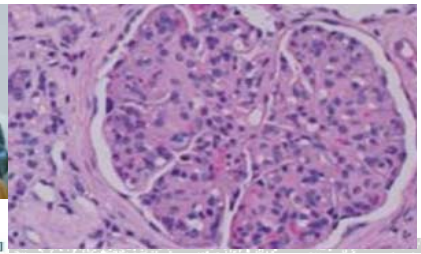
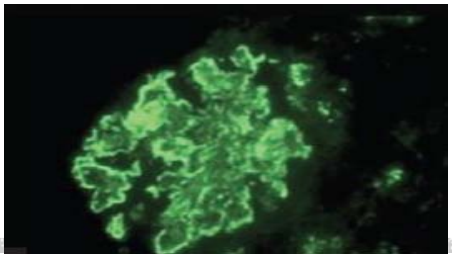
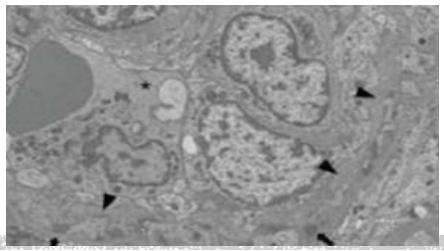
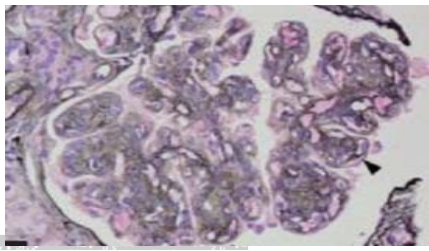
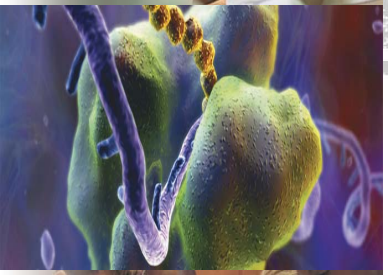










C3 GLOMERULOPATHY

By
Happy Sawires
Professor of Pediatrics and Pediatric Nephrology
Cairo University

Agenda

- What is C3 Glomerulopathy (C3G) ?
- The COMPLEMENT system.
- Pathogenesis / Pathology of C3G.
- Clinical Presentations.
- Investigations.
- Treatment.

1. What is C3G?

C3G is an entity with glomerular deposits made solely (?!) of complement C3.

- Dysregulation of AP through inherited or acquired defects.
- Presence of C3 nephritic factors (C3NeFs).
- Substantial risk for ESRD.
- Substantial risk for recurrence after RTX.

Clinical Nephrology 2013; 80(6): 395-403

Definition of C3 glomerulopathy based on 'C3 only' was impractical, since it excluded many DDD cases identified on EM.

- Predominant glomerular C3 intensity of ≥ 2 levels of magnitude greater than any combination of IgG, IgM, IgA and C1q.

Nephrol Dial Transplant (2014) 0: 1–9

Box 2 | C3 glomerulopathy

Inclusion criteria

- Glomerular deposition of complement C3
- Absence (or only scanty deposition) of immunoglobulin within glomeruli

Examples

- Dense deposit disease
- Idiopathic C3 glomerulonephritis[1]
- Membranoproliferative glomerulonephritis type I with isolated subendothelial deposition of complement C3[5]
- Familial membranoproliferative glomerulonephritis type III[22,23]
- CFHR5 nephropathy (familial C3 glomerulonephritis associated with heterozygous mutation in *CFHR5*)[24]

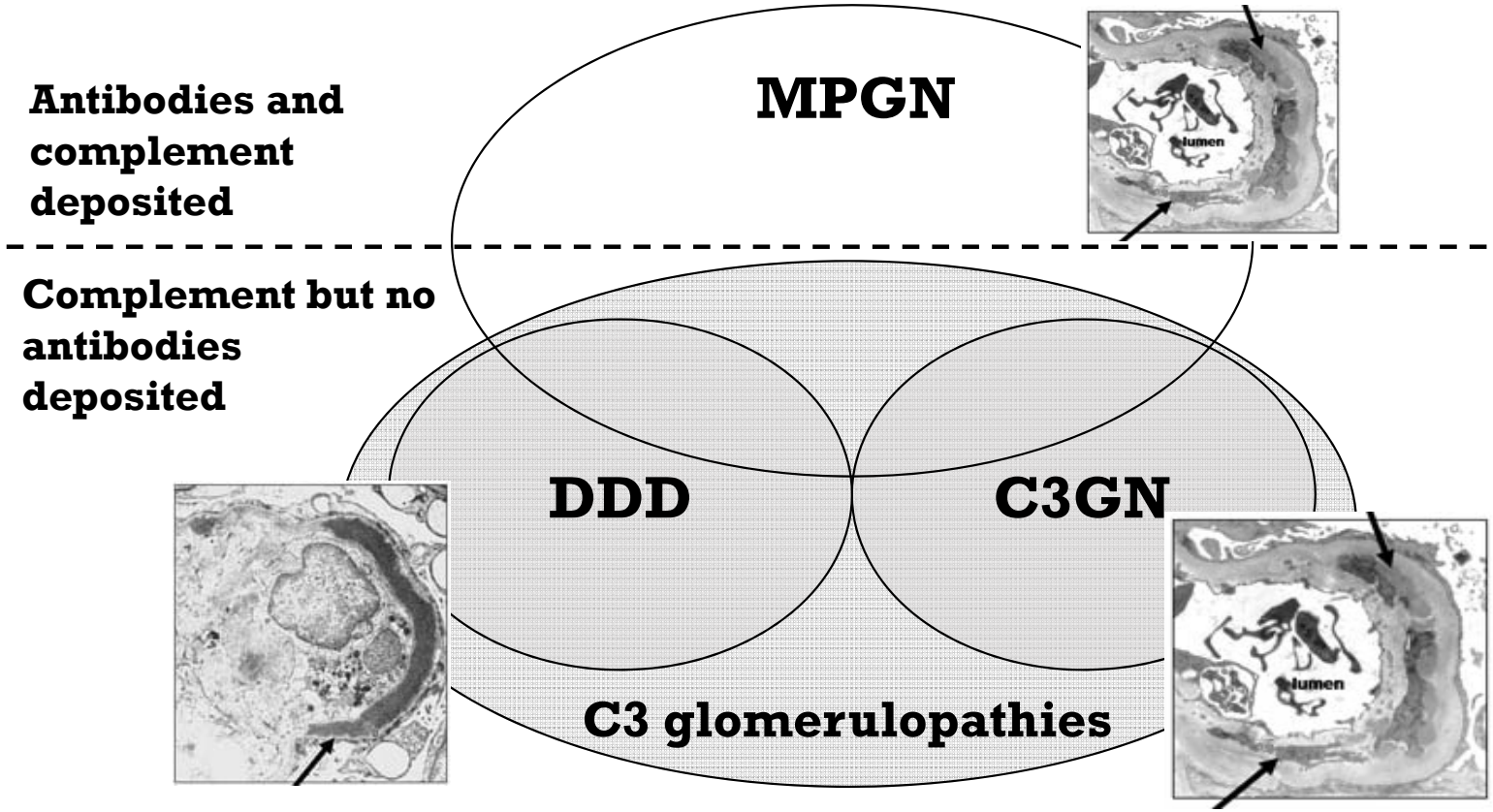
OPINION

C3 glomerulopathy: a new classification

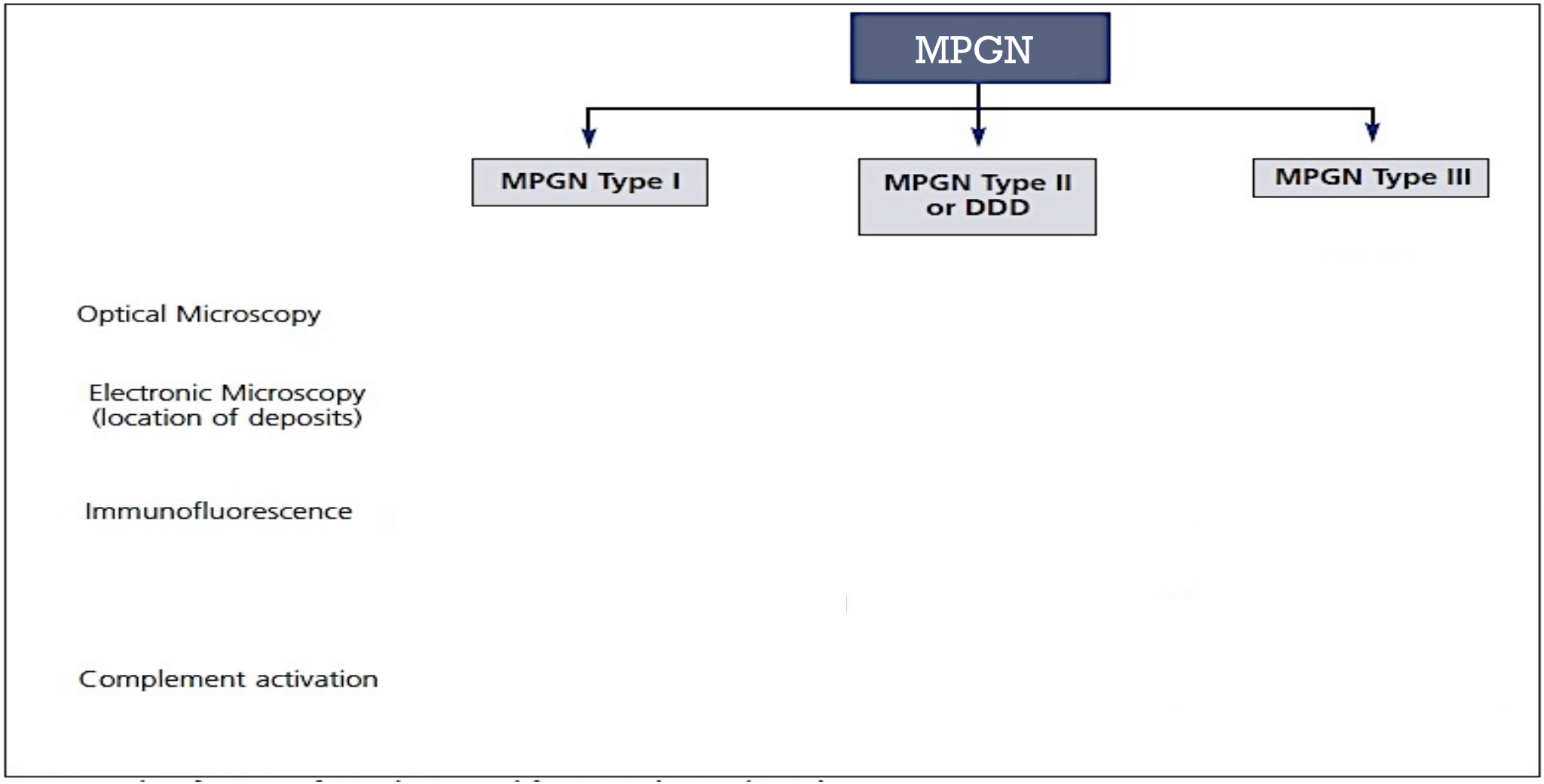
Fadi Fakhouri, Véronique Frémeaux-Bacchi, Laure-Hélène Noël, H. Terence Cook and Matthew C. Pickering

