Riunione della Società Italiana di Pediatria per la formazione continua dei PLS del FVG

Le novità che cambiano la pratica

Autoimmunità e Rene

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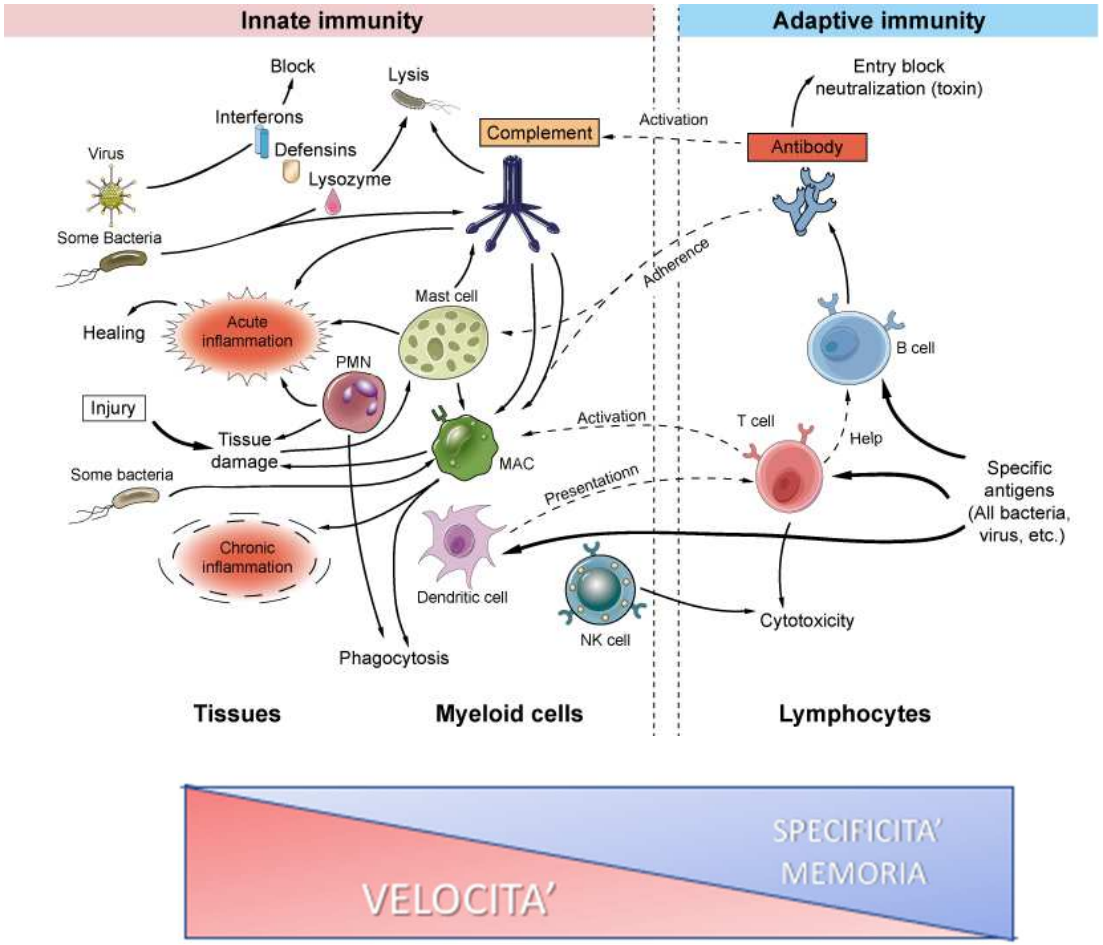
UNIVERSITÀ DEGLI STUDI DI UDINE

ASU FC
Azienda sanitaria universitaria Friuli Centrale

REGIONE AUTONOMA FRIULI VENEZIA GIULIA

Innate versus adaptive immunity



(Auto)Immunità e Rene

- Il **rene**, in aggiunta alla milza, ha un ruolo centrale nel processo immunitario, specie per il **mantenimento della tolleranza immunologica**:
  - Antigeni filtrati di basso peso molecolare (ormoni, proteine alimentari) vengono presentati ad alte concentrazioni (10x quelle ematiche) alle cellule del nefrone distale ed intercettati da un denso network di cellule dendritiche che poi presentano gli antigeni ai linfociti T

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- I reni sono suscettibili a malattie immuno-mediate da perdita dell'**omeostasi immunologica**.

Innate versus adaptive immunity in kidney immunopathology

Hans-Joachim Anders

	Innate immunity	Adaptive immunity
Recognition receptors (R)	Complement-R	B cell receptors
	Mannose-R	T cell receptors
	Toll-like-R	MHC I
	Inflammasomes	MHCII
	Low affinity immunoglobulins	High affinity IgG
Receptor clonality	Non-clonal	clonal
Receptor genes	Single gene, no rearrangement required	Encoded in gene segments Rearrangement required
Receptor agonists	Molecular patterns	Antigenic epitopes
Time delay of response	Immediate	Delayed
Effector mechanism	Opsonization, phagocytosis, granuloma formation, leukocyte recruitment, complement lysis, inflammation, healing responses	Clonal expansion of antigen-specific B and T cells, antigen-specific immunoglobulins
Paradigmatic kidney diseases	Urinary tract infection, acute kidney injury, glomerulosclerosis, tubulointerstitial fibrosis, crystal nephropathies C3 glomerulopathy	IC glomerulonephritis, allograft rejection, interstitial nephritis

Anders *BMC Nephrology* 2013, **14**:138
http://www.biomedcentral.com/1471-2369/14/138

Classificazione anatomopatologica delle possibili lesioni renali

- Malattia glomerulare
- Malattia tubulo-interstiziale
- Malattia dei piccoli vasi

Classificazione anatomopatologica delle possibili lesioni renali

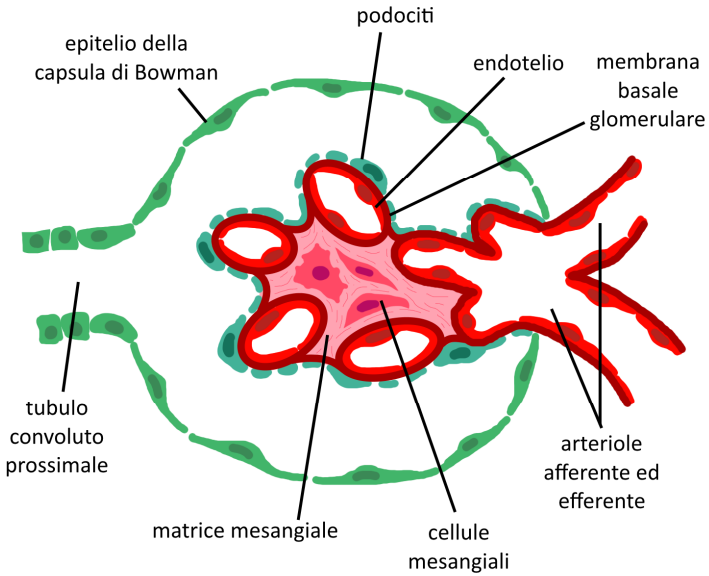
- Malattia glomerulare
  1. **Primitiva**
     - Solo coinvolgimento renale
     - Risposta infiammatoria sistemica contenuta
  2. **Secondaria**
     - Coinvolgimento glomerulare nel contesto di una malattia sistemica

Risposta del glomerulo all'insulto

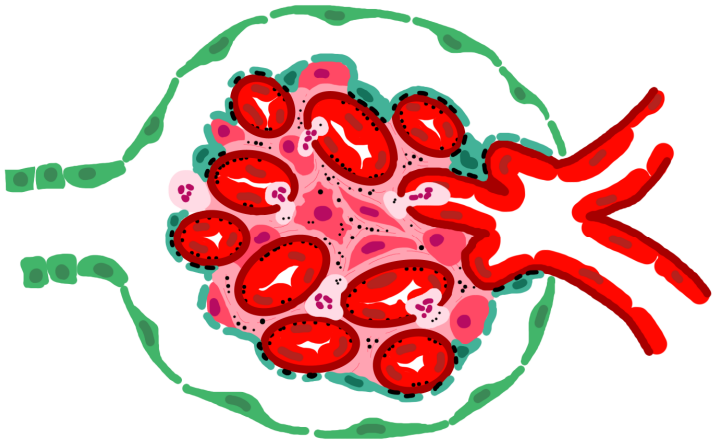
- Aumento della cellularità (ipercellularità):
  - Glomerulonefriti proliferativa
  - Aumento della cellularità endoteliale, mesangiale ed epiteliale
  - Infiltrazione leucocitaria (neutrofili, monociti, linfociti)

Risposta del glomerulo all'insulto

Glomerulo normale



Glomerulonefrite proliferativa



Risposta del glomerulo all'insulto

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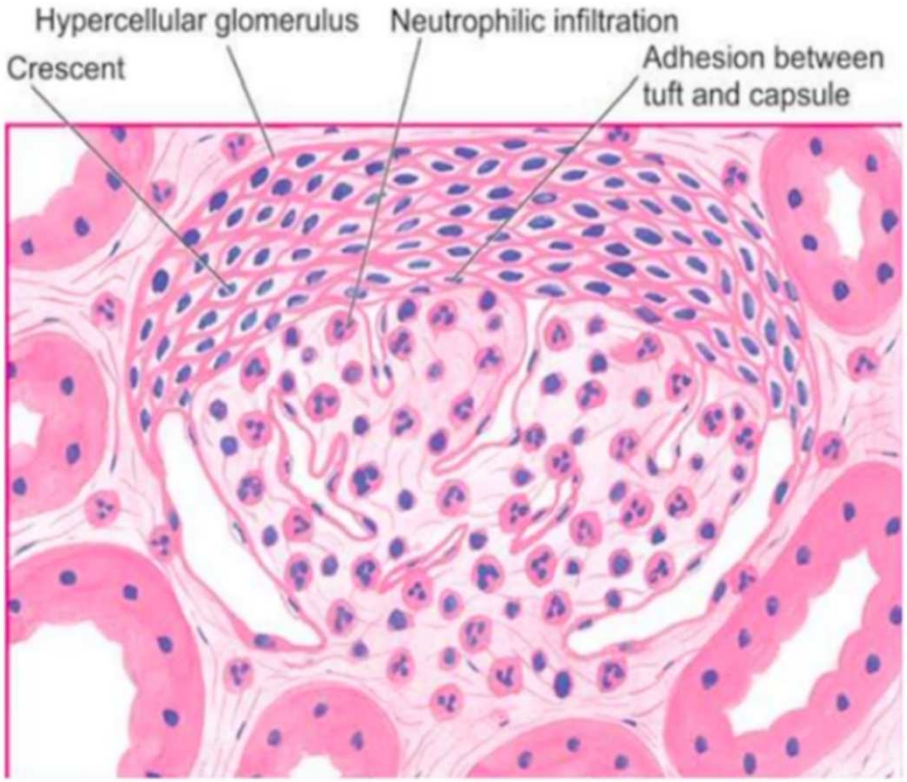
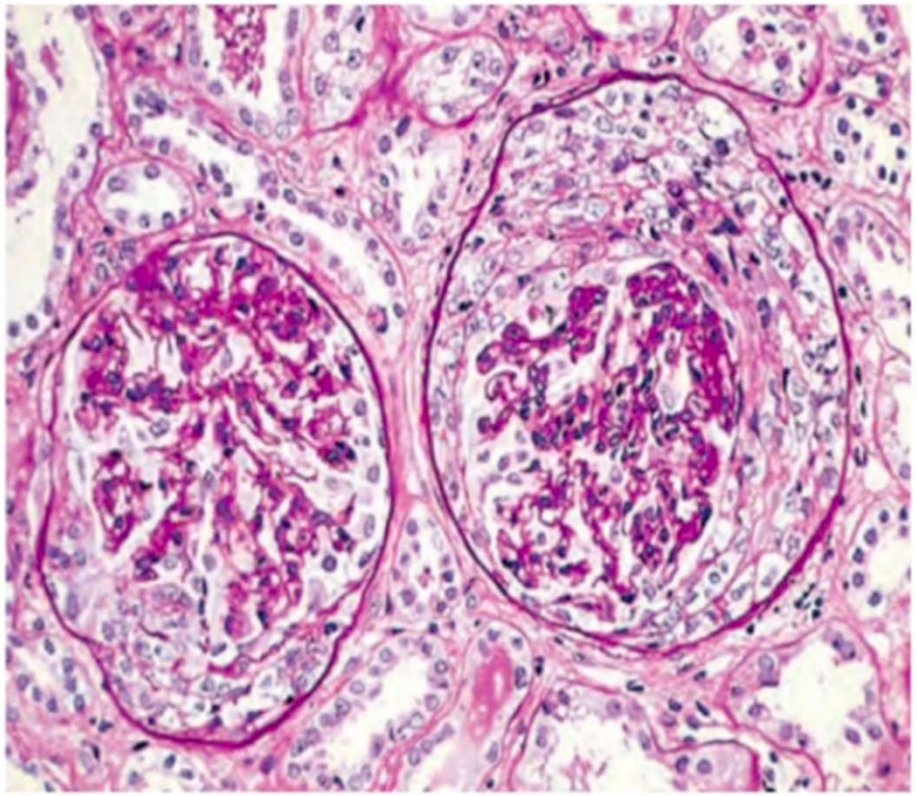
  - Glomerulonefriti profliferativa
  - Aumento della cellularità endoteliale, mesangiale ed epiteliale
  - Infiltrazione leucocitaria (neutrofili, monociti, linfociti)

  - Formazione dei ***crescent*** (semilune): proliferazione delle cellule parietali epiteliali (capsula del Bowmann), con infiltrato leucocitario e depositi di fibrina

Risposta del glomerulo all'insulto



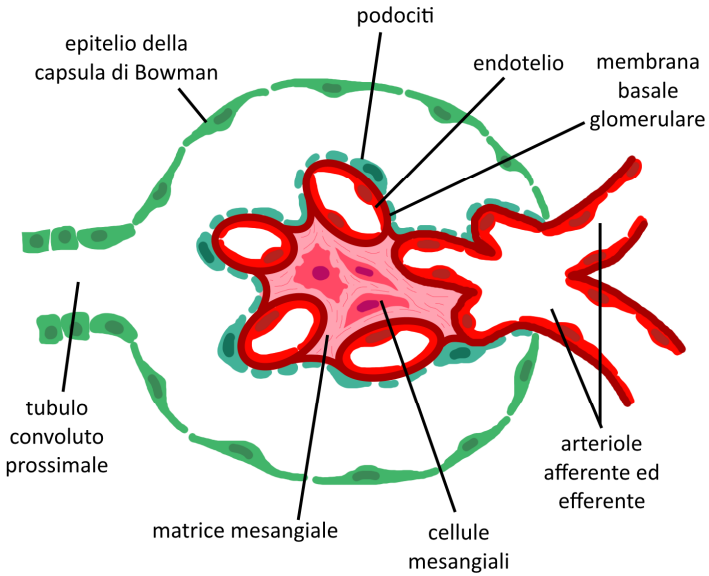


Risposta del glomerulo all'insulto

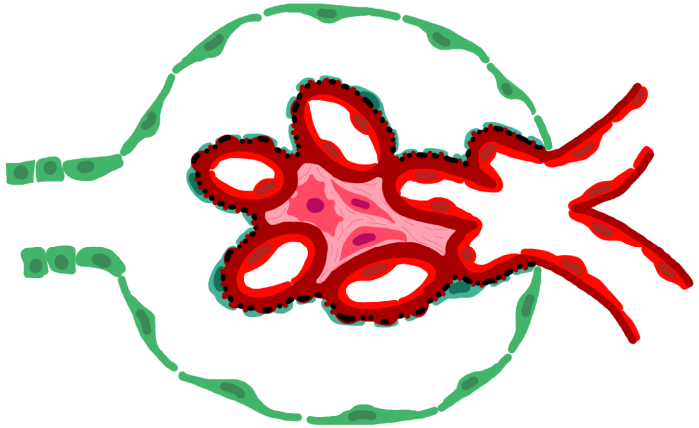
- Ispessimento della membrana basale (***thickening***):
  - Deposito di materiale amorfo elettrondenso o di immunocomplessi sul versante epiteliale, intramembranoso o endoteliale
  - Duplicazione della lamina densa

Risposta del glomerulo all'insulto

Glomerulo normale

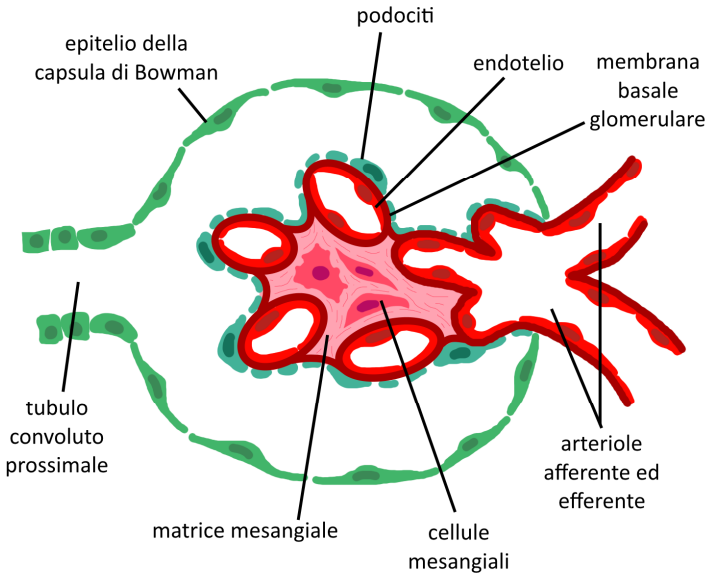


Glomerulonefrite membranosa

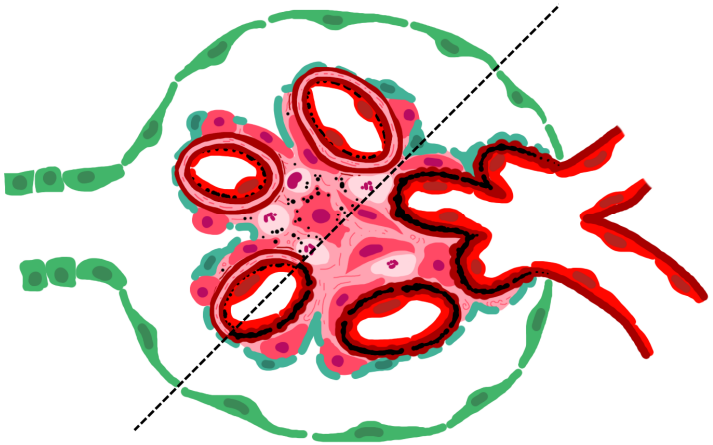


Risposta del glomerulo all'insulto

Glomerulo normale



Glomerulonefrite membranoproliferativa

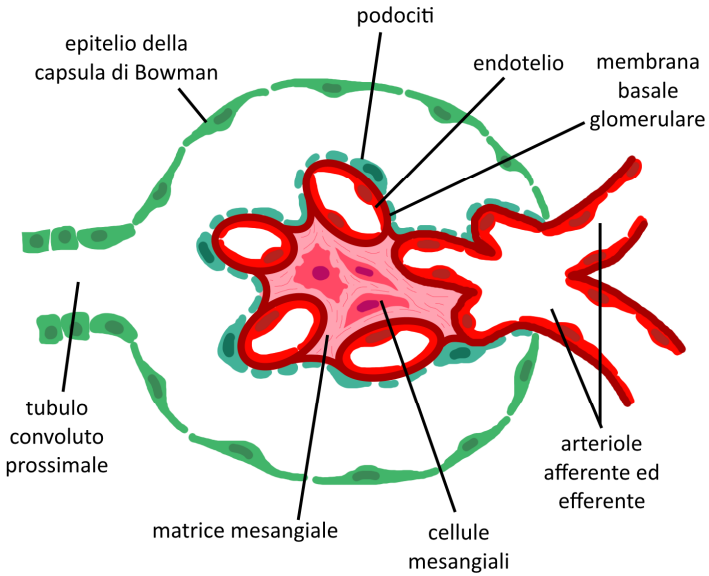


Risposta del glomerulo all'insulto

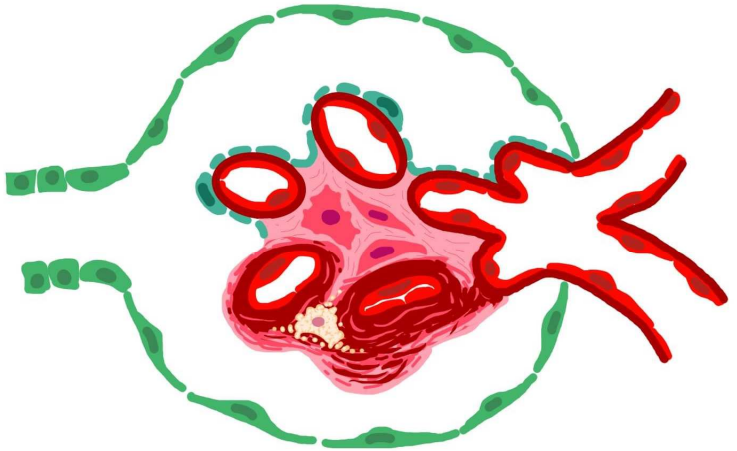
- Sclerosi
  - Deposito extracellulare di matrice collagene
  - In ambito mesangiale o capillare

