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Introduction

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Manipulate Innate Immunity: Complement

Innate and acquired immunity

Innate immunity

Cells:

NK cells
macrophages
dendritic cells
granulocytes

Soluble mediators:

Cytokines
Chemokines
Defensins
Pentraxins
Complement
Etc.

Acquired immunity

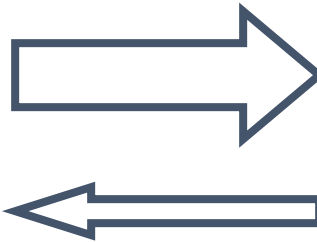
Cells:

T lymphocytes
B lymphocytes

Soluble products:

Cytokines
Chemokines

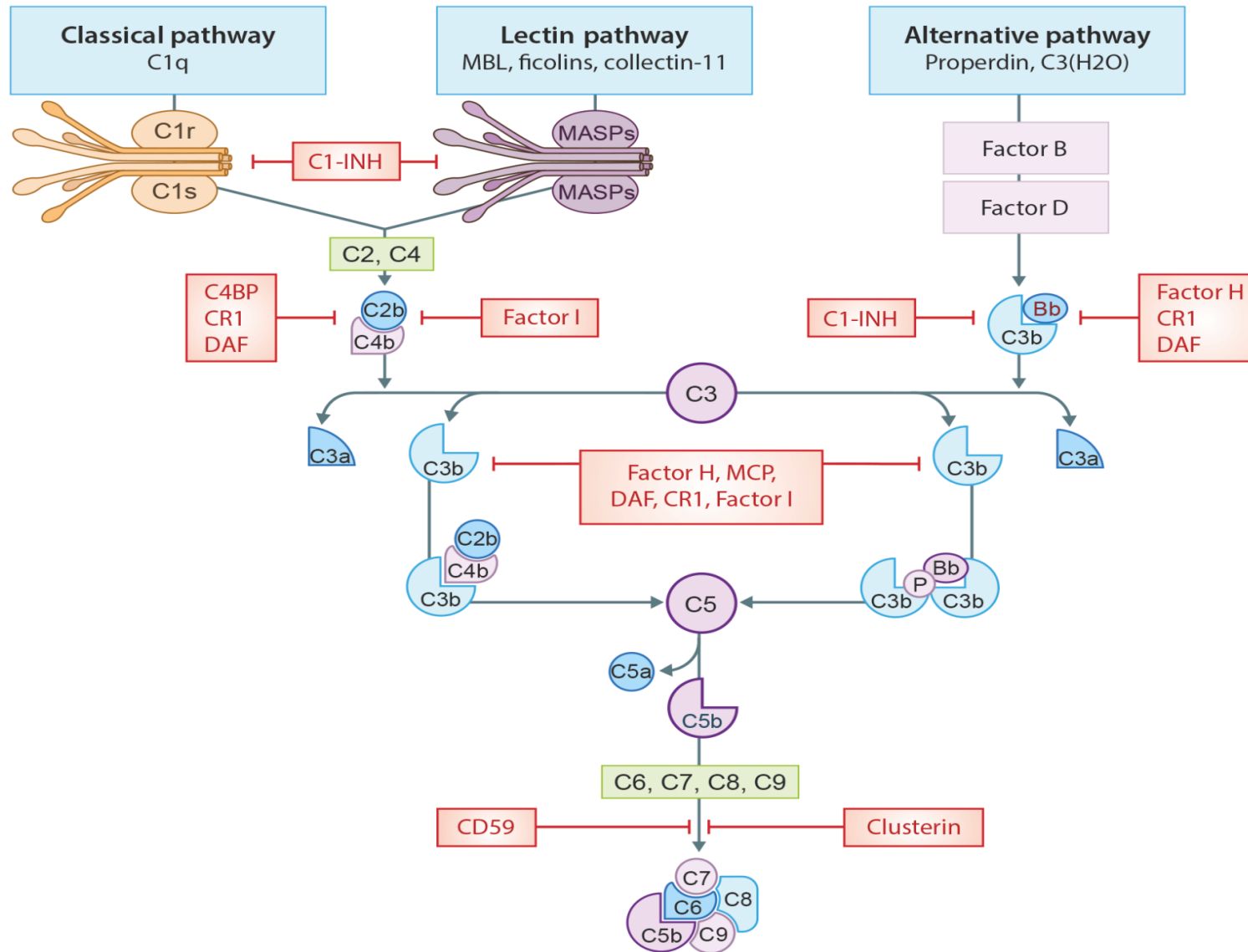
Antibodies



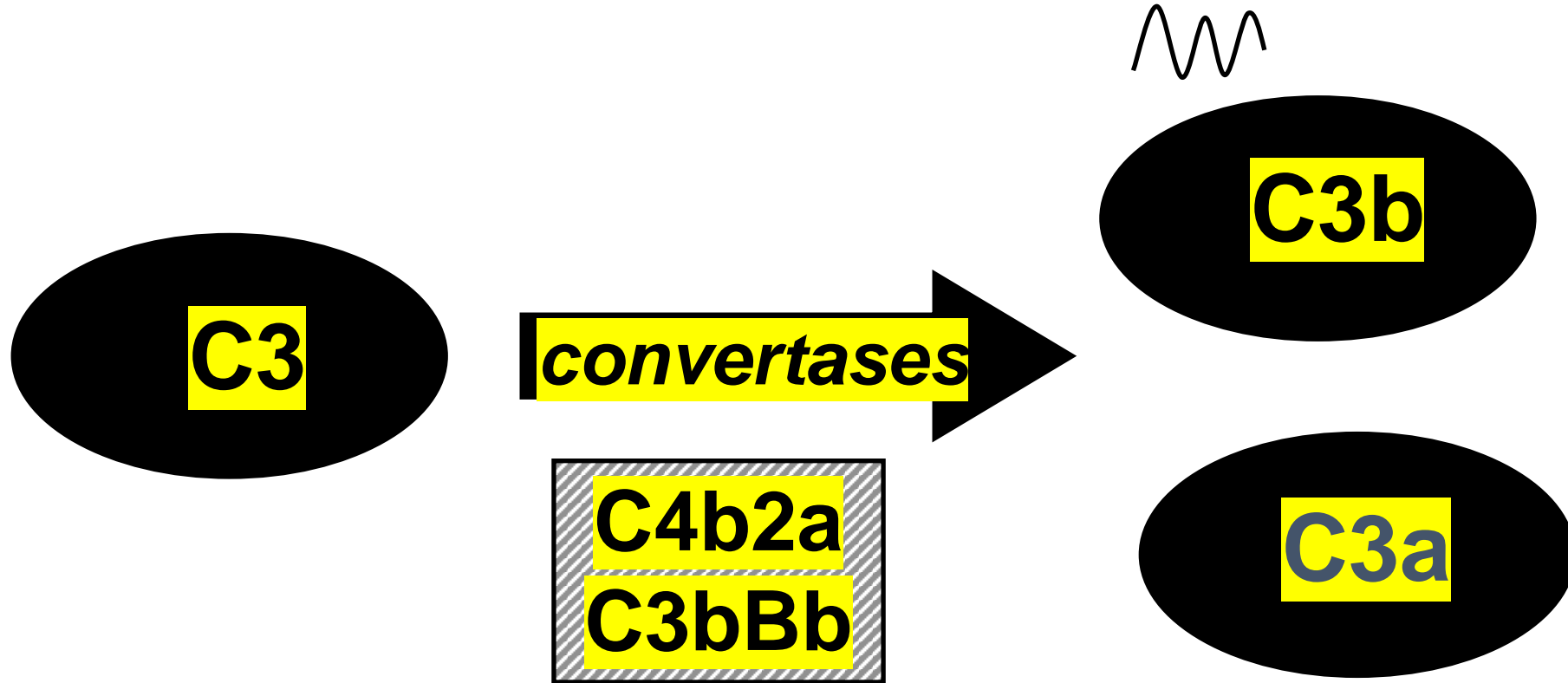
Biological functions of complement

- Direct pathogen elimination
- Induction of phagocytosis via opsonization
- Induction of inflammation and chemotaxis
- Interface between innate and adaptive immunity
- Clearance of immune complexes and self debris

