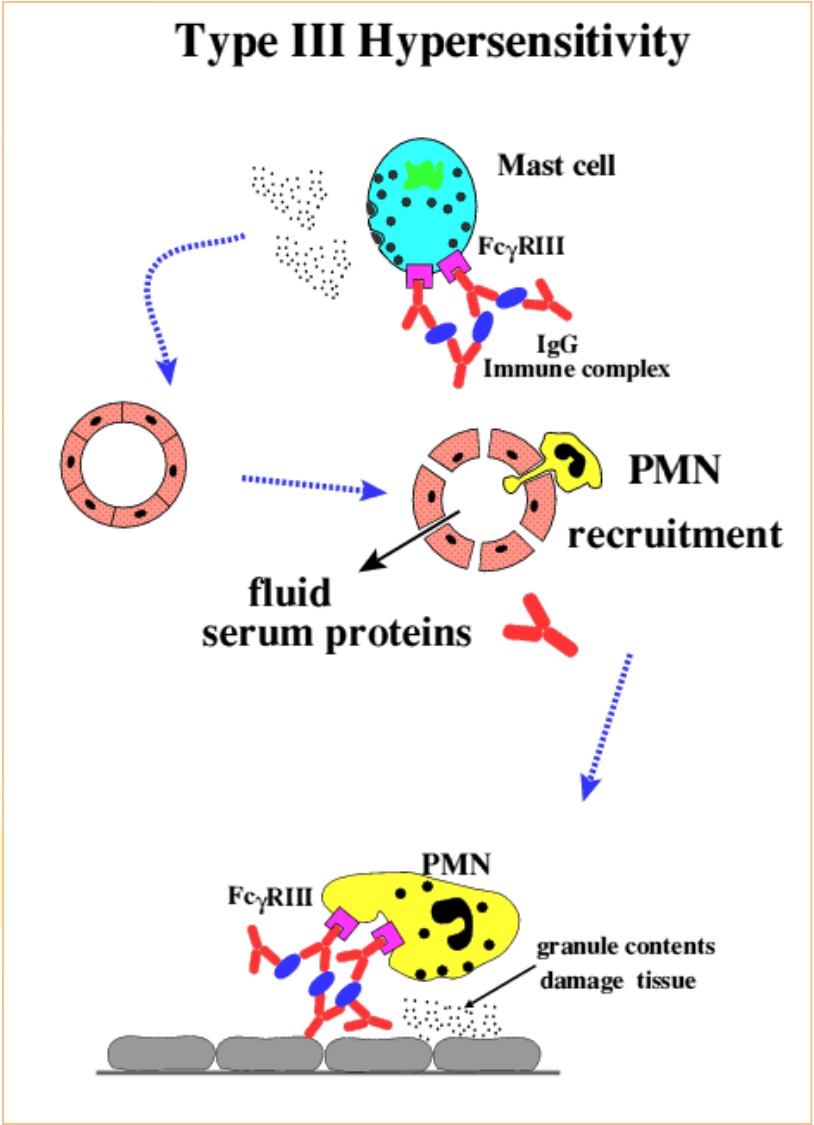
Receptor de TSH

- Diabetes insulinoresistente

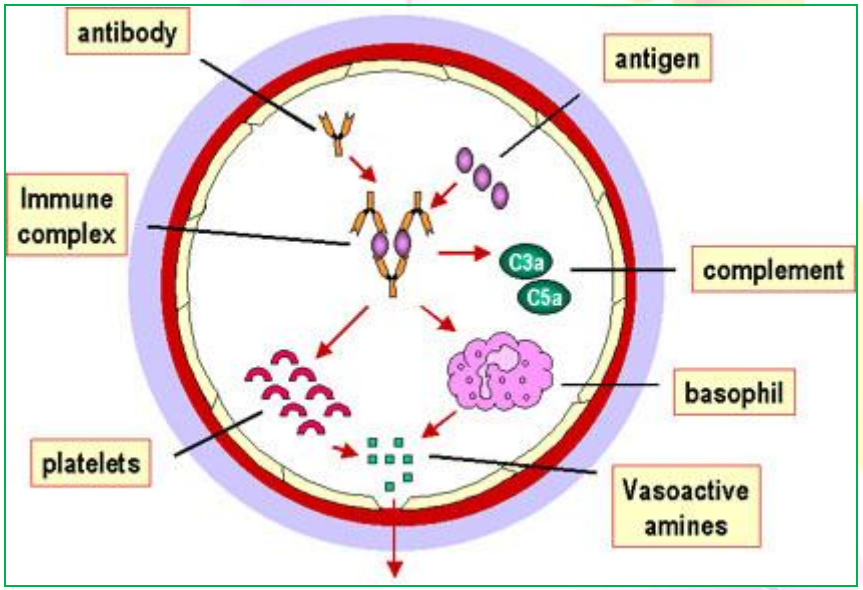
Receptor de insulina