Risposta del glomerulo all'insulto

Glomerulo normale



GSFS



(Auto)Immunità e Rene

- Le malattie renali immuno-mediate da perdita dell'omeostasi immunologica si distinguono in:
  - Malattie renali da danno immune diretto
    - Glomerulonefrite da anticorpi anti-GBM
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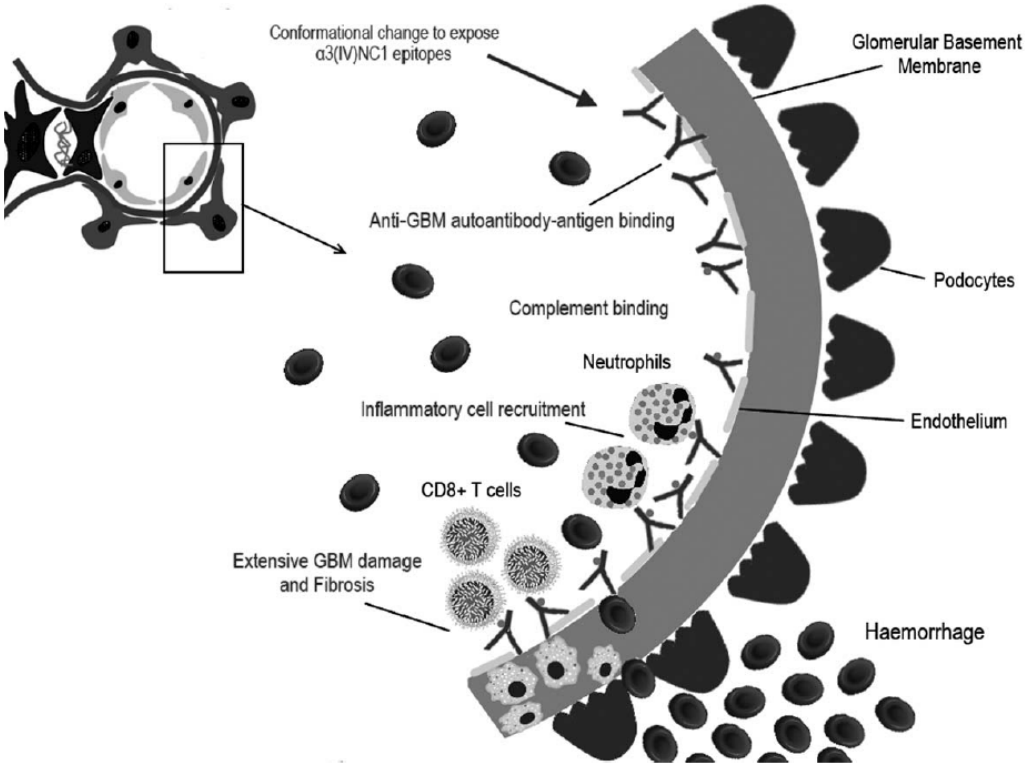
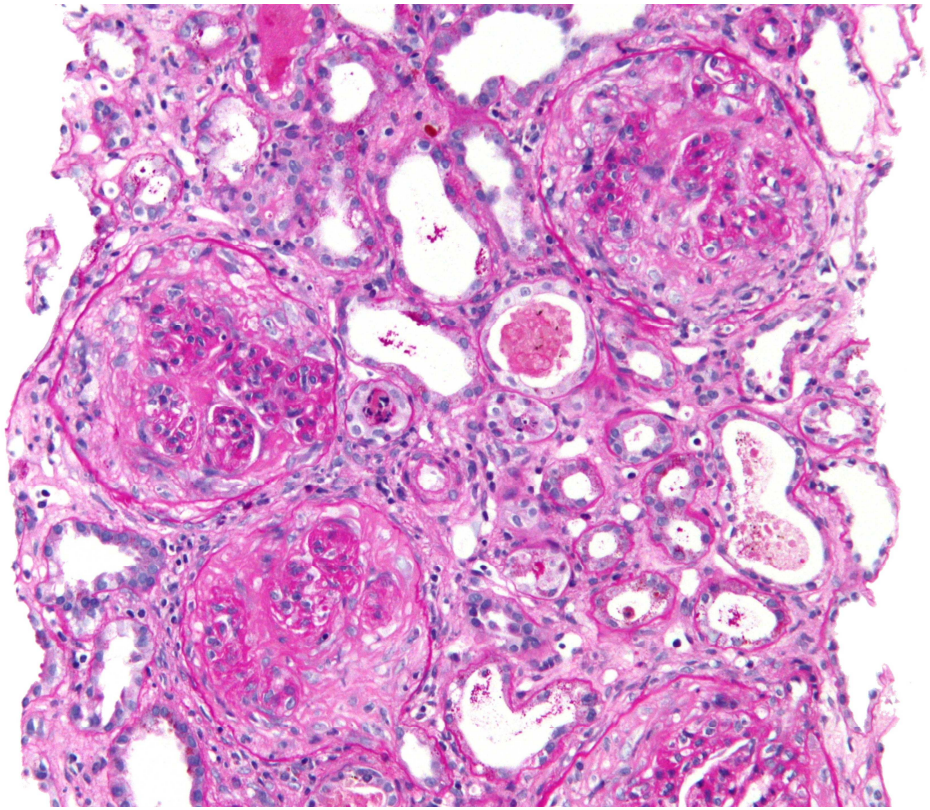
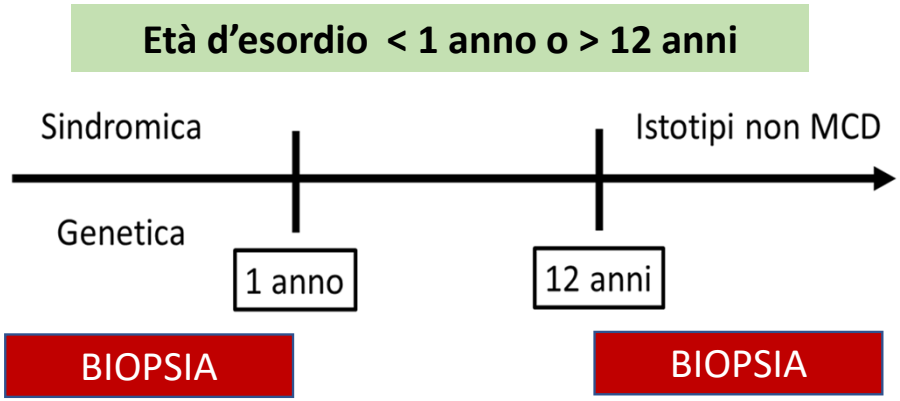
Sindrome di Goodpasture



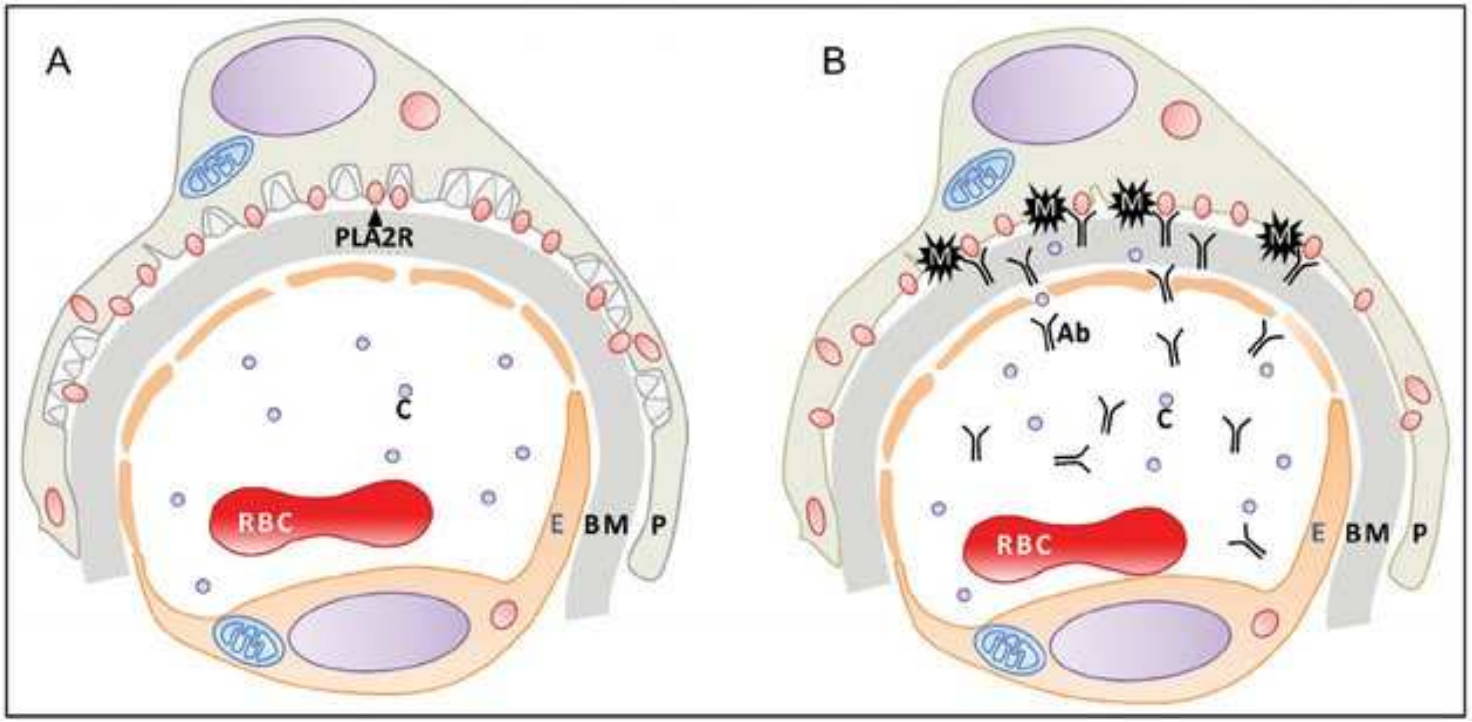


Glomerulonefrite membranosa

- Incidenza: 1-2 casi/100.000/anno
- 6-10% delle biopsie dell'adulto
- Nell'80% dei casi è una forma primitiva
- Nell'80% dei casi si manifesta con **sindrome nefrosica**



Glomerulonefrite membranosa



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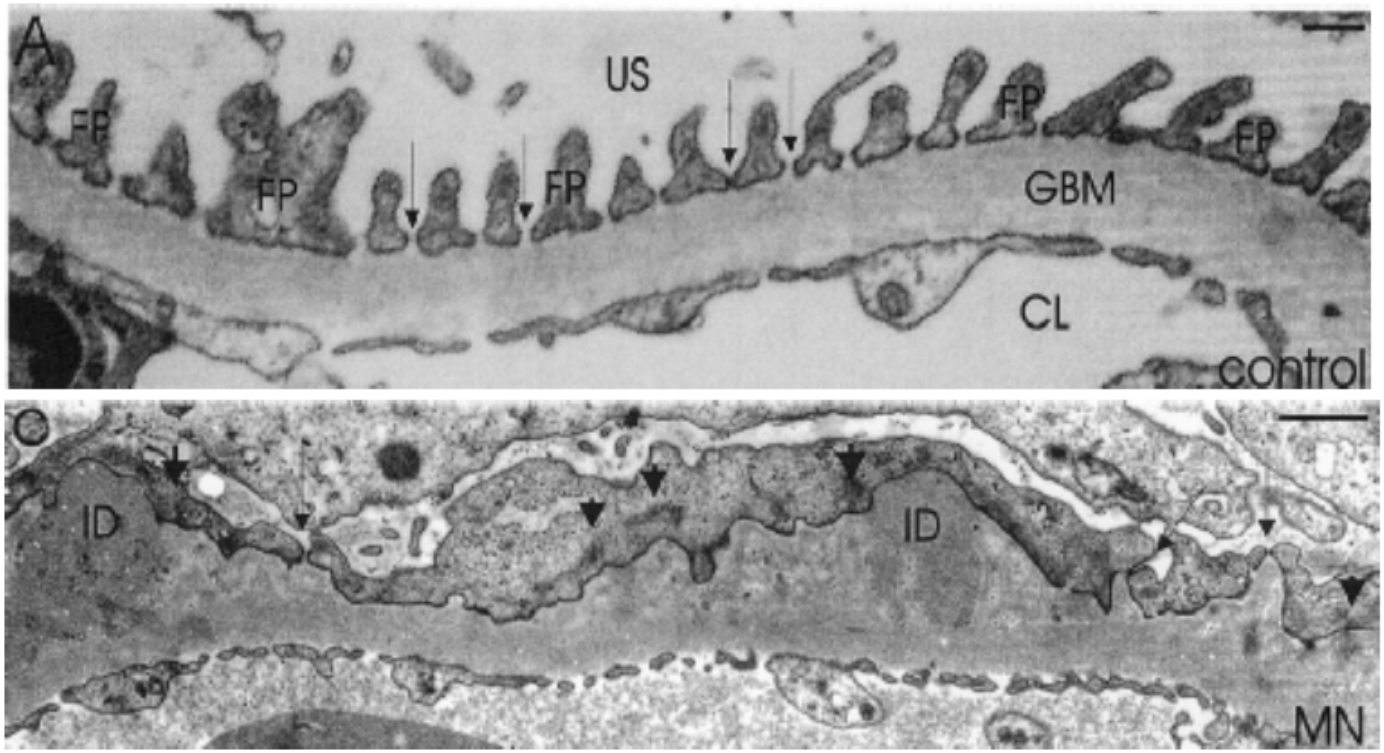

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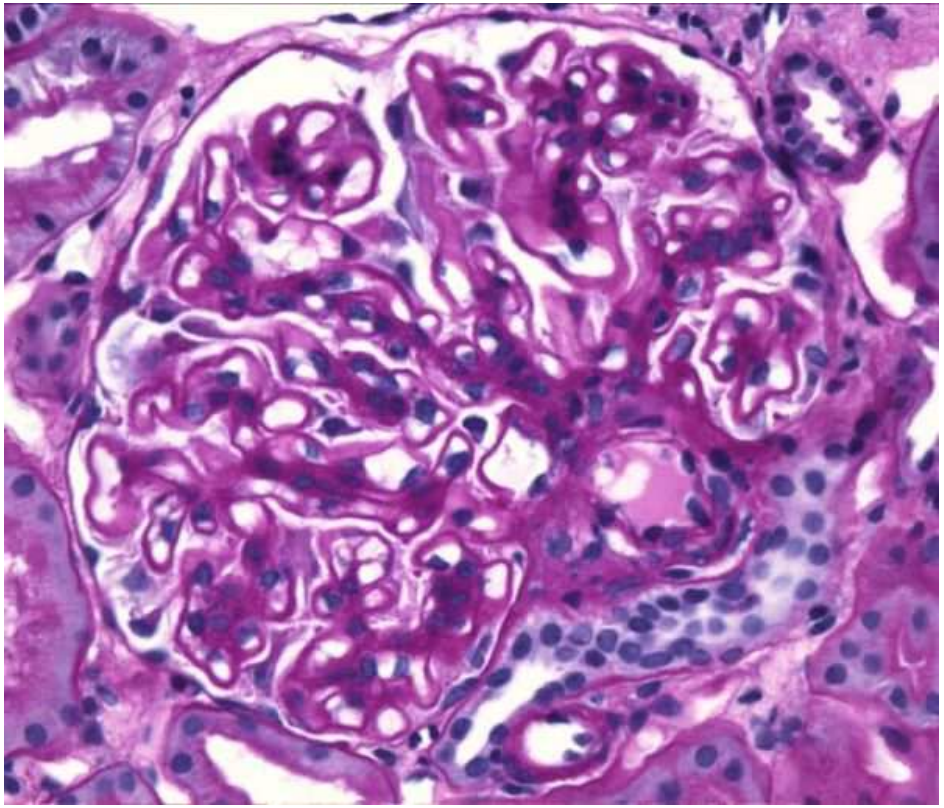
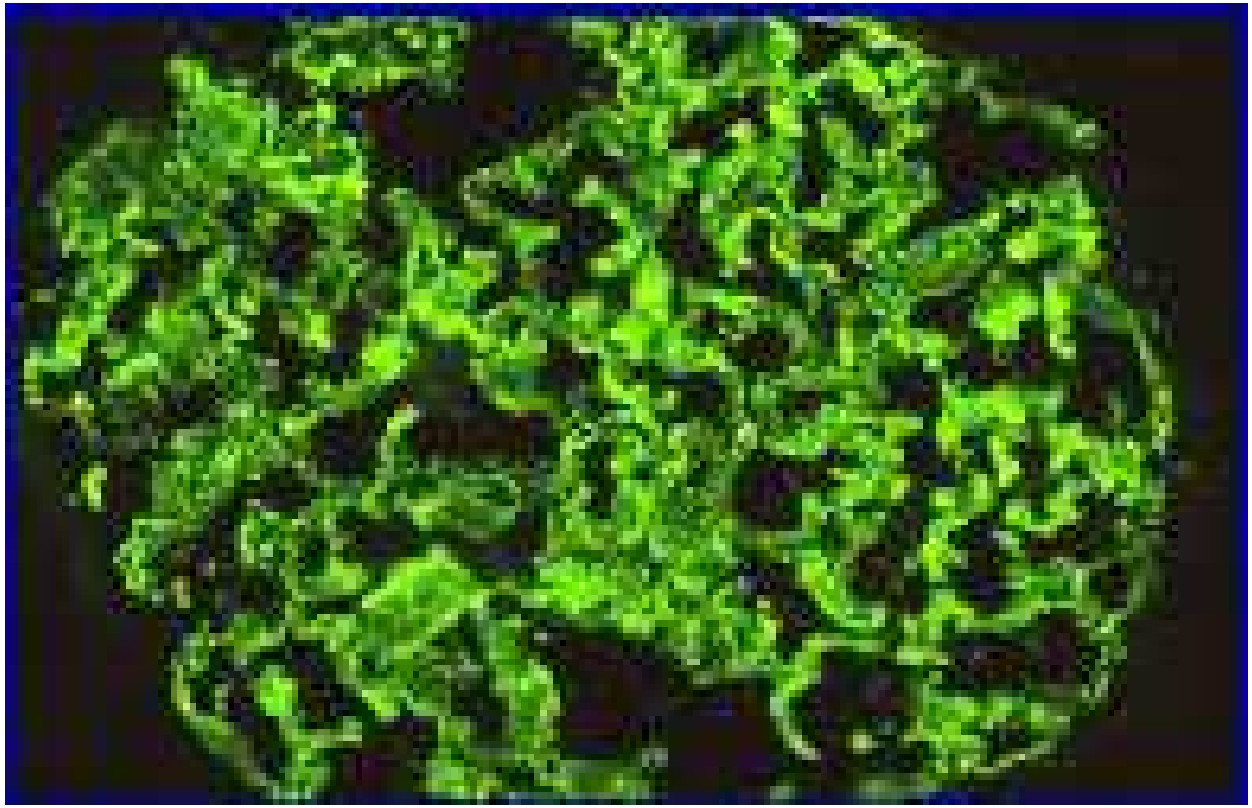


