SINDROME URÉMICO HEMOLÍTICO ATÍPICO
SUHa

FISIOPATOLOGÍA

DIAGNÓSTICO

SUHa Y TRANSPLANTE

HERNÁN TRIMARCHI

2014

Mammals
5,600 species estimated
5,501 (**98**%) species discovered

Birds
10,500
10,064 (**96**%)

Reptiles
12,000
9,547 (**80**%)

Amphibians
15,000
6,771 (**45**%)

Fish
45,000
32,400 (**72**%)

Crustaceans
150,000
47,000 (**31**%)

Mollusks
200,000
85,000 (**43**%)

Arachnids
600,000
102,248 (**17**%)

Insects
5,000,000
1,000,000 (**20**%)

Pertea and Salzberg *Genome Biology* 2010, 11:206
http://genomebiology.com/2010/11/5/206

Genome Biology

REVIEW

Between a chicken and a grape: estimating the number of human genes

Mihaela Pertea and Steven L Salzberg*

Abstract

Many people expected the question 'How many genes in the human genome?' to be resolved with the publication of the genome sequence in 2001, but estimates continue to fluctuate.

Ever since the discovery of the genetic code, scientists have been trying to catalog all the genes in the human genome. Over the years, the best estimate of the number of human genes has grown steadily smaller, but we still do not have an accurate count. Here we review the history of efforts to establish the human gene count and present the current best estimates.

The first attempt to estimate the number of genes in the human genome appeared more than 45 years ago, while the genetic code was still being deciphered. Friedrich Vogel published his 'preliminary estimate' in 1964 [1], based on the number of amino acids in the alpha- and beta-chains of hemoglobin (141 and 146, respectively). Knowing that three nucleotides corresponded to each amino acid, he extrapolated to compute the molecular weight of the DNA comprising these genes. He then made several assumptions in order to produce his estimate: that these proteins were typical in size (they are actually smaller than average); that nucleotide sequences were uninterrupted on the chromosomes (introns were discovered more than 10 years later [2,3]); and that the entire genome was protein coding. All these assumptions were reasonable at the time, but later discoveries would reveal that none of them was correct. Vogel then used the molecular weight of the human haploid chromosomes to correctly calculate the genome size as 3×10^9 nucleotides, and dividing that by the size of a 'typical' gene, came up with an estimate of 6.7 million genes.

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Even at the time, Vogel found this number 'disturbingly high,' but no one suspected in 1964 that most human genes were interrupted by multiple introns, nor did anyone know that vast regions of the human genome would turn out to contain seemingly meaningless repetitive sequences. Since Vogel's initial attempt, many scientists have tried to estimate the number of genes in the human genome, using increasingly sophisticated molecular tools. Over the years, the number has gradually come down, in a process that has been humbling at times, as we realized that many other species - even plants - are predicted to have more genes than we do (Figure 1). An estimate of 100,000 genes appeared in the 1990 joint National Institutes of Health (NIH)/Department of Energy (DOE) report on the Human Genome Project [4]; this was apparently based on a very rough (and incorrect) calculation that typical human genes are 30,000 bases long, and that genes cover the entire 3-gigabase genome.

Many people, including many geneticists, expected that we would have a definitive gene count when the human genome was finally completed, and indeed one of the main surprises upon the initial publication of the human genome in February 2001 [5,6] was that the number had again dropped, quite precipitously. However, as we shall see, the publication of the human genome did not come anywhere close to producing a precise gene list or even a gene count, and in the years since the number has continued to fluctuate. As a result, even today's best estimates still have a large amount of uncertainty associated with them.

In order to count genes, we need to define what we mean by a 'gene', a term whose meaning has changed dramatically over the past century. For our discussion, we will restrict the definition of gene to a region of the genome that is transcribed into messenger RNA and translated into one or more proteins. When multiple proteins are translated from the same region due to alternative mRNA splicing, we will consider this collection of alternative isoforms to be a single gene. In this respect, our definition of a gene is equivalent to what may also be called a chromosomal locus. We will exclude non-protein-coding RNA genes (such as microRNAs (miRNAs) and small nuclear RNAs (snRNAs)), in part

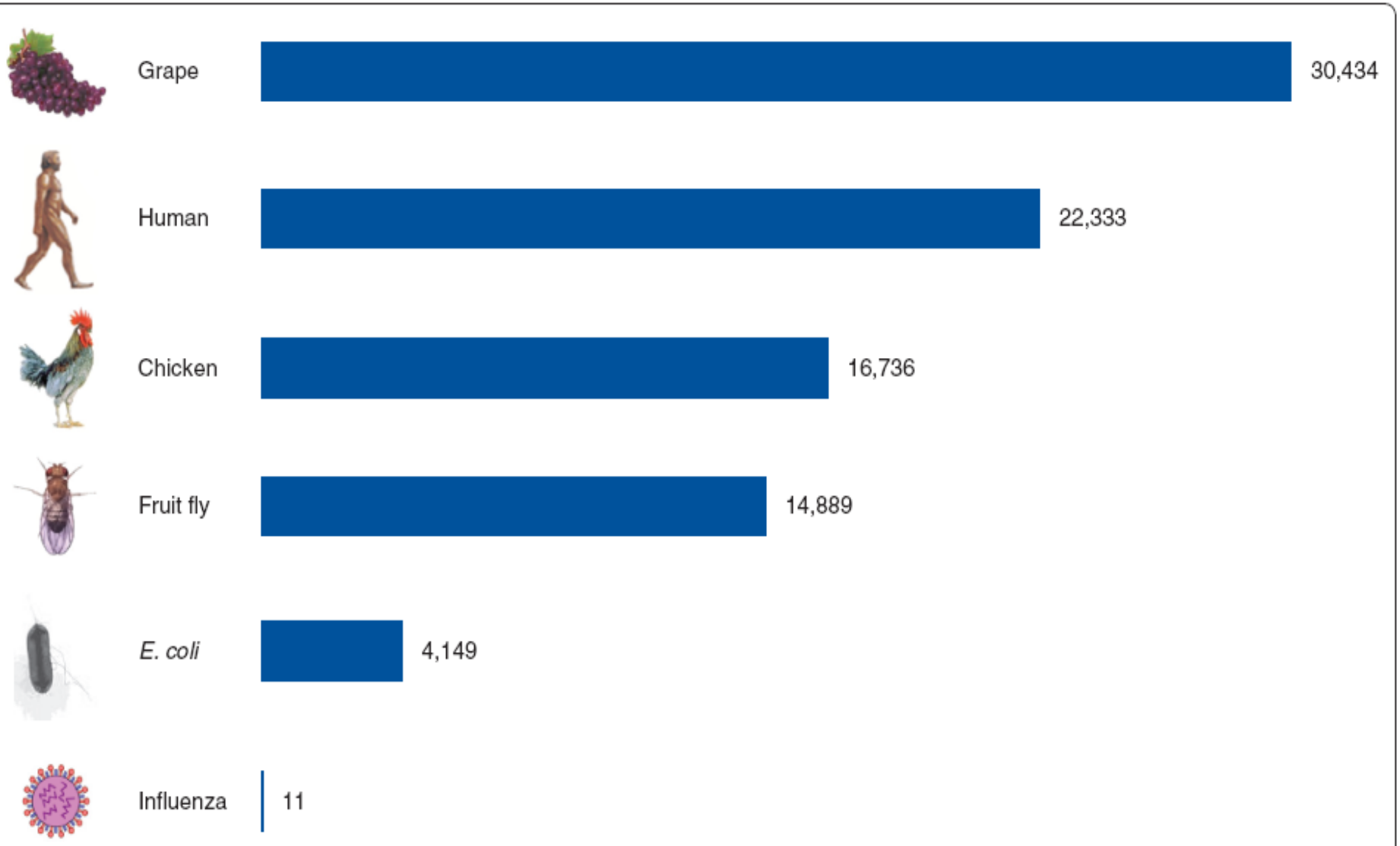
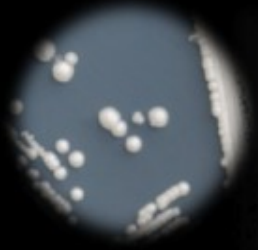


Figure 1. Gene counts in a variety of species. Viruses, the simplest living entities, have only a handful of genes but are exquisitely well adapted to their environments. Bacteria such as *Escherichia coli* have a few thousand genes, and multicellular plants and animals have two to ten times more. Beyond these simple divisions, the number of genes in a species bears little relation to its size or to intuitive measures of complexity. The chicken and grape gene counts shown here are based on draft genomes [50,51] and may be revised substantially in the future.

Fruit Fly
44%

Mouse
92%

Yeast
26%

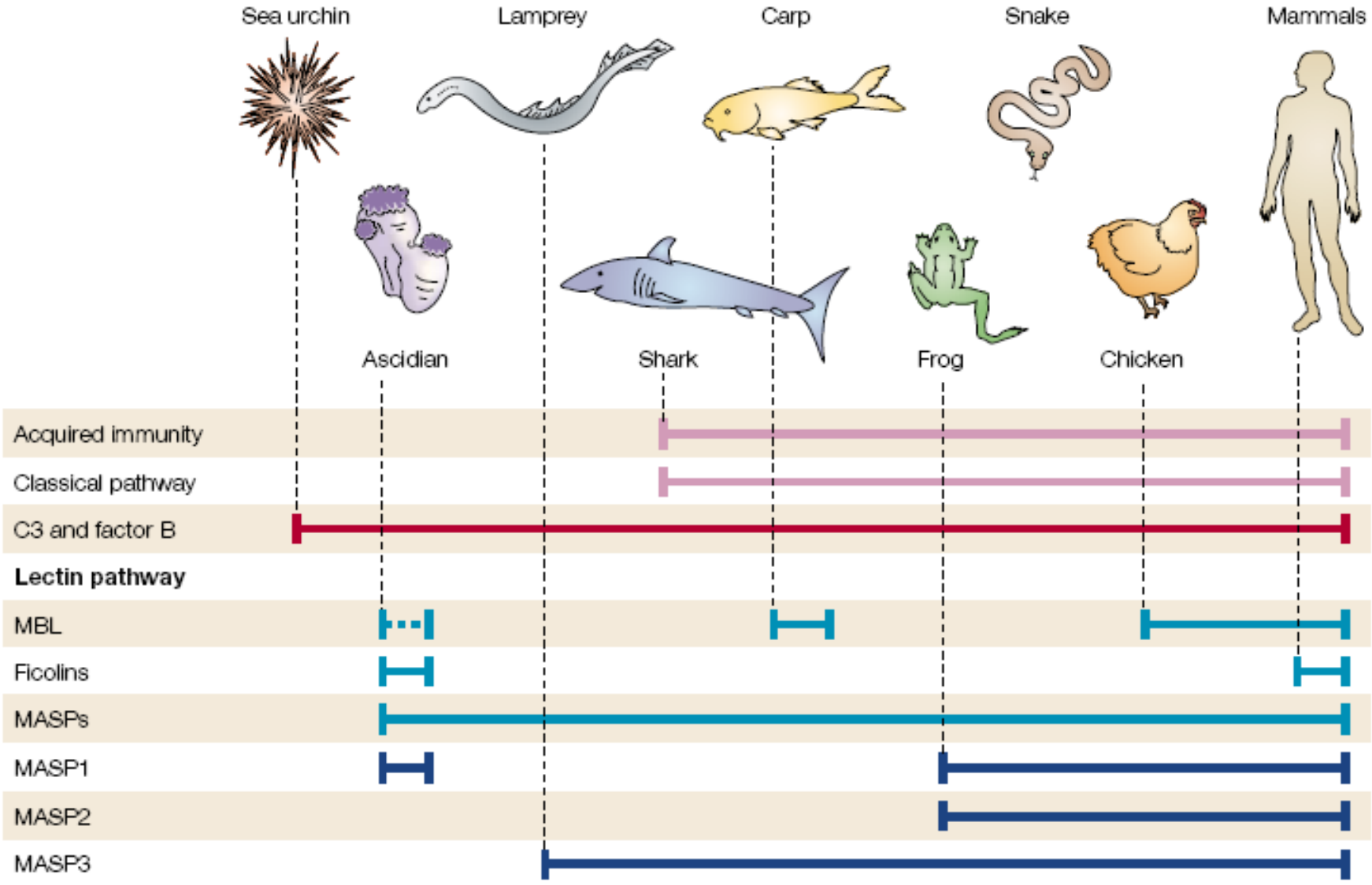


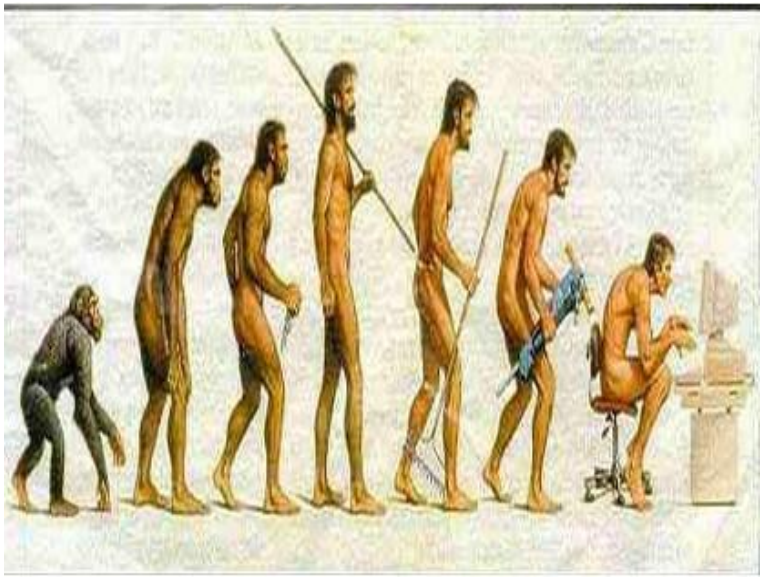
Chimp
98%

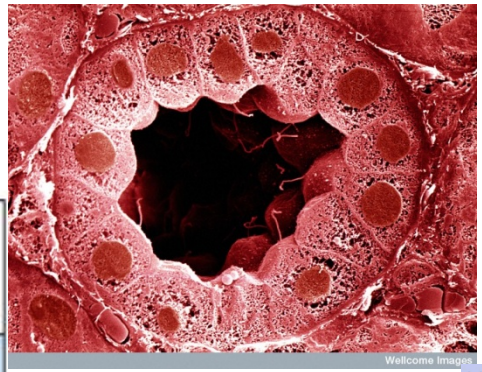
Plant
18%

What percent of your genes do you share?

