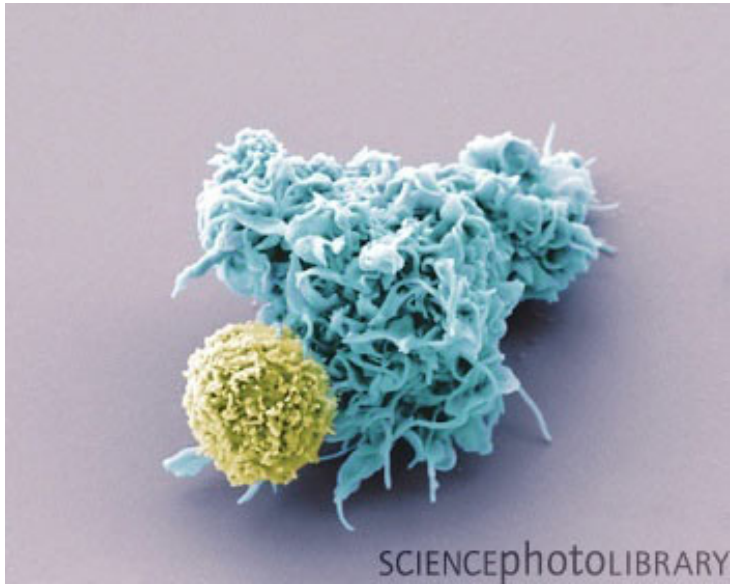
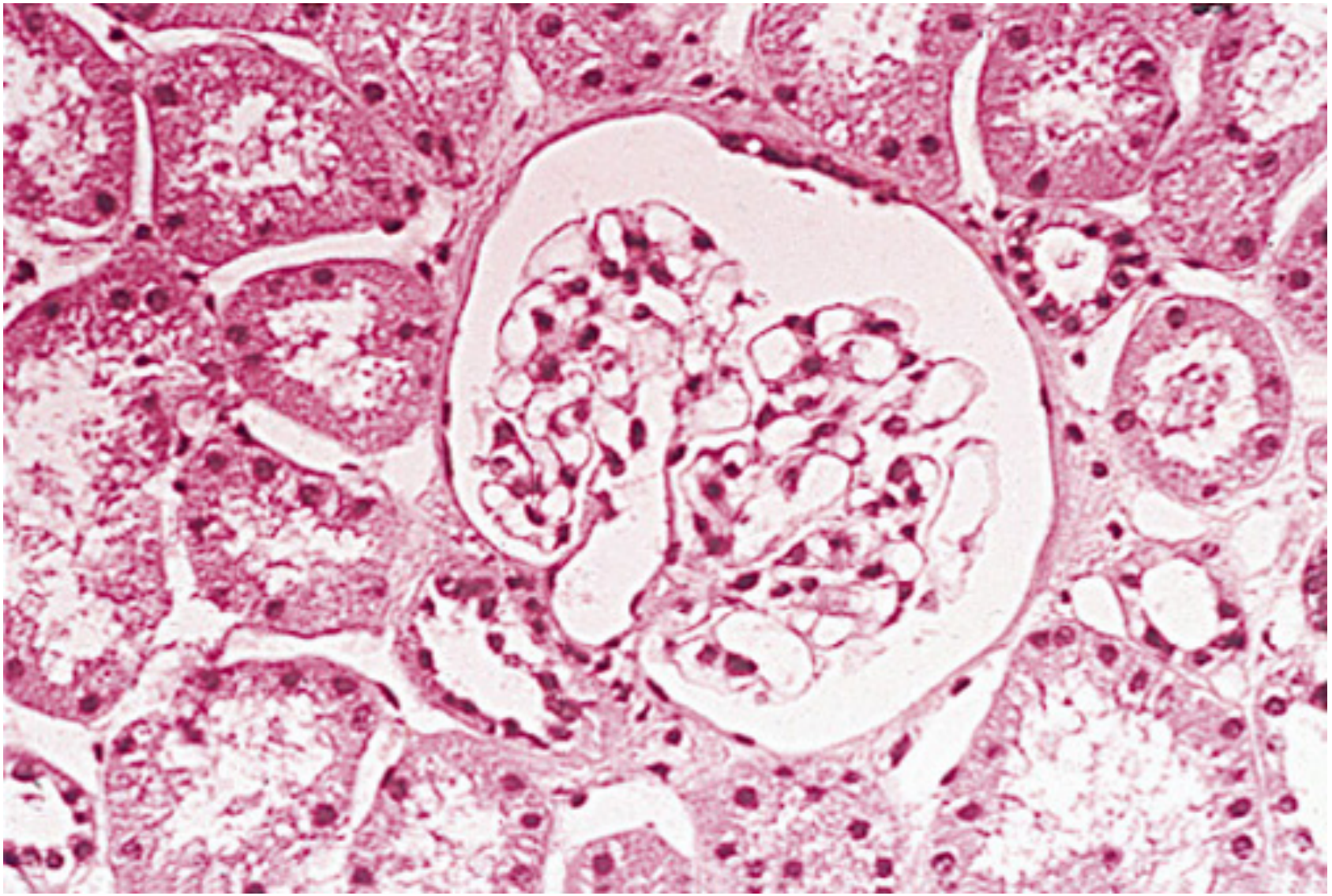
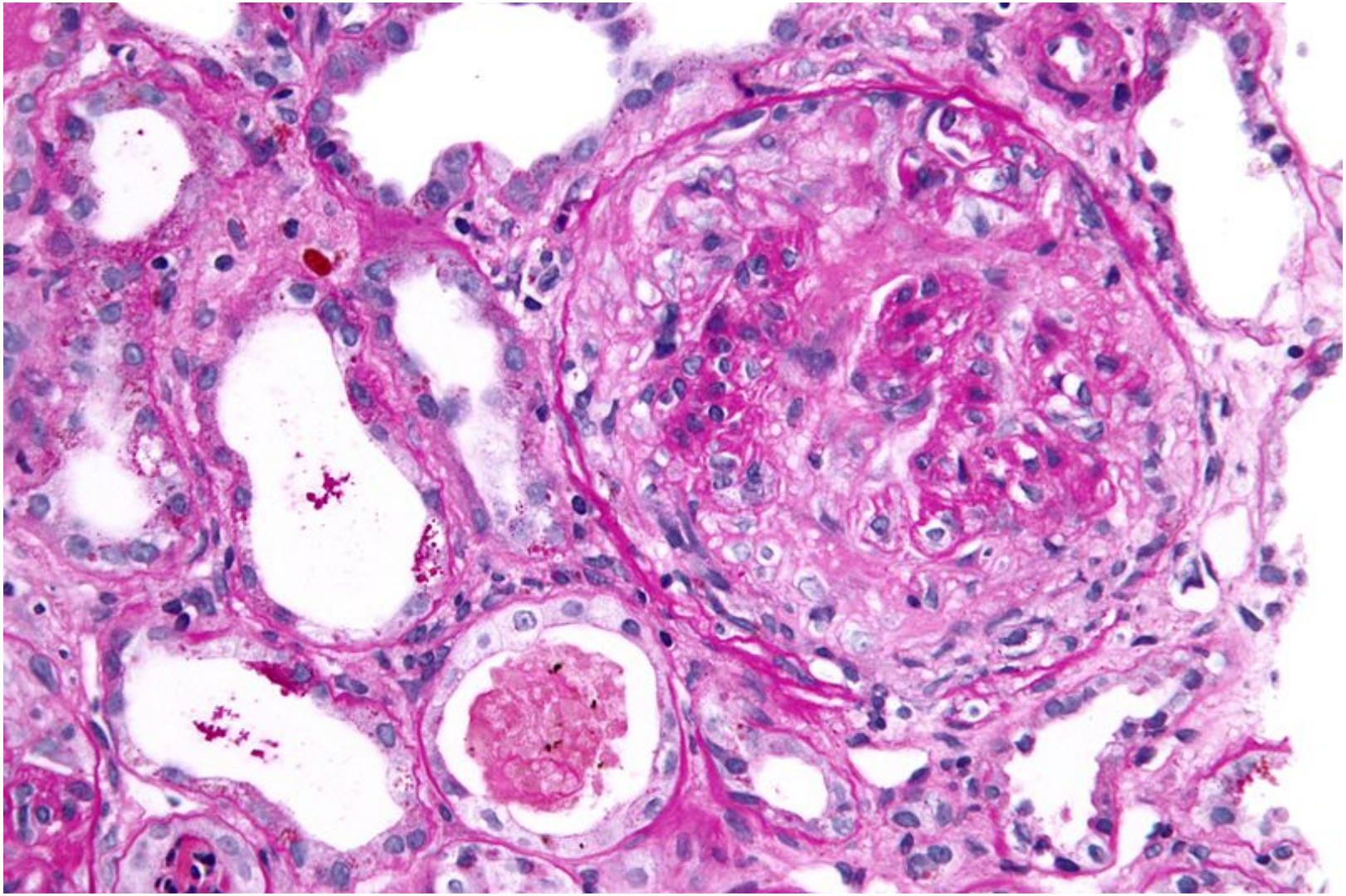
INMUNOSUPRESIÓN EN LAS GLOMERULOPATÍAS



Qué es una glomerulopatía?



Qué es una glomerulonefritis?



¿QUÉ ES UNA GLOMERULONEFRITIS?

EL término “glomerulonefritis” (GN) se reserva a enfermedades en los cuales los glomérulos contienen células inflamatorias, básicamente polimorfonucleares (PMNs), macrógafos tisulares, o linfocitos, más allá del número hallado en condiciones normales.

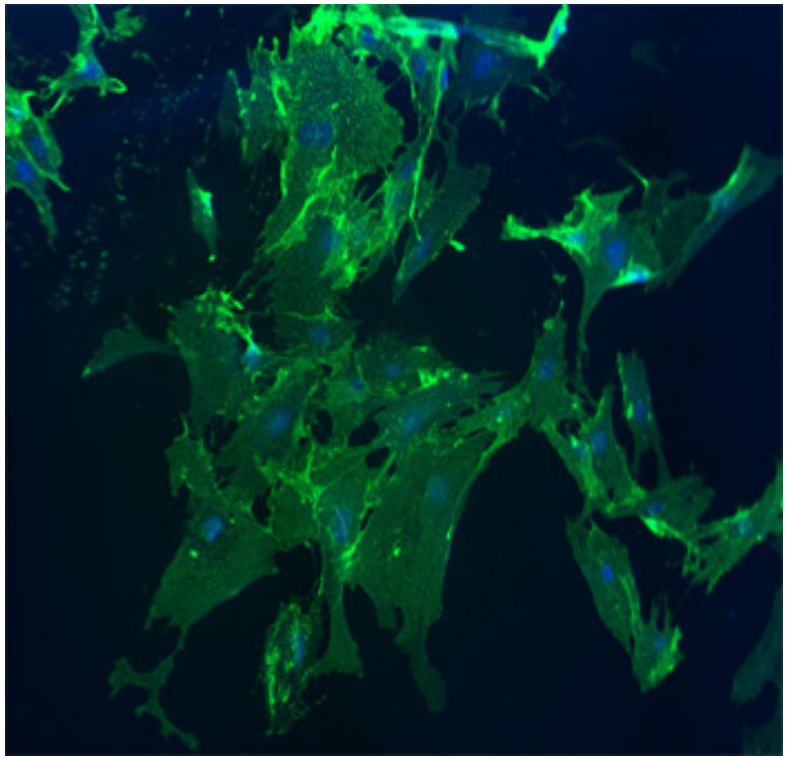
En la gran mayoría de las GN, se hallan depósitos inmunes (ICs antígeno-anticuerpo) en localizaciones
mesangiales,
subendoteliales, o
subepiteliales.

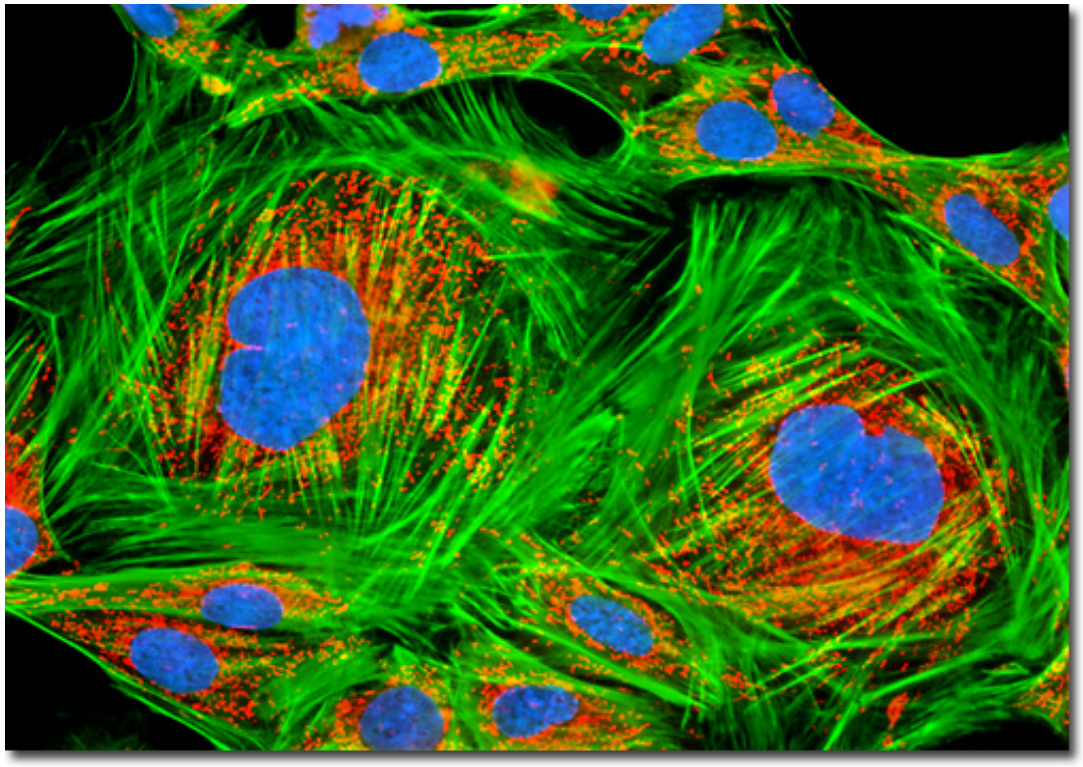
En algunos casos, como en la nefropatía membranosa, los cambios inflamatorios no siempre se ven en las técnicas de rutina de microscopía de luz. Sin embargo, un análisis exhaustivo y molecular de estos glomérulos, revela un número elevado de macrófagos activados.

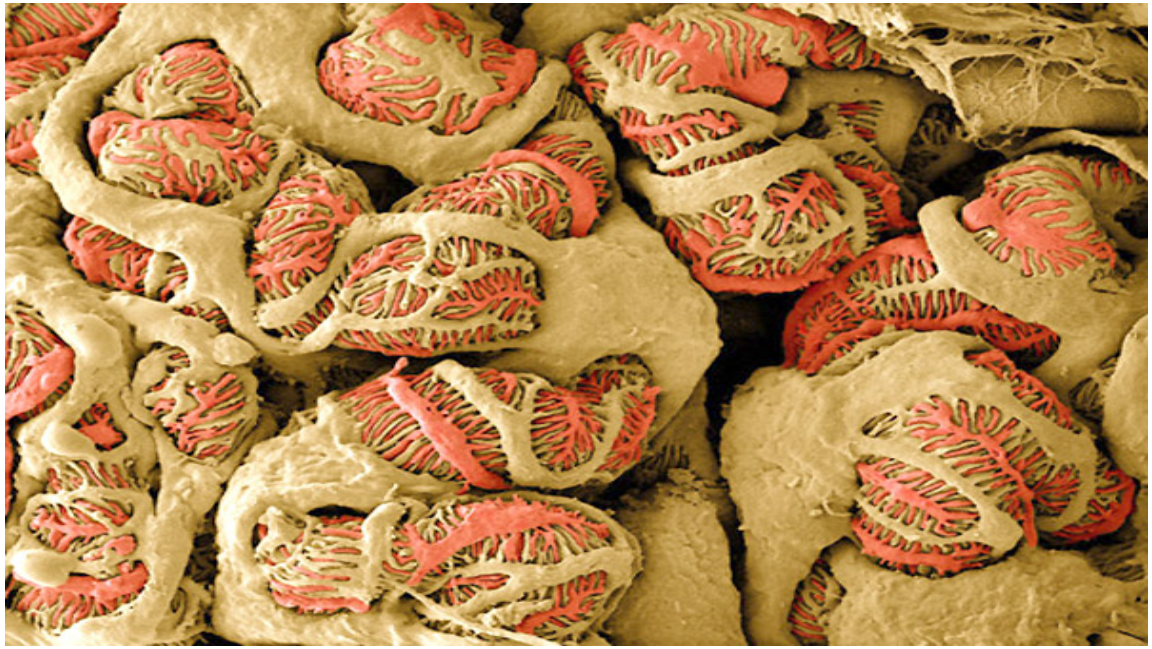
La presencia de leucocitos infiltrantes es el resultado de estímulos quimioatractantes, como los que producen el componente C5a del complemento y el leukotrieno B4 los cuales, a su vez, son liberados por el depósito de ICs y la ola inicial de infiltración de PMNs dentro del glomérulo.

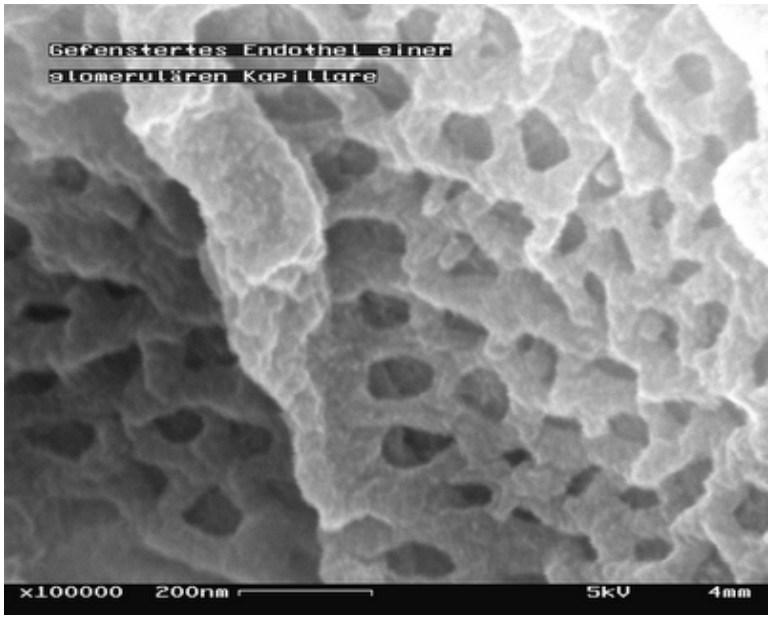
Por ello, la glomerulonefritis es esencialmente una enfermedad inflamatoria autodestructiva.

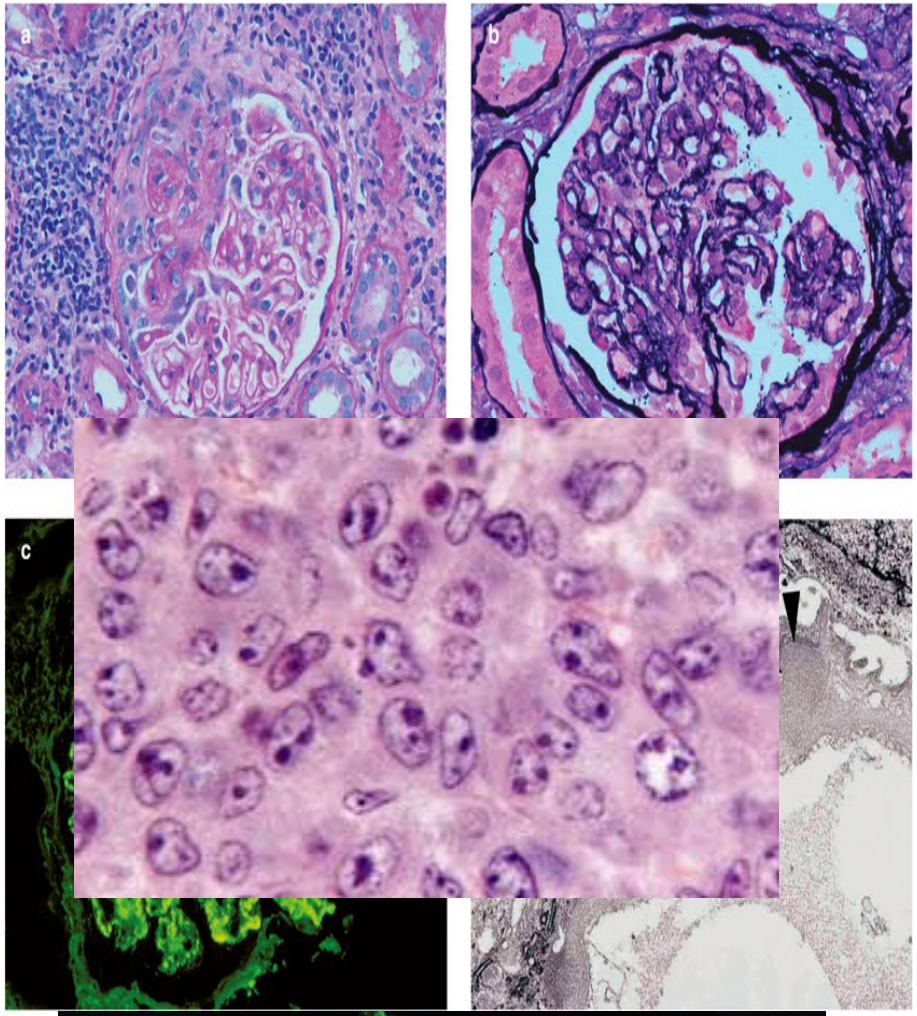
En muchos casos, también depende del aflujo de células inflamatorias
que en un principio no son residentes del parénquima renal,
sino que son reclutadas en los inicios de una GN