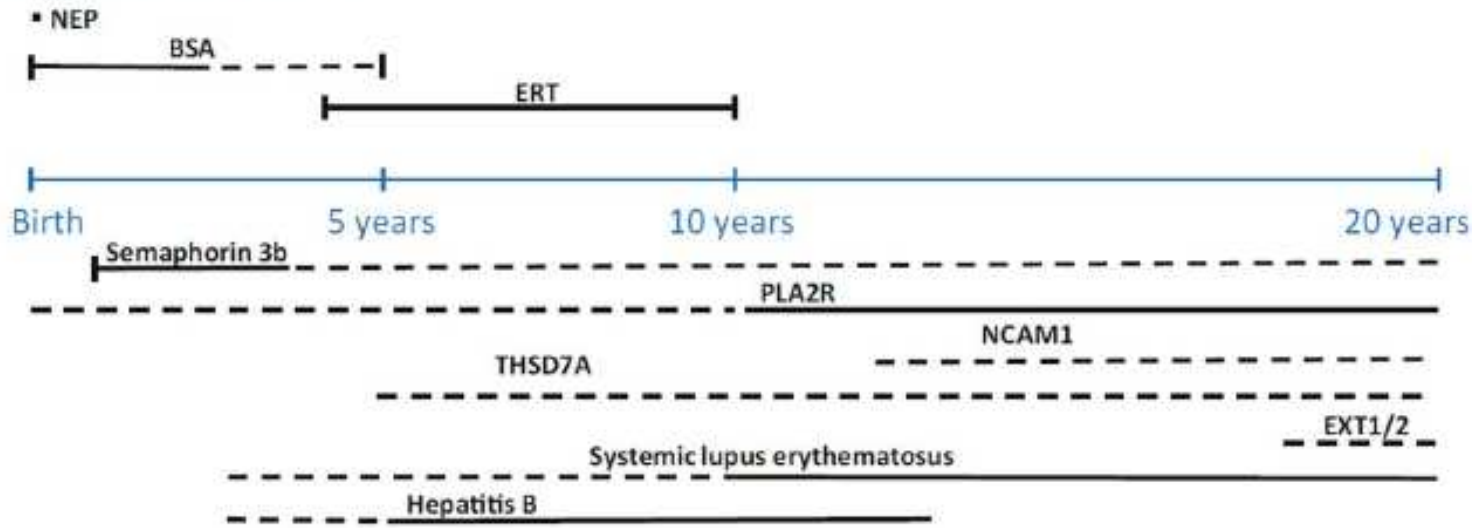
Diffuso ispessimento della parete capillare glomerulare, scarsa componente proliferativa



Depositi parietali granulari diffusi di IgG

New advances in membranous nephropathy: the antigenic revolution

Distribution of antigens according to age



Ronco P, Vivarelli M, Ayalon R & Debiec H Chapter 94.1 Pediatric Nephrology, 2021

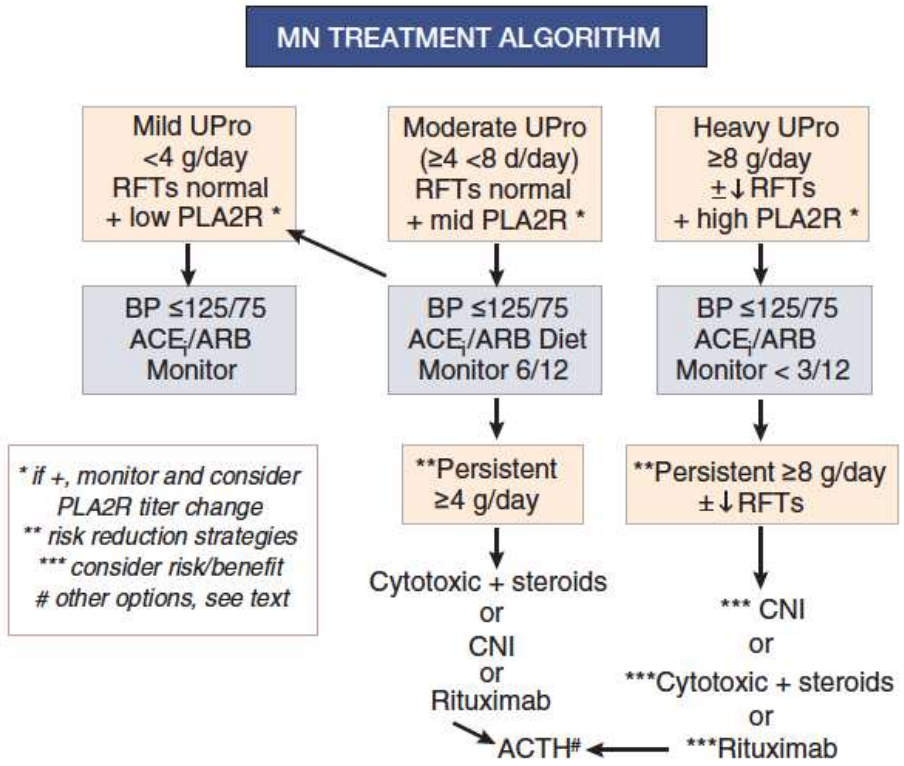
Membranous nephropathy: integrating basic science into improved clinical management

Daniel C. Cattran[1] and Paul E. Brenchley[2]

[1]Toronto General Research Institute, University Health Network, Toronto, Ontario, Canada; and [2]Renal Research Labs, Institute of Cardiovascular Sciences, University of Manchester, Manchester, United Kingdom

How knowledge of the autoimmune mechanism and the sequential measurement of these autoantibodies is likely to change the clinical management and trajectory of AMN by more precisely defining its diagnosis, prognosis, and treatment is discussed. Their application early in the disease course to new and old therapies will provide additional precision to AMN management. We also review innovative therapeutic approaches on the horizon that are expected to lead to our ultimate goal of improved patient care in A(I)MN.

Kidney International (2017) **91,** 566–574; http://dx.doi.org/10.1016/j.kint.2016.09.048



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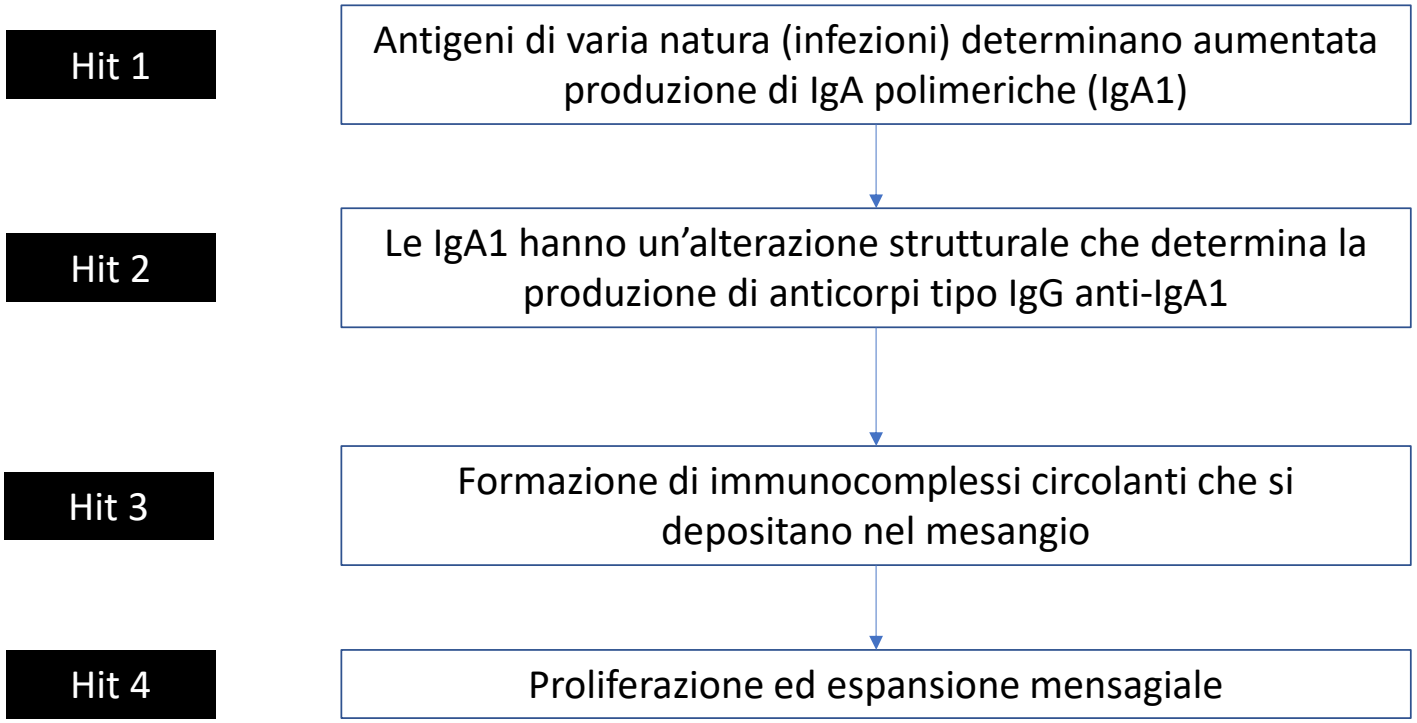
Nefropatia a depositi di IgA

- È una glomerulonefrite ad andamento cronico progressivo, che determina lo sviluppo di insufficienza renale terminale nel 30% dei casi dopo 20 anni di malattia

- Rappresenta la glomerulonefrite cronica più diffusa al mondo, con 30 casi per milione di abitanti.

Nefropatia a depositi di IgA



Nefropatia a depositi di IgA

Antigeni di varia natura (infezioni) determinano aumentata produzione di IgA polimeriche (IgA1)

↓

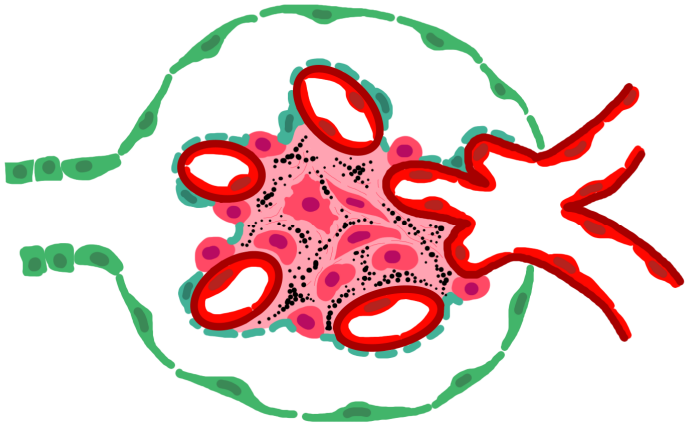
Le IgA1 hanno un'alterazione strutturale che determina la produzione di anticorpi tipo IgG anti-IgA1

↓

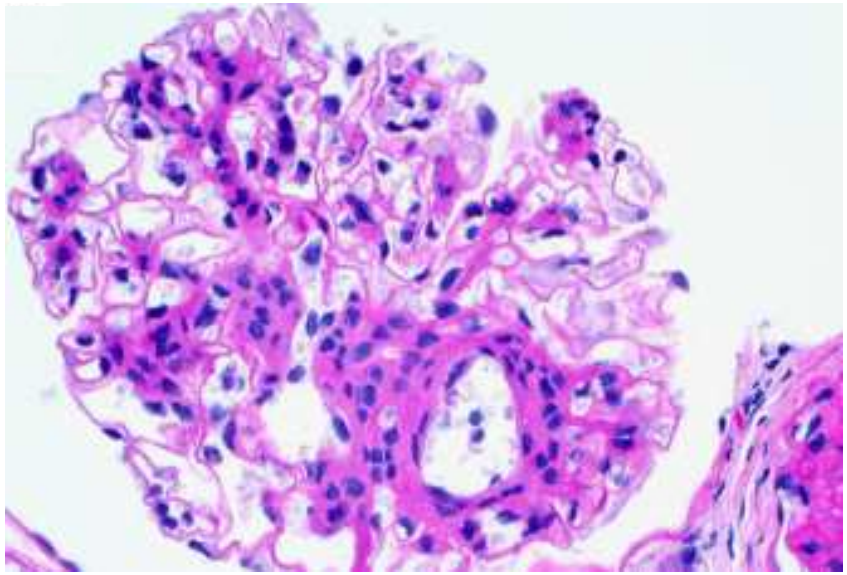
Formazione di immunocomplessi circolanti che si depositano nel mesangio

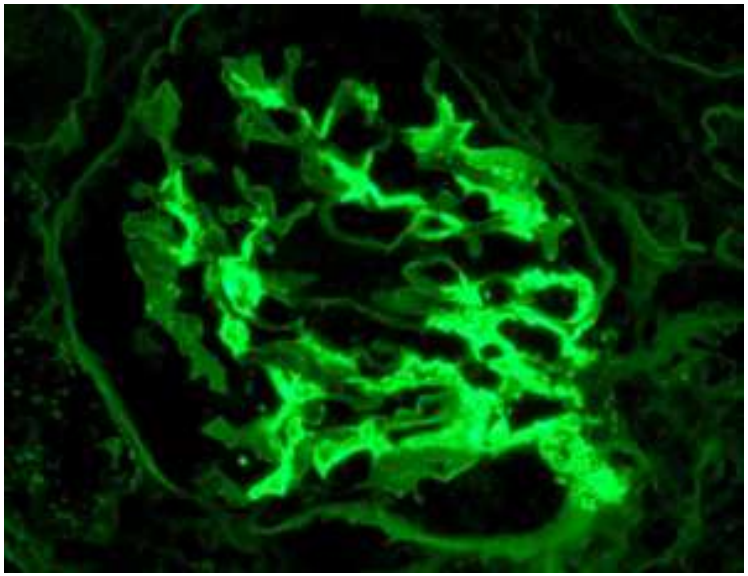
↓

Proliferazione ed espansione mensagiale



Nefropatia a depositi di IgA





Nefropatia a depositi di IgA: clinica

- È caratterizzata da:
  - **Episodi ricorrenti di macroematuria** in concomitanza di un processo infettivo delle alte vie respirarorie.
  - La macroematuria è di durata variabile e può ripetersi nel tempo in rapporto alla carica antigenica
  - **Microematuria persistente** negli intervalli
  - Progressiva comparsa di proteinuria patologica

  - Nel 3% dei casi può esordire con sindrome nefritica e nel 3-6% dei casi con sindrome nefrosica

  - **Raramente come forma rapidamente progressiva**

Perché le semilune?

Il processo infiammatorio può causare la rottura dei capillari glomerulari, con passaggio di cellule e proteine plasmatiche nella capsula di Bowman

↓

Accumulo di monociti

↓

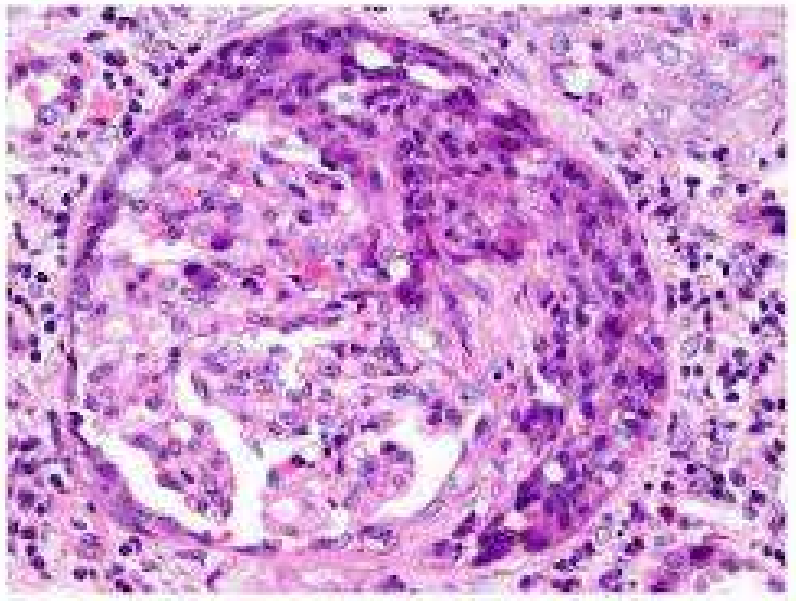
Proliferazione locale di cellule epiteliali viscerali e parietali

↓

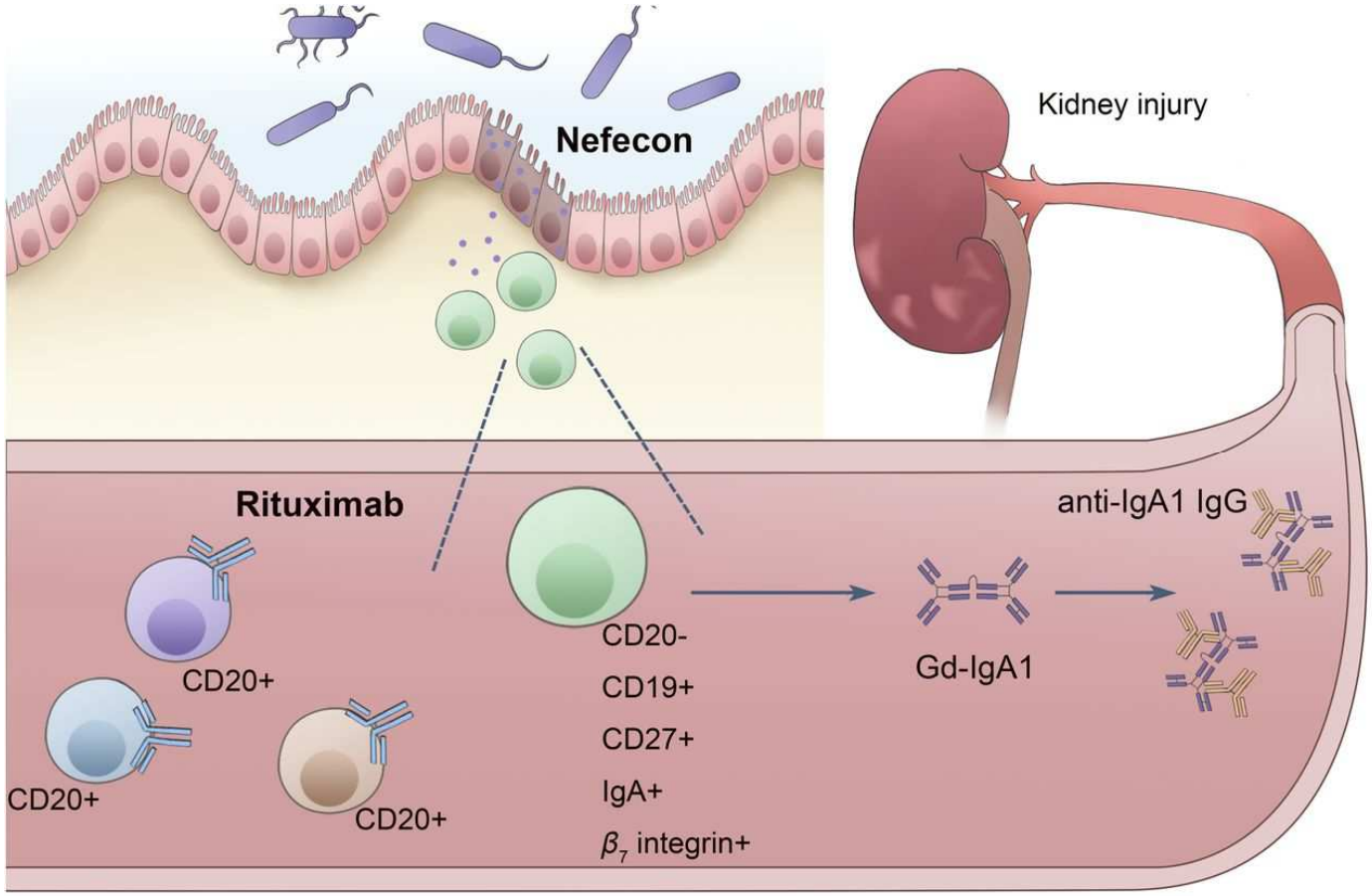
Formazione di semilune

↓

Fibrosi e sclerosi



Plasmablasts with a mucosal phenotype may contribute to the failure of rituximab and the clinical success of Nefecon in IgA nephropathy.