Nat Rev Nephrol 2010; 6(8): 494-499

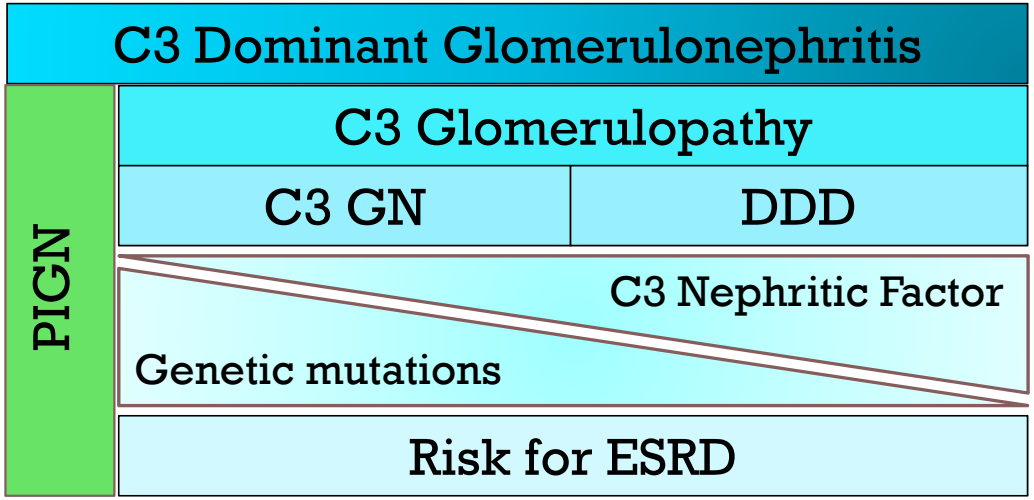
Overlap between MPGN & C3G



MPGN and C3 Glomerulopathy



Classification



Dense Deposit Disease (DDD)

C3 Glomerulonephritis (C3GN)

Cypriot Cohort (CFHR5)

2. Complement System

- Discovered by **Bordet**
- Lytic activity of fresh serum between 0°C and 56°C
- Can be destroyed at 56°C for 30 mnin.

1894

William C Gunn
The association between CN and ↓ complement levels

1915

Muller-Eberhard H J
Revolution in complement biology
Detection of C3

1960

Clark D West
Reports that DDD was C3 and ruptures glomerular capillaries in Glomerulonephritis and MPGN

1964
1965

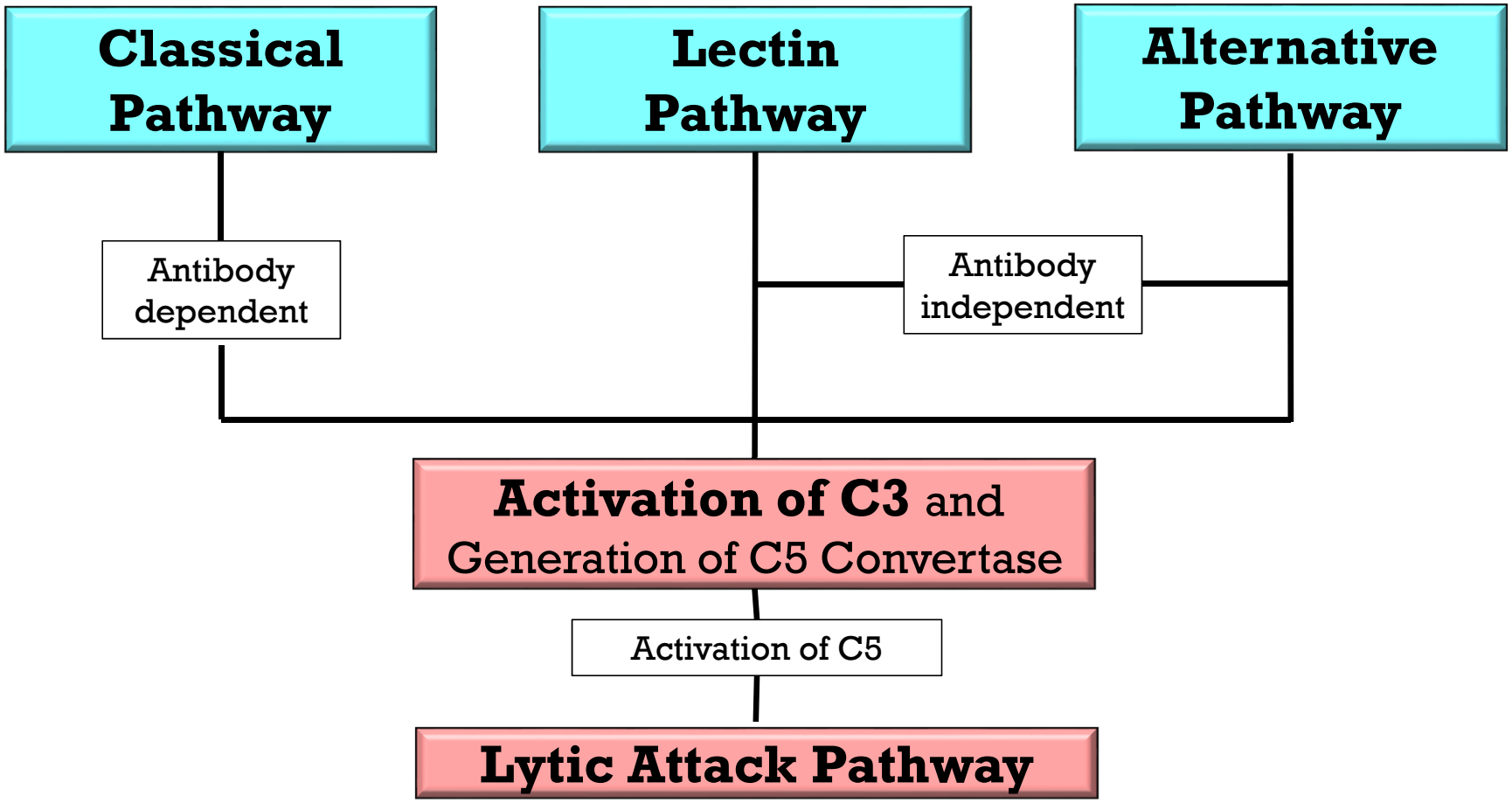
Mathew TH
DDD was C3 and ruptures glomerular capillaries in Glomerulonephritis and MPGN