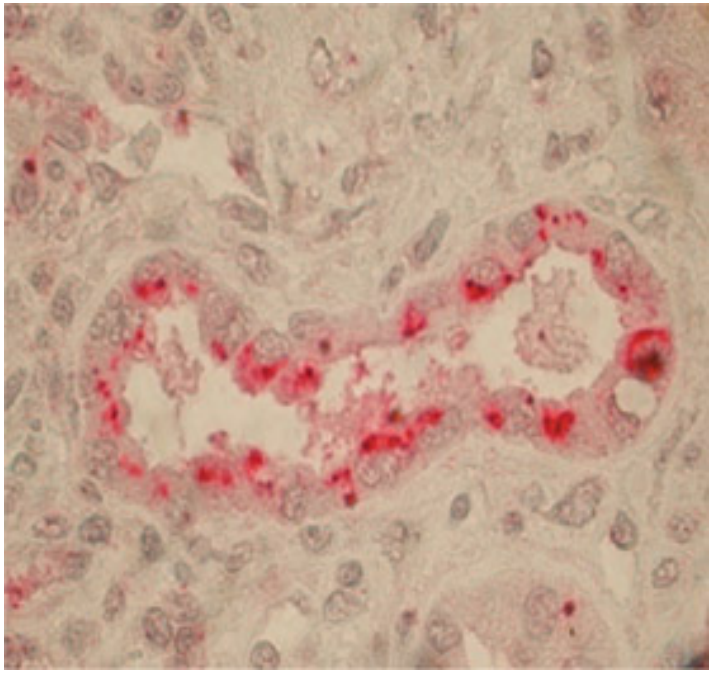


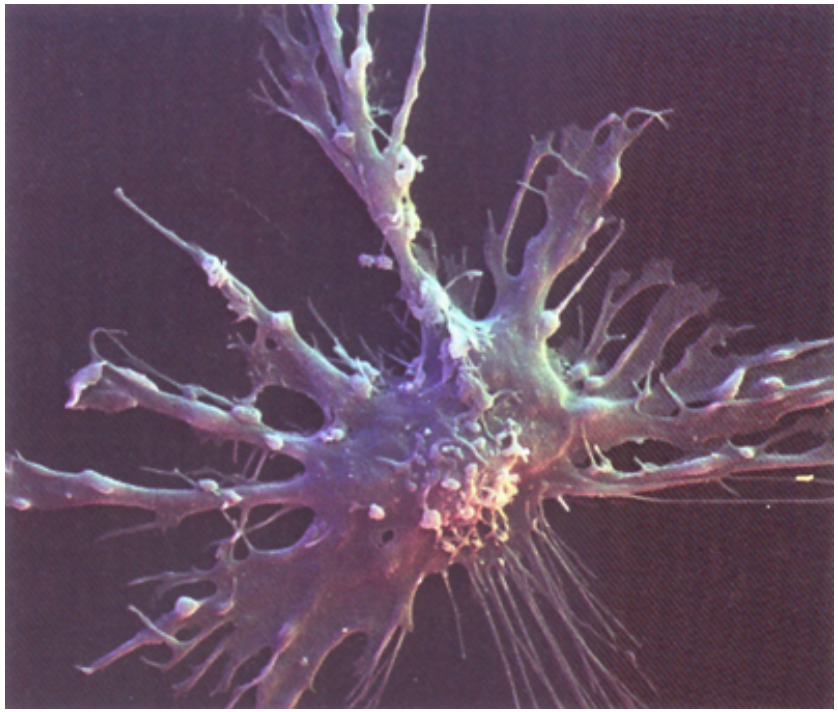


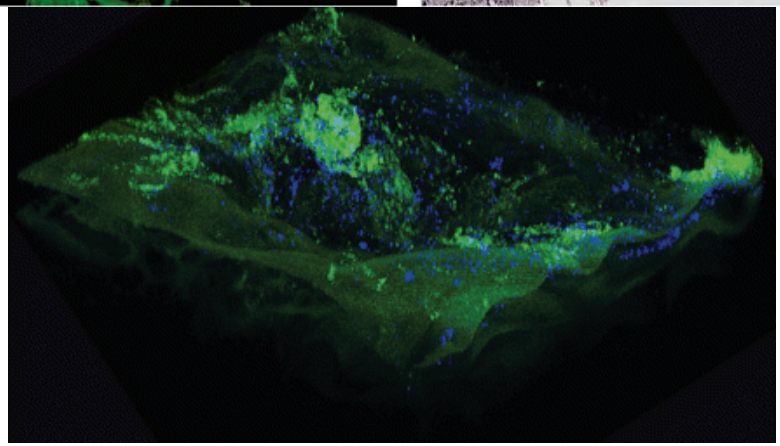


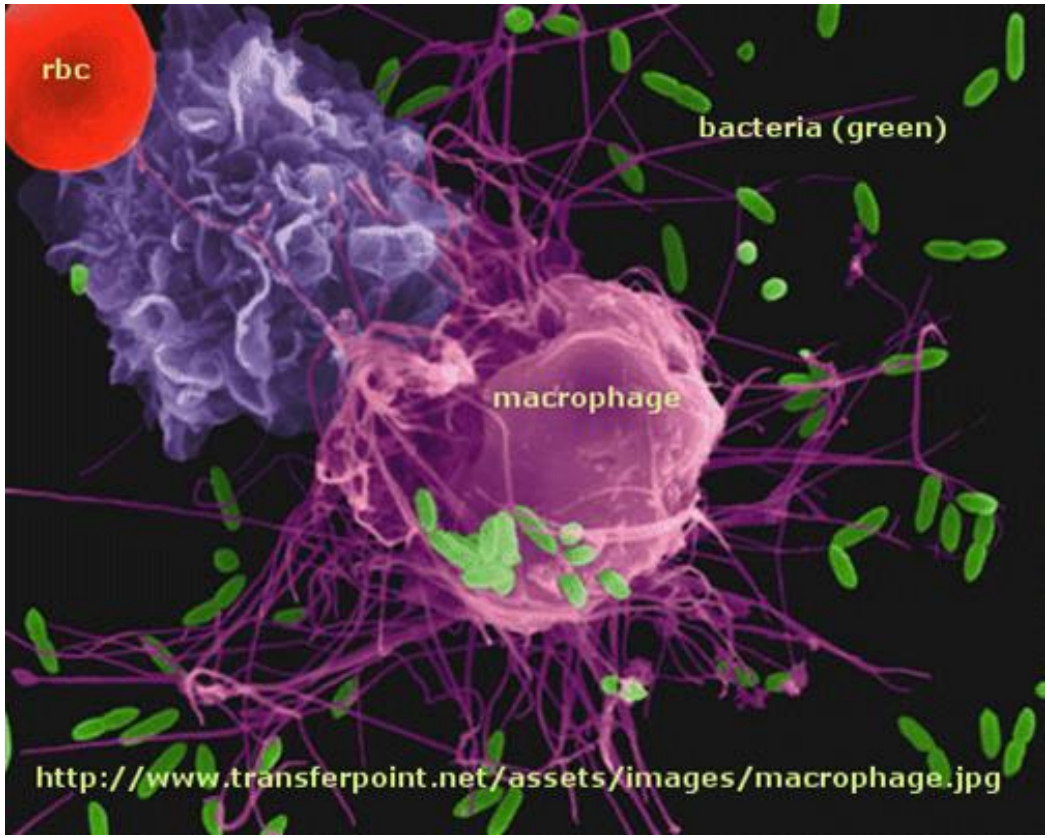

Gefenstertes Endothel einer
glomerulären Kapillare
x100000 200nm 5kV 4mm

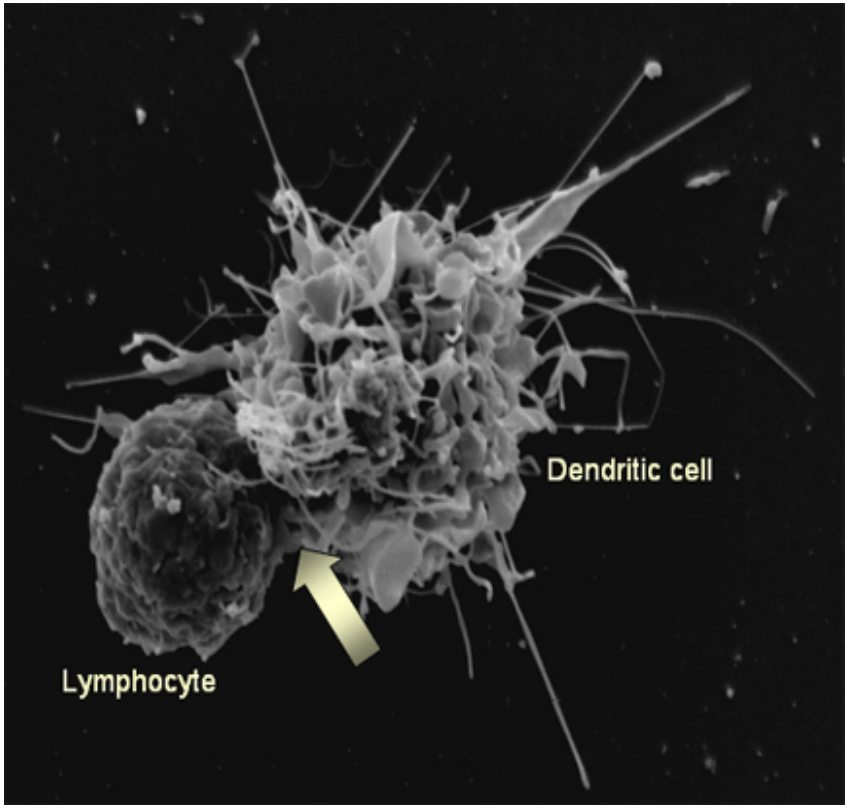

a
b
c

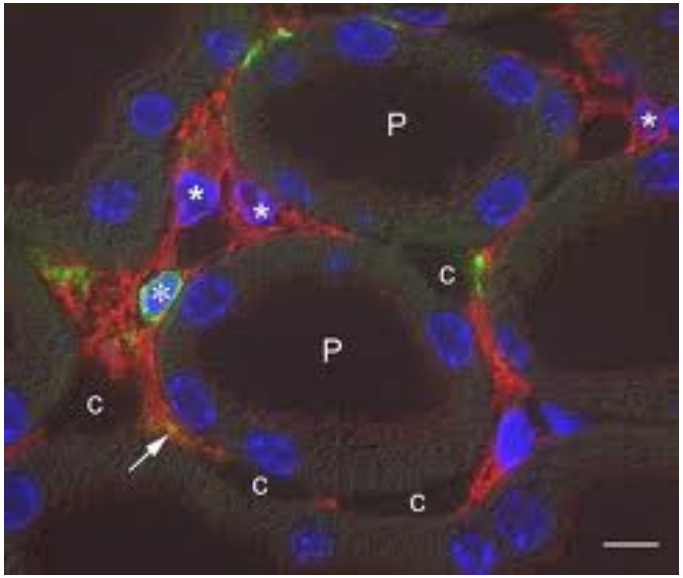


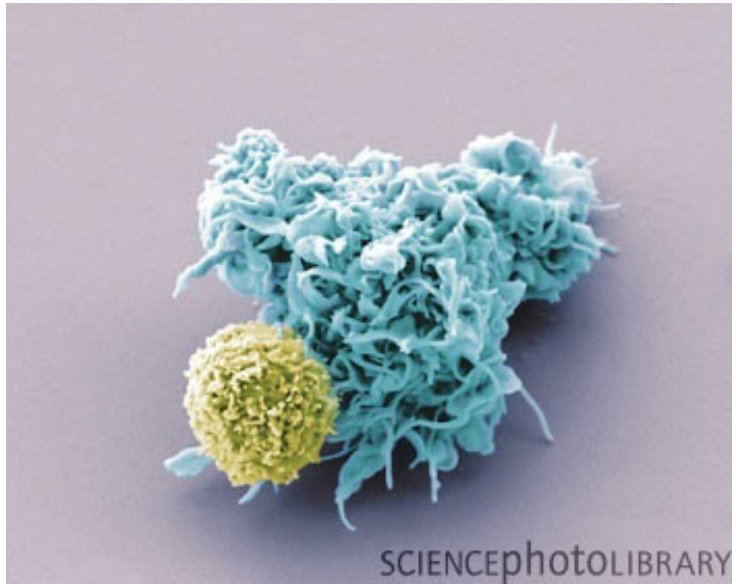




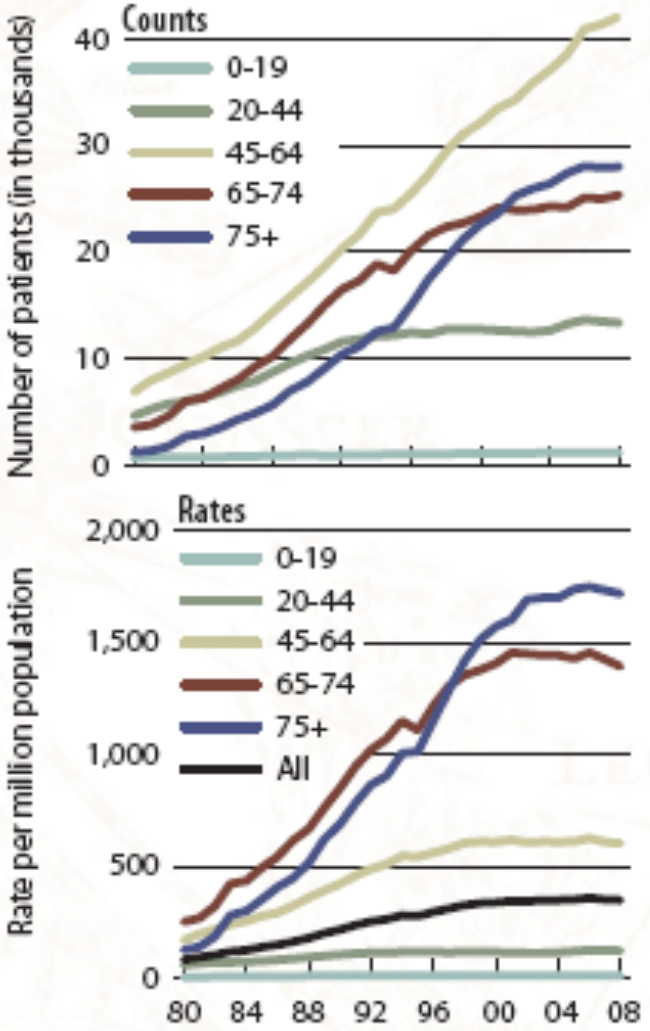

rbc
bacteria (green)
macrophage
http://www.transferpoint.net/assets/images/macrophage.jpg


Dendritic cell
Lymphocyte

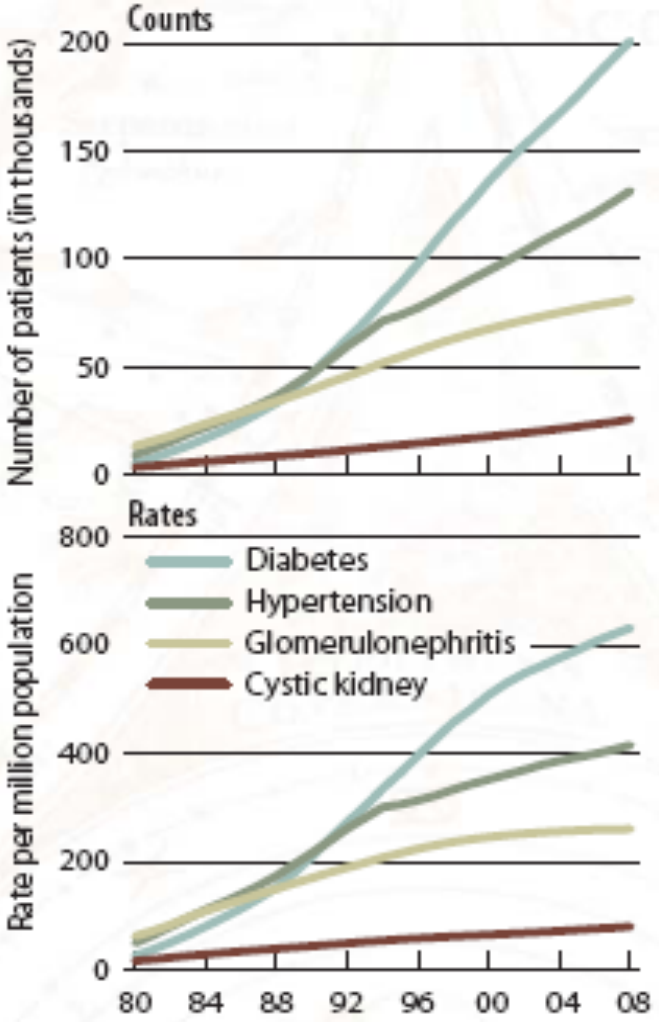

P
P
c
c
c
c

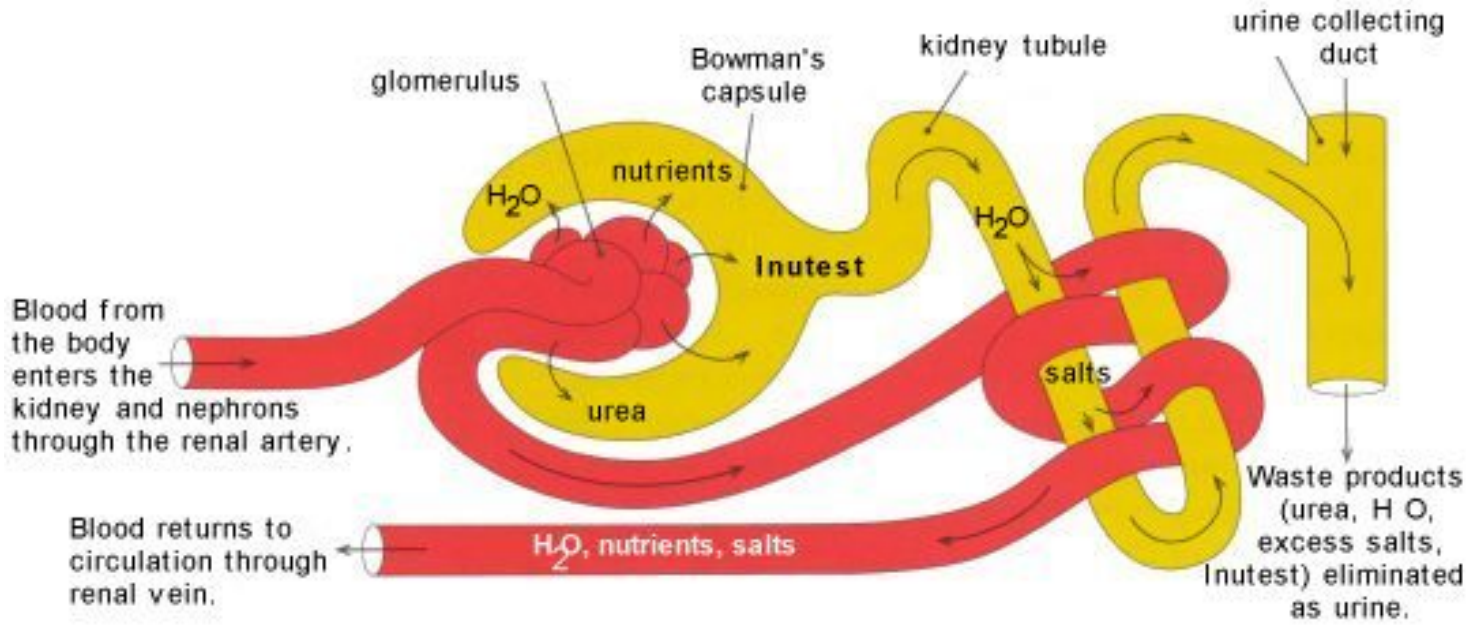

SCIENCEphotoLIBRARY

[2]4.ii Incident counts & adjusted rates of ESRD, by age

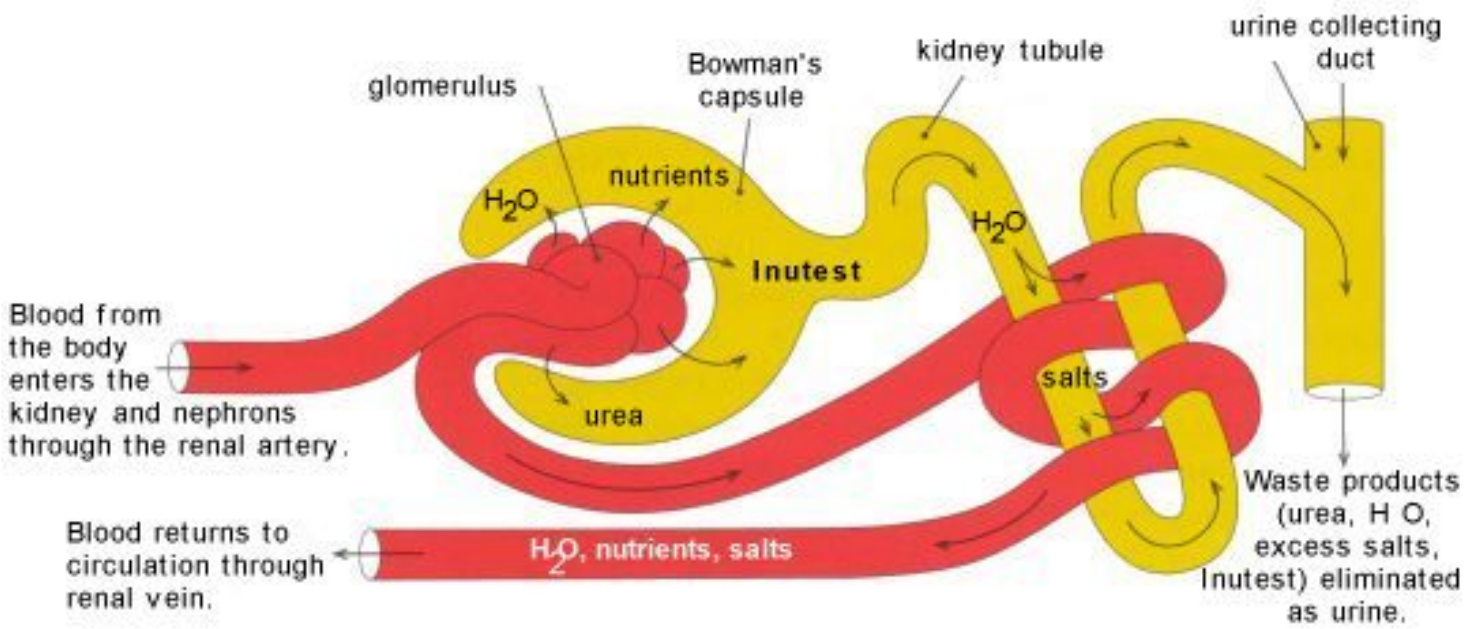


[2]15.ii Prevalent counts & adjusted rates of ESRD, by primary diagnosis





La elevación aguda de la presión capilar glomerular (QA) en el glomérulo normal no produce proteinuria significativa pero lo hará si se perpetúa por períodos prolongados (nefropatía por hiperfiltración .



En presencia de injuria glomerular inflamatoria, sin embargo, disminuyendo la presión intraglomerular se asocia con una caída en la proteinuria.
Esta disminución sugiere que en la presencia de una patología preexistente en la estructura del podocito o en su función, la presión glomerular elevada exacerba el pasaje anormal de proteínas.
Además de la presión capilar elevada, la proteinuria puede exacerbarse por tasas disminuidas de fracciones de filtrado por cada nefrona, como resultado de un tiempo prolongado de contacto local y de un fenómeno de pasaje de proteínas liderado por la difusión más que por convección.

