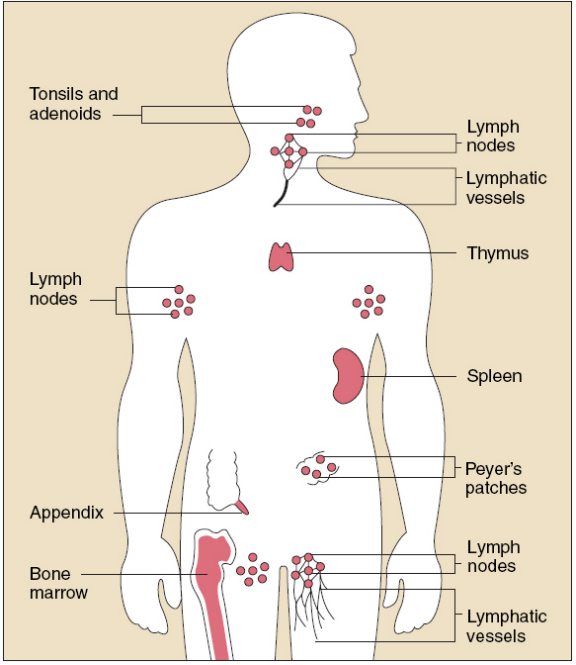
MECANISMOS DE ACCIÓN DE LA DROGAS INMUNOSUPRESORAS EMPLEADAS EN LAS GLOMERULOPATÍAS Y EN EL TRANSPLANTE

HERNÁN TRIMARCHI

2014



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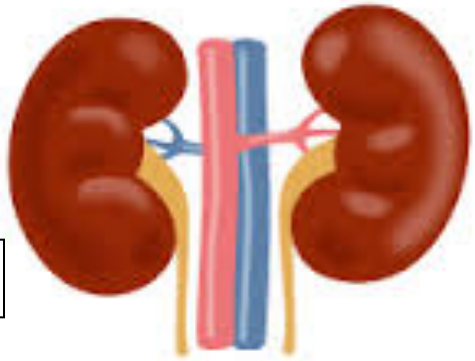
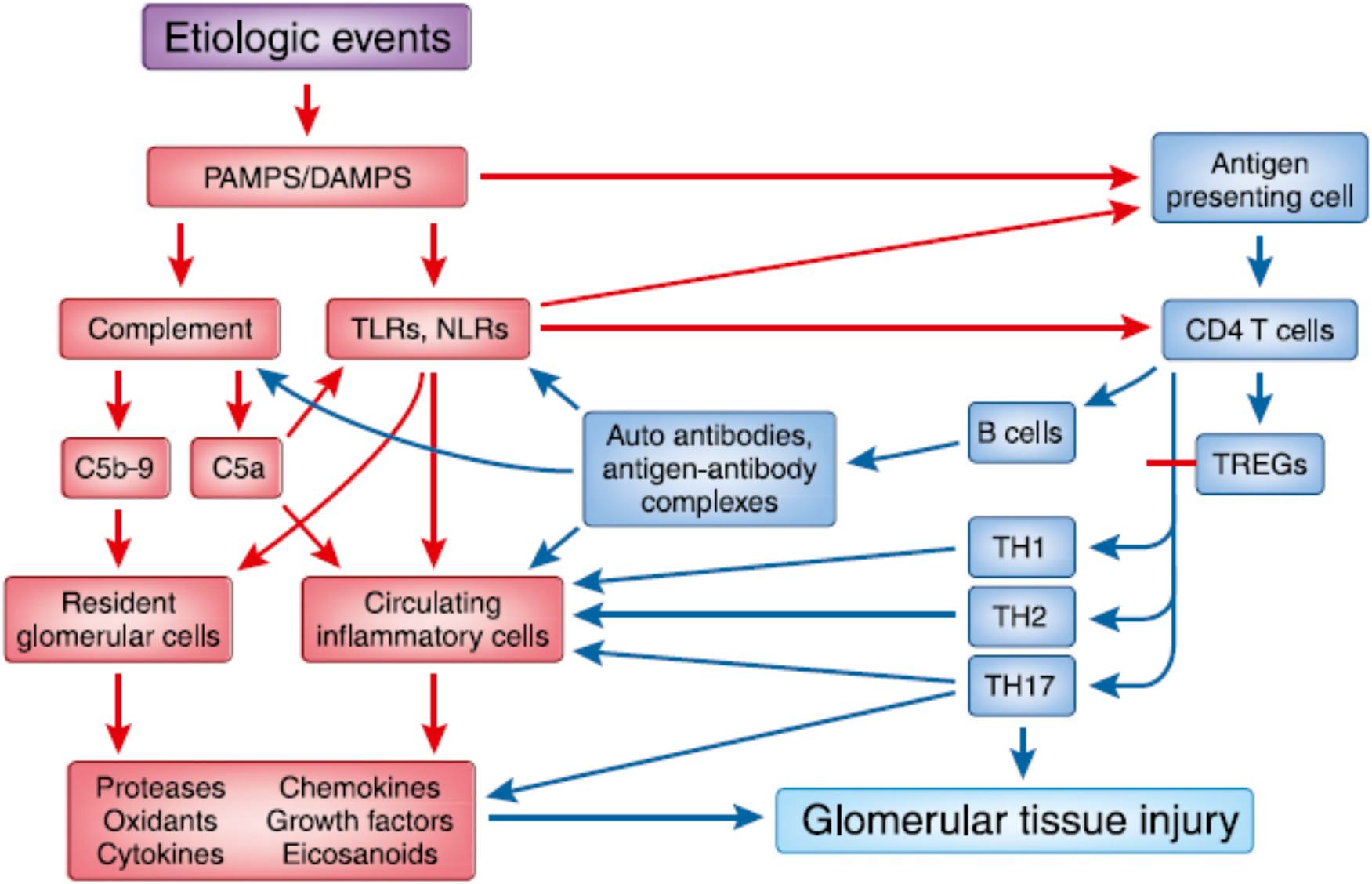
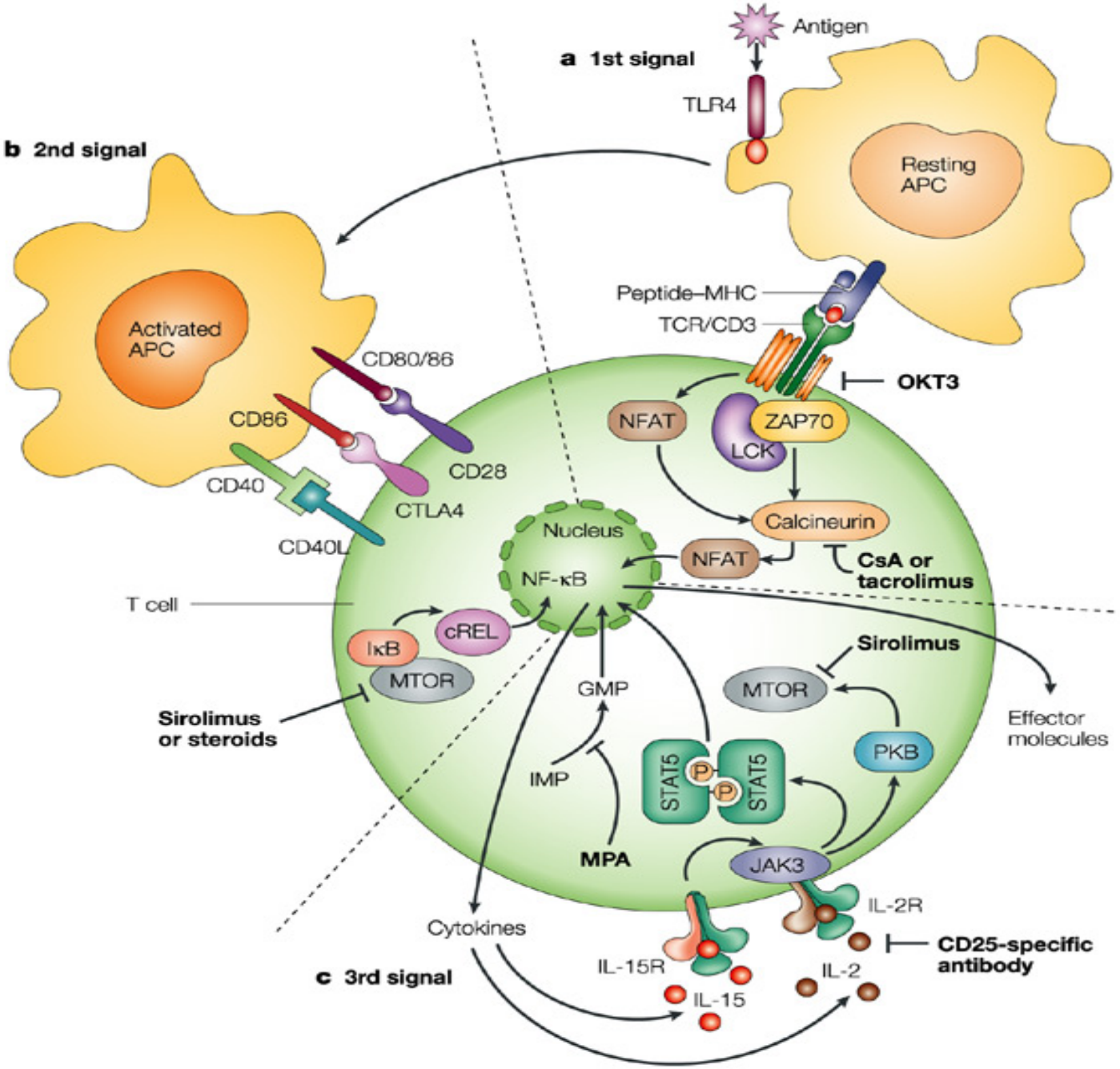


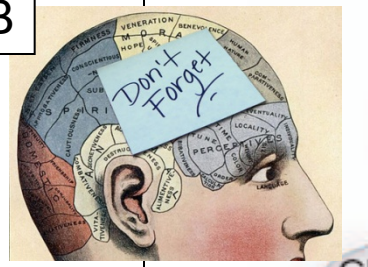
MEMBRANA BASAL GLOMERULAR

TÚBULO-INTERSTICIO

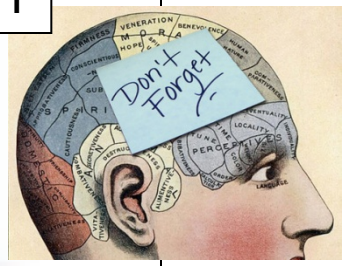

Etiologic events
PAMPS/DAMPS
Antigen presenting cell
Complement
TLRs, NLRs
CD4 T cells
C5b-9
C5a
Auto antibodies, antigen-antibody complexes
B cells
TREGs
TH1
TH2
TH17
Resident glomerular cells
Circulating inflammatory cells
Proteases
Oxidants
Cytokines
Chemokines
Growth factors
Eicosanoids
Glomerular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

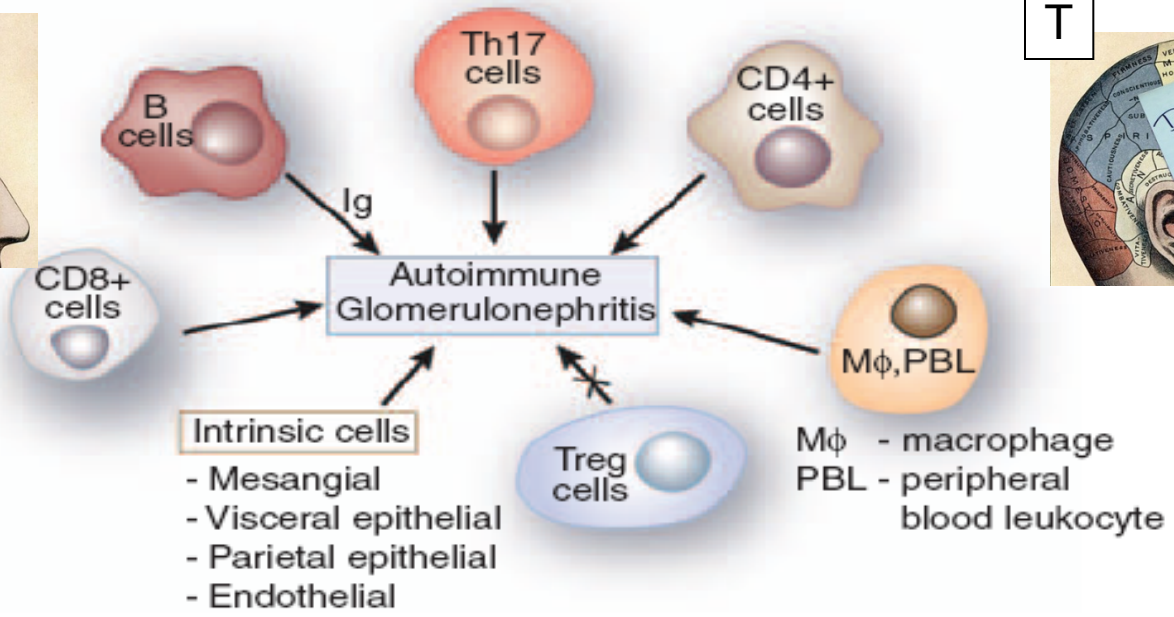

Antigen
a 1st signal
TLR4
Resting APC
b 2nd signal
Activated APC
Peptide–MHC
TCR/CD3
OKT3
CD80/86
CD86
CD28
CD40
CTLA4
CD40L
NFAT
ZAP70
LCK
Calcineurin
NFAT
CsA or tacrolimus
Nucleus
NF-κB
T cell
cREL
IκB
MTOR
Sirolimus or steroids
GMP
IMP
MPA
MTOR
Sirolimus
Effector molecules
PKB
STAT5
STAT5
P
P
JAK3
IL-2R
CD25-specific antibody
Cytokines
IL-15R
IL-15
IL-2
c 3rd signal

B



T

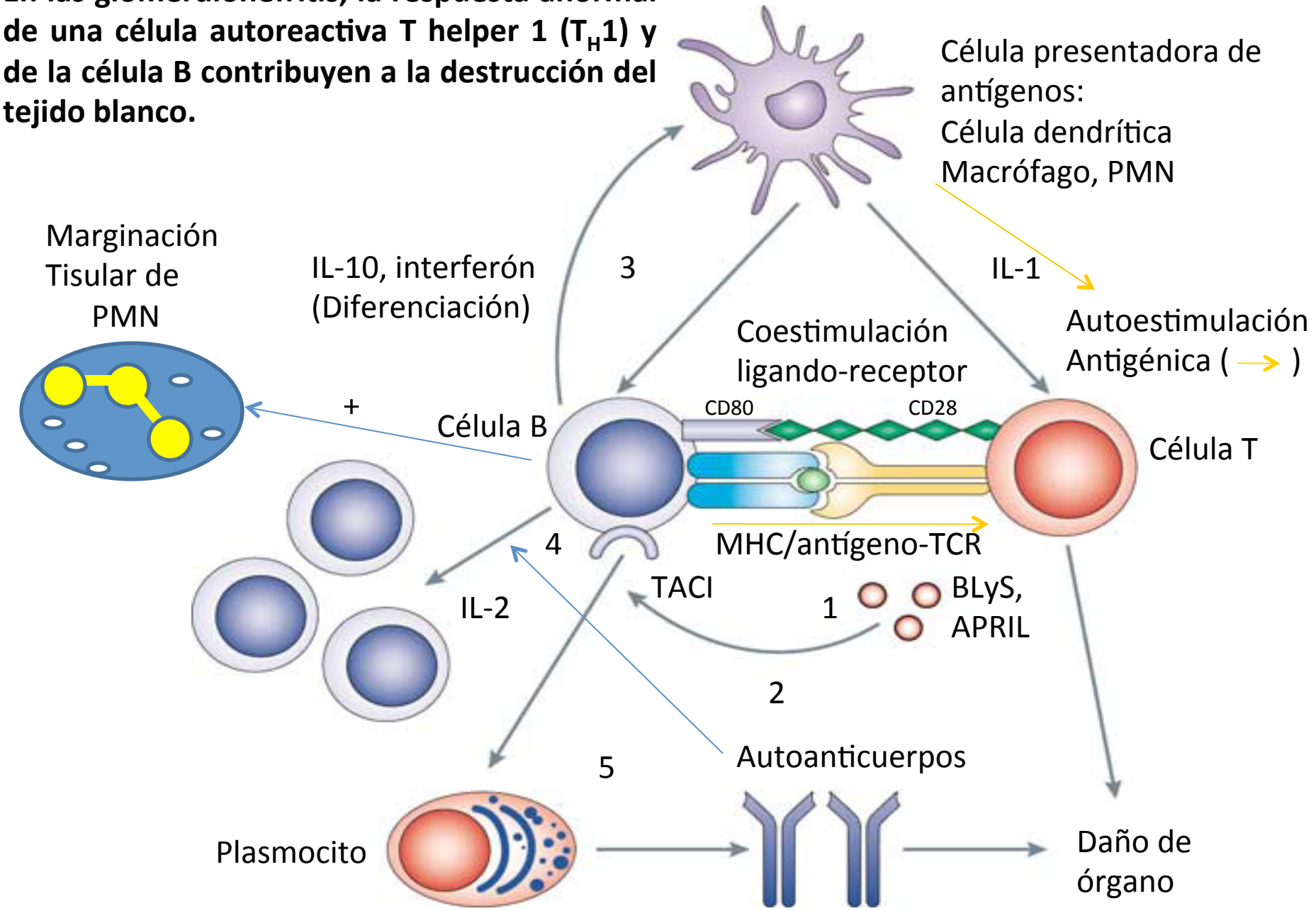


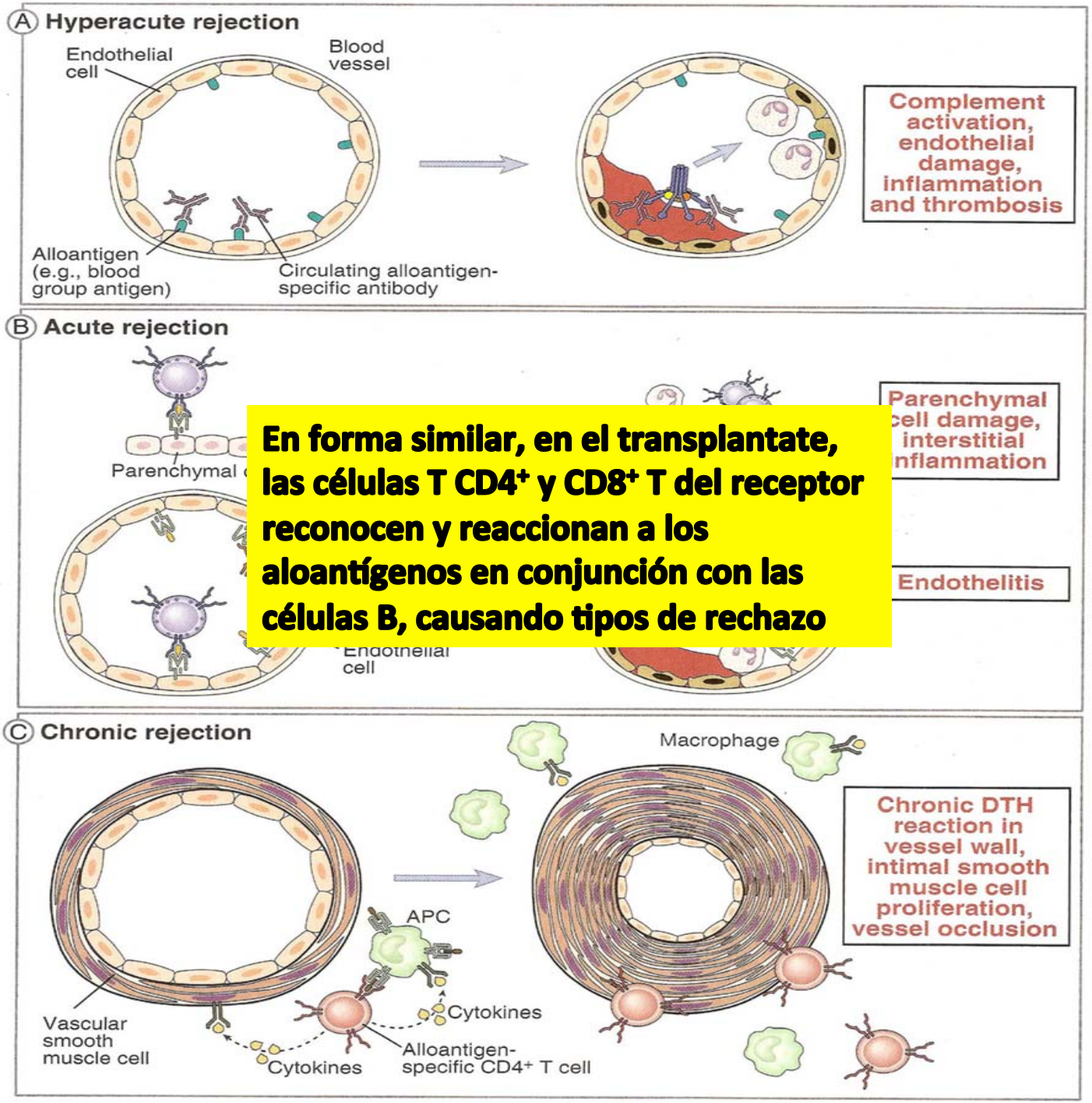


Broken tolerance,↓suppressor/regulatory cells, epitope mimetics, cryptic antigens, autoimmunity to complementary peptides

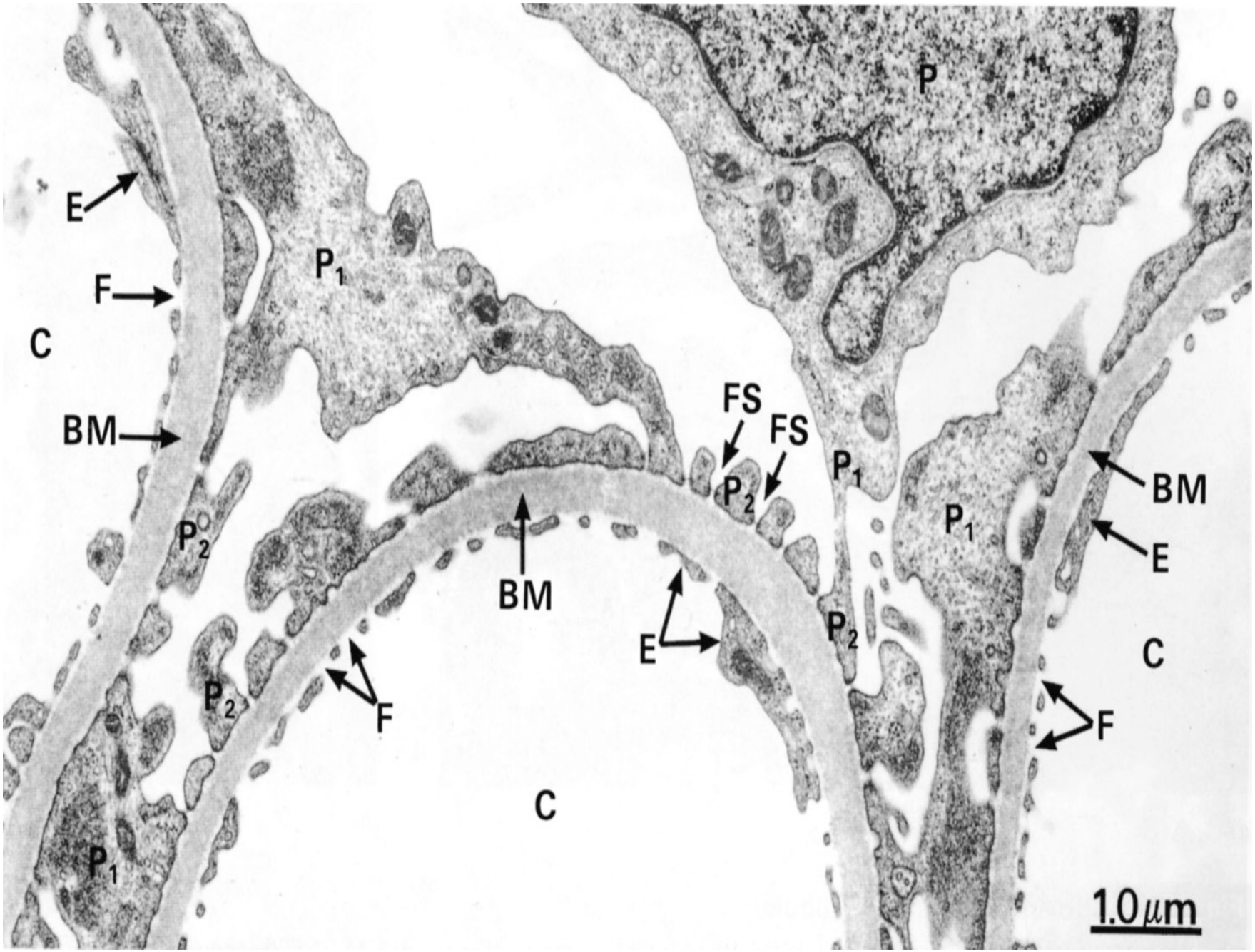
Figure 1 | Cells in GN. Figure 1 represents an aggregate of data derived from animal models. B cells were classically considered to be involved in the pathogenesis of GN by elaboration of immunoglobulin (Ig). Th-17, $CD4^+$, and $CD8^+$ cells have a significant role as shown by abrogation of activity 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.