1971

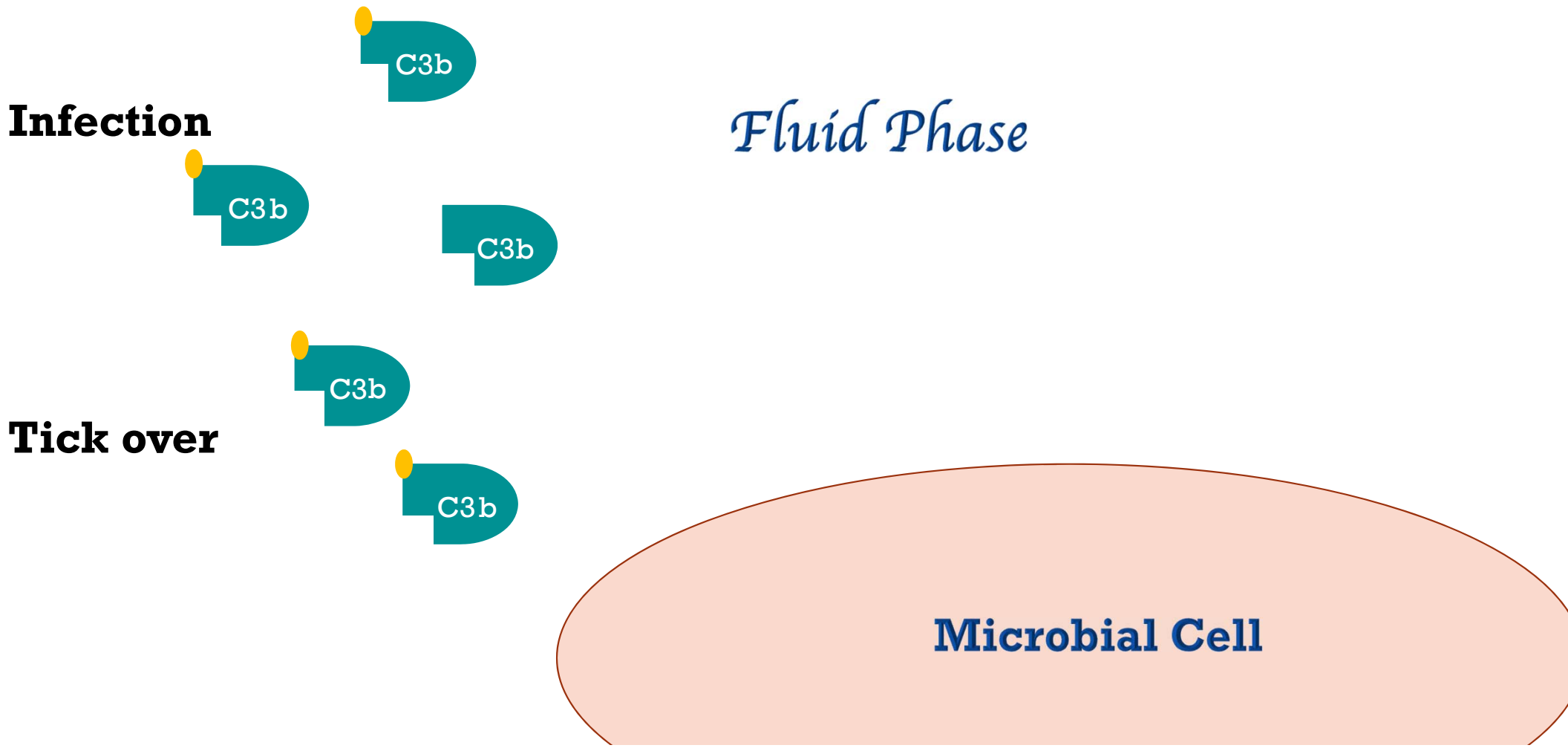
Aude Servas
First description of C3GN

2007

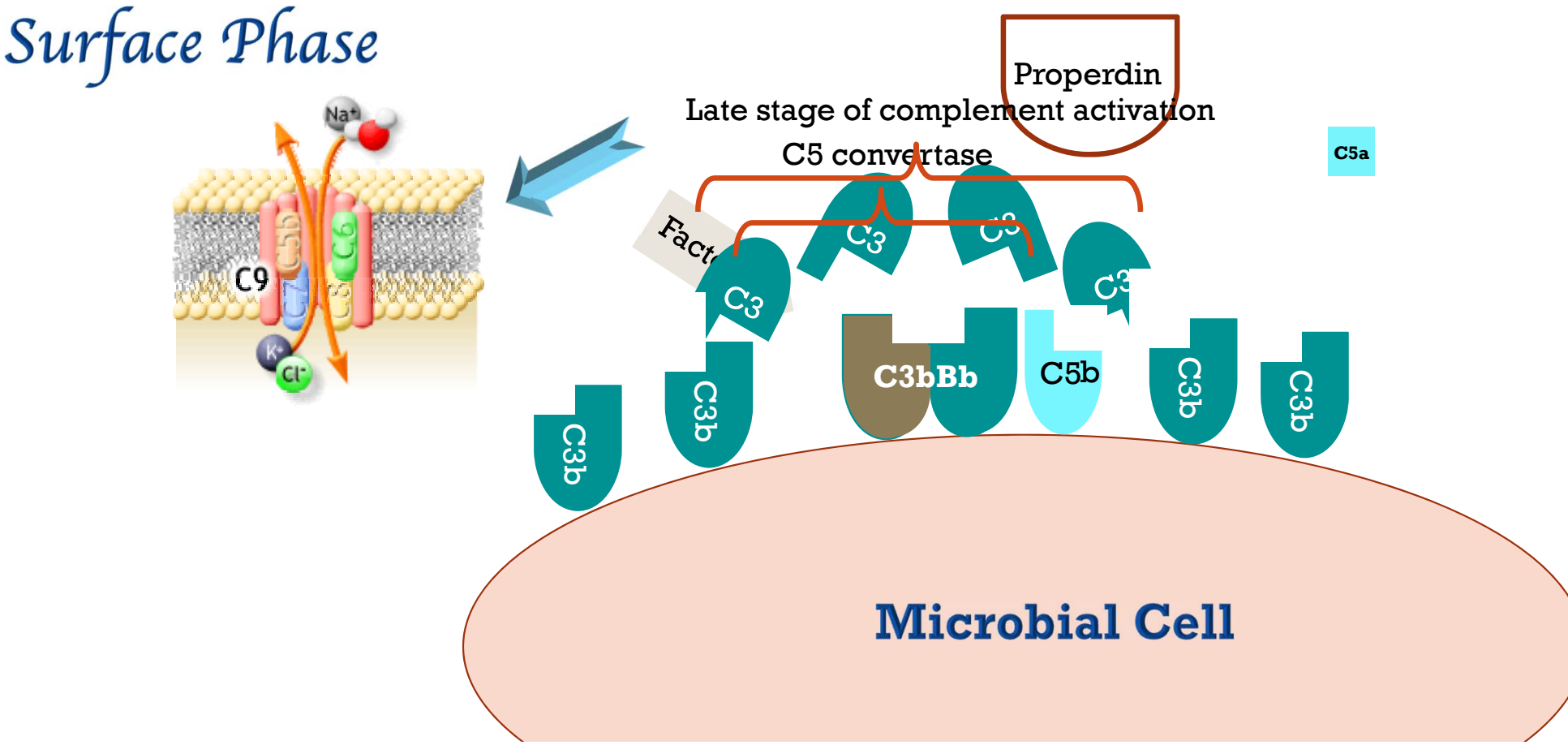
Pathways for complement activation



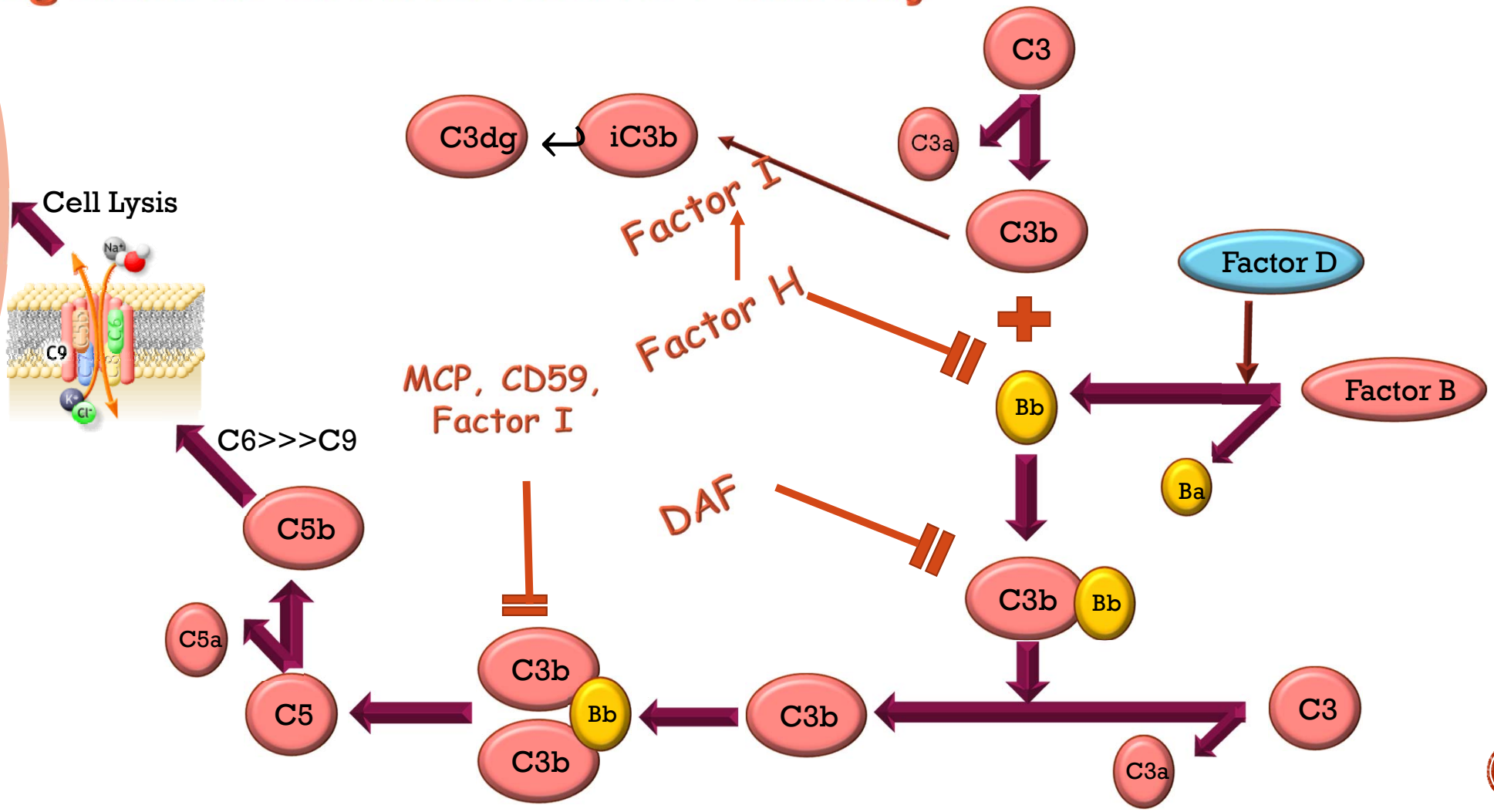
Activation of Alternative Pathway



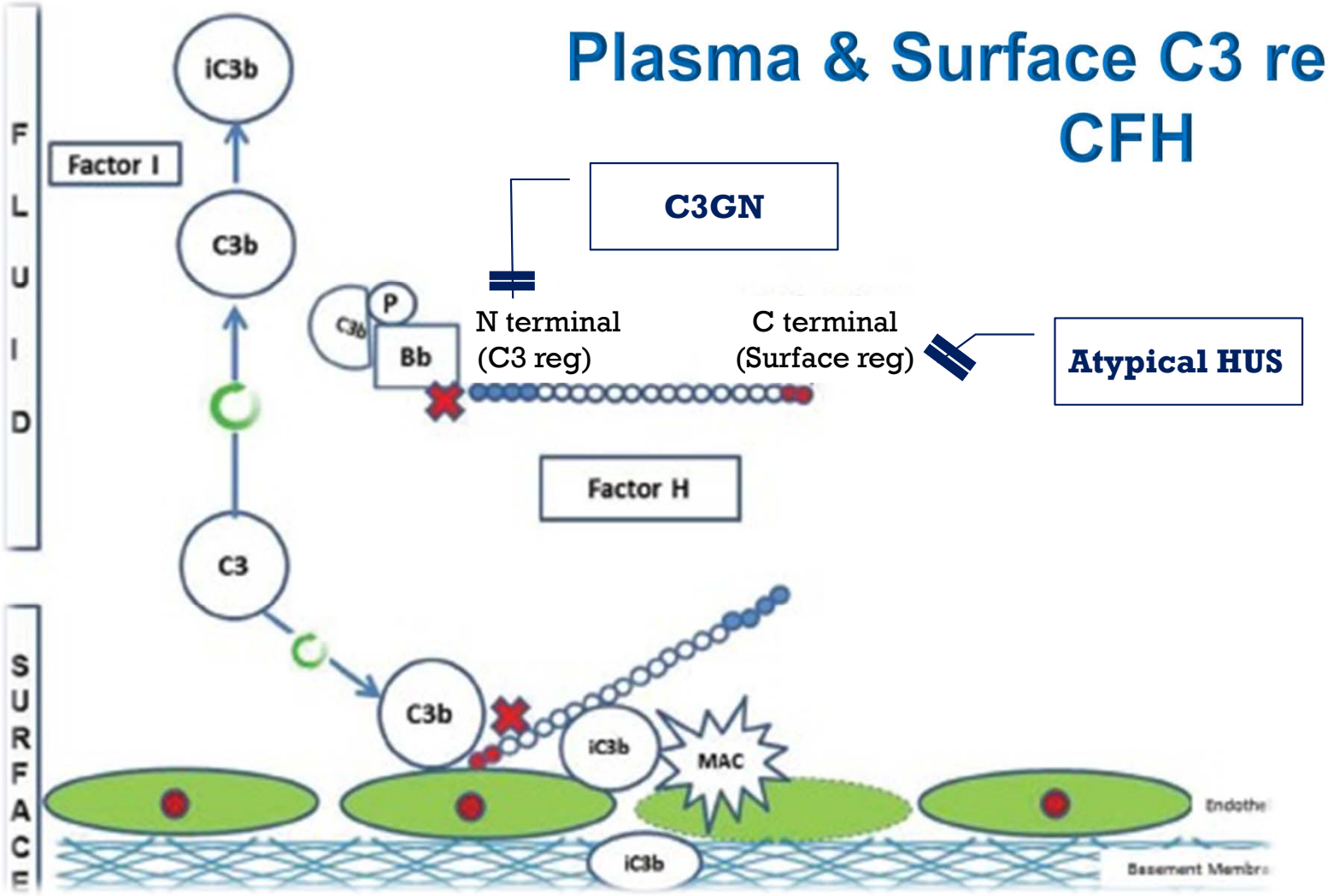