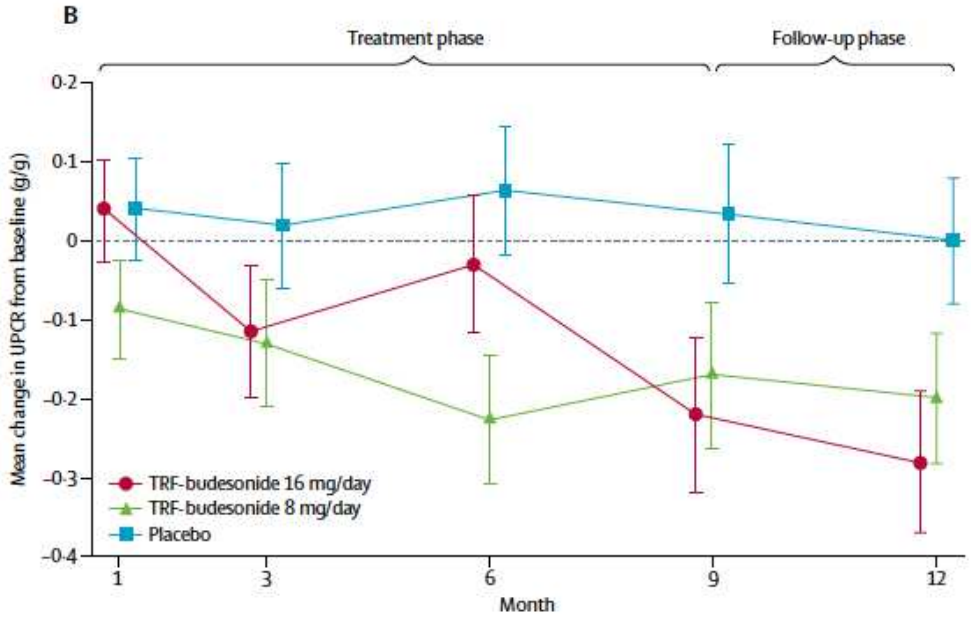
Yue-miao Zhang, and Hong Zhang CJASN 2018;13:1584-1586

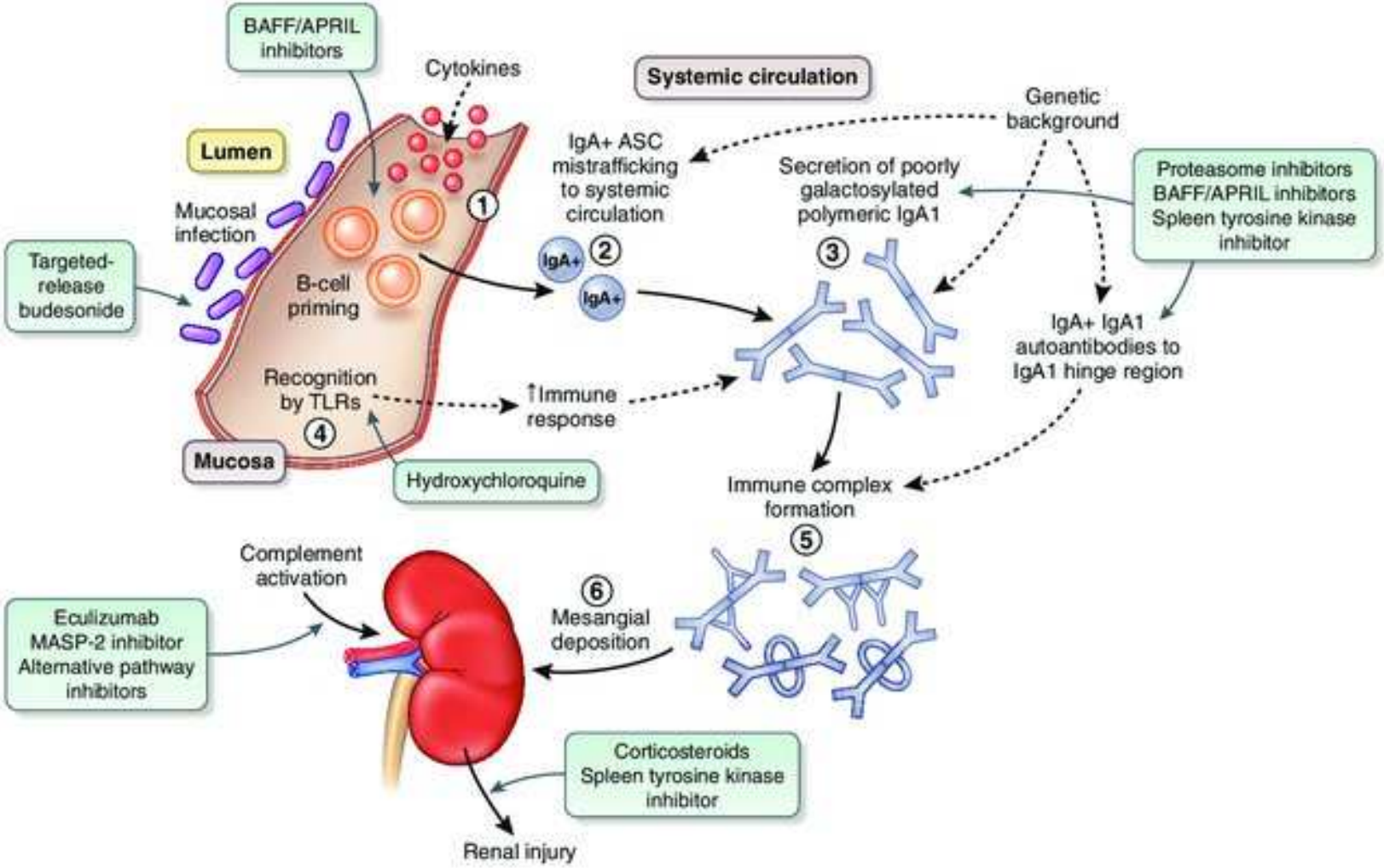
CJASN
Clinical Journal of the American Society of Nephrology

Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

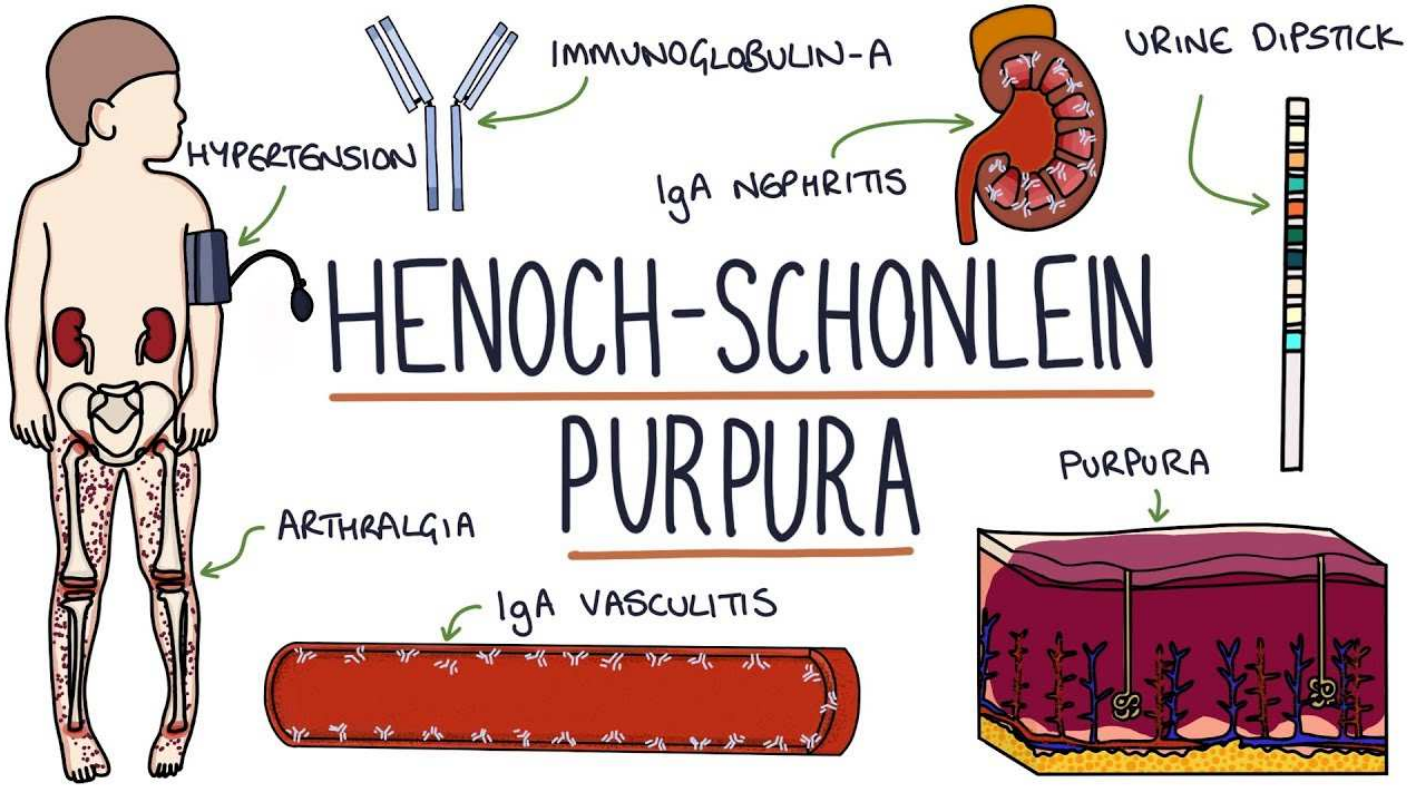
Bengt C Fellström, Jonathan Barratt, Heather Cook, Rosanna Coppo, John Feehally, Johan W de Fijter, Jürgen Floege, Gerd Hetzel, Alan G Jardine, Francesco Locatelli, Bart D Maes, Alex Mercer, Fernanda Ortiz, Manuel Praga, Søren S Sørensen, Vladimir Tesar, Lucia Del Vecchio, for the NEFIGAN Trial Investigators

www.thelancet.com **Vol 389 May 27, 2017**




BAFF/APRIL inhibitors
Cytokines
Systemic circulation
Genetic background
Lumen
IgA+ ASC mistrafficking to systemic circulation
Secretion of poorly galactosylated polymeric IgA1
Proteasome inhibitors
BAFF/APRIL inhibitors
Spleen tyrosine kinase inhibitor
Mucosal infection
1
Targeted-release budesonide
B-cell priming
IgA+
2
IgA+
3
IgA+ IgA1 autoantibodies to IgA1 hinge region
Recognition by TLRs
4
↑Immune response
Mucosa
Hydroxychloroquine
Immune complex formation
5
Complement activation
6
Mesangial deposition
Eculizumab
MASP-2 inhibitor
Alternative pathway inhibitors
Corticosteroids
Spleen tyrosine kinase inhibitor
Renal injury

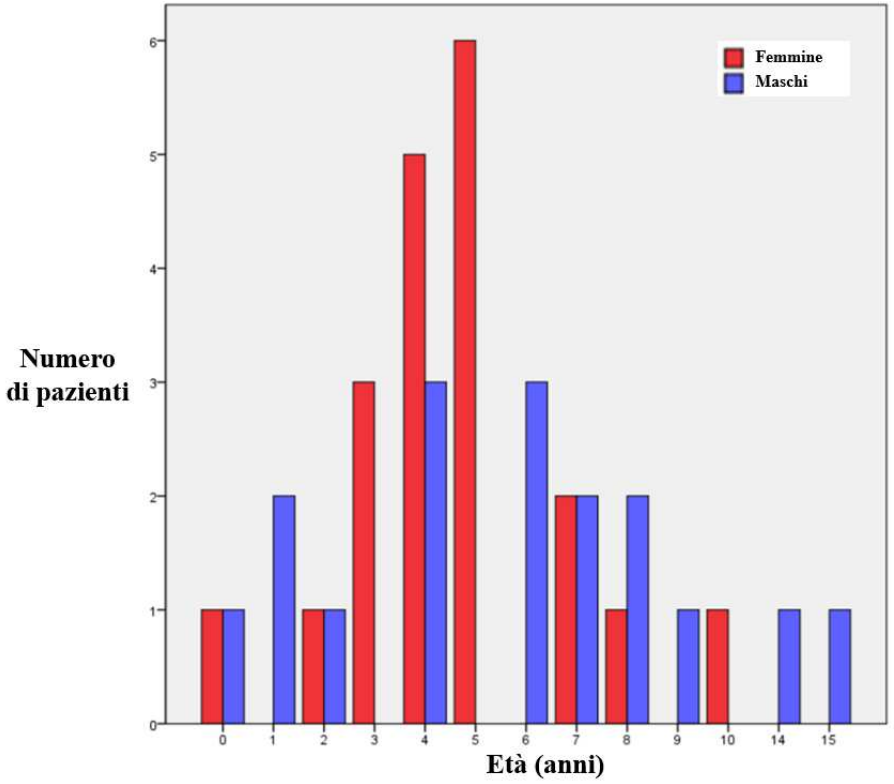
Vasculite ad IgA



Vasculite ad IgA
Esperienza della Clinica Pediatrica di Udine

- Accessi in PSP e ricoveri con diagnosi di PSH dal 01.01.2015 al 31.12.2021
- N=37

Sesso	♀ 54,1%	♂ 45,1 %	M:F 1: 1,18
Età	5,73 ± 3,24	Min: 4 mesi Max: 15 anni	< 2 aa: 16% 3-10 aa: 78%