Overview of the complement system



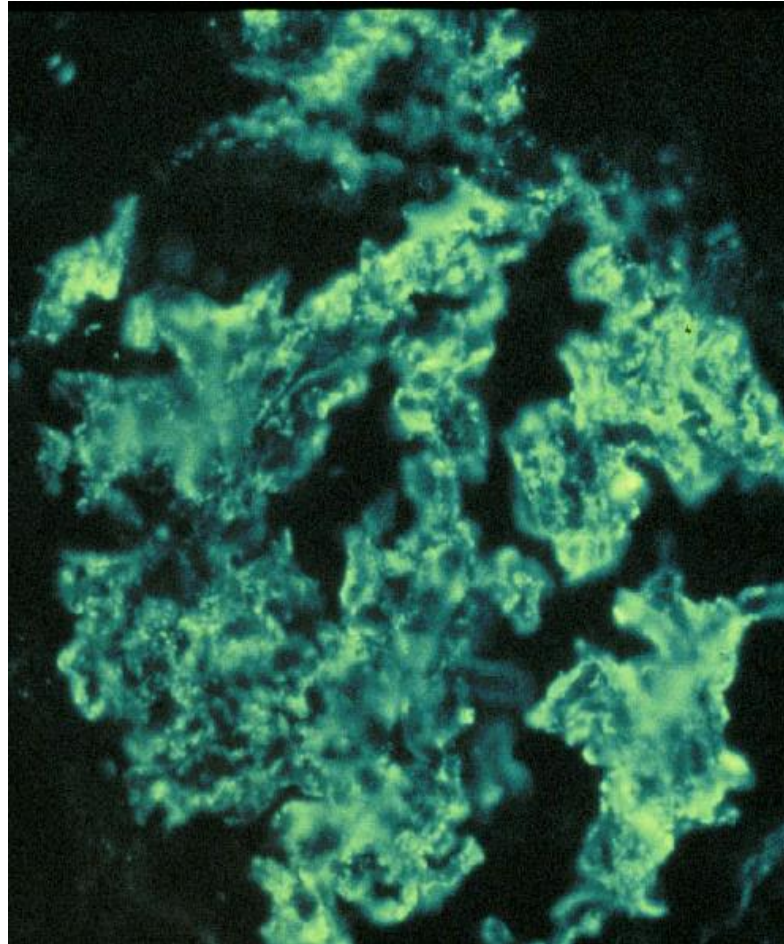
Activation of C3



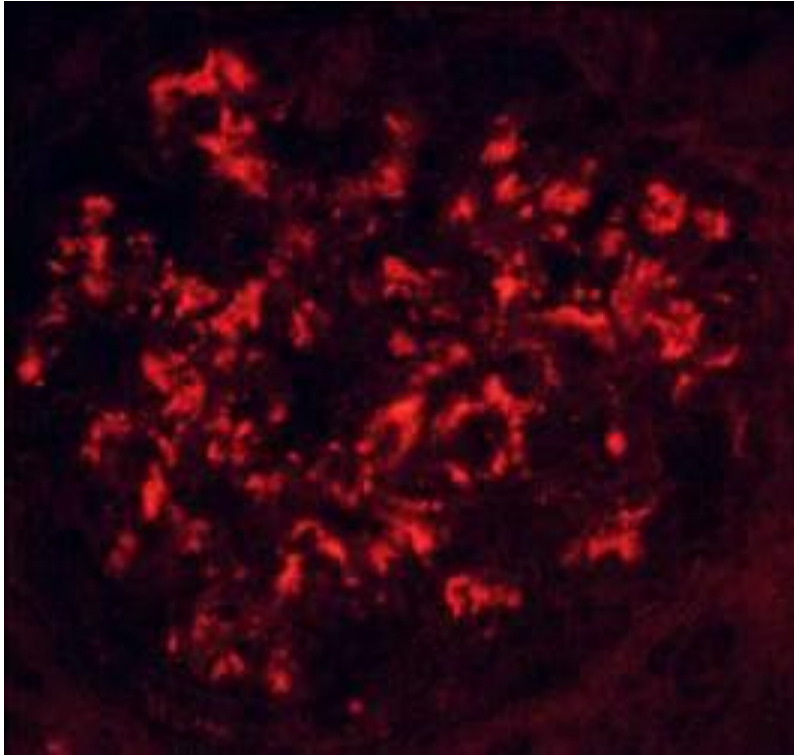
Complement plays a role in different types of GN's

- SLE
- IgAN
- Membranous nephropathy
- ANCA associated vasculitis
- Atypical HUS
- C3GN

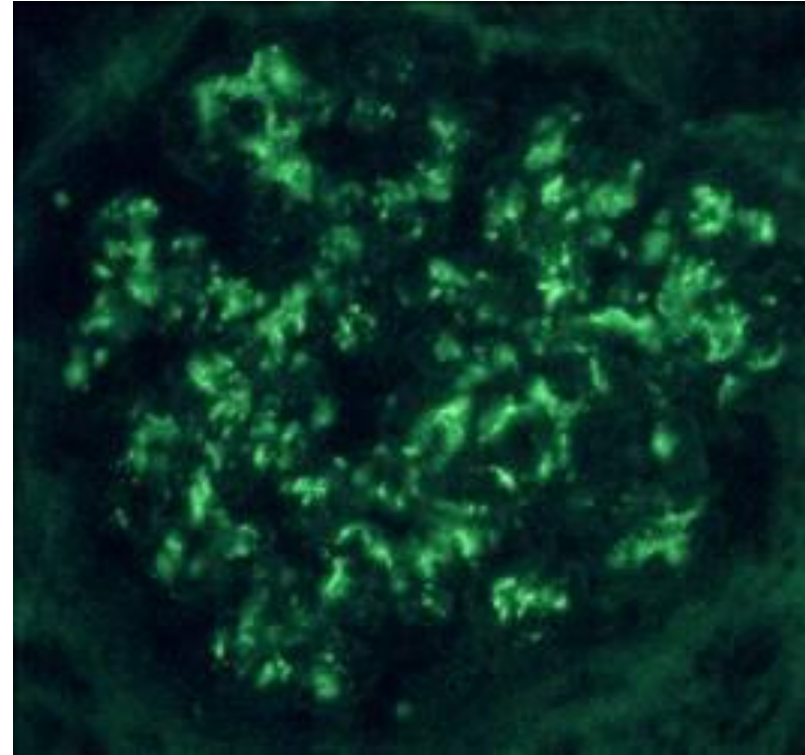
C1q deposition in a SLE patient



Complement activation in IgA nephropathy

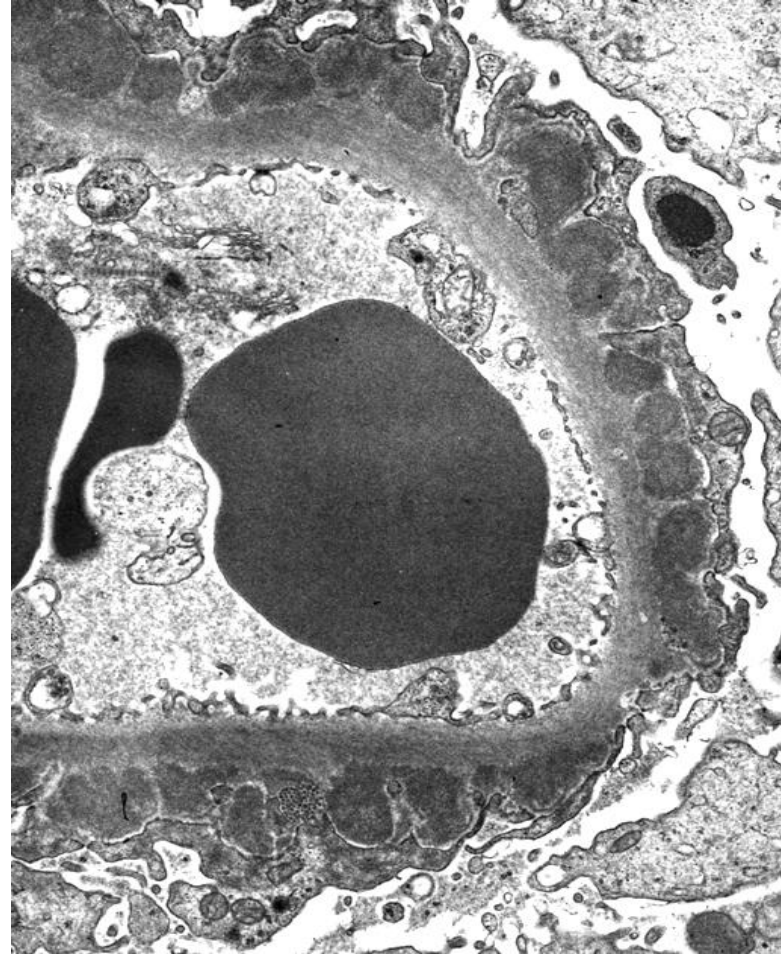
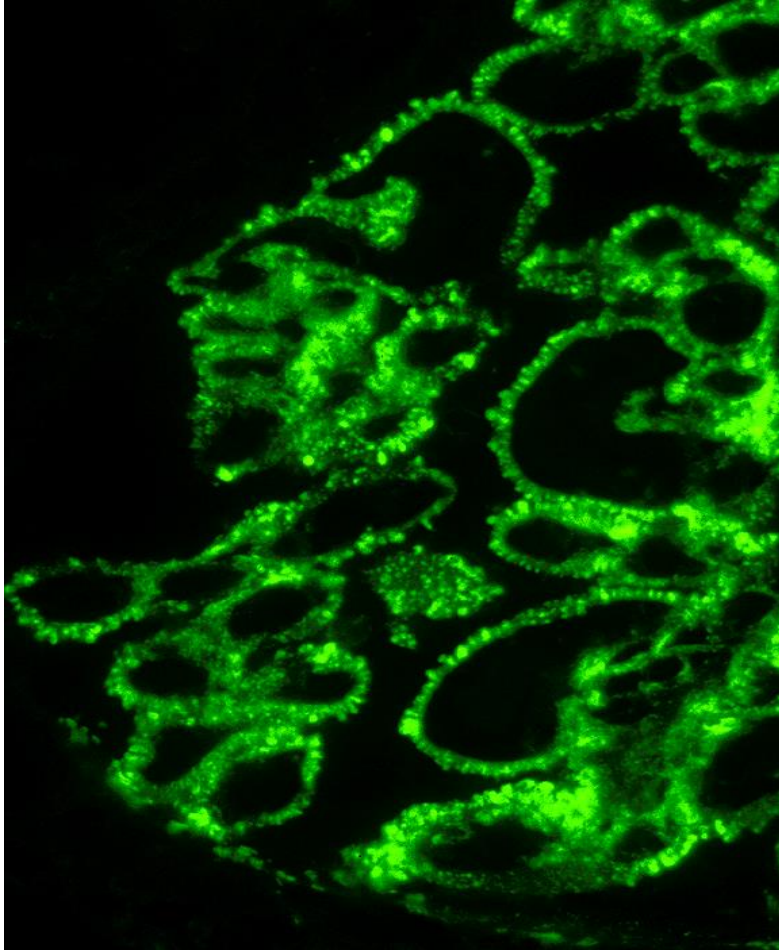