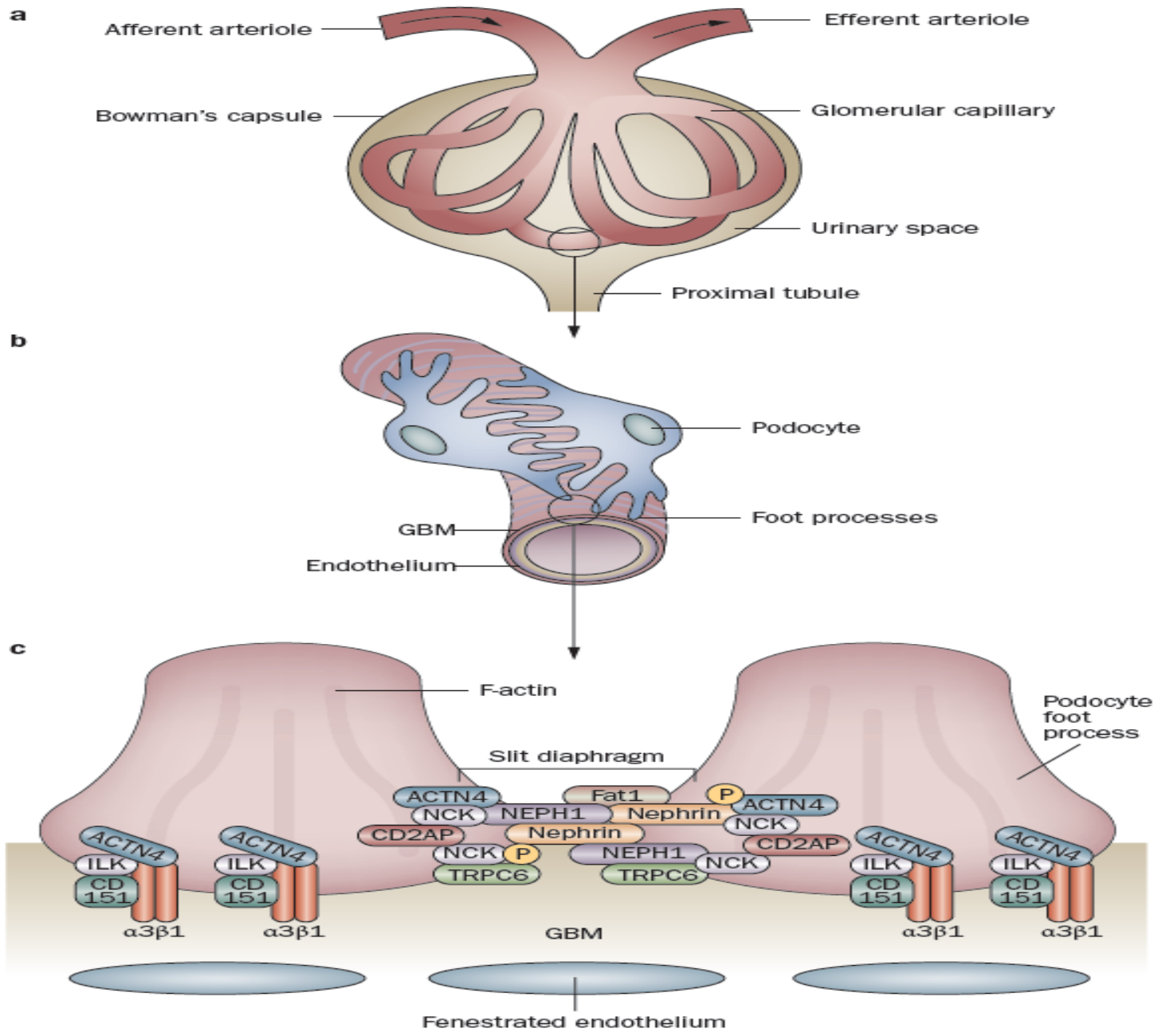
En las glomerulonefritis, la respuesta anormal de una célula autoreactiva T helper 1 (T_H1) y de la célula B contribuyen a la destrucción del tejido blanco.

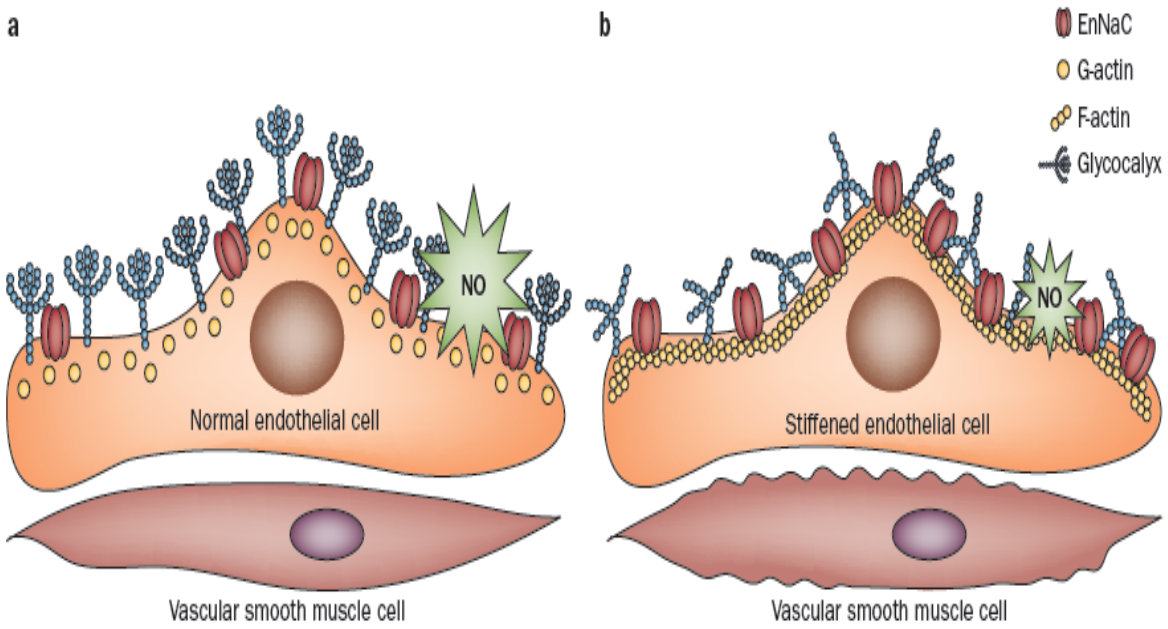




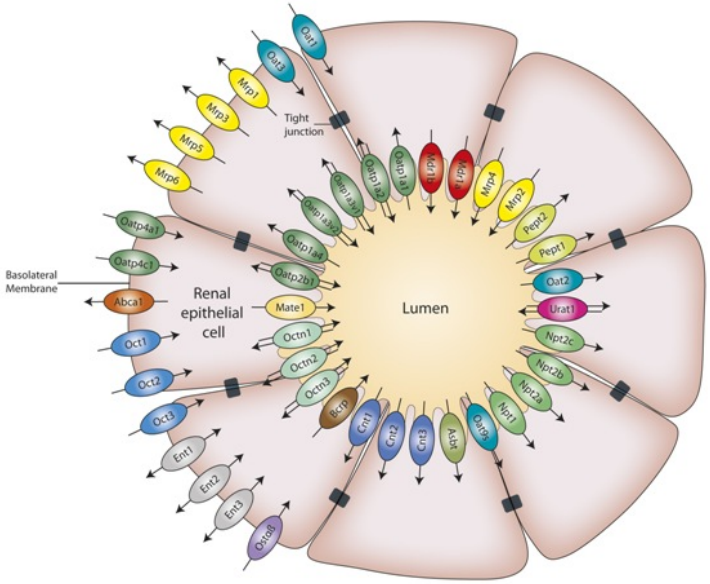
En forma similar, en el transplantate, las células T CD4⁺ y CD8⁺ T del receptor reconocen y reaccionan a los aloantígenos en conjunción con las células B, causando tipos de rechazo

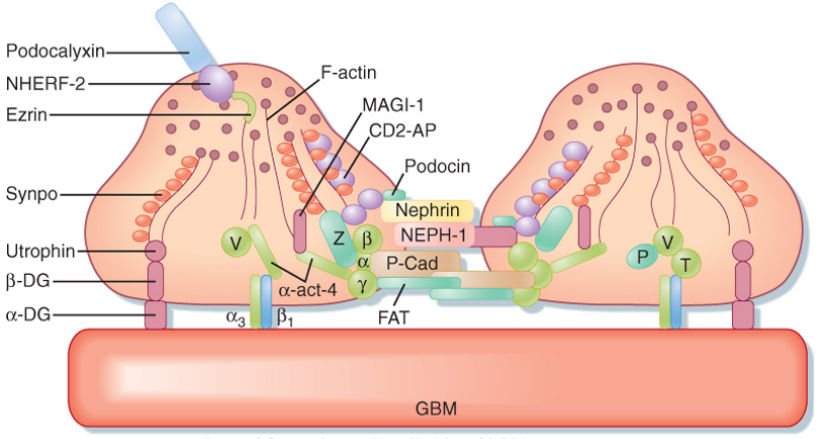

P
E
F
C
BM
P1
P2
FS
FS
P2
P1
BM
E
C
F
BM
E
P2
P2
F
C
P1
P1
BM
E
C
F
1.0 μm


a
Afferent arteriole
Efferent arteriole
Bowman's capsule
Glomerular capillary
Urinary space
Proximal tubule
b
Podocyte
Foot processes
GBM
Endothelium
c
F-actin
Podocyte foot process
Slit diaphragm
ACTN4
Fat1
P
ACTN4
NCK
NEPH1
Nephrin
NCK
CD2AP
Nephrin
CD2AP
NCK
P
NEPH1
NCK
TRPC6
TRPC6
ACTN4
ILK
CD 151
α3β1
GBM
Fenestrated endothelium



Warnock, D. G. *et al. Nat. Rev. Nephrol. 2014; 10: 146–157*





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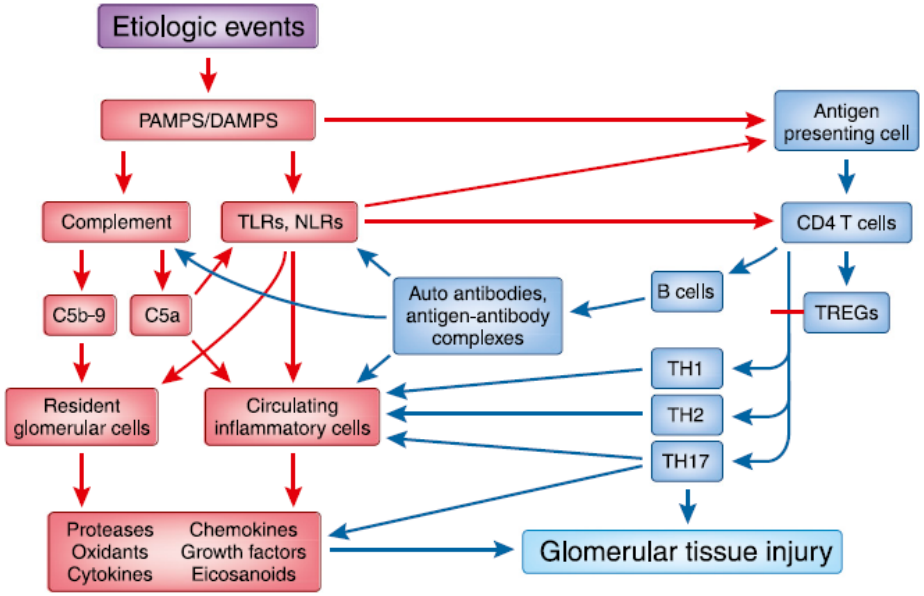
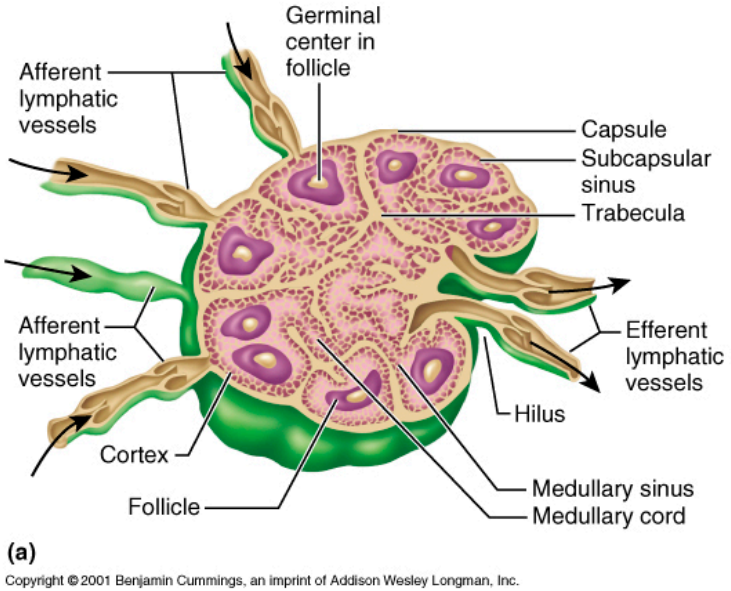
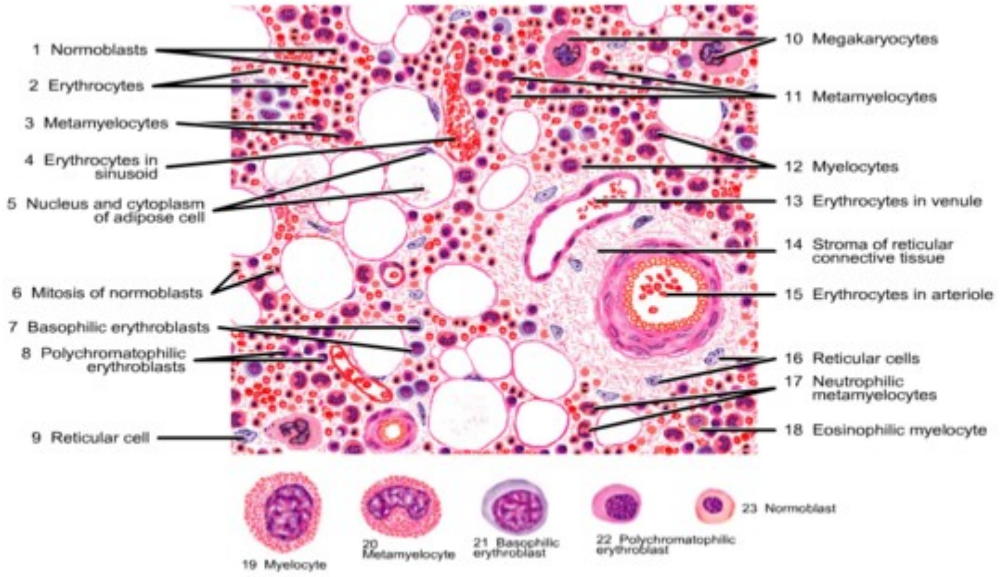
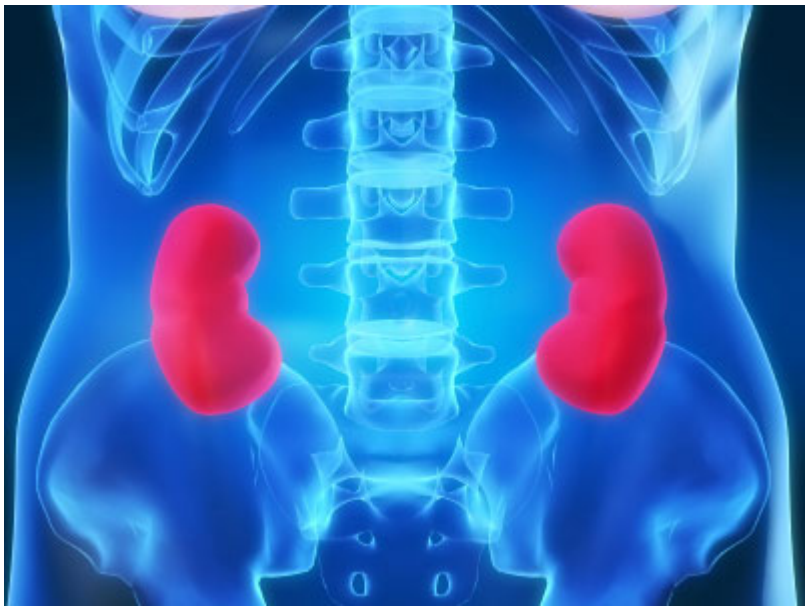








DROGAS INMUNOSUPRESORAS

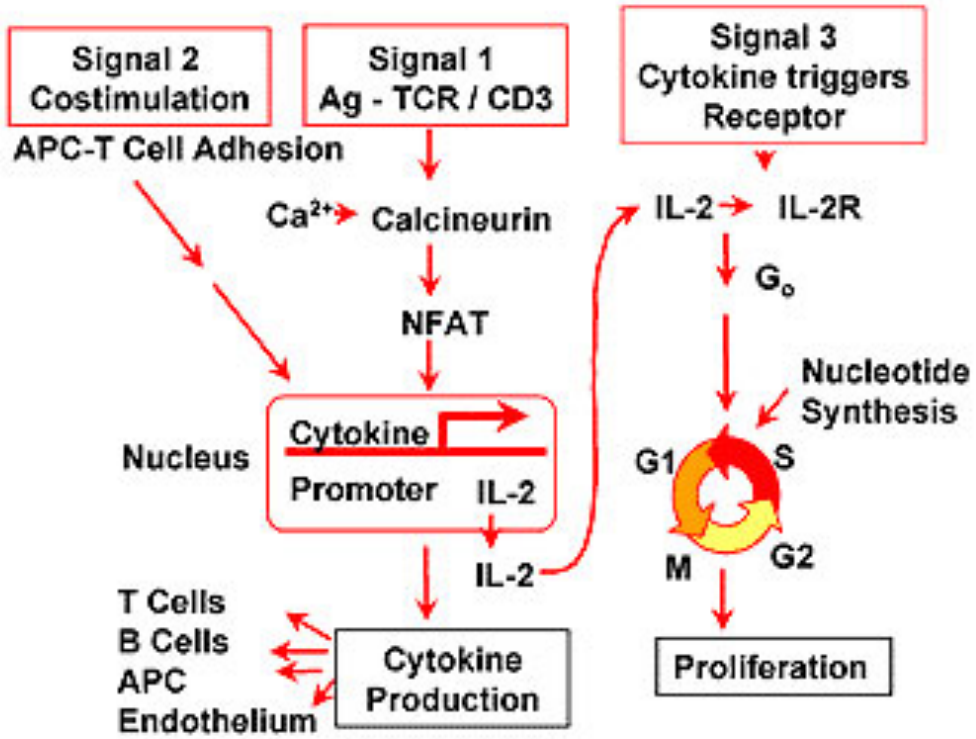


Figure 27. T cell activation.

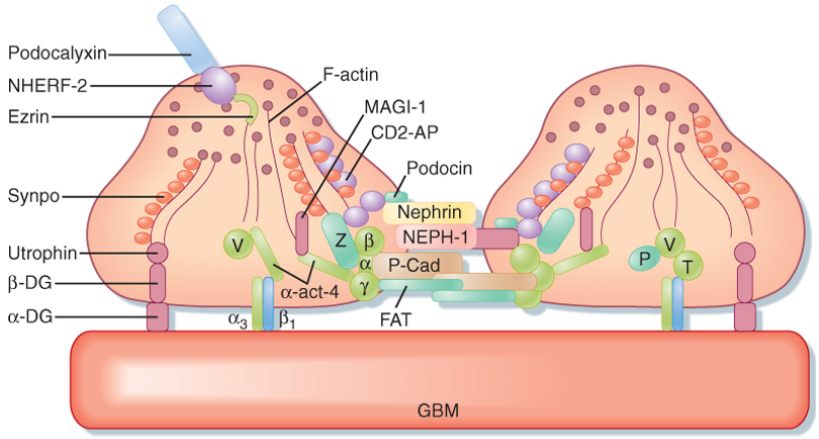
CORTICOIDES

Los esteroides poseen efectos inmunosupresores y antiinflamatorios.

Los podocitos expresan receptores glucocorticoideos, que se traslocan al núcleo luego de la unión al esteroide.

Los esteroides son citoprotectores y facilitan la recuperación podocitaria luego de la injuria.

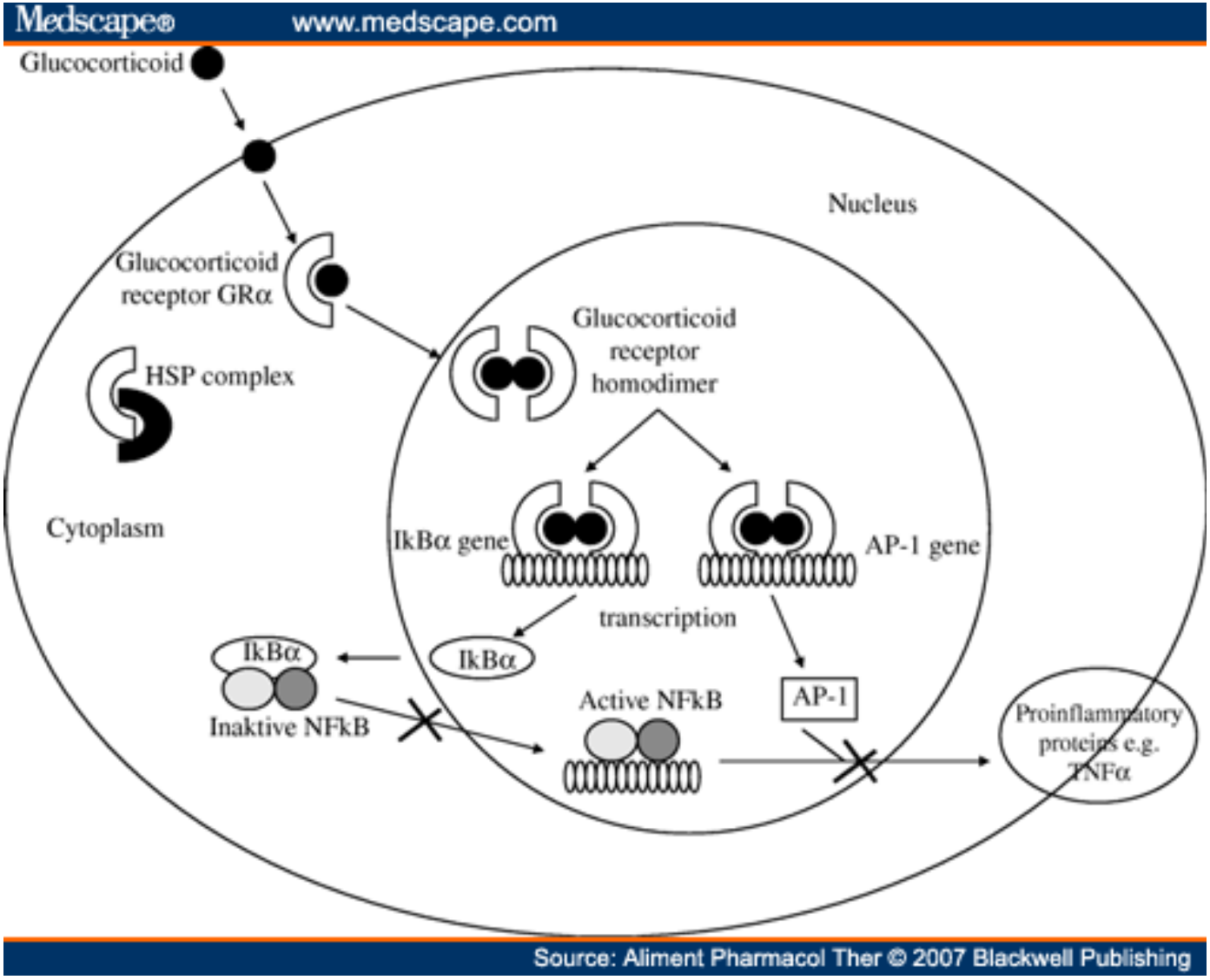
Los mecanismos protectores incluyen:



Reducción de la apoptosis podocitaria
Estabilización de los filamentos de actina
Aumento en la actividad de la GTPasa RhoA
Estabilización del complejo de la hendidura diafragmática

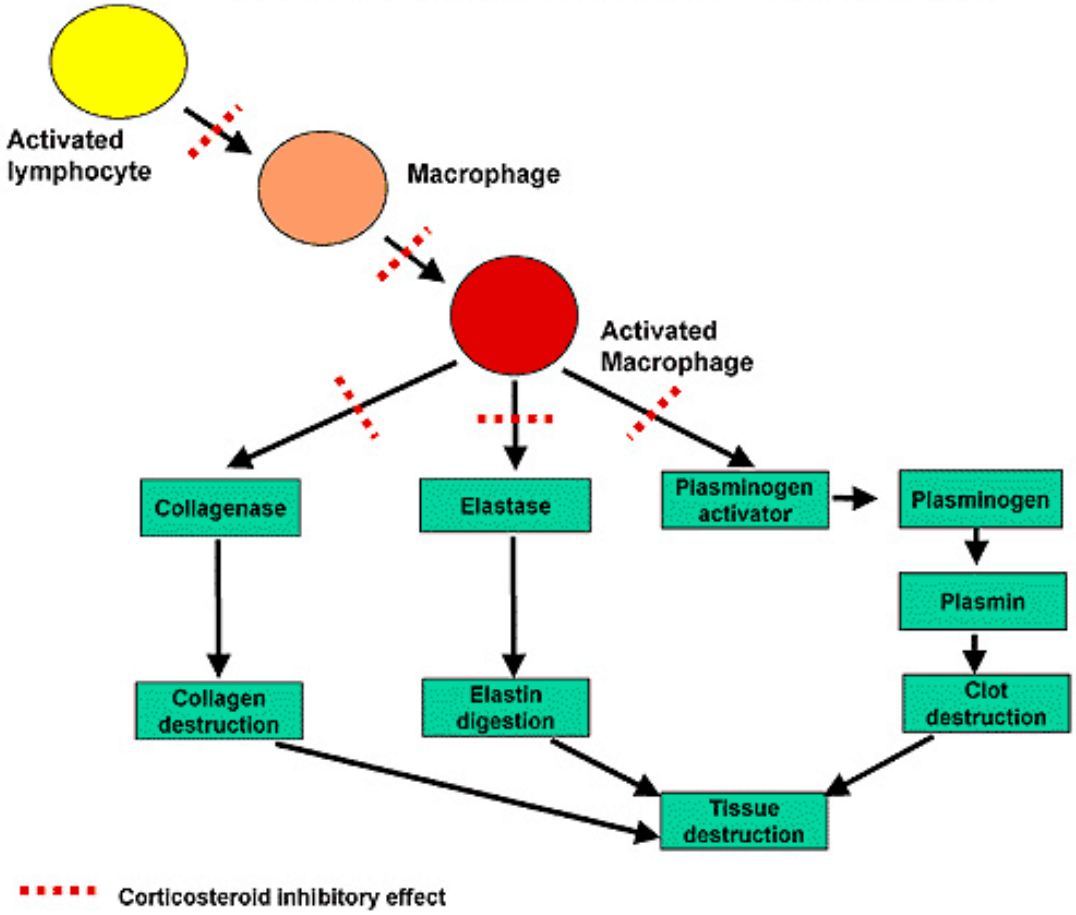
Beneficio local y sistémico de los esteroides en las enfermedades podocitarias

Am J Kidney Dis. 2011 November ; 58(5): 835–845.