Activation of Alternative Pathway



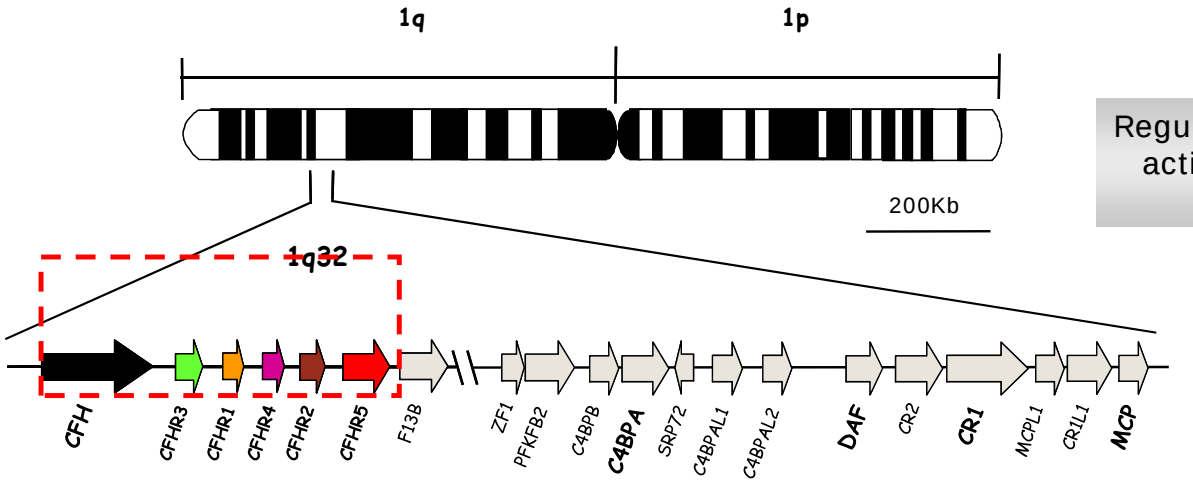
Regulators of Alternative Pathway



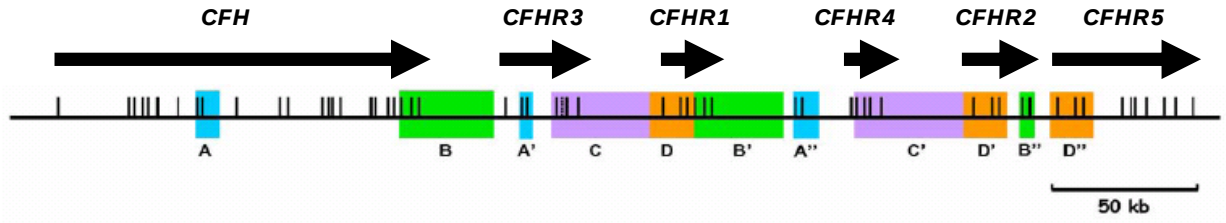
Plasma & Surface C3 regulation by CFH

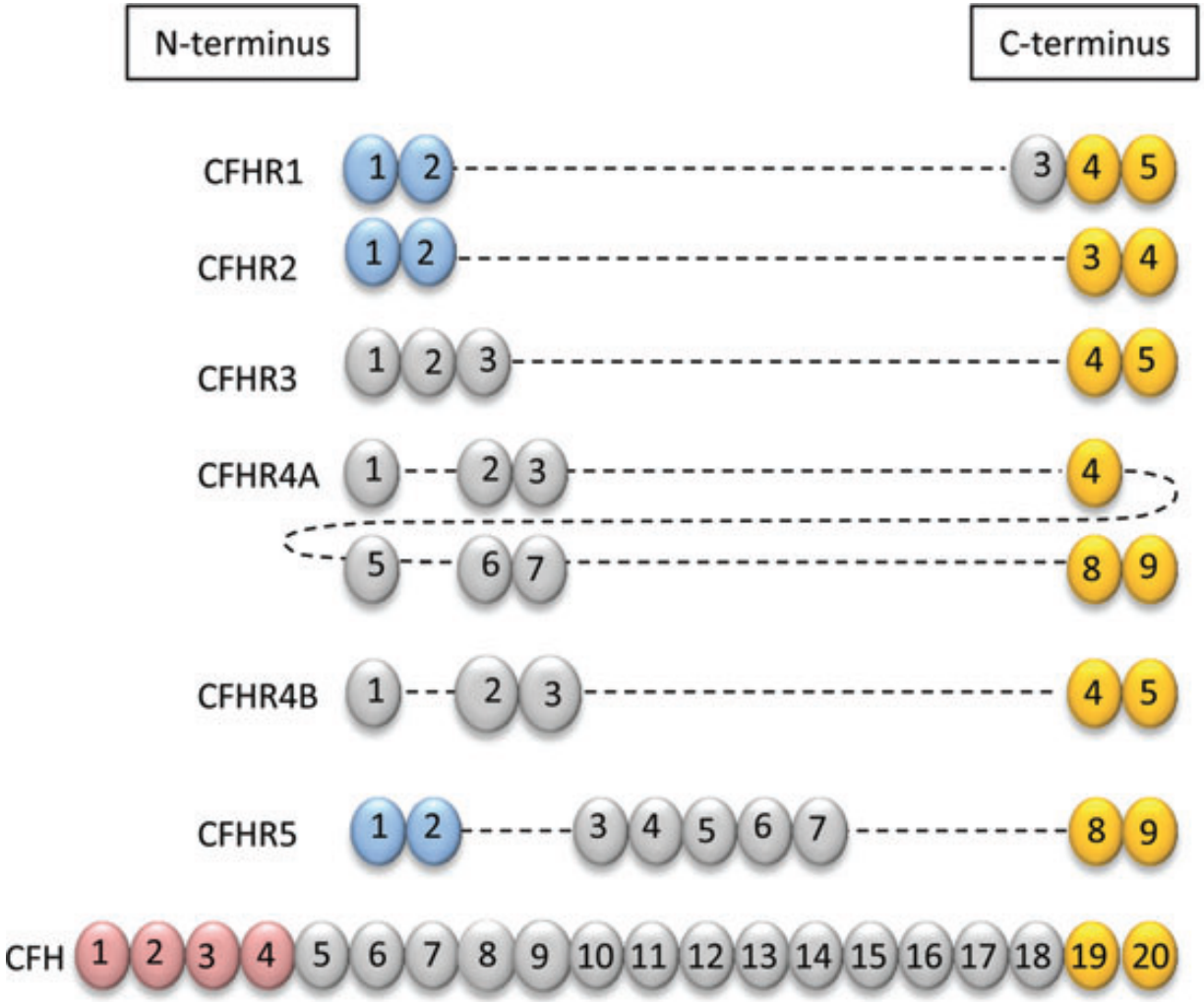


The factor H family



Regulators of complement activation gene cluster (RCA)