Immunoglobulin A



C3

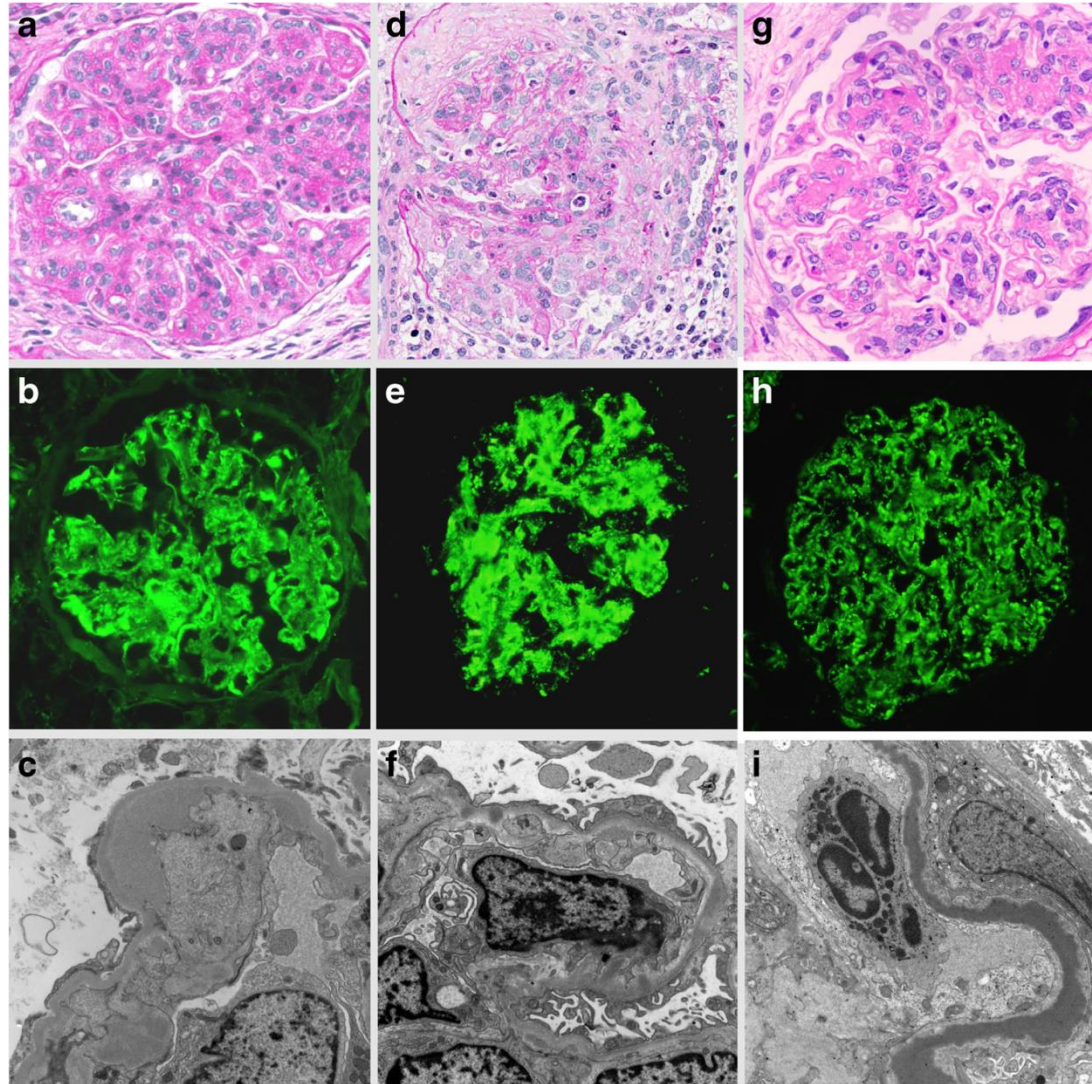
Membranous Nephropathy



Major cause of nephrotic syndrome and chronic renal failure
(Pierre Ronco)

Histological findings in C3G (*MPGN, C3G, DDD*)