Medscape®
www.medscape.com
Glucocorticoid
Nucleus
Glucocorticoid receptor GRα
HSP complex
Glucocorticoid receptor homodimer
Cytoplasm
IkBα gene
AP-1 gene
transcription
IkBα
IkBα
Inaktive NFkB
Active NFkB
AP-1
Proinflammatory proteins e.g. TNFα
Source: Aliment Pharmacol Ther © 2007 Blackwell Publishing

IL-1
TNF-α

Figure 1. Anti-inflammatory actions of corticosteroids.



MICOFENOLATO

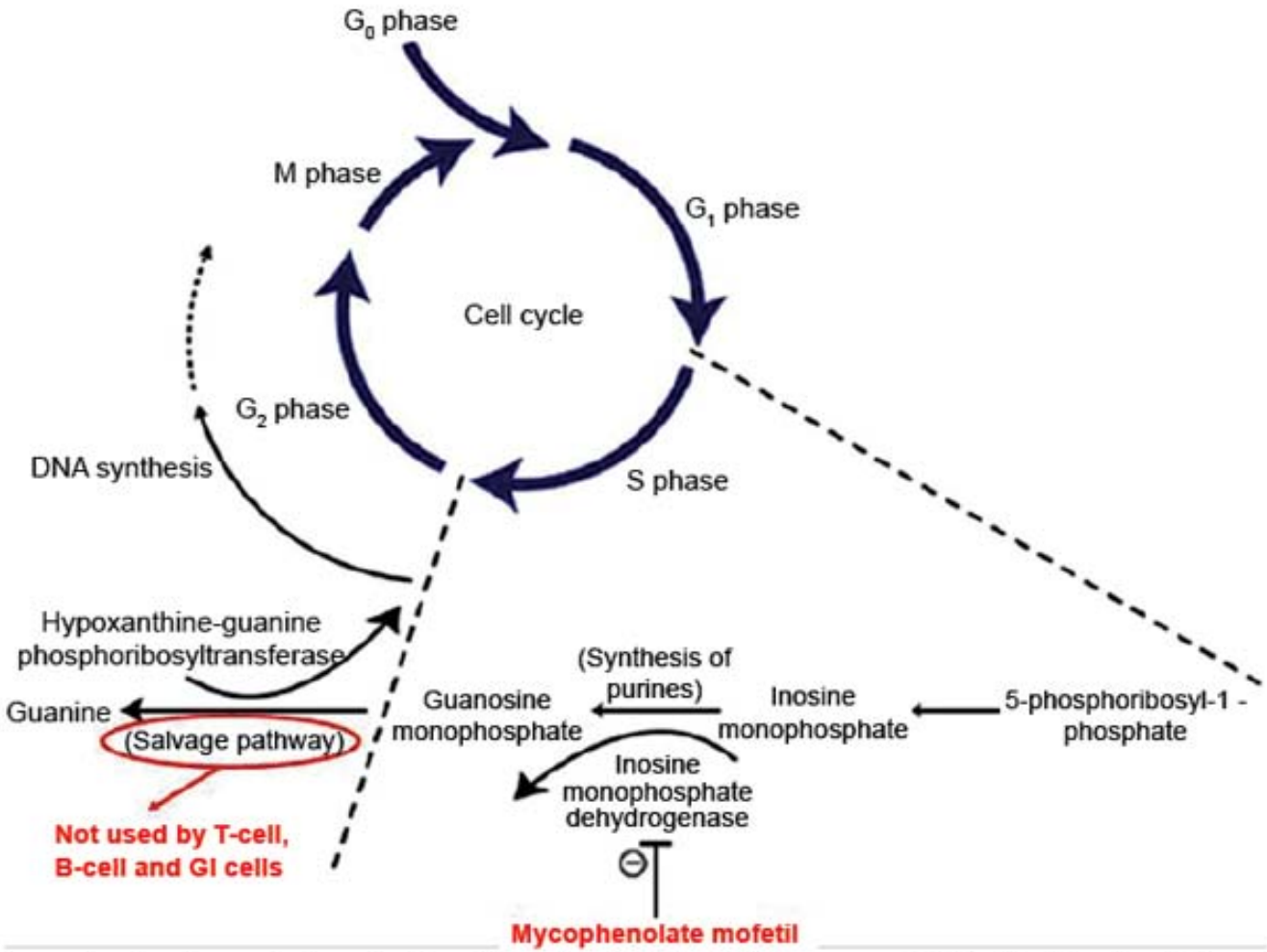
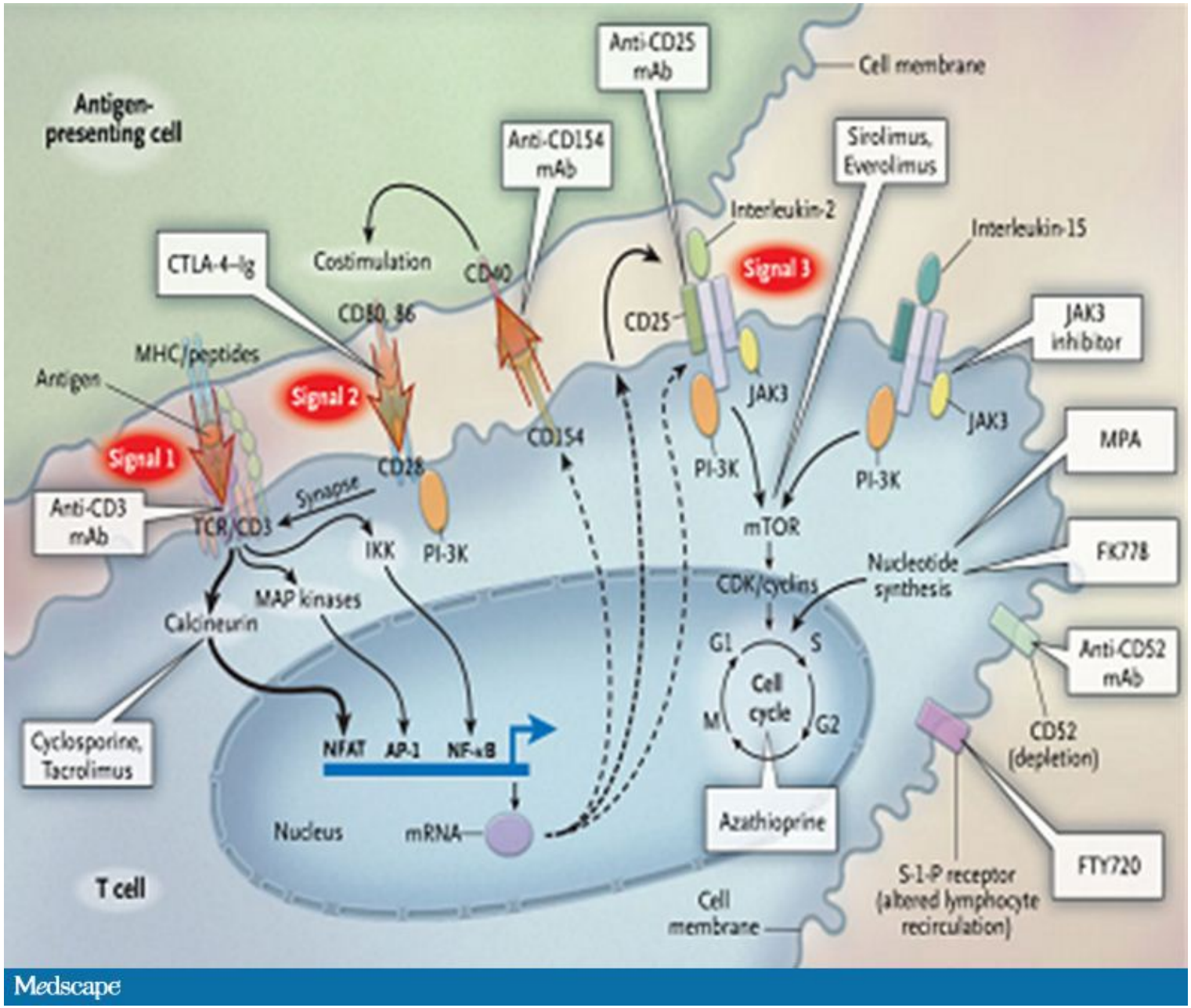
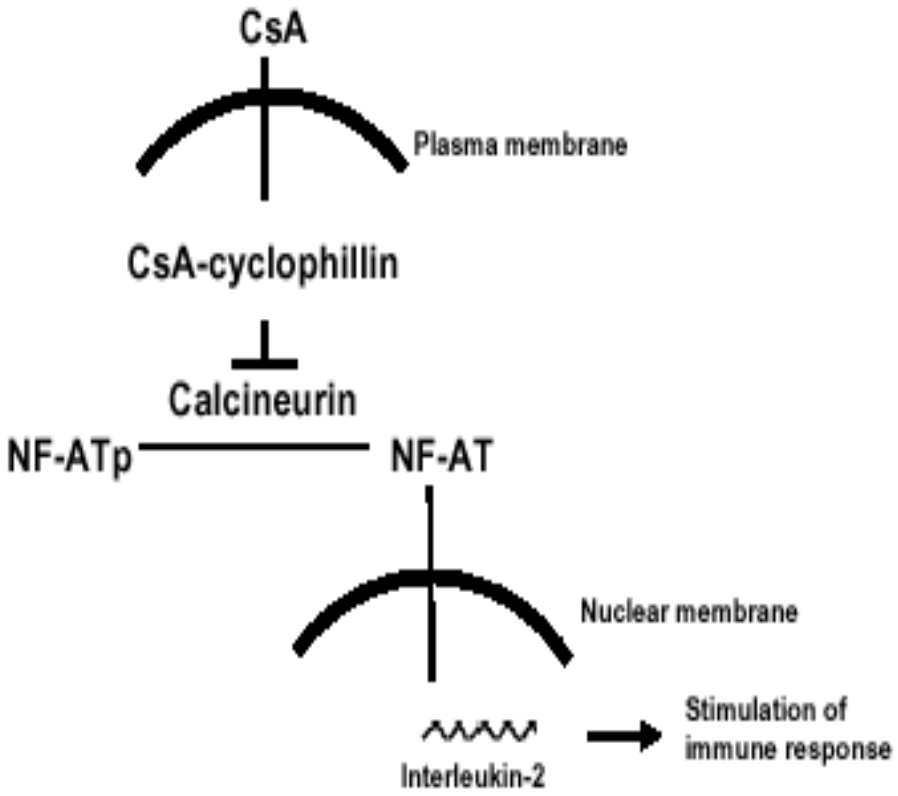


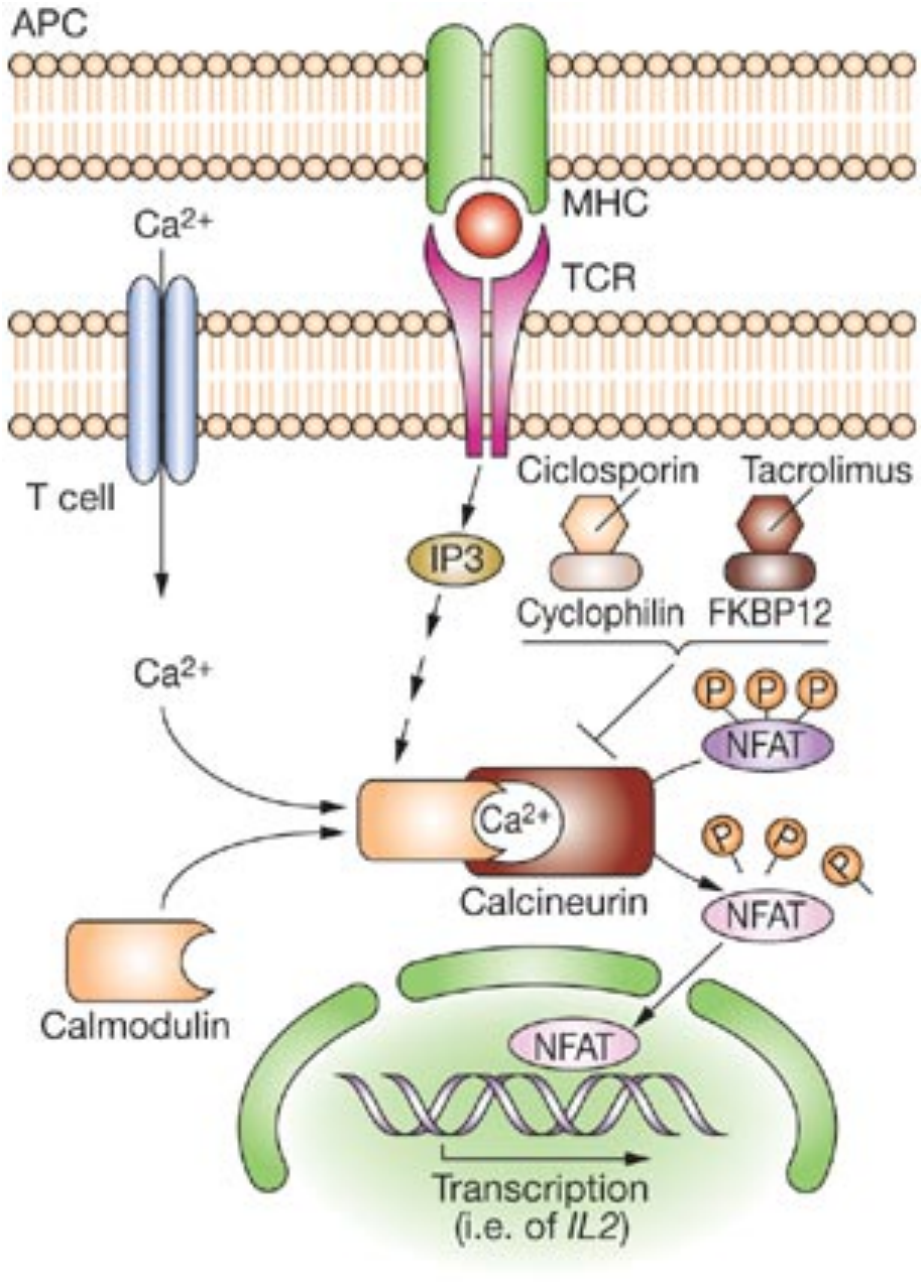
Fig. 1 : Diagram showing the mechanism of action of Mycophenolate. IMPDH is the enzyme inhibited by Mycophenolate, arresting the cell cycle in the S phase. All cells of the body except lymphocytes and GI cells use the salvage pathway with help of the enzyme HGPRT to complete the cell cycle.

AZATIOPRINA



CICLOSPORINA



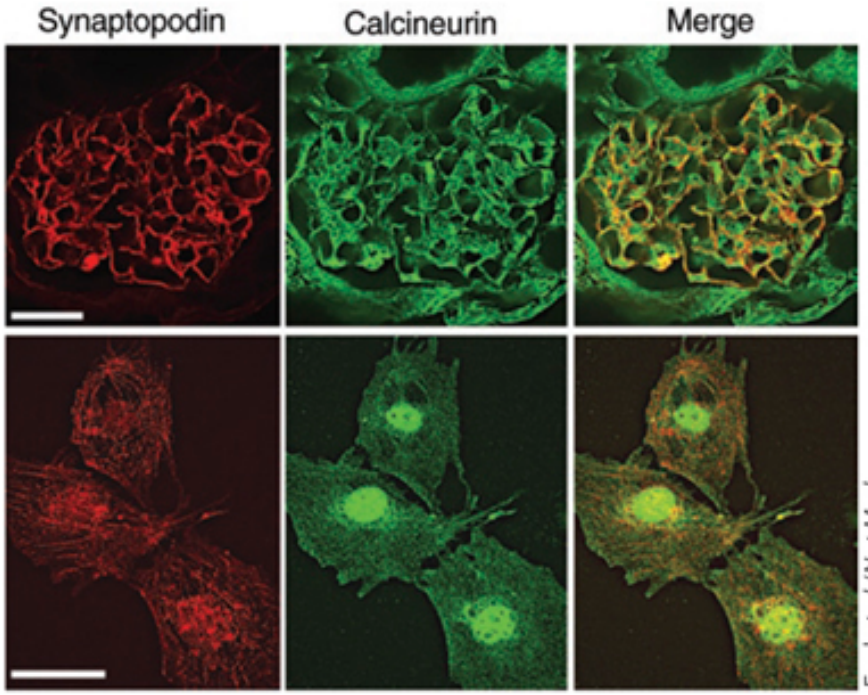


Welsh, G. I. & Saleem, M. A. *Nat. Rev. Nephrol.* **8**, 14–21 (2012);

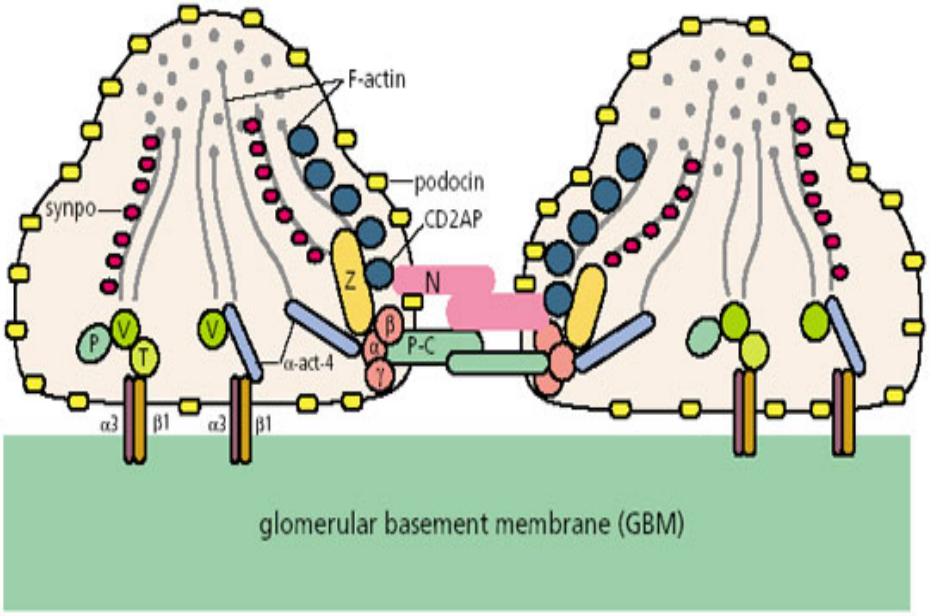
CICLOSPORINA

La CsA bloquea la defosforilación de la sinaptopodina, una proteína organizadora de la α-actinina-4 del podocito (contracción) y de la CD2AP (filopodesis).
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.
La expresión de calcineurinas en el podocito resulta en la degradación de la sinaptopodina y el desarrollo de proteinuria.