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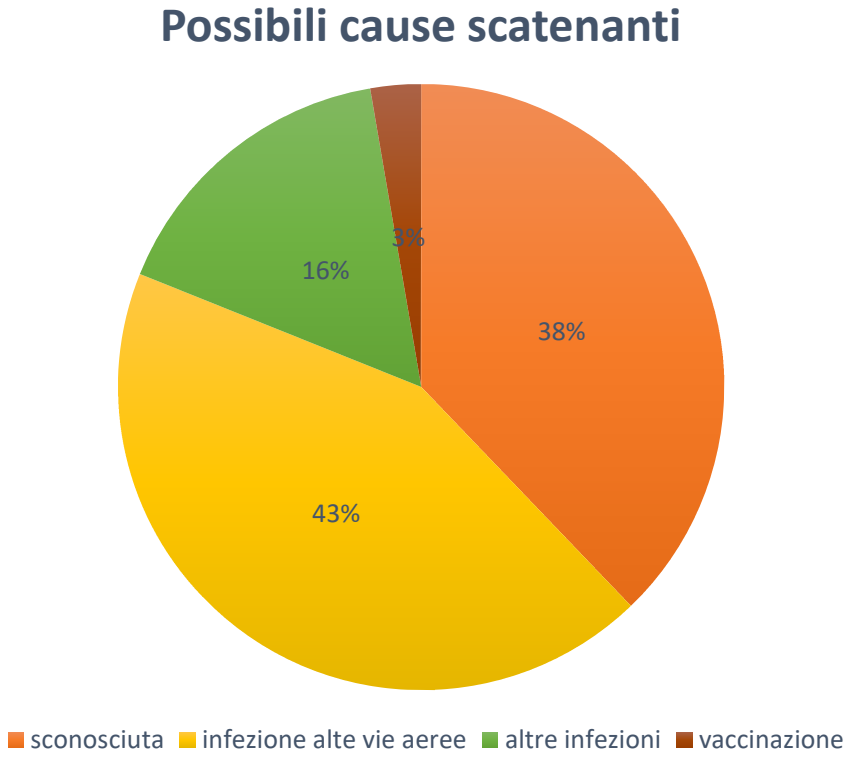
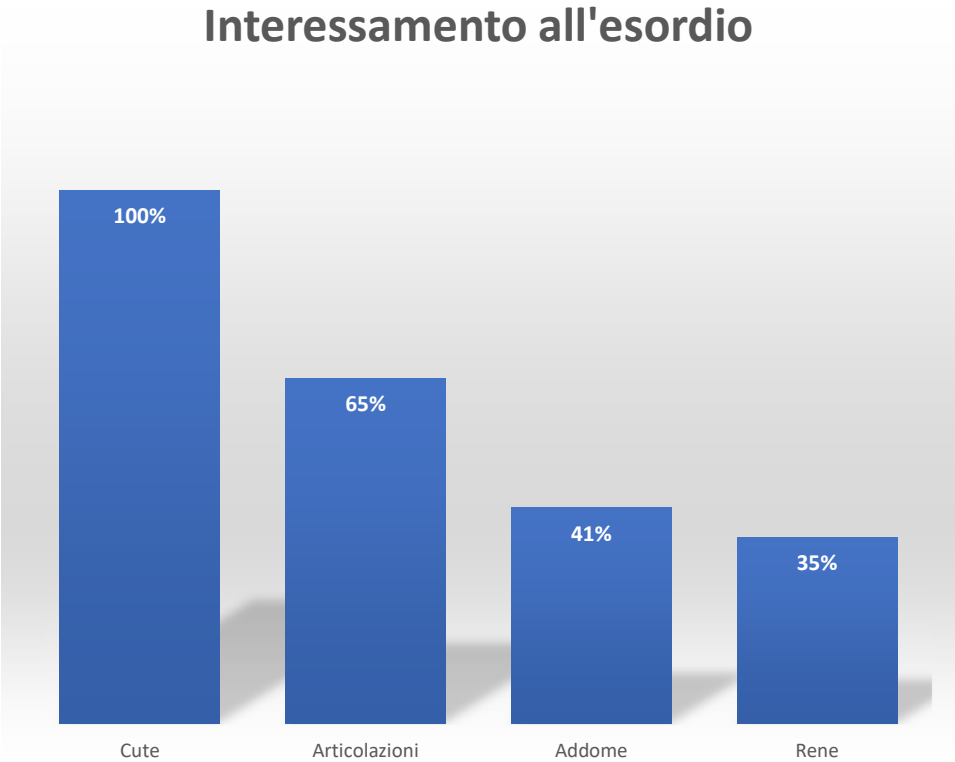
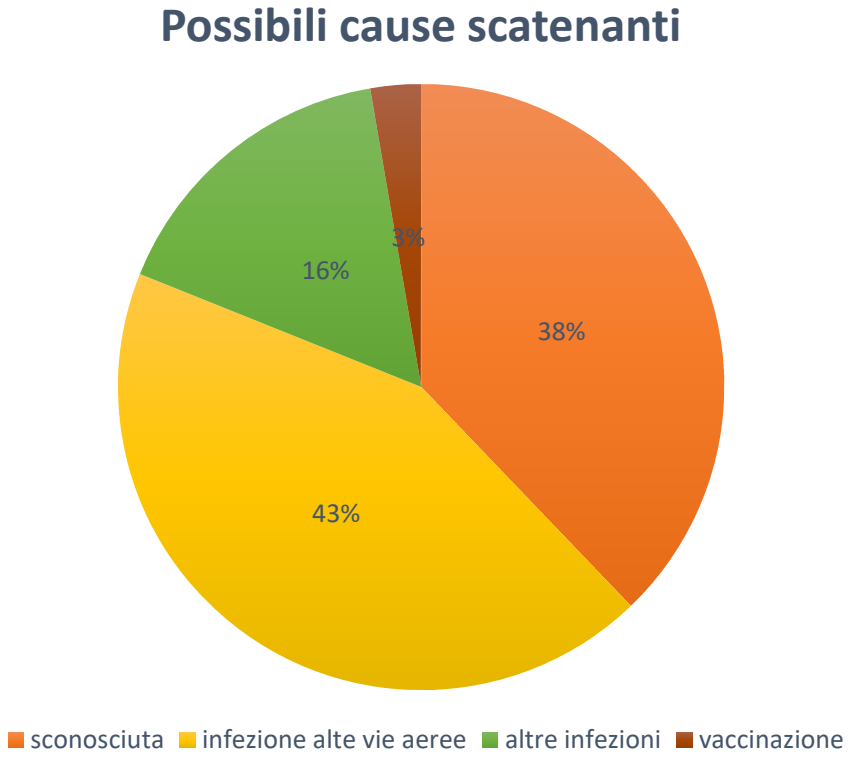
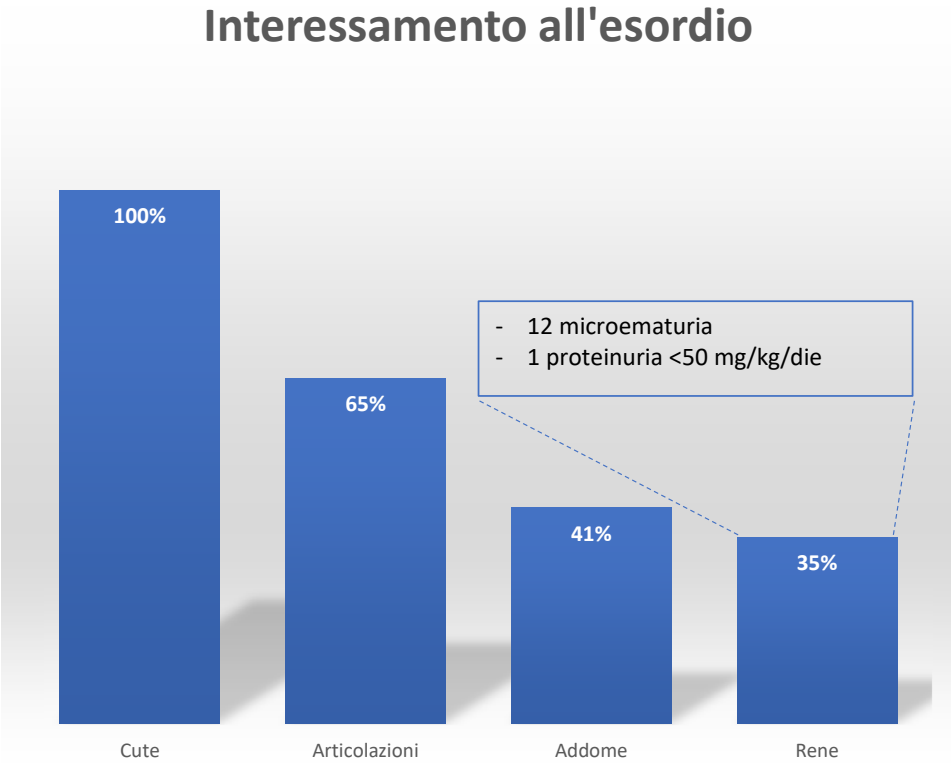




Silvia Bertolo, Scuola di Specializzazione in Pediatria, UniUD

Vasculite ad IgA
Esperienza della Clinica Pediatrica di Udine





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Vasculite ad IgA
Esperienza della Clinica Pediatrica di Udine

- Tutti i casi con microematuria si sono negativizzati entro 3 mesi.
- Il caso con proteinuria patologica ha avuto una regolarizzazione del reperto urinario entro 3 mesi.

- In 4 pazienti l'interessamento renale è stato più tardivo, a 7, 11, 15 e 40 giorni dall'esordio:
  - 3 casi con microematuria
  - 1 caso con proteinuria patologica

Monitoraggio stick urine 1 volta alla settimana nel primo mese, ogni 15 giorni nel II e III mese, poi a 6 e 12 mesi

Indicazioni alla biopsia renale:

- Presentazione con sindrome nefritica
- Evoluzione a proteinuria nefrosica (*gross* proteinuria)
- Proteinuria patologica persistente per più di 2-3 mesi dall'esordio

Silvia Bertolo, Scuola di Specializzazione in Pediatria, UniUD

Kidney International, Vol. 59 (2001), pp. 823–834

PERSPECTIVES IN RENAL MEDICINE

What is the difference between IgA nephropathy and Henoch-Schönlein purpura nephritis?

JEAN-CLAUDE DAVIN, INEKE J. TEN BERGE, and JAN J. WEENING

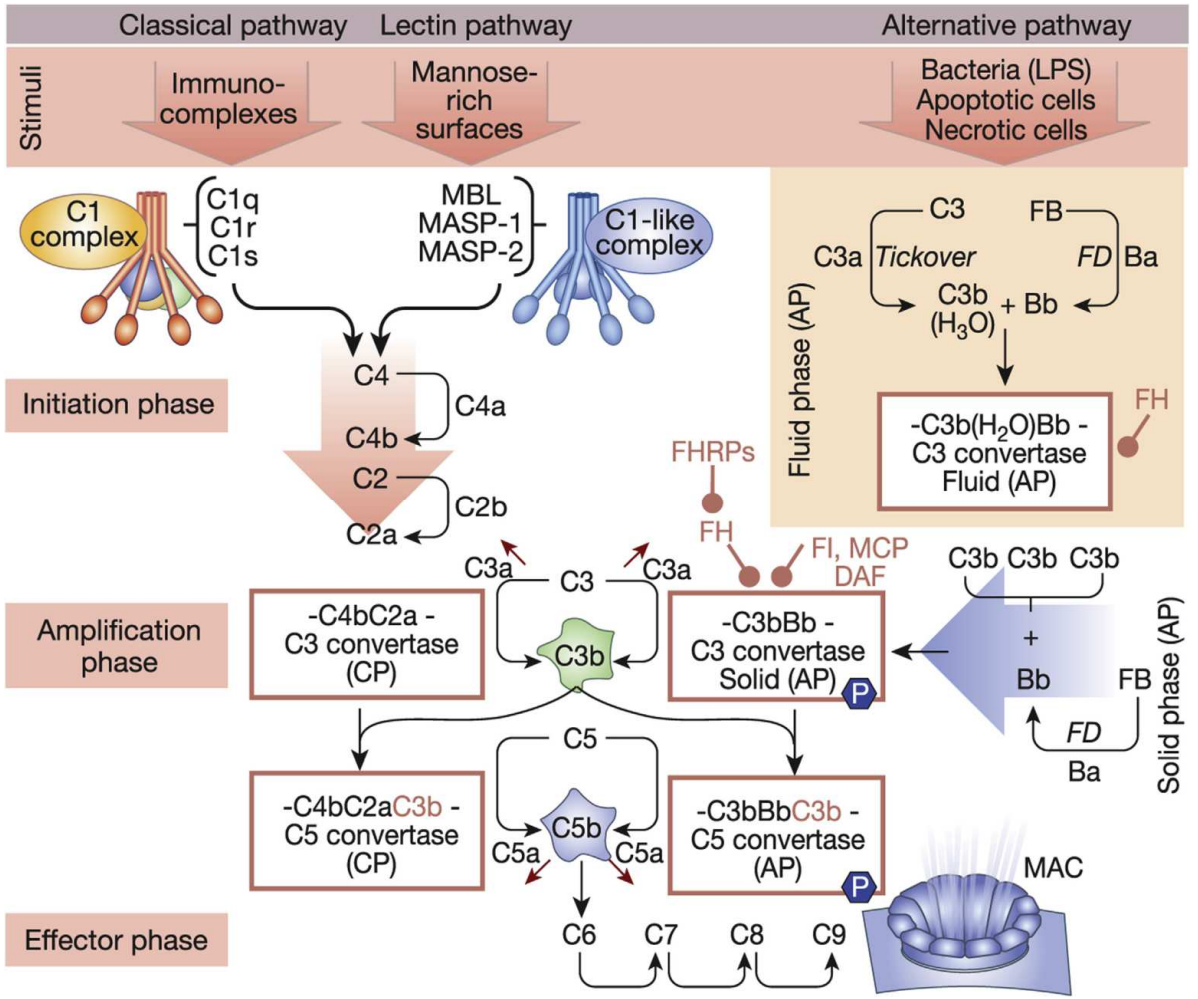
Departments of Pediatrics, Internal Medicine, and Pathology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

What is the difference between IgA nephropathy and Henoch-Schönlein purpura nephritis? Henoch-Schönlein purpura nephritis (HSPN) and IgA nephropathy (IgAN) are considered to be related diseases since both can be encountered consecutively in the same patient, they have been described in twins, and bear identical pathological and biological abnormalities. Apart from the presence of extrarenal clinical signs found only in HSPN, other differences are noticed between the two diseases. The peak age ranges between 15 and 30 years for a diagnosis of IgAN, whereas HSPN is mainly seen in childhood. Nephritic and/or nephrotic syndromes are more often seen at presentation in HSPN. In contrast to IgAN, HSPN has been described in association with hypersensitivity. Endocapillary and extracapillary inflammations as well as fibrin deposits in the glomerulus are more frequent in HSPN. No major biological differences have been found between the two illnesses, except for a larger size of circulating IgA-containing complexes (IgA-CC) and a greater incidence of increased plasma IgE levels in HSPN. As tissue infiltration by leukocytes is a major feature of HSPN vasculitis, a possible role of a more potent activation of the latter cells by IgA-CC and/or circulating chemokines in HSPN should be considered. Further studies are required to elucidate this possible mechanism as well as the role of hypersensitivity in HSPN.

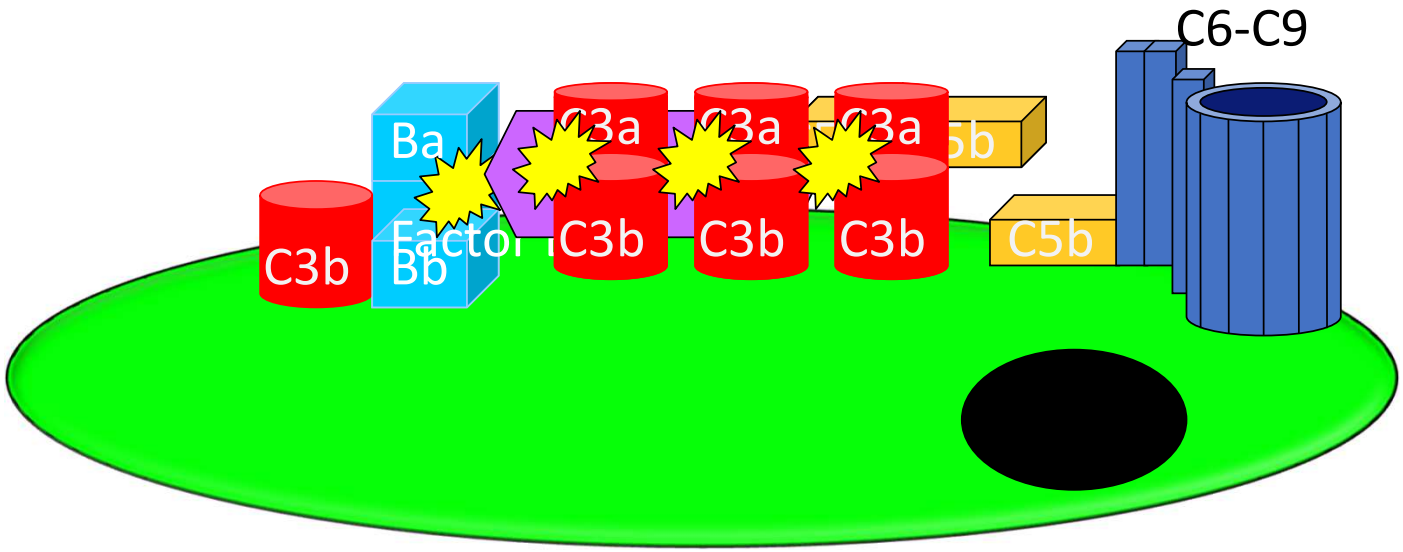
(Auto)Immunità e Rene

- Le malattie renali immuno-mediate da perdita dell'omeostasi immunologica si distinguono in:
  - Malattie renali da danno immune diretto
    - Glomerulonefrite da anticorpi anti-GBM
    - Glomerulonefrite membranosa
  - Malattie renali da danno immune indiretto
    - Glomerulonefriti da immunocomplessi
    - Glomerulonefriti da alterazioni della via alternativa del complemento