- From:
- *Riedl, Thorner and Licht 2017*

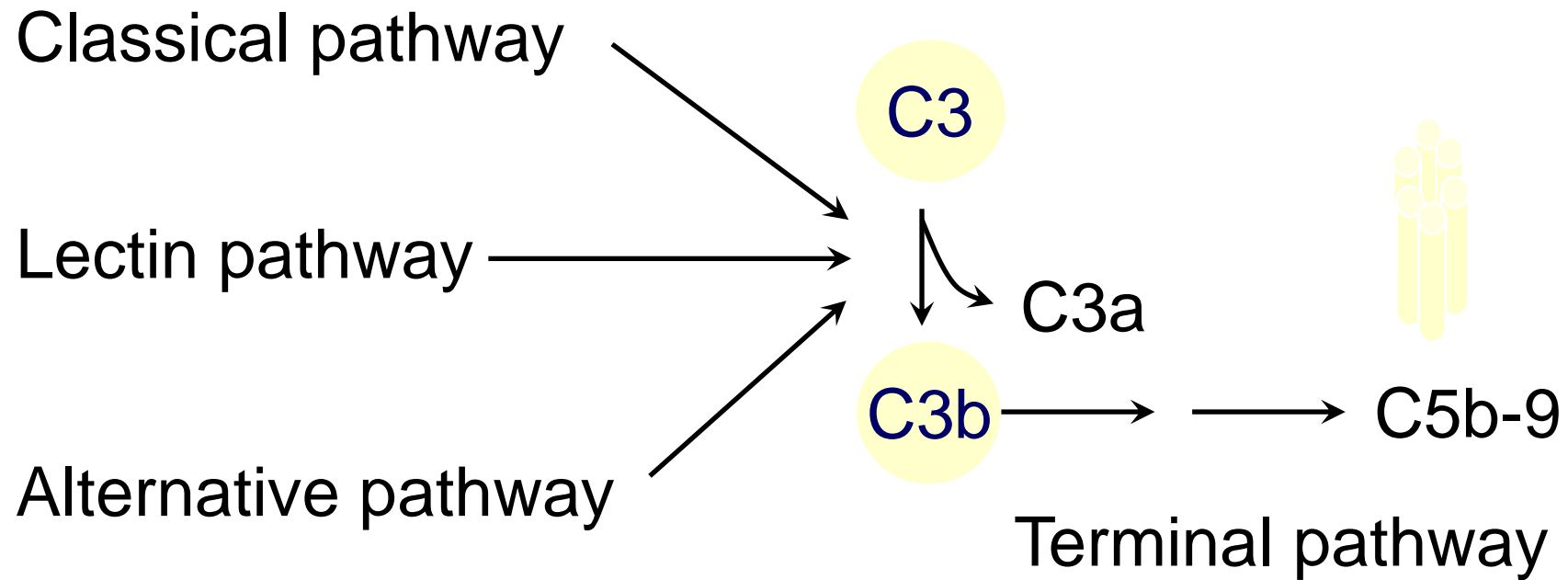


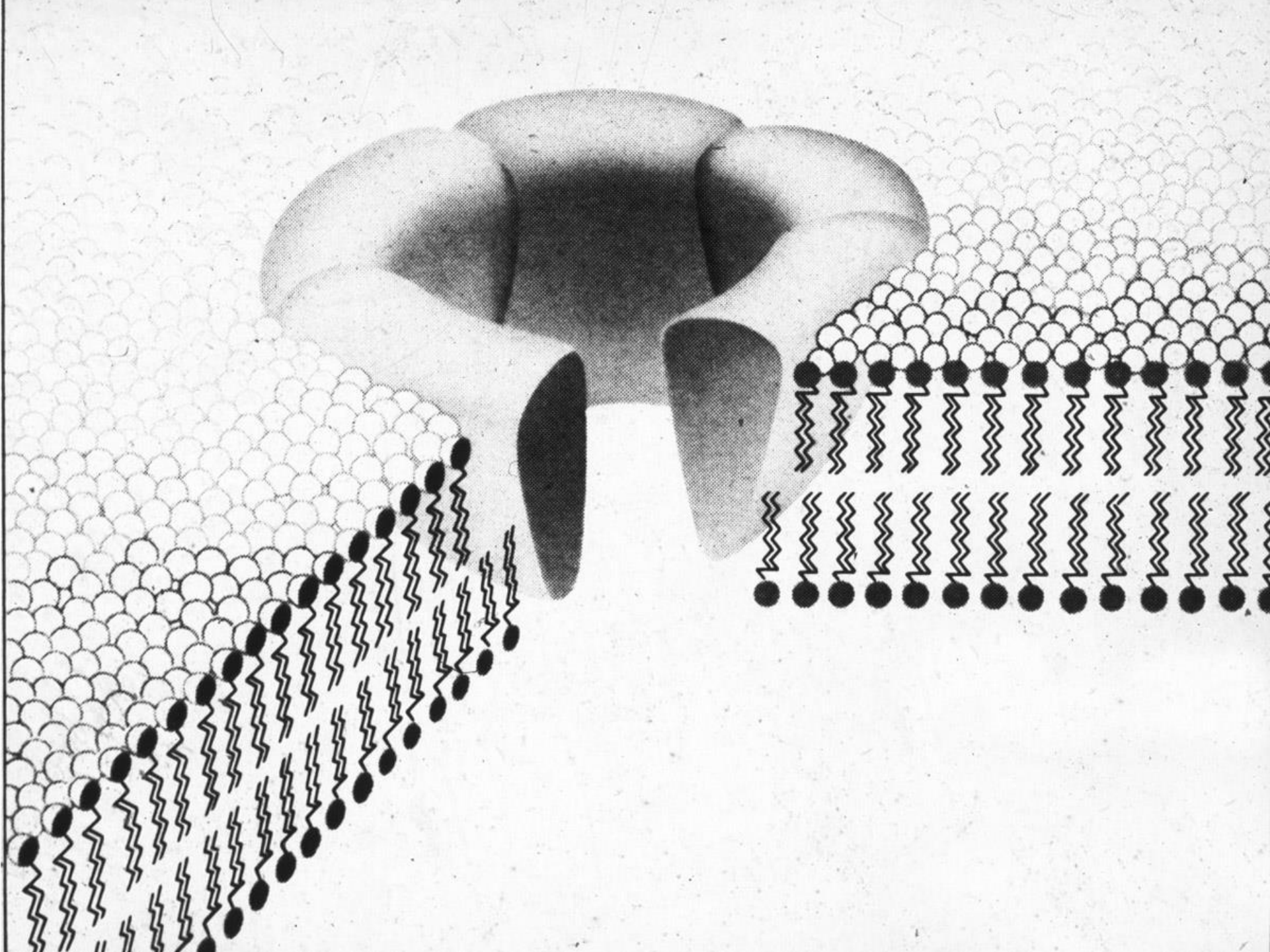
- *Riedl, Thorn and Licht 2017*

- **Causes:**

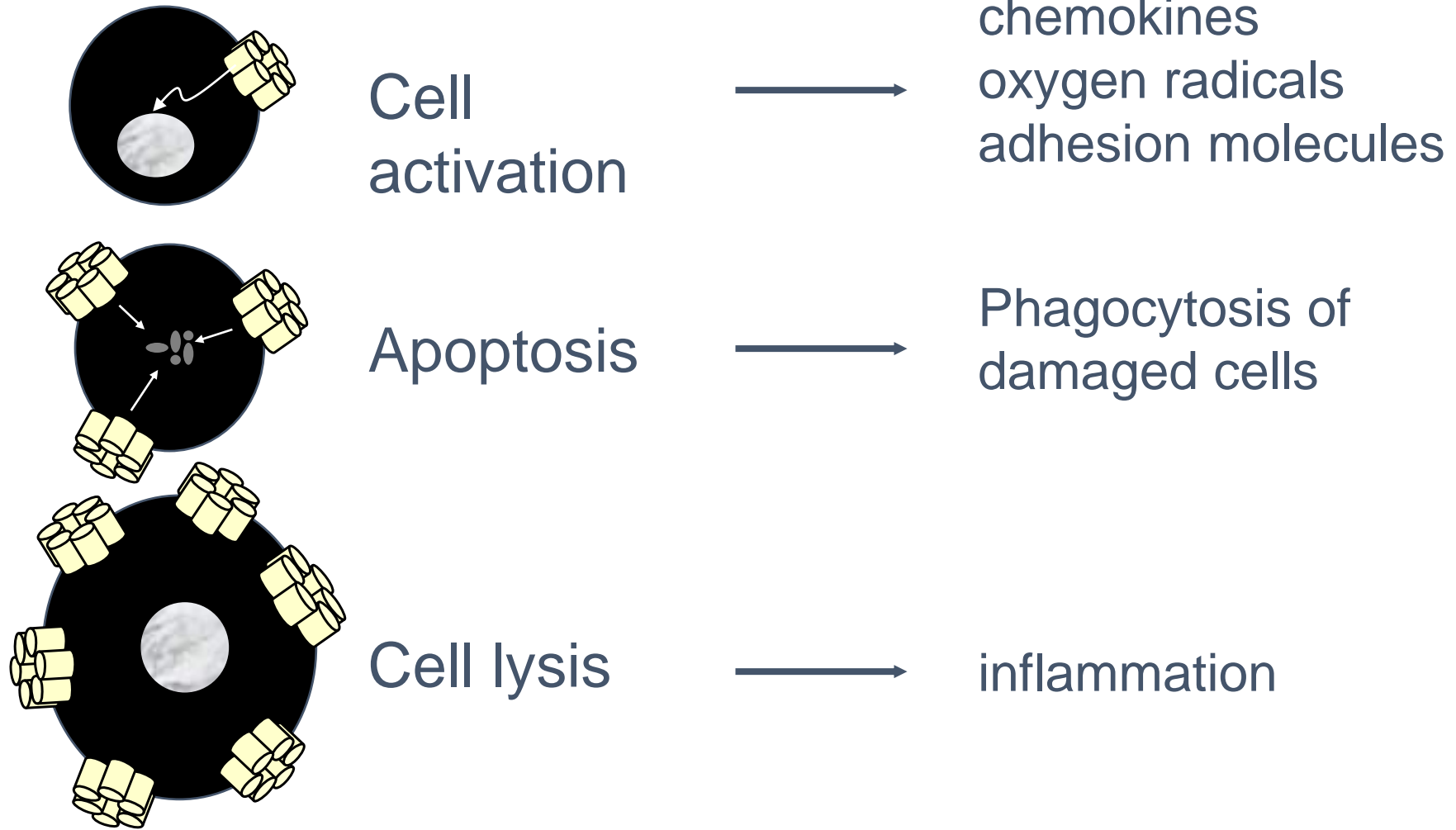
- *deregulation of FF and Membrane regulators, gain of function mutations etc.*