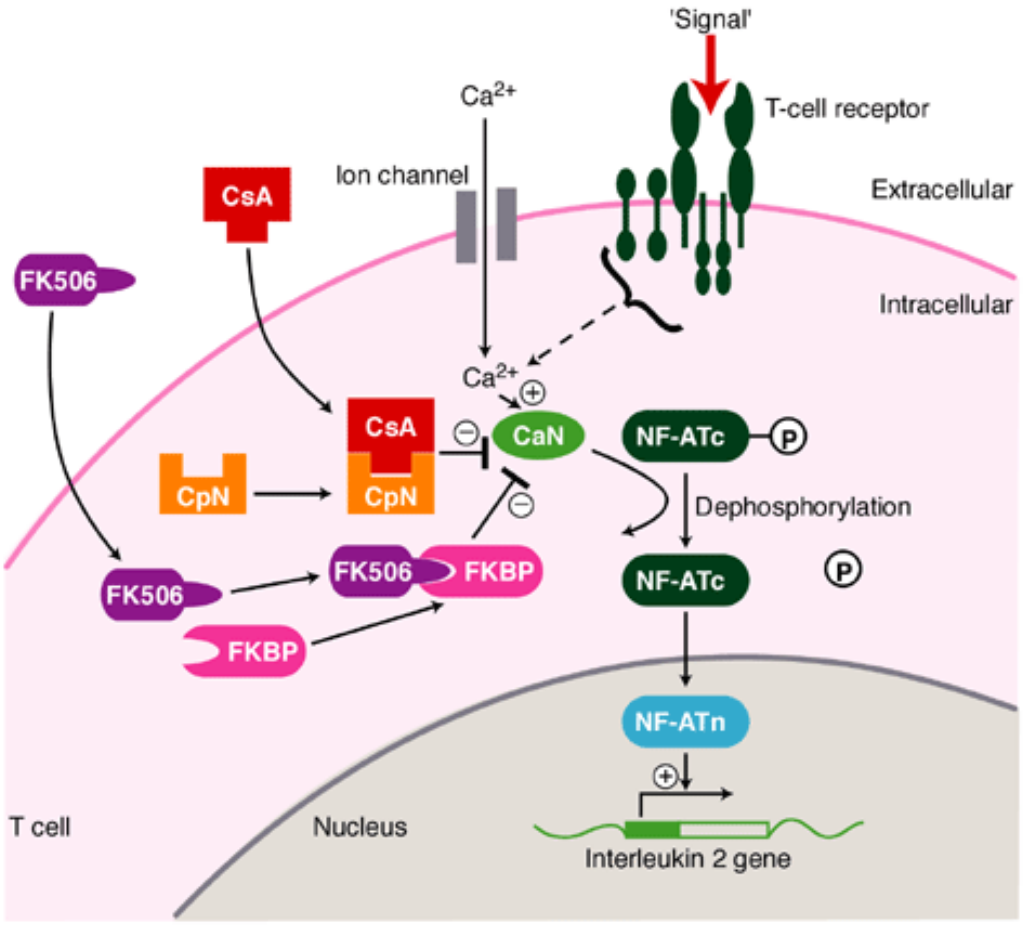


Faul *et al.*/*Nat Med*



Welsh, G. I. & Saleem, M. A. *Nat. Rev. Nephrol.* **8**, 14–21 (2012);

TACROLIMUS



Mechanism of action of cyclosporine or tacrolimus (FK506)

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

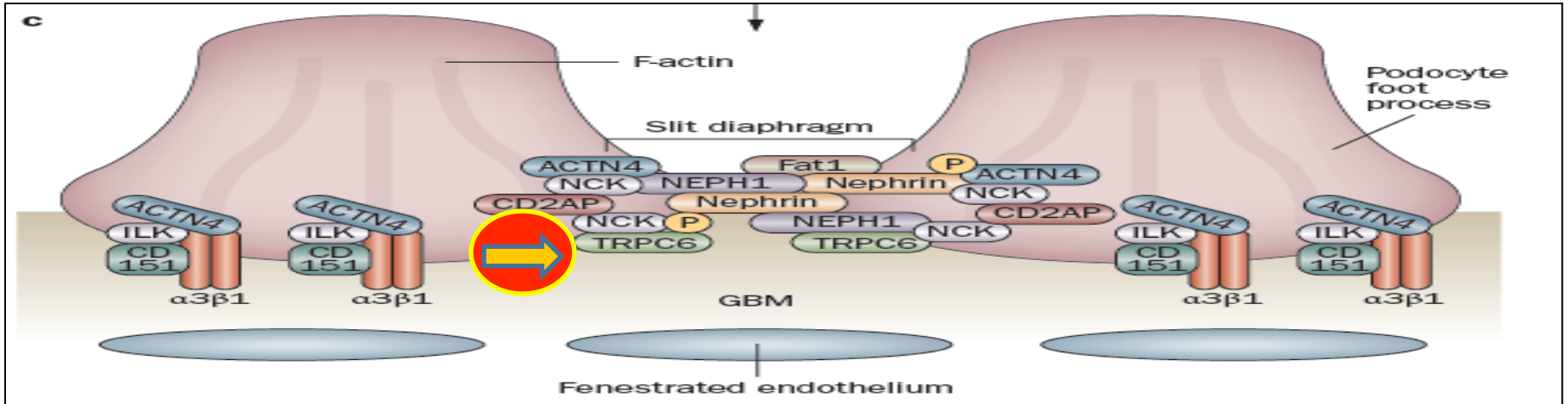
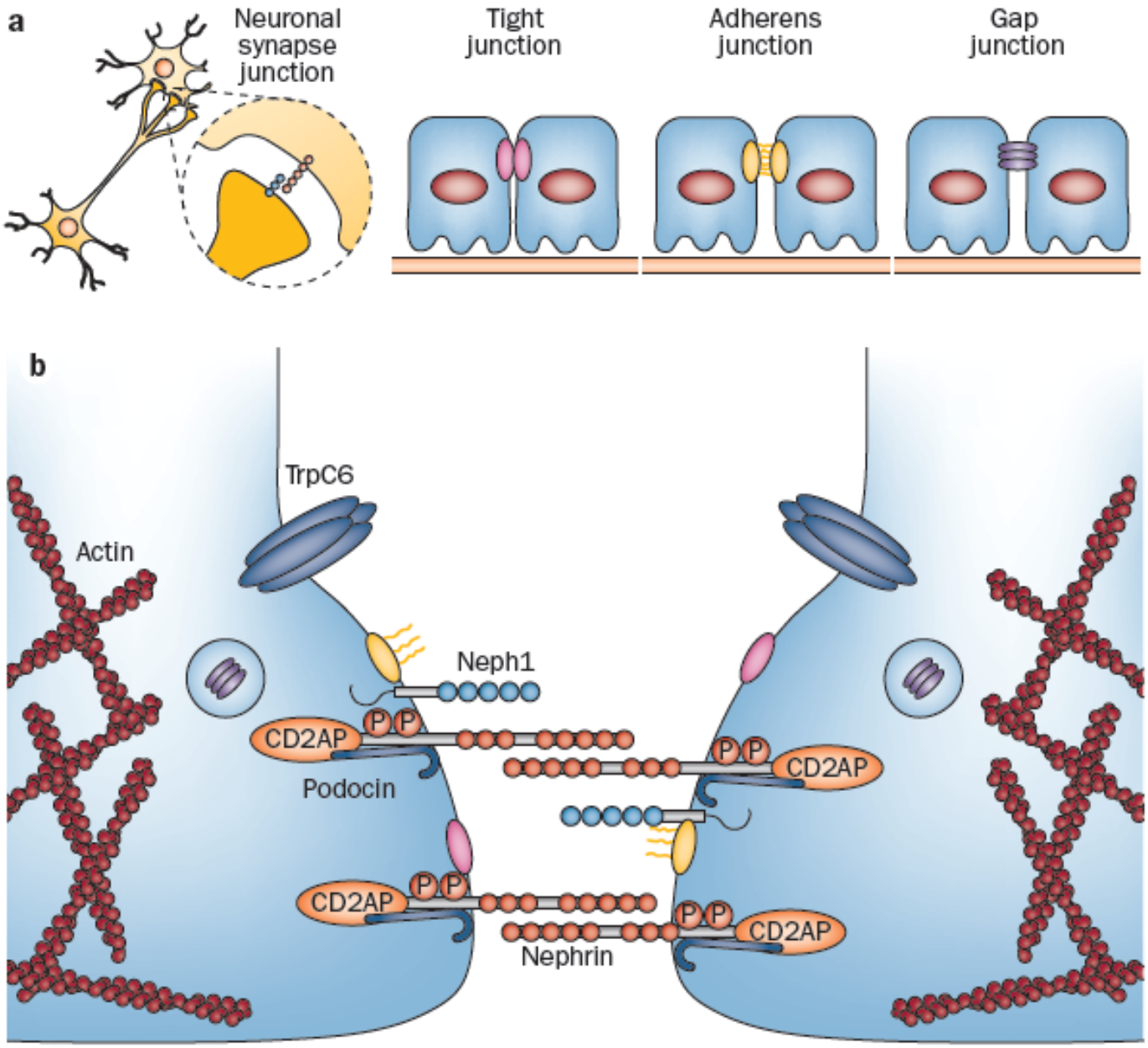


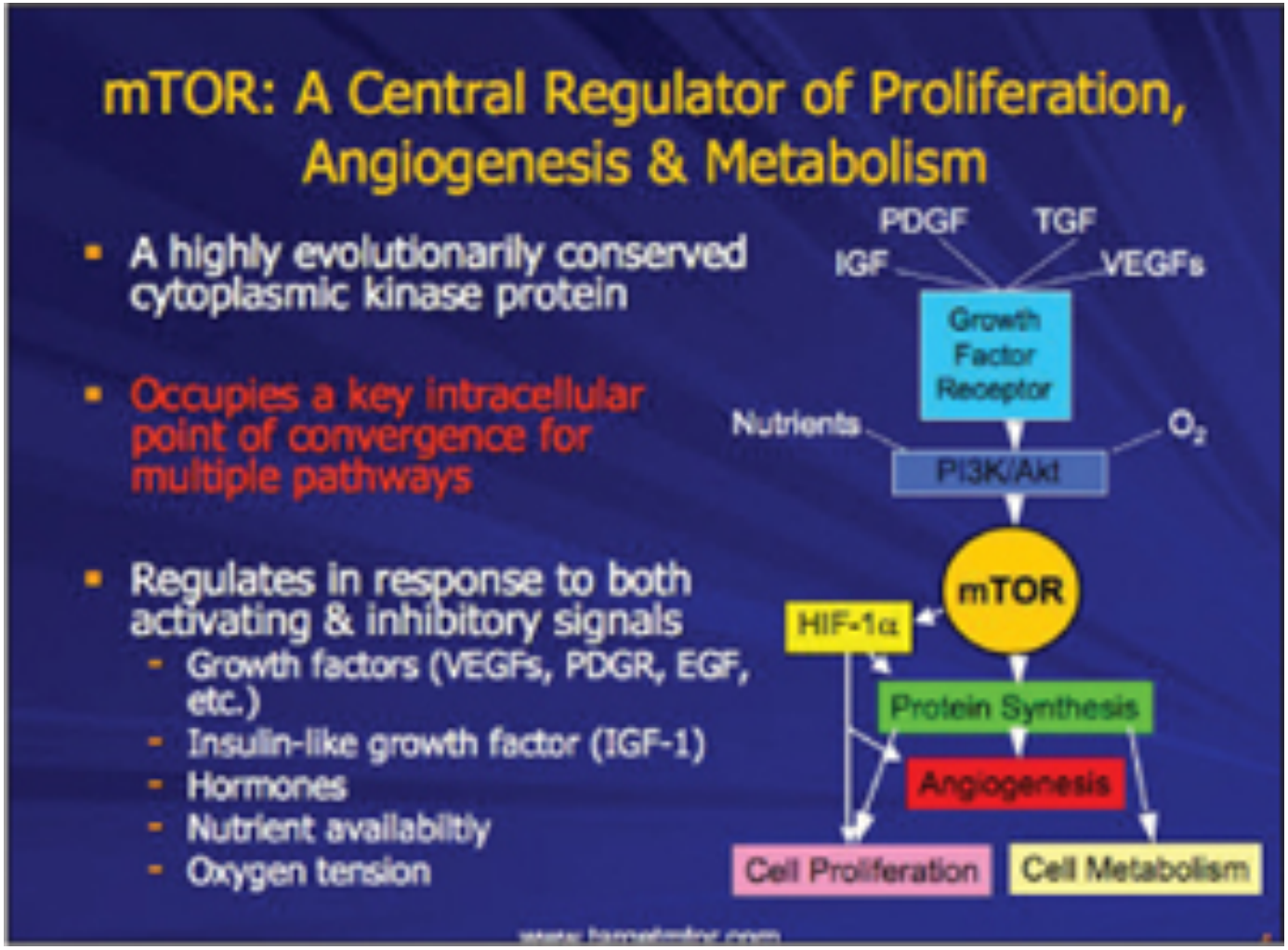
Figure 1 | Structure of the glomerular filtration barrier. **a** | Glomerular filtration occurs through the capillary wall into the urinary space, which empties into the proximal tubules. **b** | The capillary wall contains an innermost fenestrated endothelium, the GBM, and a layer of podocytes with 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.

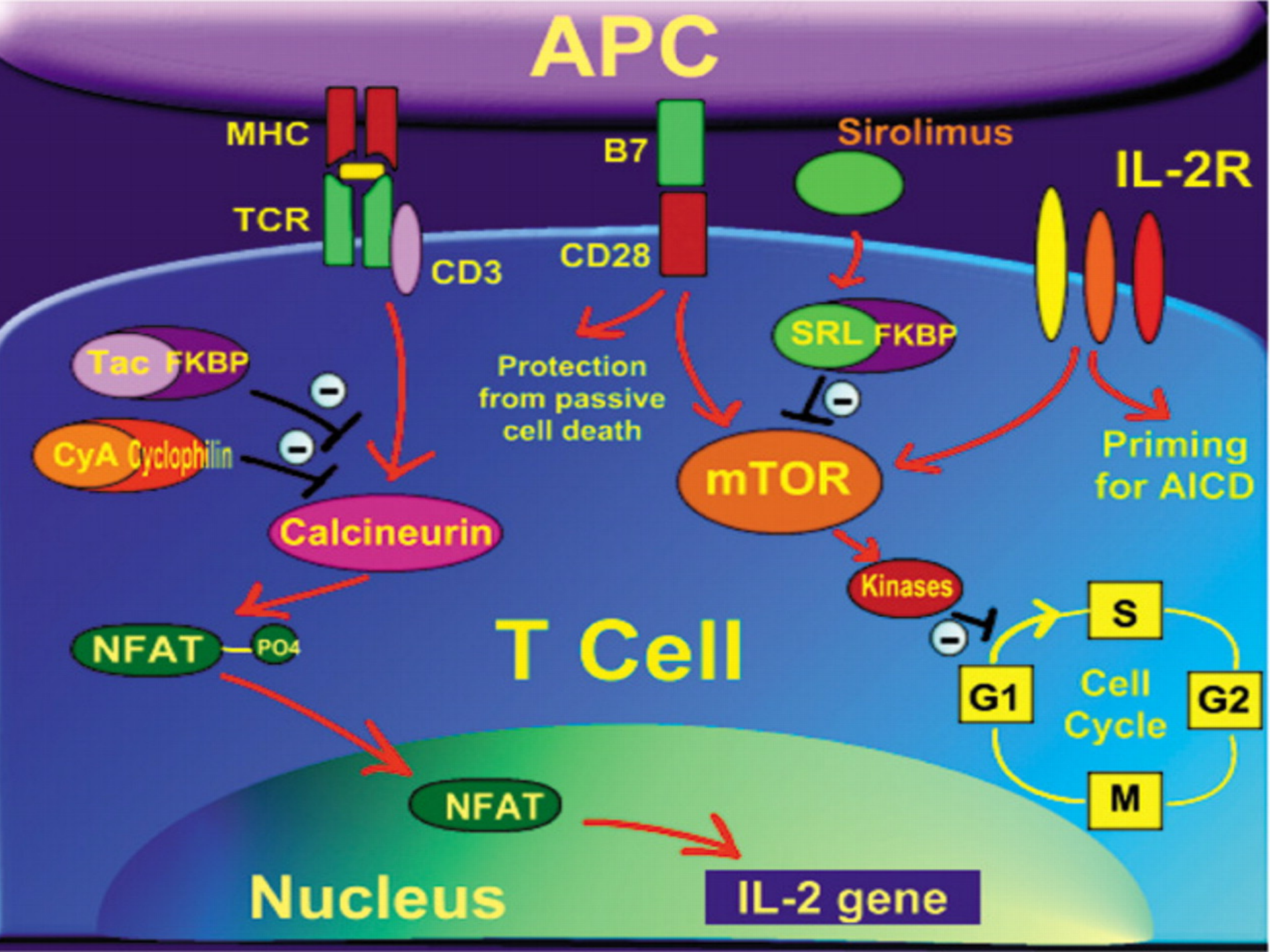
Welsh, G. I. & Saleem, M. A. *Nat. Rev. Nephrol.* **8**, 14–21 (2012);



Grahammer, F. *et al. Nat. Rev. Nephrol.* **9**, 587–598 (2013)

SIROLIMUS-EVEROLIMUS




APC
MHC
TCR
CD3
B7
CD28
Sirolimus
IL-2R
Tac FKBP
CyA Cyclophilin
Calcineurin
Protection from passive cell death
SRL FKBP
mTOR
Priming for AICD
Kinases
NFAT
PO4
T Cell
S
G1
Cell Cycle
G2
M
NFAT
Nucleus
IL-2 gene

RAPAMICINA- EVEROLIMUS

Review Article

Is There a Role for Mammalian Target of Rapamycin Inhibition in Renal Failure due to Mesangioproliferative Nephrotic Syndrome?

Hernán Trimarchi, Mariano Forrester, Fernando Lombi, Vanesa Pomeranz, Romina Iriarte, María Soledad Raña, and Pablo Young

International Journal of Nephrology
Volume 2012, Article ID 427060, 6 pages
doi:10.1155/2012/427060

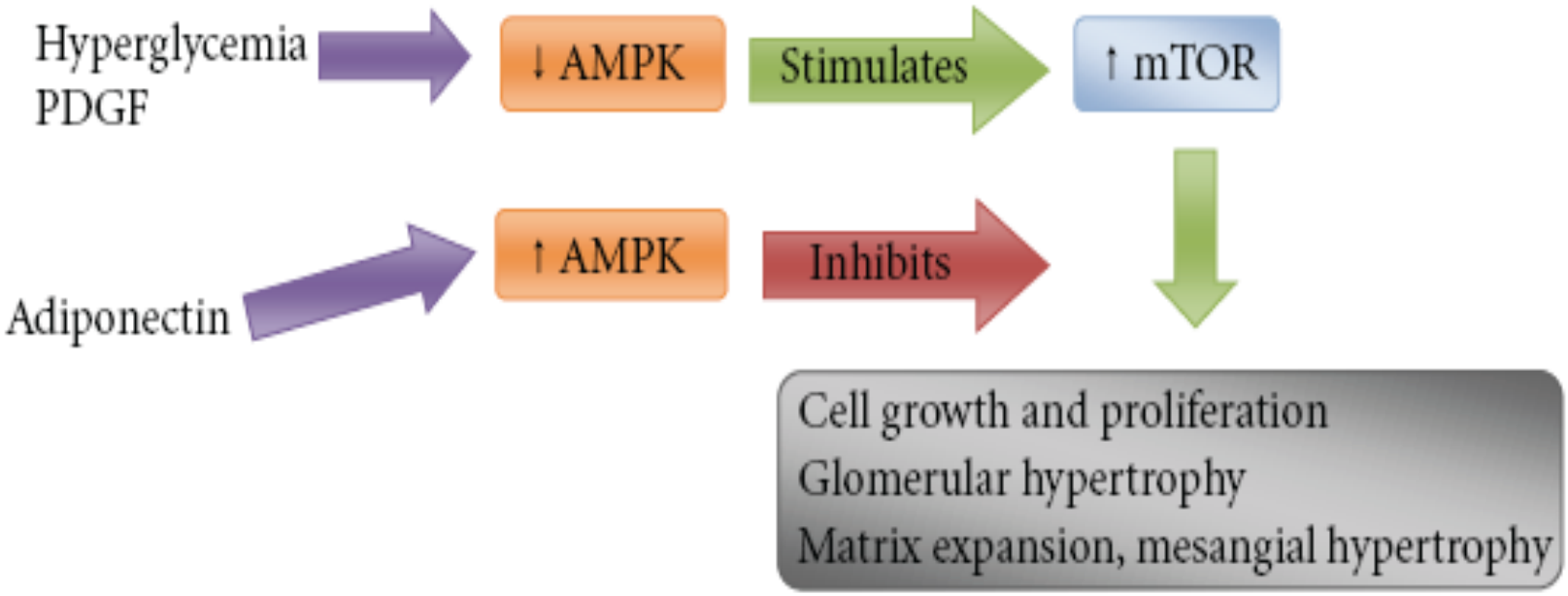


Figure 1: Hyperglycemia and PDGF stimulate mTOR, which in turn contribute to the nuclear translation of mRNAs necessary for cell growth and proliferation, clinically evident as hematuria, proteinuria, and glomerular filtration rate alterations.

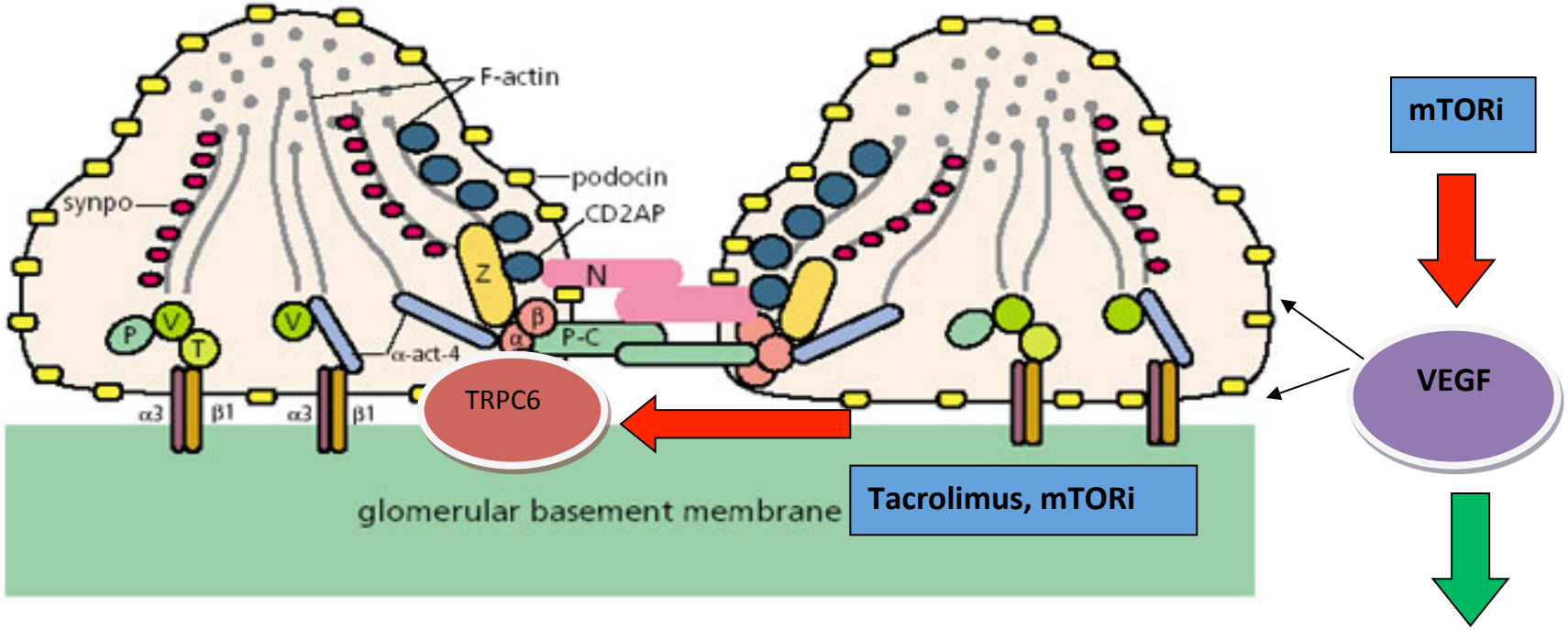
International Journal of Nephrology
Volume 2012, Article ID 427060, 6 pages
doi:10.1155/2012/427060

¿Cómo interpretar la proteinuria en el trasplante?

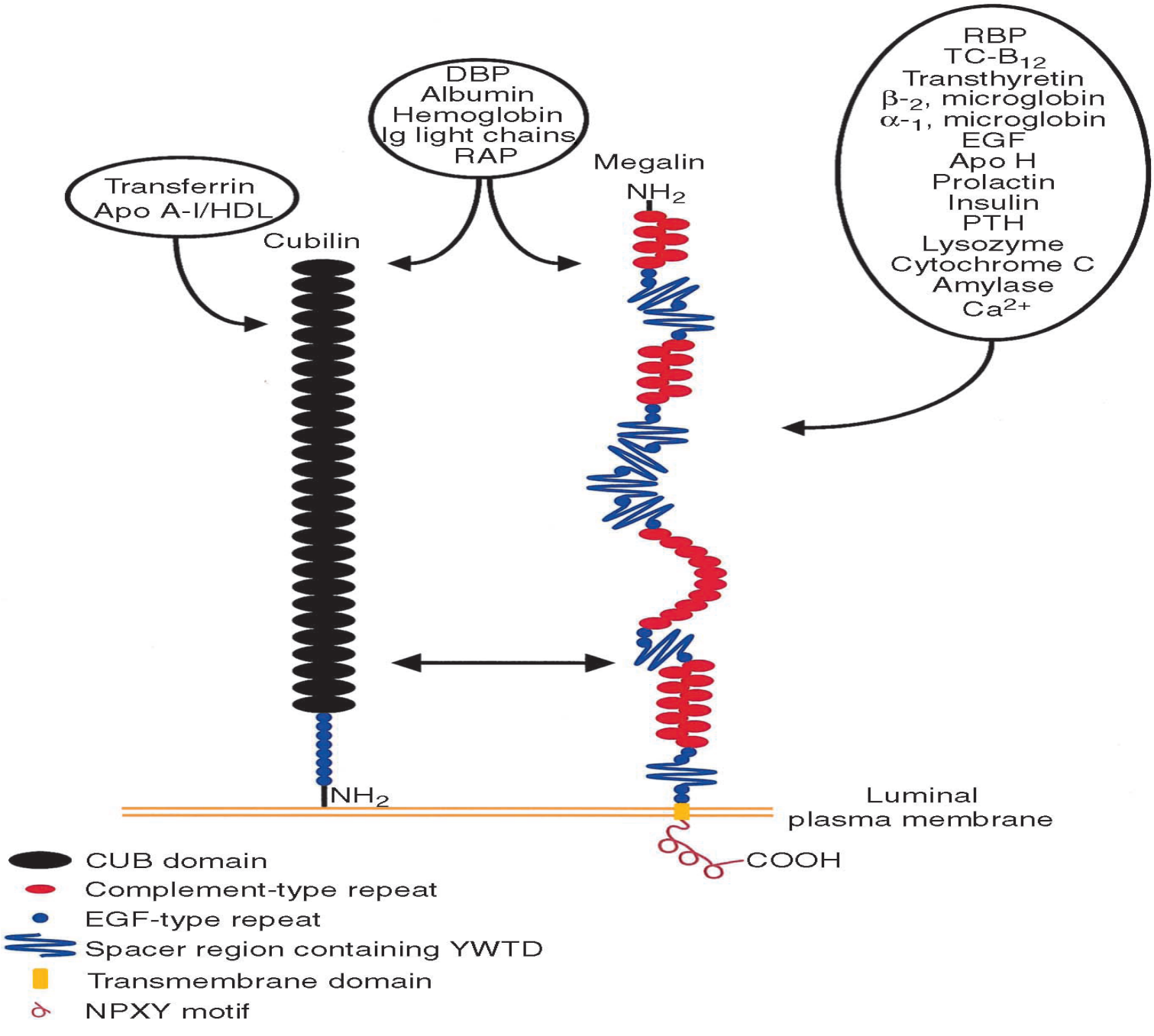
Hernán Trimarchi[1, 2] *y Vanesa Pomeranz*[1]

[1] Servicio de Nefrología, Hospital Británico de Buenos Aires, Argentina
[2] Equipo de Trasplante Renal, Hospital Británico de Buenos Aires, Argentina.