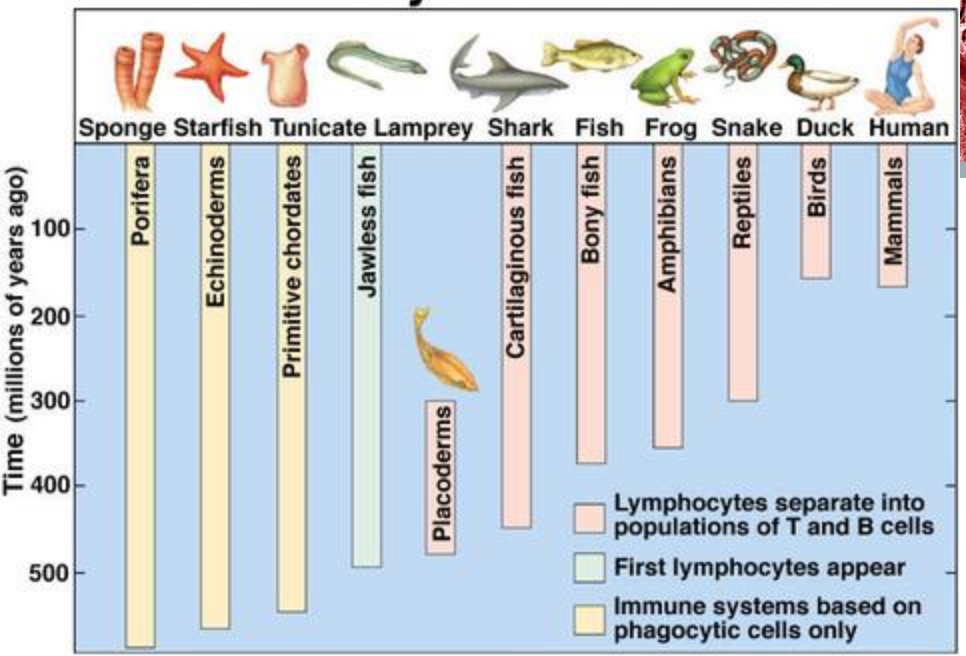
www.23andme.com

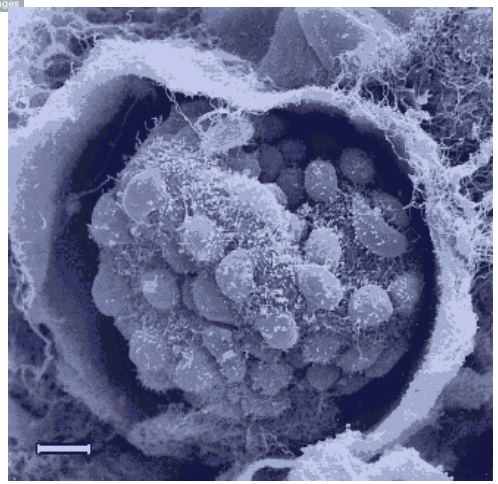

Sea urchin
Lamprey
Carp
Snake
Mammals
Ascidian
Shark
Frog
Chicken
Acquired immunity
Classical pathway
C3 and factor B
Lectin pathway
MBL
Ficolins
MASPs
MASP1
MASP2
MASP3





Immune System Evolution





Overview of Complement Activation and Regulation

Marina Noris, PhD, and Giuseppe Remuzzi, MD

Table 1. The Main Physiologic Activities of the Complement System

Activity	Complement Protein Responsible for the Activity
Host defense against infection	
Oponization	Covalently bound fragments of C3 and C4 (C3b, C4b)
Chemotaxis and activation of leukocytes	hylatoxins (C5a, C3a); anaphylatoxin receptors on leukocytes (C5aR, C3aR)
Lysis of bacteria and cells	Membrane-attack complex (C5b-9)
Interface between innate and adaptive immunity	
Augmentation of antibody response	b and ments bound to immune complexes and to antigens; CR1-4 receptors on B PC
Enhancement of T-cell response to APC	C3a and 5a, C3 aR on T cells and APC
Reduction of Treg function	and C5a, C3aR and C5aR on T cells and APC
Disposal of waste	
Clearance of immune complexes from tissues	C1q; covalently bound fragments of C3 (C3b) and C4 (C4b), CR1 on erythrocytes, CR1-4 receptors on phagocytes
Clearance of apoptotic cells	C1q; covalently bound fragments of C3 (C3b) and C4 (C4b), CR1 on erythrocytes, CR1-4 receptors on phagocytes

Abbreviations: APC, antigen presenting cells; Treg, regulatory T cells.

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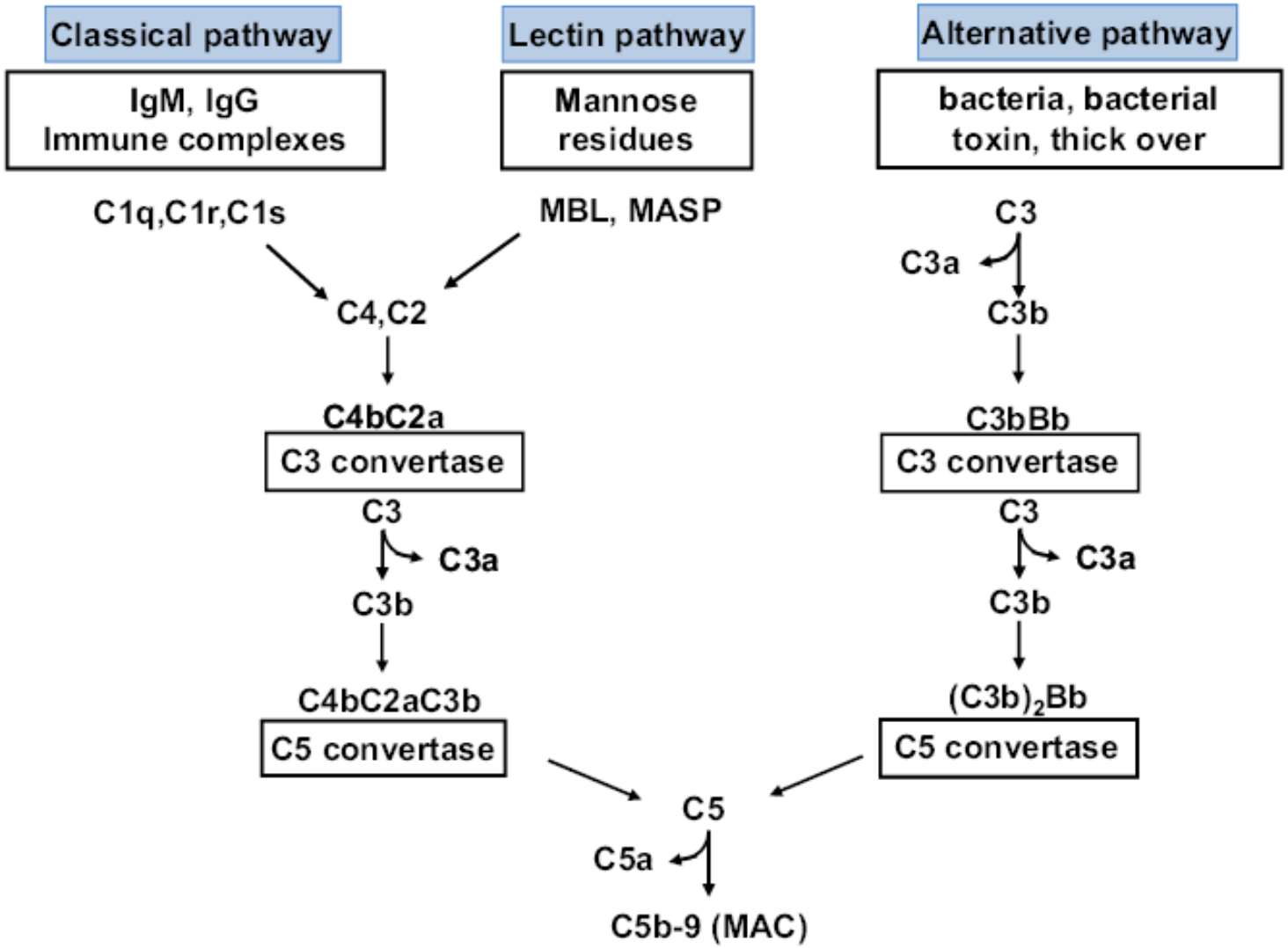
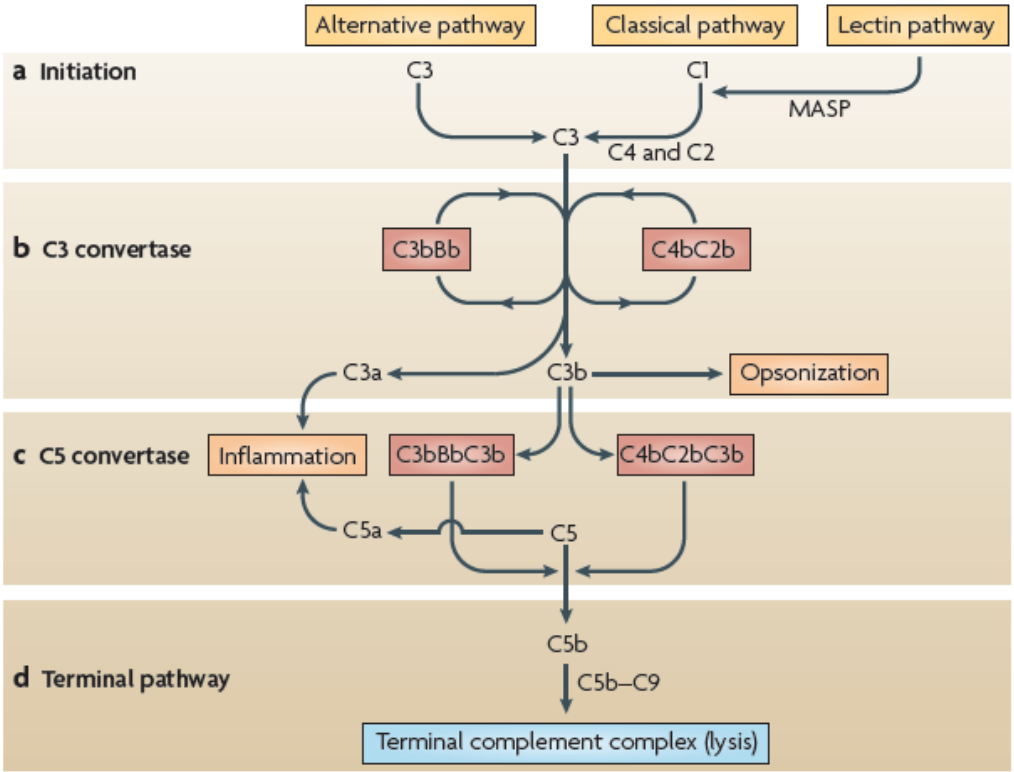
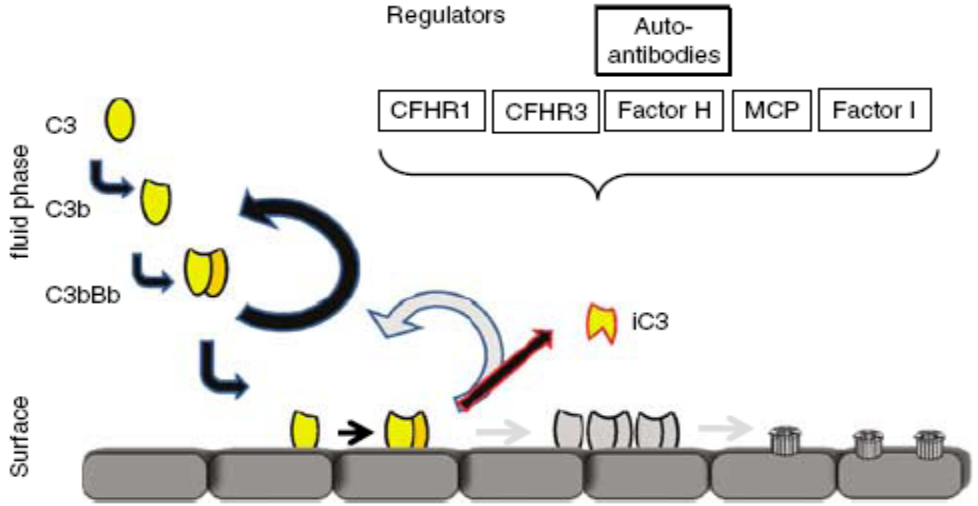

Classical pathway
IgM, IgG
Immune complexes
C1q,C1r,C1s
Lectin pathway
Mannose
residues
MBL, MASP
Alternative pathway
bacteria, bacterial
toxin, thick over
C3
C3a
C3b
C4,C2
C4bC2a
C3 convertase
C3
C3a
C3b
C4bC2aC3b
C5 convertase
C3bBb
C3 convertase
C3
C3a
C3b
(C3b)2Bb
C5 convertase
C5
C5a
C5b-9 (MAC)





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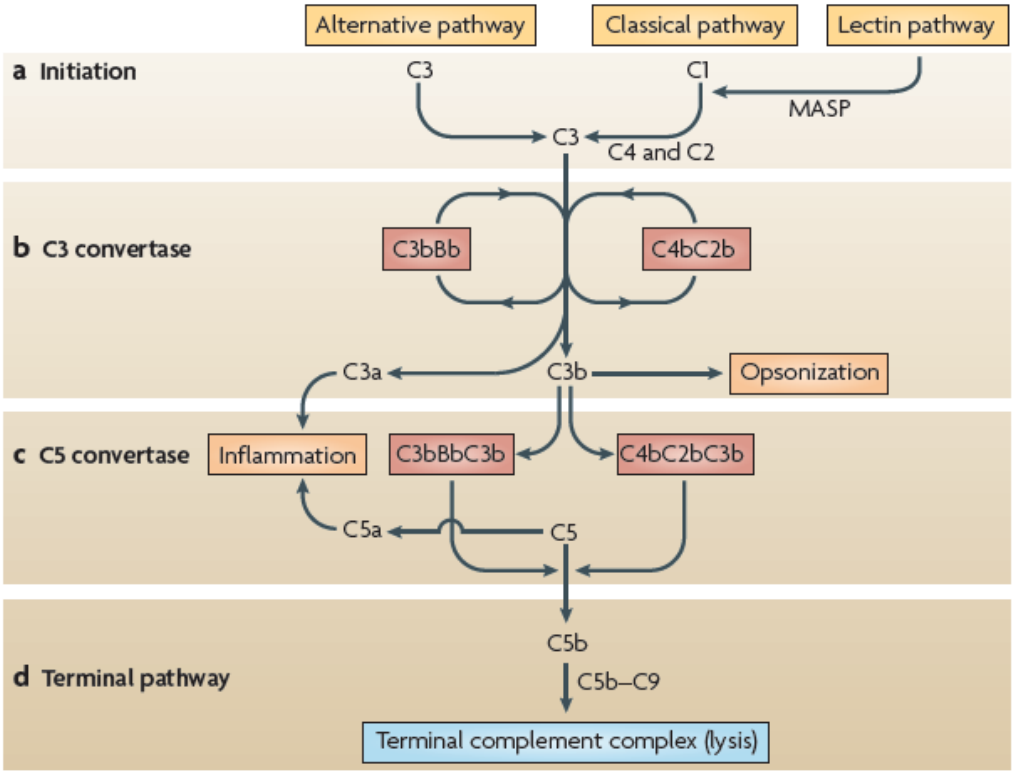
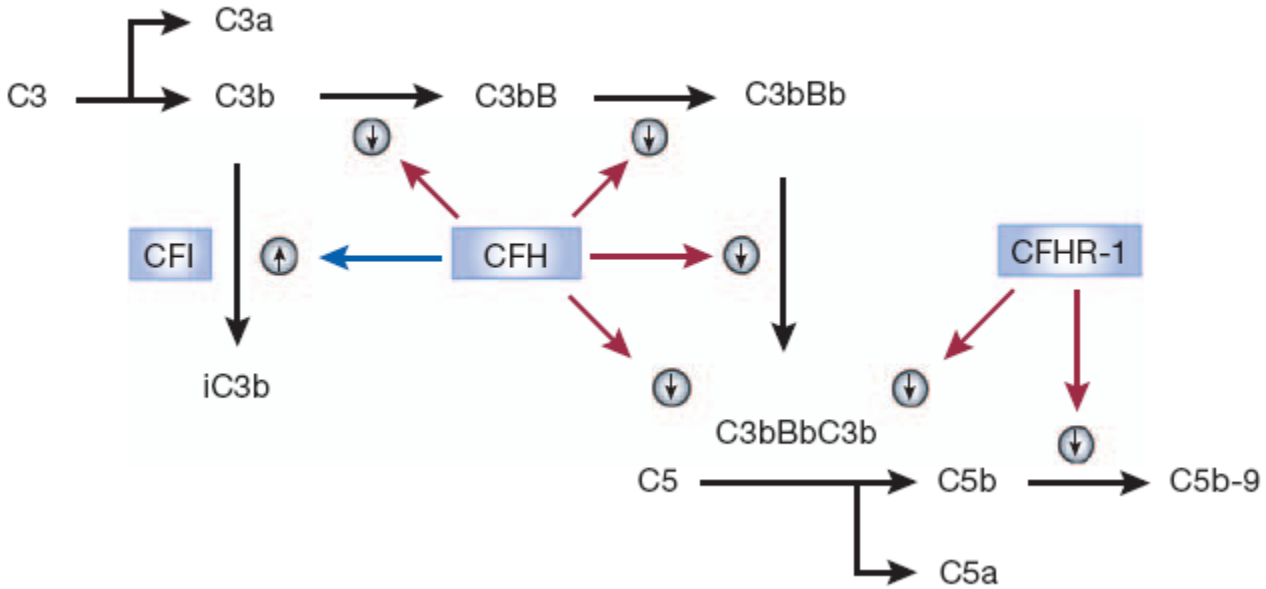
DE BUENOS AIRES