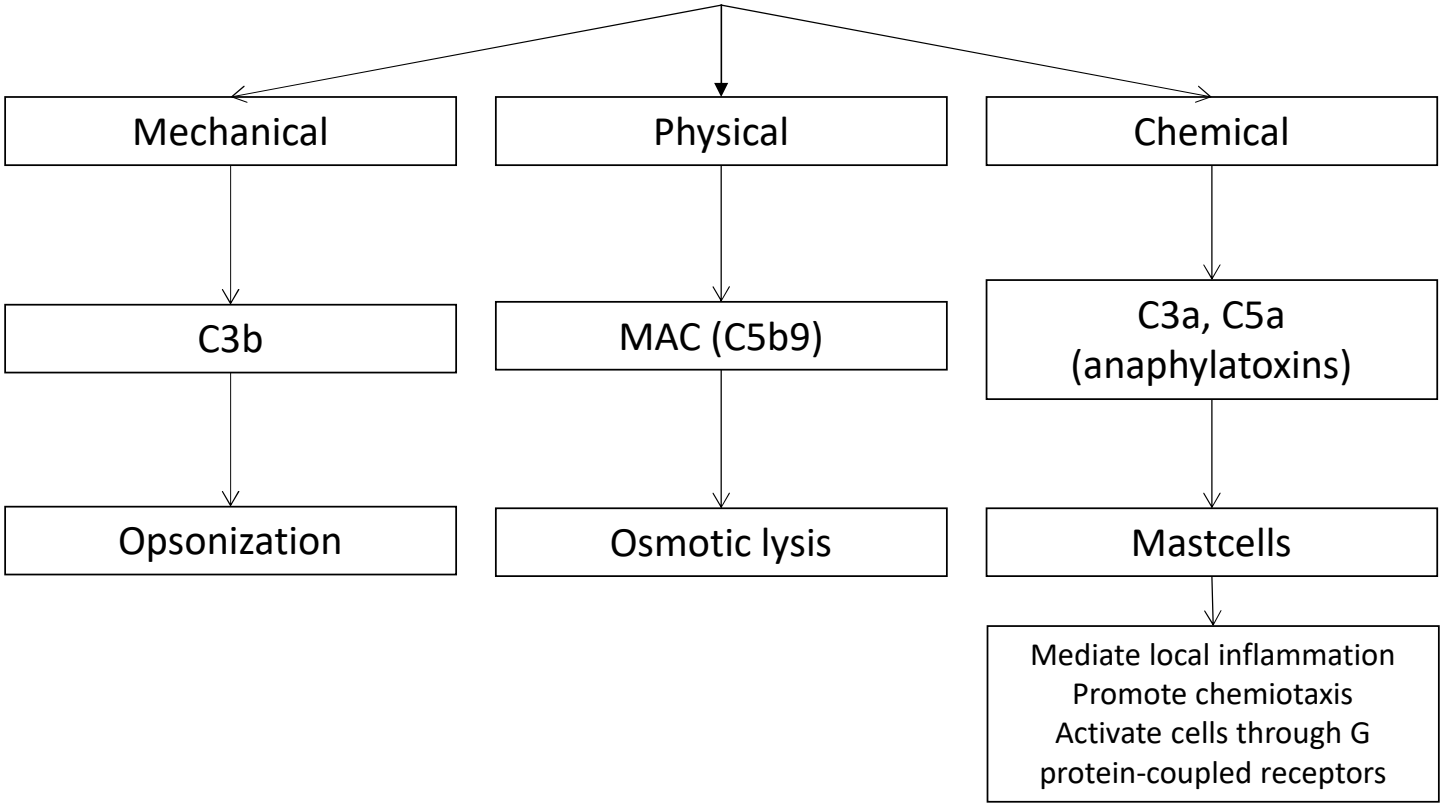
The normal complement pathway



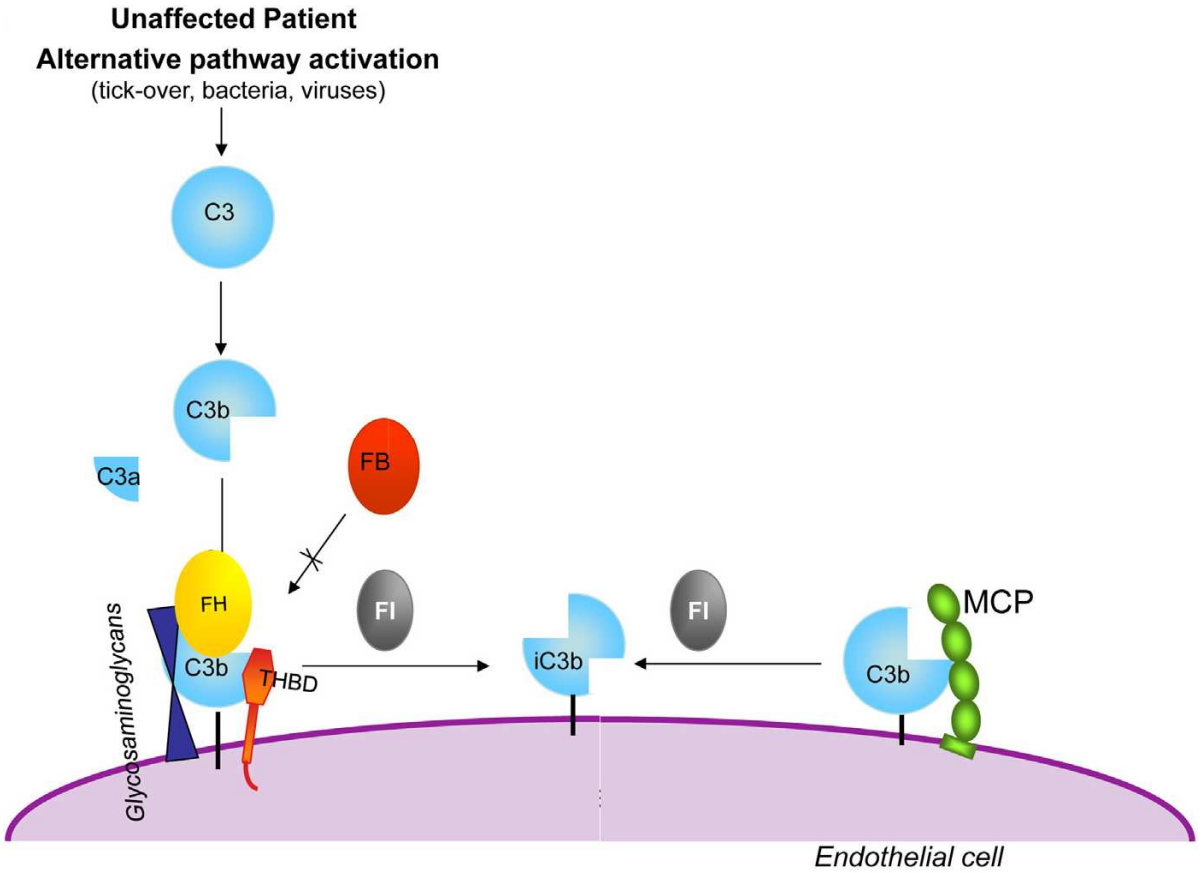
The alternative complement pathway



Complement pathway effector functions

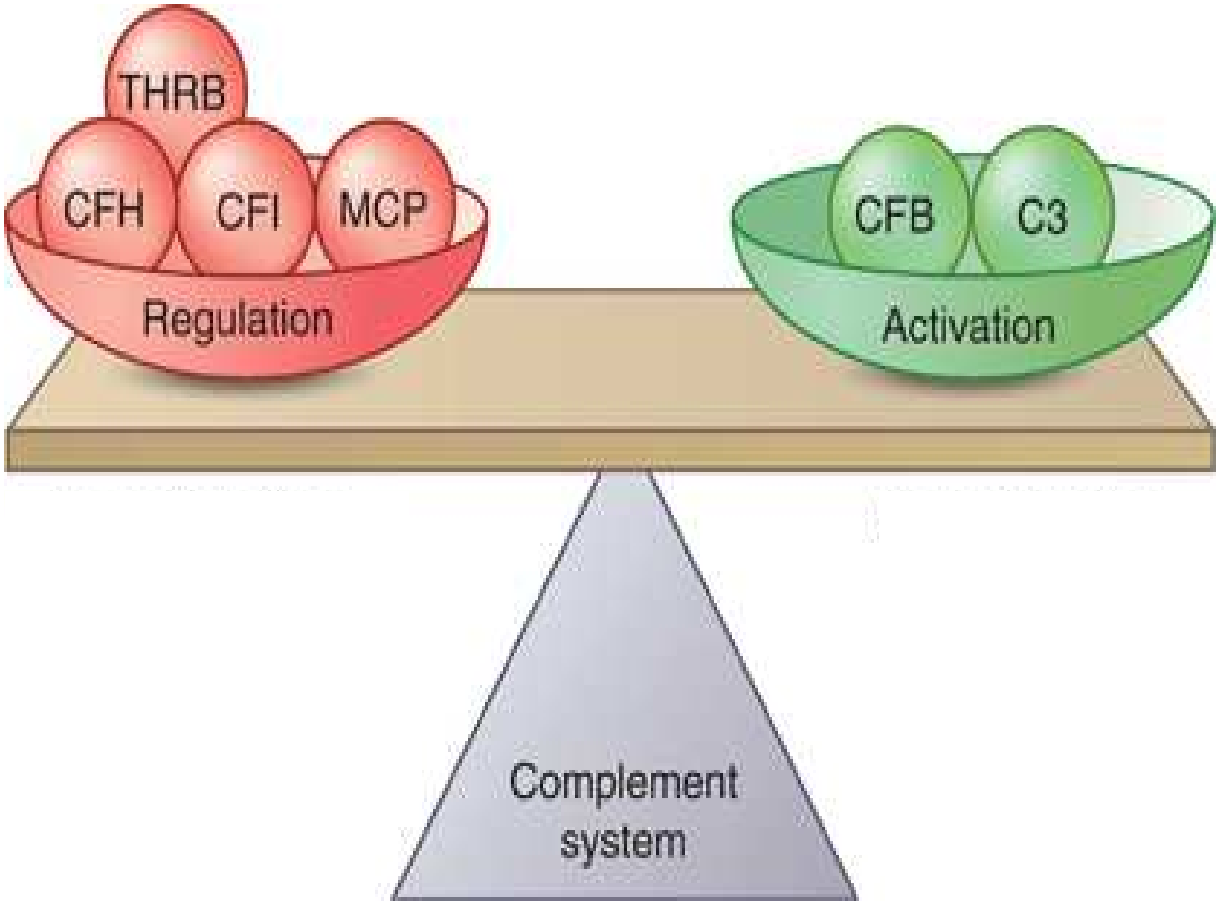


Complement activation in physiological conditions

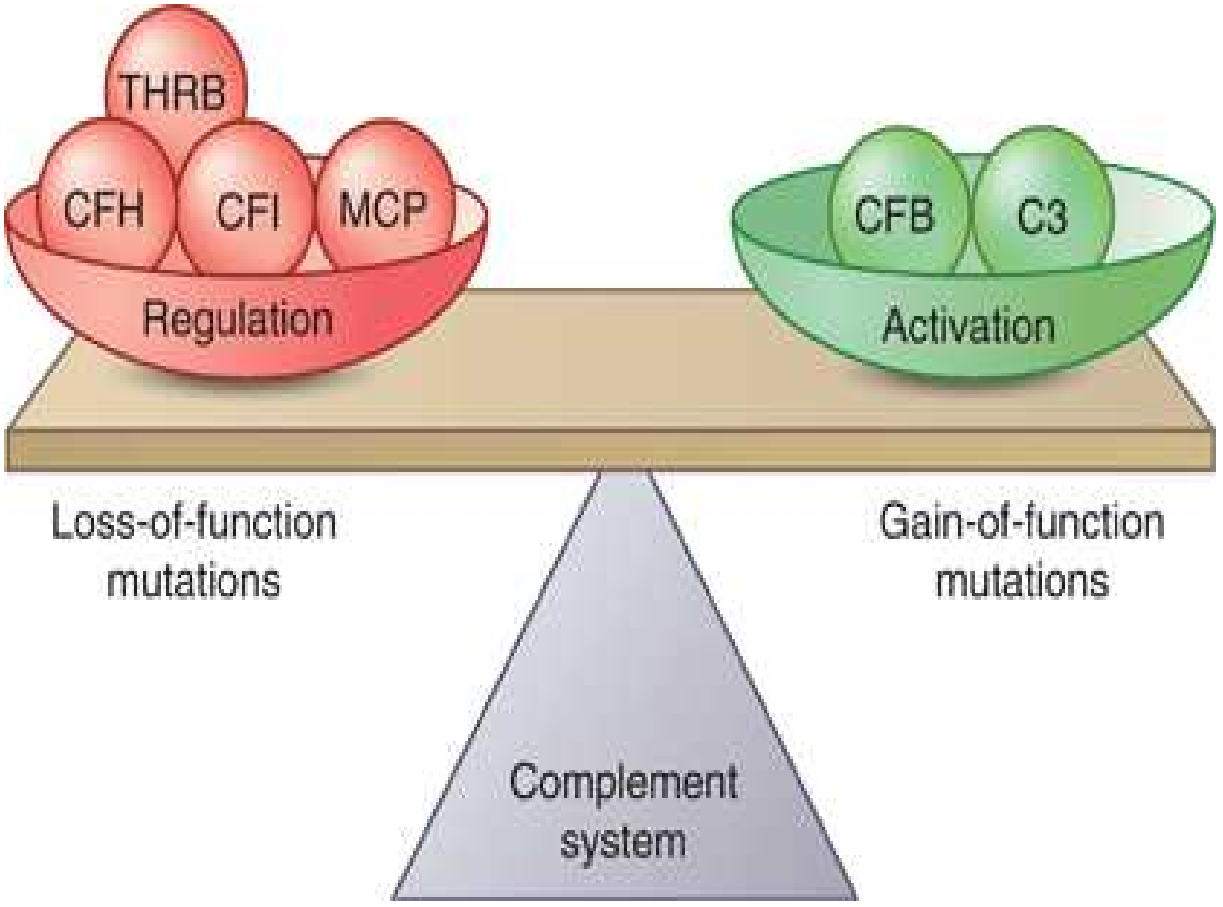


Noris et al. AJKD 2015;66(2):359-375

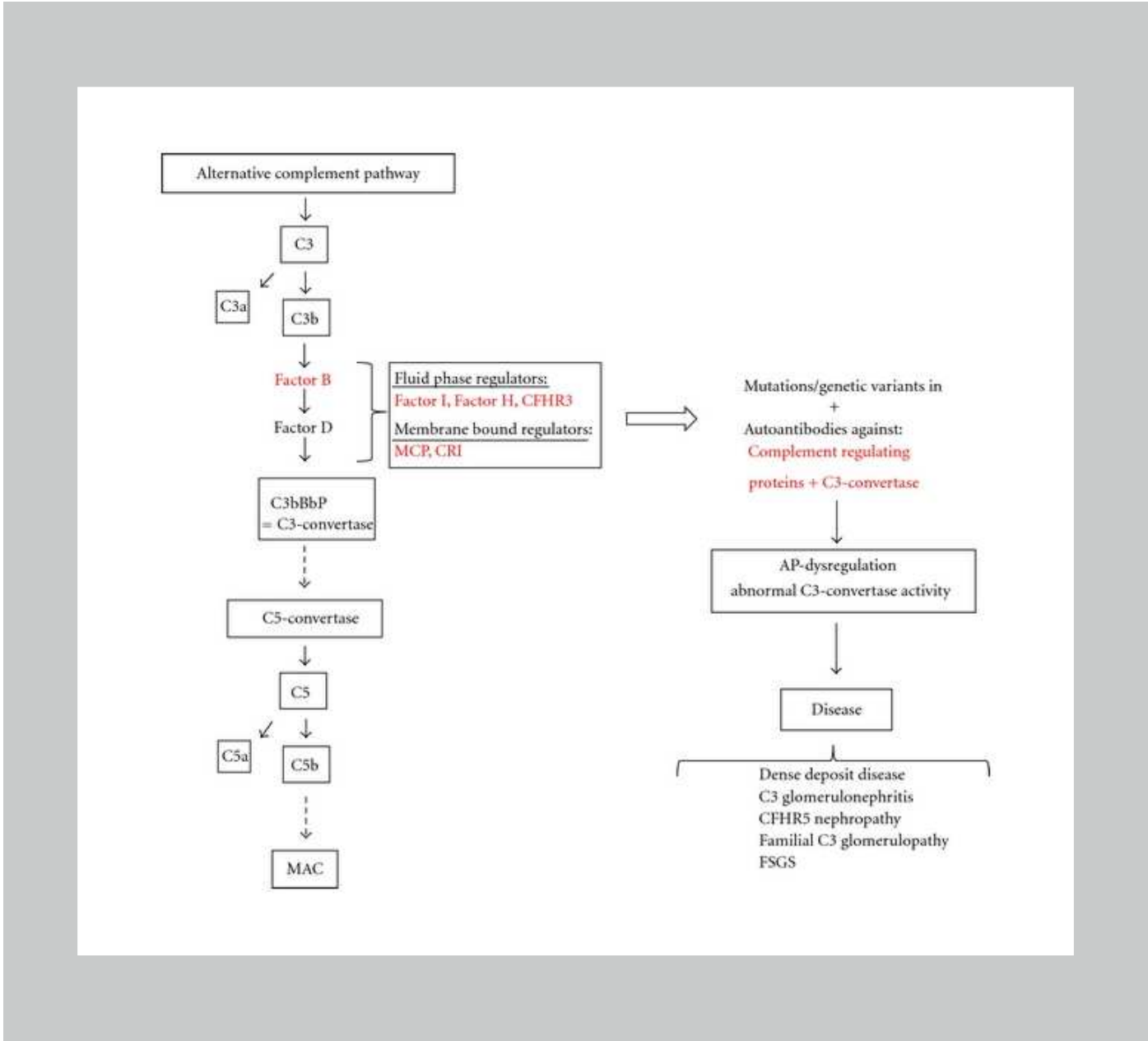
The balance between activation and regulation



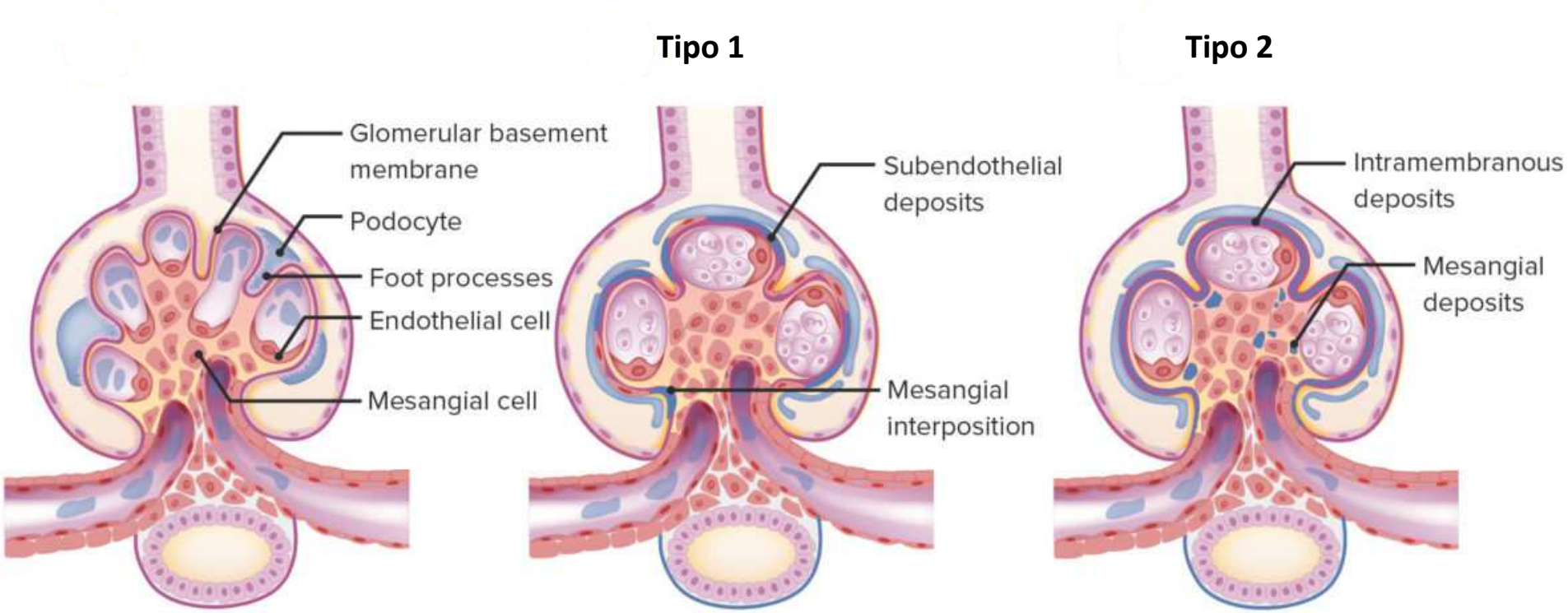
The balance between activation and regulation



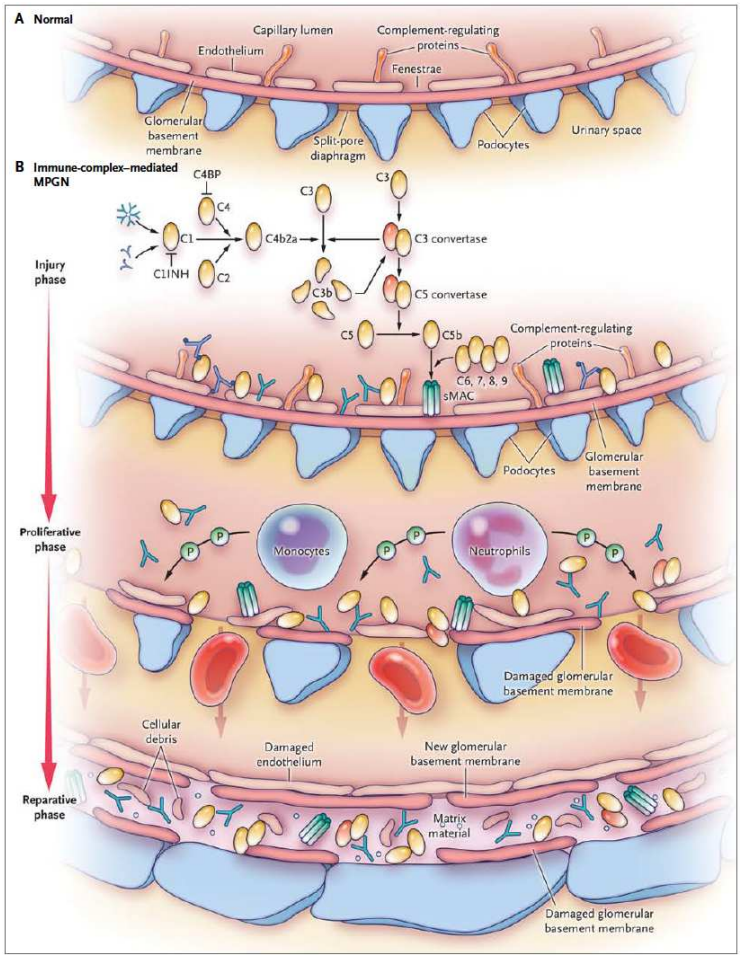
Kidney diseases resulting from complement activation/dysregulation