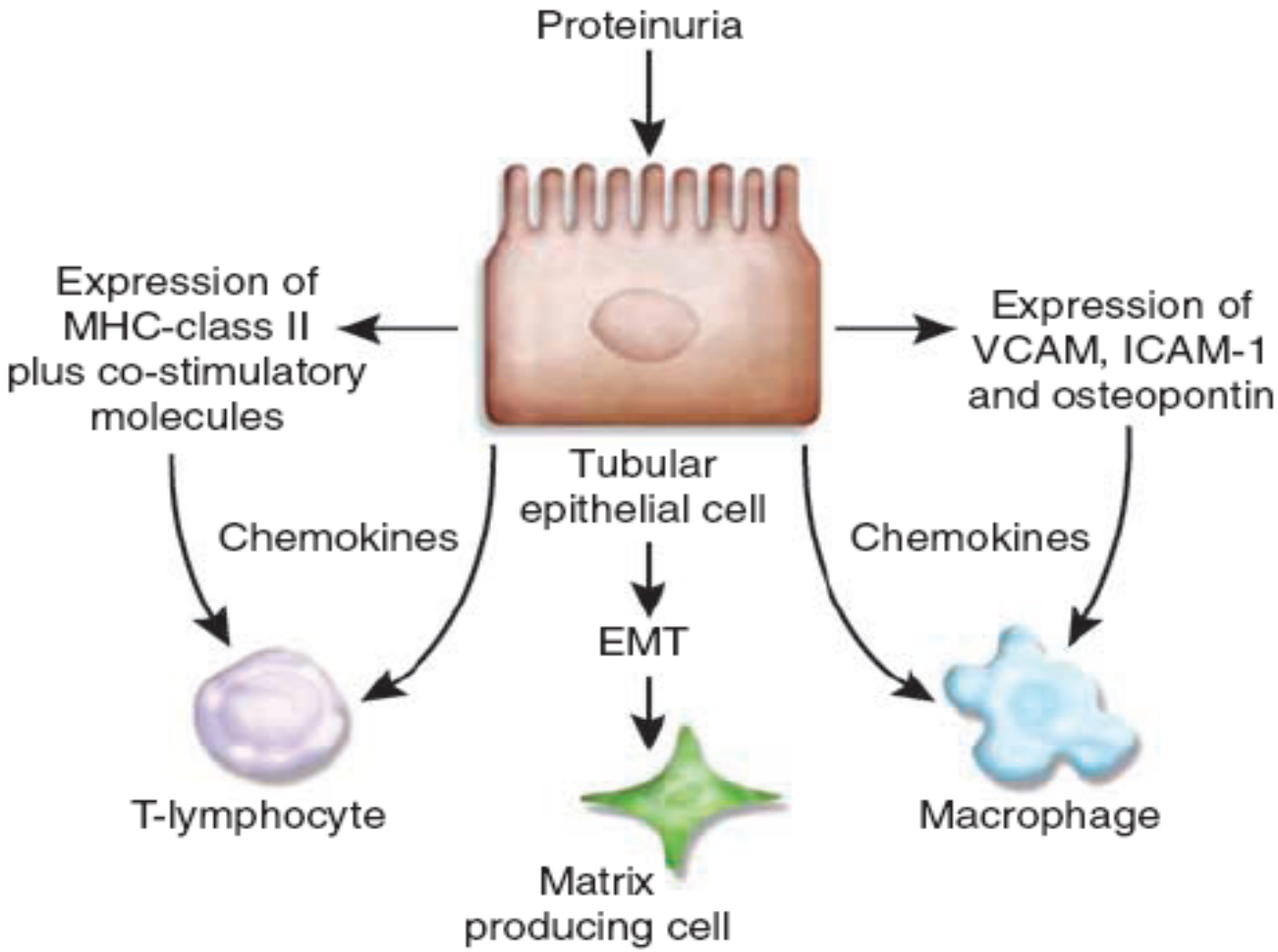
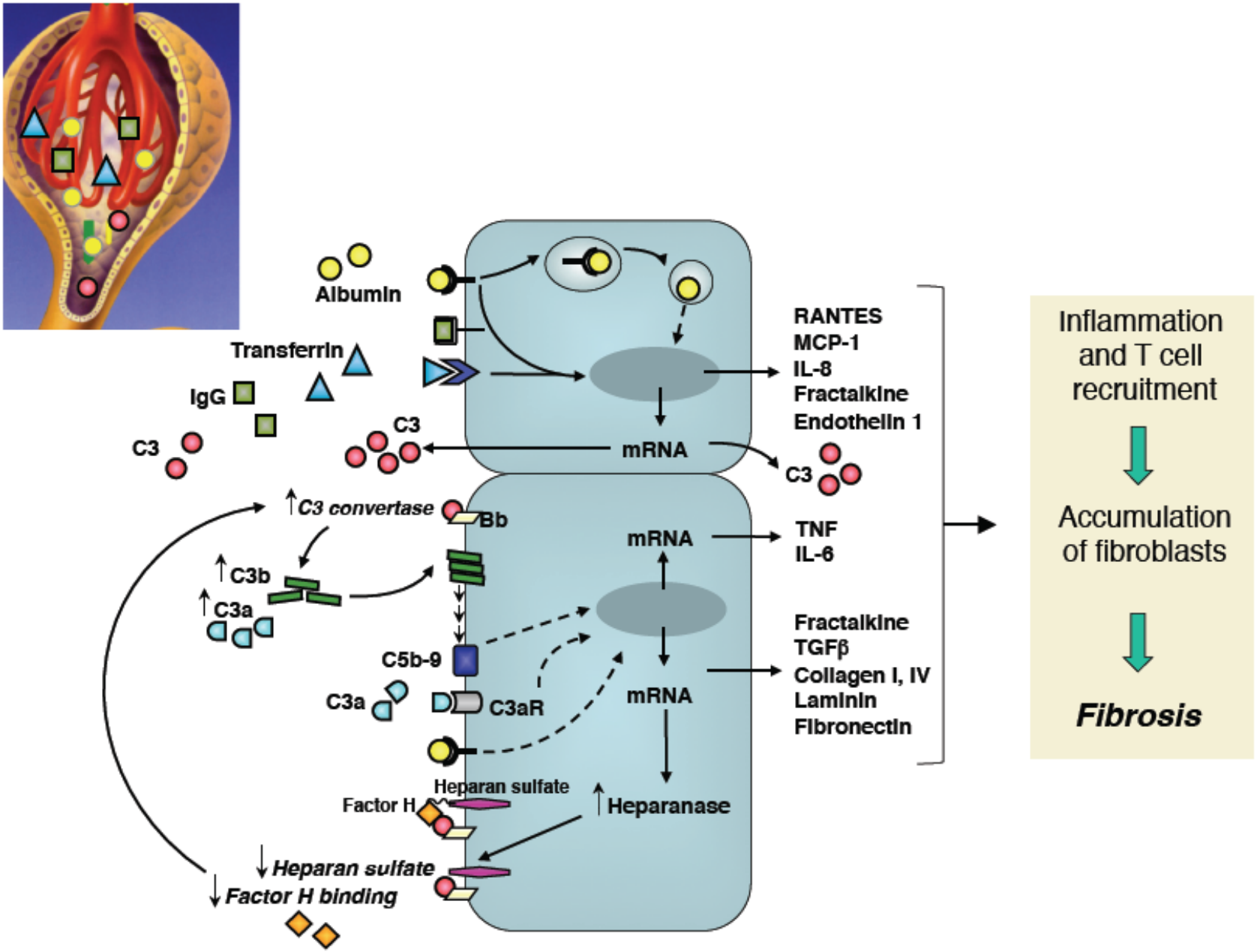
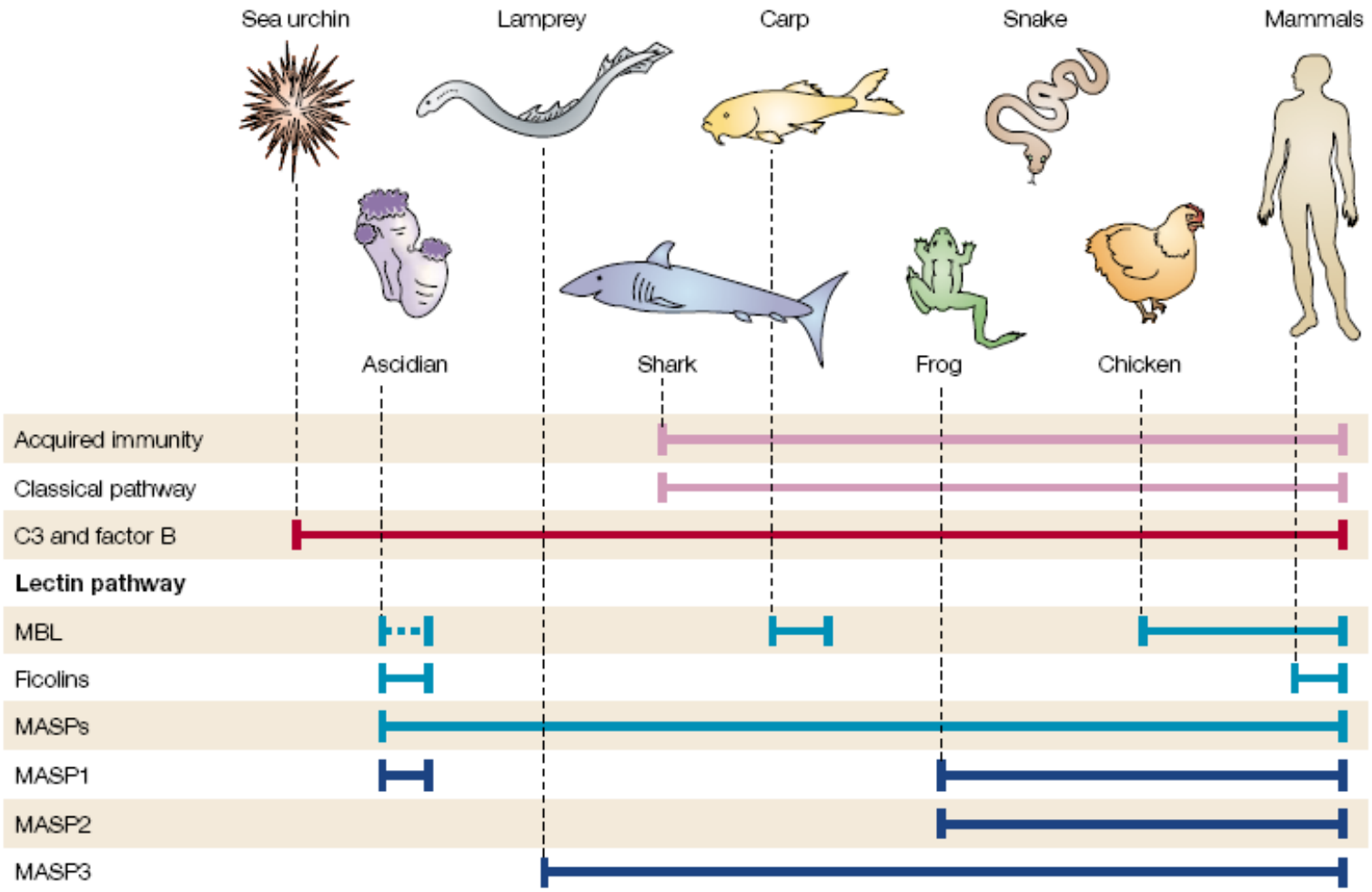
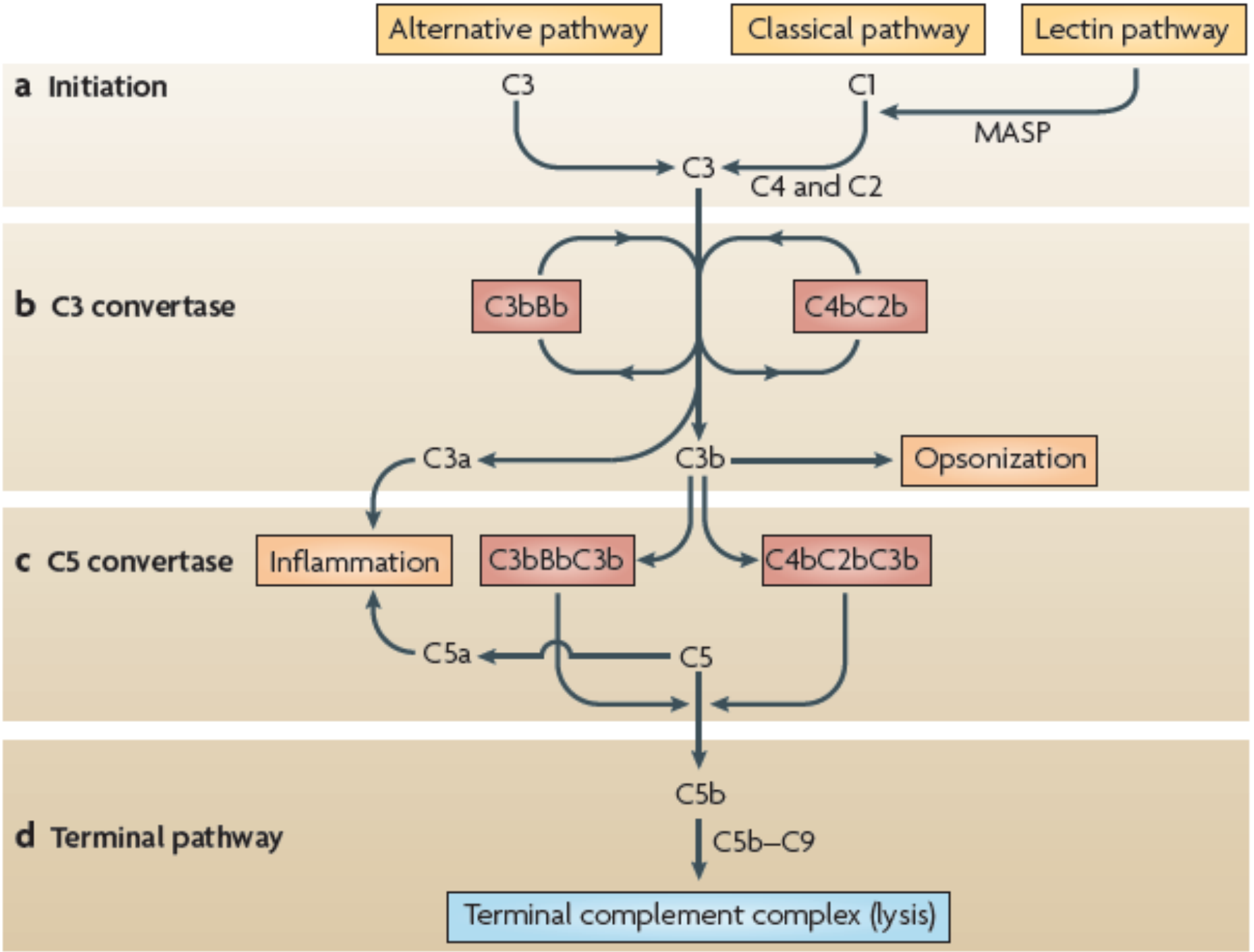
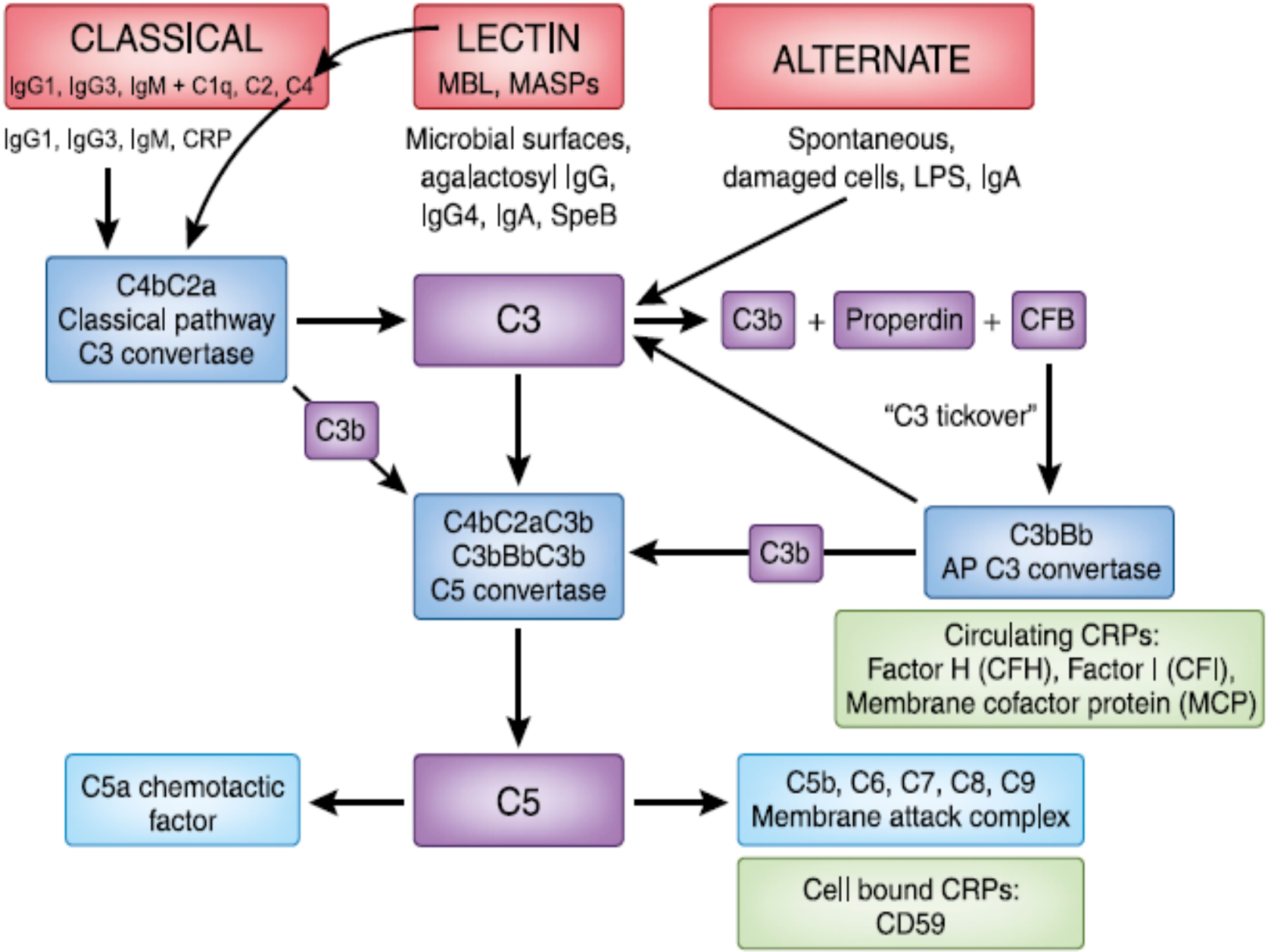


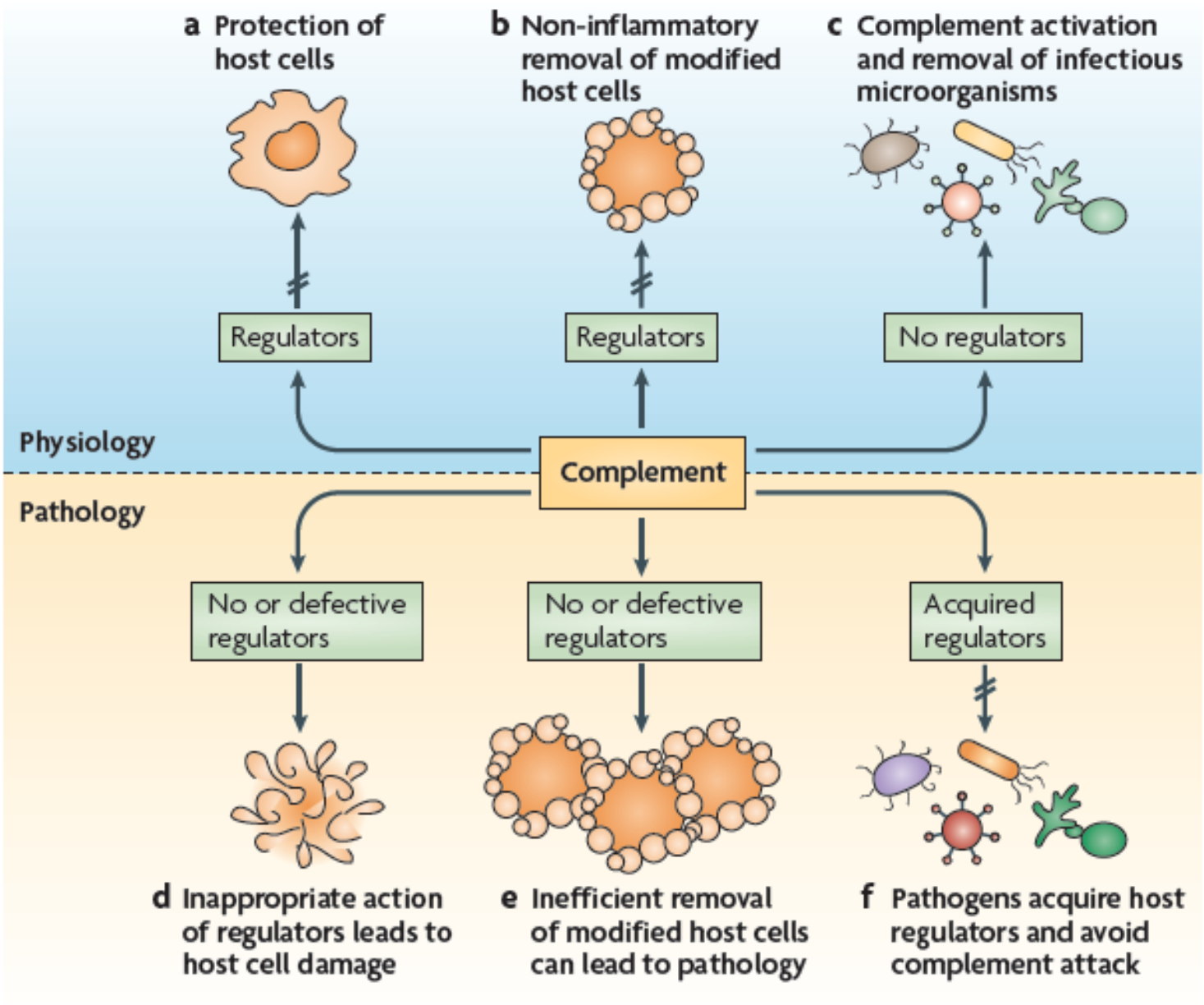
Figure 1 | Effects of proteinuria on tubular epithelial cells. Increased protein absorption by tubular cells may result in direct tubular toxicity, release of chemokines and cytokines, increased expression of adhesion and MHC class II molecules along with co-stimulatory molecules. The net effect is an increased influx of mononuclear inflammatory cells. The evidence for direct proteinuria induced EMT is weak.


Albumin
Transferrin
IgG
C3
C3
C3 convertase
Bb
C3b
C3a
C5b-9
C3a
C3aR
Heparan sulfate
Factor H
Heparanase
Heparan sulfate
Factor H binding
mRNA
mRNA
mRNA
RANTES
MCP-1
IL-8
Fractalkine
Endothelin 1
C3
TNF
IL-6
Fractalkine
TGFβ
Collagen I, IV
Laminin
Fibronectin
Inflammation and T cell recruitment
Accumulation of fibroblasts
Fibrosis


Sea urchin
Lamprey
Carp
Snake
Mammals
Ascidian
Shark
Frog
Chicken
Acquired immunity
Classical pathway
C3 and factor B
Lectin pathway
MBL
Ficolins
MASPs
MASP1
MASP2
MASP3


Alternative pathway
Classical pathway
Lectin pathway
a Initiation
C3
C1
MASP
C3
C4 and C2
b C3 convertase
C3bBb
C4bC2b
C3a
C3b
Opsonization
c C5 convertase
Inflammation
C3bBbC3b
C4bC2bC3b
C5a
C5
C5b
d Terminal pathway
C5b–C9
Terminal complement complex (lysis)


CLASSICAL
IgG1, IgG3, IgM + C1q, C2, C4
LECTIN
MBL, MASPs
ALTERNATE
IgG1, IgG3, IgM, CRP
Microbial surfaces,
agalactosyl IgG,
IgG4, IgA, SpeB
Spontaneous,
damaged cells, LPS, IgA
C4bC2a
Classical pathway
C3 convertase
C3
C3b + Properdin + CFB
C3b
"C3 tickover"
C4bC2aC3b
C3bBbC3b
C5 convertase
C3b
C3bBb
AP C3 convertase
Circulating CRPs:
Factor H (CFH), Factor I (CFI),
Membrane cofactor protein (MCP)
C5a chemotactic
factor
C5
C5b, C6, C7, C8, C9
Membrane attack complex
Cell bound CRPs:
CD59


a Protection of host cells
b Non-inflammatory removal of modified host cells
c Complement activation and removal of infectious microorganisms
Regulators
Regulators
No regulators
Physiology
Complement
Pathology
No or defective regulators
No or defective regulators
Acquired regulators
d Inappropriate action of regulators leads to host cell damage
e Inefficient removal of modified host cells can lead to pathology
f Pathogens acquire host regulators and avoid complement attack

QUÉ FACTORES INMUNOLÓGICOS PROPIOS INTERVIENEN EN EL CAMINO A SEGUIR EN UNA GN?

Dentro de la respuesta inmune innata, están los Toll-Like Receptors (TLRs)

Los TLRs son receptores muy antiguos presentes en todas las membranas celulares y a nivel intracelular entre el citoplasma y los endosomas y que reconocen patrones antigénicos estereotipados determinados.

Los TLRs reconocen patrones inmunoestimuladores conservados (antígenos) como péptidoglicanos, LPSs, y ácidos nucleicos bacterianos y virales (pathogen-associated molecular patterns [PAMPs]) así como componentes endógenos (danger-associated molecular patterns [DAMPs]).