The complement system: Terminal pathway

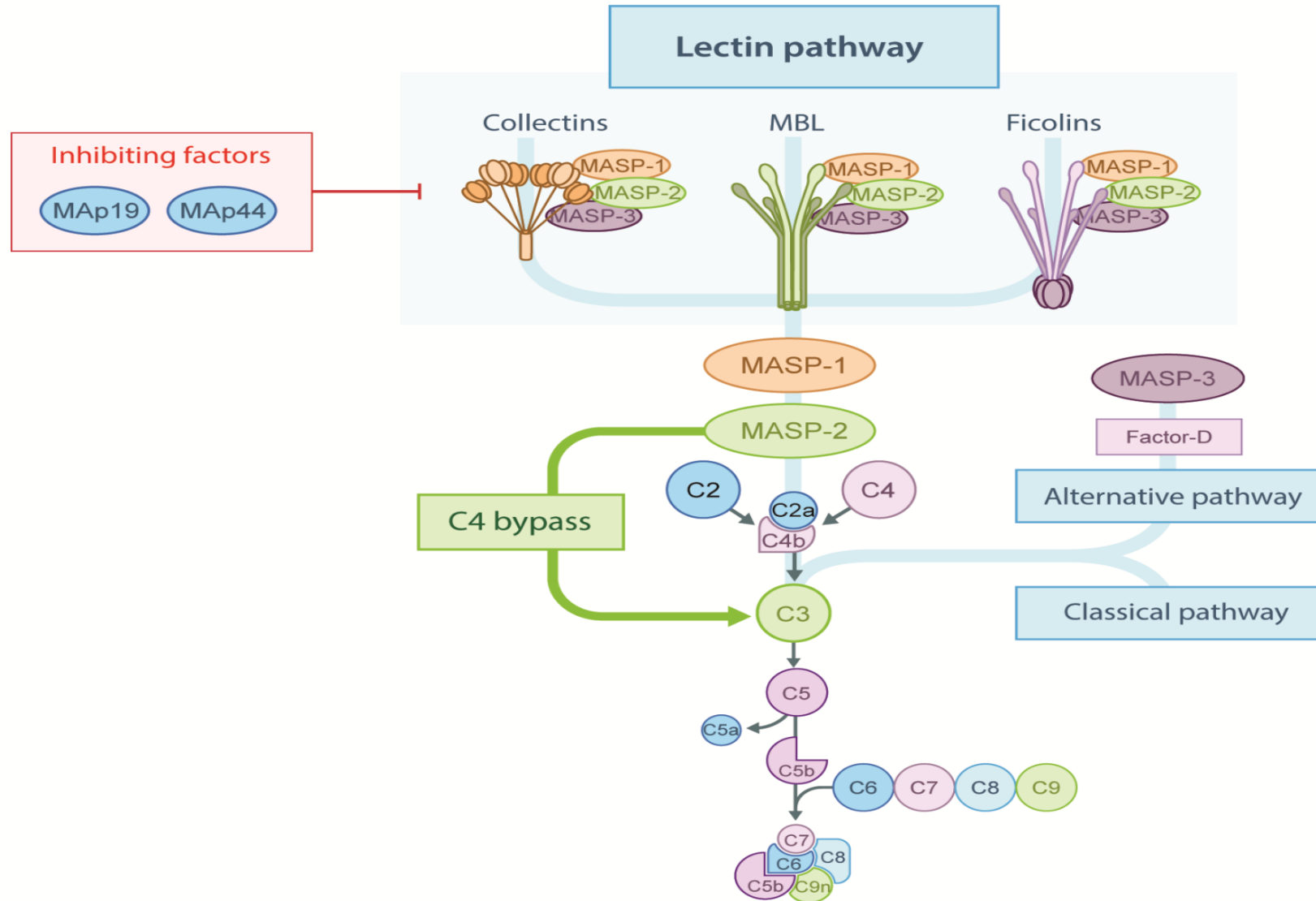




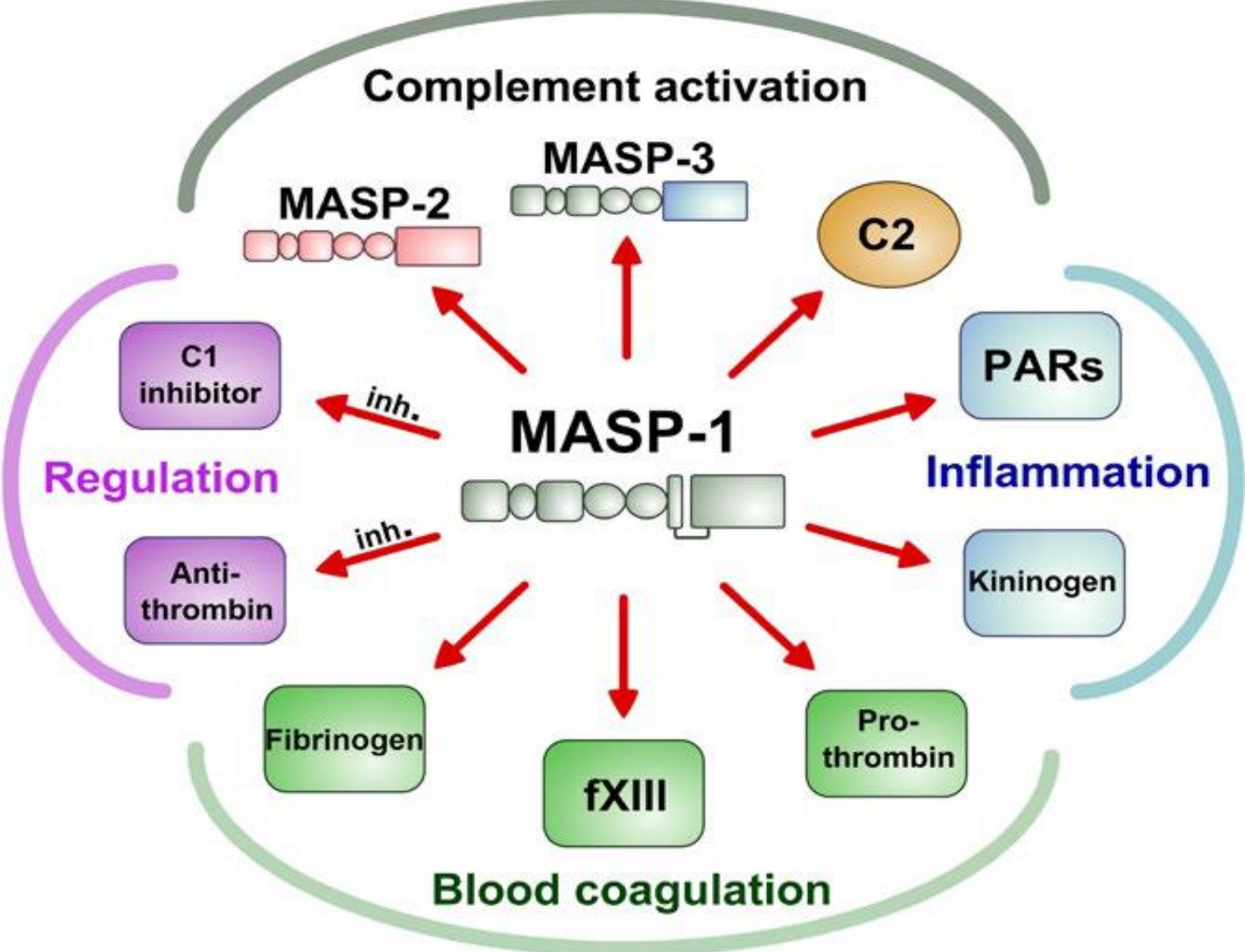
Dose-dependent effects of terminal complement C5b-9



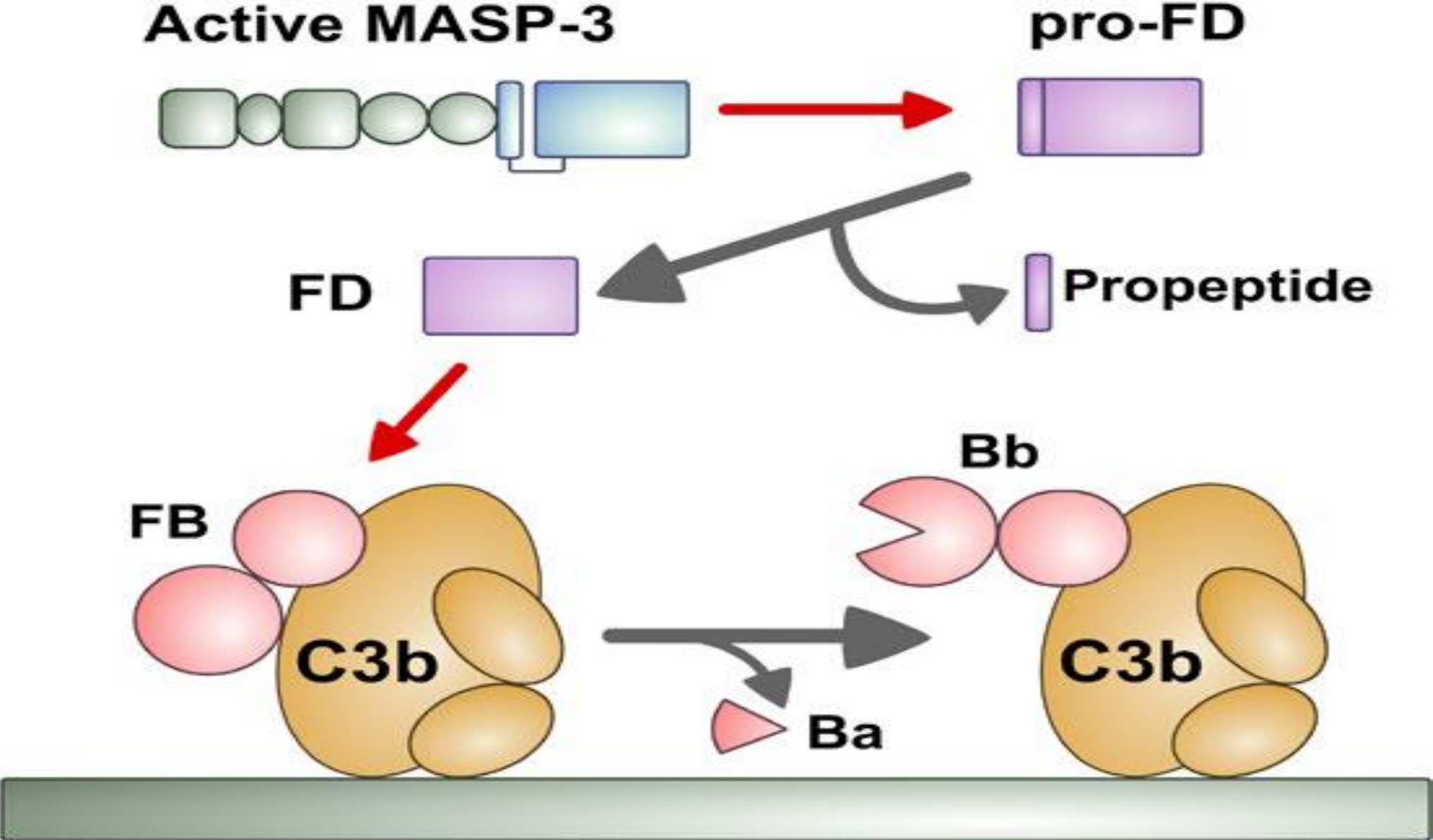
Overview of the C4 bypass mechanism



Promiscuity of MASP-1: *it's many functions*



Link between the Lectin pathway and Alternative pathway following MASP-3 activation

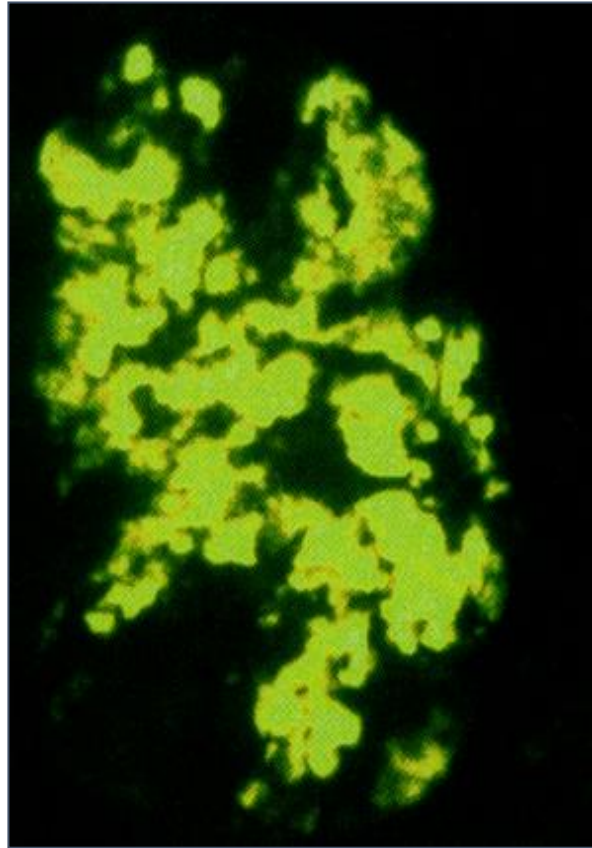


Question

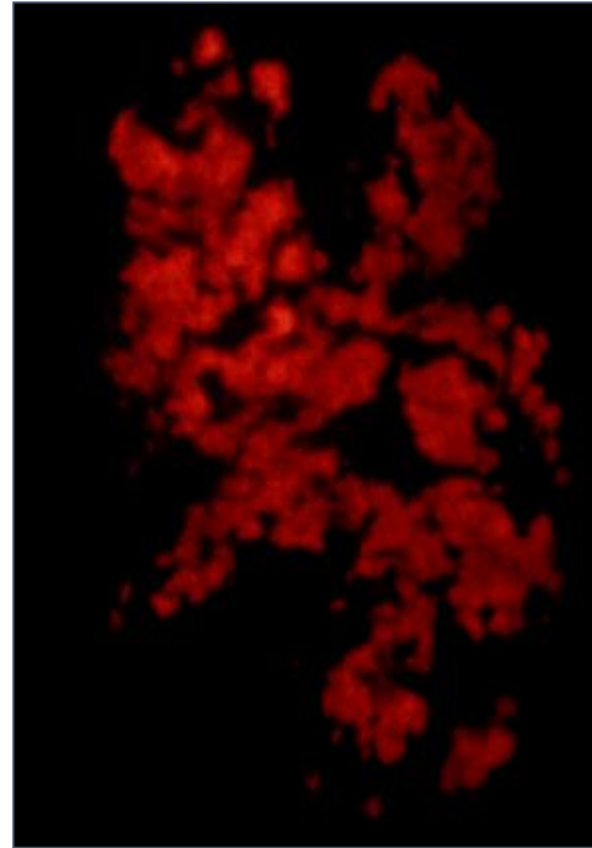
More to know about complement activation in IgAN?