Revista Argentina de Trasplantes - Pág X
Hernán Trimarchi y Vanesa Pomeranz. ¿Cómo interpretar la proteinuria en el trasplante?. 201 I; I: X-X



Proliferación del endotelio
Angiogénesis
Permeabilidad capilar
Integridad de la MBG


RBP
TC-B12
Transthyretin
β-2, microglobin
α-1, microglobin
EGF
Apo H
Prolactin
Insulin
PTH
Lysozyme
Cytochrome C
Amylase
Ca2+
DBP
Albumin
Hemoglobin
Ig light chains
RAP
Transferrin
Apo A-I/HDL
Megalin
NH2
Cubilin
NH2
Luminal
plasma membrane
COOH
CUB domain
Complement-type repeat
EGF-type repeat
Spacer region containing YWTD
Transmembrane domain
NPXY motif

Los mTORi **bloquean** el tráfico de proteínas desde la luz tubular al intersticio

El reclutamiento de macrófagos y linfocitos

La transdiferenciación de pericitos a fibroblastos (Transición Epitelio o Endotelio-Mesenquimatosa, EMT)

La aparición de fibrosis intersticial irreversible

TFG-β
PDGF
MCP-1 ↓

Los mTORi y el Micofenolato ⊘ EMT y de atenuar el daño túbulointersticial y el depósito local de colágeno

Finalmente, los mTORi

↓ infiltración de células inflamatorias
TGF-β
CTGF
PDGF
α-SMA

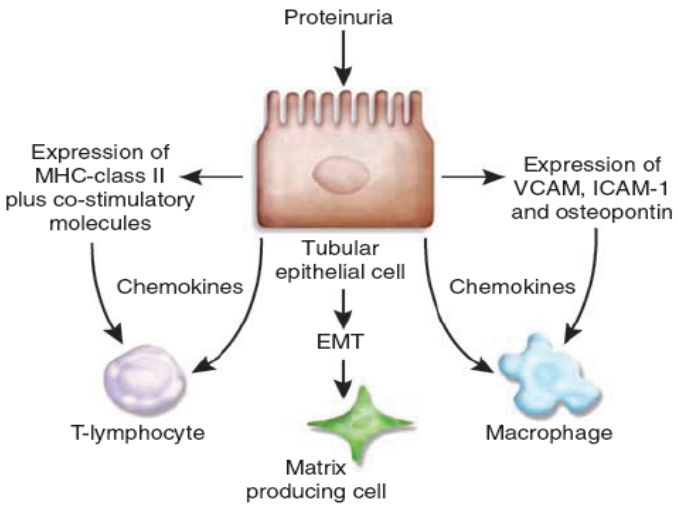
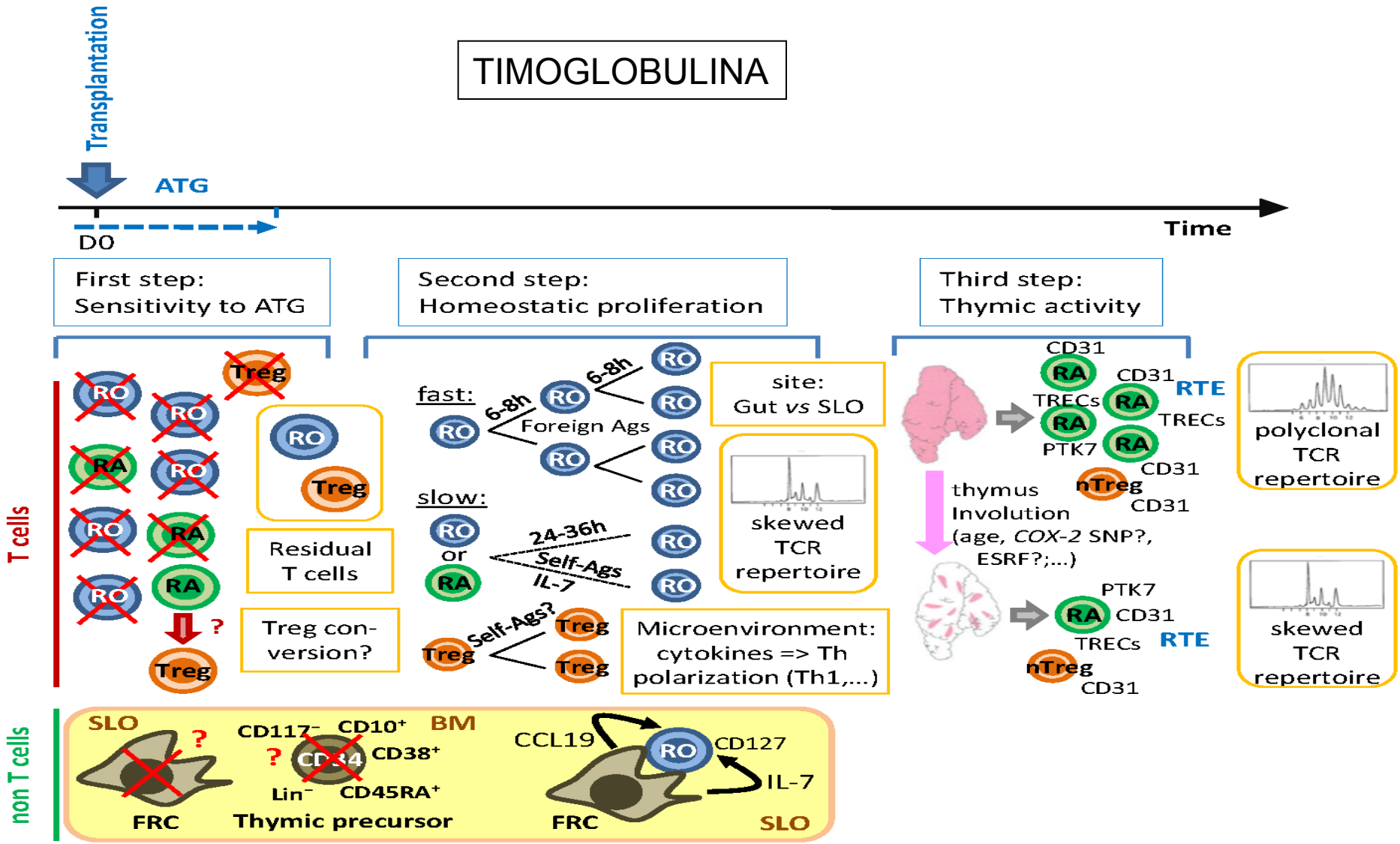


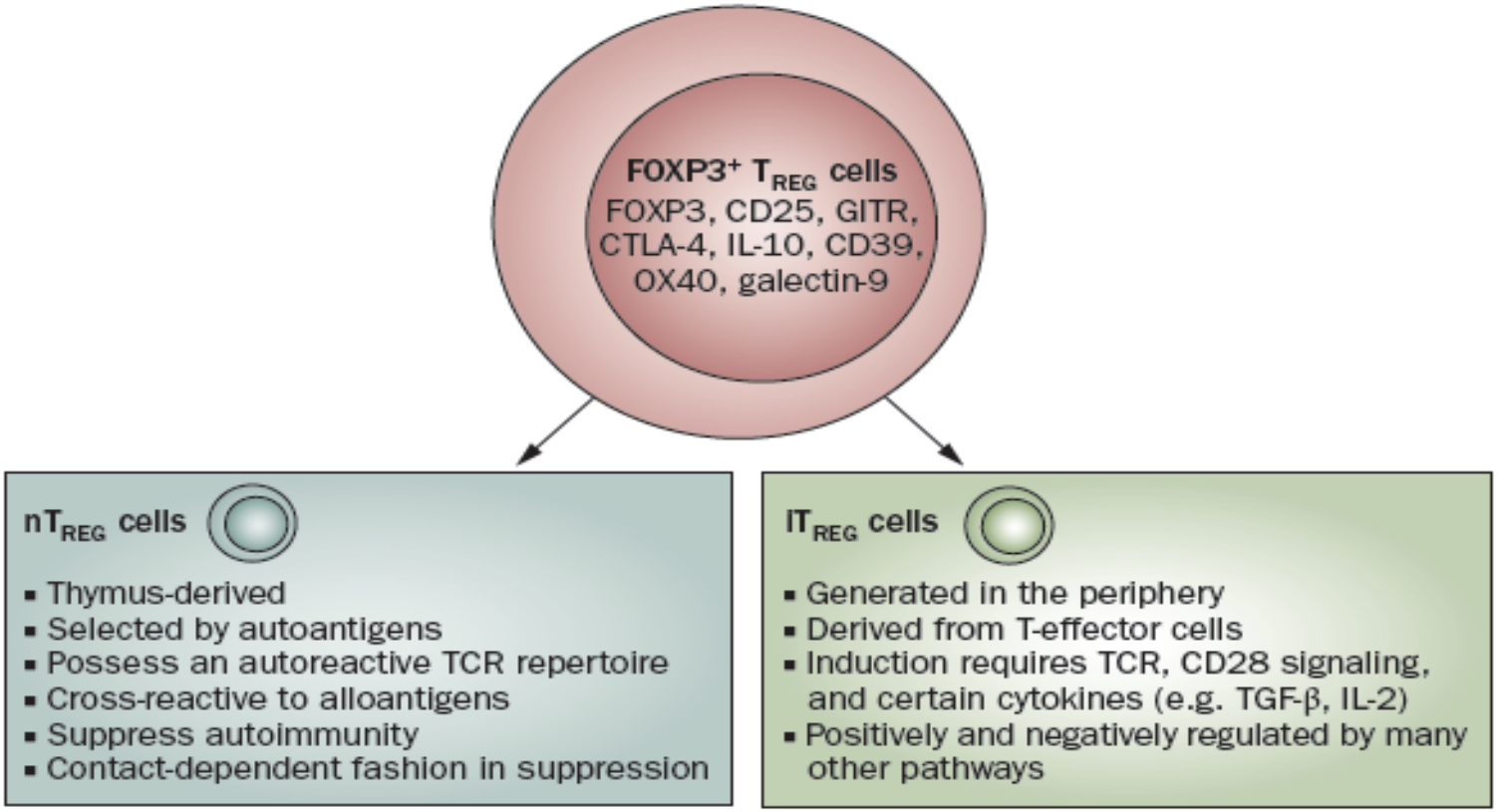
Figure 1 | Effects of proteinuria on tubular epithelial cells. Increased protein absorption by tubular cells may result in direct tubular toxicity, release of chemokines and cytokines, increased expression of adhesion and MHC class II molecules along with co-stimulatory molecules. The net effect is an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

TIMOGLOBULINA



Consequences for RTR:	Immunodeficiency	Altered T cell responses T cell exhaustion	Persistent lymphopenia => LIP
Leading to:	=> Infections => Cancers	=> Accelerated atherosclerosis => Cancers	=> Accelerated atherosclerosis => Cancers

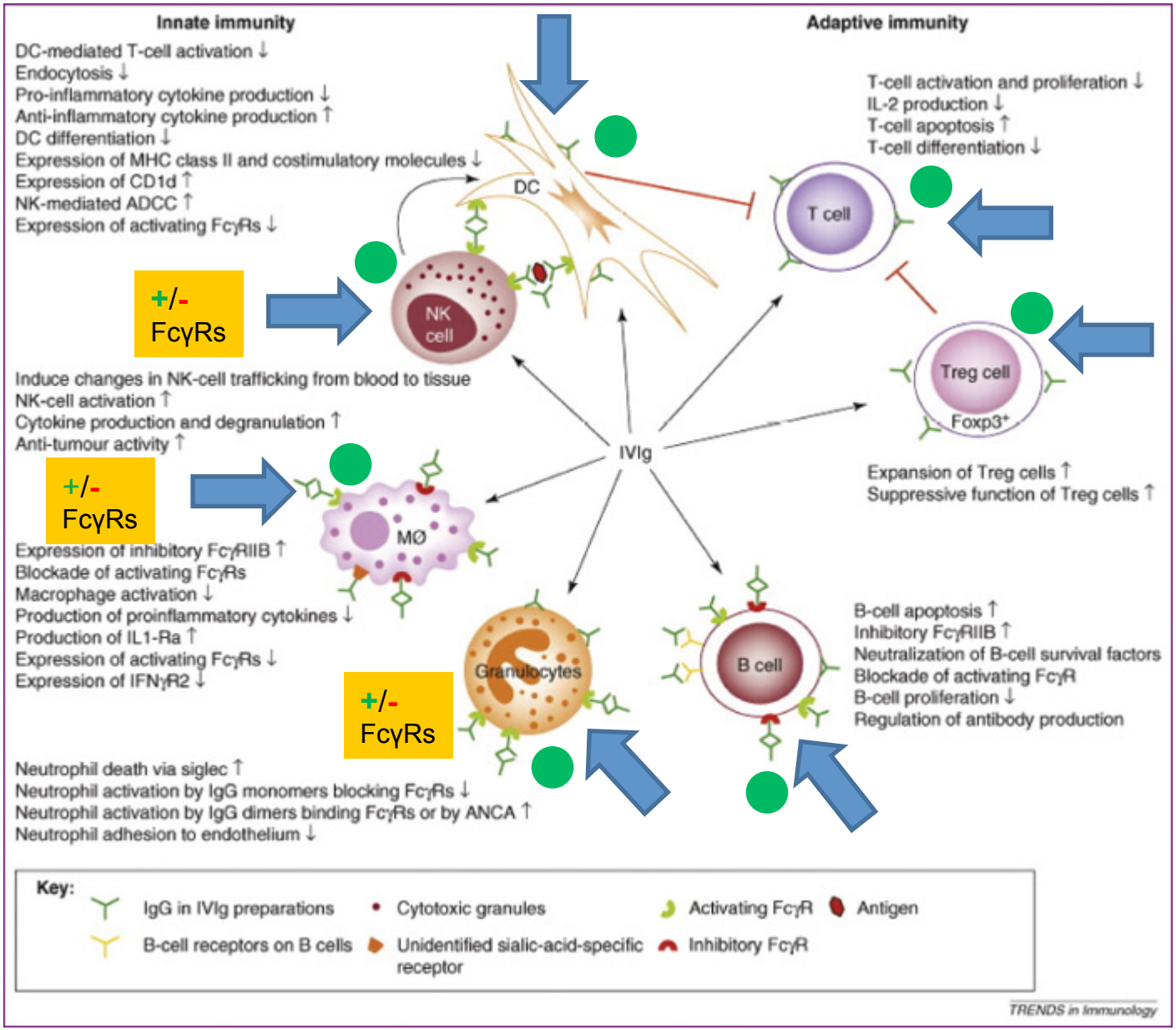
Legend: naive CD4⁺ T cells: RA ; activated/memory CD4⁺ T cells: RO ; CD4⁺ regulatory T cells: Treg



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

INMUNOGLOBULINA INTRAVENOSA



Trends Immunol. 2008;29:608-615

BELATACEPT

Proteína de fusión soluble

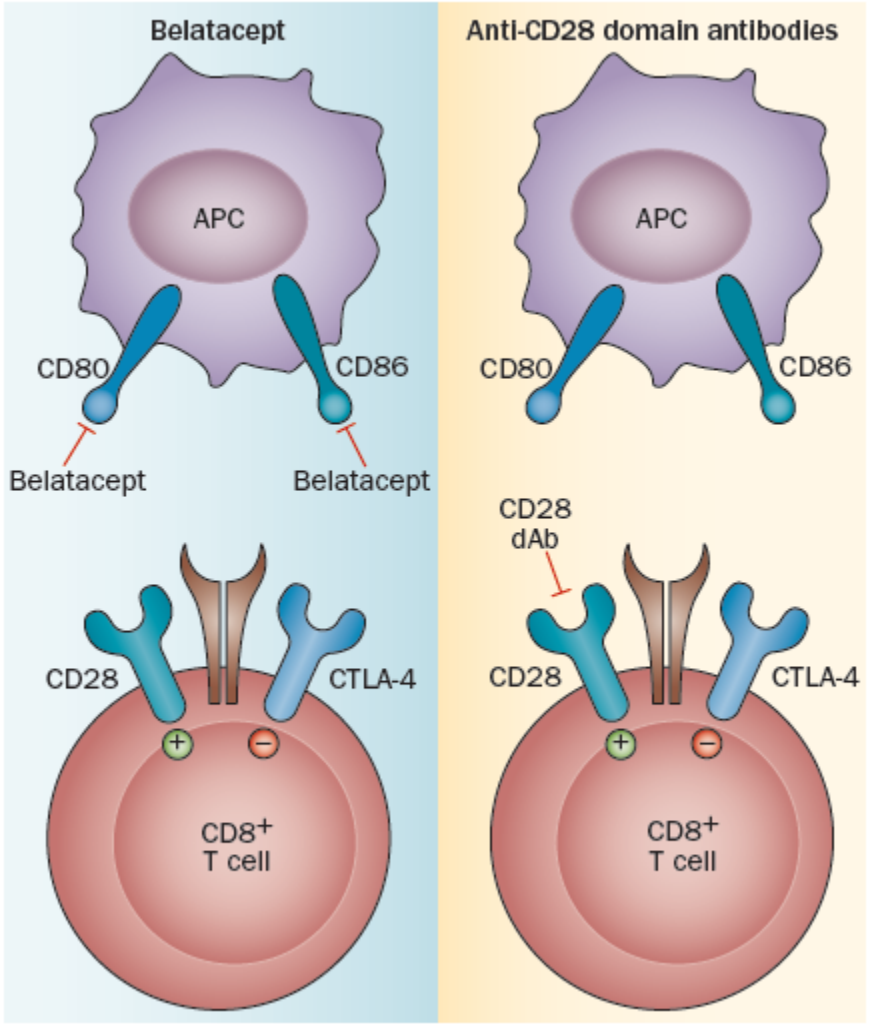
Bloqueador de la coestimulación selectiva de los linfocitos T.

Se une al **CD80 (B-7)** y al **CD86** en las células presentadoras de antígenos.

Bloquea la coestimulación mediada por CD28 de los linfocitos T.

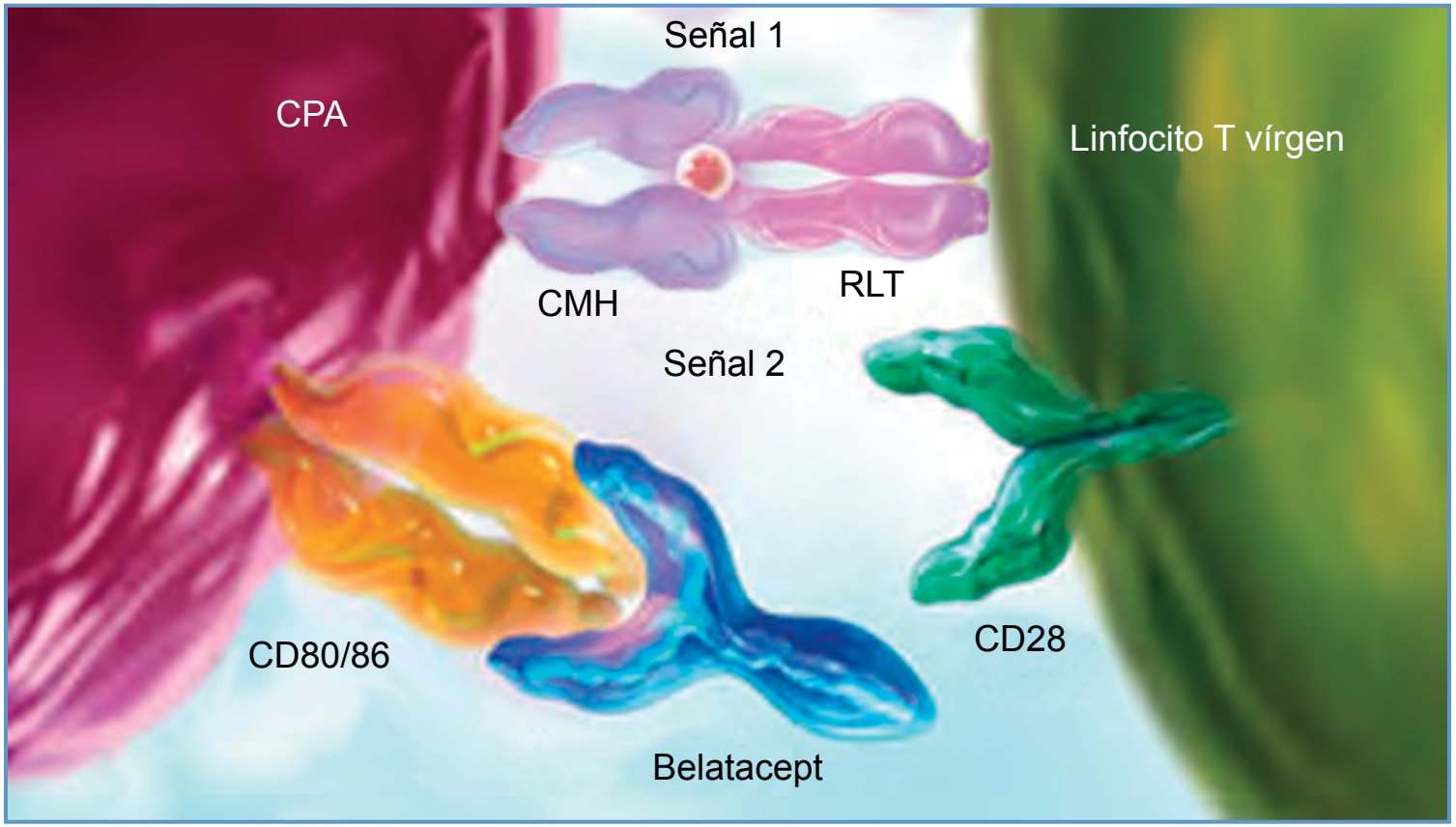
Inhibe la proliferación de linfocitos T.

Inhibe la producción de IL-2, interferón-γ, IL-4, y TNF-α.