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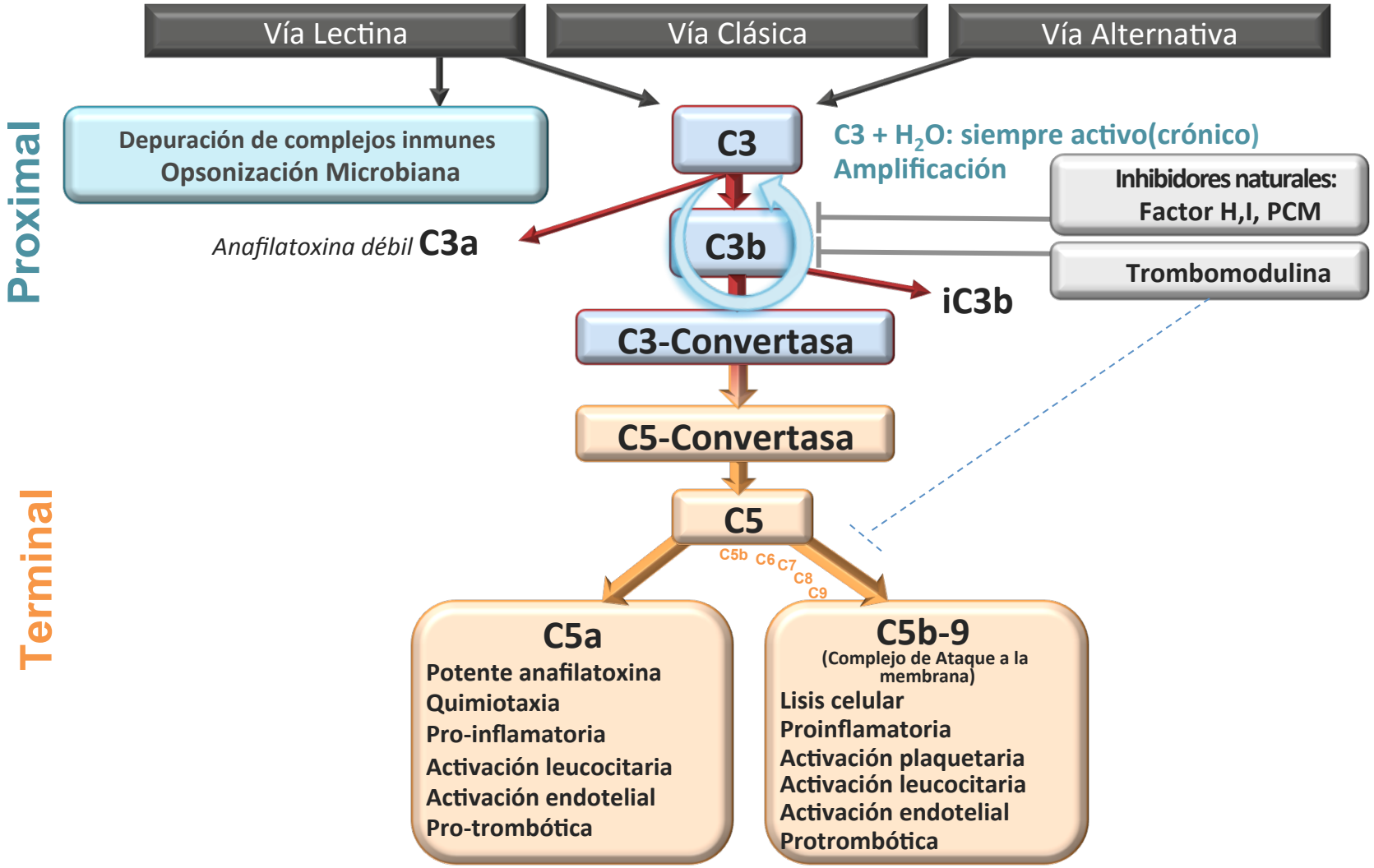
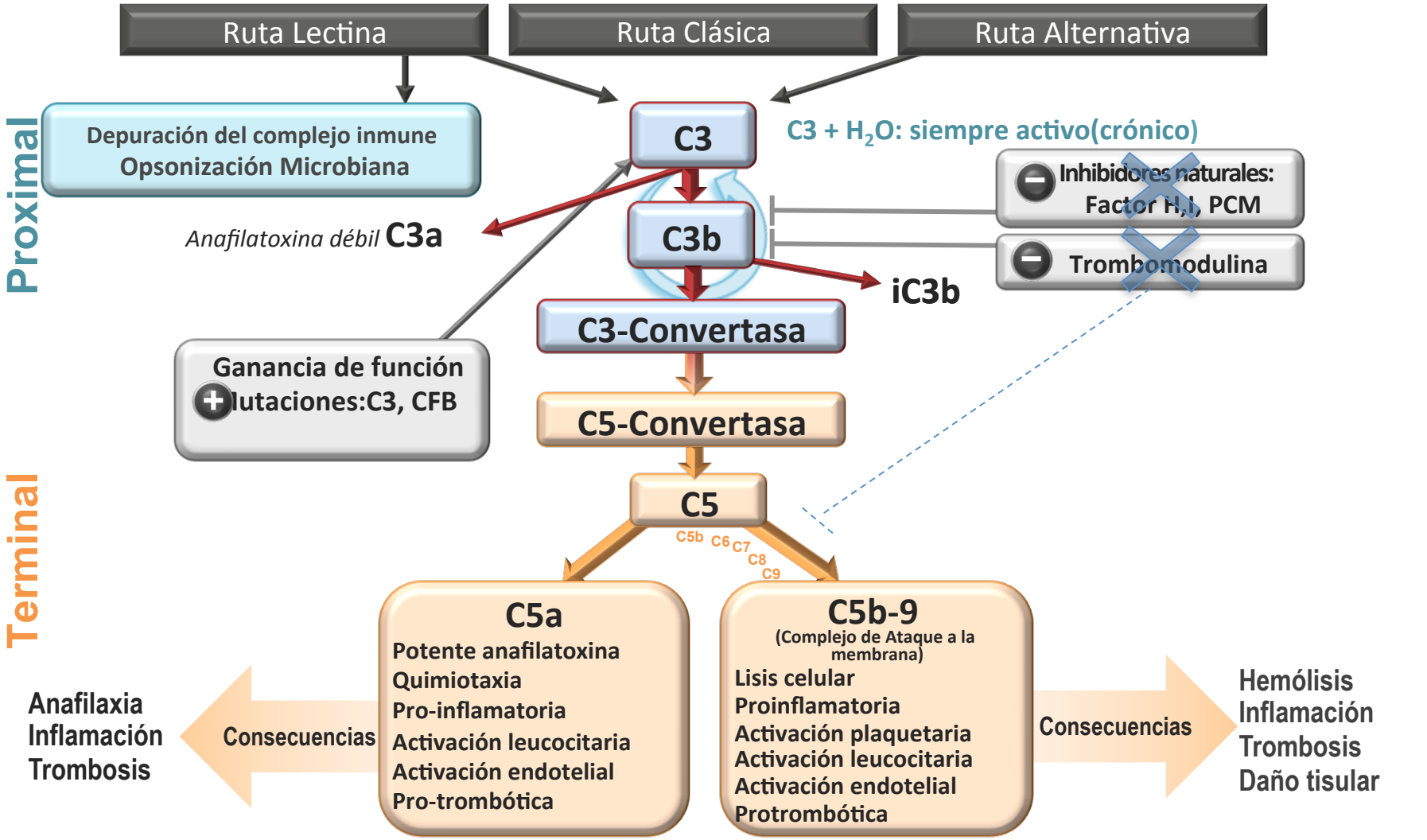
Los inhibidores naturales son necesarios para controlar el sistema del complemento



En el SHUa, la actividad crónica no controlada del complemento lleva daños severos



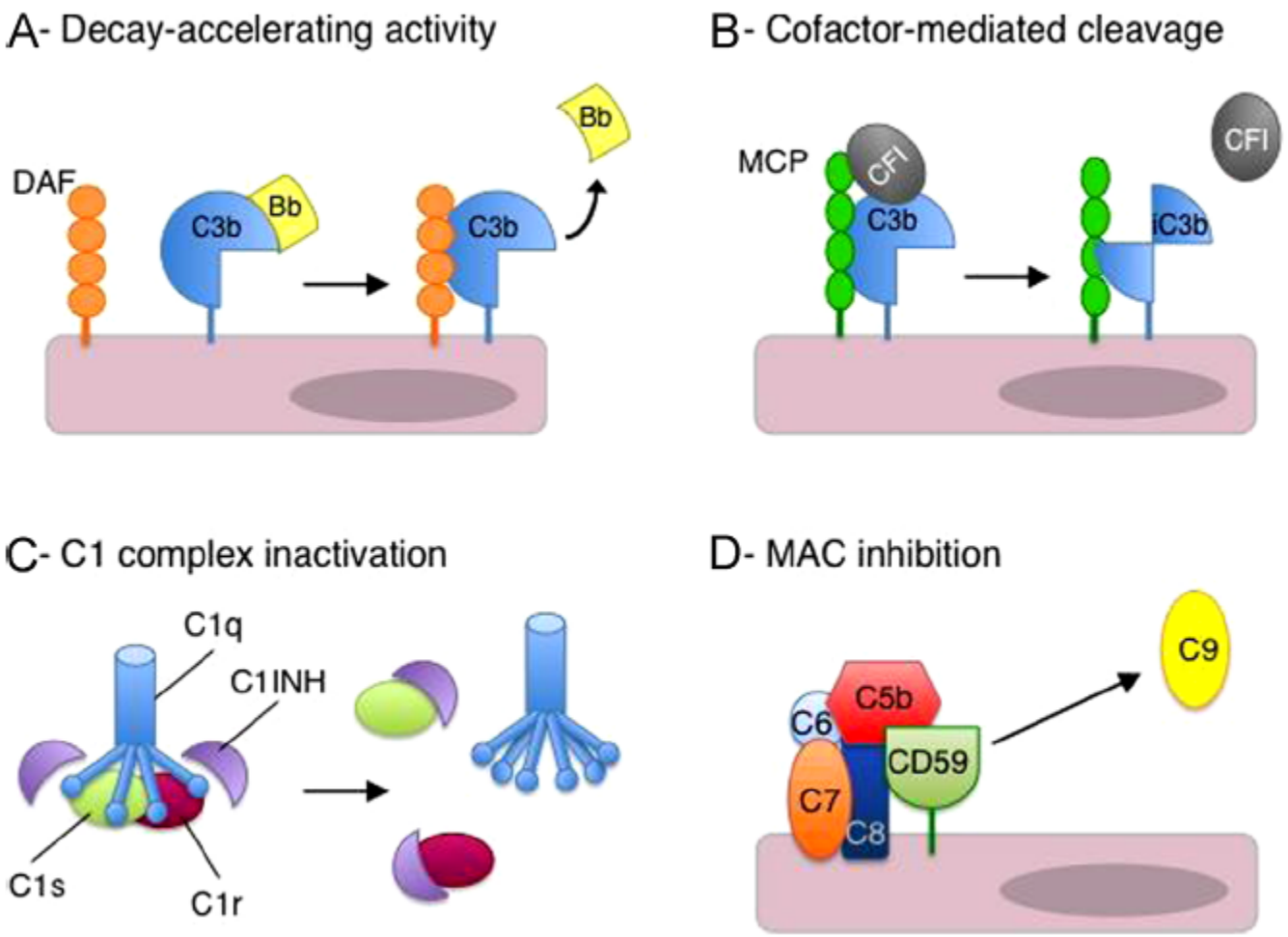


Figure 3. Mechanisms of complement regulation. (A) DAF (or CFH, CR1) destabilizes C3 convertases and accelerates the dissociation of C3bBb (depicted) and C4bC2a. (B) Cofactor activity: MCP (or CFH, CR1) binds to C3b and serves as a cofactor for CFI-mediated cleavage and inactivation of C3b (or C4b). (C) C1 complex inactivation. C1INH binds to C1r and C1s to inactivate the C1 enzyme complex. (D) MAC inhibition: CD59 inhibits C9 association with C5b-8 and prevents MAC (C5b-9) formation.

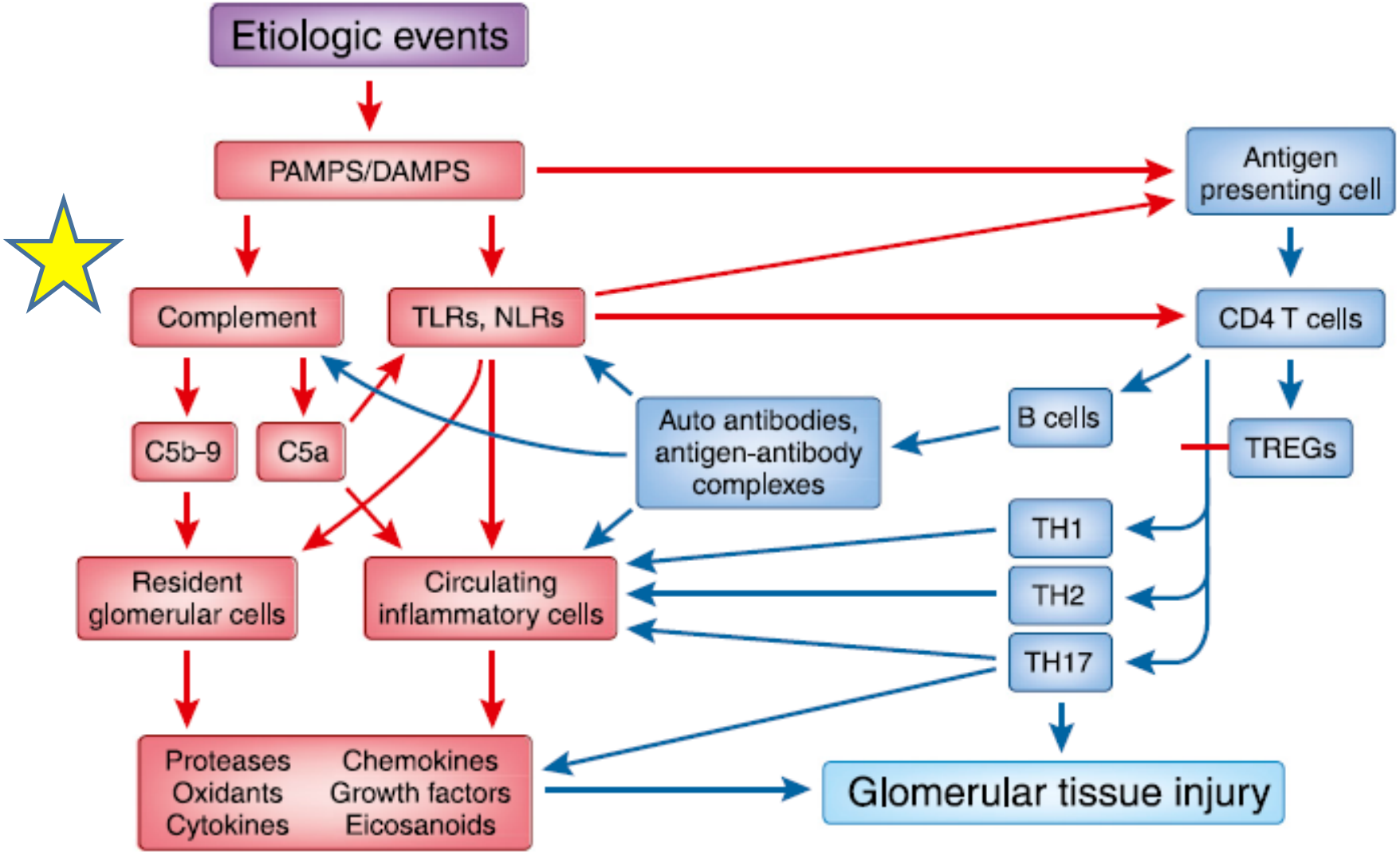

Etiologic events
PAMPS/DAMPS
Antigen presenting cell
Complement
TLRs, NLRs
CD4 T cells
C5b-9
C5a
Auto antibodies, antigen-antibody complexes
B cells
TREGs
TH1
TH2
TH17
Resident glomerular cells
Circulating inflammatory cells
Proteases
Oxidants
Cytokines
Chemokines
Growth factors
Eicosanoids
Glomerular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

Figure 1. Complement activation and regulation. The proteins relevant to complement activation beginning with ICs in the classic pathway are shown. Regulators of complement activation are in the boxes adjacent to their site(s) of action. Classic pathway activation can recruit the alternative pathway; if intrinsic regulation is overwhelmed, activation and generation of C3a, C3b, C5a, and C5b-9 ensues, each of which has pathophysiologic relevance in kidney diseases. CPN, carboxypeptidase N.