Mesangial IgA deposition in the glomerulus of a patient with IgAN

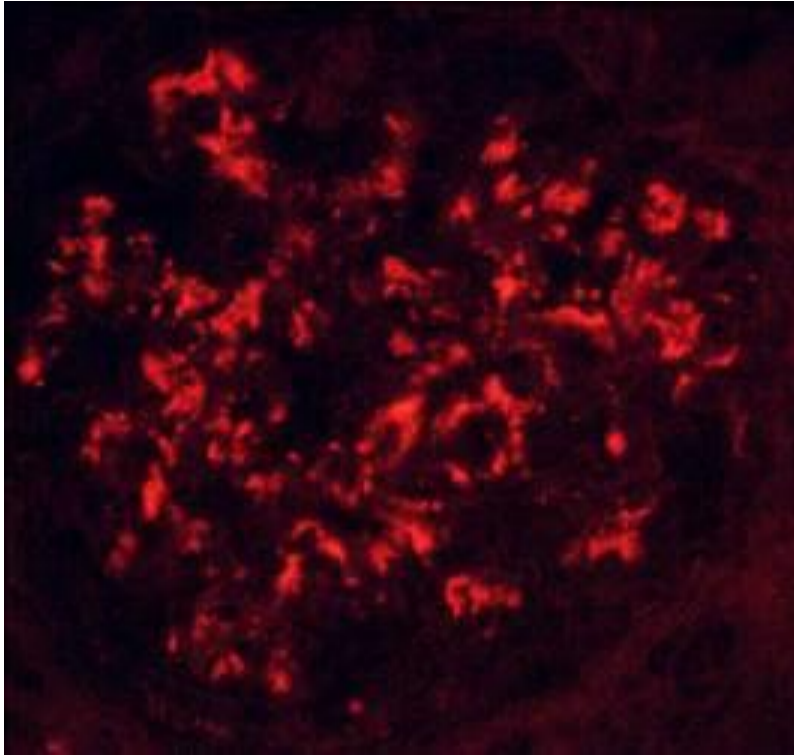
IgA staining



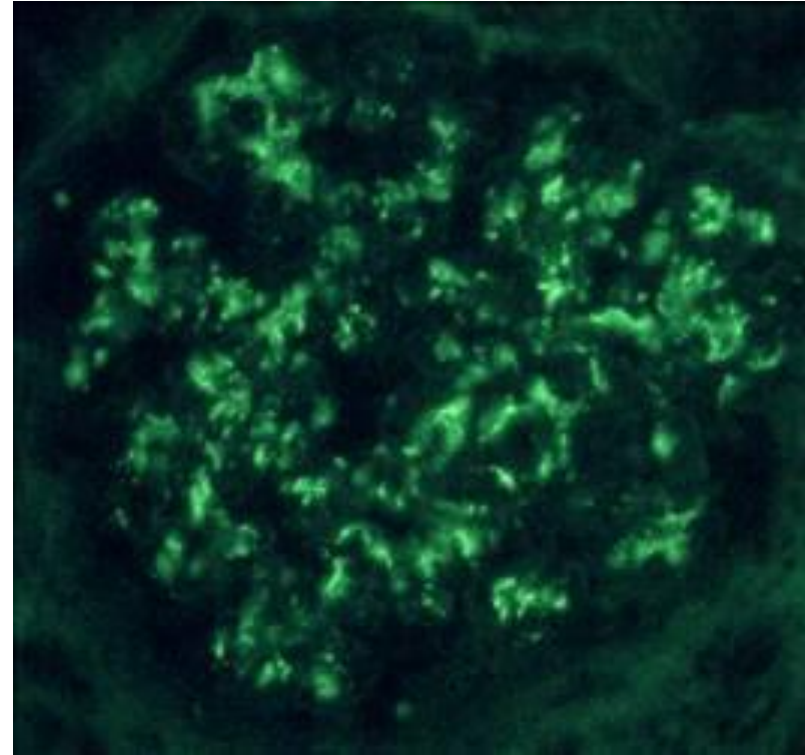
IgA1 staining



Complement activation in IgA nephropathy



Immunoglobulin A



C3

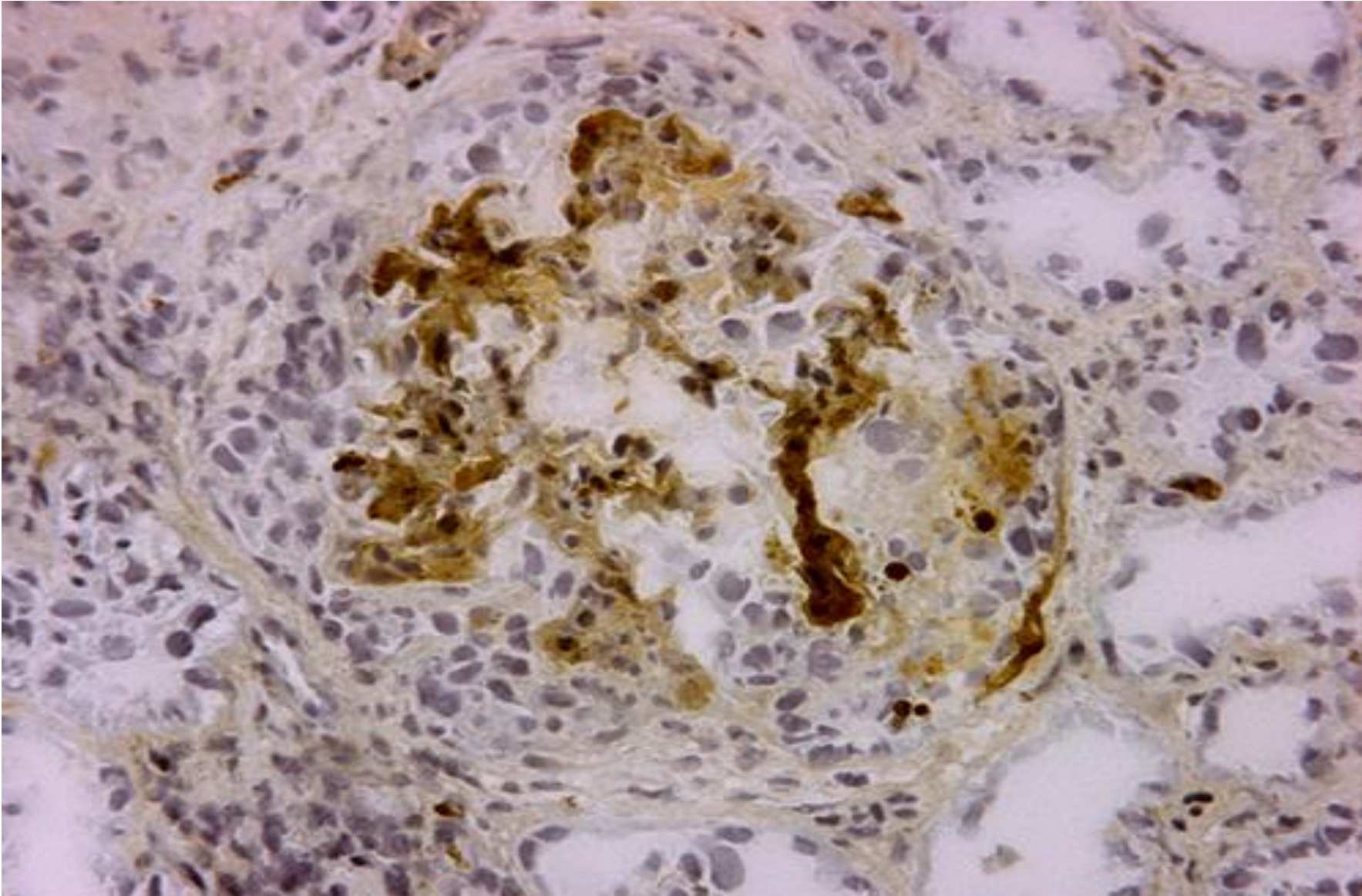
IgAN and complement

Various studies have indicated that the alternative pathway of complement is activated in IgAN