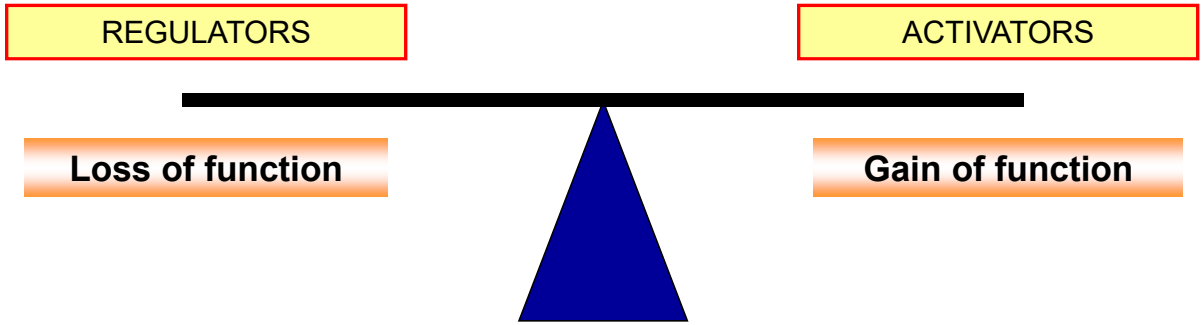




Nephrol Dial Transplant (2014) 0: 1–9

COMPLEMENT DYSREGULATION AND DISEASE:

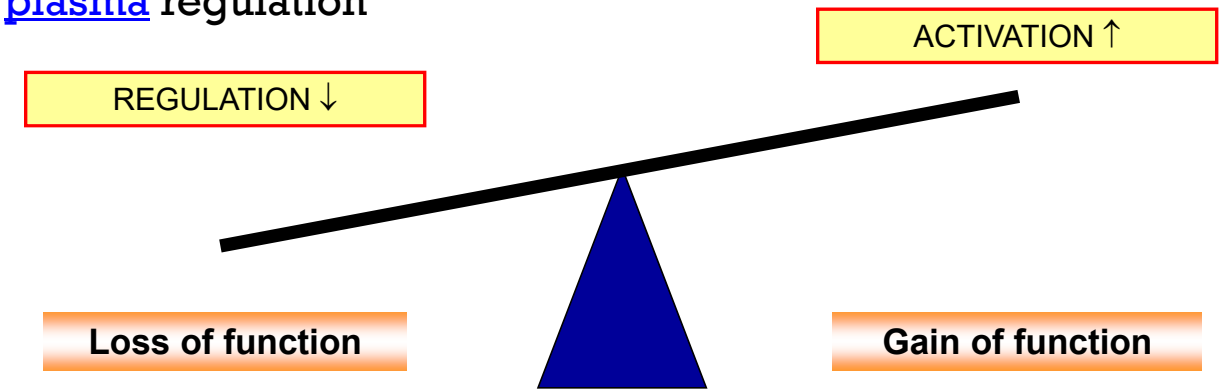
- Physiological control of complement activation



The balance is influenced by mutations (extreme) and/or polymorphisms ('fine tuning')

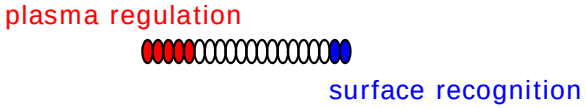
3. Pathogenesis of C3G?

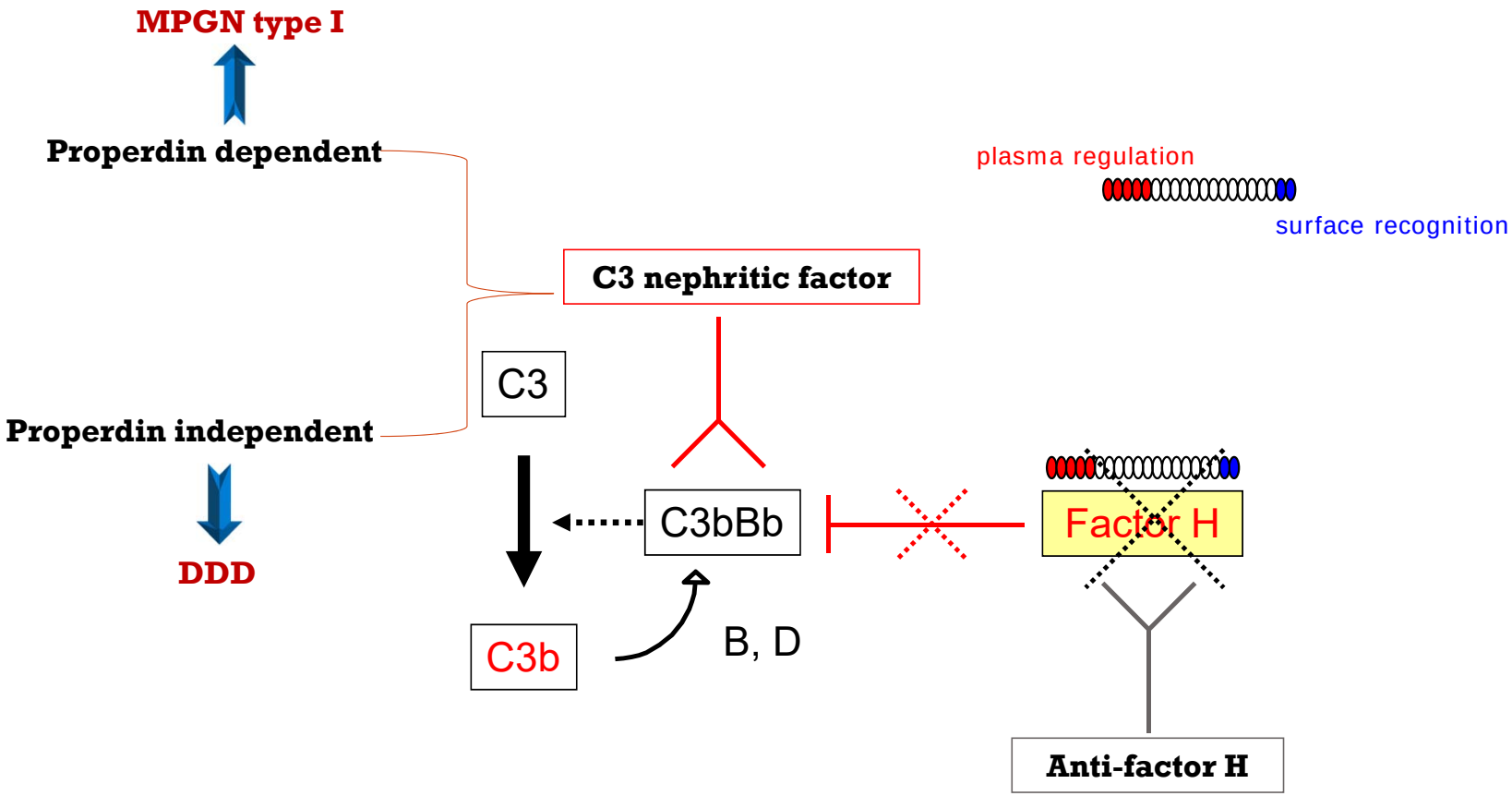
- Impaired plasma regulation



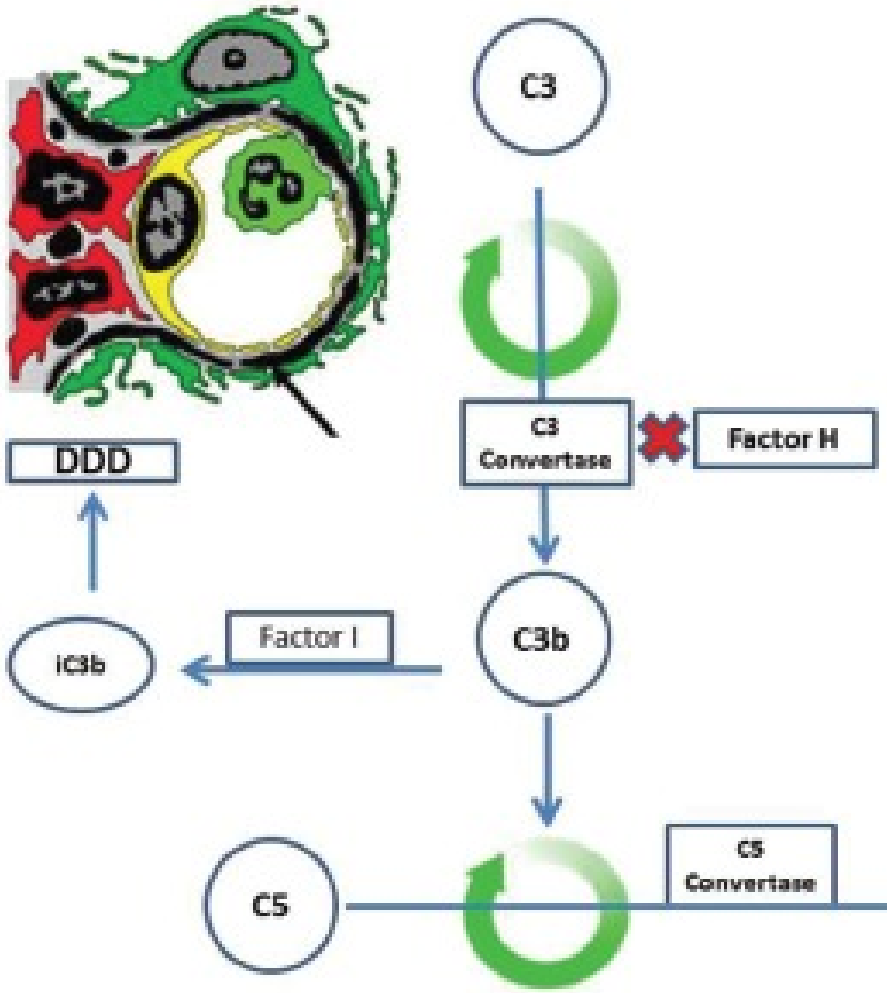
FACTOR H

C3

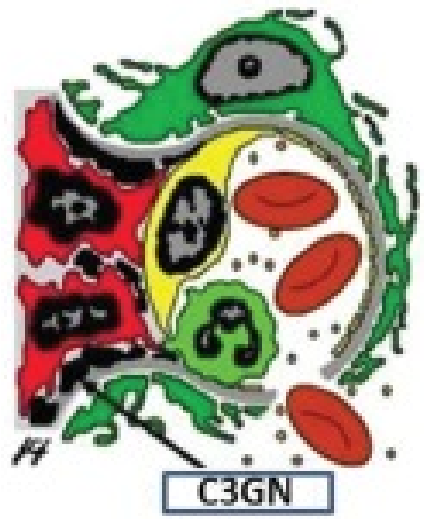



MPGN type I
Properdin dependent
Properdin independent
DDD
C3 nephritic factor
C3
C3bBb
C3b
B, D
plasma regulation
surface recognition
Factor H
Anti-factor H