La unión al TLR es central para activar inmediatamente al sistema innato en respuesta a patógenos , pero la activación de los TLRs es también fundamental para lograr respuestas adaptativas a fenómenos antígeno-específicos facilitando la conversión de células dendríticas a células presentadoras de antígeno

Los TLRs activan múltiples vías de señalización celular que conllevan a la secreción de citokinas, quimokinas, etc

Los TLRs conectan eventos iniciales con la mediación de la injuria tisular en GN asociadas con infecciones o autoinmunidad o ambas

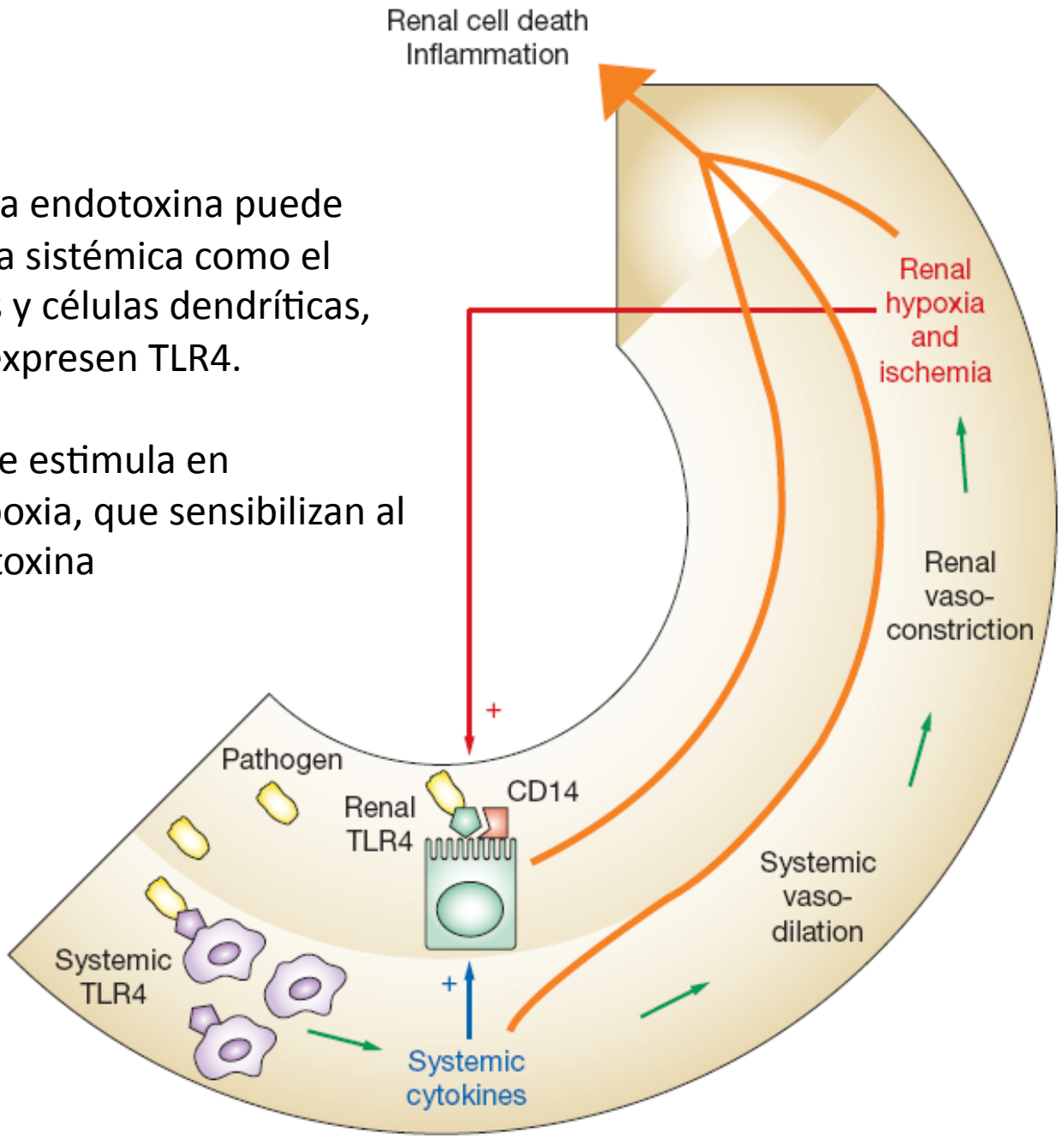
Table 2 | TLRs involved in the onset or aggravation of renal conditions

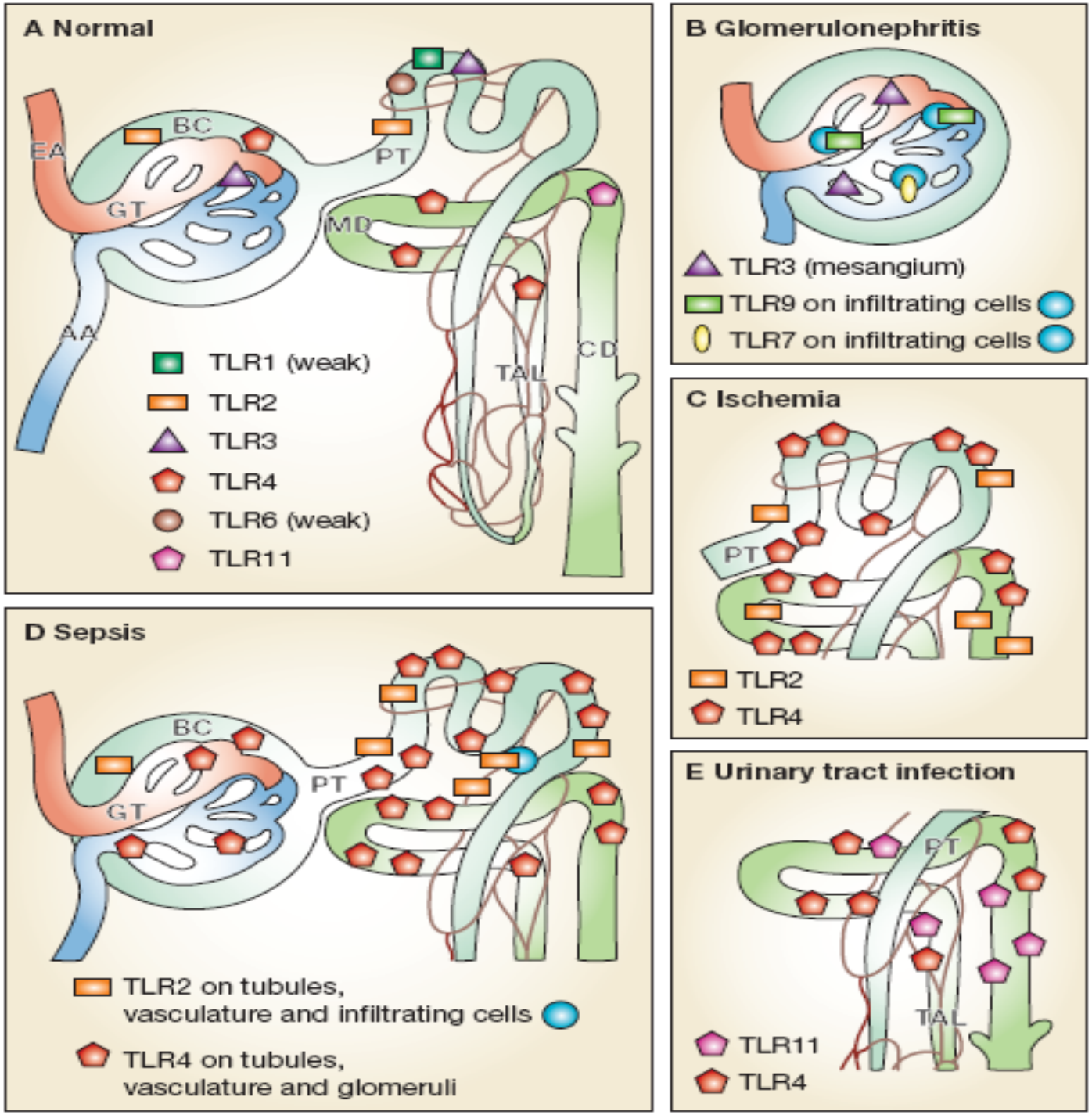
TLR	Ligand	Renal condition
TLR4[23,69]	LPs, β-defensin 2	AKI
TLR4[72]	Unknown	AKI caused by cisplatin nephrotoxicity
TLR2[76] TLR4[77] TLR9[78]	Pam3Cys, LPs LPs LPs	Crescentic glomerulonephritis
TLR3[91,92] TLR4[87] TLR7[84–86] TLR9[80–82]	dsRNA, poly(I:C) LPs ssRNA CpG-DNA	Lupus nephritis and immune-complex glomerulonephritis
TLR2[47] TLR4[96,98,99]	Lipoteichoic acid, Pam3Cys Peptidoglycan, LPs	Allograft rejection
TLR4[100]	HMG-1, heparan sulfate, hyaluronic acid, fibronectin, etc.	Transplantation-induced ischemic kidney disease
TLR2[4,115] TLR4[114]	DAMPs LPs	Ischemic renal injury

Abbreviations: AKI, acute kidney injury; CpG, unmethylated cytidine–guanosine dinucleotide; DAMP, damage-associated molecular pattern; dsRNA, double-stranded RNA; LP, lipopolysaccharide; poly(I:C), polyinosinic:polycytidylic acid; ssRNA, single-stranded RNA.

De acuerdo a este modelo, una endotoxina puede causar injuria renal por una vía sistémica como el TLR4, presente en macrófagos y células dendríticas, como en células renales que expresen TLR4.

Un diálogo entre ambas vías se estimula en condiciones de isquemia e hipoxia, que sensibilizan al riñón a los efectos de la endotoxina




A Normal
BC
EA
GT
PT
MD
AA
TAL
CD
TLR1 (weak)
TLR2
TLR3
TLR4
TLR6 (weak)
TLR11
B Glomerulonephritis
TLR3 (mesangium)
TLR9 on infiltrating cells
TLR7 on infiltrating cells
C Ischemia
PT
TLR2
TLR4
D Sepsis
BC
GT
PT
TLR2 on tubules,
vasculature and infiltrating cells
TLR4 on tubules,
vasculature and glomeruli
E Urinary tract infection
PT
TAL
TLR11
TLR4

Dos vías principales han sido descriptas como mediadores de la injuria al podocito durante una GN aguda y crónica:

Ataque directo por el complemento (particularmente el complejo C5b-9) o,

más aún en la fase crónica,

la disrupción de las funciones del podocito por autacoides del proceso inflamatorio que provienen de la activación de los

PMNs,
macrófagos,
células mononucleares, y
células glomerulares mesangiales o
dendríticas

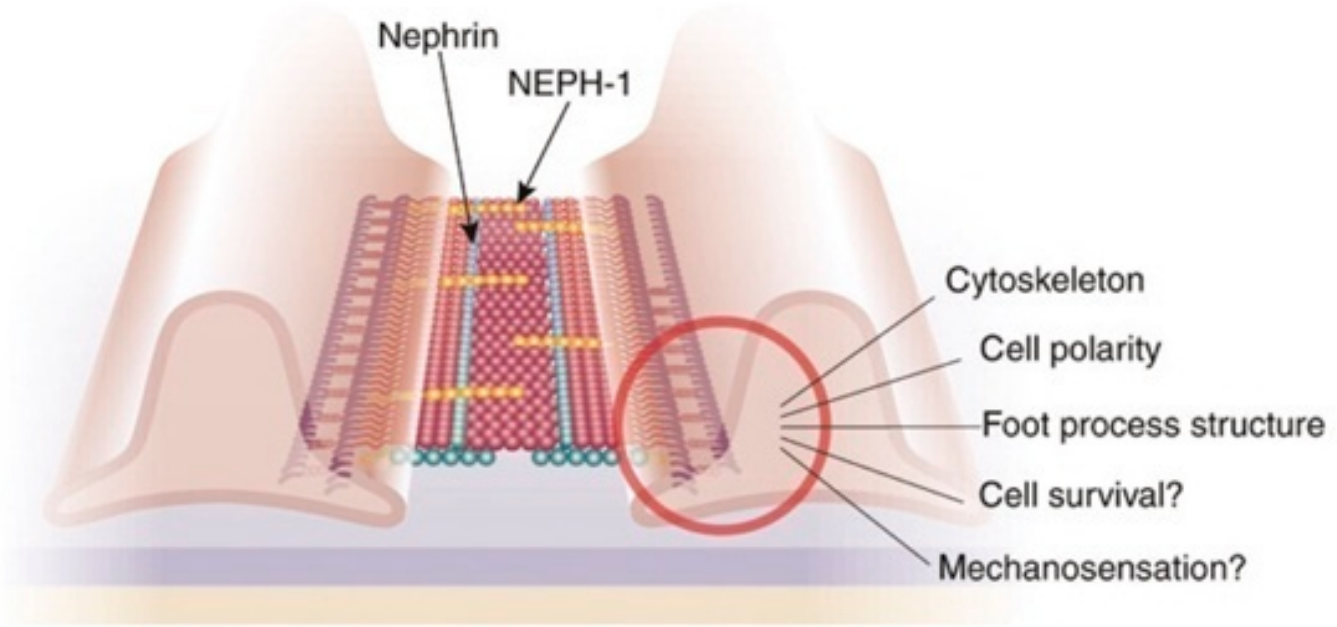
Sin embargo, en la mayoría de las GNs la infiltración aguda de PMNs no es muy evidente en la biopsia renal.

En su lugar, se ve una reacción crónica (amplificación) en la cual
componentes del complemento,
células T,
citokinas,
autacoides,
mediadores lipídicos,
y otras moléculas secretadas por células nativas e infiltrantes
participan en el reconocimiento del antígeno, en la amplificación y la perpetuación de la injuria inicial.

La activación de las células glomerulares nativas, leucocitos infiltrantes y plaquetas media las consecuencias funcionales.

El grado de proteinuria y la magnitud de la disminución del VFG son muy variables, no sólo entre las distintas GNs, sino entre distintos individuos con la misma enfermedad.

Es más que claro que en el control del fino filtrado glomerular, los procesos pedicelares, el endotelio, la MBG y fundamentalmente los diafragmas poseen una interrelación funcional tan estrecha que un mínimo daño en una molécula de uno de ellos puede resultar en una gran repercusión clínica, como proteinuria masiva e IRA.
Que el VFG se aproxime a 180 litros/día resulta en una drástica amplificación de la filtración anormal de cada nefrona enferma que lleva a la proteinuria severa.



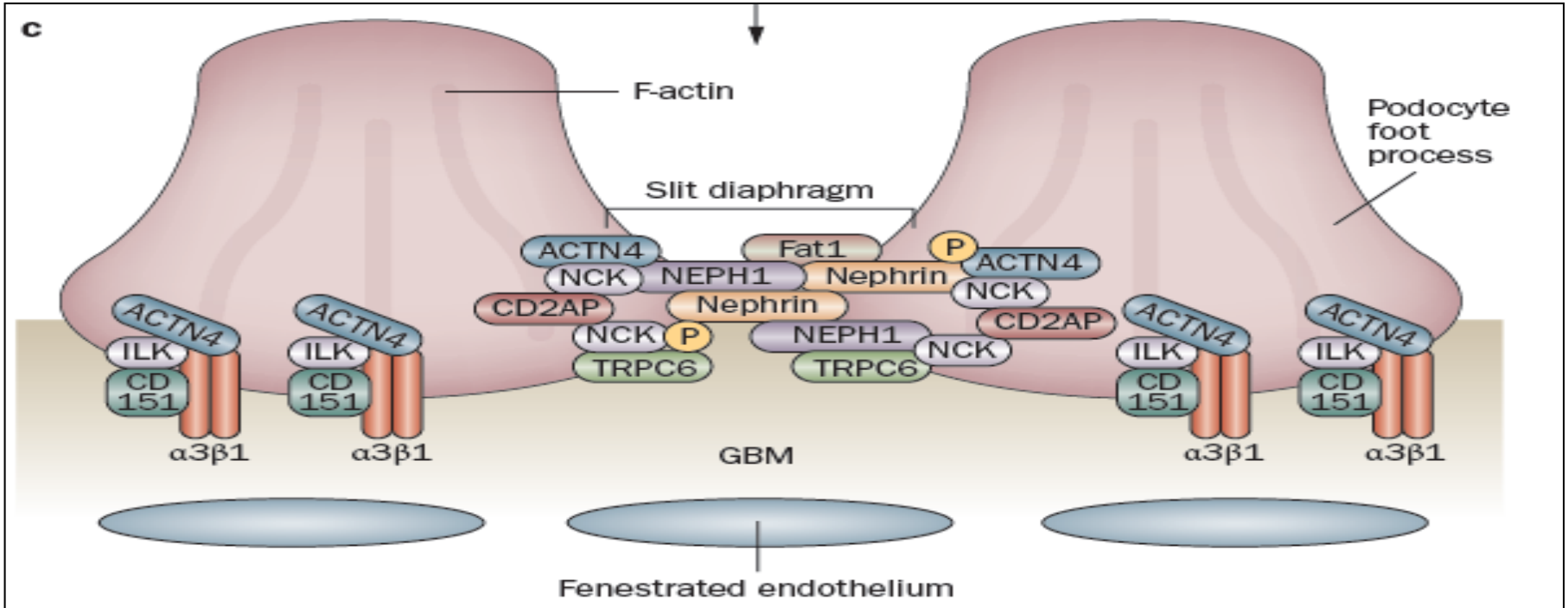
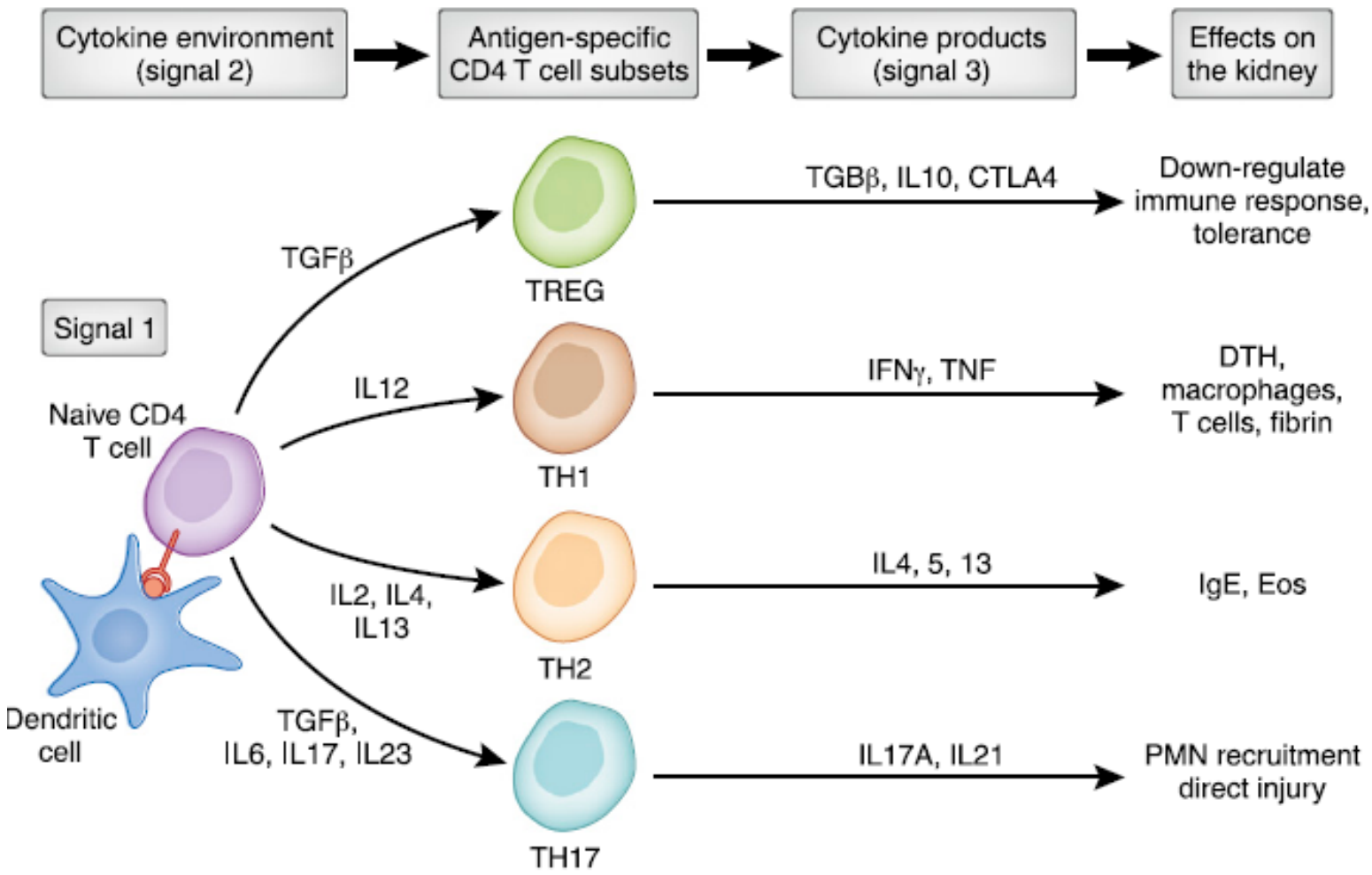
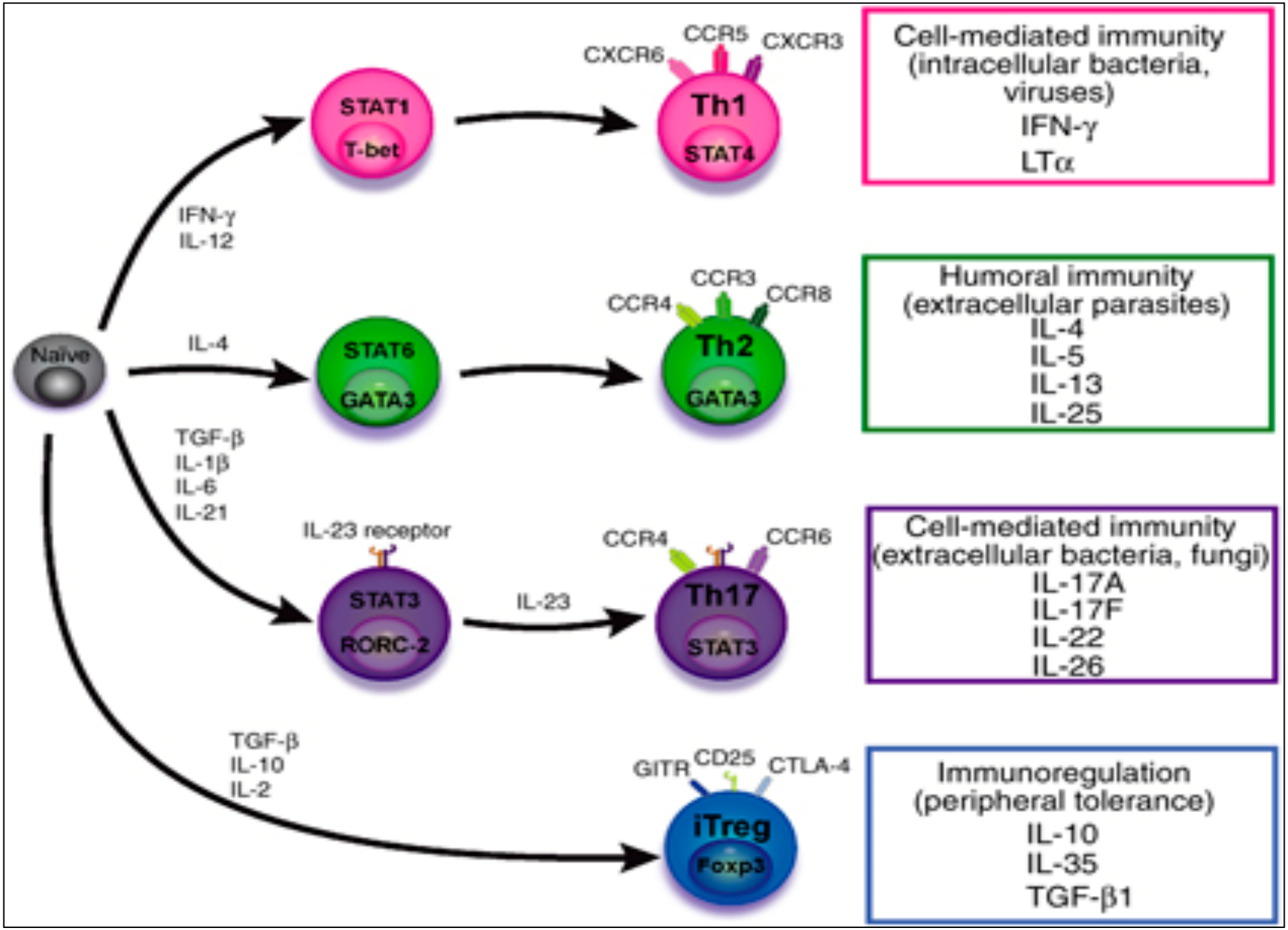
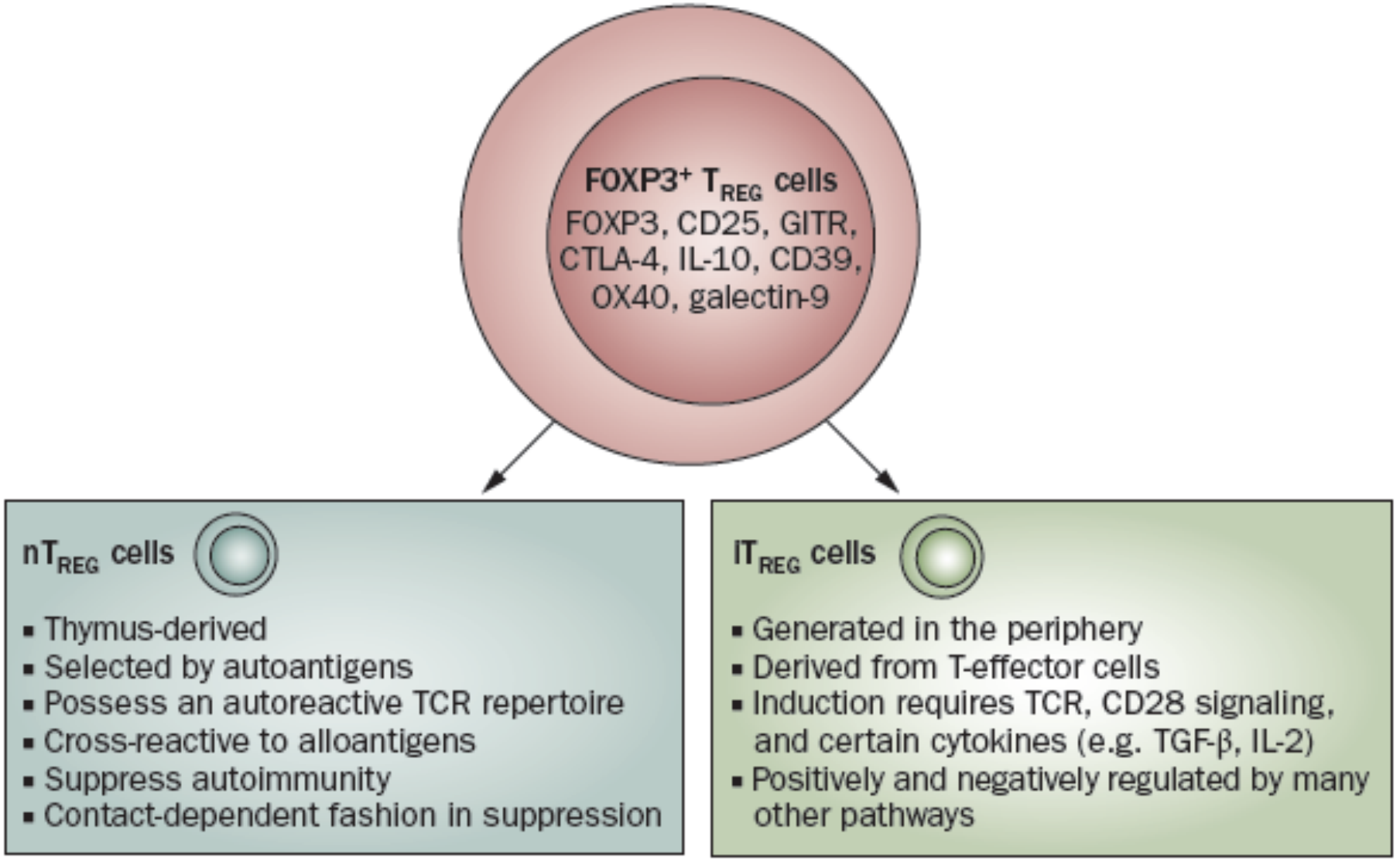