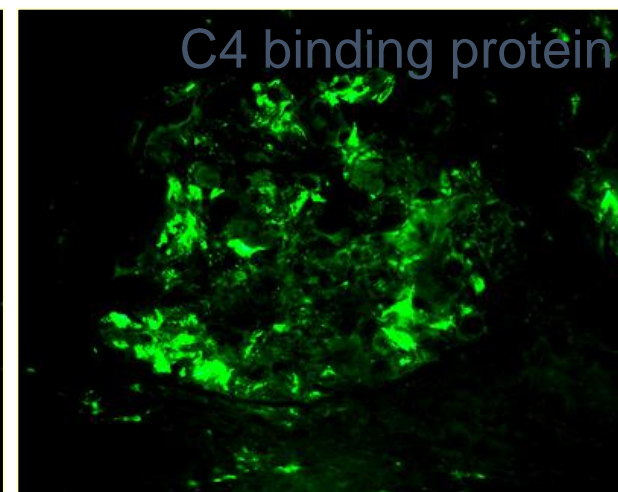
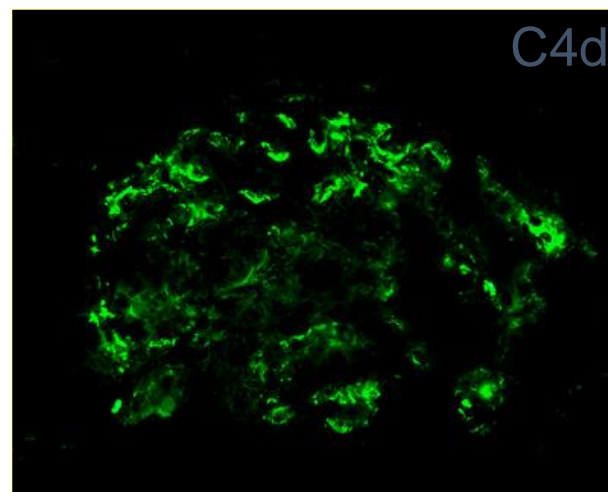
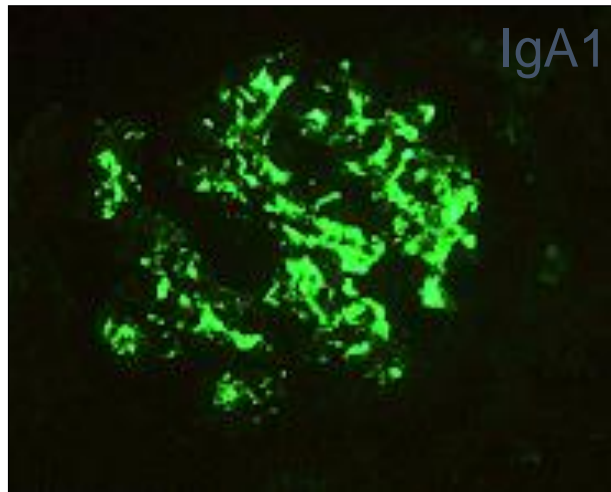
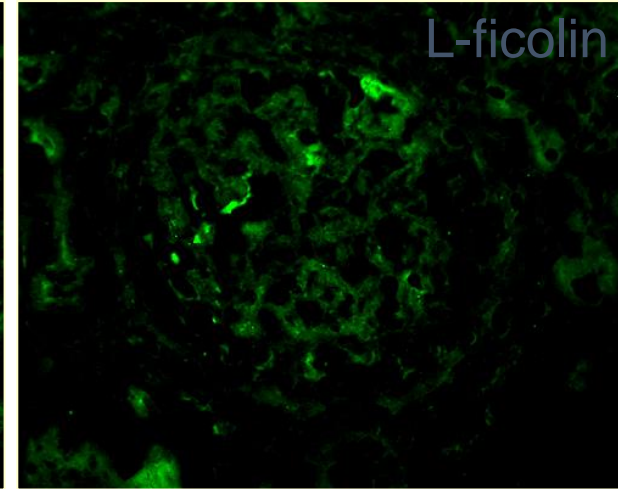
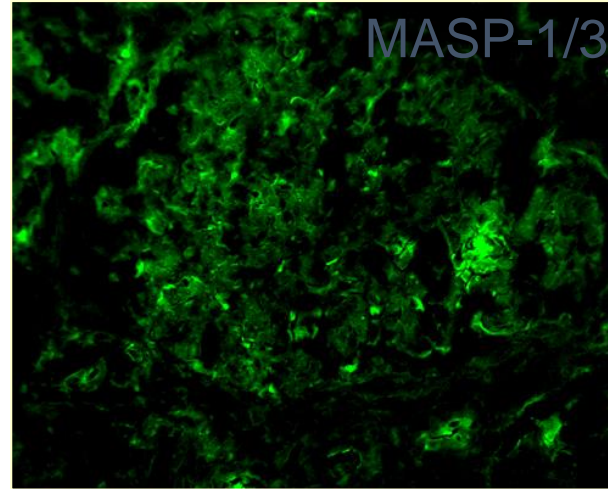
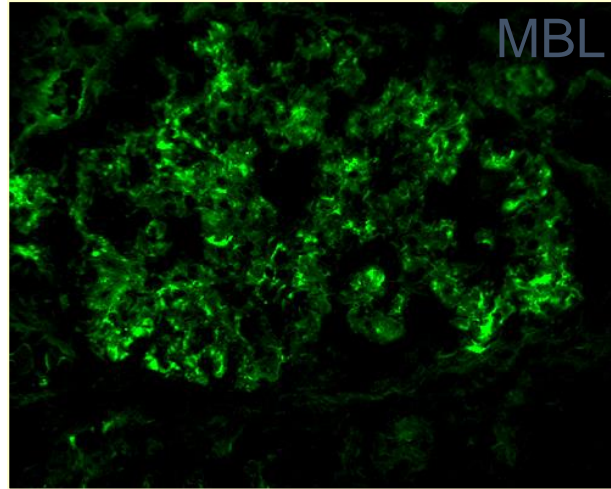
There is strong evidence that this is associated with deposition of the terminal complex, C5b-9 in biopsies of patients with IgAN

Is there also a role for the MBL pathway in IgAN?

Glomerular MBL deposition in IgA nephropathy



Glomerular deposition of MBL and L-ficolin in IgA nephropathy



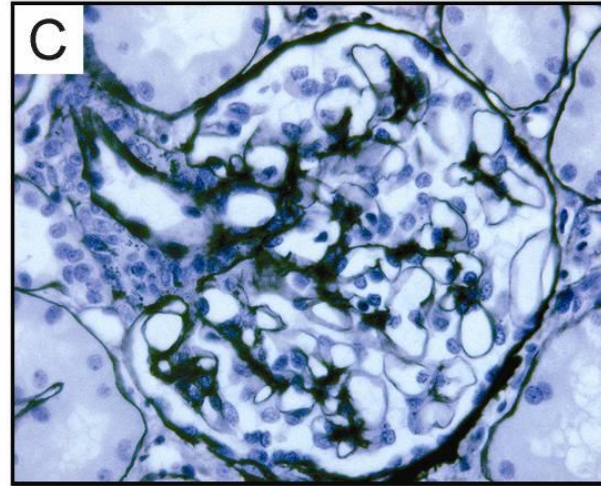
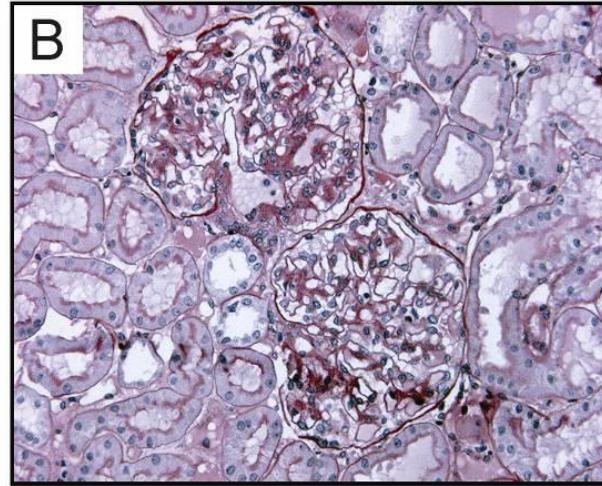
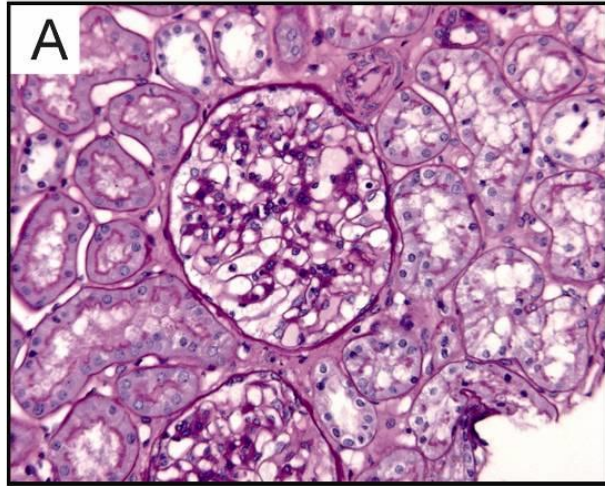
Glomerular C4 activation in IgA nephropathy is restricted to cases with MBL and ficolin deposition

MBL staining	MASP-1/3	L-ficolin	C4d	C4 binding protein	C1q	C3	IgA1	IgA2
Positive (15)	100 %	100 %	100 %	100 %	0 %	60 %	100 %	0 %
Negative (45)	0 %	0 %	0 %	0 %	0 %	82 %	100 %	0 %

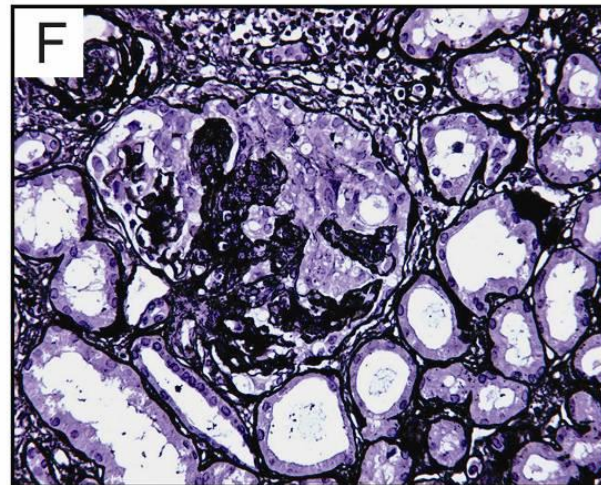
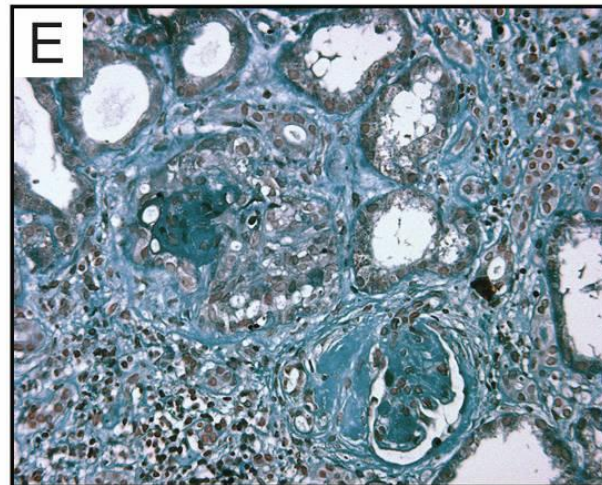
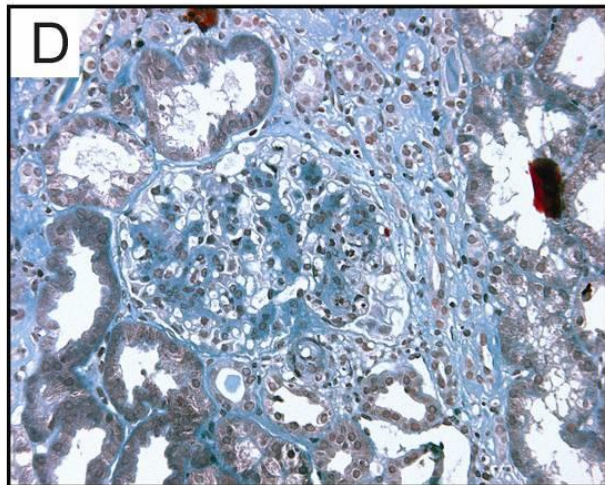
Two patterns of glomerular complement activation in IgAN