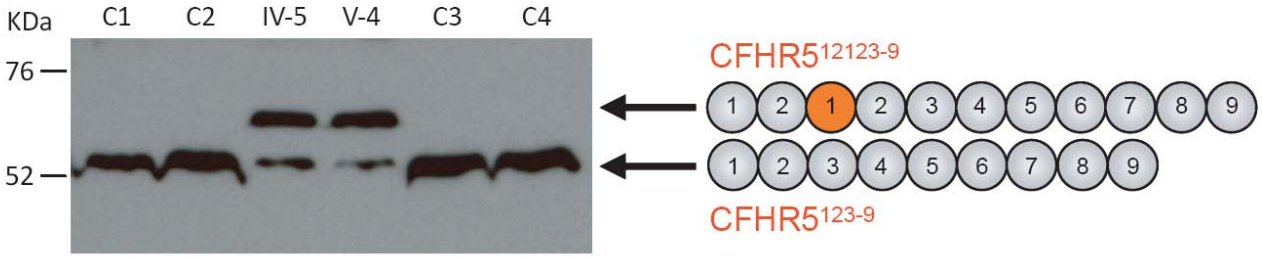
PATHOPHYSIOLOGY OF C3G



	DDD	C3GN
C3 con	↑↑	↑
C5 con	↑	↑↑



CFHR5 NEPHROPATHY



Aberrantly increased size protein detected in sera

- FHR have analogous domains with factor H at the surface regulatory end and compete with factor H for binding with C3B, leading to familial C3GN.
- The internal duplication of CFHR5, leads to Cypriot Nephropathy.

$CFHR5_{121-9}$
(Gale *et al.* (2010) [2],
Medjeral-Thomas *et al.* (2014) [6])

Hybrid $CFHR3_{12}$-CFHR1
(Malik *et al.* (2012) [3])

$CFHR1_{12341-5}$
(Tortajada *et al.* (2013) [5])

Hybrid $CFHR2_{12}$-CFHR5
(Chen *et al.* (2014) [7])

TWO HIT THEORY

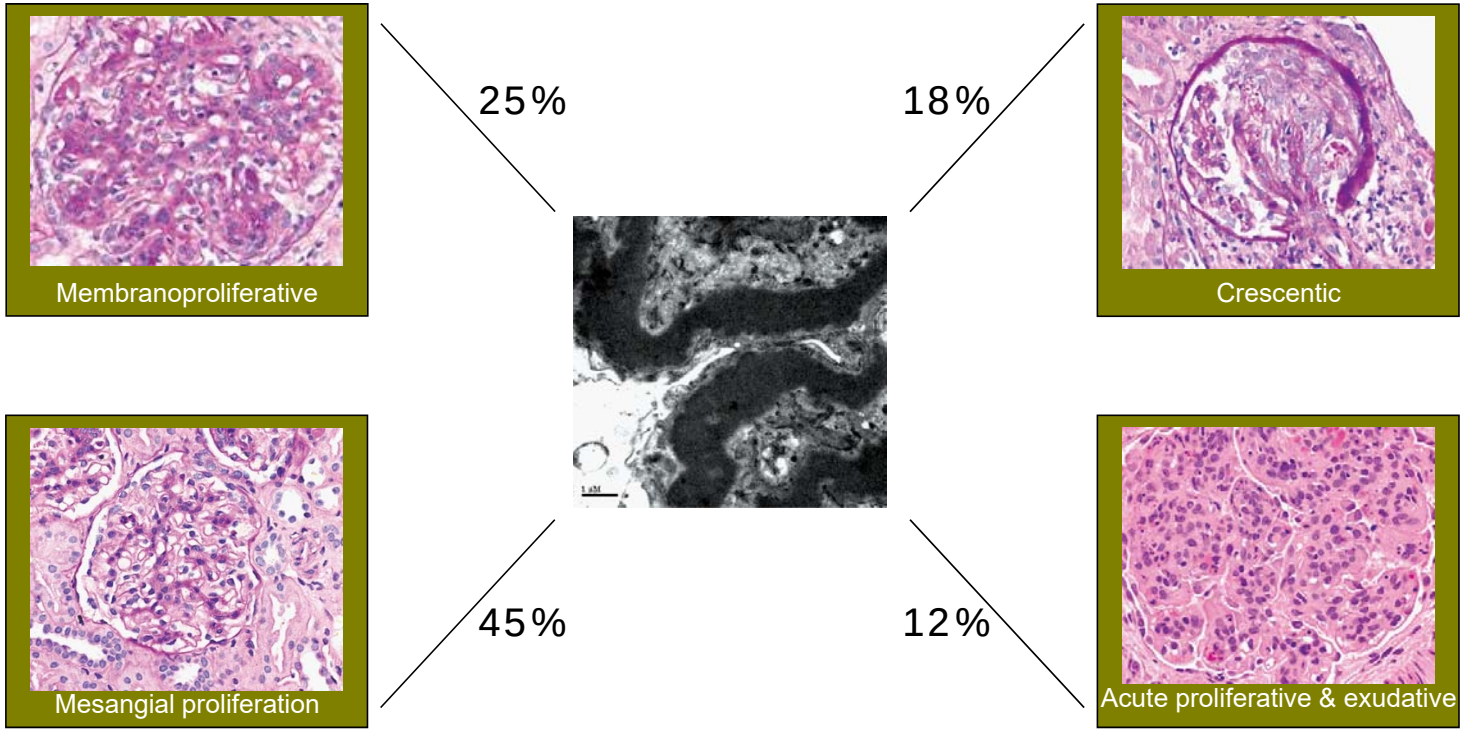
- The presence of unaffected relatives with genetic abnormalities implies that a single hit may not be sufficient to cause disease.

- As a ***Second hit***, an inciting event like an infection, or an accumulation of mutations of AP leads to uncontrolled "C3 tick over" activity.

Pathology

DENSE DEPOSIT DISEASE

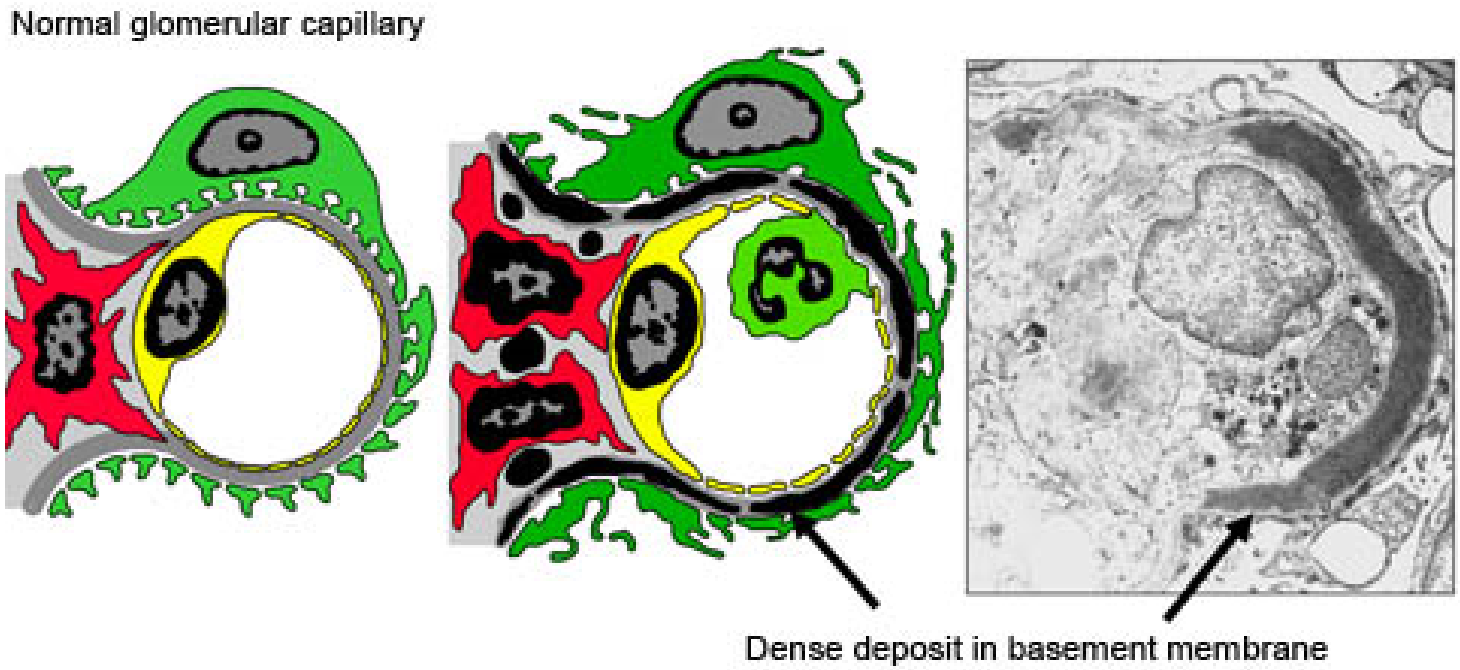
Heterogeneous light microscopic appearances