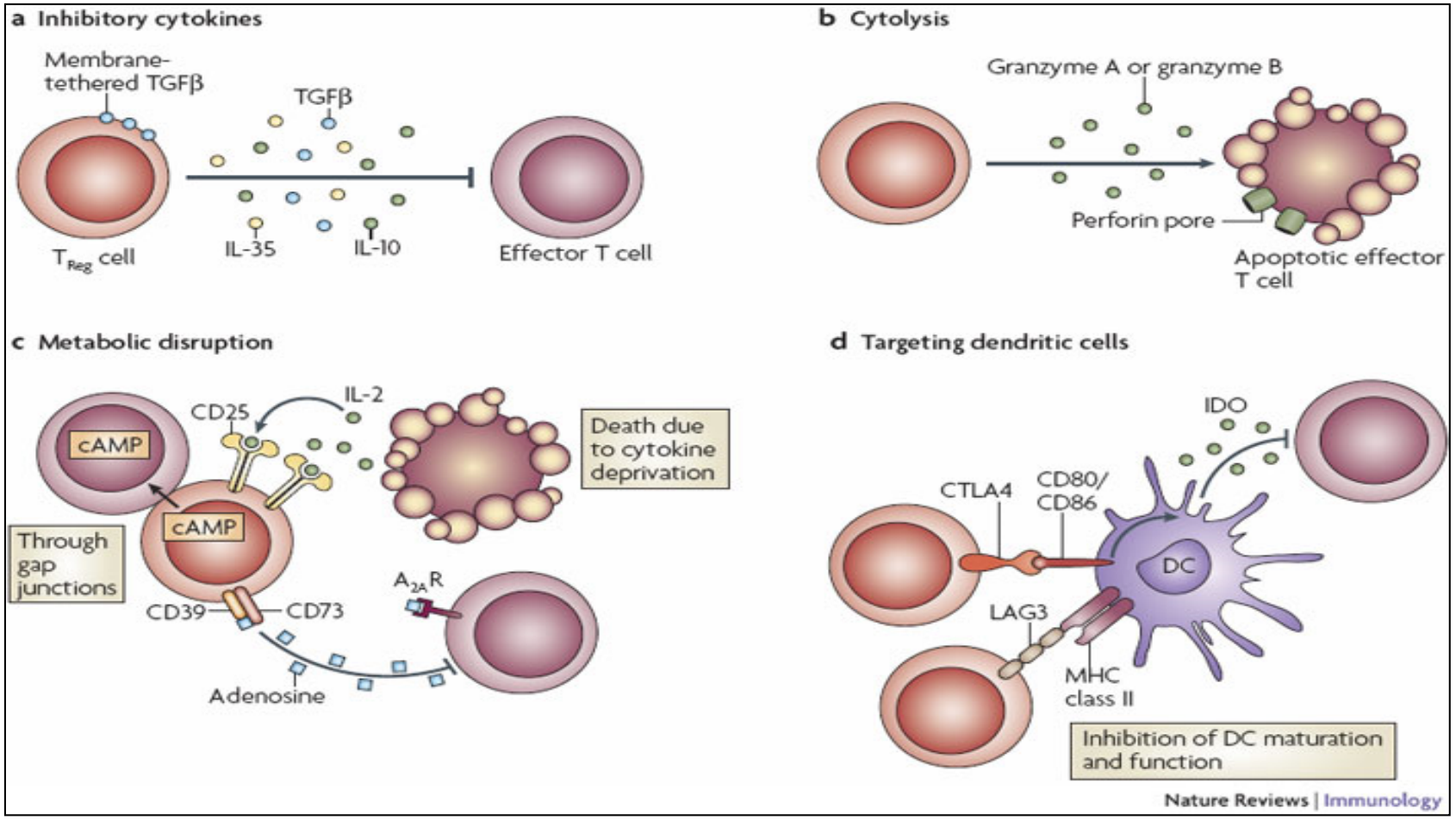
Figure 1 | Structure of the glomerular filtration barrier. **a** | Glomerular filtration occurs through the capillary wall into the urinary space, which empties into the proximal tubules. **b** | The capillary wall contains an innermost fenestrated endothelium, the GBM, and a layer of podocytes with interdigitating foot processes. **c** | Podocyte foot processes, interconnected by slit diaphragms, form the final barrier for filtration. Proteins that anchor the foot processes to the GBM (α3β1 integrin, ACTN4, ILK and the tetraspanin CD151) as well as those that are associated with the slit diaphragm (nephrin, NEPH1, podocin, Fat1, ACTN4, the adaptor protein NCK, CD2AP, and TRPC6) are crucial for normal function of the filtration barrier. Abbreviations: ACTN4, α-actinin-4; CD2AP, CD2-associated protein; GBM, glomerular basement membrane; ILK, integrin-linked kinase; P, podocin; TRPC6, transient receptor potential cation channel 6.


Cytokine environment (signal 2)
Antigen-specific CD4 T cell subsets
Cytokine products (signal 3)
Effects on the kidney
Signal 1
Naive CD4 T cell
Dendritic cell
TGFβ
IL12
IL2, IL4, IL13
TGFβ, IL6, IL17, IL23
TREG
TH1
TH2
TH17
TGBβ, IL10, CTLA4
IFNγ, TNF
IL4, 5, 13
IL17A, IL21
Down-regulate immune response, tolerance
DTH, macrophages, T cells, fibrin
IgE, Eos
PMN recruitment direct injury

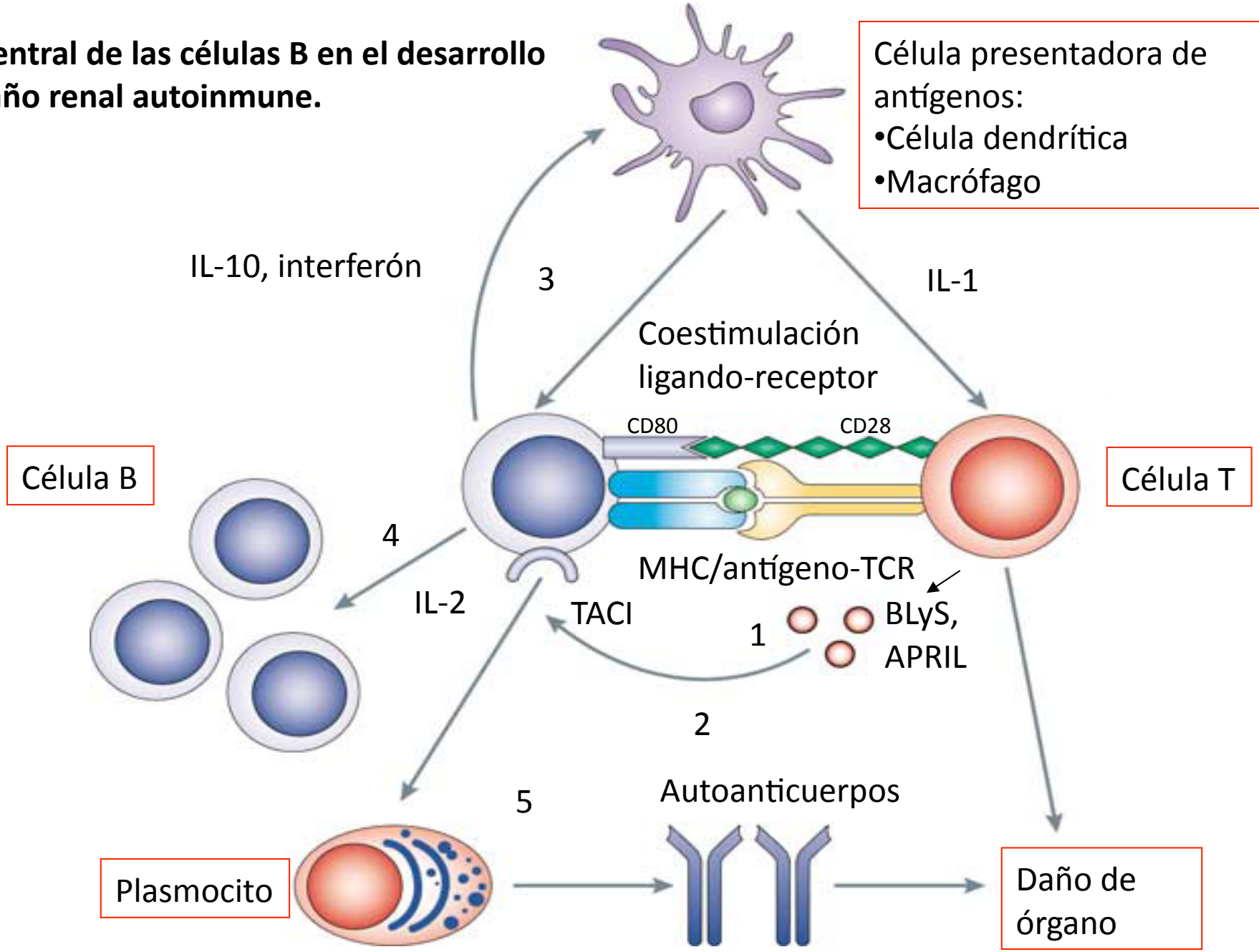

Naive
IFN-γ
IL-12
STAT1
T-bet
CXCR6
CCR5
CXCR3
Th1
STAT4
Cell-mediated immunity
(intracellular bacteria,
viruses)
IFN-γ
LTα
IL-4
STAT6
GATA3
CCR4
CCR3
CCR8
Th2
GATA3
Humoral immunity
(extracellular parasites)
IL-4
IL-5
IL-13
IL-25
TGF-β
IL-1β
IL-6
IL-21
IL-23 receptor
STAT3
RORC-2
IL-23
CCR4
CCR6
Th17
STAT3
Cell-mediated immunity
(extracellular bacteria, fungi)
IL-17A
IL-17F
IL-22
IL-26
TGF-β
IL-10
IL-2
GITR
CD25
CTLA-4
iTreg
Foxp3
Immunoregulation
(peripheral tolerance)
IL-10
IL-35
TGF-β1

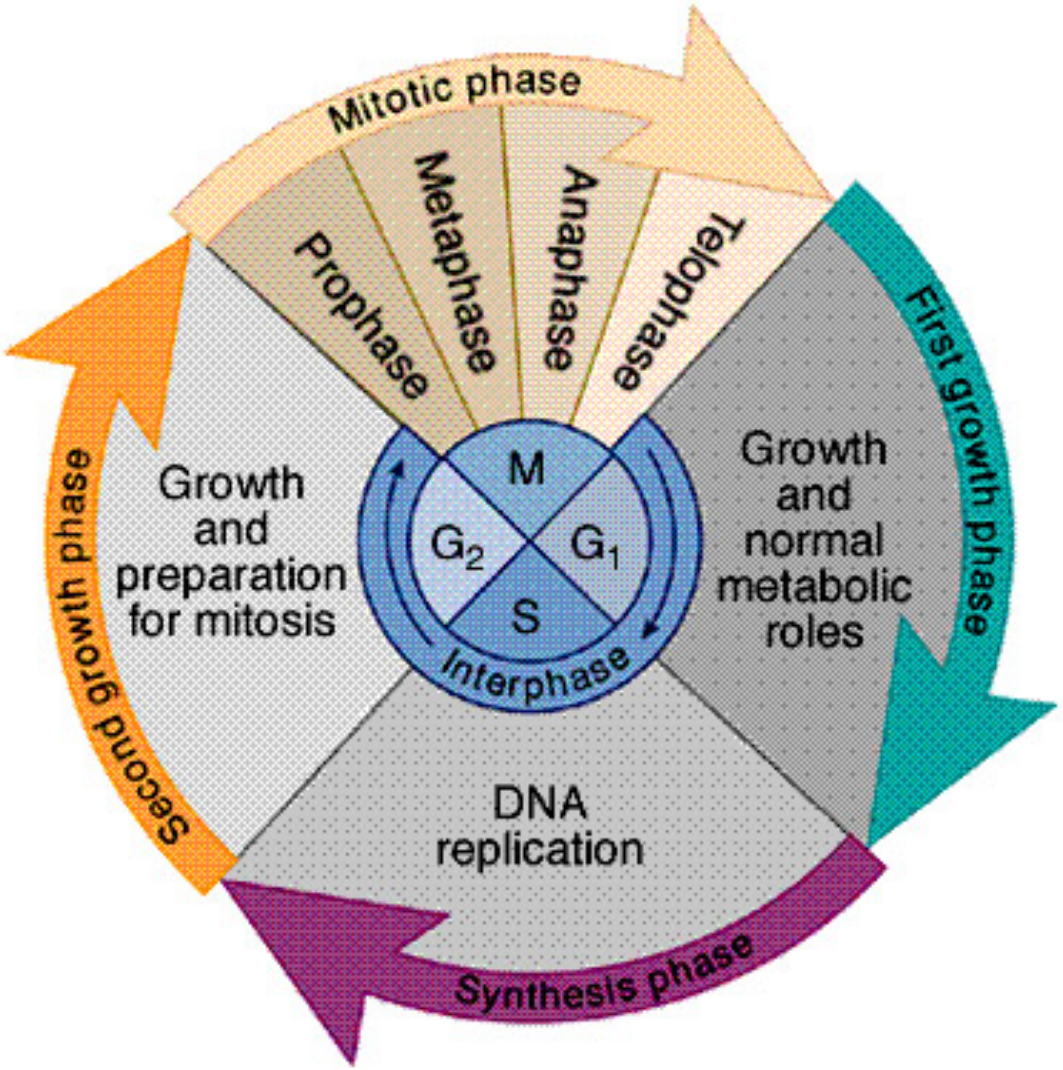

FOXP3+ TREG cells
FOXP3, CD25, GITR, CTLA-4, IL-10, CD39, OX40, galectin-9
nTREG cells
▪ Thymus-derived
▪ Selected by autoantigens
▪ Possess an autoreactive TCR repertoire
▪ Cross-reactive to alloantigens
▪ Suppress autoimmunity
▪ Contact-dependent fashion in suppression
ITREG cells
▪ Generated in the periphery
▪ Derived from T-effector cells
▪ Induction requires TCR, CD28 signaling, and certain cytokines (e.g. TGF-β, IL-2)
▪ Positively and negatively regulated by many other pathways

Las T reguladoras naturales e inducidas pueden tornarse hiporespondedoras y anérgicas a un estímulo antigénico en una GN. Las T reguladoras pueden bloquear a las T efectoras por contacto directo célula-célula, por secretar citokinas antiinflamatorias como el TGF-β y la IL-10, e inhibir la generación de células T de memoria.
The transcription factor FOXP3 es un marcador específico de las Tregs y su deficiencia se asocia a autoinmunidad e inflamación.



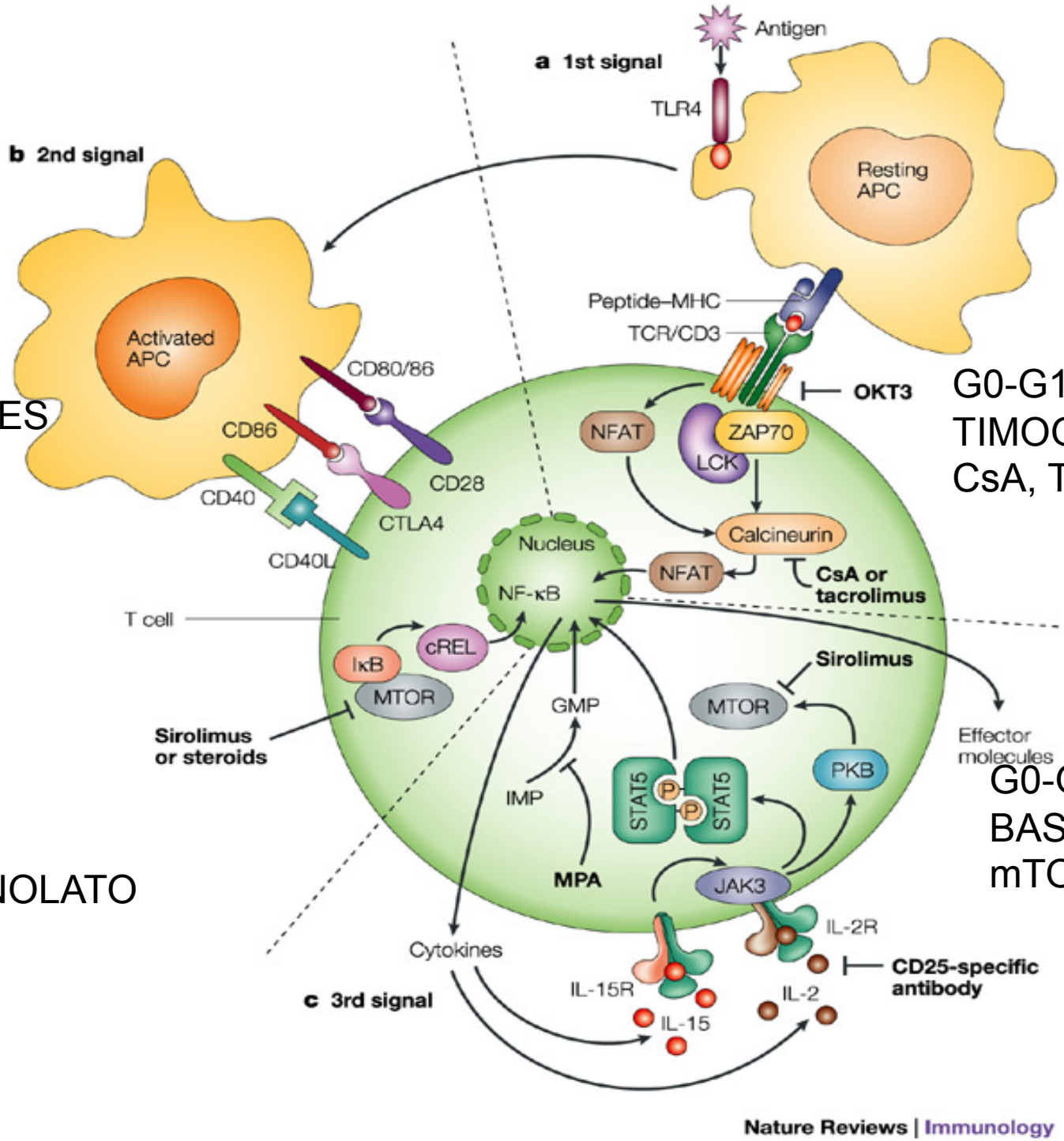
Rol central de las células B en el desarrollo de daño renal autoinmune.




Mitotic phase
Prophase
Metaphase
Anaphase
Telophase
First growth phase
Growth and normal metabolic roles
DNA replication
Synthesis phase
Second growth phase
Growth and preparation for mitosis
M
G2
G1
S
Interphase