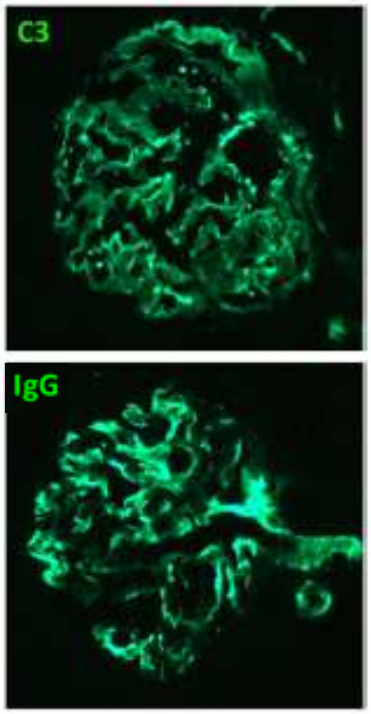


Glomerulonefrite membranoproliferativa



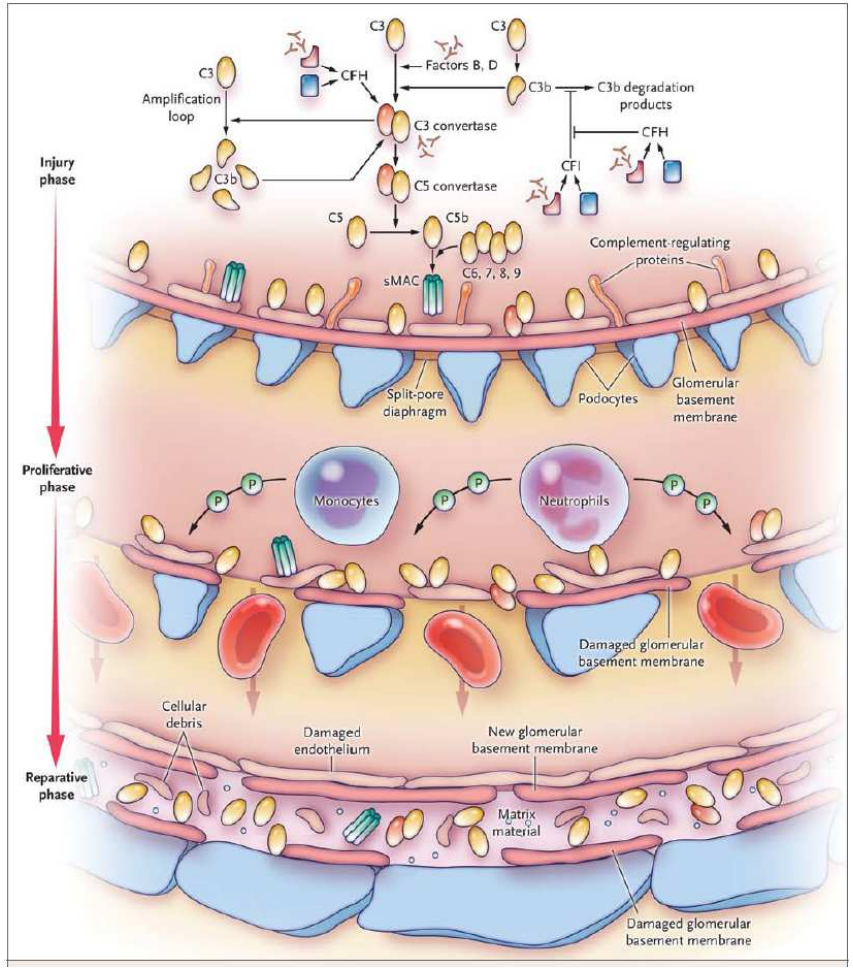
GNMP da immunocomplessi

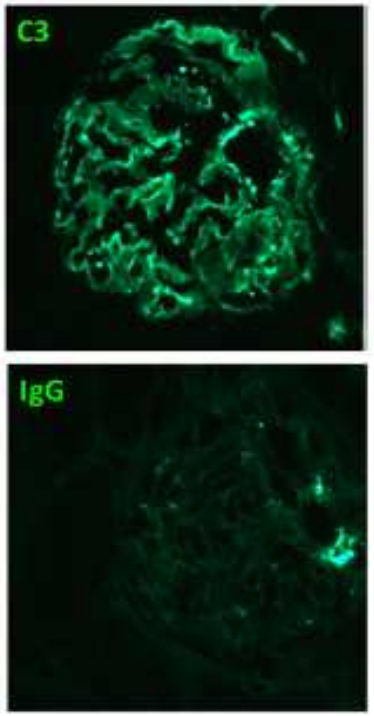




N ENGL J MED 366;12 NEJM.ORG MARCH 22, 2012

GNMP complemento-mediata

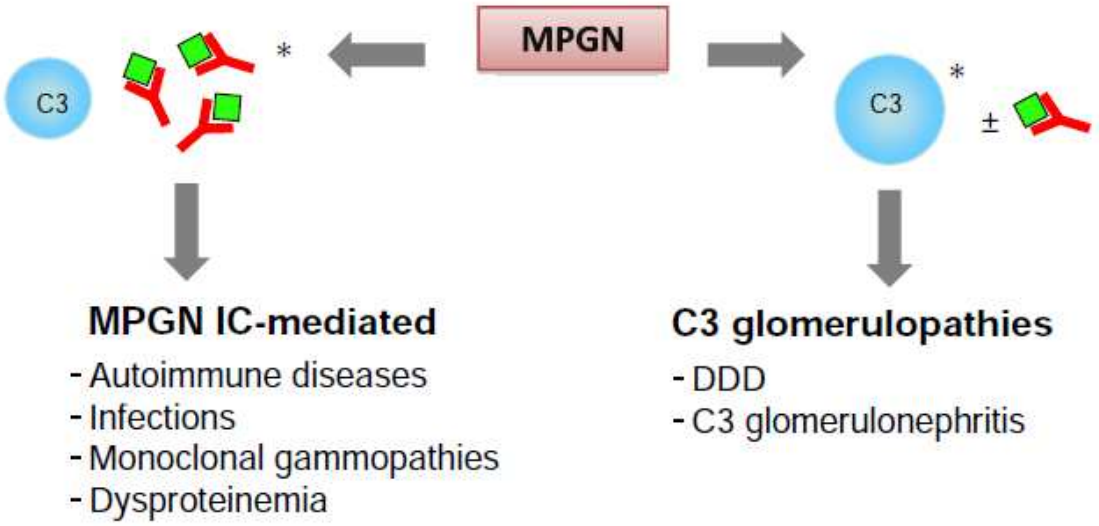




MEDICAL PROGRESS

Membranoproliferative Glomerulonephritis — A New Look at an Old Entity

Sanjeev Sethi, M.D., Ph.D., and Fernando C. Fervenza, M.D., Ph.D.

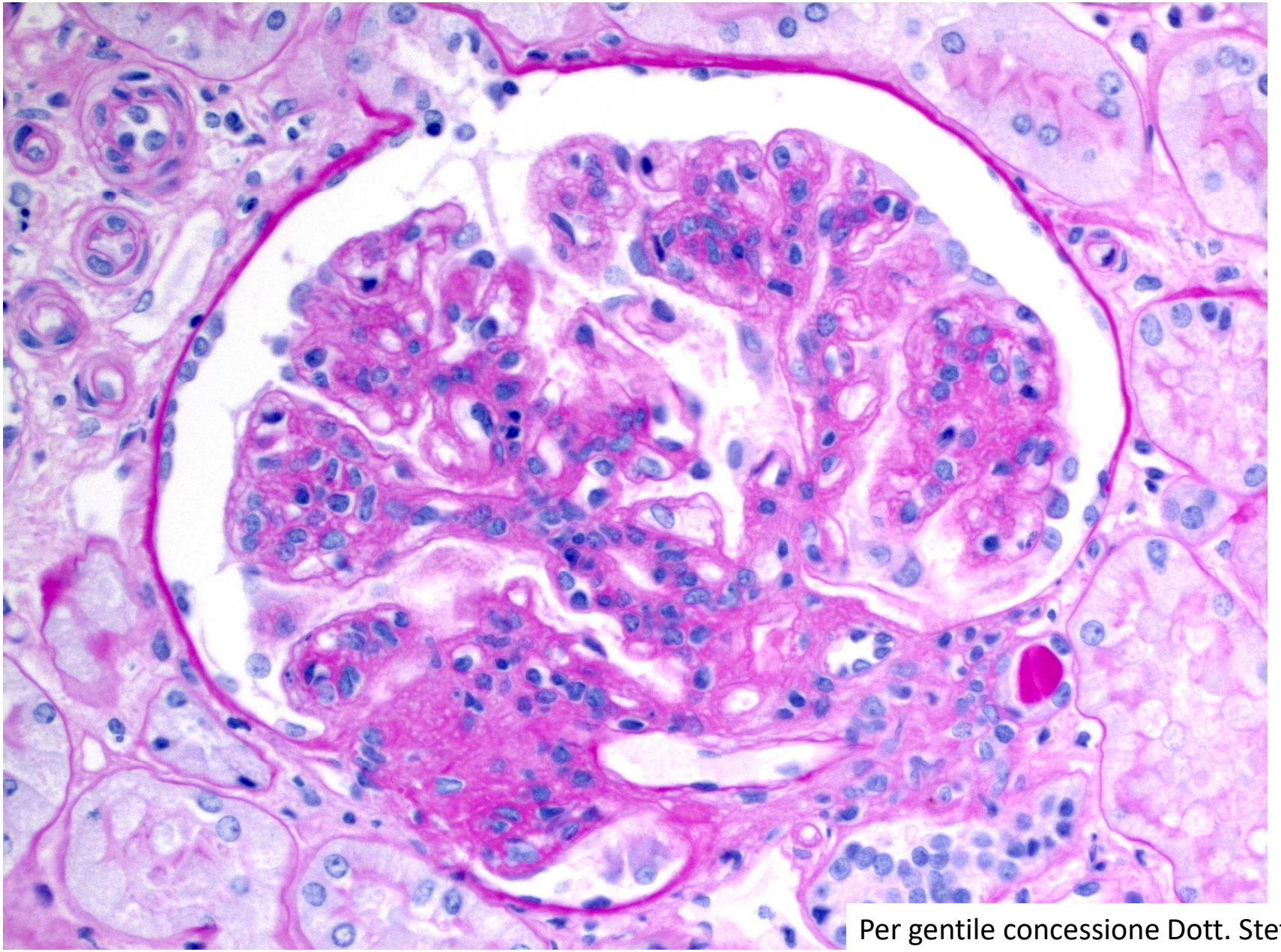


Sethi et al. NEJM 2012;366:1119-31

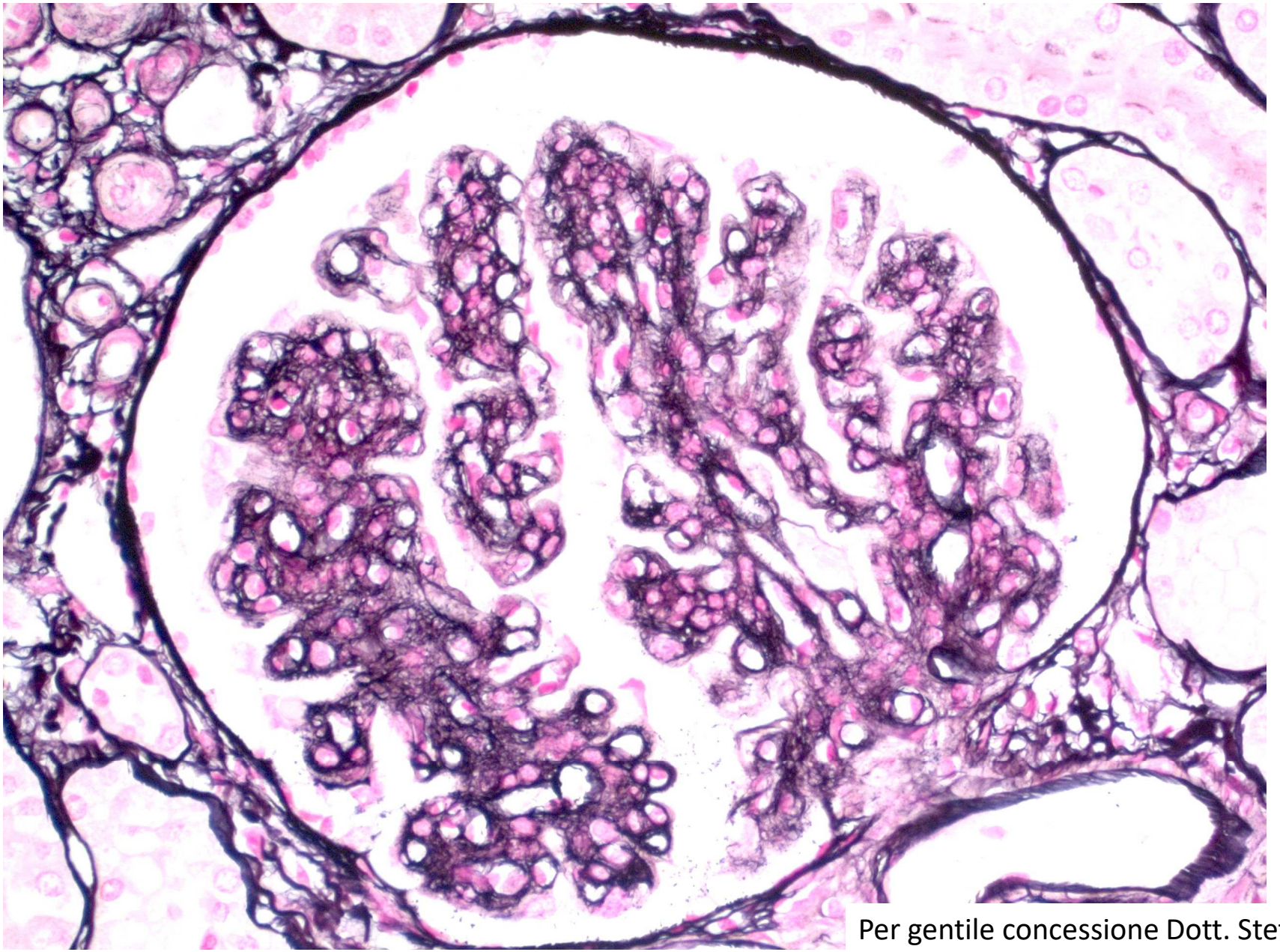
Noris et al. AJKD 2015;66(2):359-375

Alice, 16 anni

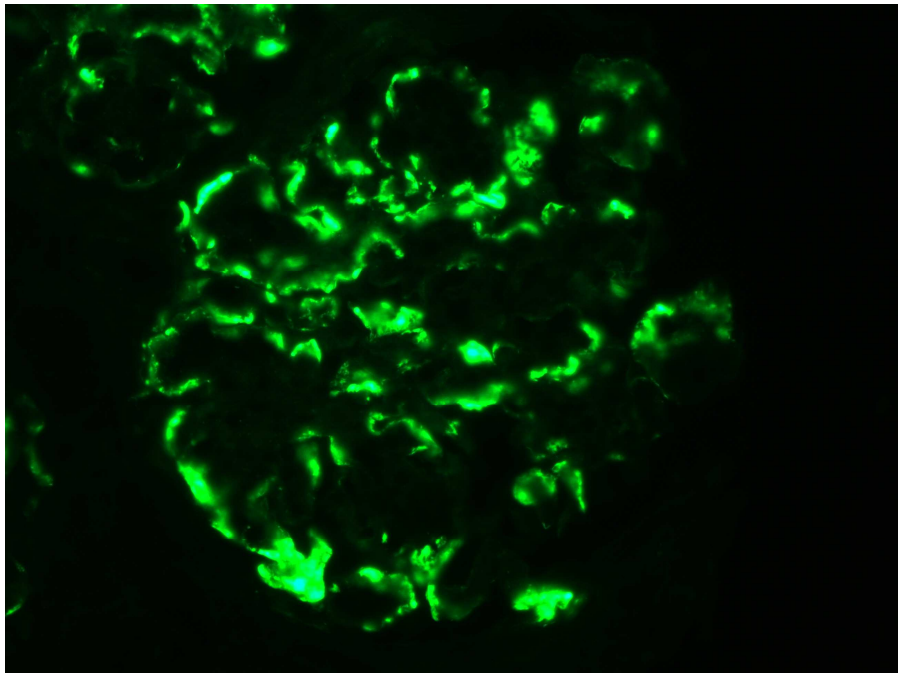
- Proteinuria patologica e microematuria persistente
- C3 e C4 sierici ai limiti bassi della norma
- Profilo autoimmunitario negativo
- Profilo microbiologico negativo



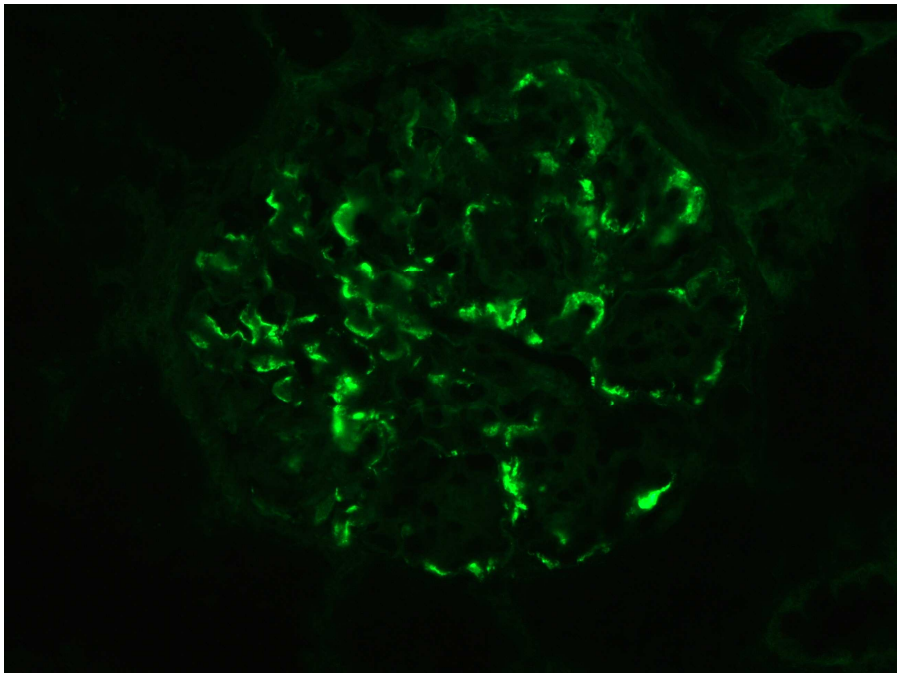
Per gentile concessione Dott. Stefano Pizzolitto



Per gentile concessione Dott. Stefano Pizzolitto



C3



IgG

Per gentile concessione Dott. Stefano Pizzolitto

Alice, 16 anni

- Proteinuria patologica e microematuria persistente
- C3 e C4 sierici ai limiti bassi della norma
- Profilo autoimmunitario negativo
- Profilo microbiologico negativo

- IC-MPGN

- Boli di metilprednisolone
- MMF

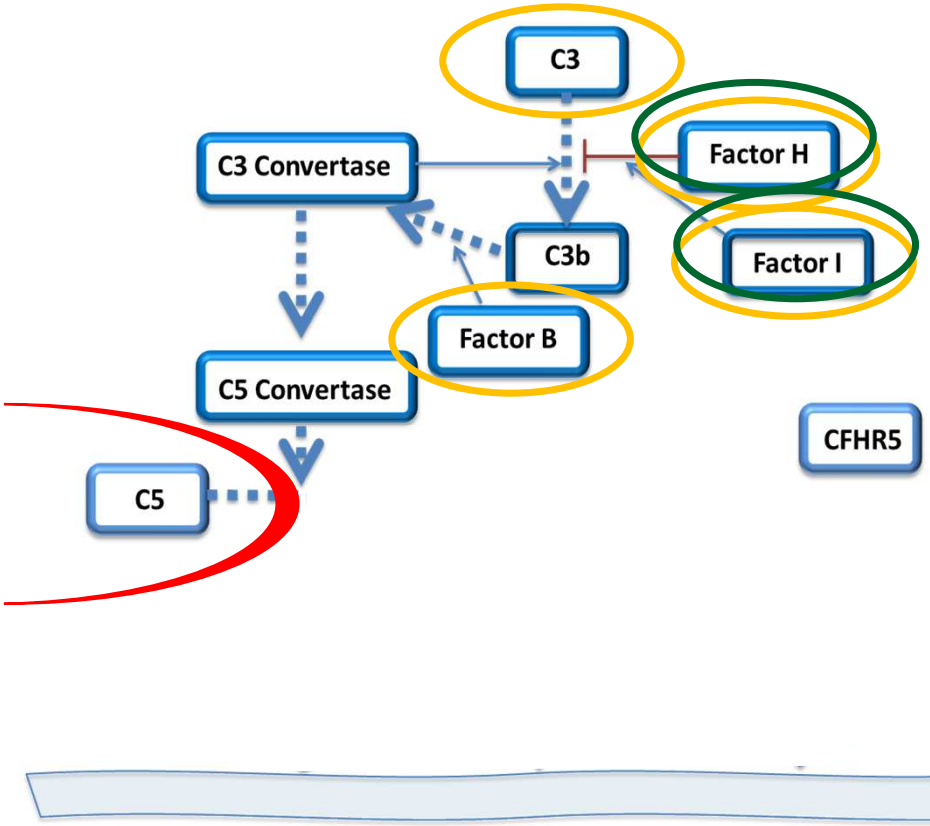
C3 glomerulopathy

Diseases	EM-findings	Alternative pathway abnormalities	Disease specific treatment options
Dense deposit disease	(i) Osmophilic wavy dense deposits within GBM, mesangial matrix, tubular BM	(i) Autoantibodies (C3Nef, FHAA, FBAA, C3-convertase AA) (ii) Mutations/genetic variations (*CFH, CFI, CFB, MCP*)	(i) Infusion of fresh frozen plasma (ii) Plasmapheresis (iii) Eculizumab (iv) Immunosuppressive treatment (in case of autoantibodies)
C3 glomerulonephritis	(i) Mesangial, subendothelial, subepithelial and intramembranous deposits	(i) Mutations/genetic variations (*CFH, CFI, MCP*) (ii) Autoantibodies (C3Nef, FHAA)	(i) Eculizumab (ii) Immunosuppressive treatment (in case of autoantibodies)
CFHR5 nephropathy	(i) Mesangial, subendothelial, subepithelial deposits	(i) *CFHR5*-mutation	(i) No treatment of proven efficacy (ii) Plasma exchange associated with good outcome
Familial C3 glomerulopathy	(i) MPGN type III (ii) Subendothelial, subepithelial deposits	(i) Familial hybrid *CFHR3-1* gene autosomal dominant inheritance	(i) No treatment of proven efficacy

Abbreviations: C3: complement component 3, CFHR5: complement factor H related protein 5, CFH: complement factor H, CFI: complement factor I, MCP: membrane cofactor protein, FHAA: factor H autoantibody, FBAA: factor B autoantibody, (G) BM; (glomerular) basement membrane, MCP: membrane cofactor protein.