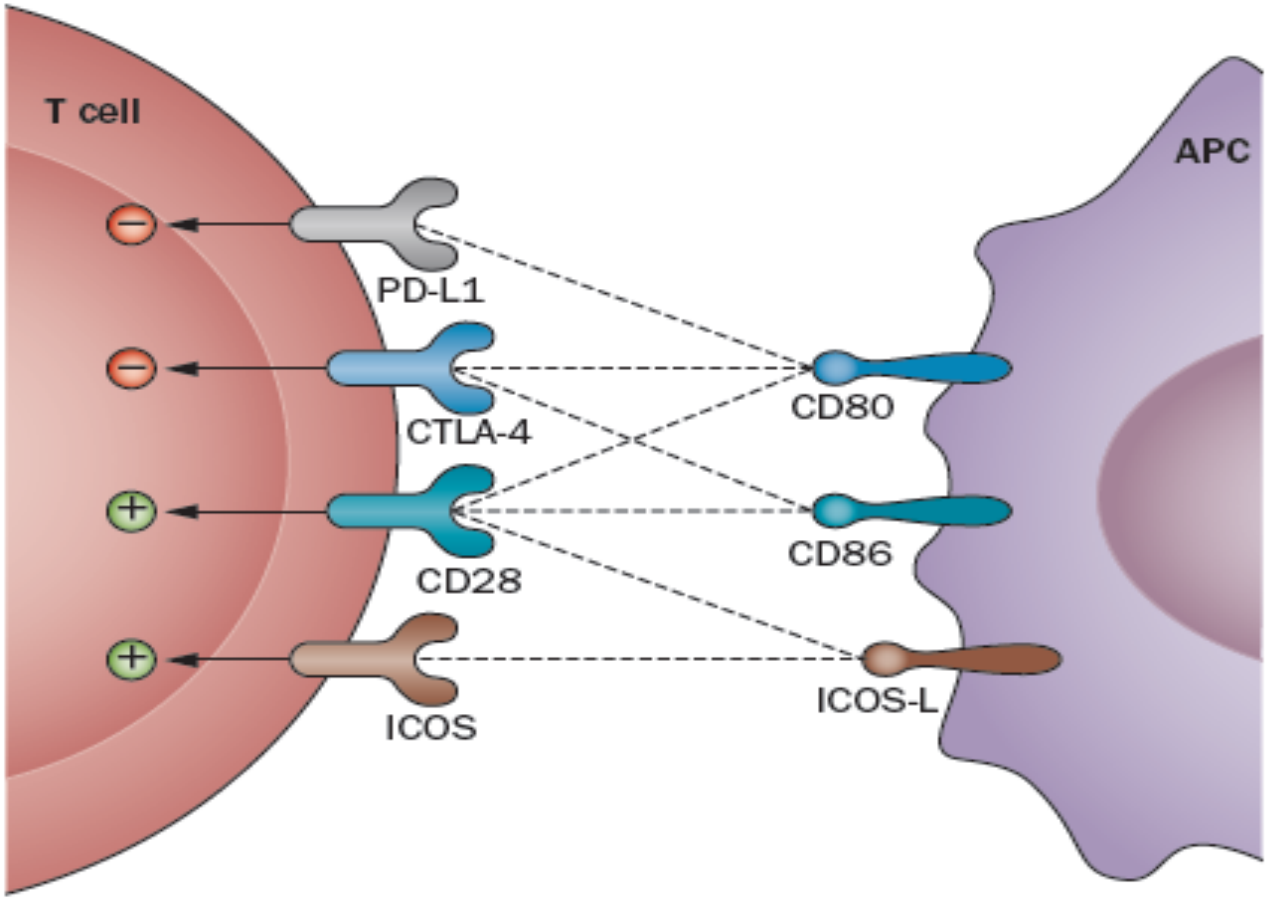


Belatacept Mecanismo de Acción

Belatacept es el primer bloqueador de la coestimulación para el mantenimiento de la inmunosupresión en el trasplante renal



Bloquea la coestimulación mediada por CD28 de los linfocitos T



CD28, T-cell-specific surface glycoprotein CD28
CD80/B7, T-lymphocyte activation antigen CD80
CD86, T-lymphocyte activation antigen CD86
CTLA-4, cytotoxic T-lymphocyte protein 4
ICOS, inducible T-cell co-stimulator
ICOS-L, inducible T-cell co-stimulator ligand
PD-L1, programmed cell death 1 ligand 1.

Ford, M. L. *et al. Nat. Rev. Nephrol.* **10**, 14–24 (2014)

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

A New Era of Podocyte-Targeted Therapy for Proteinuric Kidney Disease

Börje Haraldsson, M.D., Ph.D.

This article was published on November 8, 2013, at NEJM.org.

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

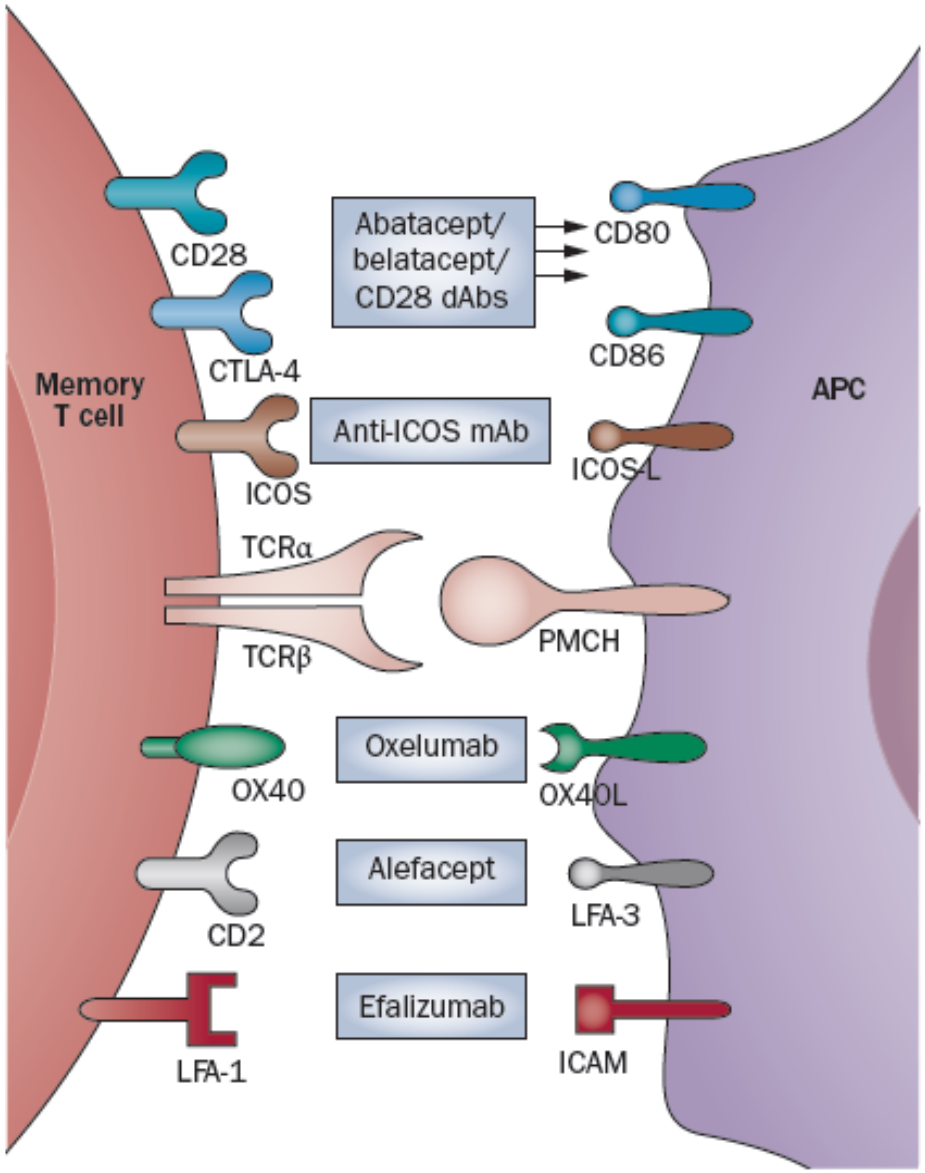
Abatacept in B7-1–Positive Proteinuric Kidney Disease

Chih-Chuan Yu, M.Sc., Alessia Fornoni, M.D., Ph.D., Astrid Weins, M.D., Ph.D., Samy Hakroush, M.D., Dony Maiguel, Ph.D., Junichiro Sageshima, M.D., Linda Chen, M.D., Gaetano Ciancio, M.D., Mohd. Hafeez Faridi, Ph.D., Daniel Behr, Kirk N. Campbell, M.D., Jer-Ming Chang, M.D., Hung-Chun Chen, M.D., Jun Oh, M.D., Christian Faul, Ph.D., M. Amin Arnaout, M.D., Paolo Fiorina, M.D., Ph.D., Vineet Gupta, Ph.D., Anna Greka, M.D., Ph.D., George W. Burke III, M.D., and Peter Mundel, M.D.

CD-80

This article was published on November 8, 2013, at NEJM.org.

N Engl J Med 2013.
DOI: 10.1056/NEJMoa1304572



Abatacept is a costimulatory inhibitor that targets **B7-1** (**CD80**).

5 patients who had **FSGS** (4 with recurrent FSGS after transplantation and 1 with primary FSGS) and proteinuria with **B7-1** immunostaining of podocytes in kidney-biopsy specimens.

Abatacept induced partial or complete remissions of **proteinuria**, suggesting that **B7-1** may be a useful biomarker for the treatment of some glomerulopathies.

Abatacept may stabilize **β1-integrin** activation in podocytes and reduce proteinuria in patients with B7-1–positive glomerular disease.

N Engl J Med 2013.
DOI: 10.1056/NEJMoa1304572

New pathophysiological insights and treatment of ANCA-associated vasculitis

Kidney International (2011) **79**, 599–612

Benjamin Wilde[1,2], Pieter van Paassen[1], Oliver Witzke[2] and Jan Willem Cohen Tervaert[1]

Principle	Mechanism	Agent	Evidence	References
Depletion of effector T cells	Antibodies directed against CD25 deplete activated T cells	Basiliximab Daclizumab	Experimental + clinical evidence (RA+Tx) Ongoing RCT in AAV	179, 180 NCT0040248
Regulation of effector T cells	Blockade of CD28/CD80 dependent T cell activation	Abatacept, Belatacept (both CTLA-4 fusion proteins)	Experimental + clinical evidence (RA+Tx) Ongoing trial in AAV	172 NCT00468208
Block adhesion of neutrophils	Blockade of CD11b/ICAM-1 mediated adhesion to endothelium		Experimental evidence	18,178
Limit activation/ recruitment of neutrophils	Inhibition of C5 cleavage. Blockade of C5a receptor on neutrophils	Eculizumab, Pexelizumab (both anti-C5)	Experimental evidence	73, 74
Enhance vascular repair	Promote EPC mobilization and function	EPO Statins	Experimental + clinical evidence	173–176
Inhibition of migration	Blockade of a4-integrins on T cells	Natalizumab	Experimental + clinical evidence in MS	169, 170
Interfere with granuloma formation	Blockade of TNF-α	Infliximab Adalimumab	Experimental + clinical evidence in AAV	90, 134–136
Depletion of B cells	B-cell depletion by antibodies recognizing CD20/CD22	Rituximab, Epratuzumab (both anti-CD20)	Experimental + clinical evidence in AAV	118–122, 166, 177
Inhibition of B-cell maturation	Neutralization of BLys. Blockade of BLys-receptors on B cells	Belimumab (anti-BLys) Atacicept (anti-TACI)	Experimental evidence	118–122, 166, 177
Anti-microbial treatment	Reduction of microbial flora that might trigger disease flares	Cotrimoxazol	Experimental + clinical evidence in AAV	45, 48–51

Targeting co-stimulatory pathways: transplantation and autoimmunity

Mandy L. Ford, Andrew B. Adams and Thomas C. Pearson

Ford, M. L. *et al. Nat. Rev. Nephrol.* **10**, 14–24 (2014)

Key points

- T-cell co-stimulatory signals, expressed either constitutively or upon activation, critically affect the magnitude and character of autoreactive or alloreactive T-cell responses
- Targeting T-cell co-stimulation pathways to reduce pathological T-cell responses has met with therapeutic success in many instances, but challenges remain
- Efficacy of co-stimulatory blockade with abatacept or belatacept could be further optimized to improve inhibition of alloreactive and autoreactive T-cell responses by leaving co-inhibitory signals intact
- Clinical application of CD154 pathway blockade has, thus far, been limited, but novel reagents in development might allow for therapeutic manipulation of this pathway to achieve immunological tolerance
- Several other T-cell co-stimulatory pathways also hold promise as therapeutic targets for the treatment of autoimmunity and transplant rejection
- Understanding the interplay between individual co-stimulatory and co-inhibitory pathways will lead to rational and targeted therapeutic interventions to manipulate T-cell responses and improve clinical outcomes

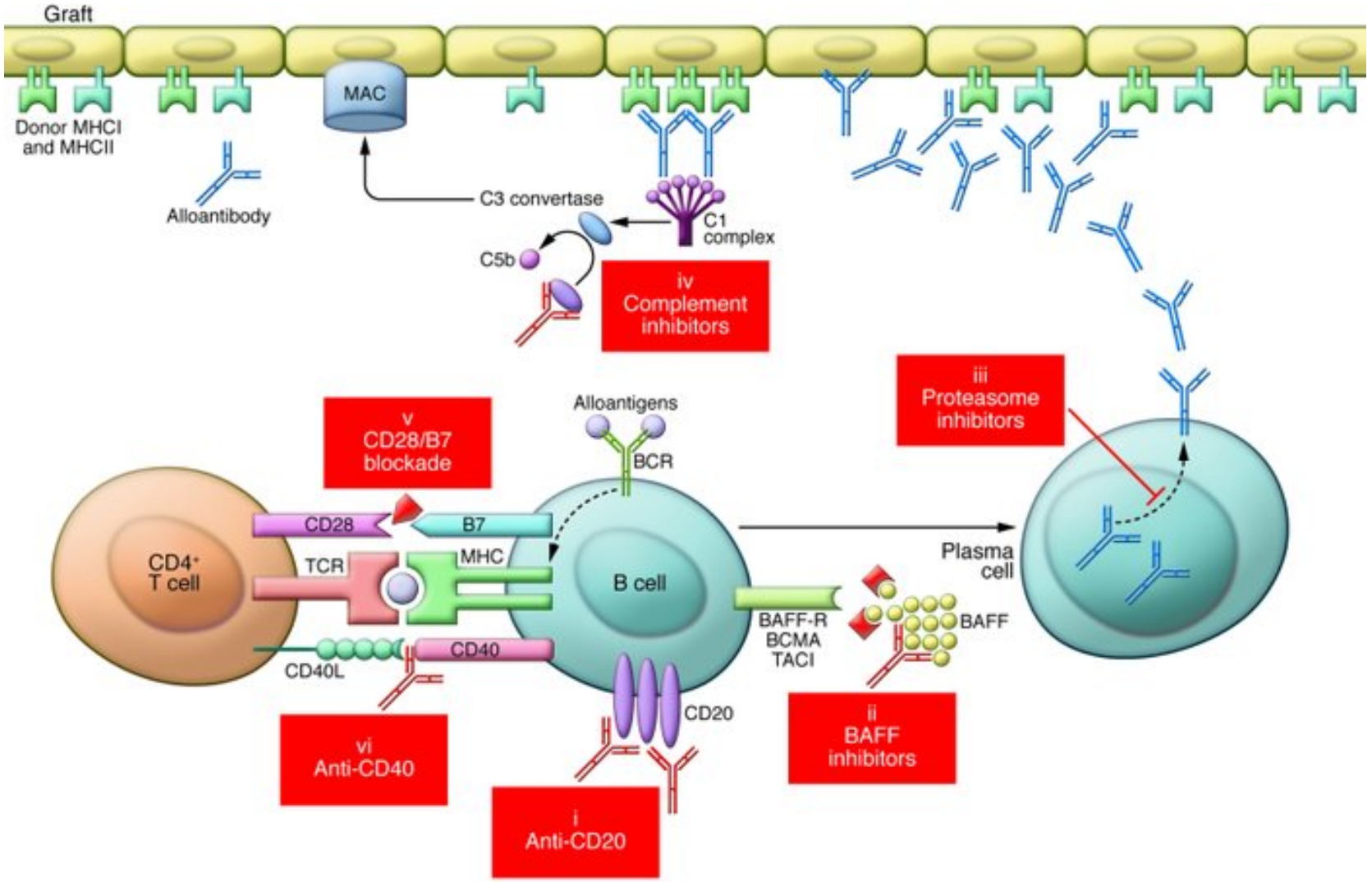
MONOCLONALES

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 -li(m)- = lymphocyte, immunomodulator -tu- = tumor (miscellaneous)	-o- = mouse -axo- = mouse–rat hybrid -xi- = chimeras -zu- = humanized -u- = human	-mab = monoclonal antibody

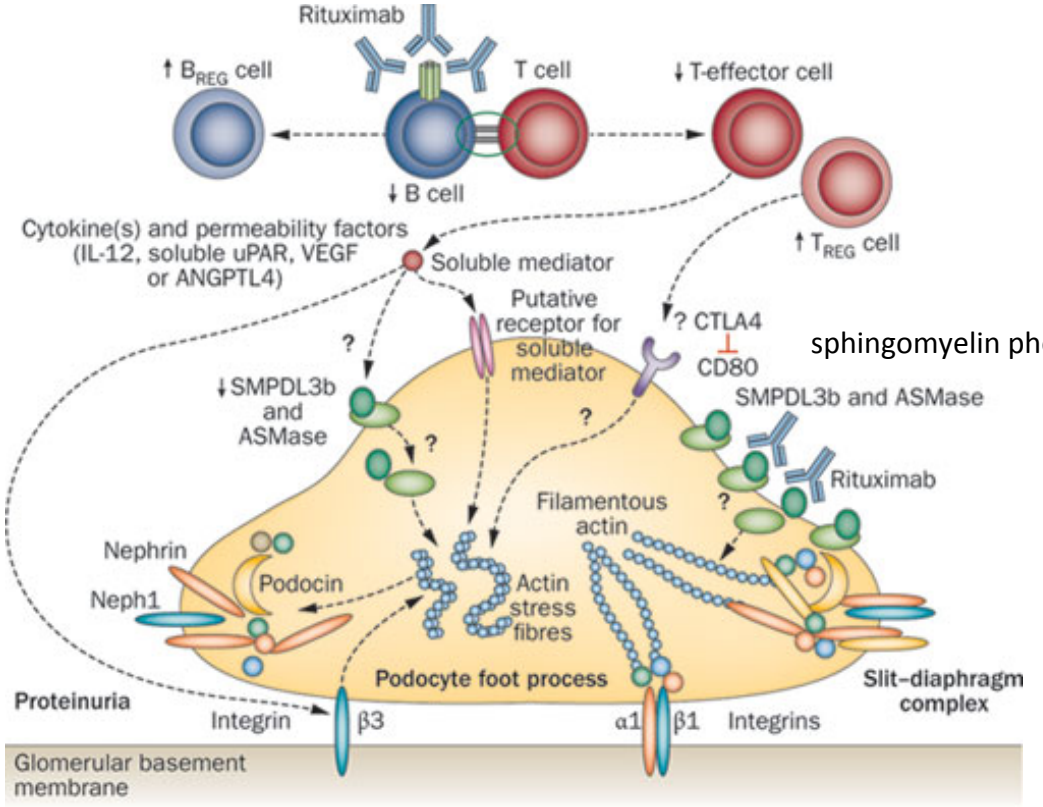
[a]Final letter of the first infix can be deleted when pronunciation is difficult. Each monoclonal antibody name consists of a unique prefix, a first infix related to the molecular target, a second infix that describes the source species of the product, and the suffix '-mab'. Names of other biologic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

RITUXIMAB


Graft
Donor MHCI and MHCII
MAC
Alloantibody
C3 convertase
C1 complex
C5b
iv Complement inhibitors
iii Proteasome inhibitors
v CD28/B7 blockade
Alloantigens
BCR
CD28
B7
CD4+ T cell
TCR
MHC
B cell
Plasma cell
BAFF-R BCMA TACI
BAFF
CD40L
CD40
CD20
vi Anti-CD40
ii BAFF inhibitors
i Anti-CD20

Rituximab therapy in nephrotic syndrome: implications for patients' management

Sinha, A. & Bagga, A. *Nat. Rev. Nephrol.* **9**, 154–169 (2013);

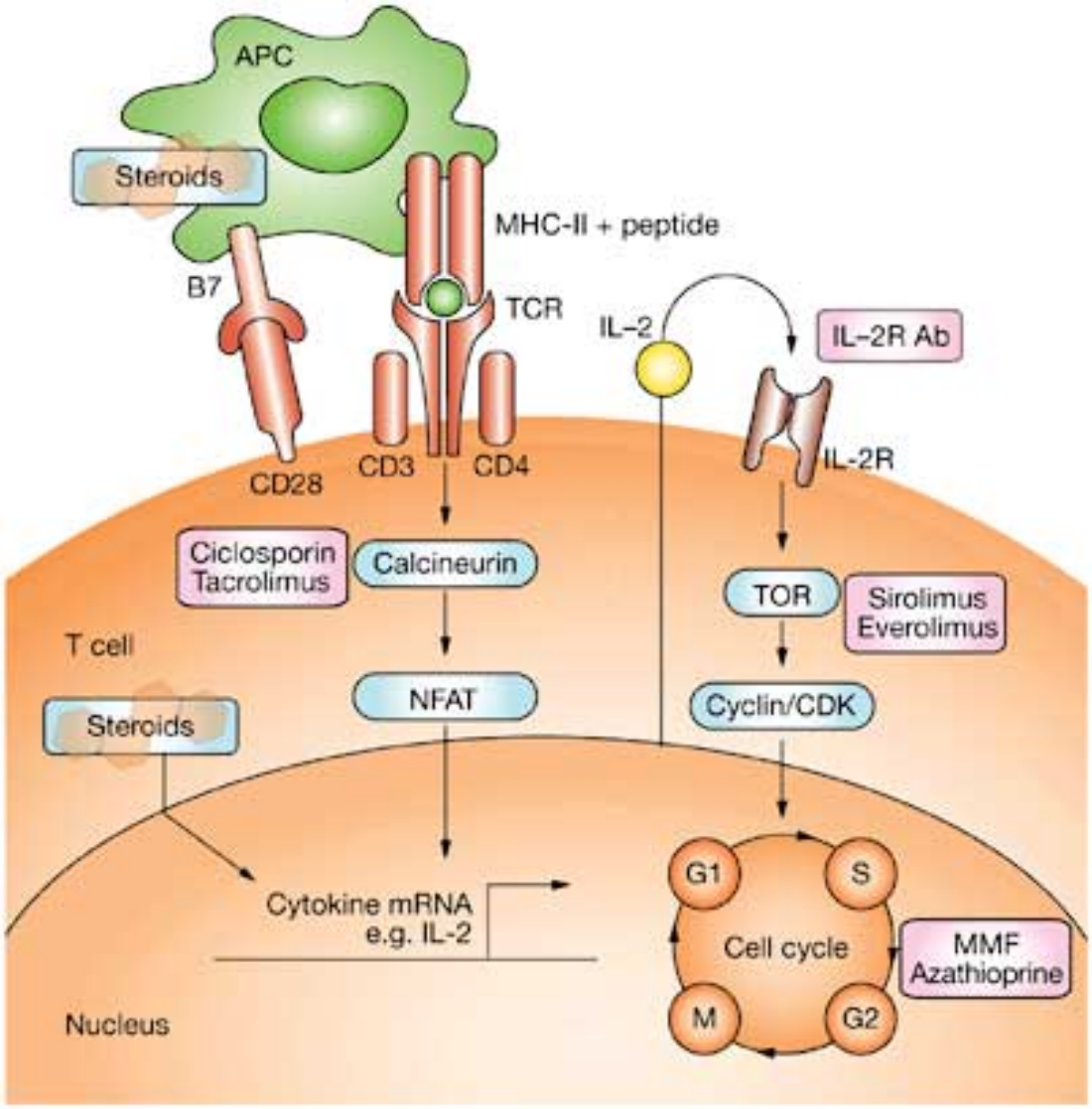


sphingomyelin phosphodiesterase acid-like 3b

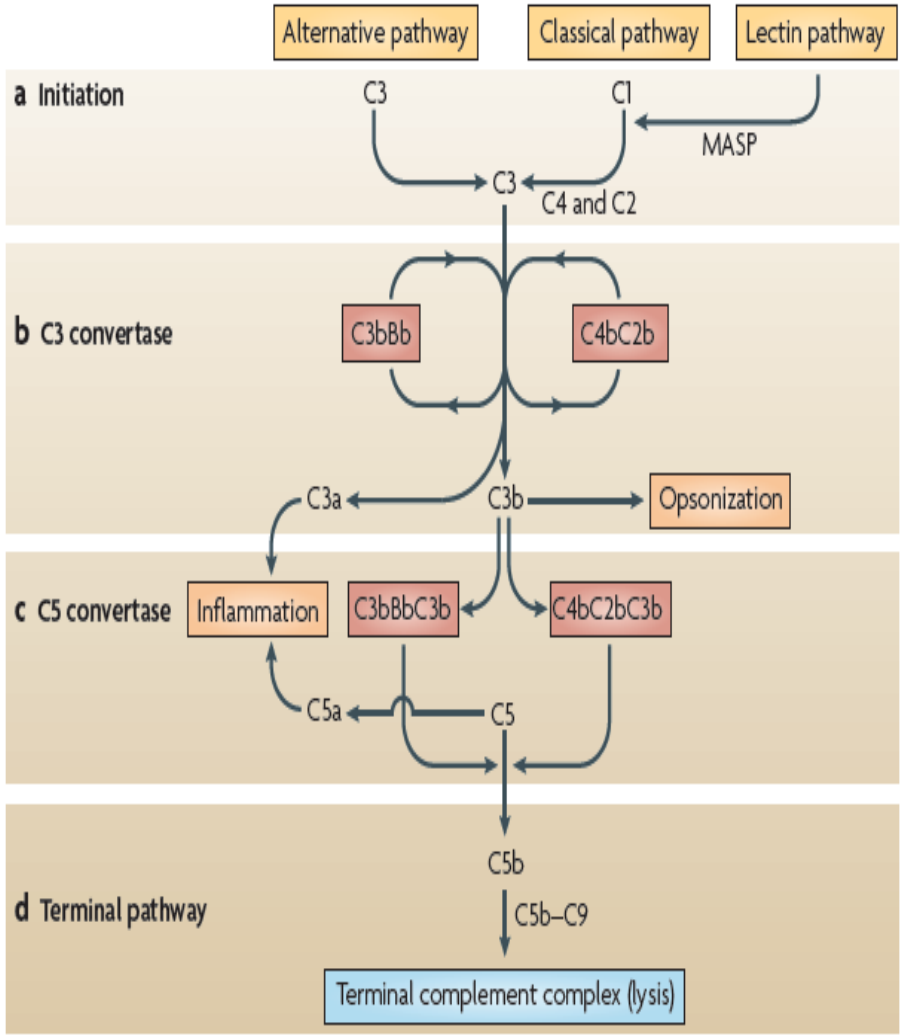
Primary focal and segmental glomerulosclerosis and soluble factor urokinase-type plasminogen activator receptor