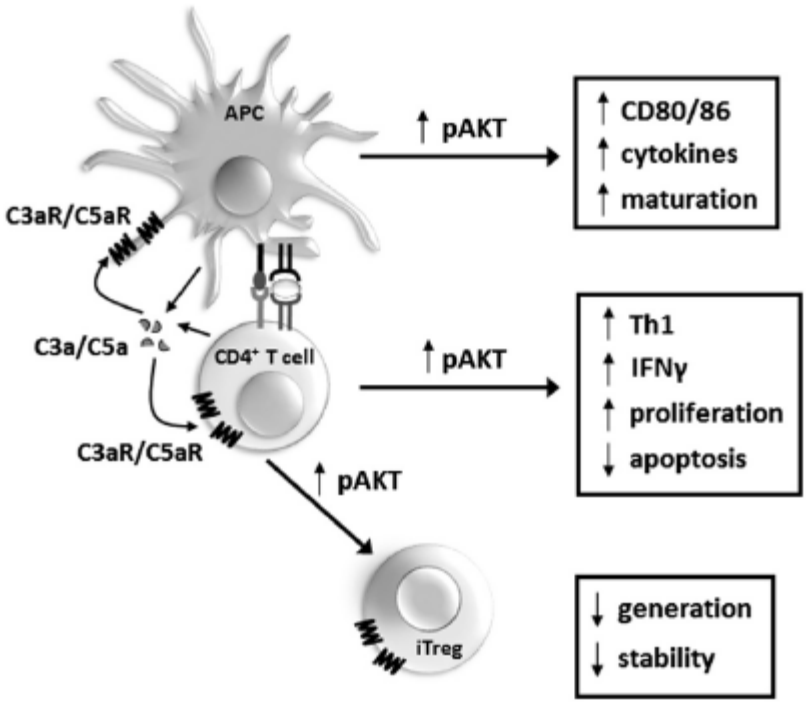


Figure 2. Schematic representation of complement-mediated effects on T cells and APCs. C3aR/C5aR signaling on both APC and T cells activates the AKT pathway by phosphorylation (among other pathways). AKT activation on the APC stimulates maturation, cytokine production, and B7 costimulatory molecule expression. AKT activation on the T cell directly promotes IFN-γ secretion, reduces susceptibility to apoptosis, and promotes cell proliferation and reduces iTreg generation and stability. In this manner, C3aR/C5aR stimulation directly and indirectly promotes T-cell maturation with an expanded effector repertoire. Modified with permission from Kwan et al.[64]

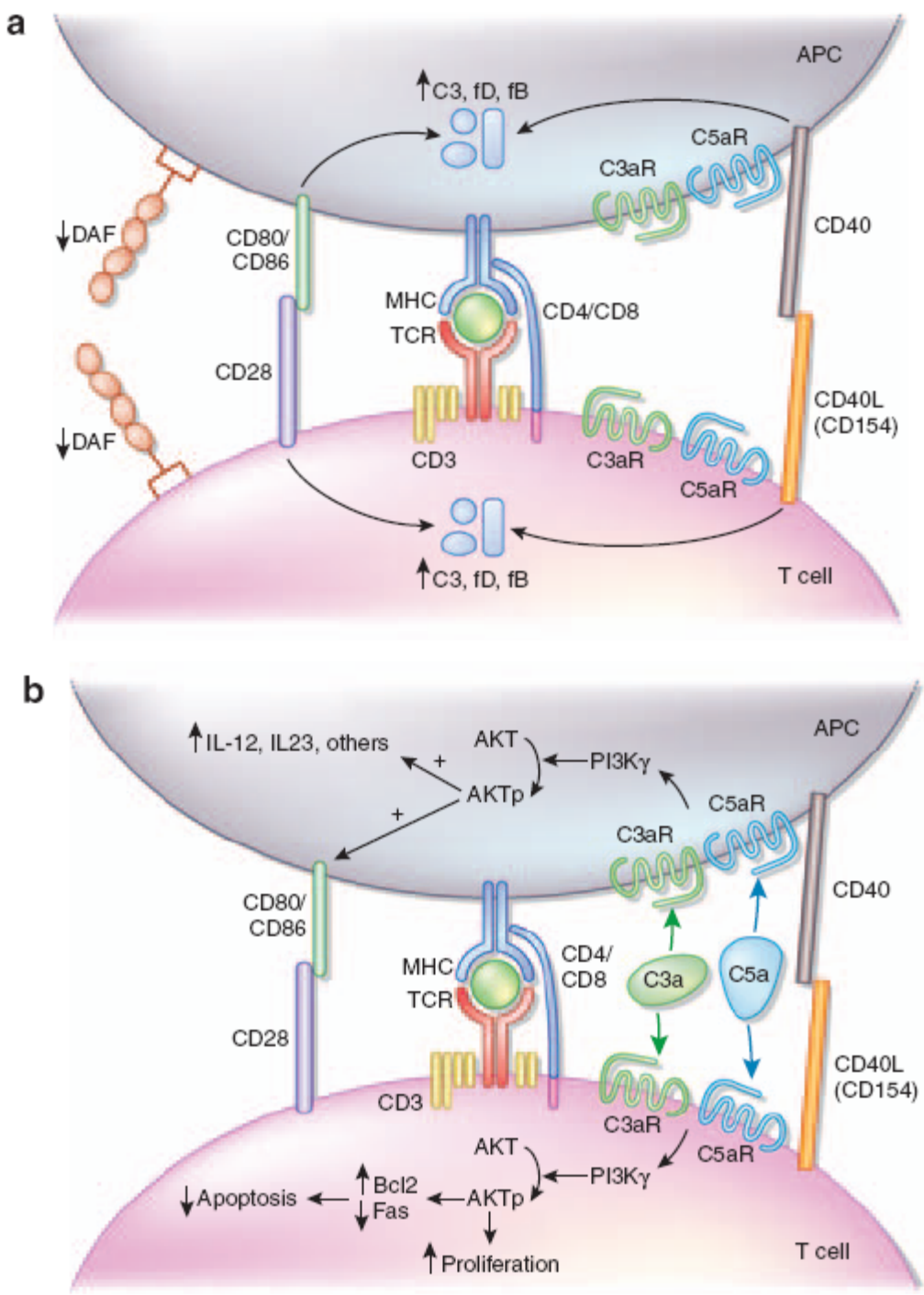
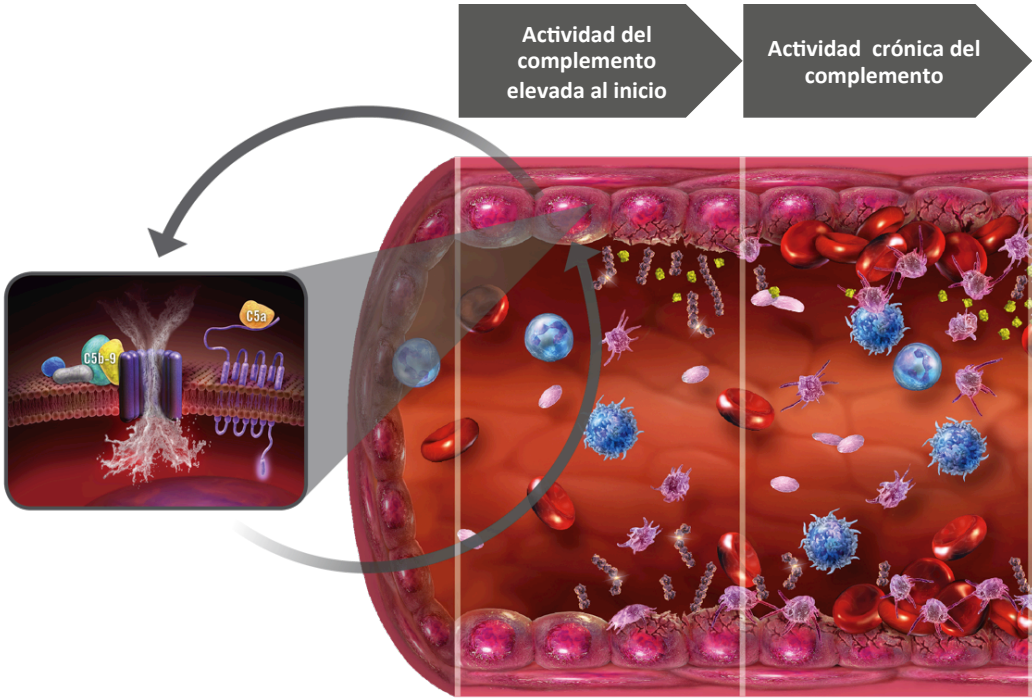


Figure 2 | Schematic depiction of how complement modulates T-cell immunity. Cognate T-cell–APC interactions result in the upregulation and release of alternative pathway complement components by both partners and in the downregulation of (**a**) cell-surface DAF, which permits local complement activation resulting in the production of (**b**) C3a and C5a. These split products bind to their G-protein-coupled receptors expressed on T cells, signaling through PI3Kγ and AKT to induce proliferation and inhibit apoptosis, while simultaneously activating APCs to upregulate B7 and innate cytokine (for example, IL-12) production. APC, antigen presenting cell; DAF, decay-accelerating factor; IL-12, interleukin-12; PI3Kγ, phosphoinositide 3-kinase-γ.

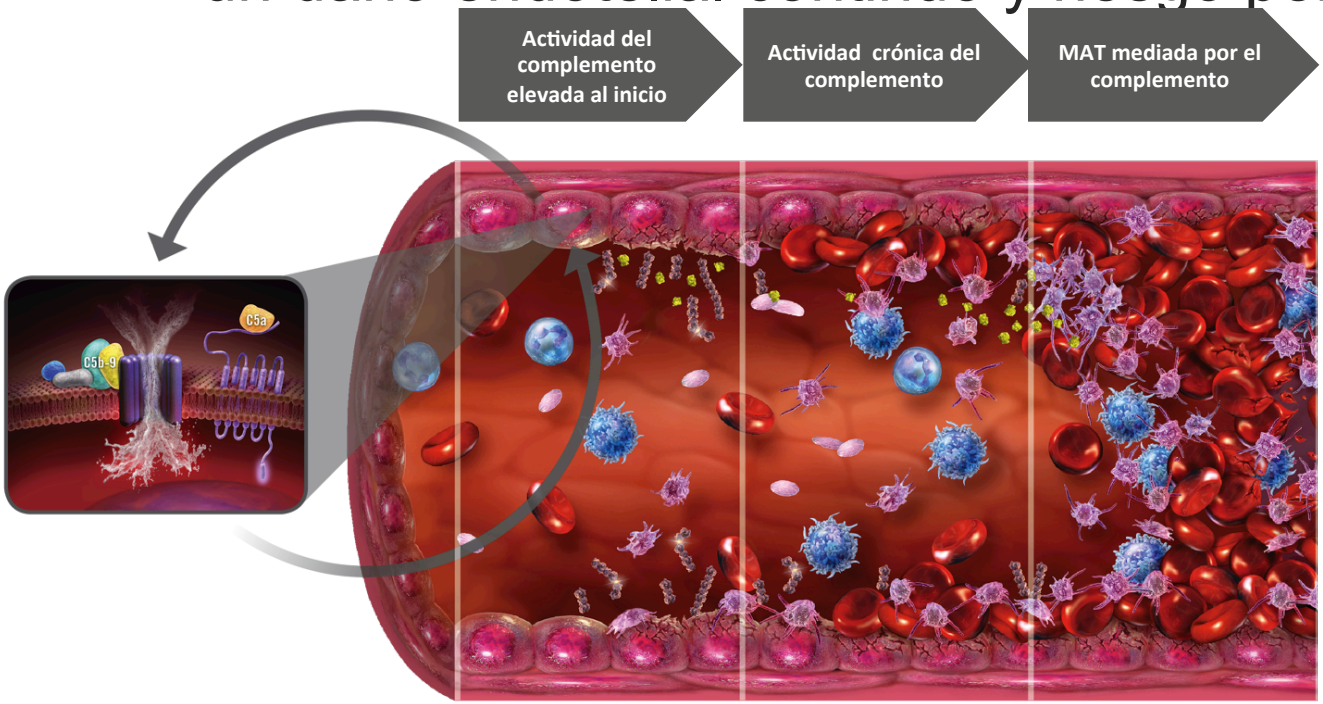
La actividad crónica no controlada del complemento resulta en un daño endotelial continuo y riesgo permanente de MAT



- El ensamblaje de múltiples complejos de C5b-9 en la superficie de las células endoteliales causa lesión endotelial y activación plauetaria[2-5]
- La unión de C5a al receptor de C5a resulta en una disminución de las propiedades anti-complemento y anti-trombóticas del endotelio[2,4,6,7]

glóbulo rojo | leucocito | plaqueta | leucocito activado | plaqueta activada | vWF | factores protrombóticos | esquistocito

La actividad crónica no controlada del complemento resulta en un daño endotelial continuo y riesgo permanente de MAT

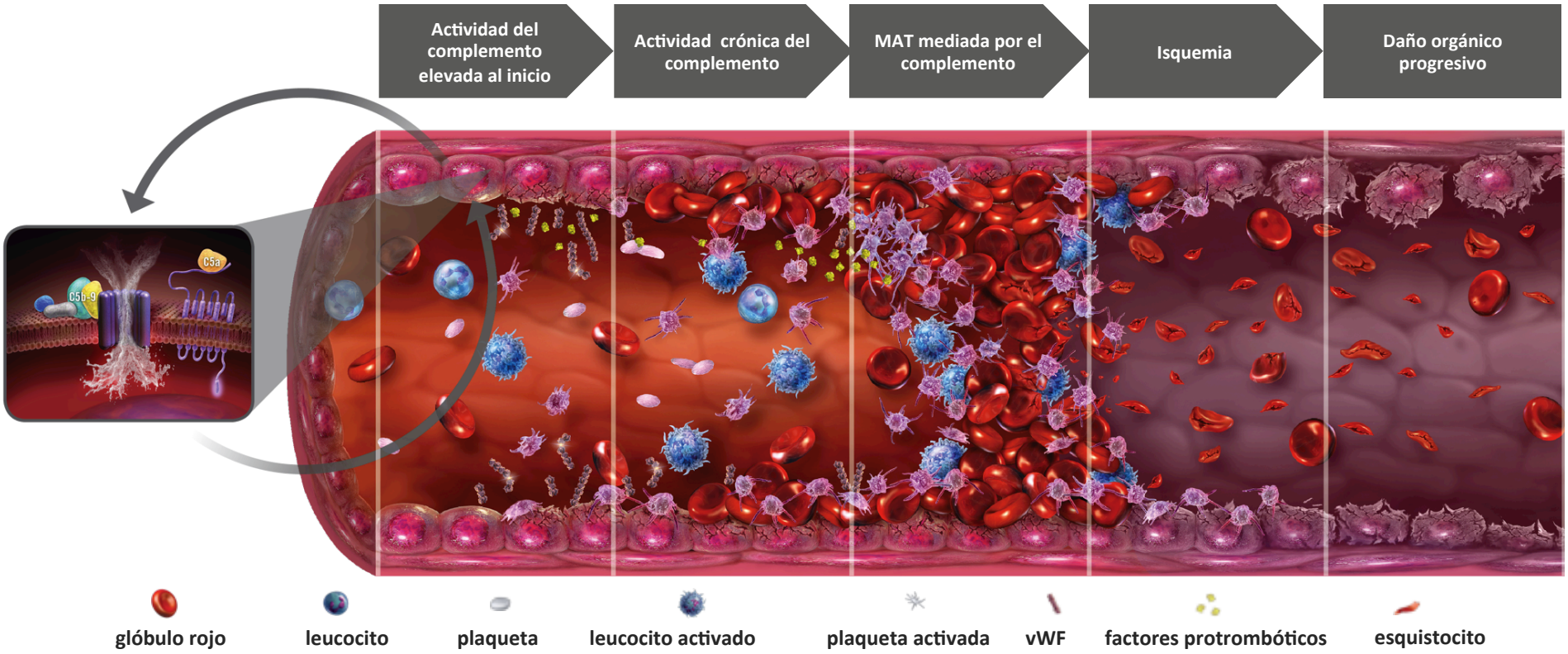


Células endoteliales interrumpidas:

- Liberan micropartículas activadoras del complemento, lo que resulta en un círculo vicioso de activación endotelial, amplificación del complemento y lesión endotelial permanente[2,3]
- Liberan proteínas de coagulación pro-trombóticas, activan las plaquetas y reclutan leucocitos, lo que resulta en la formación de trombos en los vasos sanguíneos pequeños en todo el cuerpo[2]

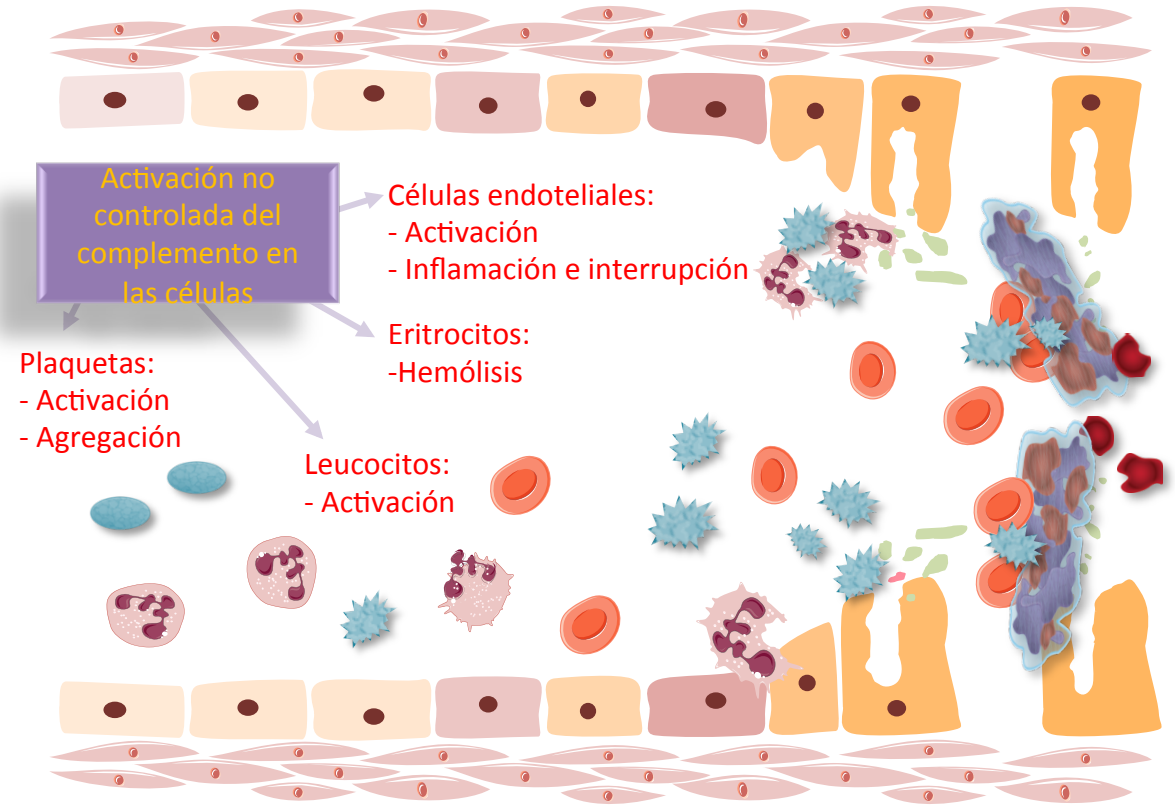
glóbulo rojo | leucocito | plaqueta | leucocito activado | plaqueta activada | vWF | factores protrombóticos | esquistocito

La actividad crónica no controlada del complemento resulta en un daño endotelial continuo y riesgo permanente de MAT



- La actividad no controlada del complemento causa lesión endotelial vascular permanente[2-5]
- Las lesiones resultantes de la MAT pueden progresar a daño multiorgánico irreversible[2-5]

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

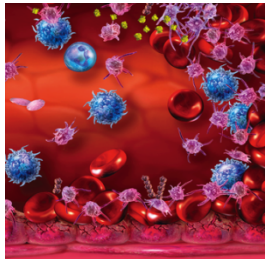
Table 1 | A molecular and etiologic classification of thrombotic microangiopathy

Renal failure: uncommon	Renal failure: common
Defective vWF proteolysis	Dysregulation of complement activation
Mutations of ADAMTS13	Mutations of CFH, IF, MCP, BF
Inhibitory antibodies of ADAMTS13	Autoantibodies of CFH
Tumor cell embolism	Shiga toxins (e.g. *E. coli* O157:H7)
Paroxysmal nocturnal hemoglobinuria	Neuraminidase (e.g. *S. pneumoniae*)
Infectious vasculitis (e.g. *C. difficile*, *R. rickettsii*, *B. anthracis*)	Drugs (e.g. calcineurin inhibitors, mitomycin, gemcitabine, quinine)
Idiopathic	Autoimmune disorders (e.g. SLE, scleroderma)
	BM/stem cell transplantation
	Miscellany (e.g. HELLP syndrome, surgery, pancreatitis)
	Idiopathic
	Graft rejection

Diferentes causas diferencian el SHUa de la PTT

MAT mediada por el complemento (SHUa)

Causa subyacente:
Actividad crónica no controlada del complemento[1-5]

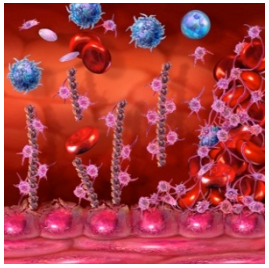


Los defectos genéticos en los activadores y/o inhibidores inducen la actividad crónica del sistema del complemento, causando daño celular endotelial y agregación plaquetaria continua[1-5]

Objetivo del tratamiento:
Regular la activación crónica y no controlada del complemento

MAT mediada por la deficiencia severa de ADAMTS13 (PTT)

Causa subyacente:
Deficiencia severa de ADAMTS13 (≤5%)[6-10]



Una actividad insuficiente de ADAMTS13 (≤5%) deja el factor de von Willebrand sin escindir, lo que causa excesiva agregación plaquetaria[8,7,11,12]

Objetivo del tratamiento:
Eliminar los auto-anticuerpos contra ADAMTS13

Differential Diagnosis for Thrombotic Microangiopathies (TMAs)

Thrombocytopenia[1,7]

Platelet count <150,000

Or

>25% Decrease from baseline

±

Microangiopathic Hemolysis[2,7]

Elevated LDH and/or
Decreased Haptoglobin and/or
Schistocytes and/or
Decreased Hemoglobin

Plus One or More of the Following:

Neurological Symptoms[3,4,9,12]

Confusion[3,4] and/or
Seizures[9,12]

Renal Impairment[5,6,7]

Elevated Creatinine[6] and/or
Decreased eGFR[6,7] and/or
Abnormal Urinalysis[5]

Gastrointestinal Symptoms[7,8,9]

Diarrhea +/- Blood[8] and/or
Nausea/Vomiting[9] and/or
Abdominal Pain[9] and/or
Gastroenteritis[7,8]

Evaluate ADAMTS13 Activity and Shiga-toxin/EHEC*Test[10,11]

≤5% ADAMTS13 Activity	>5% ADAMTS13 Activity	Shiga-toxin/EHEC Positive
TTP	aHUS	STEC-HUS

*Shiga-toxin/EHEC test is warranted in history/presence of GI symptoms.

1. Data on file. Alexion Pharmaceuticals, Inc. 2. Noris et al. *NEJM*. 2009;361:1676-1687. 3. Neuhaus et al. *Arch Dis Childl*. 1997;76:518-21. 4. Noris et al. *JASN*. 2005;16: 1177-1183. 5. Al-Akash et al. *Pediatr Nephrol*. 2011;26:613-619. 6. Sellier-Leclerc AL. *JASN*. 2007;18:2392-2400. 7. Caprioli et al *Blood.* 2006; 108(4)1267-7. 8. Noris M et al. *Clin J Am Soc Nephrol.* 2010;5:1844-1859. 9. Dragon-Durey et al. *J Am Soc Nephrol*. 2010;21:2180-2187. 10.Tsai H-M. *Int J Hematol*. 2010;91:1-19.11. Bitzan M. *Semin Thromb Hemost*. 2010;36:594-610. 12. Davin et al. *Am J Kid Dis*. 2010;55:708-777.

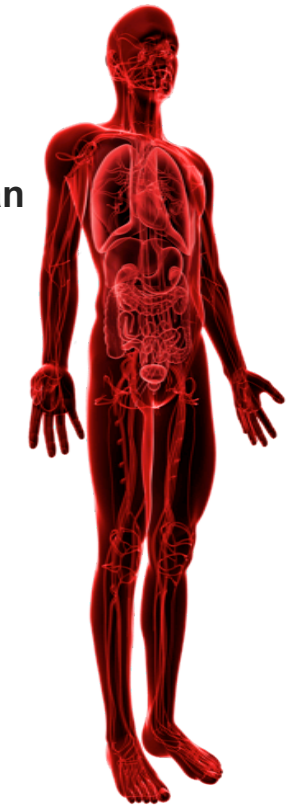
La MAT sistémica mediada por el complementio afecta en forma sistémica

Renal: Más del 50% de los pacientes progresan a ERET[1]
- Elevada creatinina[2,3]
- Proteinuria[4]
- Edema,[3] hipertensión maligna[5]
- Disminución en TFGe[6]

SNC: Hasta 48% de los pacientes presentan síntomas neurológicos[4]
- Desorientación[7]
- Apoplejía[7]
- Encefalopatía[5]
- Convulsión[4]

Blood:
- Trombocitopenia[1]
- Disminución en haptoglobina[1]
- Elevada LDH[1]
- Disminución en hemoglobina[1]
- Esquistocitos[1]

Visual:
- Oclusión ocular[8]



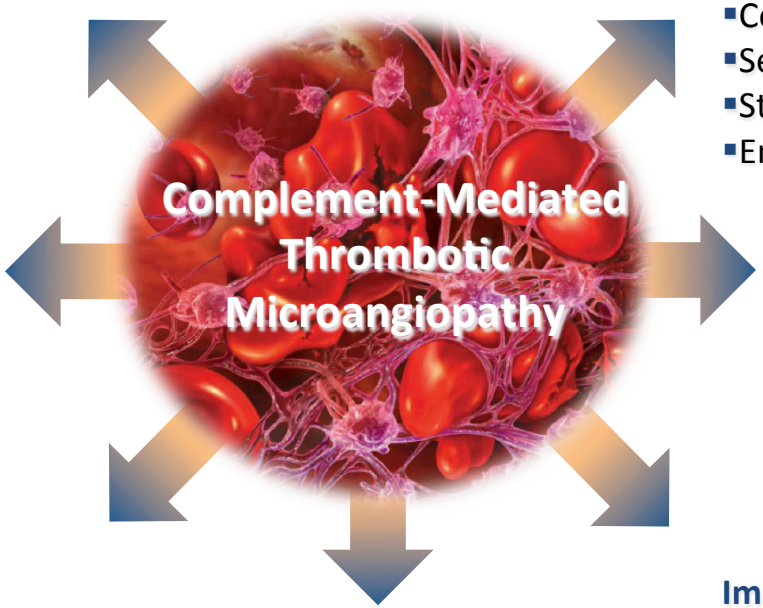
Cardiovascular: Hasta 43% de los pacientes experimentan síntomas cardiovasculares[4]
- Infarto del miocardio[9,16]
- Hipertensión[10]
- Vasculopatía difusa[6]
- Gangrena periférica[11,16]

Gastrointestinal: 37% de los pacientes experimentan síntomas GI[12]
- Diarrea[13]
- Colitis[7]
- Náusea/Vómito[14]
- Pancreatitis[14]
- Dolor abdominal[7]
- Gastroenteritis[4]
- Necrosis hepática[4]

Pulmonar:
- Disnea[9]
- Hemorragia pulmonar[15]
- Edema pulmonar[9]

- Una evaluación clínica completa debe evaluar múltiples sistemas orgánicos

Complement-Mediated TMA Leads to the Morbidities and Mortality in aHUS



Cardiovascular[2,3,4,6]
- Myocardial infarction
- Thromboembolism
- Cardiomyopathy
- Diffuse vasculopathy

CNS[1,2,3,4,5]
- Confusion
- Seizures
- Stroke
- Encephalopathy

Renal[7,8,9,11,12]
- Elevated creatinine
- Edema, malignant hypertension
- Renal failure
- Dialysis, transplant

Gastrointestinal[2,3,5,10,11,12]
- Liver necrosis
- Pancreatitis, DM
- Colitis, Diarrhea
- Nausea/vomiting
- Abdominal pain

Pulmonary[1]
- Dyspnea
- Pulmonary edema
- Pulmonary embolism

Blood[11]
- Hemolysis
- Decreased platelets
- Fatigue
- Transfusions

Impaired Quality of Life[1]
- Fatigue
- Pain/Anxiety
- Reduced mobility

1. George et al. *Blood*. 2010;116:4060-69. 2. Hosler et al. *Arch Pathol Lab Med*. 2003;127:834-39. 3. Noris et al. *CJASN.* 2010;10:1844-59. 4. Neuhaus et al. *Arch Dis Childl*. 1997;76:518-21. 5. Vesely et al *Blood*. 2003;102:60-8. 6. Sallee et al. *Nephron Dial Trans*. 2010; 25:2028-32. 7. Kose et al. *Semin Thromb Hemost*. 2010;36:669-72. 8. Davin et al. *Am J Kid Dis*. 2010;55:708-77. 9. Caprioli et al. *Blood*. 2006;108:1267-7. 10. Dragon-Durey et al. *J Am Soc Nephrol*. 2010;21:2180-87. 11. Loirat et al. *Pediatr Nephrol*. 2008;23:1957-72. 12. Stahl et al. *Blood*. 2008;111:5307-15.

Seminars in NEPHROLOGY

VOL. 33, NO. 6 NOVEMBER 2013

Introduction: Complement-Mediated Kidney Diseases

Table 1. Triggers of aHUS

Trigger	Reference
Non-Stx toxin diarrheal illnesses	51,94,95
Norovirus	161,162
Campylobacter upsaliensis	163
Clostridium difficile	164
Respiratory infections	51
Bordetella pertussis infection	10,165
Streptococcus pneumonia	166
Haemophilus influenzae	10
Other bacterial	
Fusobacterium necrophorum	167
Viral illnesses	
Varicella	168
Cytomegalovirus	169
Influenza H1N1	170
Hepatitis A	171
Hepatitis C	172
Human immunodeficiency virus	173
Coxsackie B virus	174
Epstein–Barr virus	175
Dengue	176
HHV6	177
Human parvovirus B19	178
Parasites	
Plasmodium falciparum	179
Pregnancy	51,98,180
Drugs	
Cisplatin	181
Gemcitabine	182
Mitomycin	183
Clopidogrel	184
Quinine	185,186
Interferon-alfa, -beta	187,188
Anti–vascular endothelial growth factor	189
Campath	190
Cyclosporin tacrolimus	191
Ciprofloxacin	192
Oral contraceptives	193–195
Illicit drugs (eg, cocaine, heroin, ecstasy)	196
Autoimmune	
Anticardiolipin	197
C3Nef	198
Systemic lupus erythematosus	199
Vaccination	
Hepatitis B	10
Bone marrow transplantation	200
Malignancy (gastric, breast, prostate, lung, colon, ovarian, pancreatic, lymphoma)	201
Combined methylmalonic aciduria and homocystinuria	202

Table 2. Complement Regulatory Proteins in Human Beings and Their Functions

Regulator	Function	Location
C1 inhibitor (C1-INH)	Inactivates C1r and C1s, MASP-1, and MASP-2	Plasma
MCP	Cofactor for factor I–mediated cleavage of C3b and C4b	Membrane-bound
DAF	Destabilizes C3/C5 convertases of the CP and AP (decay accelerating activity)	Membrane-bound
CR1	Decay accelerating activity as well as cofactor activity for factor I–mediated cleavage of C3b and C4b	Membrane-bound
C4 binding protein (C4BP)	Binds to C4b; decay accelerating and cofactor activity	Plasma
Factor H	Binds to C3b; has decay accelerating activity of the AP C3 and C5 convertases and cofactor activity	Plasma
Thrombomodulin	Increases CFH cofactor activity, activates TAFI-mediated C3a and C5a inactivation	Membrane-bound
Factor I	Degrades C3b and C4b aided by cofactors	Plasma
CD59	Blocks the C9 association with C5b-8 to prevent C5b-9 formation on host cells	Membrane-bound
S-protein (vitronectin)	Binds to C5b-7 and inhibits C9 polymerization	Plasma
Clusterin (SP-40,40)	Binds to C5b-7 and inhibits generation of C5b-9	Plasma

Abbreviation: TAFI, thrombin activatable fibrinolysis inhibitor.