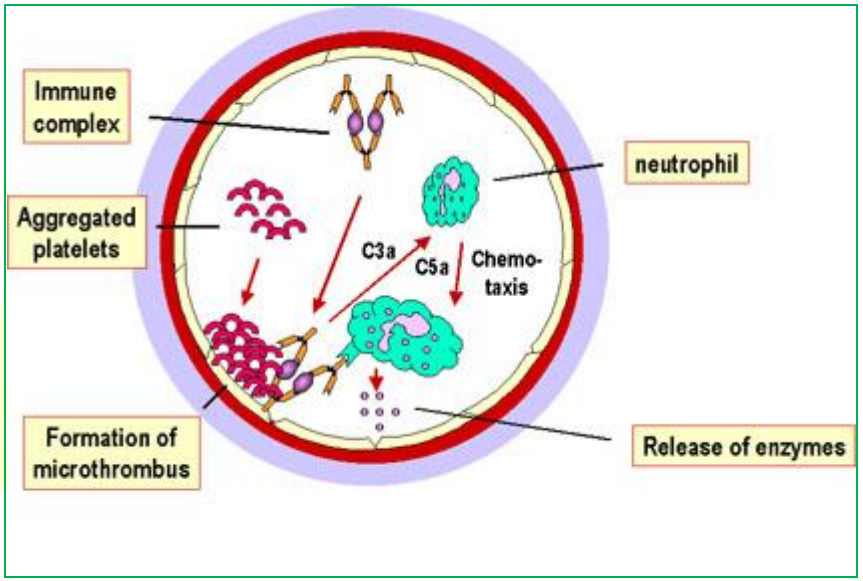
Hipersensibilidad tipo III.

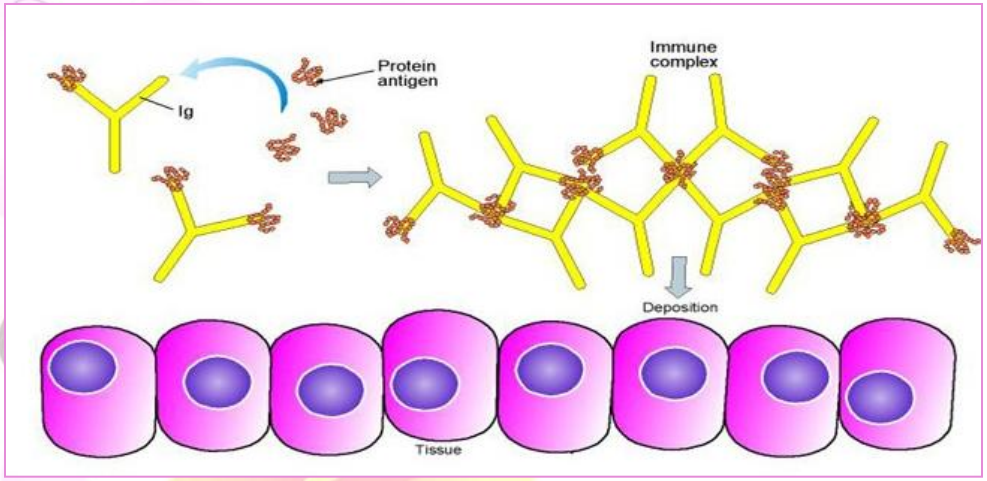
Hipersensibilidad mediada por complejos inmunes