G0-G1
mTORi
ESTEROIDES

S
MICOFENOLATO



G0-G1
TIMOGLOBULINA
CsA, Tac

G0-G1
BASILIXIMAB
mTORi

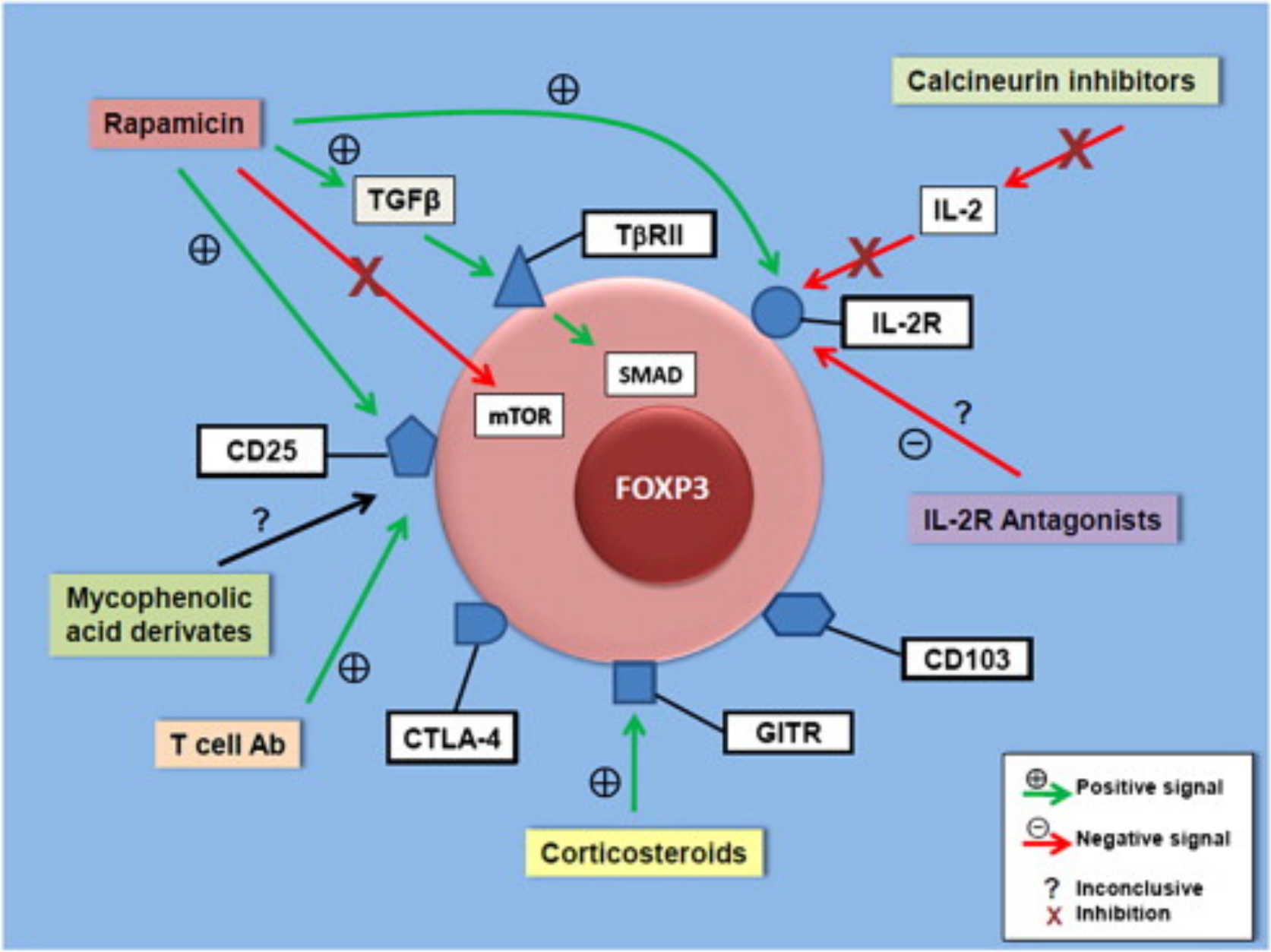
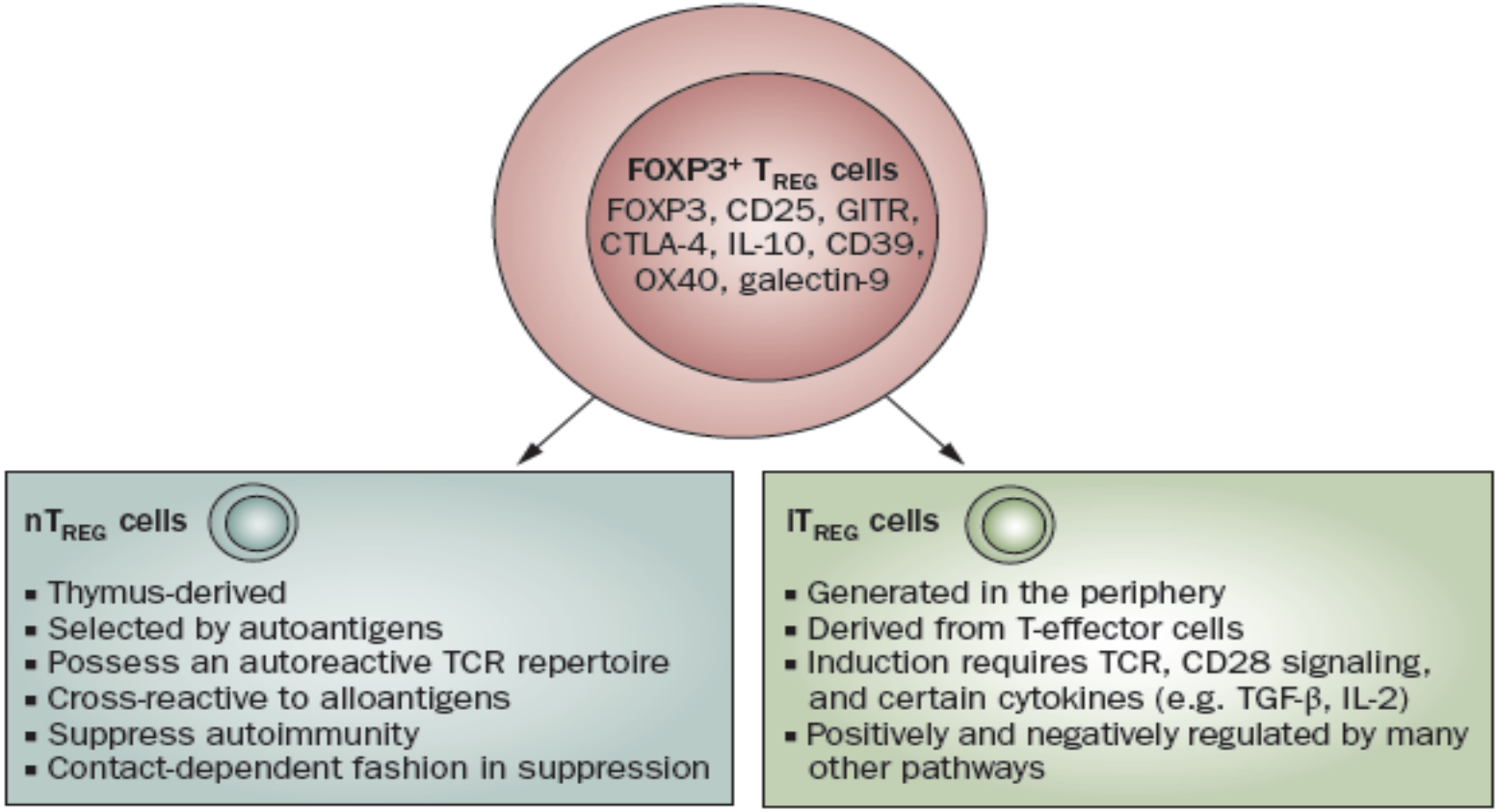

Rapamicin
TGFβ
TβRII
Calcineurin inhibitors
IL-2
IL-2R
SMAD
mTOR
CD25
FOXP3
?
IL-2R Antagonists
Mycophenolic acid derivates
?
T cell Ab
CTLA-4
CD103
GITR
Corticosteroids
Positive signal
Negative signal
? Inconclusive
X Inhibition

Table 1 | **Immunosuppressive agents**

Immunosuppressive drug	Mechanism of immunosuppressive action	Cell target (molecule)	References
Pharmacologicals			
Azathioprine	Dampens the proliferation of rapidly dividing cells	Many purine synthesis pathways (competitive inhibitor)	11,16
Mycophenolate mofetil	Dampens the proliferation of rapidly dividing cells	Guanosine base synthesis (inosine monophosphate dehydrogenase)	13,14
Corticosteroids	Suppresses co-stimulatory signals (IL-1 and IL-6, platelet activating factor, prostaglandins leukotrienes and tumour-necrosis factor), oxygen burst, and chemotactic and cytotoxic activities	APCs (IκB kinase)	15
Cyclosporine, tacrolimus	Blocks promoters of gene transcription, such as NFAT	Lymphoid cells (calcineurin)	31,33,91
Sirolimus, everolimus*	Prevents dissociation of IκB and cytokine-driven G_1 accumulation	Co-stimulatory pathway for the production of cytokines and signal transduction after cytokine signalling (mammalian target of rapamycin, MTOR)	36,92
FTY720*	Reversibly sequesters 85% of circulating lymphocytes in secondary lymphoid structures	Lymphocytes (sphingosine-1-phosphate receptors)	62
Antibodies			
OKT3	Induces selective modulation and inactivation of T cells	T cells (ε chain of CD3 complex)	28
Daclizumab (humanized)/ Basiliximab (chimeric)	Blocks IL-2R	Lymphoid and other cells (IL-2Rα; CD25)	29,30
Rituximab‡	Depletes B cells	CD20	43
Alemtuzumab‡	Produces severe depletion of lymphoid cells	T and B cells, most monocytes, macrophages, eosinophils, NK cells and dendritic cells (CD25)	24
LEA294*	Blocks co-stimulatory signals	APCs (CD80 and CD86)	71

*Pending completion of registration process. ‡Not registered for use in transplantation: off-label use at present. APC, antigen-presenting cell; IκB, inhibitor of nuclear factor-κB, IL, interleukin; NFAT, nuclear factor of activated T cells; R, receptor.



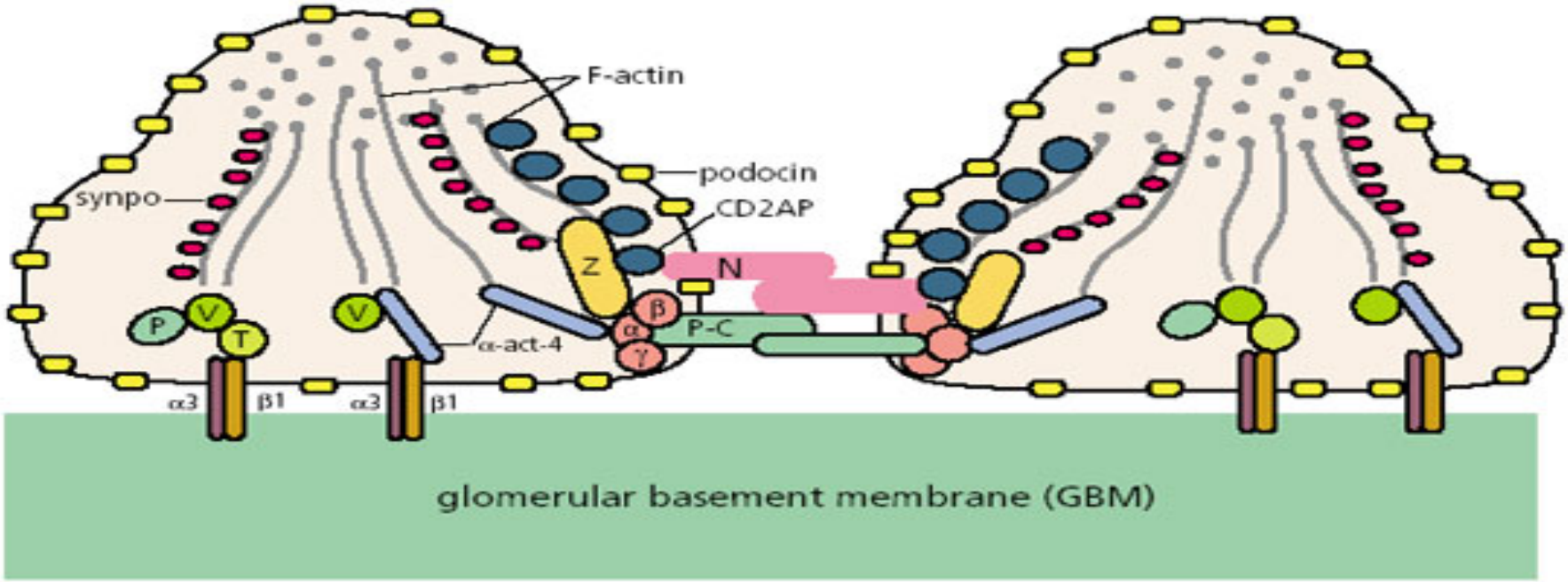
Existen drogas Inmunosupresoras que modulan el número y la función de las células Tregs y la expresión de FOXP3: mTORi actúan positivamente sobre estas células y los CNI negativamente.
Timoglobulina?

Los IECASs y los ARA II producen cambios reversibles en la estructura y función de la pared capilar glomerular y de las células mesangiales y de la matriz, al inhibir la acción de la angiotensina II:

Reordenan y estabilizan las hendiduras diafragmáticas, al polimerizar la actina en el citoesqueleto de los podocitos

Reducen la síntesis del TGF-β, colágenos I y III

Reducen la hipertrofia celular inducida por la angiotensina II

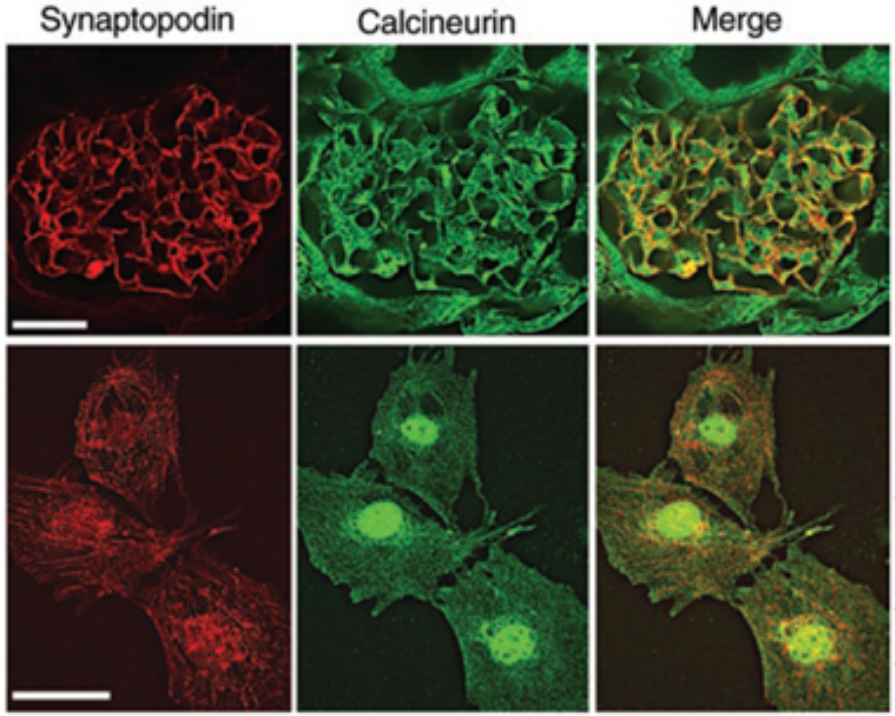


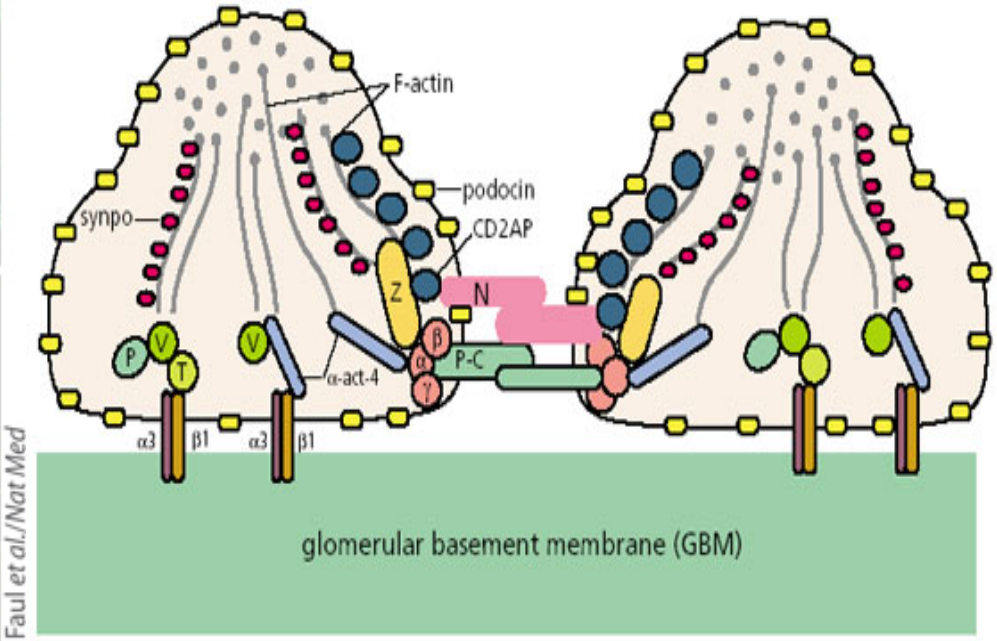
CICLOSPORINA

La CsA bloquea la defosforilación de la sinaptopodina, una proteína organizadora de la actina del podocito. Este bloqueo inhibe la proteólisis de la sinaptopodina, estabilizando las hendiduras diafragmáticas y la contracción-relajación normal del podocito.

Este efecto es independiente de la acción sobre las células B y T.

Interesante: La expresión de calcineurinas en el podocito resulta en la degradación de la sinaptopodina y el desarrollo de proteinuria.





Rol del TRPC6 Transient receptor potential cation channel 6 (trPC6)

Sobreexpresada en familias con FsGs autosómica-dominante.
Estos canales regulan la entrada de calcio intracelular.

En los podocitos, el trPC6 se localiza en la hendidura del diafragma, y participa en la señalización.

Su sobreexpresión resulta en proteinuria. Es blanco del Tacrolimus

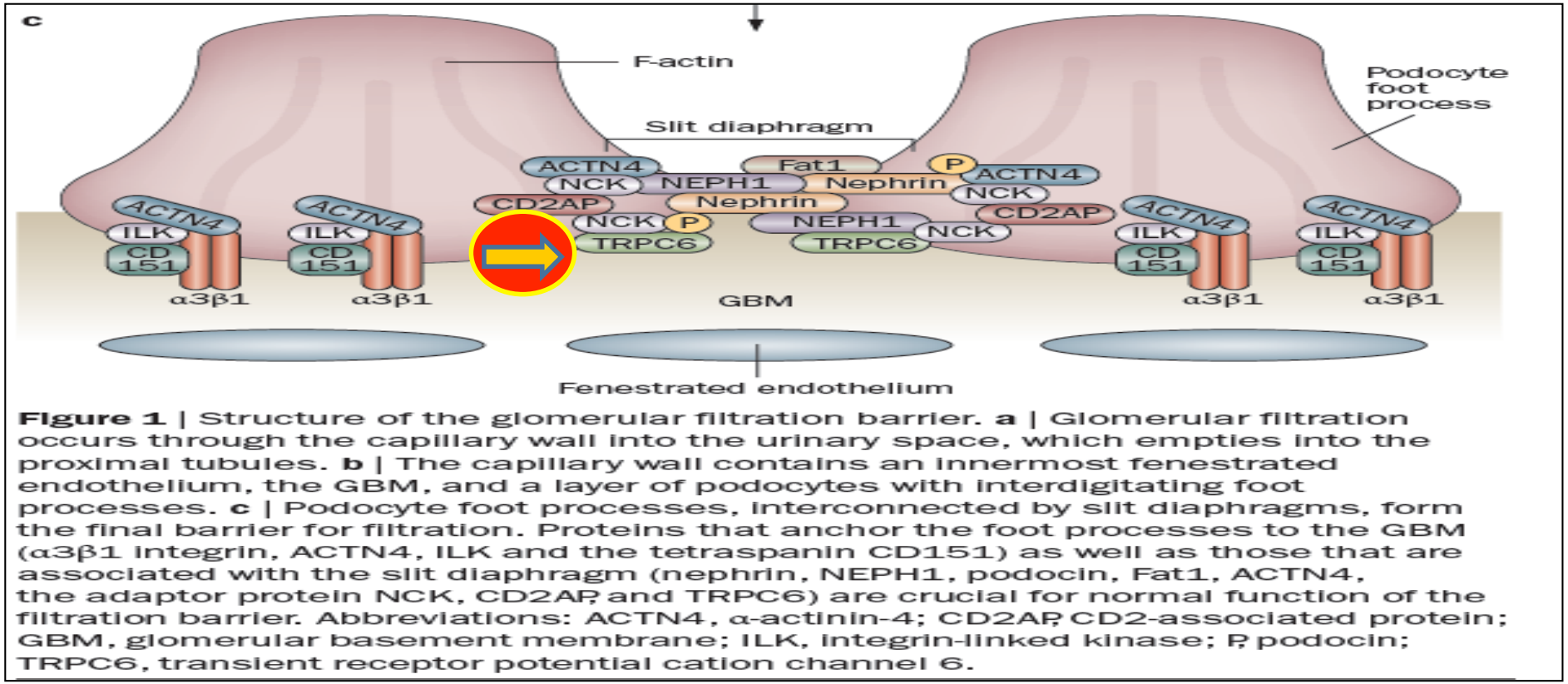
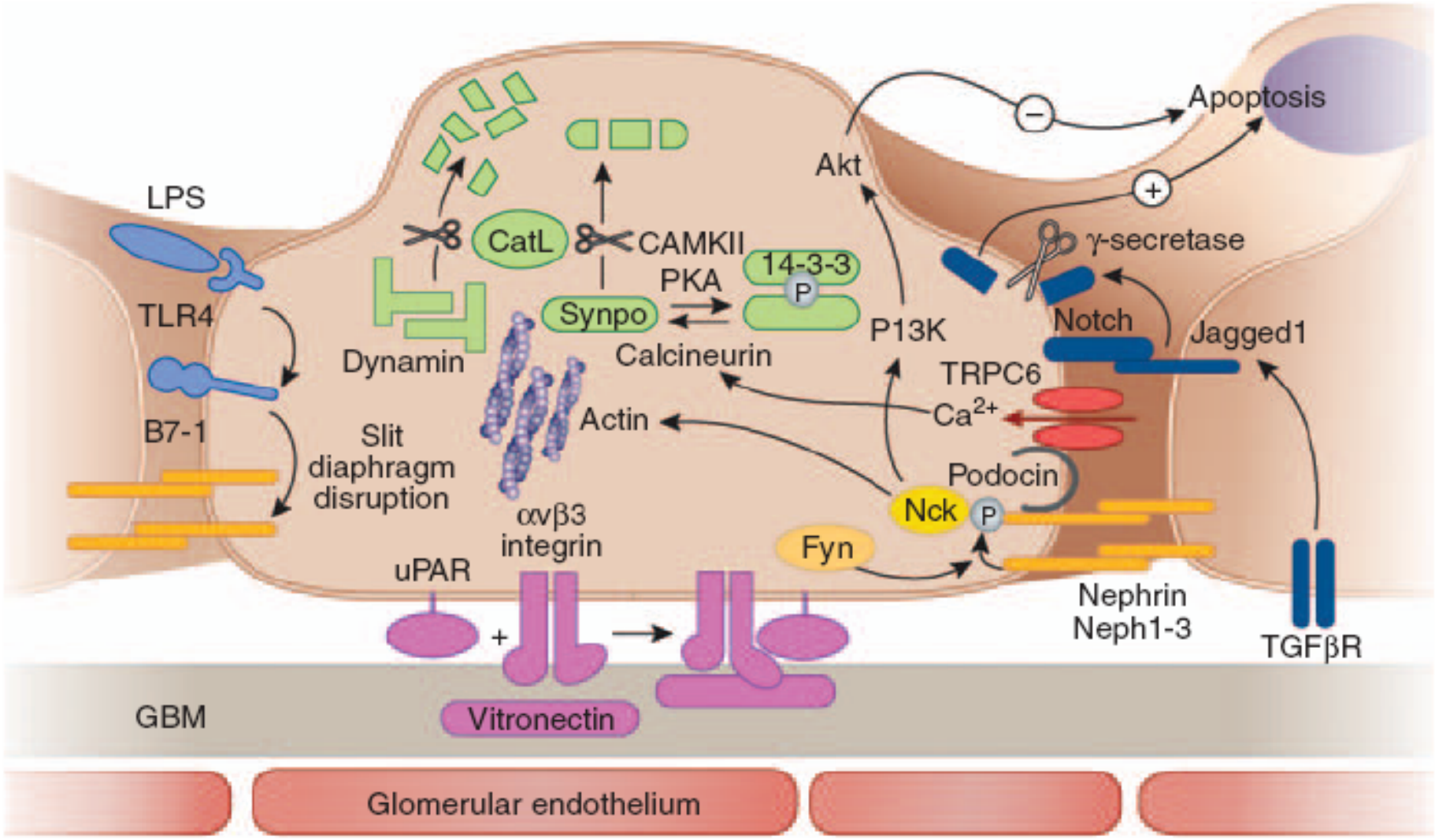


Figure 1 | Structure of the glomerular filtration barrier. **a** | Glomerular filtration occurs through the capillary wall into the urinary space, which empties into the proximal tubules. **b** | The capillary wall contains an innermost fenestrated endothelium, the GBM, and a layer of podocytes with interdigitating foot processes. **c** | Podocyte foot processes, interconnected by slit diaphragms, form the final barrier for filtration. Proteins that anchor the foot processes to the GBM (α3β1 integrin, ACTN4, ILK and the tetraspanin CD151) as well as those that are associated with the slit diaphragm (nephrin, NEPH1, podocin, Fat1, ACTN4, the adaptor protein NCK, CD2AP, and TRPC6) are crucial for normal function of the filtration barrier. Abbreviations: ACTN4, α-actinin-4; CD2AP, CD2-associated protein; GBM, glomerular basement membrane; ILK, integrin-linked kinase; P, podocin; TRPC6, transient receptor potential cation channel 6.