Modern Pathology (2007) 20, 605–616

Pathology

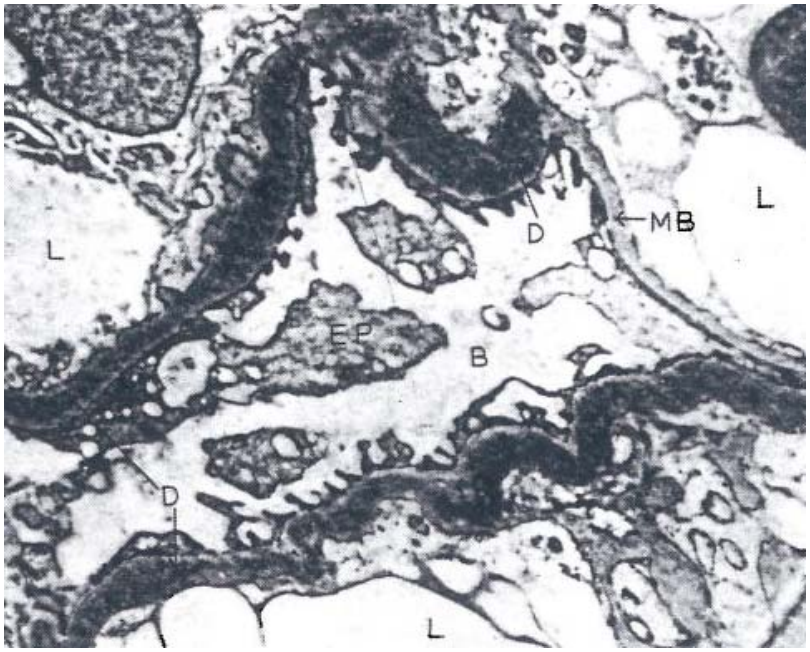
DENSE DEPOSIT DISEASE

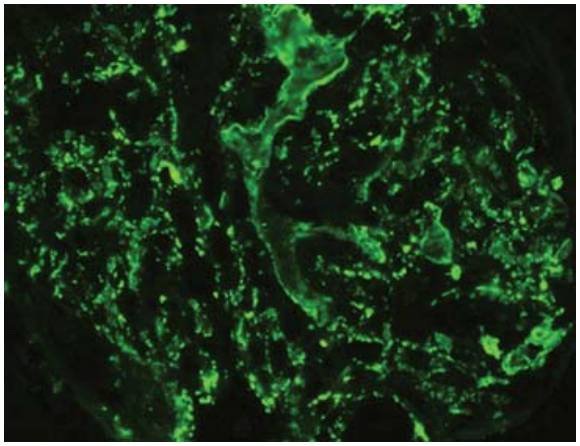


Intramembranous location of dense deposits
>>> ribbons

Pathology

DENSE DEPOSIT DISEASE



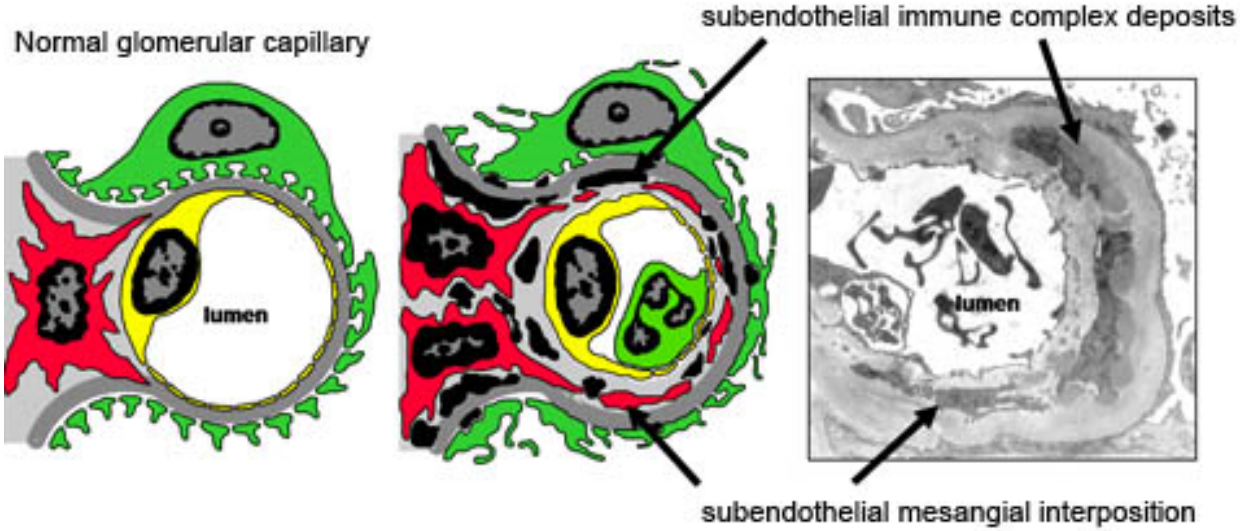


Glomerular C3 staining in DDD

Modern Pathology (2007) 20, 605–616

Pathology

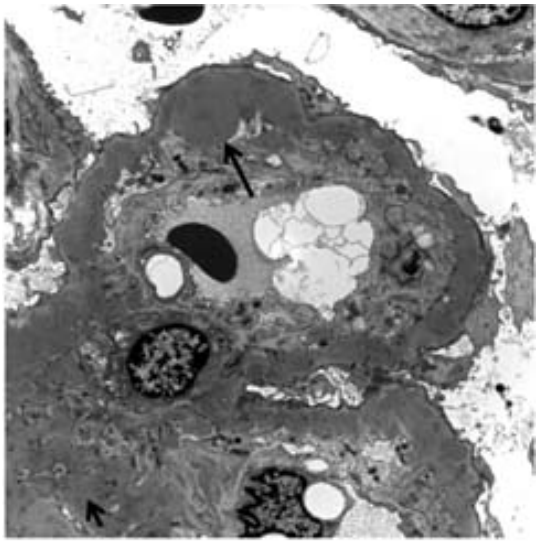
C3 GLOMERULONEPHRITIS

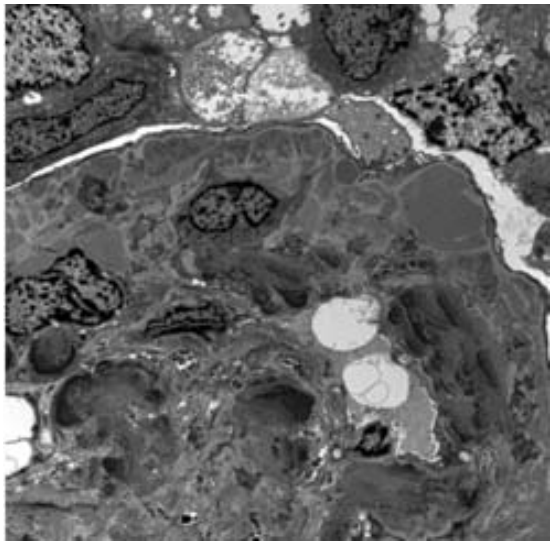


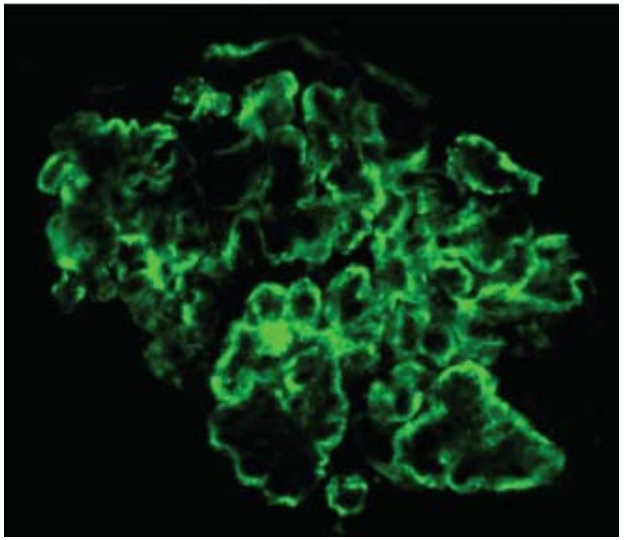
Deposits are found in the mesangium and the capillary wall (subendothelial, subepithelial).
No ribbons