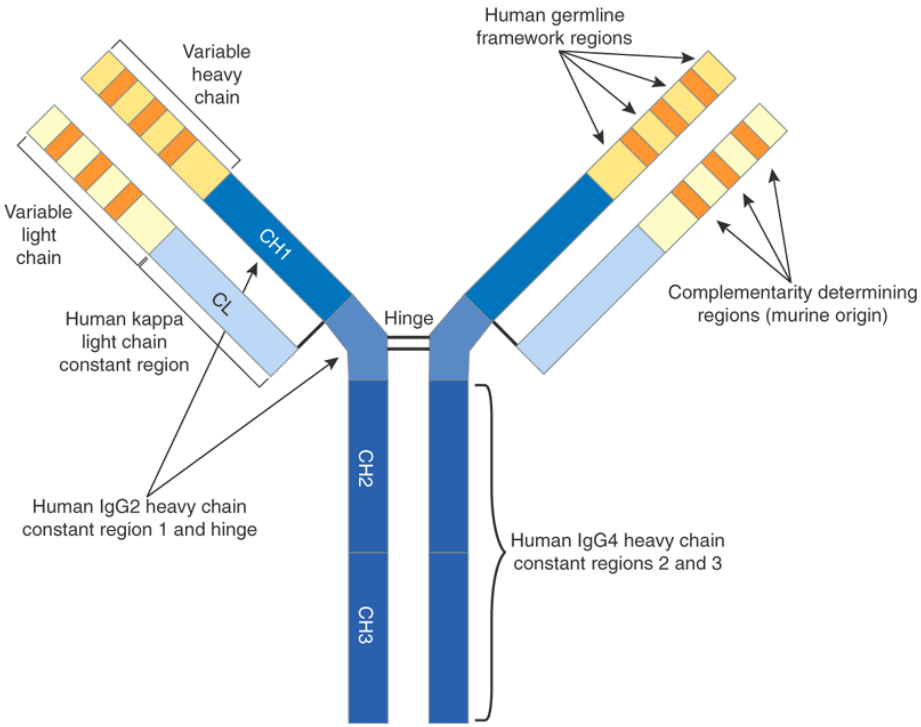
Heeringa et al. Clinical and Developmental Immunology 2012, Article ID 695131

Therapeutic options



1. Remove abnormal proteins
2. Replace deficient proteins
3. Block terminal complement

Eculizumab



- Recombinant, humanized, monoclonal antibody directed against C5 – specifically preventing its cleavage by the C5 convertase.
- Prevents production of C5a and the generation of the terminal complement complex C5b-9.
- The single most expensive drug in the world. ($409,500/yr – *Forbes Magazine*)

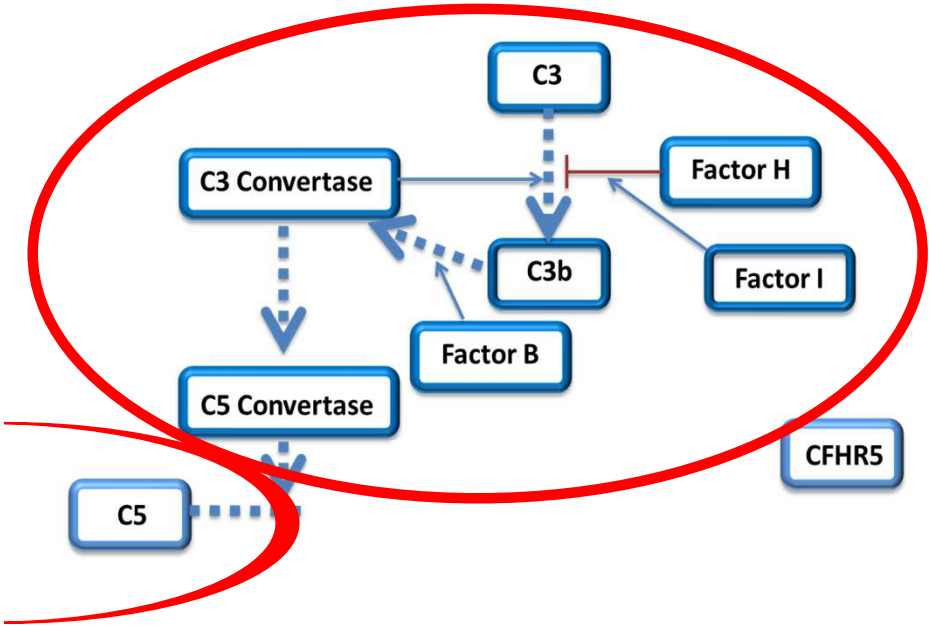
Nature Biotechnology 25, 1256 - 1264 (2007)

Treatment of C3 Glomerulopathy with Complement Blockers

Patient	Reference	C3	C3Nef	S-C5b-9	Genetics	Response	Proteinuria reduction	Renal function	Relapse at discontinuation
1	Vivarelli et al.	↓↓	+	Elevated	FB polymorphism	Yes	Yes	Normal	Yes
2	Daina et al.	↓↓	+	Elevated	FH mutation	Yes	Yes	Improved	ND
3	Radhakrishnan et al.	↓↓	+	Elevated	Absent CFHR1	Yes	Yes	Improved	ND
4	Bomback et al.	↓↓	-	Elevated	FH mutation	Yes	-	Improved	Yes
5	Bomback et al.	↓	-	ND	No mutation	Yes	Yes	Stable	No
6	Bomback et al.	↓	+	Elevated	No mutation	Yes	No	Stable	Yes
7	Bomback et al.	↓	+	Borderline	MCP mutation	Yes	-	Improved	No
8	McCaughan et al.	↓↓	+	ND	No mutation	Yes	Yes	Improved	ND
9	Gurkan et al.	↓↓	+	Elevated	No mutation	Partial	Yes, initially	Improved	ND
10	Bomback et al.	↓↓	+	Normal	No mutation	No	No	Worsened	ND
11	Bomback et al.	±	-	Normal	No mutation	No	±	Worsened	No

Vivarelli and Emma, Semin Thromb Hemost 2014 Jun;40(4):472-7

Therapeutic options



Novel complement therapeutics

- **Different classes of molecules**:
  - Protein therapeutics (Biotech):
    - Monoclonal antibodies
    - Purified plasma proteins
    - Engineered/recombinant proteins
  - Small molecules (<1kDA)
  - Small interfering RNA (siRNA therapeutics) to "*knock down*" complement protein production in the liver (=silenziamento genico)

Practical considerations in the development of complement therapeutics

	Biotech	Small molecules	siRNAs
Cost	↑↑↑	↑	↑↑
Route of administration	IV	OS	IV/SC
Half-life	↑↑	↑	↑↑↑
Toxicity	Minimal off-target effects Potentially immunogenic	More off-target effects	

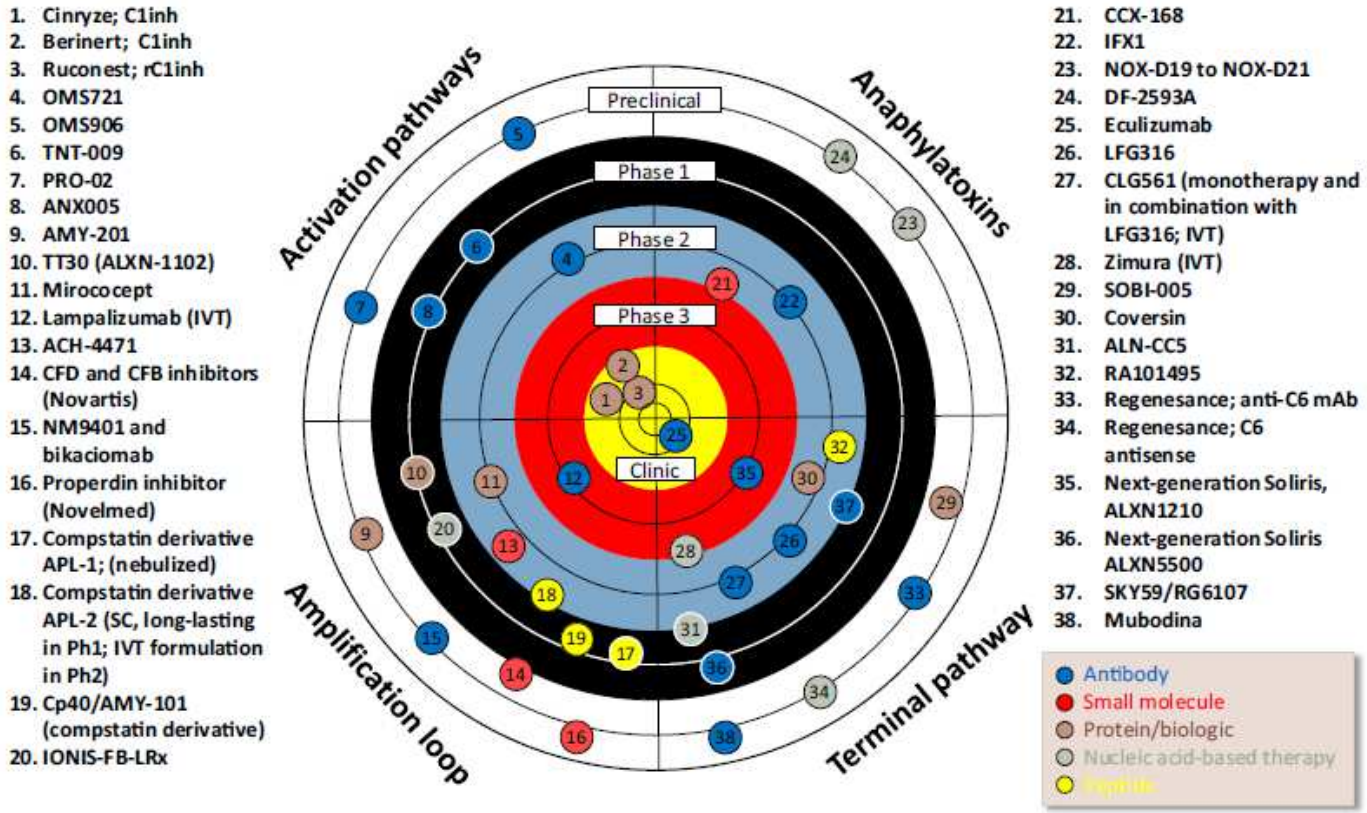
Targeting complement initiation and amplification

Target	Drug (Company)	Entity	Clinical phase (Trial No.)	Indications
C1-INH preparations C1r, C1s, MASPs	Cinryze (Shire)	Protein	P1 (NCT02435732) P3 (NCT02547220)	Transplantation Transplantation
	Berinert (CSL Behring)	Protein	P1/2 (NCT02134314) P2 (NCT02936479)	Transplantation Transplantation
	Cetor (Sanquin)	Protein	P3 (NCT01275976) term P2 (NCT02251041)	Trauma /Sepsis Transplantation
	Ruconest (Pharming)	Protein	P2 (NCT02869347)	Contrast-inducen nephropathy
Anti-C1s	TNT009 (True North)	Antibody	P1 (NCT02502903)	Cold agglutinin disease Bullous pemphigoid Autoimmune hemolytic anemia
Anti-MASP-2	OMS721 (Omeros)	Antibody	P2 (NCT02222545) P2 (NCT02682407)	TMA IgAN, LES, MN, C3G
Anti-FP	CLG561 (Novartis)	Antibody	P2 (NCT02515942)	Age-related Macular Degeneration (AMD)
C3	AMY-101 (Amyndas) 3rd generation compstatin	Peptide	P1 (N/A)	C3G, Transplantation
	APL-1 (Apellis)	Peptide	P1 (N/A)	COPD
	APL-2 (Apellis)	Peptide	P1 (NCT02588833) P1 (NCT02264639) P1 (NCT02461771) comp P2 (NCT0250332)	PNH PNH AMD AMD
FD	Lampalizumab (Genetech)	Antibody (Intravitreally)	P2 (NCT02288559) P3 (NCT02745119) P3 (NCT02247531) P3 (NCT02247479)	AMD AMD AMD AMD
	ACH-4471 (Achillion)	Small molecule	P1 (ACTRN1216000082404p) P2 (NCT03053102)	PNH PNH

Targeting terminal complement pathway

Target	Drug (Company)	Entity	Clinical phase (Trial No.)	Indications
C5	ALXN1210 (Alexion)	Antibody	P1/2 (NCT02598583) P2 (NCT02605993) P3 (NCT02946463) P3 (NCT03066040) P3 (NCT02949128)	PNH PNH PNH (naive) PNH (treated) aHUS (naive)
	Tesidolumab /LGF316 (Novartis)	Antibody	P1 (NCT02878616) P2 (NCT02763644) P2 (NCT01527500) comp P2 (NCT02515942) P2 (NCT02534909) P2 (NCT01526889)	Transplantation TMA AMD AMD PNH Uveitis/Panuveitis
	Coversin (Akari)	Protein	P2 (NCT02591862)	PNH
	RA101495 (Ra Pharma)	Peptide	P1 (ACTRN12615001143516) P2 (NCT03030183) P2 (NCT03078582)	PNH PNH (poor responder) PNH
	Zimura (Ophtotech)	Nucleotide	P2 (NCT02397954) comp P2/3 (NCT02686658)	Idiopathic Polypoidal Choroidal Vasculopathy AMD
	ALN-CC5 (Alnylam)	Nucleotide	P1/2 (NCT02352493)	PNH
C5a	IFX-1 (InflaRx)	Antibody	P2 (NCT02246595) comp P2 (NCT02866825) comp P2 (NCT03001622)	Sepsis SIRS Hidradenitis suppurativa
	ALXN1007 (Alexion)	Antibody	P2 (NCT02245412) term P2 (NCT02128269) comp	GVHD Antiphospholipid syndrome
C5aR1	Avacopan/CCX168 (Chemocentryx)	Small molecule	P2 (NCT02464891) term P2 (NCT02384317) comp P3 (NCT02994927)	aHUS IgAN ANCA-vasculitis

The current complement drug development landscape



Harris er al. Semin Immunopathol 2018;40:125-140

Conclusioni

- I reni sono molto suscettibili a patologie di tipo immunomediato.
- La perdita dell'omeostasi immunologica può colpire il rene in maniera diretta o indiretta.
- La conoscenza dei meccanismi fisiopatologici e dei quadri istologici glomerulari è alla base di una vera medicina personalizzata.
- Negli ultimi anni il trattamento aspecifico delle glomerulopatie è stato implementato dalla diffusione di farmaci di precisione ad alto costo.

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Grazie per l'attenzione

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Innate immunity as a driving force in renal disease

E de Heer[1] and DJM Peters[2]

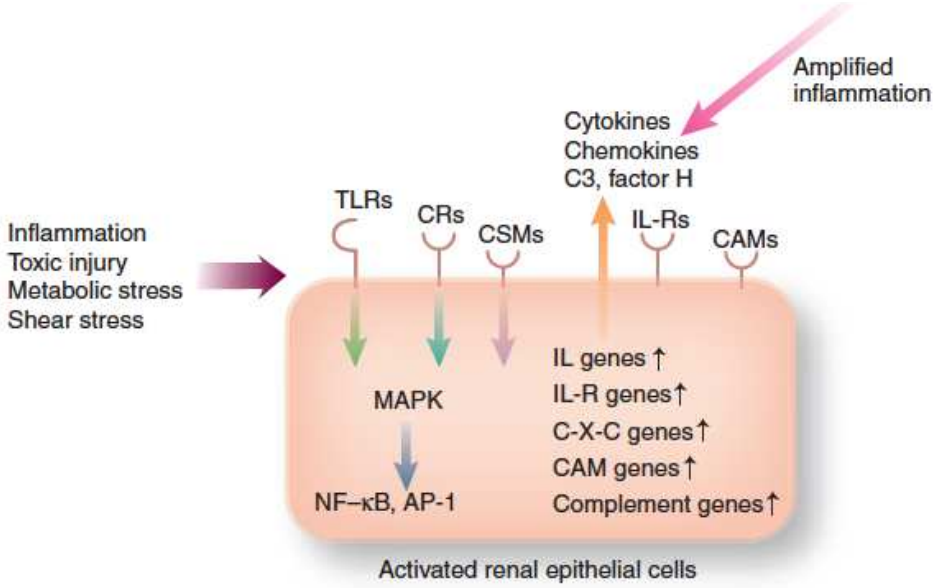

Figure 1 | Innate immunity and renal cells. AP-1, activator protein-1; CAM, cellular adhesion molecule; CRs, complement receptors; CSMs, co-stimulation molecules; IL, interleukin; IL-R, interleukin receptor; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; TLR, Toll-like receptor.