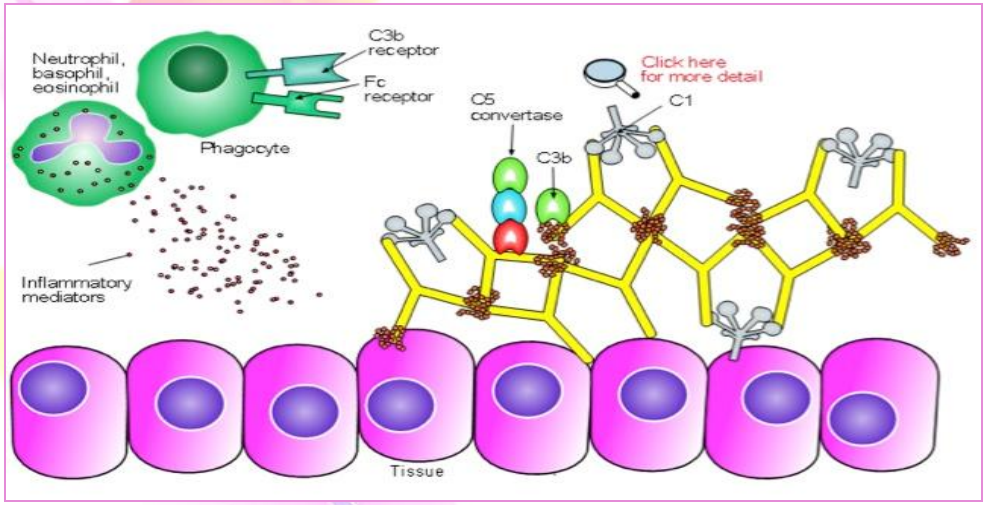


Vasculitis secundaria a depósito de CI






Protein antigen
Ig
Immune complex
Deposition
Tissue


Neutrophil, basophil, eosinophil
C3b receptor
Fc receptor
Phagocyte
Inflammatory mediators
Click here for more detail
C5 convertase
C1
C3b
Tissue

Enfermedades mediadas por inmunocomplejos

- Lupus eritematoso sistémico:

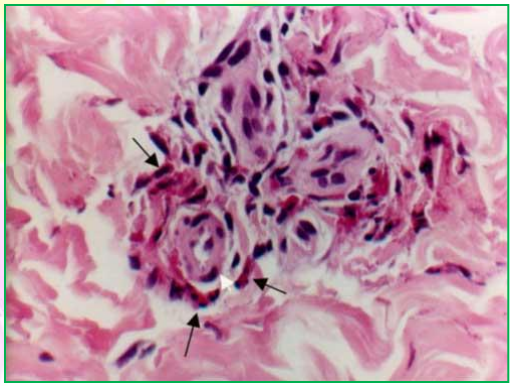
Inflamación mediada por complemento y Fc:

Nefritis, artritis, vasculitis

- Poliarteritis nodosa: vasculitis
- Glomerulonefritis

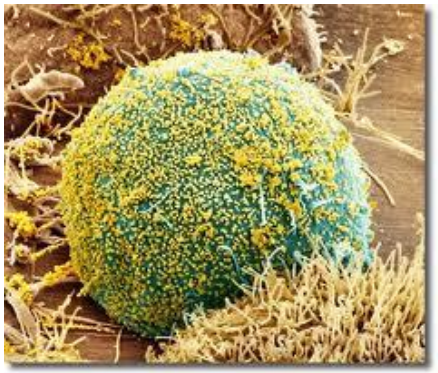
postestreptocóccica:

