

## THE COMPLEMENT SYSTEM AND RELATED KIDNEY DISEASES





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The complement system is triggered by the detection of non-host, pathogen and damage-associated molecular patterns by any of the **three** up-stream pathways:

the <b>Classical</b> (see left)	Lectin (see top)	Alternative (see right)	
The <b>Classical Pathway</b> is triggered when the C1q complex (C1q+C1r+C1s) binds immune complexes.	The Lectin Pathway is triggered when its complex of pattern recognition molecules (MBL, collectins (Col) or ficolins (Fic)) and MBL-associated proteins (MASP) bind carbohydrate moieties, typically on immunoglobulin or cell surfaces.	The Alternative Pathway is constitutively activated by the spontaneous hydrolysis of the C3 thioester bond to form C3(H <sub>2</sub> O). This reveals a promiscuous thioester domain that binds nearby surfaces and molecules.	
	Complement initiation via the classical and lectin pathways cleaves and activates C4 and C2 to form a C3 convertase, C4bC2b.	Activated C3 (C3(H <sub>2</sub> 0) or C3b) interacts with factor B (FB), which has itself been activated by factor D (FD), to form a C3 convertase (C3bBb). The C3 convertase cleaves and activates C3 to C3b and C3a, an anaphylatoxin.	
All th	nree triggering branches converge at C3 amplification (see ce	enter).	
This occurs via an amplification loop w As the density of C3b increases, b	hereby C3b forms new C3 convertases (C3bBb), which them inding of additional C3b to existing C3 convertases form C5 c	selves activate more C3 to C3b and C3a. onvertases (C4b2aC3b, C3bBbC3b).	
C5 convertases activate the terminal p C8, and several C9 mol	athway by cleaving C5 into C5b and C5a, a potent anaphylate ecules forms the membrane attack complex (C5b9), which ca	oxin (see bottom). C5b binding to C6, C7, auses target cell damage.	
Several fluid phase and membr	ane-bound regulators tightly control complement activation	at various steps of the pathway.	
Eactor H (H) is the major possible res	sulator of the alternative Nearly all calls everys me	ambrana bound regulators including CD46	

Factor H (H) is the major negative regulator of the alternative pathway and, with factor I (FI), controls C3b formation (see center).

Nearly all cells express membrane bound regulators including CD46 (MCP), CD55 (DAF), CD35 (CR1), and CD59. Properdin (P) stabilises the alternative pathway C3 convertase and is the only known positive regulator of the complement system.

Evidence of complement activity has been identified in a wide range of kidney disease and indicates the complement system is an important, pathogenic factor for many patients. These include, but are not limited to:

<ul> <li>Anti GBM Disease,</li> <li>Cryoglobulinaemia,</li> <li>IgA nephropathy (IgAN),</li> <li>focal segmental glomerulosclerosis (FSGS),</li> <li>and ANCA associated vasculitis (AAV).</li> </ul>	•	lupus nephritis (LN),	•	antibody mediated rejection (ABMR) of	•	C3 glomerulopathy (C3G),	1
<ul> <li>Cryoglobulinaemia,</li> <li>IgA nephropathy (IgAN),</li> <li>focal segmental glomerulosclerosis (FSGS),</li> <li>and ANCA associated vasculitis (AAV).</li> </ul>	•	Anti GBM Disease,		transplanted kidney,	•	post infectious glomerulonephritis (PIGN),	
IgA nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), and ANCA associated vasculitis (AAV).	•	Cryoglobulinaemia,	•	membranous nephropathy (MN),	•	atypical haemolytic uraemic syndrome (aHUS),	
	•	IgA nephropathy (IgAN),	•	focal segmental glomerulosclerosis (FSGS),	•	and ANCA associated vasculitis (AAV).	





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## **ABBREVIATIONS**

Abbreviation	Meaning
AAV	ANCA Associated Vasculitis
ABMR	Antibody Mediated Rejection (ABMR) of Transplanted Kidney
aHUS	Atypical Haemolytic Uraemic Syndrome
C1q+C1r+C1s	C1q complex
C3(H2O) or C3b	Activated C3
C3bBb	a C3 Convertase
C3G	C3 Glomerulopathy
C4b2aC3b, C3bBbC3b	C5 Convertases
C4bC2b	A C3 Convertase
C5b9	the membrane attack complex
СМКД	Complement-Mediated Kidney Disease
FB	Factor B
FD	Factor D
FI	Factor I
FSGS	Focal Segmental Glomerulosclerosis
Н	Factor H
IgAN	IgA Nephropathy
LN	Lupus Nephritis
MASP	MBL-associated proteins
MBL	Mannan binding lectin
MBL/Co/Fic	MBL, collectins (Col) or ficolins (Fic)
MN	Membranous Nephropathy
Р	Properdin
PIGN	Post Infectious Glomerulonephritis

## **GENERAL COMPLEMENT SYSTEM REFERENCES:**

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For funding and support information, see: https://www.theisn.org/initiatives/toolkits/complement-mediated-kidney-disease-toolkit/#Support