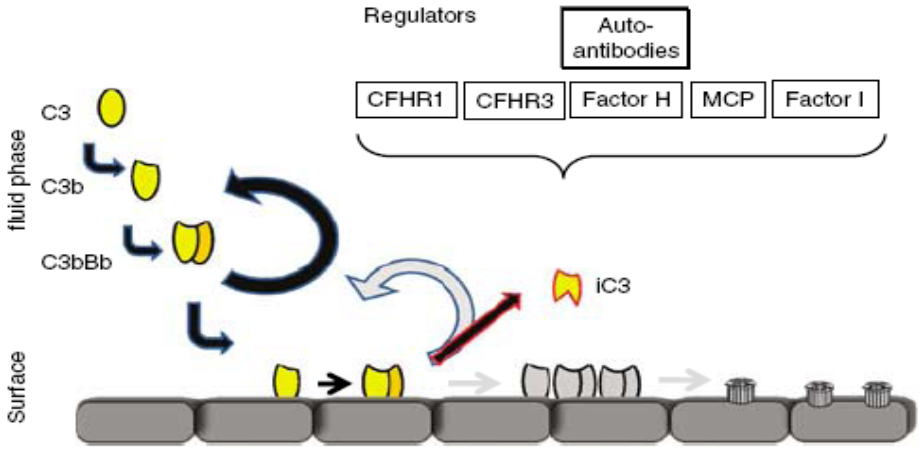
Hernán Trimarchi *World J Nephrol* 2013 November 6; 2(4): 103-110

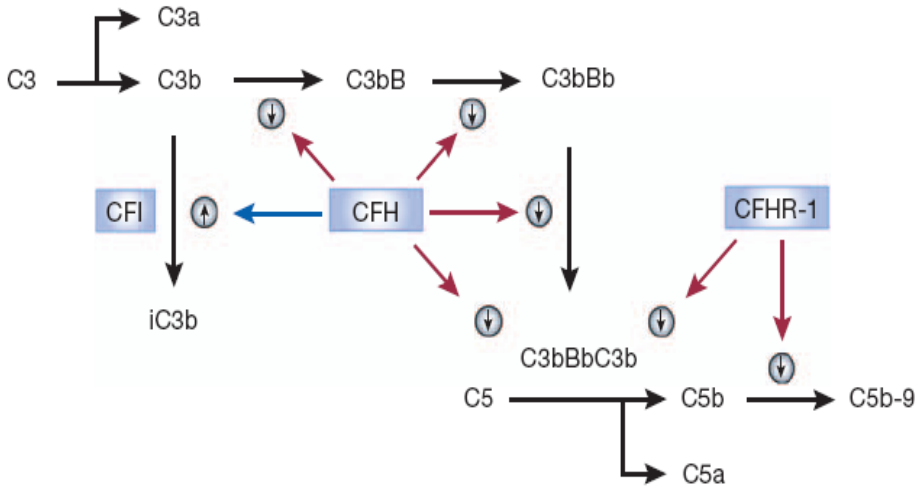
BASILIXIMAB



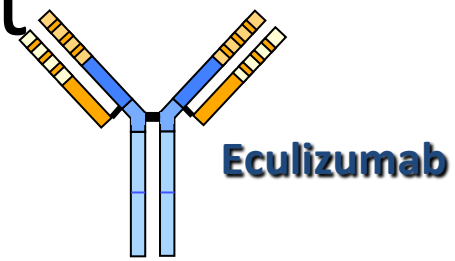
ECULIZUMAB


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)

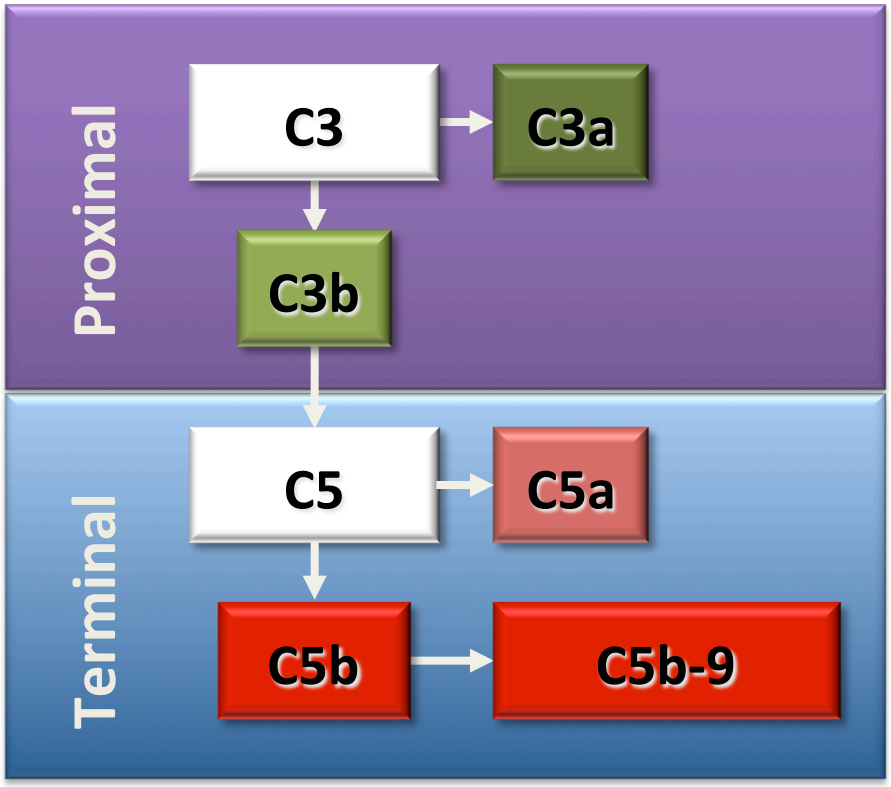

Regulators
Auto-antibodies
CFHR1
CFHR3
Factor H
MCP
Factor I
fluid phase
Surface
C3
C3b
C3bBb
iC3


C3
C3a
C3b
C3bB
C3bBb
CFI
CFH
CFHR-1
iC3b
C3bBbC3b
C5
C5b
C5b-9
C5a

ECULIZUMAB Blocks Terminal Complement



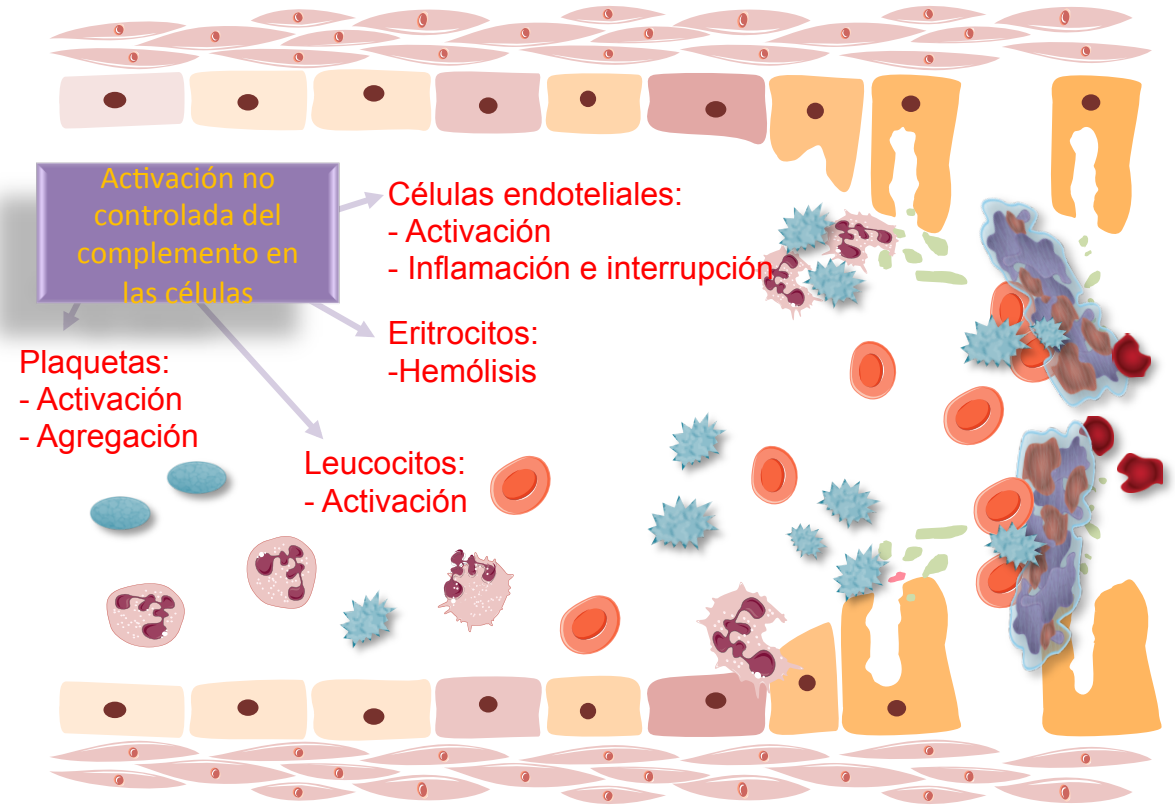
Complement Cascade



- 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.

Activación Crónica No Controlada del Complemento lleva a Daño endotelial y del órgano terminal



Consecuencias clínicas:

Consumo plaquetario

Hemólisis mecánica

Trombos vasculares

Oclusión de vasos

Inflamación

Isquemia

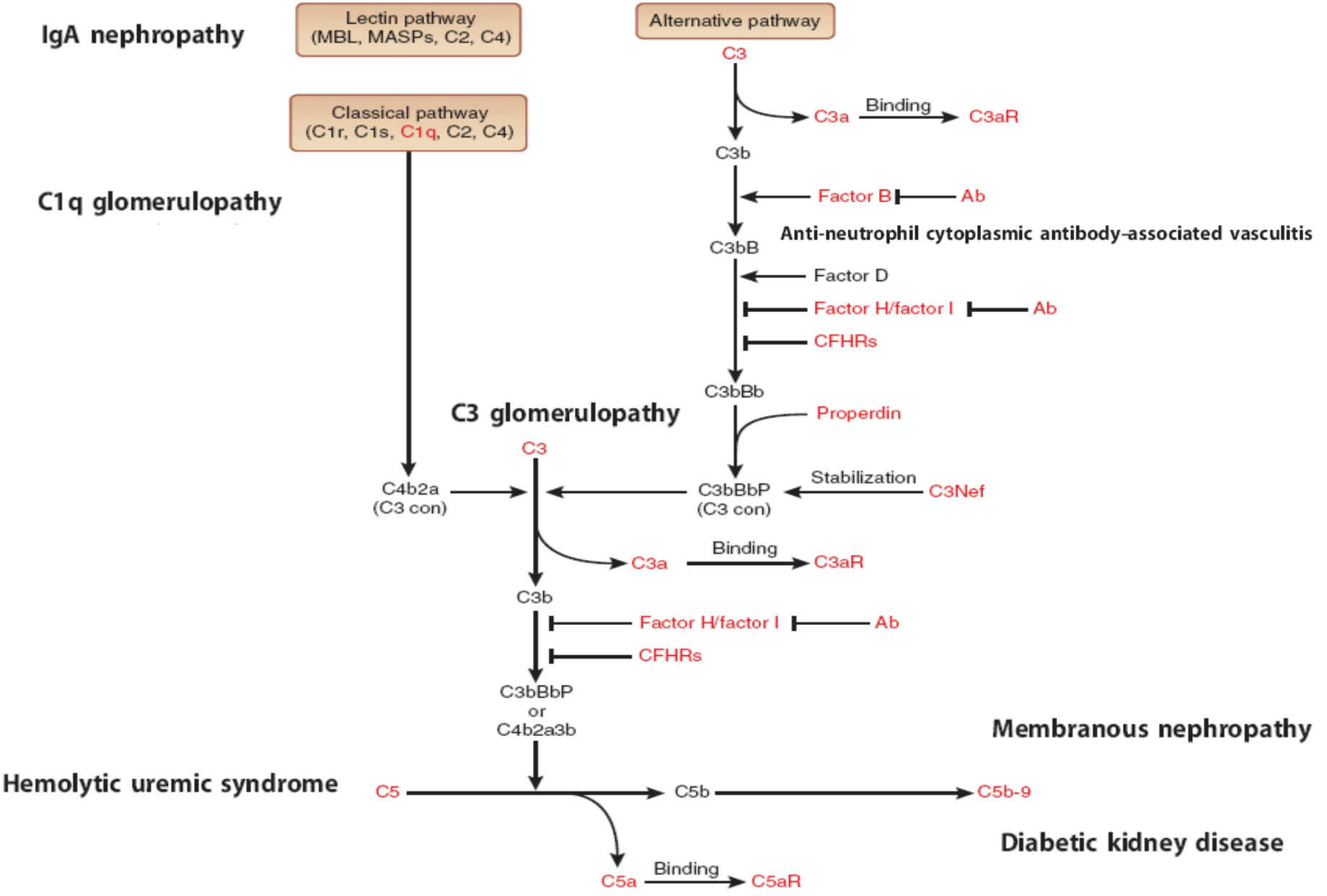
↓

Complicaciones sistémicas multiorgánicas

Modificada por Zipfel y Jokiranta de Desch *et al. JASN* 2007;18:2457–6240; Licht C *et al. Blood* 2009 114:4538–4545; Noris M *et al. NEJM* 2009;361:1676–687; Stahl A *et al. Blood* 2008;111:5307–5315; Morigi *et al. J Immunol* 2011

Novel roles of complement in renal diseases and their therapeutic consequences

Kidney International (2013) **84**, 441–450



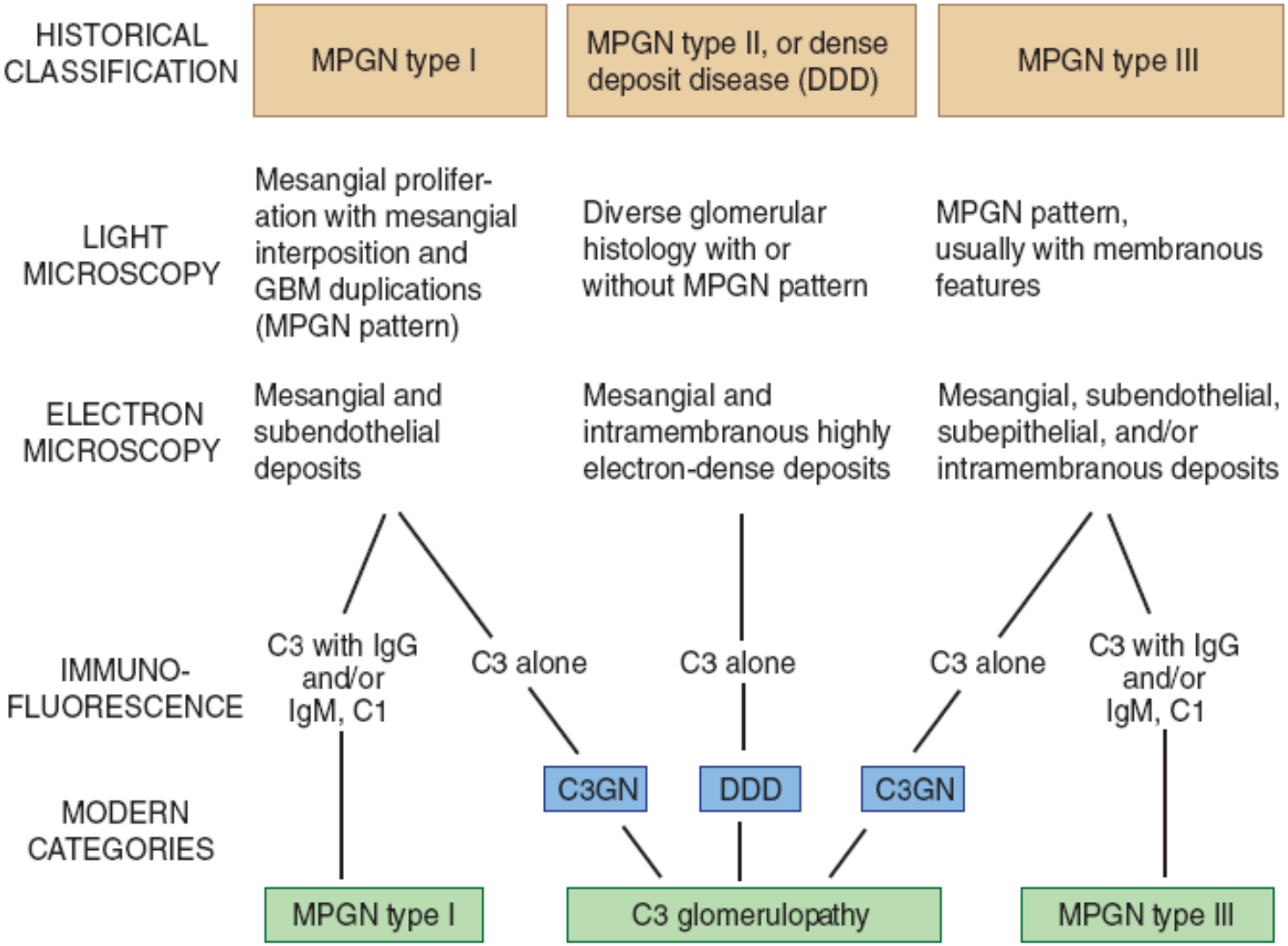
C3 glomerulopathy: what's in a name?

Vivette D. D'Agati[1] and Andrew S. Bomback[2]

Kidney International (2012) **82,** 379–381. doi:10.1038/ki.2012.80

GLOMERULOPATÍA POR C3

DDD
Glomerulonefritis x C3
CFRH5



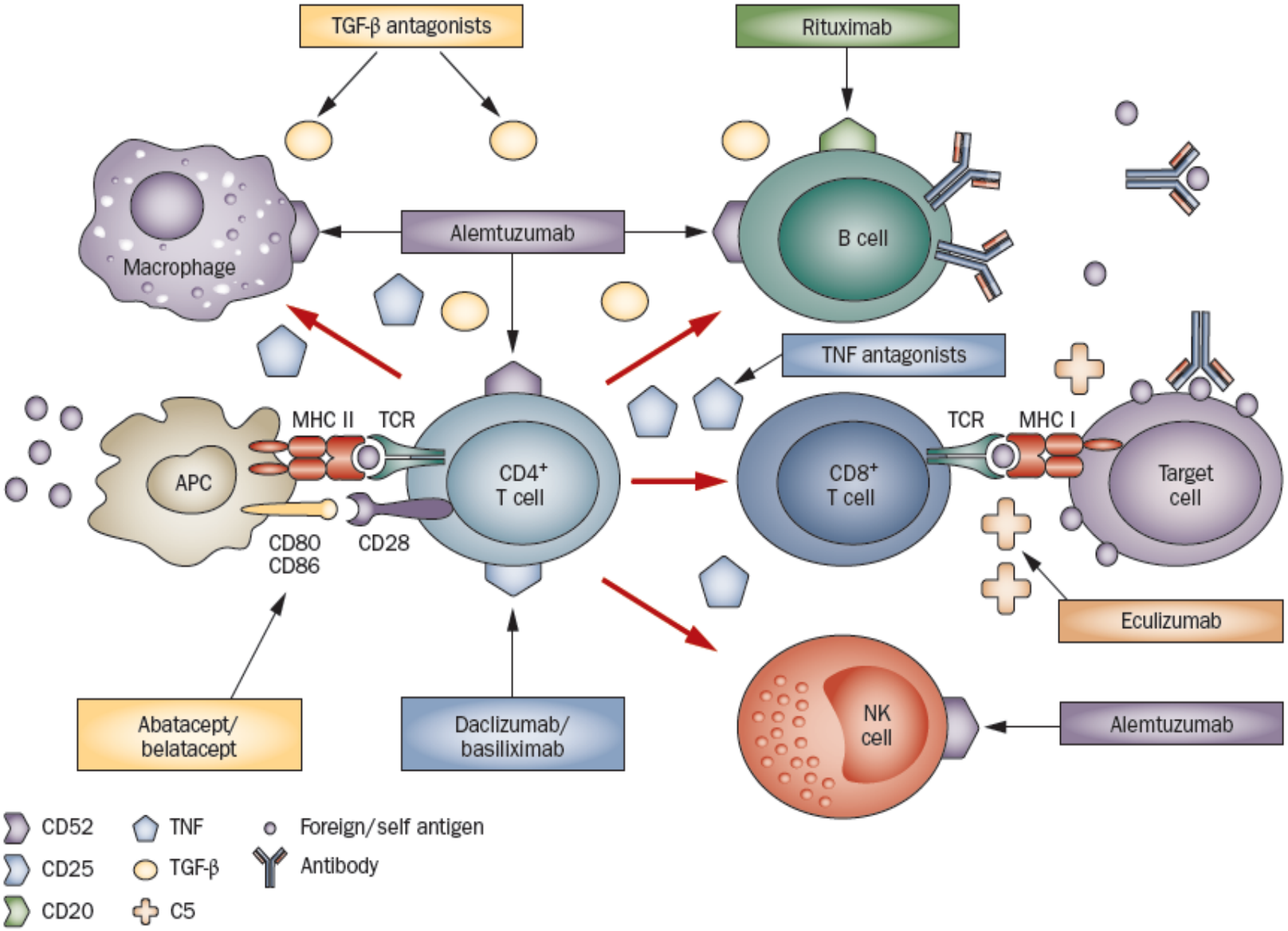
Kidney International (2012) **82,** 379–381. doi:10.1038/ki.2012.80

Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies

Julien Zuber, Fadi Fakhouri, Lubka T. Roumenina, Chantal Loirat and Véronique Frémeaux-Bacchi on behalf of the French Study Group for aHUS/C3G

Zuber, J. *et al. Nat. Rev. Nephrol.* **8**, 643–657 (2012)

NO ES TRATAMIENTO DE PRIMERA LÍNEA Y ES OFF-LABEL AL AÑO 2014


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

J Artif Organs (2011) 14:9–22
DOI 10.1007/s10047-010-0529-5

REVIEW

Benefits and limitations of plasmapheresis in renal diseases: an evidence-based approach

Sanjeev Baweja · Kate Wiggins · Darren Lee · Susan Blair · Margaret Fraenkel · Lawrence P. McMahon

Received: 21 September 2010 / Accepted: 8 November 2010 / Published online: 10 December 2010

Abstract In use for over 50 years, the rationale for plasmapheresis remains based largely on case series and retrospective studies. Recently, results from several randomized controlled trials, meta-analyses, and prospective studies have shown plasmapheresis may be of benefit in various renal diseases, and have provided insights into more rational use of this therapy. A multicenter trial by the European Vasculitis Study Group has shown it is the preferred additional form of therapy for patients with anti-neutrophil cytoplasmic antibody-associated glomerulonephritis and severe renal failure. A recent study conducted at Mayo Clinic also found it effective at reversing renal failure from myeloma-related cast nephropathy if serum free light chain levels were reduced by at least 50%. In addition, a Cochrane review has analyzed the available evidence for its use in thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. The objective of this article is to review recent and past evidence and, thereby, the current indications for treatment in renal disease.

Keywords Plasmapheresis · Renal failure · Renal transplantation · Renal diseases

S. Baweja (✉) · K. Wiggins · D. Lee · S. Blair · M. Fraenkel · L. P. McMahon (✉)
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Introduction

Plasmapheresis, or plasma exchange, is an extracorporeal blood-purification process whereby plasma is removed from the patient and artificially replaced. Abel [1] first described the process in the dog in 1914 but the first therapeutic plasmapheresis was performed by Schwab and Fehay [2] in two patients with macroglobulinemia in 1960. Since then, it has been widely used to remove either proven or presumed large-molecular-weight pathogens from the circulation. These include antibodies, immune complexes, monoclonal proteins, endotoxins, drugs, and cholesterol-containing lipoproteins [3]. It is essentially symptomatic therapy, removing or replacing a product rather than addressing any underlying pathology, although some theoretical immune-modulatory effects of plasmapheresis have also been proposed [4–7].