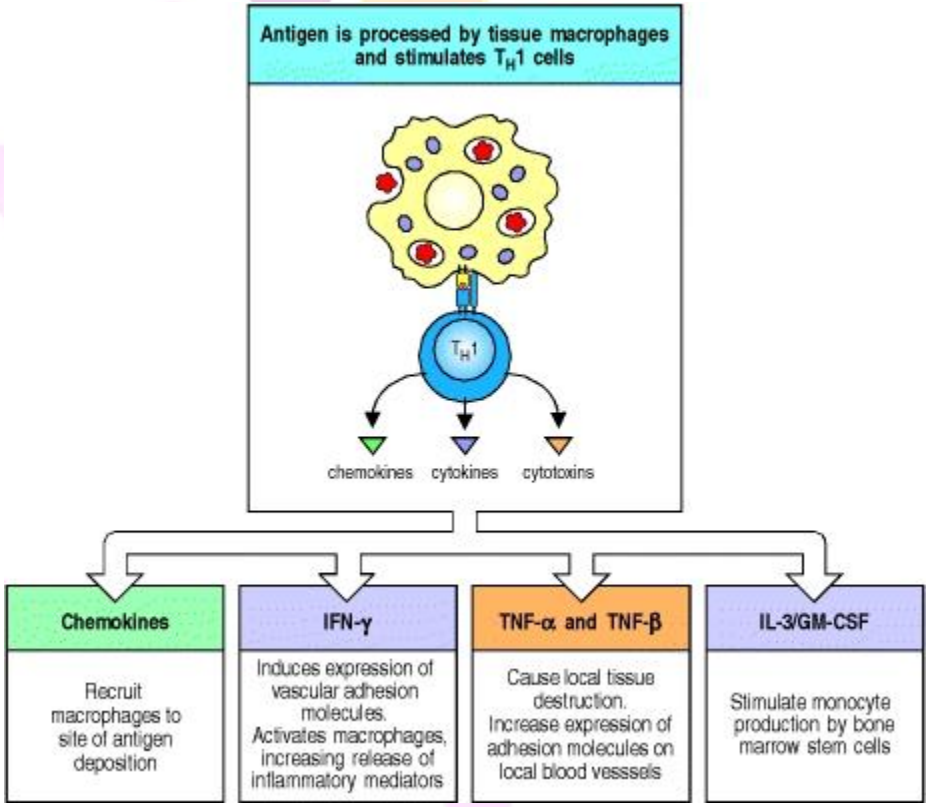
Nefritis

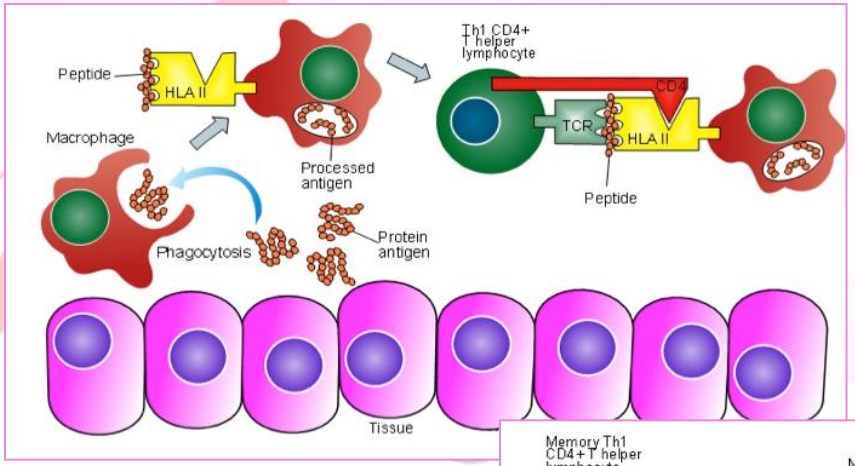


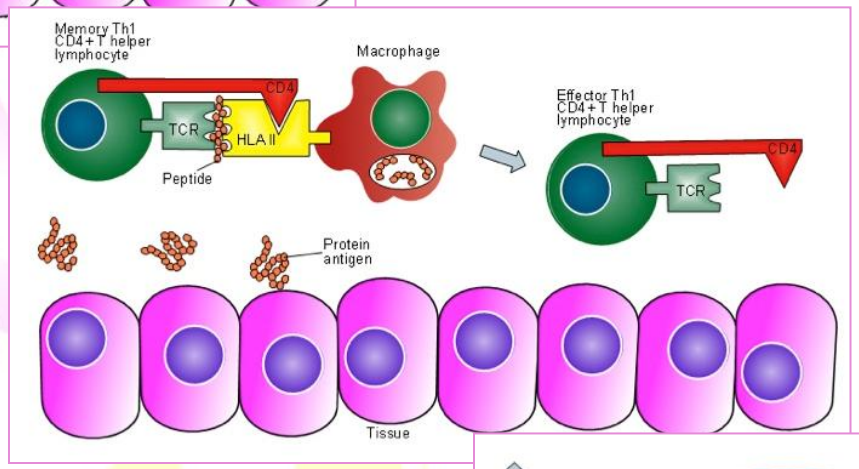
Hipersensibilidad tipo IV.