Table 2. Summary Data for Genetic Mutations in aHUS

Mutations	CFH*		CFH*	MCP		MCP	CFI		CFI	C3		C3	THBD		THBD
Reference	49		51	49		51	49		51	49		51	49		51
Percentage	27.5		24	9.3		7	8.4		4	8.4		4	0		5
Type I mutation	56%		14%†	91%		88%†	42%		9%†	-		-	N/A		0%†
Type II mutation	44%		86%†	9%		12%†	58%		91%†	-		-	N/A		100%†
Homozygous	1.8%		4%	2.8%		1%	0%		0%	0%		0%	N/A		0%
Heterozygous	25.7%		20%	6.5%		6%	8.4%		4%	8.4%		4%	N/A		5%
	Ped	Ad		Ped	Ad		Ped	Ad		Ped	Ad		Ped	Ad	
Low C3 levels	70%	52%	47%	0%	11%	27%	60%	50%	20%	70%	85%	73%	N/A	N/A	50%
ESRF	52%‡	65%‡	53%§	17%‡	63%‡	6%§	17%‡	83%‡	60%§	43%‡	63%‡	67%§	N/A	N/A	23%§
Death	11%‡	2.5%‡	23%§	0%‡	0%‡	0%§	33%‡	0%‡	0%§	0%‡	0%‡	0%§	N/A	N/A	31%§
Death/ESRF	63%‡	68%‡	77% c	17%‡	63%‡	6%§	50%‡	83%‡	60%§	43%‡	63%‡	67%§	N/A	N/A	54%§

Table 3. Summary of the Main Complement-Associated Renal Diseases

Disease	Pathogenesis	Complement Pathway
Lupus nephritis	Anti-DNA antibodies, accumulation of apoptotic cells	CP
Post-streptococcal glomerulonephritis	Antibody mediated, circulating or planted antigens	CP
Goodpasture syndrome	Anti-GBM antibodies	CP
IgA nephropathy	Deposition of polymeric IgA	CP/AP
ANCA-associated vasculitis	Antibodies directed against neutrophil components	CP/AP
Membranous nephritis	Antibody-antigen complexes subepithelially	CP AP/LP
MPGN I	Immune complexes, C3NeF, complement gene mutations	CP/AP
C3 glomerulopathies	C3NeF, complement gene mutations	AP
STEC-HUS	Shiga-toxin mediated endothelial injury/activation	AP
aHUS	Complement gene mutations, anti-CFH antibodies	AP
Tubulointerstitial injury in proteinuric progressive glomerulopathies	Proteins (including complement components) abnormally ultrafiltered by the glomeruli	AP
I/R injury	Ischemic tissue injury, oxygen radicals	AP/LP

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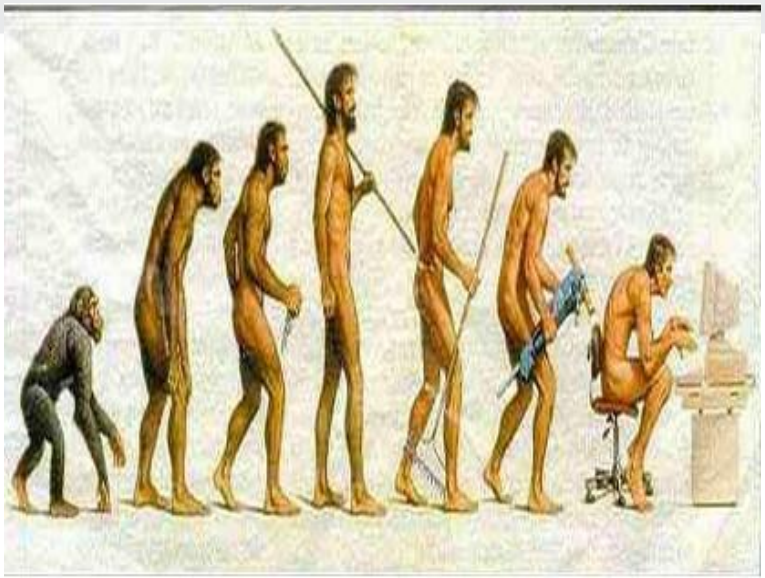
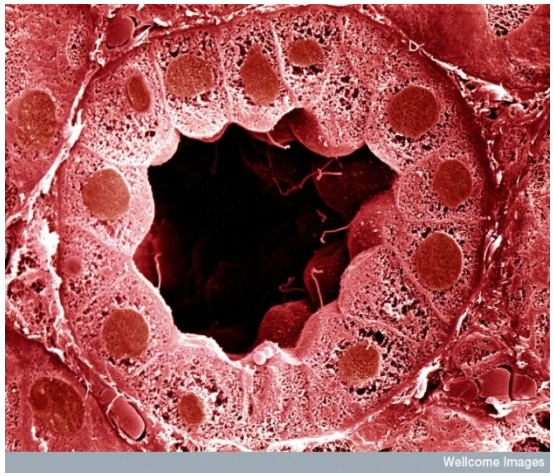
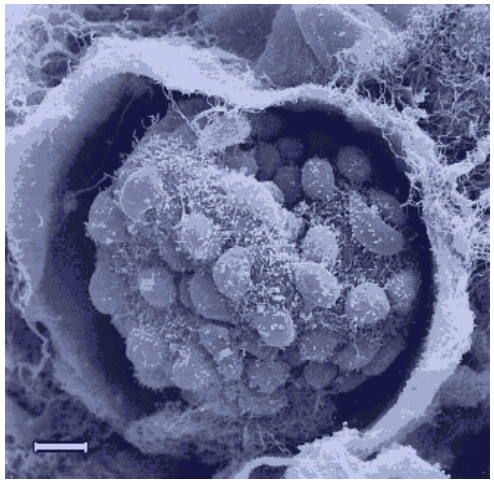


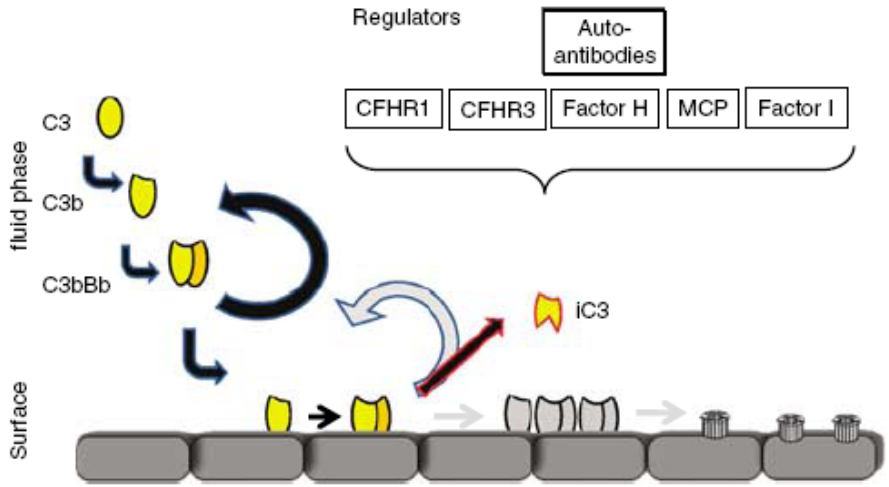




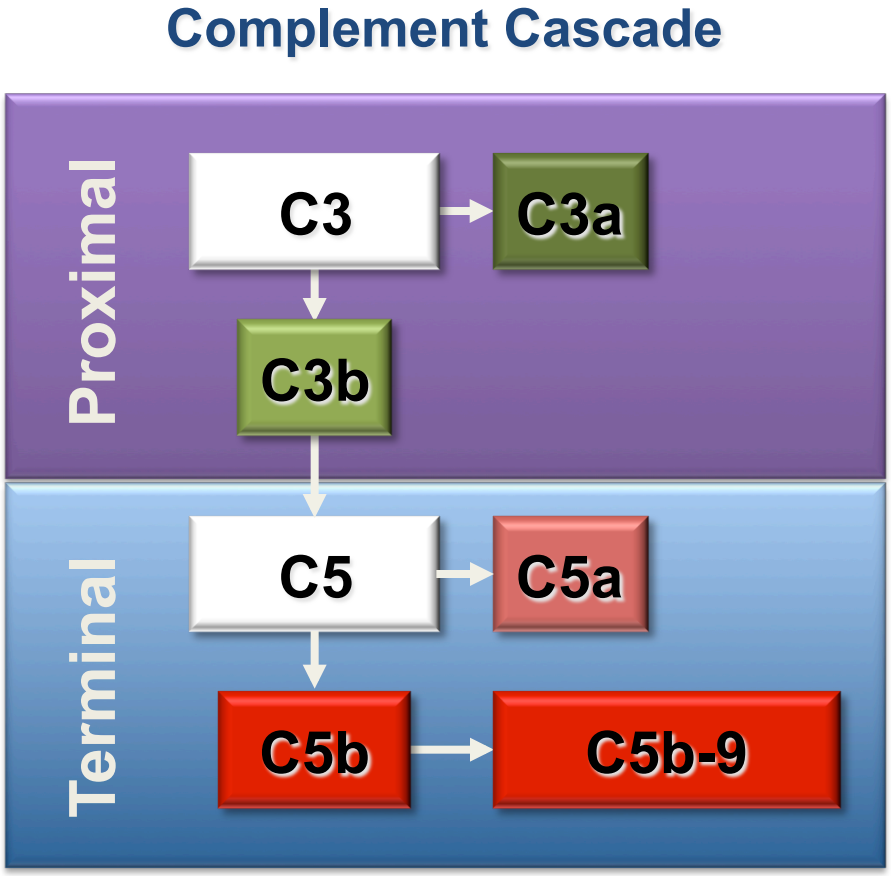
Desórdenes del Complemento

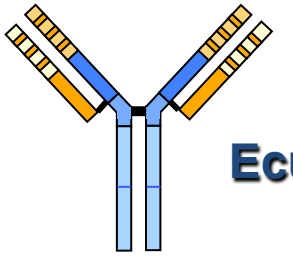
- 30% mutaciones del gen que codifica la porción soluble del factor H (FH)
- 10% autoanticuerpos contra FH (mas frecuente en niños), asociado a deficiencia de la proteína relacionada al factor H
- 10% mutaciones del CD46 (MCP)
- 10% mutaciones del factor I (FI)
- Mutaciones activadoras del factor B y C3

LAS MUTACIONES O POLIMORFISMOS DE MÁS DE UNO DE ESTOS GENES AUMENTAN LAS POSIBILIDADES DE SUH ATIPICO



El eculizumab bloquea la fase terminal de activación del complemento





Eculizumab

- 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.

Novel roles of complement in renal diseases and their therapeutic consequences

Takehiko Wada[1] and Masaomi Nangaku[1]

[1]*Division of Nephrology and Endocrinology, University of Tokyo School of Medicine, Bunkyo-ku, Tokyo, Japan*

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

Table 1 | Representative abnormalities in complement leading to renal disease

Components/related molecules	Diseases/phenotypes	Species	Notes
Complement C3	C3 glomerulopathy (DDD)	Human	Mutation (923ΔDG)
	aHUS	Human	Mutations
Factor H	C3 glomerulopathy (DDD/C3GN)	Human	Mutations
	aHUS	Human	Mutations
Factor I	C3 glomerulopathy (C3GN)	Human	Mutations
	aHUS	Human	Mutations
MCP	aHUS	Human	Mutations
Factor B	aHUS	Human	Mutations
CFHR5	Familial C3 glomerulopathy (CFHR5 nephropathy)	Human	Mutation (internal duplication)
CFHR3-1	Familial C3 glomerulopathy	Human	Mutation (hybrid gene)
CFHR1/3	IgA nephropathy	Human	Combined deletion
	aHUS	Human	Combined deletion
Factor B autoantibody	C3 glomerulopathy (DDD)	Human	Positive in serum
Factor H autoantibody	C3 glomerulopathy (DDD/C3GN)	Human	Positive in serum
C3Nef	C3 glomerulopathy (DDD/C3GN)	Human	Positive in serum
Bb (activated factor B)	HUS	Human	Plasma level↑
	ANCA-associated vasculitis	Human	Plasma level↑
Soluble C5b-9	HUS	Human	Plasma level↑
	TTP	Human	Plasma level↑
	ANCA-associated vasculitis	Human	Plasma level↑
C3a	ANCA-associated vasculitis	Human	Plasma level↑
	TTP	Human	Plasma level↑
C5a	ANCA-associated vasculitis	Human	Plasma level↑
C1q/C1qR	C1q nephropathy	Human	Positive in glomeruli
Properdin	TI injury due to massive proteinuria	Rat	Binding to tubular heparan sulfate
C5	ANCA-associated vasculitis	Mouse	Deficient mice were protected from disease
Factor B	ANCA-associated vasculitis	Mouse	Deficient mice were protected from disease
C3aR	TI inflammation	Mouse	Deficient mice were protected from disease
	IRI	Mouse	Deficient mice were protected from disease
C5aR	IRI	Mouse	Deficient mice were protected from disease
Factor H	IRI	Mouse	Deficient mice were protected from disease
C5b-9	IRI	Mouse	Deficient mice were protected from disease
CD59	IRI	Mouse	Deficient mice were protected from disease

Table 1. Most common complement profiles and autoimmune features in GN

Disease	Serum C Profile	Autoimmune Features
Poststreptococcal GN	AP or MBL normal C1q, low C3-C9	Anti-C1q, IgG AECA*, anti-DNA, ANCA, protein disulfide Isomerase (PDI), cardiac myosin
IgAN	Normal	Antiglycan, endothelial cell, mesangial cell, IgG, C1q
Anti-GBM nephritis	Normal	Anti-GBM, ANCA (20%), anti-C1q
ANCA-positive GN	Normal	Anti-MPO, PR3, cPR3, NET, DNA, endothelial cell, ? LAMP2
Lupus nephritis	CP, low C1q-C9	Anti-dsDNA, annexin, MPO, PR3, nucleosome, IgG, C1q, C1s,C1-INH, C4, cardiolipin, MBL, NET, H-ficolin, C3Nef
MPGN I	CP, low C1q-C9	Anti-C3 Nef, C4 Nef, C1q
MCD/FSGS	Normal	None
Membranous nephropathy	Normal	Anti-PLA2R, DNA, NEP, aldose reductase, SOD2, C1q
DDD	AP, normal C1q, low C3-C9	Anti-C3Nef, C4 Nef, CFH, factor B, C1q
C3 nephropathy	AP, normal C1q, low C3-C9	C3Nef, CFH, factor B

CP, classic pathway; AP, alternastive pathway; MBL, mannose binding lectin pathway; LAMP2, lysosomal membrane protein 2.