Several plasmapheresis techniques are currently available. Centrifugation-based plasma separators are most widely used, because the required blood flow can easily be achieved by cannulating a large peripheral vein, thus avoiding the need to access central veins. Other conventional forms of plasmapheresis include membrane plasma separation, cryofiltration apheresis, immunoadsorption, and chemical affinity column apheresis [8]. Compared with centrifugal devices, membrane filtration has the advantages of less platelet loss, less hemolysis, and minimum equipment requirements. Membrane filtration can be performed by using standard hemodialysis equipment, and patients with kidney injury who require both hemodialysis and plasmapheresis can receive each sequentially. However, although faster and more efficient, there seems little or no clinical advantage compared with centrifugal devices [9–11].

The amount of plasma to be replaced during plasmapheresis must be determined in relation to the patient's

estimated plasma volume (EPV), which can be calculate by use of the formula [12]:

$$EPV = [0.065 \times \text{weight (kg)}] \times (1 - \text{hematocrit}).$$

The decline in immunoglobulin levels after a single plasmapheresis is misleading, because extravascular immunoglobulins enter the vascular space at the rate of 1–3% per hour, yielding a post-treatment increase which begins to plateau after 24 h, at which time there will be a further opportunity for immunoglobulin removal. Usually, if production rates are modest, at least daily exchanges for 3 days will be required to remove 70% of the patient's initial burden, and 5 separate treatments during a 7 to 10-day period will remove 90% of the patient's initial total body burden. If production rates are high, additional treatments may be required [12–14].

The overall complication rate during plasmapheresis is approximately 10% (reports vary from 1.4 to 20%) and mostly occurs in patients receiving fresh frozen plasma (FFP) as replacement fluid. The most frequent complications are symptoms of hypocalcemia, hypovolemia, and anaphylactoid reactions [15] Serious adverse events occur in <3% of patients and the procedure-related mortality rate is very low (0.0–0.05%) [16, 17]. In particular, the infection rate does not seem to be higher in immunocompromized patients [18]. Some patients taking ACE inhibitors may experience atypical symptoms such as flushing, hypotension, bradycardia, dyspnea, and abdominal cramping [19].

The latest guidelines for use of plasmapheresis were published by the American Society for Apheresis in June 2007 [20–23]. Current indications for renal diseases are displayed in Table 1. Recently, results from several randomized controlled trials (RCTs), meta-analyses, and prospective studies have shown plasmapheresis may be of benefit in various renal diseases, and have provided some insight into more rational use of this therapy, although many of the guidelines are still not based on results from RCTs.

Anti-glomerular basement membrane (Anti-GBM) disease

Anti-glomerular basement membrane disease, when accompanied by pulmonary hemorrhage, is known as Goodpasture's disease [24]. It is caused by circulating antibodies directed against the non-collagenous domain of the α-3 chain of type IV collagen [25]. In 1975, before the introduction of plasmapheresis [26], mortality was 86–96% either from pulmonary hemorrhage or renal failure [27–29]. Since then, many uncontrolled trials or case reports have demonstrated the clinical benefits of plasmapheresis [30–36].

Table 1 Indications for plasmapheresis in renal diseases (modified from Ref. [20])

Disease	Rating
Anti-GBM disease	1
Rapidly progressive glomerulonephritis	2
Thrombotic thrombocytopenic purpura	1
Hemolytic uremic syndrome	3–4
Cryoglobulinemia	1
Multiple myeloma cast nephropathy	3
Hyperviscosity syndrome (Waldenström's macroglobulinemia)	1
Removal of cytotoxic antibodies in transplant candidate	2
Renal allograft rejection	2
Focal segmental glomerulosclerosis (recurrence after transplantation)	2
Rheumatoid arthritis/rheumatoid vasculitis	2
Antiphospholipid antibody syndrome	2
Systemic lupus erythematosis	4
Scleroderma	4

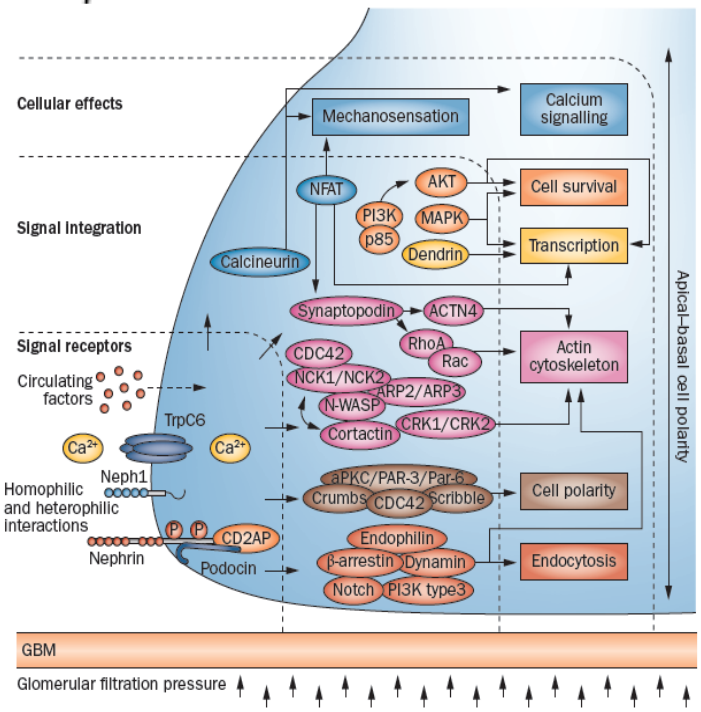
Rating: 1, standard therapy, but not mandatory; 2, available evidence tends to suggest efficacy, conventional therapy usually tried first; 3, inadequately tested at this time; 4, no demonstrated value in controlled trials

[illegible]ne randomized study has compared the immunosuppressive therapy alone (prednisone and cyclophosphamide) with immunosuppression and plasmapheresis [37]. Seventeen patients with anti-GBM disease were studied. Only 2 of 8 patients who received plasmapheresis became dialysis-dependent, in comparison with 6 of 9 in the immunosuppression alone group. Patients treated with plasmapheresis had a more rapid disappearance of anti-GBM antibodies, with mean serum creatinine value half that of the control group. Patients with <30% crescents and well preserved renal functions did well with either treatment, whereas patients with severe crescentic involvement and impaired glomerular filtration rate uniformly did poorly.

The largest published series of long-term outcomes of anti-GBM disease is from the Hammersmith Hospital, London [38]. All 71 patients received a standard regimen of plasmapheresis, oral prednisolone, and oral cyclophosphamide. Plasmapheresis (50 mL/kg to a maximum of 4 L) was performed daily for at least 14 days or until anti-GBM titers were undetectable. One-year patient and renal survival were 100 and 95%, respectively, when creatinine was <500 μmol/L (5.7 mg/dL), 83 and 82% when creatinine was ≥500 μmol/L but not dialysis-dependent, and 65 and 8% when patients were dialysis-dependent at onset. Five-year patient and renal survival were 94 and 94%, 80 and 50%, and 44 and 13%, respectively. All patients who required immediate dialysis and had 100% crescents on

Table 1 | Pathways involved in acquired glomerular diseases

Molecular pathways	Human diseases
Transmembrane receptors	
Nephrin	DNP, MCD
B7-1	LN
uPAR	FSGS, DNP
Notch	FSGS, DNP
PLA_2R	MN
Ion channels	
TRPC6	MCD, MN
Growth factors	
VEGF-A	Preeclampsia
TGF-β	DNP
Proteases	
Cathepsin L → dynamin, synaptopodin	MN, FSGS, DNP



Abbreviations: DNP, diabetic nephropathy; FSGS, focal segmental glomerulosclerosis; LN, lupus nephritis; MCD, minimal change disease; MN, membranous nephropathy; TGF-β, transforming growth factor-β; TRPC6, transient receptor potential cation channel-6; uPAR, urokinase plasminogen-activator receptor; VEGF-A, vascular endothelial growth factor A.

Only those pathways that have been shown to be involved in acquired human glomerular diseases are listed.

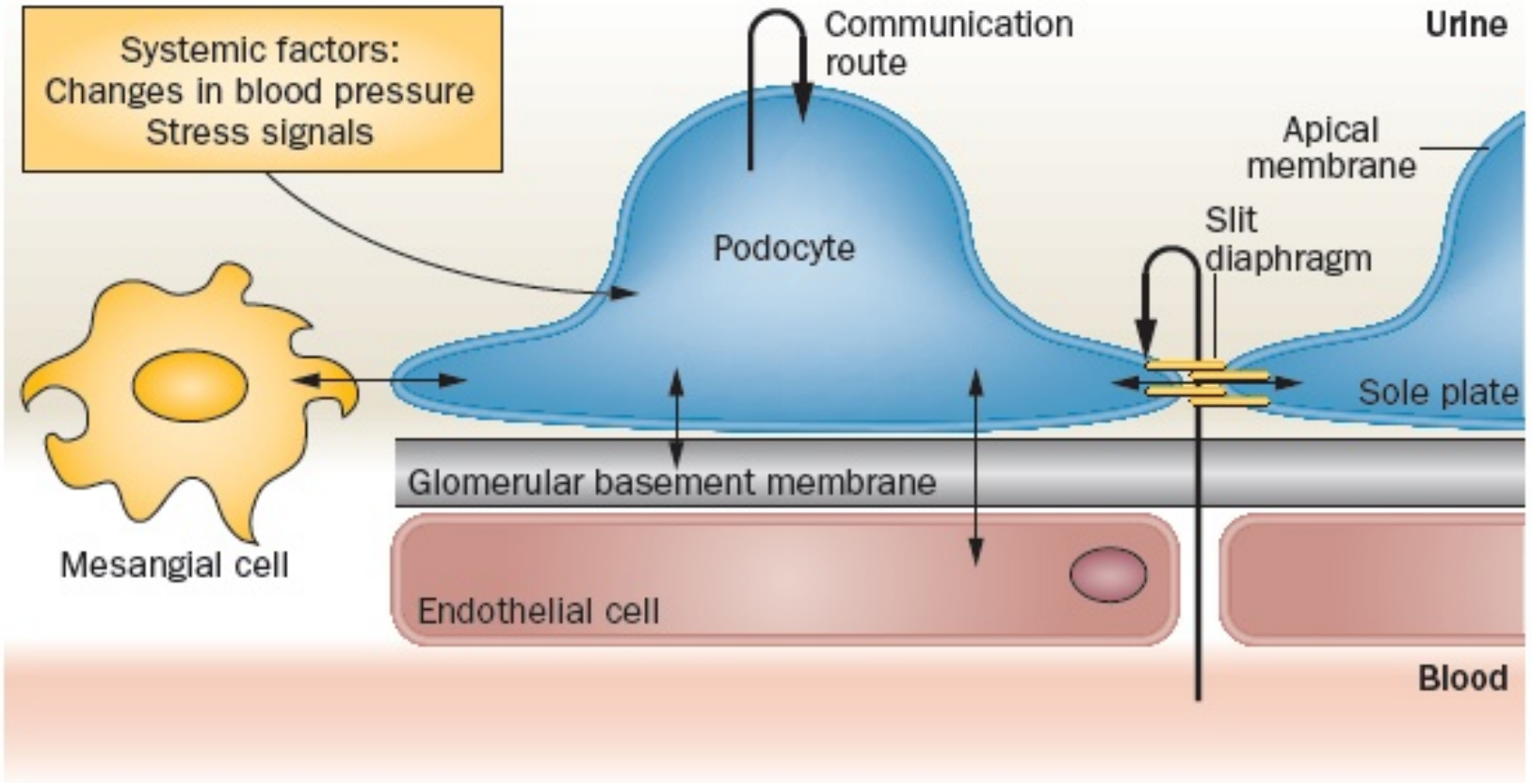
Grahammer, F. *et al. Nat. Rev. Nephrol.* **9**, 587–598 (2013)

GLOMERULOPATÍAS

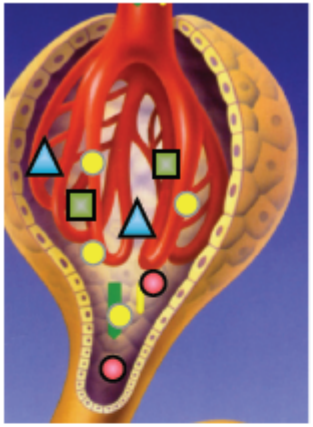
GN 1-2

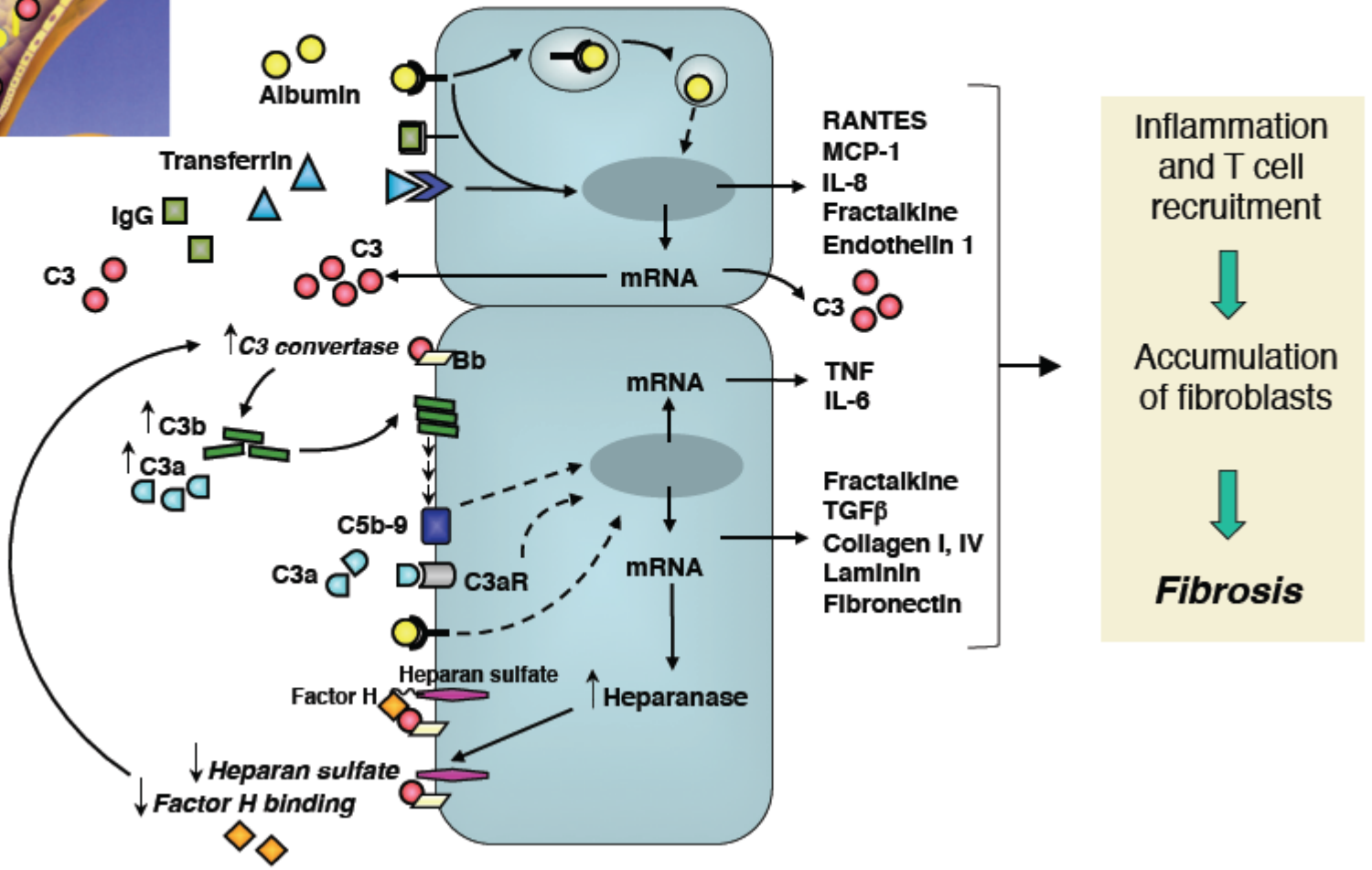
GN-TX

PROTEINURIA



Reiser, J. *et al. Nat. Rev. Nephrol.* **10**, 104–115 (2014);




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

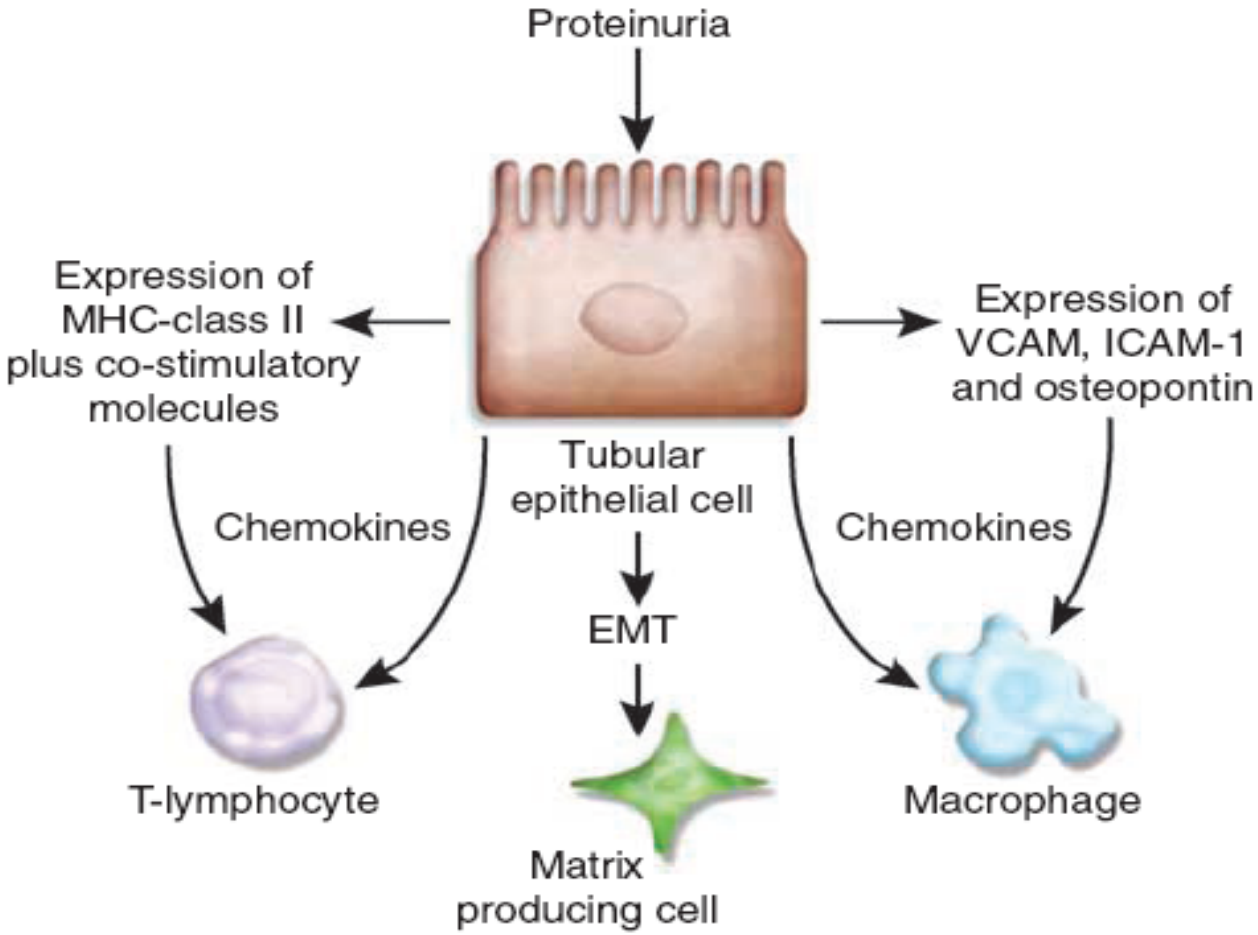
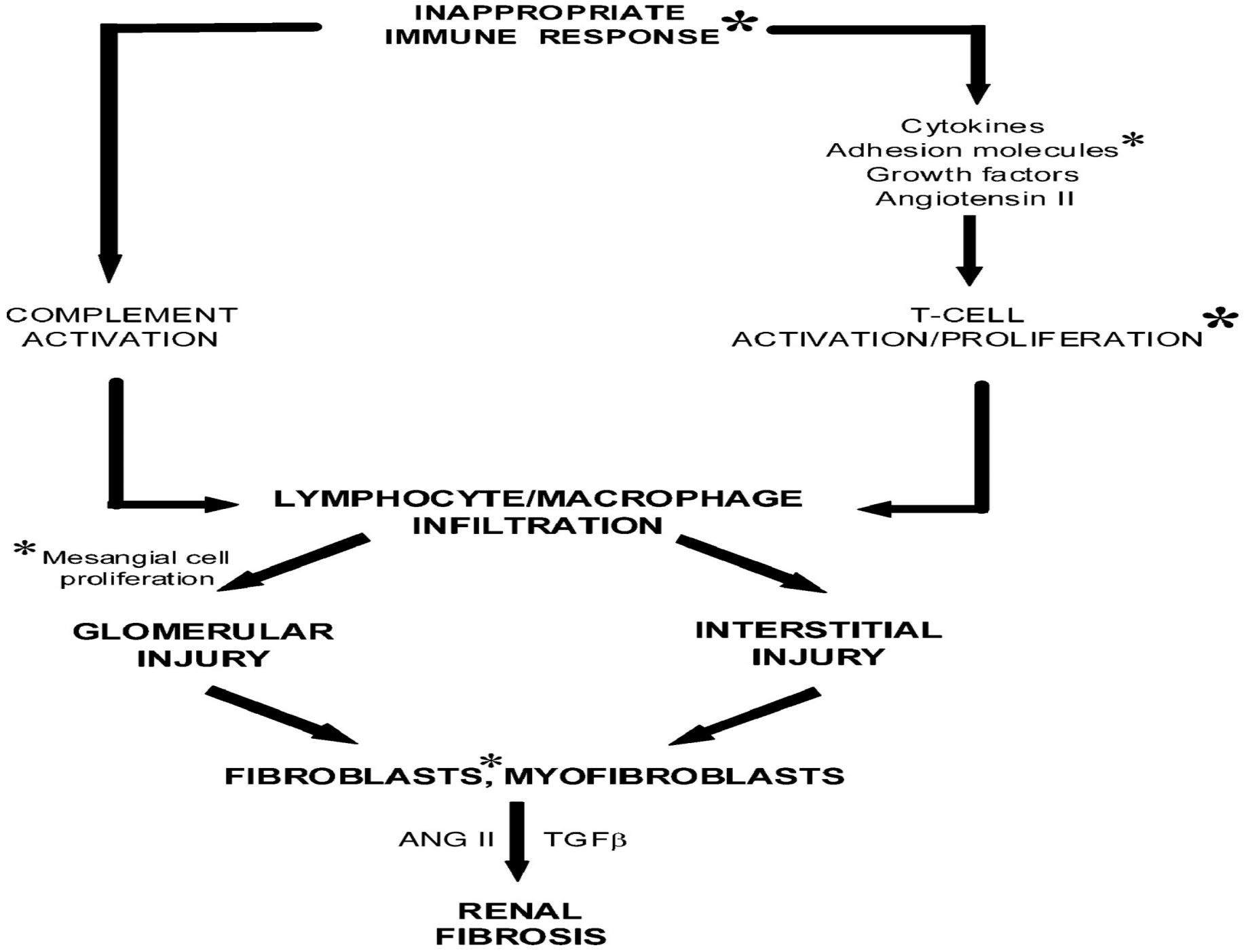


Figure 1 | Effects of proteinuria on tubular epithelial cells. Increased protein absorption by tubular cells may result in direct tubular toxicity, release of chemokines and cytokines, increased expression of adhesion and MHC class II molecules along with co-stimulatory molecules. The net effect is an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


INAPPROPRIATE IMMUNE RESPONSE*
Cytokines
Adhesion molecules*
Growth factors
Angiotensin II
COMPLEMENT ACTIVATION
T-CELL ACTIVATION/PROLIFERATION*
LYMPHOCYTE/MACROPHAGE INFILTRATION
* Mesangial cell proliferation
GLOMERULAR INJURY
INTERSTITIAL INJURY
FIBROBLASTS,* MYOFIBROBLASTS
ANG II
TGFβ
RENAL FIBROSIS