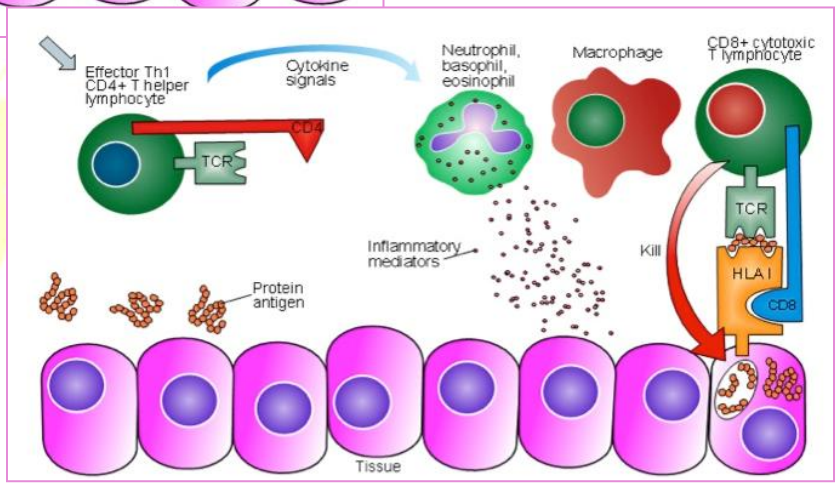
Hipersensibilidad mediada por células



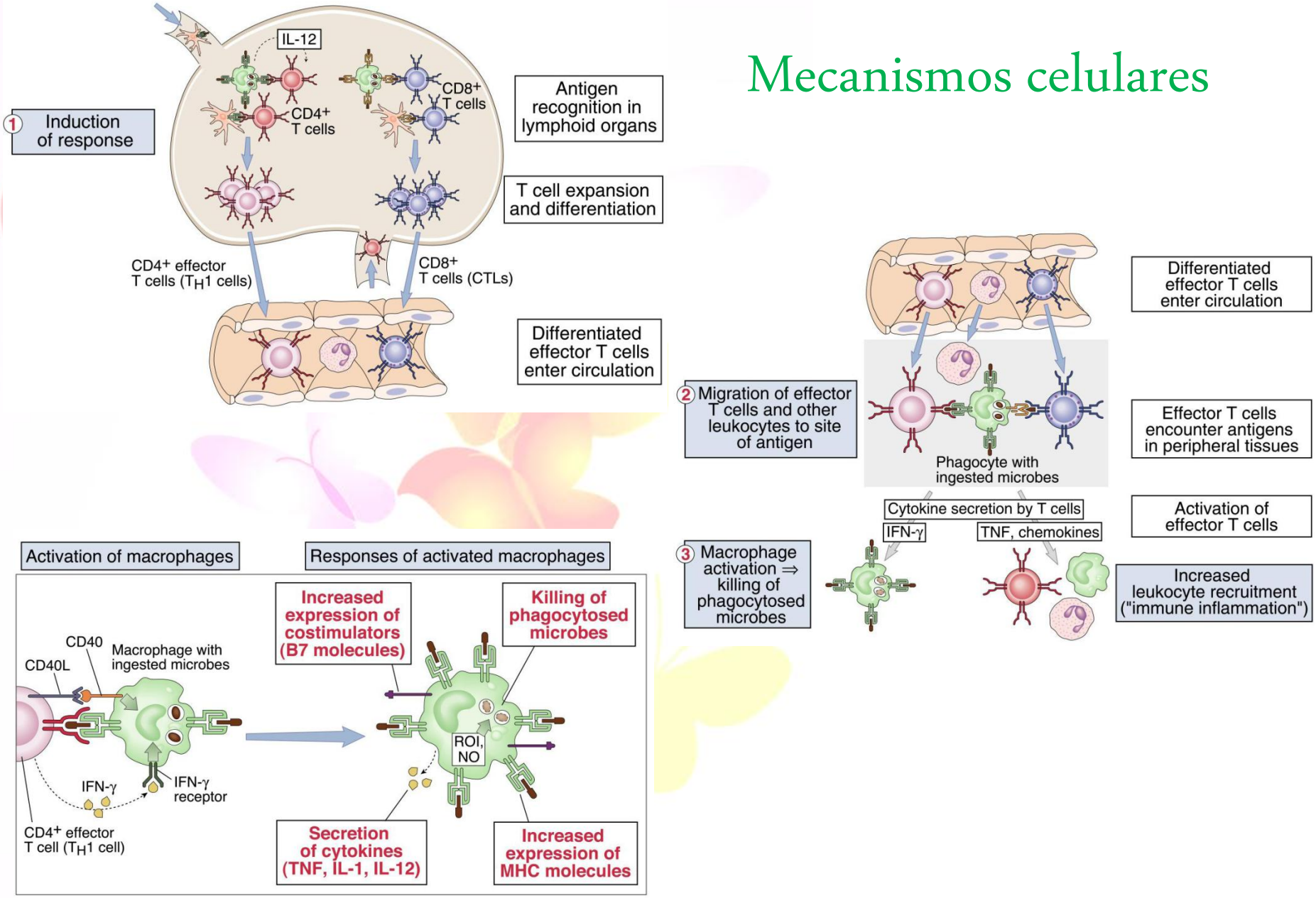



Peptide
HLA II
Macrophage
Processed antigen
Phagocytosis
Protein antigen
Tissue
Th1 CD4+ T helper lymphocyte
CD4
TCR
HLA II
Peptide