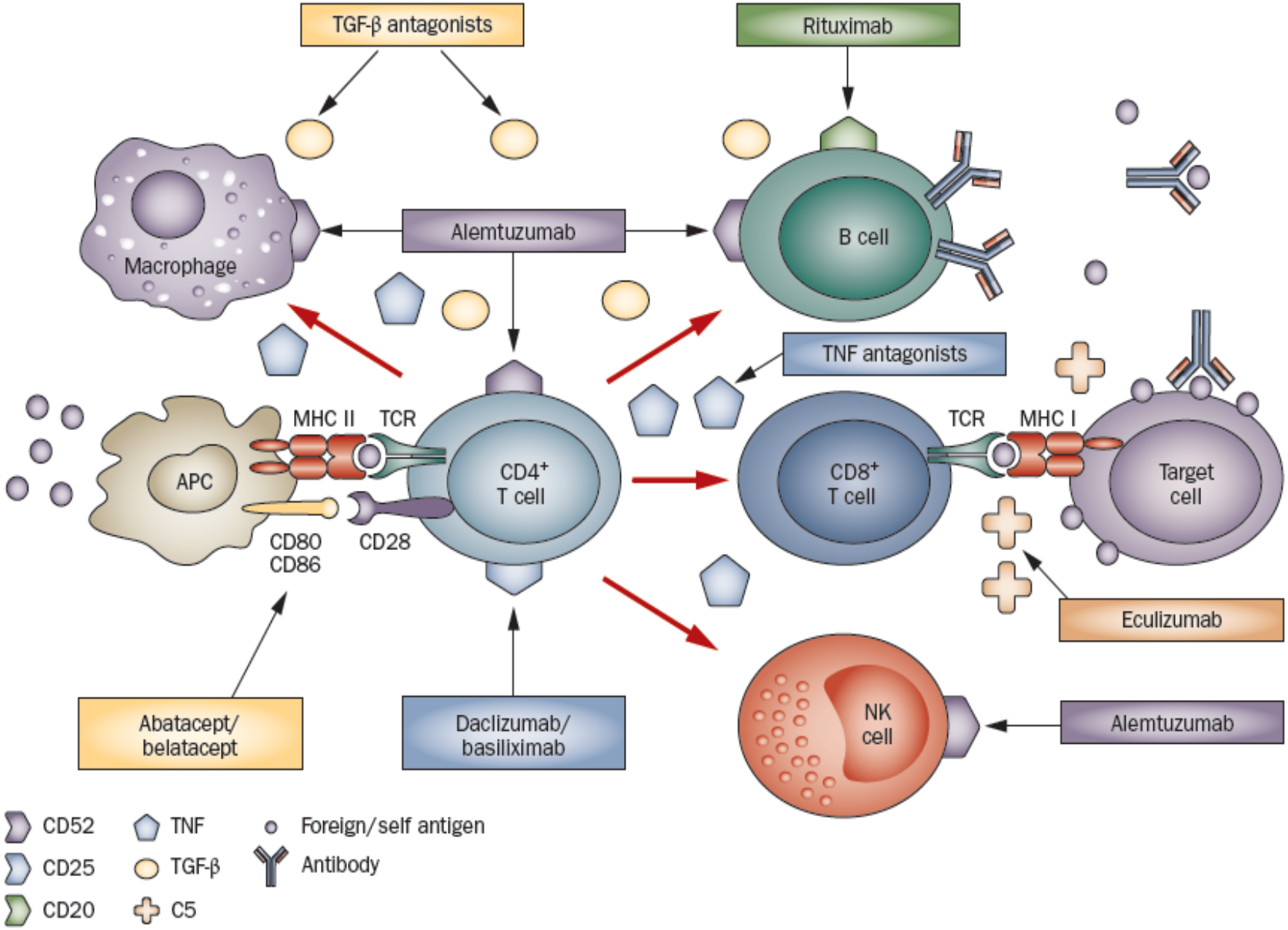

LPS
TLR4
B7-1
Slit
diaphragm
disruption
CatL
Dynamin
CAMKII
PKA
14-3-3
P
Synpo
Calcineurin
Actin
αvβ3
integrin
uPAR
Vitronectin
GBM
Akt
P13K
Apoptosis
γ-secretase
Notch
Jagged1
TRPC6
Ca2+
Podocin
Nck
P
Fyn
Nephrin
Neph1-3
TGFβR
Glomerular endothelium

RITUXIMAB
ECULIZUMAB
PLASMAFÉRESIS

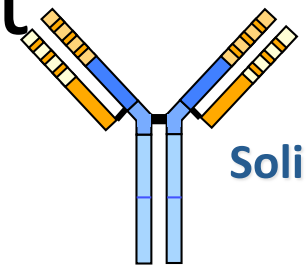
Table 1 | Naming system for monoclonal antibodies developed by the International Nonproprietary Names program

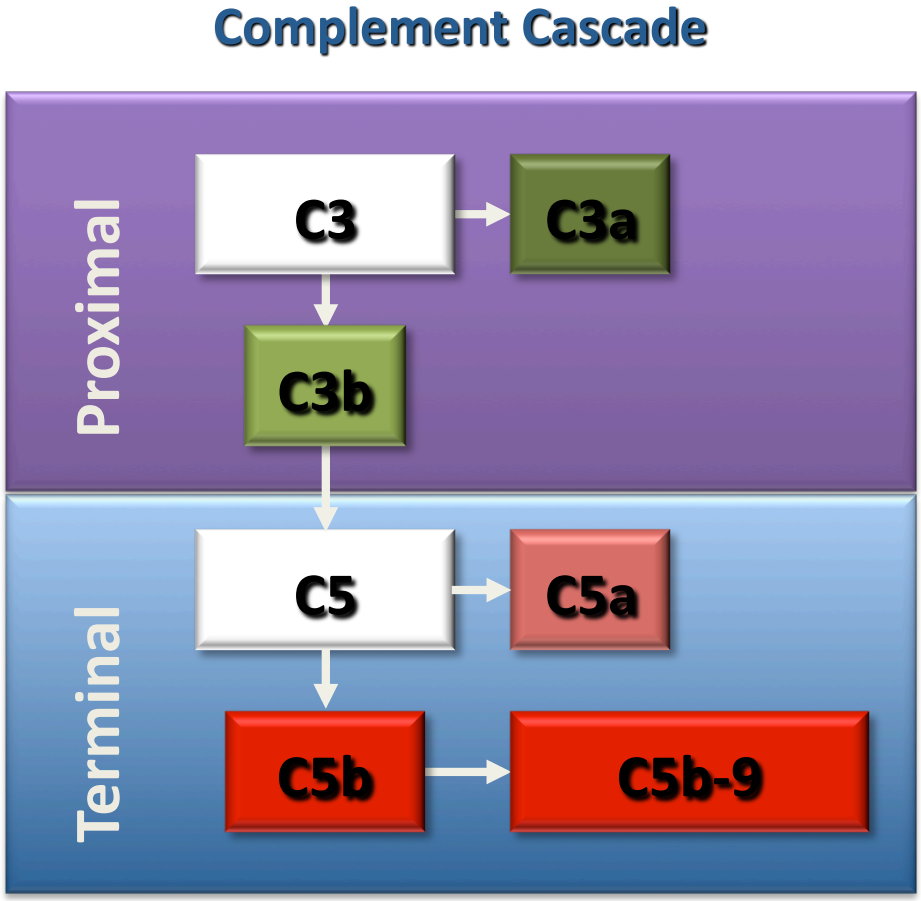
Prefix	First infix[a] = target	Second infix = source of the product	Suffix = class
Varies	-ki(n)- = interleukin	-o- = mouse	-mab = monoclonal antibody
	-li(m)- = lymphocyte, immunomodulator	-axo- = mouse–rat hybrid	
	-tu- = tumor (miscellaneous)	-xi- = chimeras	
		-zu- = humanized	
		-u- = human	

[a]Final letter of the first infix can be deleted when pronunciation is difficult. Each monoclonal antibody name consists of a unique prefix, a first infix related to the molecular target, a second infix that describes the source species of the product, and the suffix '-mab'. Names of other biologic therapies include the suffixes -atacept (CTLA-4 antagonist) and -nercept (tumor necrosis factor antagonist).[40]


TGF-β antagonists
Rituximab
Macrophage
Alemtuzumab
B cell
TNF antagonists
MHC II
TCR
APC
CD4+
T cell
CD8+
T cell
TCR
MHC I
Target
cell
CD80
CD86
CD28
Eculizumab
Abatacept/
belatacept
Daclizumab/
basiliximab
NK
cell
Alemtuzumab
CD52
CD25
CD20
TNF
TGF-β
C5
Foreign/self antigen
Antibody

ECULIZUMAB Blocks Terminal Complement





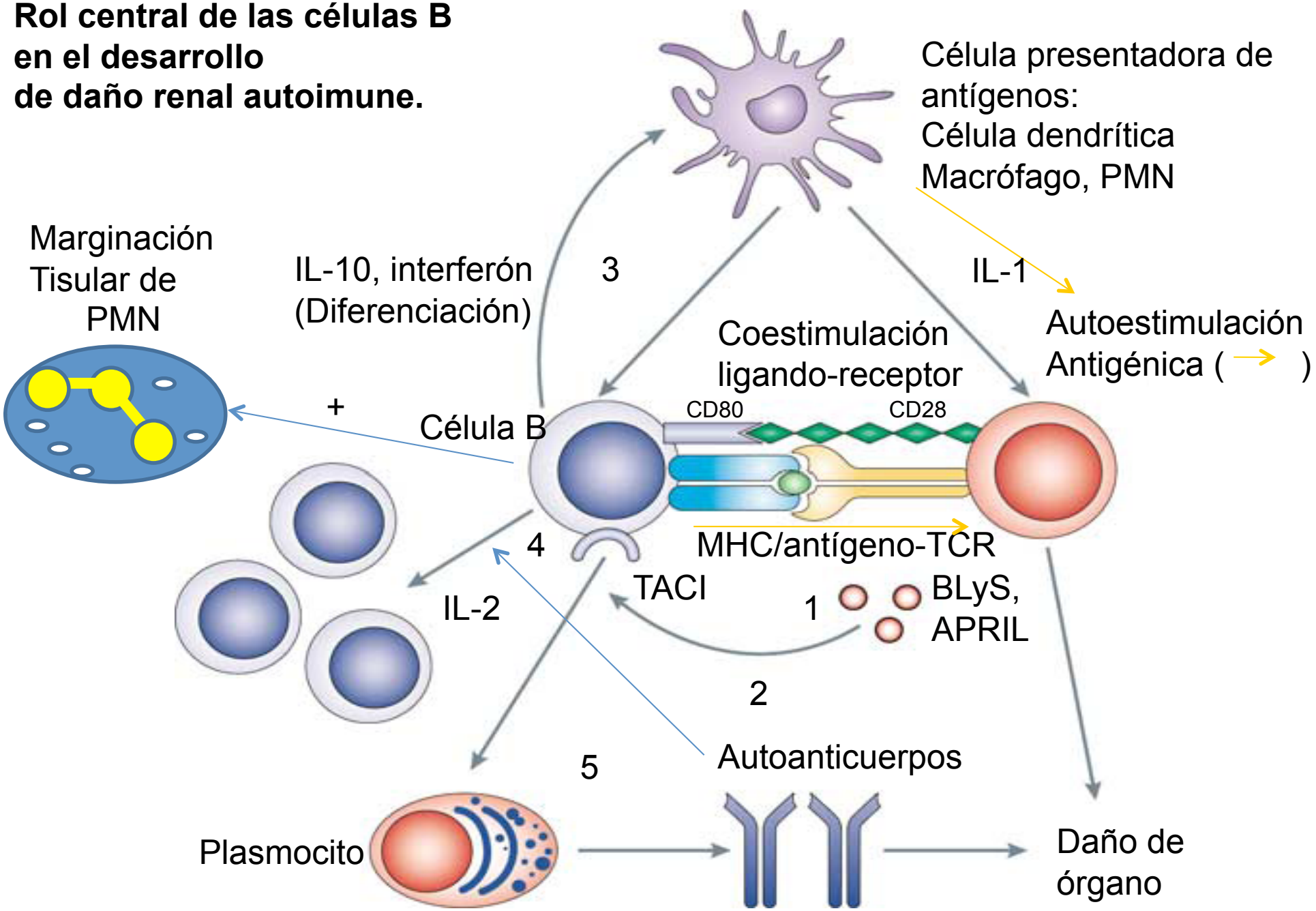
- Soliris binds with high affinity to C5
- Terminal complement - C5a and C5b-9 activity blocked
- Proximal functions of complement remain intact
  - Weak anaphylatoxin
  - Immune complex clearance
  - Microbial opsonization

Figueroa JE, Densen P. *Clin Microbiol Rev*. 1991;4(3):359-395. Walport MJ. *N Engl J Med*. 2001;344(14):1058-66. Soliris® (eculizumab) [package insert]. Alexion Pharmaceuticals; 2011. Rother RP et al. *Nature Biotech*. 2007;25(11):1256-64.

Table 2 | **Complement deficiencies and complement-mediated diseases**

Disease	Major defects	Causes	Genes affected
Atypical haemolytic uraemic syndrome (aHUS) and possibly some cases of thrombotic thrombocytopenic purpura (TTP)	Defective C3 convertase, stabilization of the convertase, defective regulation, and increased stability and turnover	Mostly heterozygous mutations, genetic defects and autoantibodies	Deficiency of CFHR1, CFHR3, factor B, factor H and factor I
Membranoproliferative glomerulonephritis, type II (MPGN II; also known as dense-deposit disease)	Defective C3 convertase	Mostly homozygous mutations, genetic defects, autoantibodies and C3 nephritic factor	Factor H and C3
Systemic lupus erythematosus (SLE)	Defective clearance of apoptotic cells and bodies	Hereditary homozygous deficiency and genetic defects	C1q, C1r, C1s, C2, C3 and C4
Pyogenic infections	Inappropriate complement attack	Infections with *Neisseria meningitidis* and *Streptococcus pneumoniae*	C3, factor H, factor I, properdin and TCC
	Deficiency of properdin	Infections with *Neisseria* spp.	Gene mutation
	Deficiency of factor I	Infections with *N. meningitidis* and *S. pneumoniae* and other respiratory tract infection	Gene mutation
	Deficiency of factor H	Infection with *N. meningitidis*	Gene mutation affecting protein secretion
Haemolysis and thrombosis	Erythrocyte lysis and thrombus formation	Unknown	CD59, factor H and deficiency of CFHR1 and CFHR3
Partial lipid dystrophy	Loss of adipose tissue	C3 nephritic factor	Unknown
Hereditary angioedema	Recurrent spontaneous non-allergic oedema of the subcutaneous tissues and mucous membranes	Mostly heterozygous mutations	C1 inhibitor
Paroxysmal nocturnal haemoglobinuria (PNH)	Failure of CD55 and CD59 expression	Genetic deficiency of PIG-A, and failure to form GPI anchor	PIGA
Age-related macular degeneration (AMD)	Drusen formation and chronic inflammation	Unknown	Factor H, C3, C2, deficiency of CFHR1 and/or CFHR3, factor B and factor I
Tumour cells	Overexpression of membrane and secreted regulators, and enhanced binding of soluble regulators	Unknown	Unknown

Rol central de las células B en el desarrollo de daño renal autoimune.



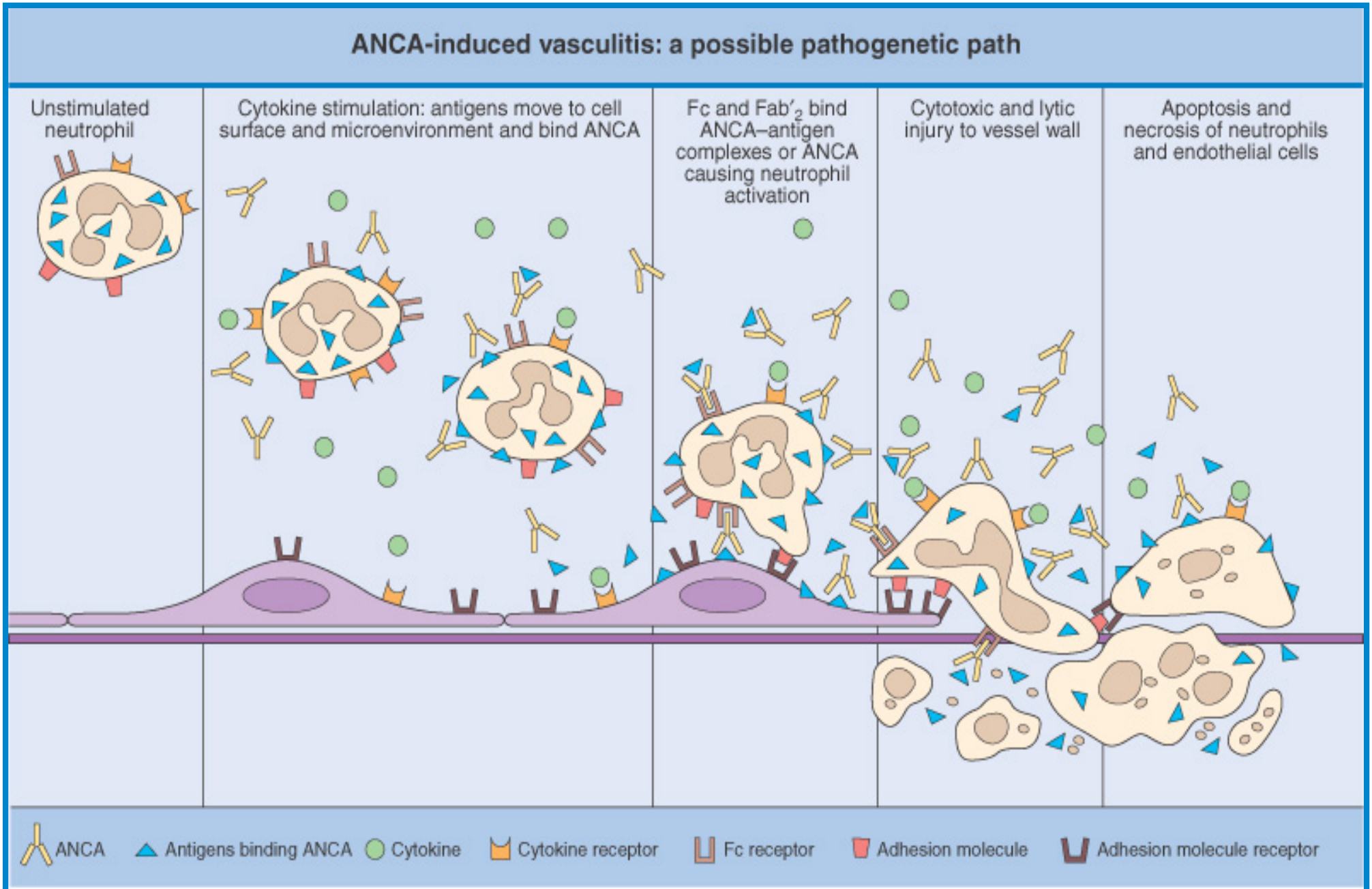
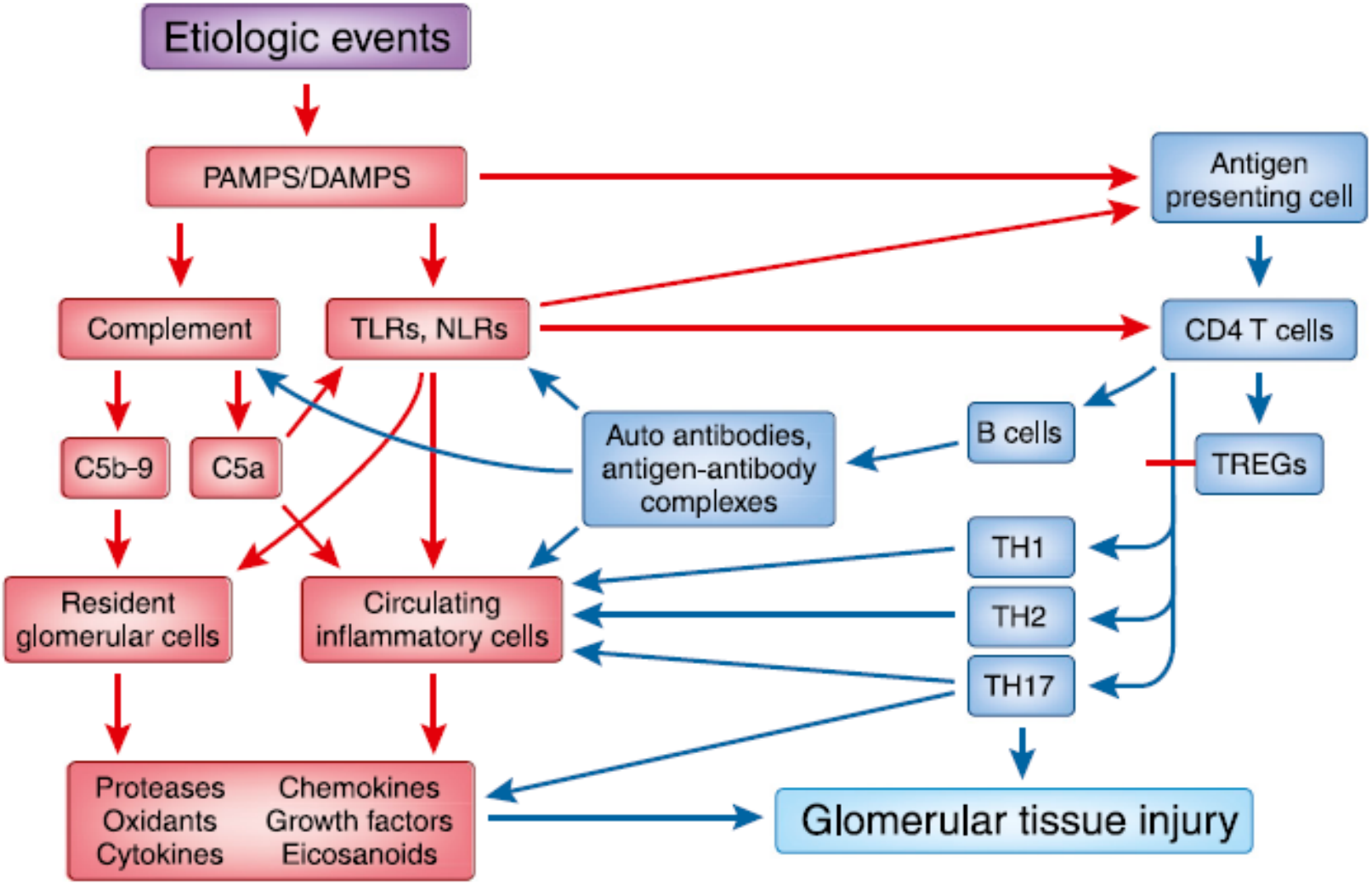


Figure 23.4 Vasculitis induced by antineutrophil cytoplasmic antibodies (ANCA): a hypothetical sequence of pathogenetic events.

(Adapted with permission from Jennette JC, Falk RJ: Pathogenesis of the vascular and glomerular damage in ANCA-positive vasculitis. Nephrol Dial Transplant 1998;13[Suppl 1]:16–20.)