Pathology

C3 GLOMERULONEPHRITIS



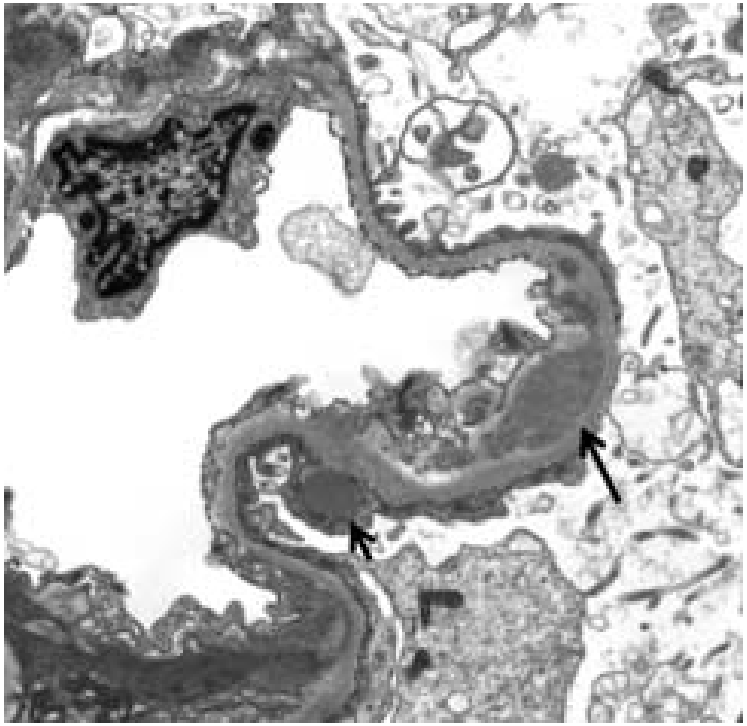




Nephrol Dial Transplant (2013) 0: 1–8

Pathology

CFHR5 NEPHROPATHY



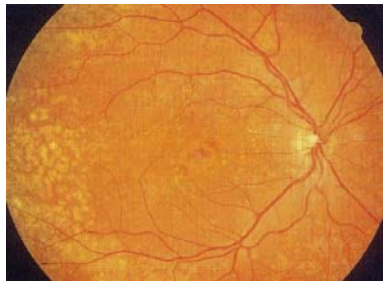
subendothelial (long arrow) and 'hump'-like subepithelial (short arrow) deposits

Nephrol Dial Transplant (2013) 0: 1–8

4. Clinical Presentations

DENSE DEPOSIT DISEASE

- **Age**: 5-15 years.
- **Renal manifestations**:
  - Nephritic-nephrotic syndrome (hematuria, proteinuria..nephrotic range).
- **Extra-renal manifestations**:
  - Brush's membrane retina (Drusen formation)>>> loss of vision (early)
  - Acquired partial lipodystrophy (Barraquer-Simons' syndrome)
  - Increased risk of IDDM
- **Progression to ESRD** in 50% within a decade
- Almost 50% **recurrence following RTX**.



DDD retinopathy

C3 GLOMERULONEPHRITIS

- **Age**: 10-30 years.
- **Renal manifestations**:
  - Nephritic-nephrotic syndrome (hematuria, proteinuria less severe than DDD).
- **Extra-renal manifestations**:
  - No
- **Progression to ESRD** in 10% within 2-3 years
- **Recurrence following RTX**.

CFHR5 NEPHROPATHY

- **Autosomal Dominant.**
- **Renal manifestations**:
  - Persistent microscopic hematuria.
  - Episodes of synpharyngitic macroscopic hematuria.
- **Progression to ESRD** mainly in males.

American Journal of Transplantation 2010; 10: 1–4
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2010.03333.x

Case Report

Recurrence of Complement Factor H-Related Protein 5 Nephropathy in a Renal Transplant

K. A. Vernon[a,*], D. P. Gale[b], E. Goicoechea de Jorge[a], A. G. McLean[b], J. Galliford[b], A. Pierides[c], P. H. Maxwell[d], D. Taube[b], M. C. Pickering[a] and H. T. Cook[a]

Received 09 August 2010, revised 19 September 2010 and accepted for publication 08 October 2010

Differences between DDD and C3GN

	DDD	C3GN
Pathogenesis	C3 convertase dysregulation	C5 convertase dysregulation
Age at diagnosis	12 years	26 years
Extra-renal	Yes	No
Low C3	60%	40%
C3NeF	80%	40-50%
MPGN on L/M	++	+
Crescents	19%	5%
Vascular disease	+	++
Chronicity	+	++
Recurrence	++	++

5. Investigations

C3 Dominant Glomerulonephritis[1]

Clinical course not typical for post-infectious glomerulonephritis[2]

Screen for a paraproteinemia in patients over 50 years old[3]

Test for autoantibodies and protein deficiencies

- C3 nephritic factors
- FHAA
- FBAA
- FH level
- FB level
- Properdin level
- CD46 expression on leukocytes
- Western blot for FHR proteins

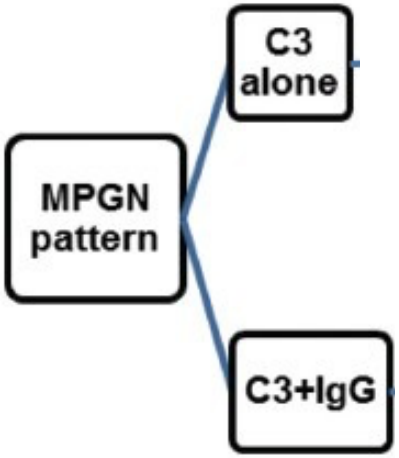
Assess serum complement activity

- Alternative pathway functional assay
- Hemolytic assay
- C3 breakdown products[4]
- C5 breakdown products[5]
- Terminal complement cascade activity[6]

Screen for genetic mutations and copy number variation

- *CFH*
- *CFI*
- *MCP*
- *C3*
- *CFB*
- *CFHR1-5*
- Copy number variation across *CFH-CFHR* region

Clin Nephrol. 2013 Dec;80(6):395-403



Indian J Nephrol. 2014; 24(6): 339–348.

6. Treatment

No treatment is proven to be beneficial in C3G.

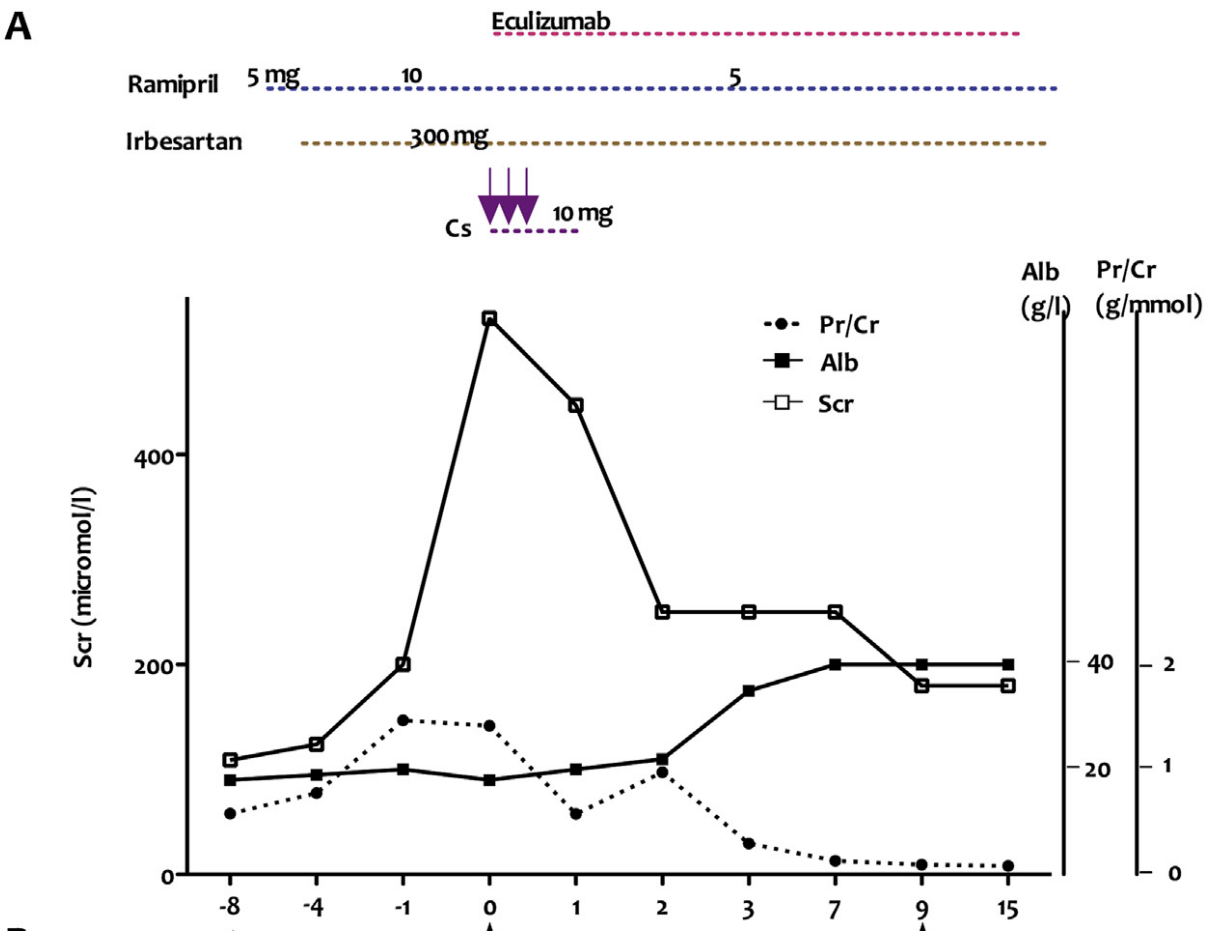
- Plasma exchange is the first-line therapy for factor H defects and elevated C3NeF.

- Treatment with Fresh frozen plasma/recombinant factor H is recommended for factor H deficiency.

- C3GN-due to autoantibodies to a complement protein may benefit from immunosuppressive therapy with steroids/Rituximab.

- ECLUZIMAB !!!

Indian J Nephrol. 2014; 24(6): 339–348.



Am J Kidney Dis. 2015;65(3):484-9.

Future

- Multicenter open label trial is underway for a new drug-soluble CR1 (CDX1135).

- CR1 is a regulator of complement activity along with factor H and MCP. It also mediates factor I dependent cleavage of iC3B to C3C and C3D and regulates C3 and C5 convertase activity.

- In mice made deficient in CF H and transgenic for human CR1, soluble CR1 therapy stopped AP activation, resulting in normalization of serum C3 levels and clearance of iC3b from GBMs.

*Take home message

1. C3G is a rare disease ch.ch. by AP dysregulation with substantial risk of ESRD and recurrence following RTX.

2. Diagnosis depends on I/F and E/M (+ genetic analysis).

3. ↓C3 and C3NeF are not essential for diagnosis.


Thank You