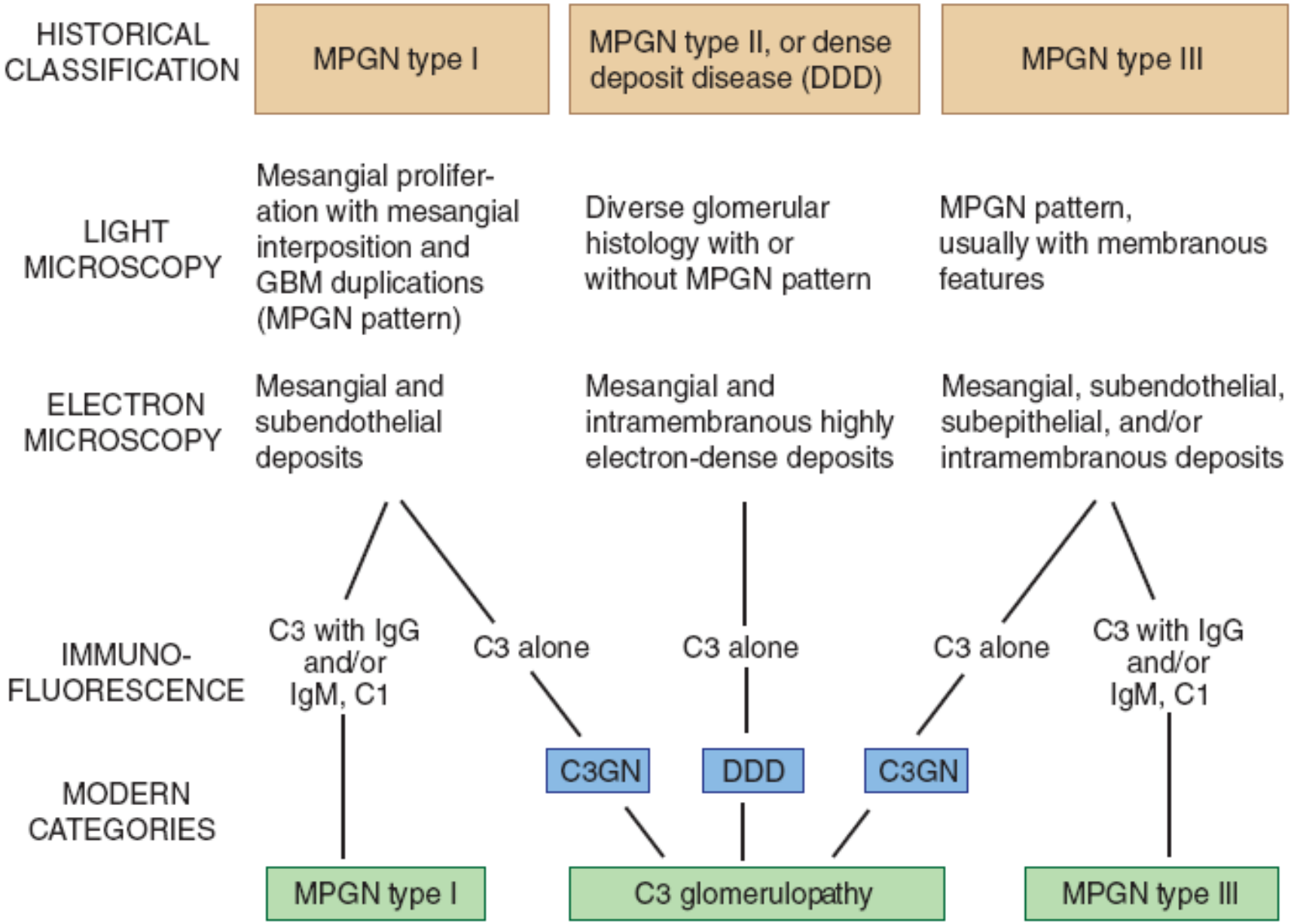
C3 glomerulopathy: what's in a name?

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


HISTORICAL CLASSIFICATION
MPGN type I
MPGN type II, or dense deposit disease (DDD)
MPGN type III
LIGHT MICROSCOPY
Mesangial proliferation with mesangial interposition and GBM duplications (MPGN pattern)
Diverse glomerular histology with or without MPGN pattern
MPGN pattern, usually with membranous features
ELECTRON MICROSCOPY
Mesangial and subendothelial deposits
Mesangial and intramembranous highly electron-dense deposits
Mesangial, subendothelial, subepithelial, and/or intramembranous deposits
IMMUNOFLUORESCENCE
C3 with IgG and/or IgM, C1
C3 alone
C3 alone
C3 alone
C3 with IgG and/or IgM, C1
MODERN CATEGORIES
C3GN
DDD
C3GN
MPGN type I
C3 glomerulopathy
MPGN type III

Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies

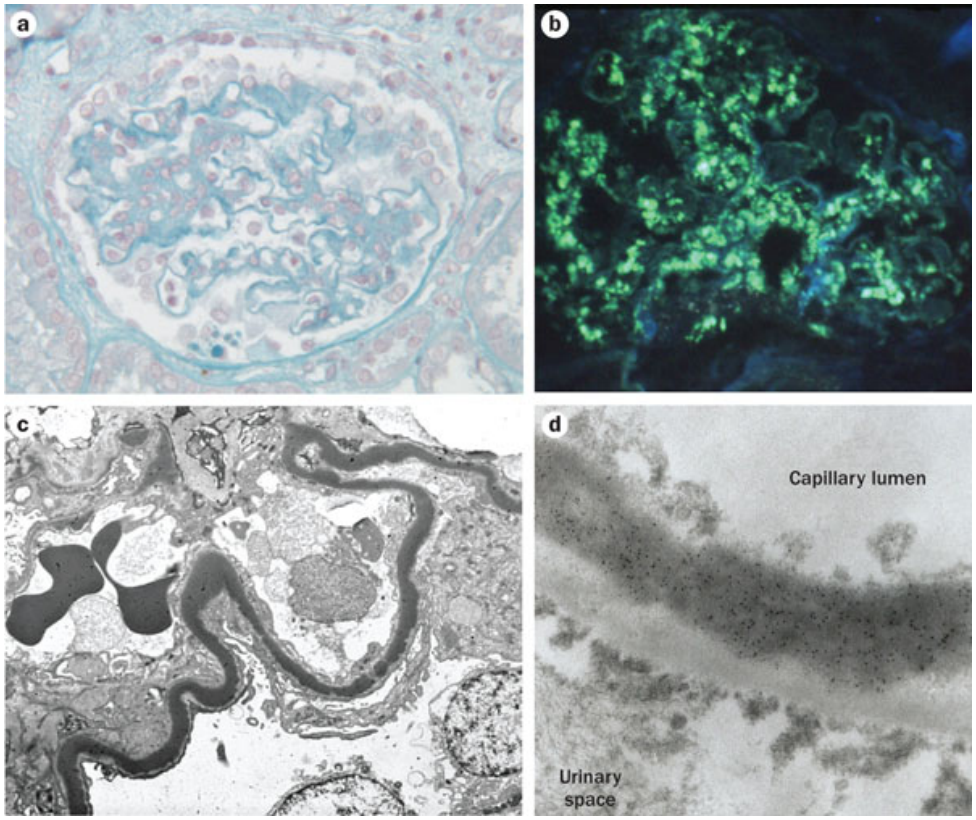
Julien Zuber, Fadi Fakhouri, Lubka T. Roumenina, Chantal Loirat and Véronique Frémeaux-Bacchi on behalf of the French Study Group for aHUS/C3G

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

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

El término ‘glomerulopatía por C3 abarca un espectro heterogéneo de nefropatías con base inmunológica que comparten un rasgo histopatológico:
Los depósitos glomerulares de C3.

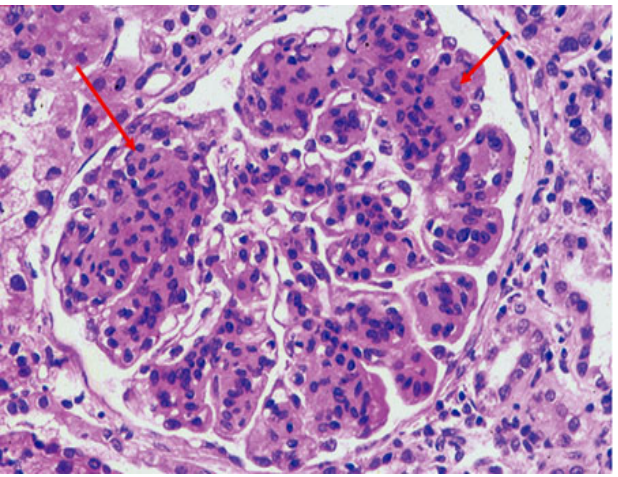
La disregulación de la vía alterna del complemento y la subsecuente siembra glomerular de los productos de degradación de la fracción C3 factor, sobre todo de C3d, son los eventos primarios que llevan al desarrollo de las glomerulopatías por C3.

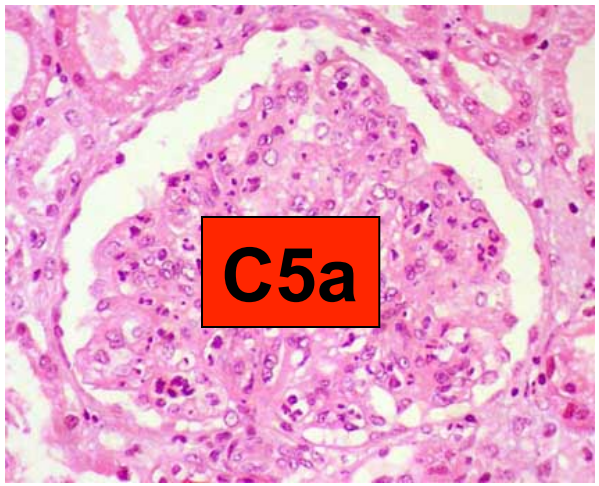


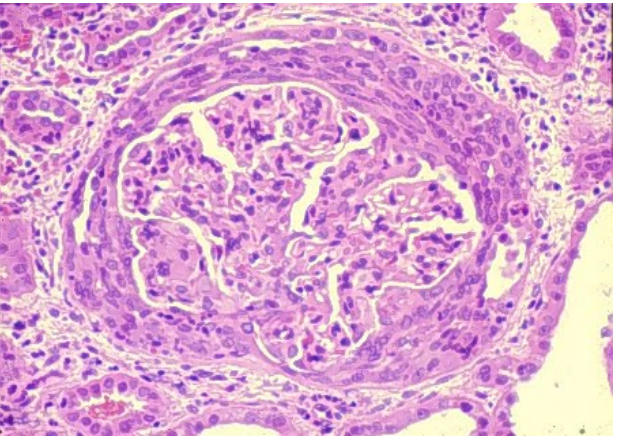
Zuber, J. *et al. Nat. Rev. Nephrol.* **8**, 643–657 (2012)

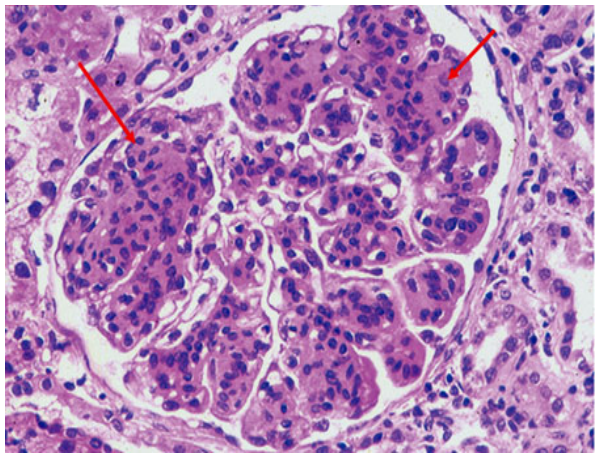
Las lesiones glomerulares de tipo inflamatorio y necróticas (expansión mesangial y proliferación endocapilar y extracapilar), que son en general gatilladas por la liberación de C5a, juegan un rol mayor en la progresión que lleva a la fibrosis y a la disfunción del riñón.

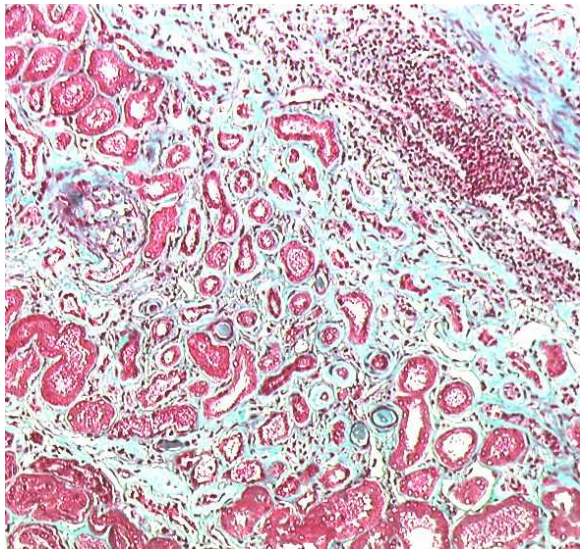
Las semilunas y en menor grado la proliferación mesangial, y no el tipo de glomerulopatía por C3, determinan el riesgo de enfermedad renal terminal y el riesgo de recurrencia en el injerto.











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

Los blancos de tratamiento en la glomerulopatías por C3 pueden dirigirse a la lesión inicial de los depósitos granulares glomerulares de C3 y/o a los cambios glomerulares inflamatorios subsecuentes.

La inhibición de la parte final de la vía del complemento a nivel del componente C5 atenúa los cambios inflamatorios glomerulares pero no alteran a los depósitos de C3 o el desarrollo de cambios en las paredes capilares

No hay drogas que bloqueen específicamente a la convertasa de C3 de la vía alterna.

Pero existe el bloqueo de la vía común final del complemento con al anticuerpo anti-C5, el eculizumab, el cual puede ser una terapia potencial para las glomerulopatías por C3.

La terapia anti-C5 ataca al componente inflamatorio de la glomerulopatía por C3, el factor C5a.

Sin embargo, las tinciones para C3 y para C5b–9 permanecen sin cambios en las biopsias post-eculizumab, indicando que el eculizumab no puede acelerar el clearance del complejo C5b–9 anterior al tratamiento.

Más aún, la inflamación glomerular y los cambios estructurales pueden prolongar la vida media de la fracción C5b–9 en el tejido renal.