Etiologic events
PAMPS/DAMPS
Antigen presenting cell
Complement
TLRs, NLRs
CD4 T cells
C5b-9
C5a
Auto antibodies, antigen-antibody complexes
B cells
TREGs
TH1
TH2
TH17
Resident glomerular cells
Circulating inflammatory cells
Proteases
Oxidants
Cytokines
Chemokines
Growth factors
Eicosanoids
Glomerular tissue injury

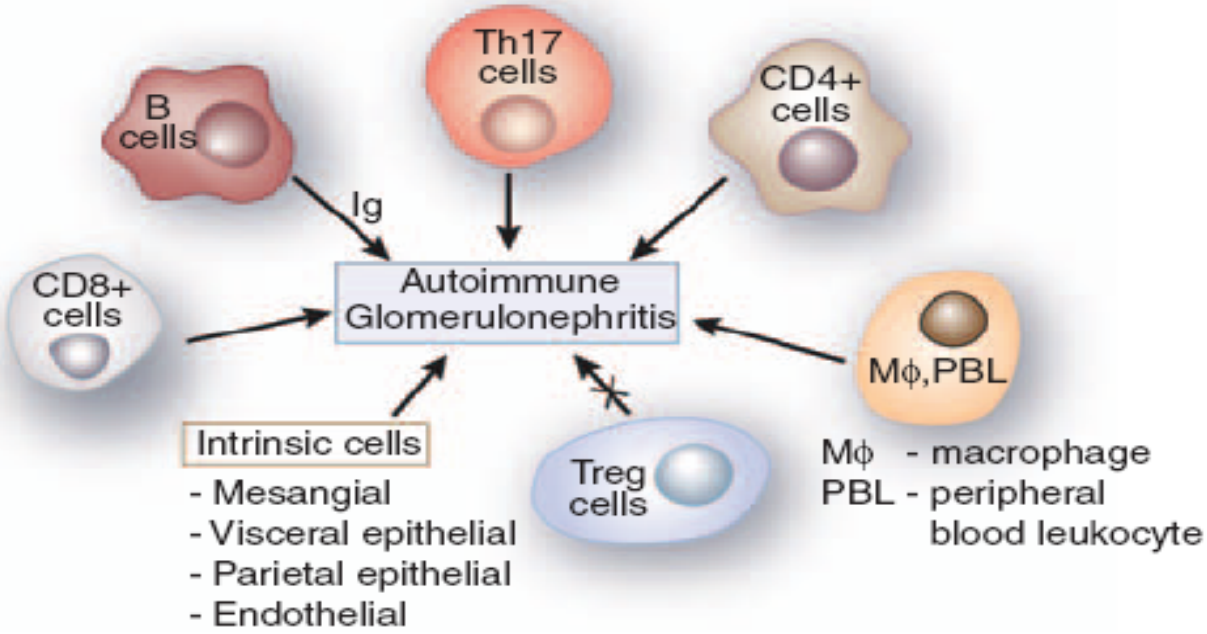
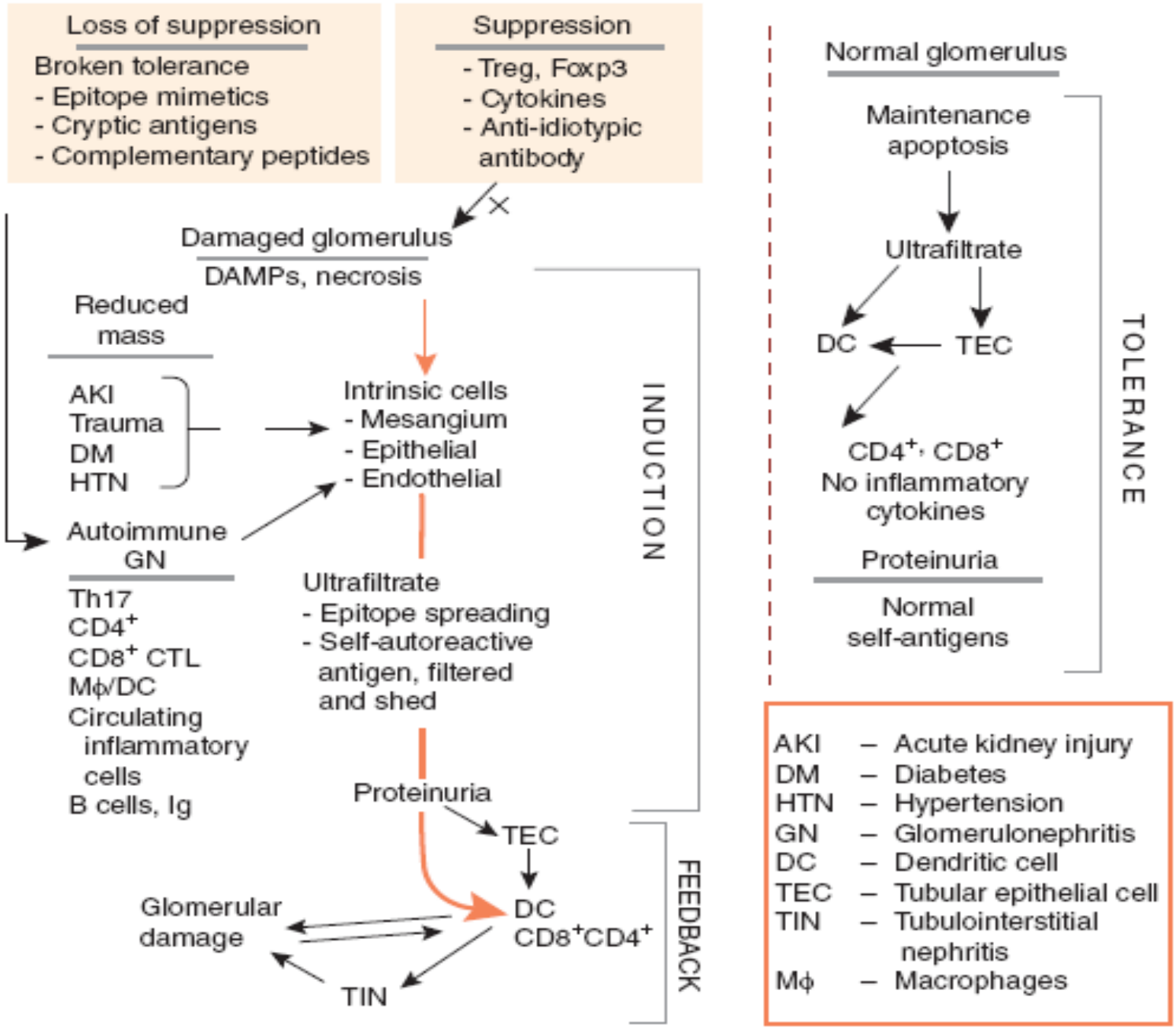
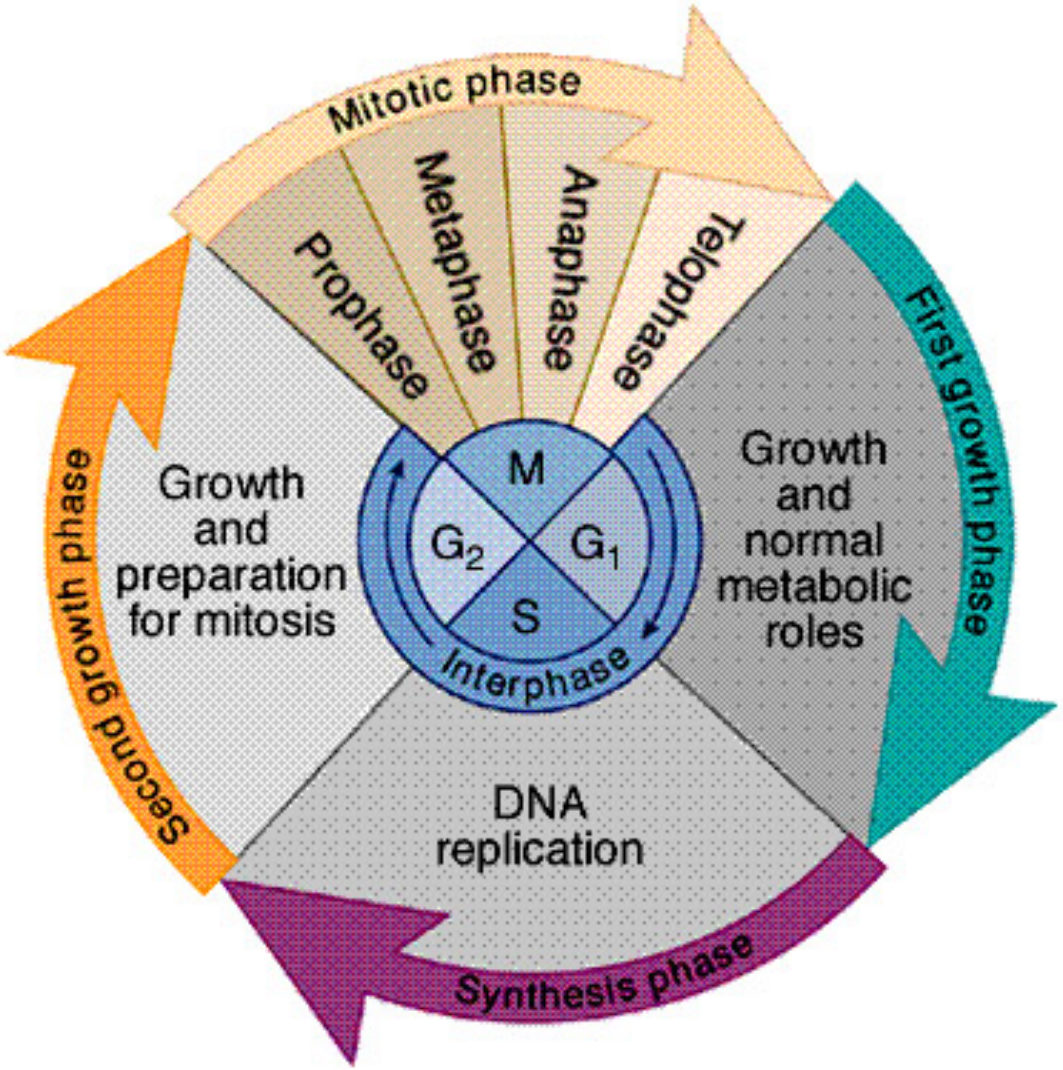


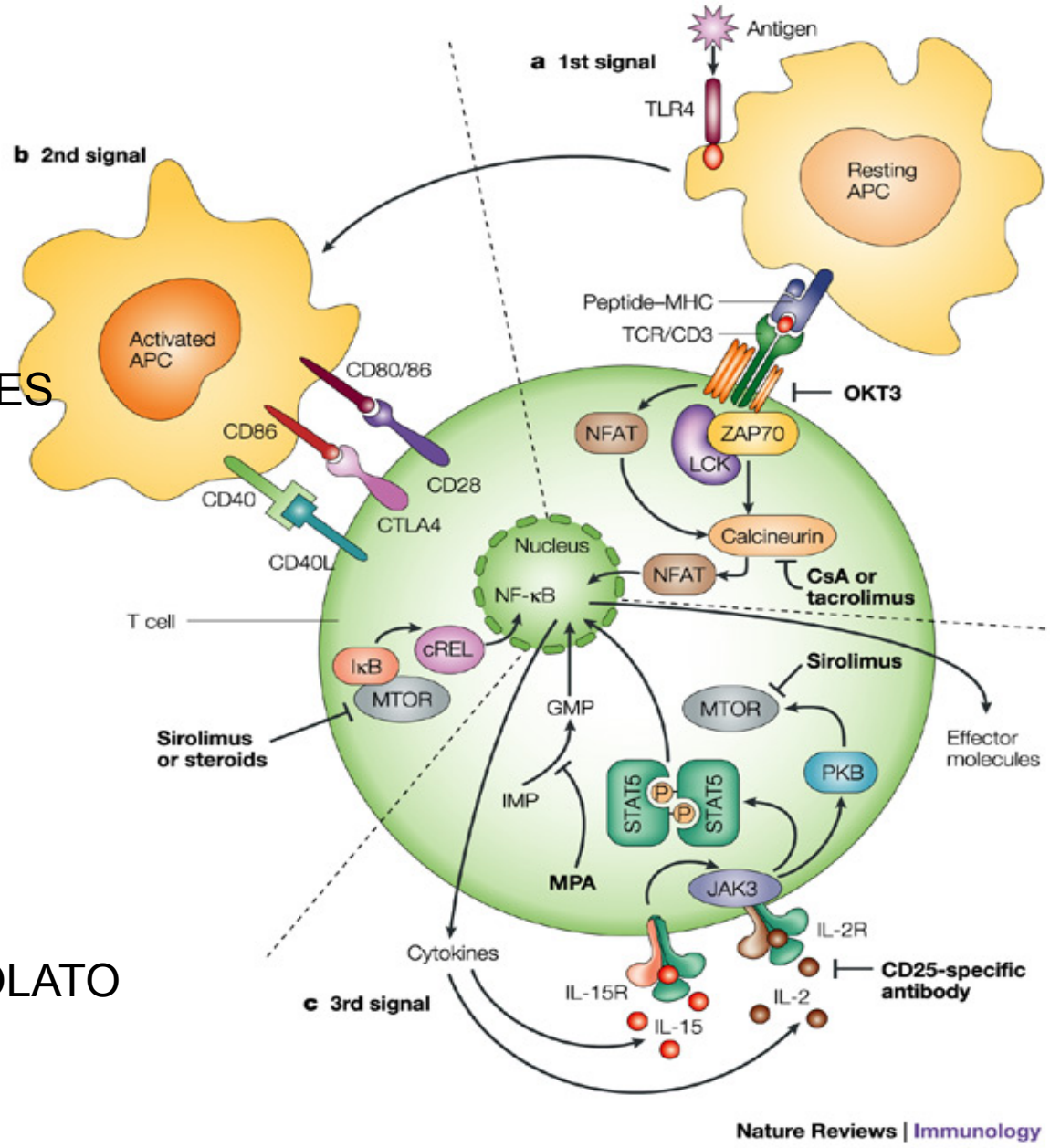
Figure 1 | Cells in GN. Figure 1 represents an aggregate of data derived from animal models. B cells were classically considered to be involved in the pathogenesis of GN by elaboration of immunoglobulin (Ig). Th-17, $CD4^+$, and $CD8^+$ cells have a significant role as shown by abrogation of activity leading to amelioration of GN. Macrophages and peripheral blood leukocyte (PBL) are essential in the histological changes of GN. All result in a variable increase in the mesangial matrix, and involvement of the visceral and parietal epithelial cells. T regulatory cells downregulate disease. Experimental autoimmune glomerulonephritis presumably arises secondary to various etiologies, including broken tolerance, a decrease in suppressor/regulatory cells, epitope mimetics, exposure of cryptic antigens, and possibly autoimmunity to complementary peptides.


Loss of suppression
Broken tolerance
- Epitope mimetics
- Cryptic antigens
- Complementary peptides
Suppression
- Treg, Foxp3
- Cytokines
- Anti-idiotypic antibody
Damaged glomerulus
DAMPs, necrosis
Reduced mass
AKI
Trauma
DM
HTN
Intrinsic cells
- Mesangium
- Epithelial
- Endothelial
Autoimmune GN
Th17
CD4+
CD8+ CTL
Mϕ/DC
Circulating inflammatory cells
B cells, Ig
Ultrafiltrate
- Epitope spreading
- Self-autoreactive antigen, filtered and shed
Proteinuria
TEC
DC
CD8+CD4+
Glomerular damage
TIN
INDUCTION
FEEDBACK
Normal glomerulus
Maintenance apoptosis
Ultrafiltrate
DC
TEC
CD4+, CD8+
No inflammatory cytokines
Proteinuria
Normal self-antigens
TOLERANCE
AKI – Acute kidney injury
DM – Diabetes
HTN – Hypertension
GN – Glomerulonephritis
DC – Dendritic cell
TEC – Tubular epithelial cell
TIN – Tubulointerstitial nephritis
Mϕ – Macrophages


Mitotic phase
Prophase
Metaphase
Anaphase
Telophase
First growth phase
Growth and normal metabolic roles
DNA replication
Synthesis phase
Second growth phase
Growth and preparation for mitosis
M
G2
G1
S
Interphase

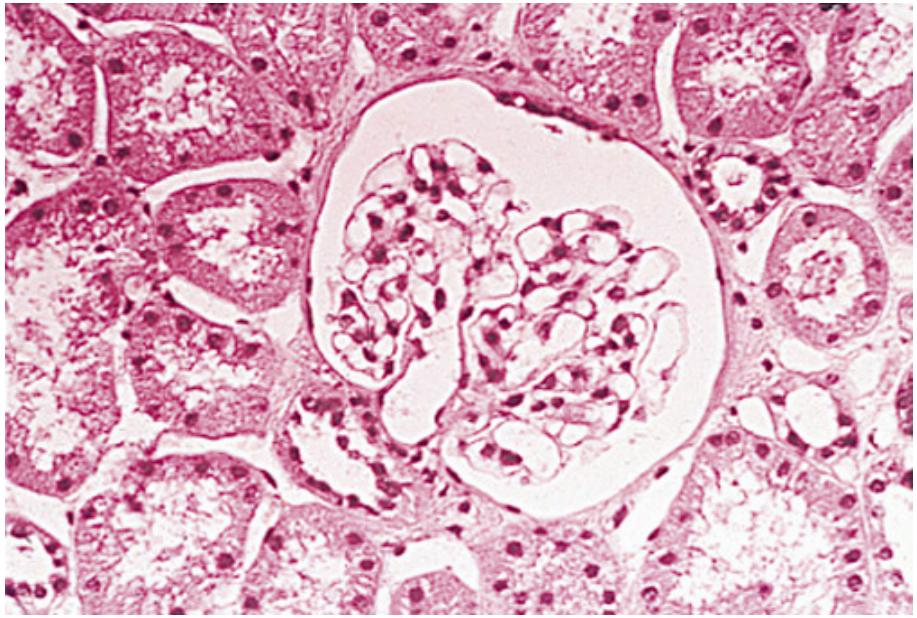
G0-G1
mTORi
ESTEROIDES

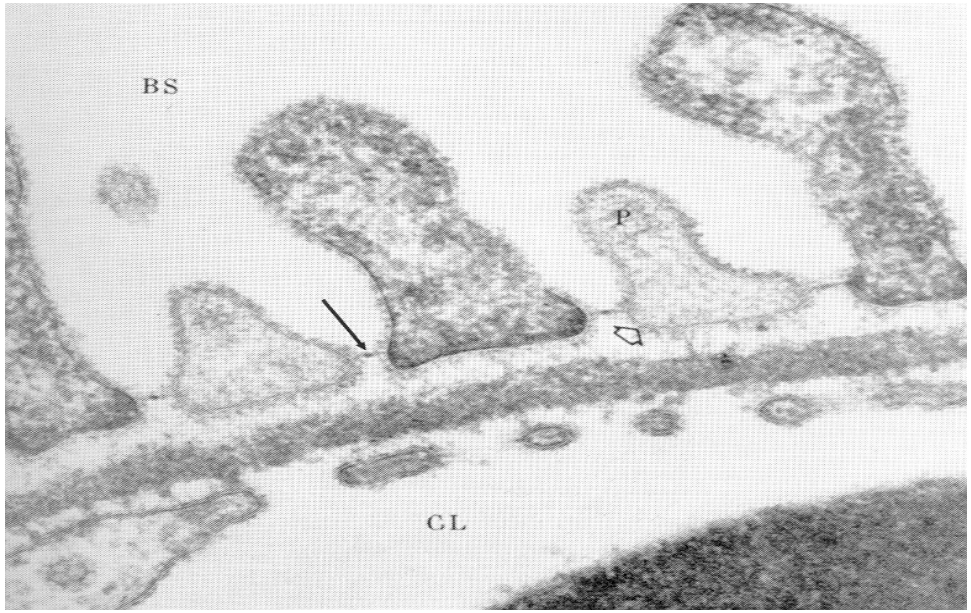
S
MICOFENOLATO

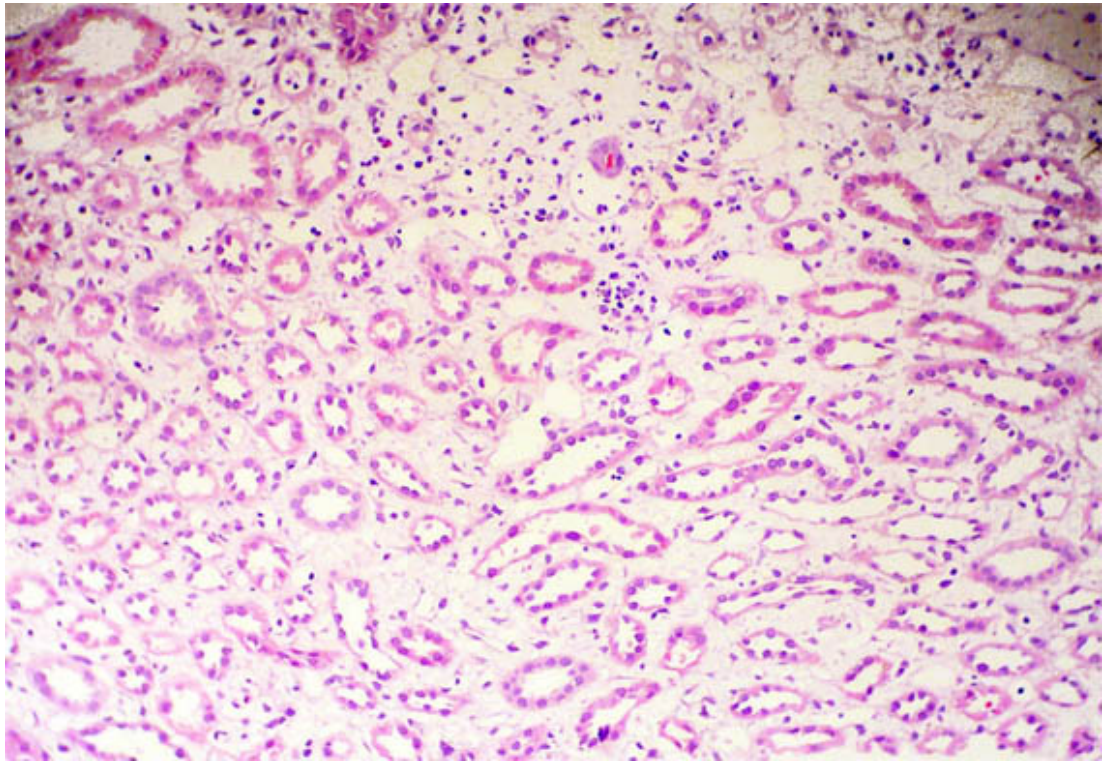


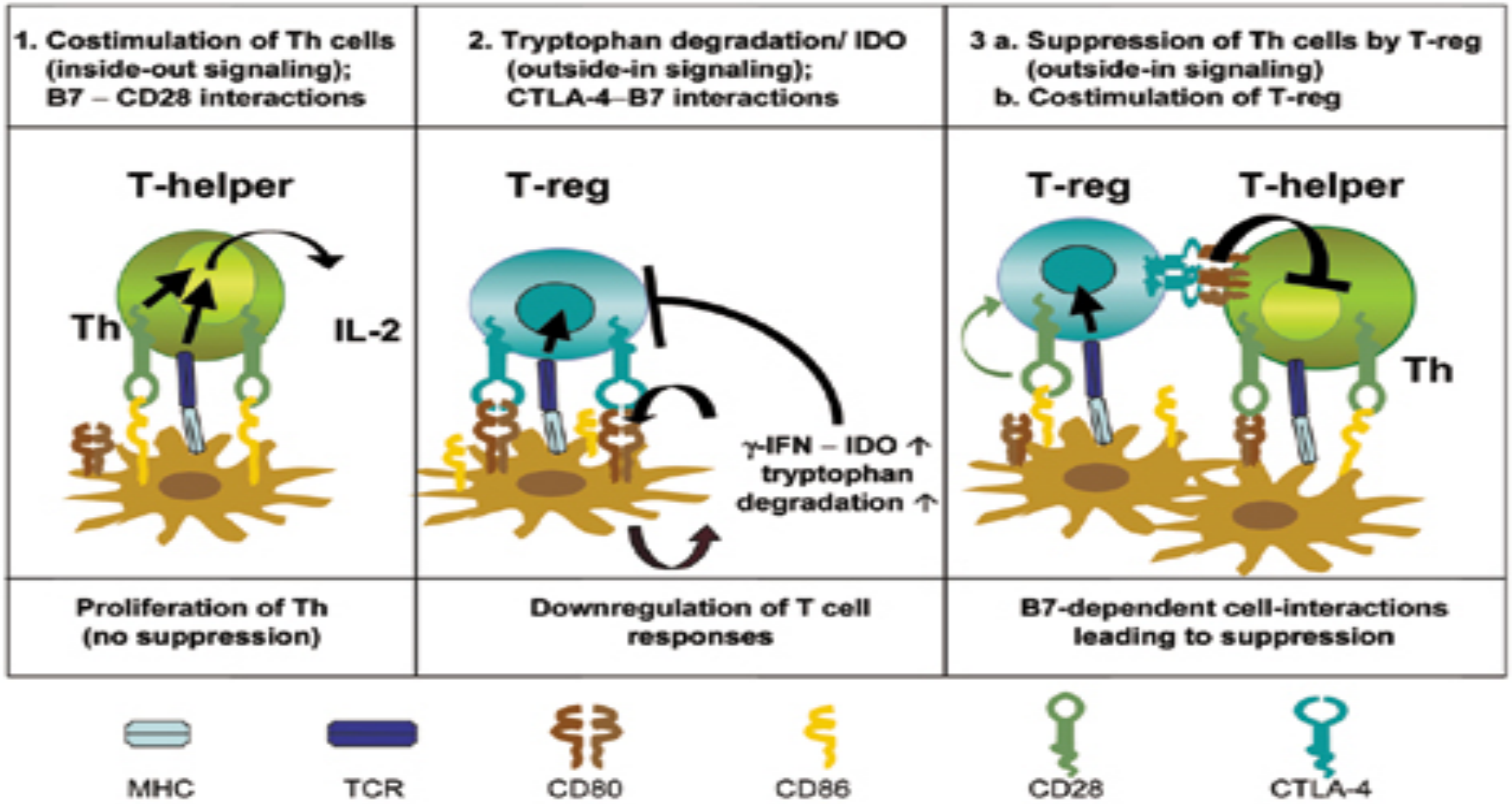
G0-G1
TIMOGLOBULINA
CsA, Tac

G0-G1
BASILIXIMAB
mTORi




BS
P
CL




1. Costimulation of Th cells (inside-out signaling); B7 – CD28 interactions
2. Tryptophan degradation/ IDO (outside-in signaling); CTLA-4–B7 interactions
3 a. Suppression of Th cells by T-reg (outside-in signaling)
b. Costimulation of T-reg
T-helper
Th
IL-2
T-reg
γ-IFN – IDO ↑
tryptophan degradation ↑
T-reg
T-helper
Th
Proliferation of Th (no suppression)
Downregulation of T cell responses
B7-dependent cell-interactions leading to suppression
MHC
TCR
CD80
CD86
CD28
CTLA-4