MBL staining	Lectin pathway							IgA1	IgA2
	MASP	L-ficolin	C4d	C1q	C3	C5b-9			
Positive (25 %)	100 %	100 %	100 %	0 %	60 %	100 %	100 %	0 %	
Negative (75 %)	0 %	0 %	0 %	0 %	82 %	100 %	100 %	0 %	
	Alternative pathway								

MBL-positive IgAN cases show more glomerular and interstitial damage

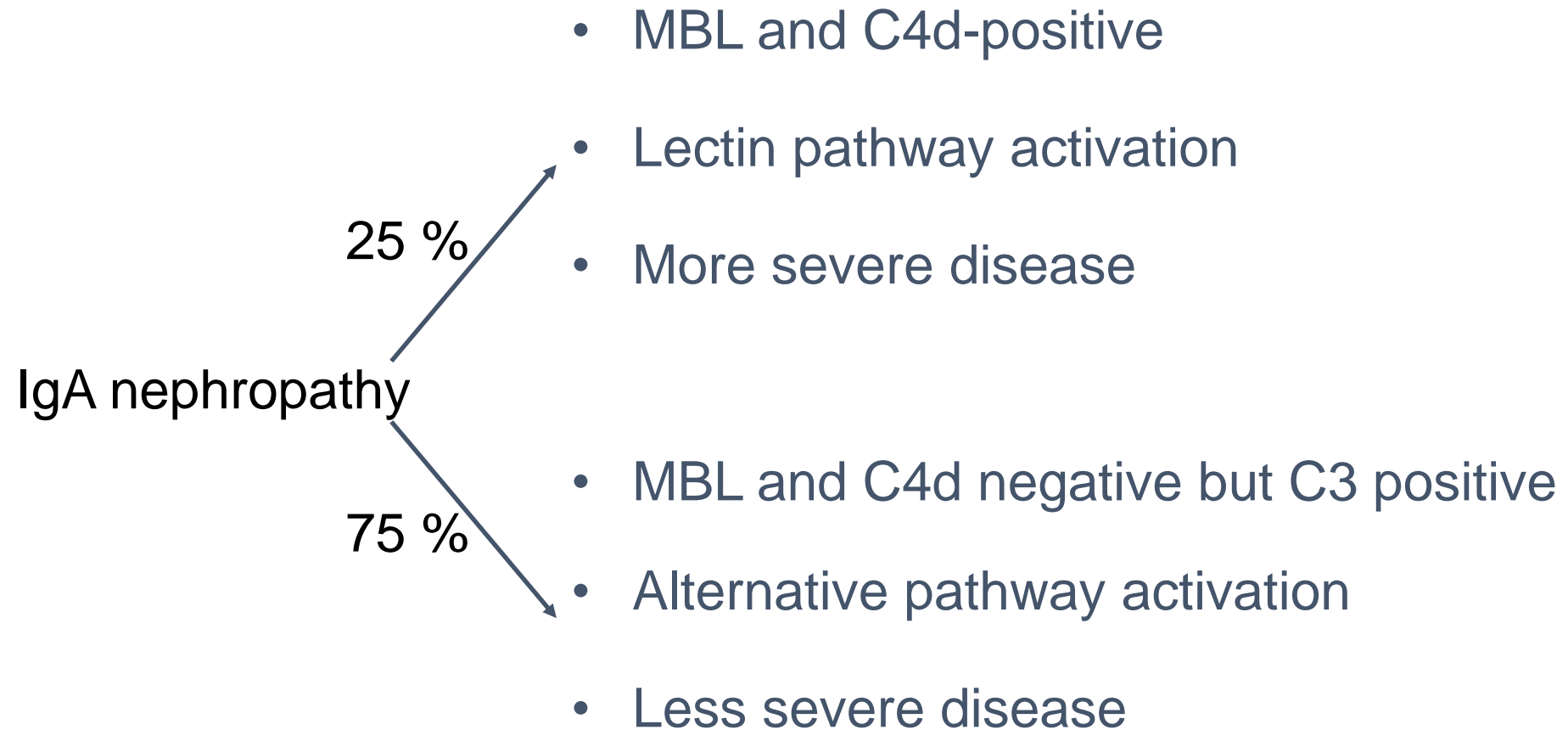


*MBL-
neg*

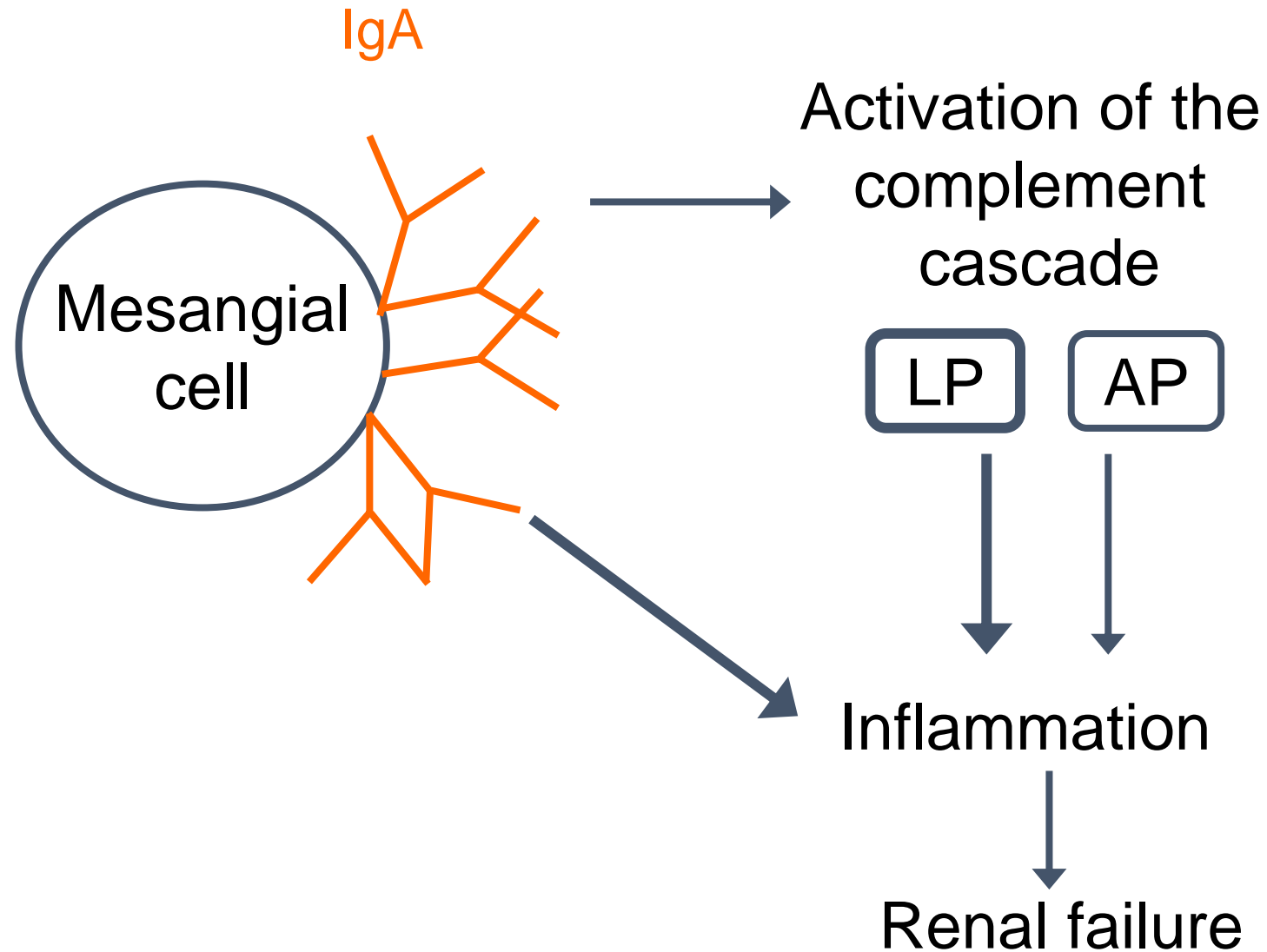


*MBL-
pos*

Lectin pathway activation in IgA nephropathy



Complement activation by IgA in IgA nephropathy



- Modulation of Complement with drugs

Ongoing Trials with complement inhibitors

<i>Trial ID</i>	<i>Target</i>	<i>Compound</i>	<i>Company</i>	<i>Design</i>
NCT03608033	MASP-2	Monoclonal antibody, intravenous injection	Omeros	Randomized, double-blind, placebo-controlled, Phase 3 study
NCT03453619	C3	Pegylated peptide, subcutaneous injection	Apellis Pharmaceuticals	Single arm open-label Phase 2 study
NCT04578834	Factor B	Small-molecule, orally administered	Novartis	Multi-center, randomized, double-blind, placebo-controlled, Phase 3 study
NCT04014335	Factor B	Antisense oligonucleotide, subcutaneous injection	Ionis Pharmaceuticals	Single arm open-label Phase 2 study
NCT04564339	C5	Monoclonal antibody, intravenous injection	Alexion Pharmaceuticals	Randomized, double-Blind, placebo-Controlled Phase 2 study

continued

NCT03841448 C5 -Small interfering RNA –subcutaneous injection - Alnylam Pharmaceuticals Randomized, -double-blind, placebocontrolled Phase 2 study *Ongoing*

NCT02384317 C5aR1 -Small-molecule, -orally administered - Chemocentryx -Single arm open-label Phase 2 study
Completed