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

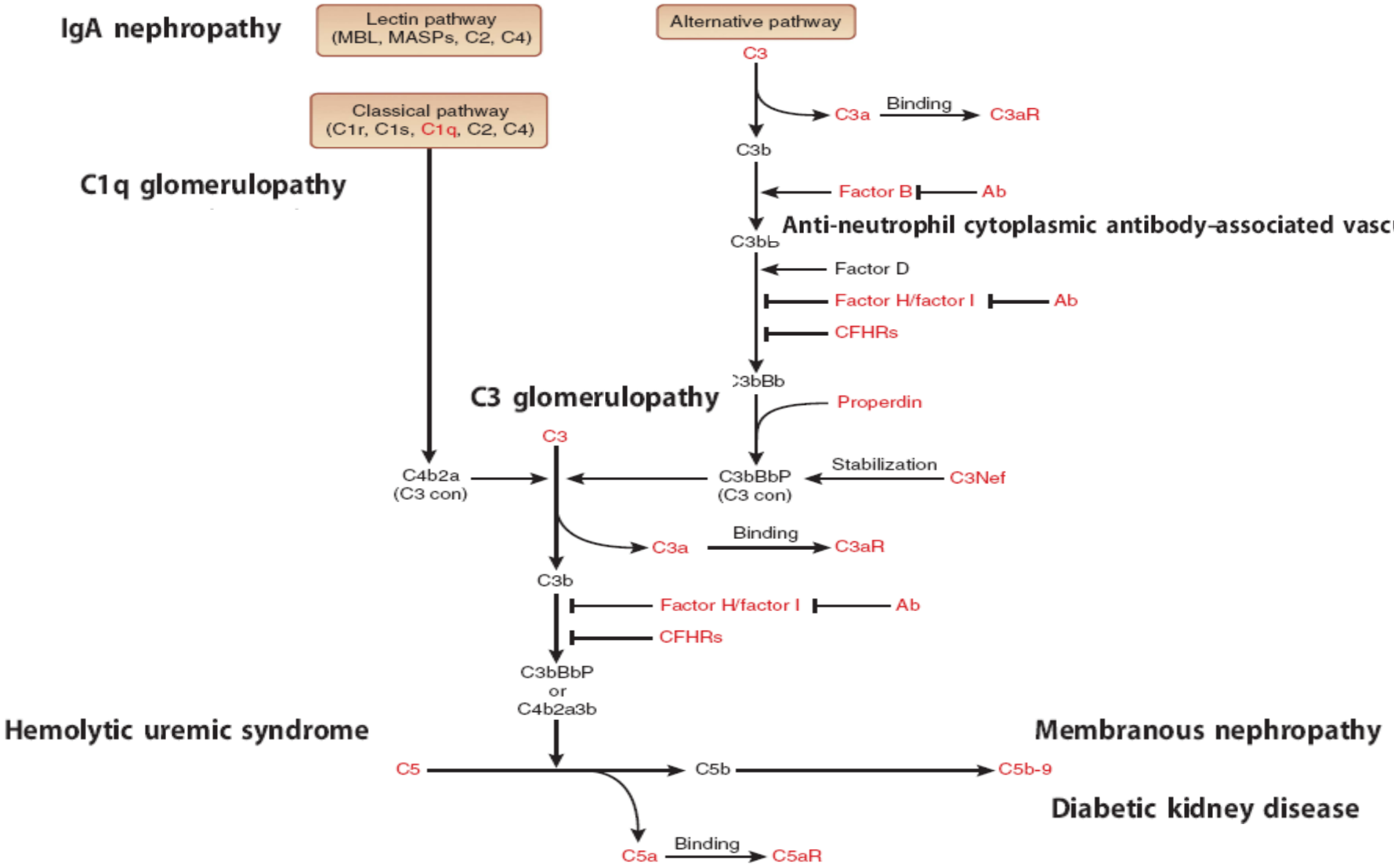


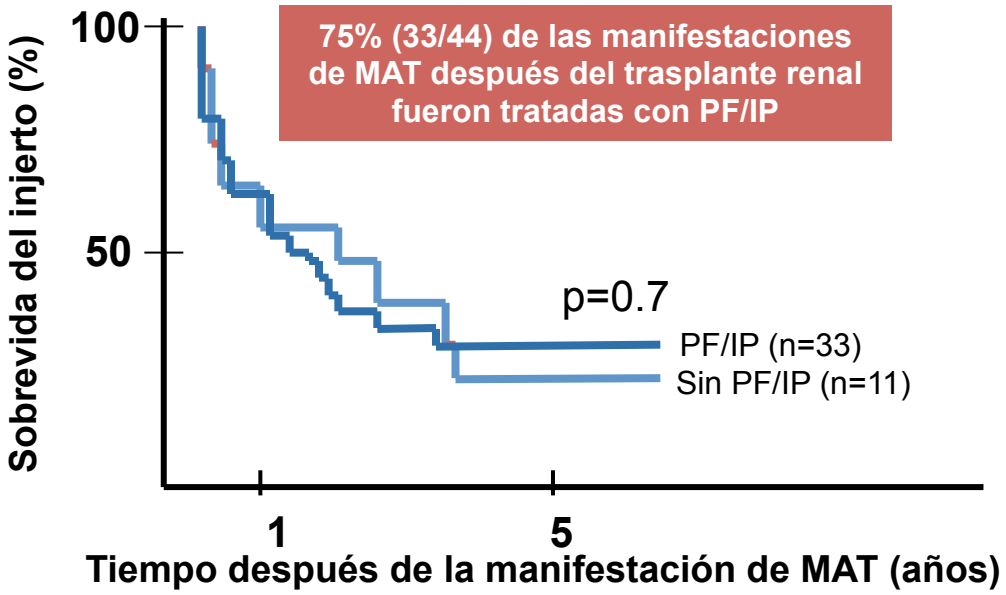
Figure 1 | Complement components and related molecules implicated in abnormal activation. The pathways of complement activation are depicted, with particular emphasis on the alternative pathway. The molecules highlighted in red are the complement components and the related molecules specifically discussed in this review. Ab, antibody; C3 con, C3 convertase; C3Nef, C3 nephritic factor; C3aR/C5aR, C3a receptor/C5a receptor; CFHRs, complement factor H–related proteins; MASPs, mannose-binding protein–associated serine proteases; MBL, mannose-binding lectin.

C + IgS	**PENSAR EN VÍA CLÁSICA**
C3	**PENSAR EN VÍA ALTERNA**
C4	**PENSAR EN VÍA DE LAS LECTINAS**

SINDROME URÉMICO HEMOLÍTICO ATÍPICO
Y
TRANSPLANTE RENAL

La PF/IP falló en mejorar la sobrevida del injerto en pacientes con SHUa posterior al trasplante renal[1]

- En la mayoría de los reportes, la PF/IP falló en la prevención de la pérdida del injerto[2-5]
- No hubo mejoría en la sobrevida del injerto en los pacientes con SHUa posterior al trasplante renal a pesar de PF/IP en la cohorte de Francia (N=44)[1]



Modificado de Le Quintrec et al. *AJT 2013*

Referencias: 1. Le Quintrec et al. Am J Transplant. 2013 3:663-75; **2.** Noris M, et al. *Clin J Am Soc Nephrol.* 2010;5:1844-1859; **3.** Loirat C et al. *Semin Thromb Hemost.* 2010; 6:673-81; **4.** Loirat C, Frémeaux-Bacchi V. *Orphanet J Rare Dis.* 2011;6:60; **5.** Zuber J, Le Quintrec M, Sberro-Soussan R, et al. *Nat Rev Nephrol.* 2011;1:23-35.

La eficacia del eculizumab ha revolucionado el manejo y el pronóstico del SUHa y ha abierto la posibilidad del transplante renal en los sujetos con SUHa.

Si bien el transplante renal con donante fallecido es la opción preferida en los pacientes con SUHa, el transplante vivo no-relacionado puede ser considerado en cada caso puntual.

El caso del donante vivo relacionado es más complejo pues el SUHa pudo haber pasado inadvertido en el donante y puede desenmascarase luego de la nefrectomía por el stress quirúrgico, por lo que no es la opción ideal

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

El riesgo de recurrencia del SUHa en el post-transplante depende básicamente de la anomalía genética del factor del complemento involucrado.

En este sentido los estudios genéticos son mandatorios.

Y servirán para ajustar a medidad la estrategia terapéutica para cada caso de transplante renal en particular

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

Pacientes con alto riesgo de recurrencia deben recibir en forma profiláctica el eculizumab, incluyendo una dosis de 1200 mg antes de la cirugía y una dosis adicional de 900 mg dentro de las 24 horas de la reperfusión.

Pacientes con riesgo moderado pueden recibir plasma o una dosis profiláctica de eculizumab, dependiendo de la accesibilidad a la droga.

Duración del tratamiento profyláctico con eculizumab post transplante?

De por vida en los de alto riesgo de recurrencia.

Se puede discontinuar en el subgrupo de moderado riesgo a los 12 meses post-transplante.

Estas recomendaciones deben ser validadas en el futuro

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

El transplante hepatorenal es efectivo en la cura el SUHa por las mutaciones en el factor H, factor I , C3 y CFB.

Si bien el procedimiento se ha tornado más seguro luego de la introducción del plasma pre-conditioning y de las técnicas quirúrgicas, sigue teniendo sus riesgos.

Tener en cuenta los costos de los tratamientos a instituir y los riesgos-beneficios en cada caso

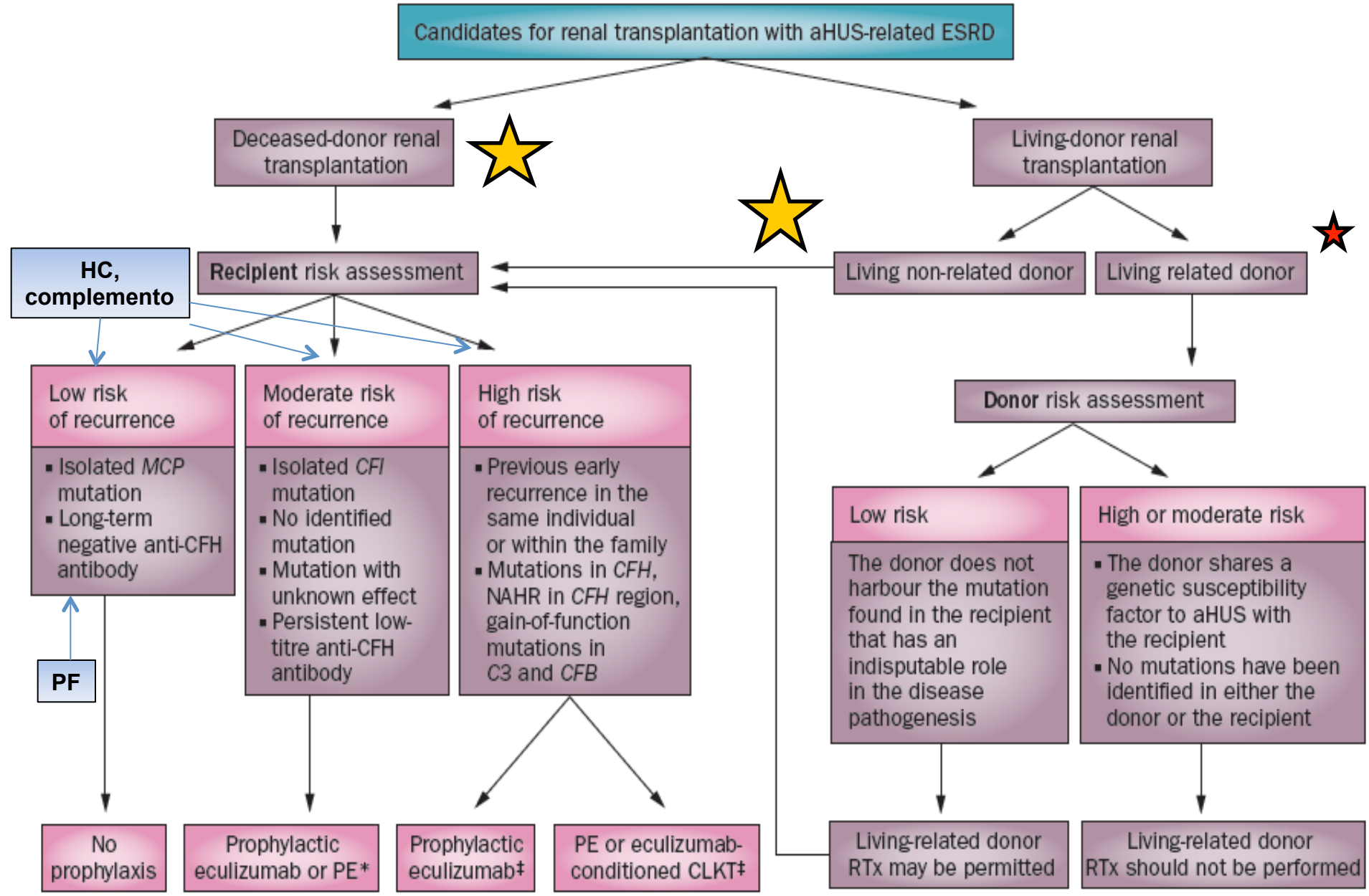
Zuber, J. *et al. Nat. Rev. Nephrol.* **8**, 643–657 (2012)

El trasplante renal no trata la causa subyacente del SHUa

Proteína afectada	Resultado del Trasplante renal[1]
Factor H	Porcentaje de pacientes con MAT permanente: **80-90%**
CFHR1, R3	Porcentaje de pacientes con MAT permanente: **20%**
MCP	Porcentaje de pacientes con MAT permanente: **15-20%**
Factor I	Porcentaje de pacientes con MAT permanente: **70-80%**
Factor B	MAT permanente en un caso publicado
C3	Porcentaje de pacientes con MAT permanente: **40-50%**
THBD	MAT permanente en un caso publicado

Más del 90% de los pacientes con SHUa en otra cohorte experimentaron pérdida del injerto, la mayoría en el primer año[2]

Referencias: 1. Noris M et al. *N Engl J Med*. 2009;361:1676-1687. **2**. Bresin E et al. International Registry of Recurrent and Familial HUS/PTT. *Clin J Am Soc Nephrol*. 2006;1:88-99.



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

Eculizumab – Approved Dosing Schedule in aHUS

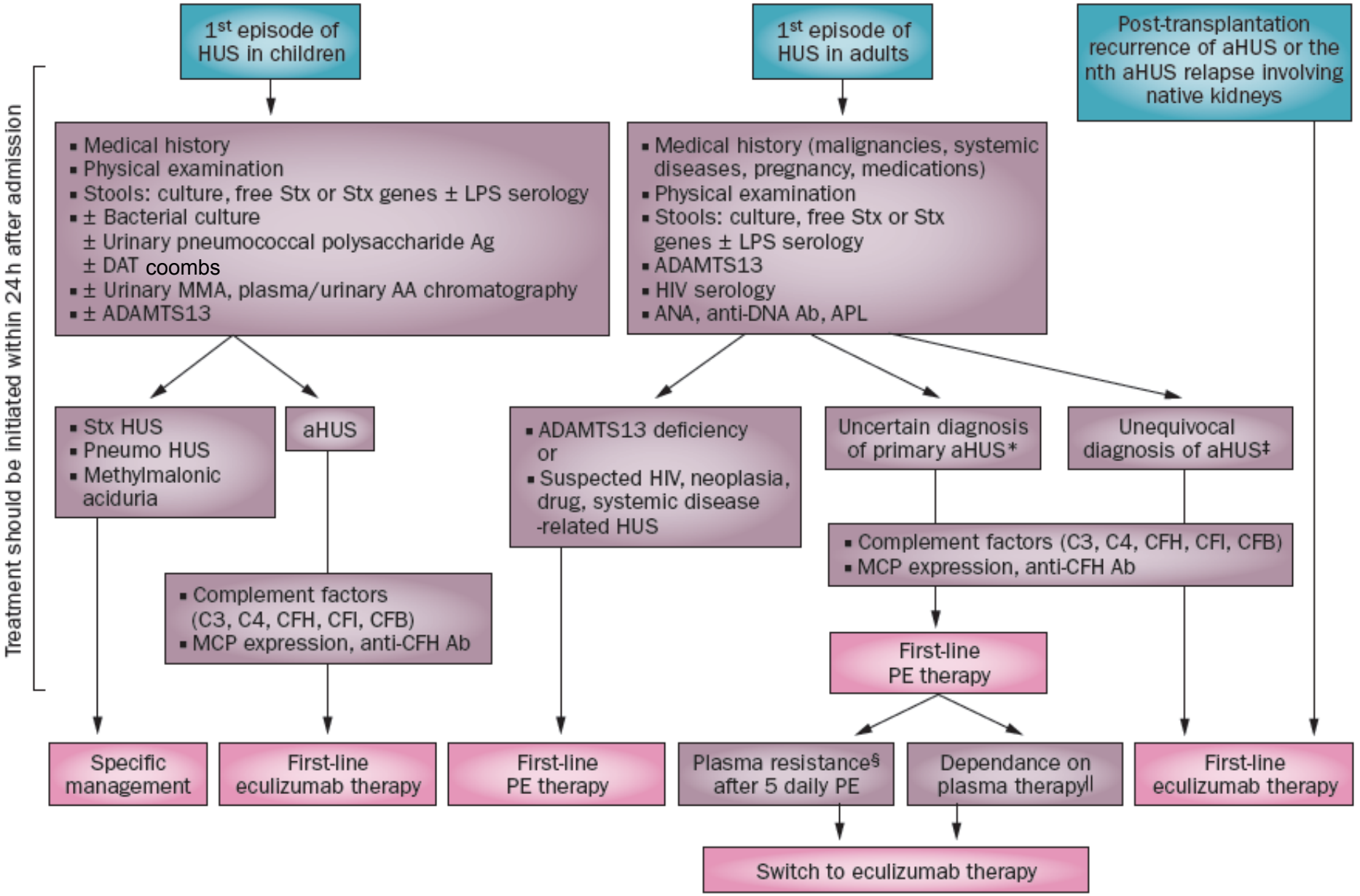
For patients ≥18 years of age, Soliris therapy consists of:

	Induction	Maintenance
	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks

For patients <18 years of age, administer Soliris based upon body weight, according to the following schedule:

Patient Body Weight	Induction	Maintenance
40 kg and over	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg less than 20 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 3 weeks

ALGORITMO DE DIAGNÓSTICO Y TRATAMIENTO DEL SUHa



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

- **NO ESPERAR EL ESTUDIO GENÉTICO PARA COMENZAR TRATAMIENTO**
- **ESTUDIO GENÉTICO CON IMPACTO A FUTURO (PLANIFICACIÓN DE TX)**
- **DIAGNÓSTICO CLÍNICO**
- **40% CURSAN CON DIARREA (SUH); 40% SON ADULTOS: A CUALQUIER EDAD**
- **80% CON C3 NORMAL; CFH NORMAL EN 87% DE CASOS**
- **PUEDE ACOMPAÑAR A OTROS CUADROS: LES, MALIGNIDAD, EMBARAZO**
- **TRATAMIENTO: CUANTO ANTES, MEJOR**
- **PLASMAFÉRESIS Y/O INFUSIÓN DE PLASMA (60% ÓBITO; 40% PROGRESAN A HD)**
- **RITUXIMAB**
- **ECULIZUMAB**
- **SUSPENSIÓN INMEDIATA DE PLASMAFERÉSIS , FUNCIÓN RENAL MEJORA EN GRAL A LA 5TA SEMANA, DURACIÓN DE TRATAMIENTO NO ESTABLECIDA; COSTO**

Some kind of happiness is measured out in miles

You can talk to me
If you're lonely, you can talk to me

Hey Bulldog Lennon & McCartney 1968