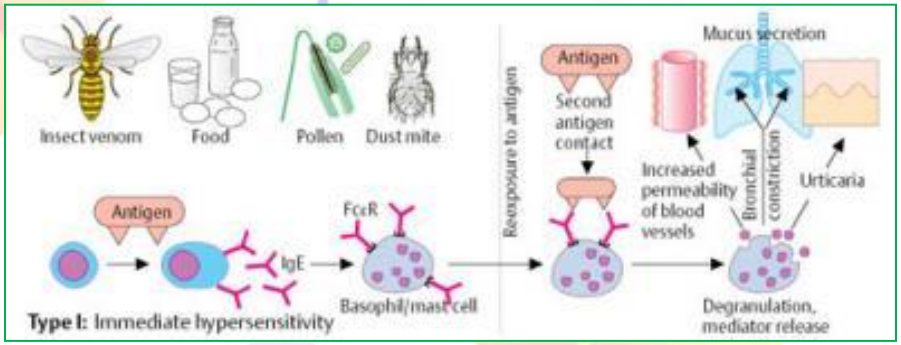

Memory Th1 CD4+ T helper lymphocyte
CD4
TCR
HLA II
Peptide
Macrophage
Effector Th1 CD4+ T helper lymphocyte
CD4
TCR
Protein antigen
Tissue

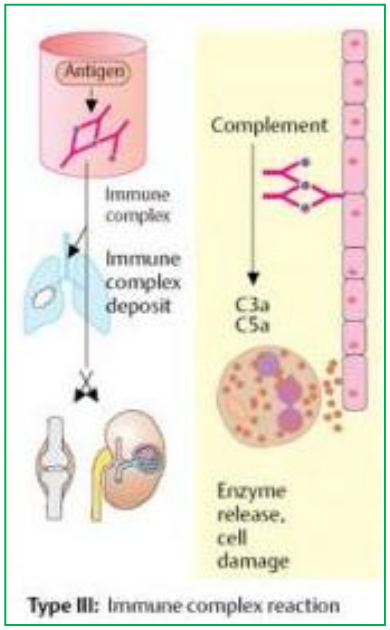

Effector Th1 CD4+ T helper lymphocyte
CD4
TCR
Cytokine signals
Neutrophil, basophil, eosinophil
Macrophage
CD8+ cytotoxic T lymphocyte
TCR
HLA I
CD8
Kill
Inflammatory mediators
Protein antigen
Tissue

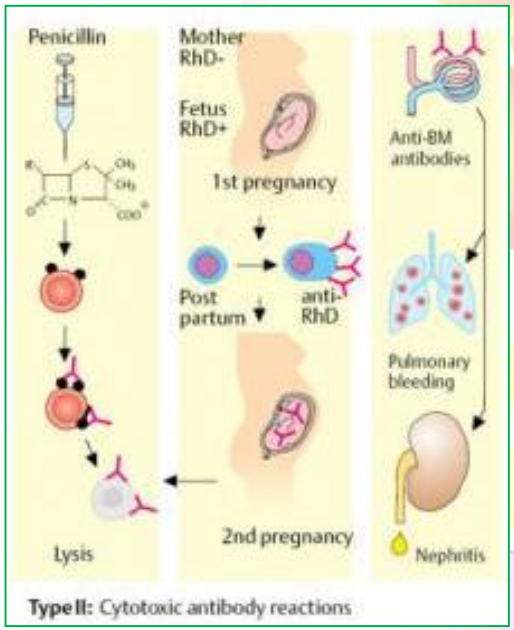
Mecanismos celulares

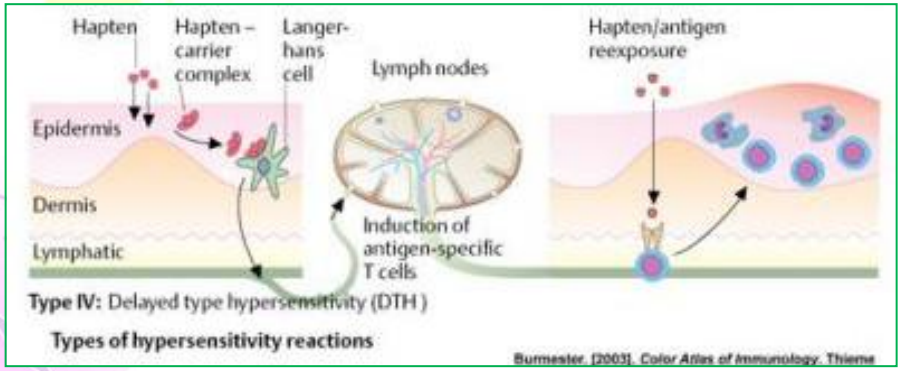


Mecanismos de lesión









Enfermedades Autoinflamatorias:

Table 1. Clinical Classification of Selected Autoinflammatory Diseases

Disease	Gene (Protein)	Proposed Mechanism*
Hereditary Recurrent Fevers		
Familial Mediterranean fever (FMF)	*MEFV* (pyrin)	Increased inflammasome activation
TNF receptor-associated periodic syndrome (TRAPS)	*TNFRSF1A* (TNFR1)	Protein misfolding
Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)	*MVK* (mevalonate kinase)	Increased inflammasome activation
Familial cold autoinflammatory syndrome (FCAS)	*NLRP3/CIAS1* (NLRP3/cryopyrin)	Intrinsic inflammasomopathy
Muckle-Wells syndrome (MWS)	*NLRP3/CIAS1* (NLRP3/cryopyrin)	Intrinsic inflammasomopathy
Neonatal-onset multisystem inflammatory disease (NOMID)	*NLRP3/CIAS1* (NLRP3/cryopyrin)	Intrinsic inflammasomopathy
Idiopathic Febrile Syndromes		
Systemic onset juvenile idiopathic arthritis (SoJIA)	Complex	Unknown
Adult-onset Still's disease	Complex	Unknown
Schnitzler syndrome	Sporadic?	Increased inflammasome activation
Pyogenic Disorders		
Pyogenic arthritis with pyoderma gangrenosum and acne (PAPA)	*PSTPIP1/CD2BP1* (PSTPIP1/CD2BP1)	Abnormal PSTPIP1 binding to pyrin causing increased IL-1β activation
Granulomatous Diseases		
Chronic granulomatous synovitis with uveitis and cranial neuropathy (Blau syndrome)	*NOD2/CARD15* (NOD2/CARD15)	NF-κB activation disorder
Crohn's disease	Complex (*NOD2*, *ATG16L1*, *IRGM*)	NF-κB activation disorder
Autoinflammatory Disorders of Skin and Bone		
Deficiency in IL-1 receptor antagonist (DIRA)	*IL1RN* (IL-1Ra)	Absence of negative regulator of IL-1α and IL-1β
Majeed syndrome	*LPIN2* (Lipin-2)	Unknown
Chronic recurrent multifocal osteomyelitis (CRMO)	Complex	Unknown
Synovitis acne pustulosis hyperostosis osteitis (SAPHO)	Complex	Unknown
Metabolic Disorders		
Gout (monosodium urate deposition)	Complex (*SLC2A9/GLUT9*, *ABCG2*)	Crystal-induced inflammasome activation
Pseudogout (calcium pyrophosphate dihydrate deposition)	Complex	Crystal-induced inflammasome activation
Type 2 diabetes mellitus	Complex	Hyperglycemia-induced inflammasome activation
Complement Disorders		
Atypical hemolytic-uremic syndrome (aHUS)	*CFH* (complement factor H), *MCP* (CD46), *CFI* (complement factor I), *CFB* (complement factor B)	Abnormal regulation of C3b
Age-related macular degeneration	Complex, *CFH*	Impaired inactivation of C3b
Vasculitis		
Behçet's disease	Complex	Unknown
Macrophage Activation Syndromes		
Familial hemophagocytic lymphohistiocytosis (HLH)	*UNC13D* (Munc13-4), *PRF1* (perforin 1), *STX11* (syntaxin 11)	Impaired efficacy of cytotoxic T lymphocytes with compensatory macrophage activation
Secondary HLH	Complex	Unknown
Storage Diseases		
Gaucher's disease	*GBA* (acid β-glucosidase)	Unknown
Atherosclerosis?	Complex	Unknown
Fibrosing Diseases		
Asbestosis/silicosis	Complex	Particle-induced inflammasome activation