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The Complement System in ANCA Vasculitis

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Innate and acquired immunity

Innate immunity

Cells:

NK cells
macrophages
dendritic cells
granulocytes

Soluble mediators:

Cytokines
Chemokines
Defensins
Pentraxins
Complement
Etc.

Acquired immunity

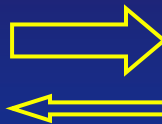
Cells:

T lymphocytes
B lymphocytes

Soluble products:

Cytokines
Chemokines

Antibodies



Sensing Functions of Complement

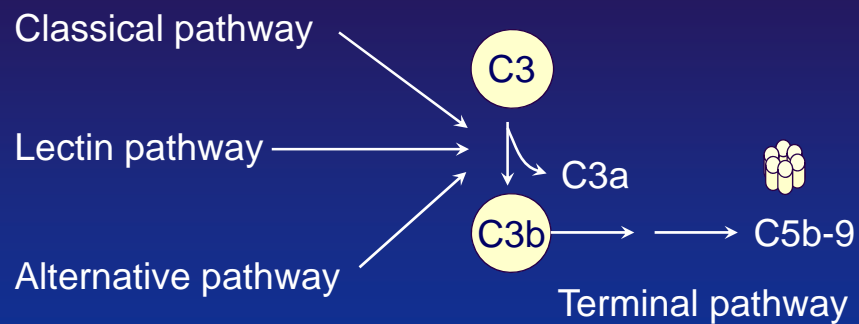
Recognition of non-self ligands:

- pathogens: viruses, bacteria, yeast, parasites

Recognition of altered self ligands:

- apoptotic and necrotic cells
- damaged tissue, tissue debris
- ischemic endothelium
- aberrant glycosylation

The complement system

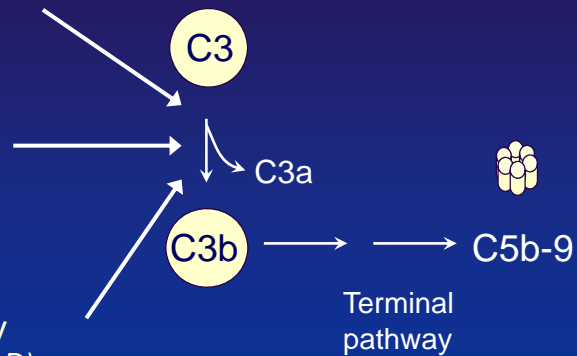


Recognition molecules of the complement system

Classical pathway
(**C1q**, C1r, C1s, C4, C2)

Lectin pathway
(**MBL, Ficolins**, MASPs, C4, C2)

Alternative pathway
(**Properdin**, factor B and D)

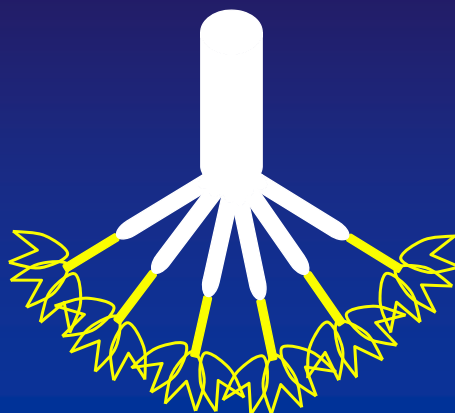


Oligomerization of MBL structural units

Trimeric structural subunit



Hexamer of trimeric subunit



Domain binds to:

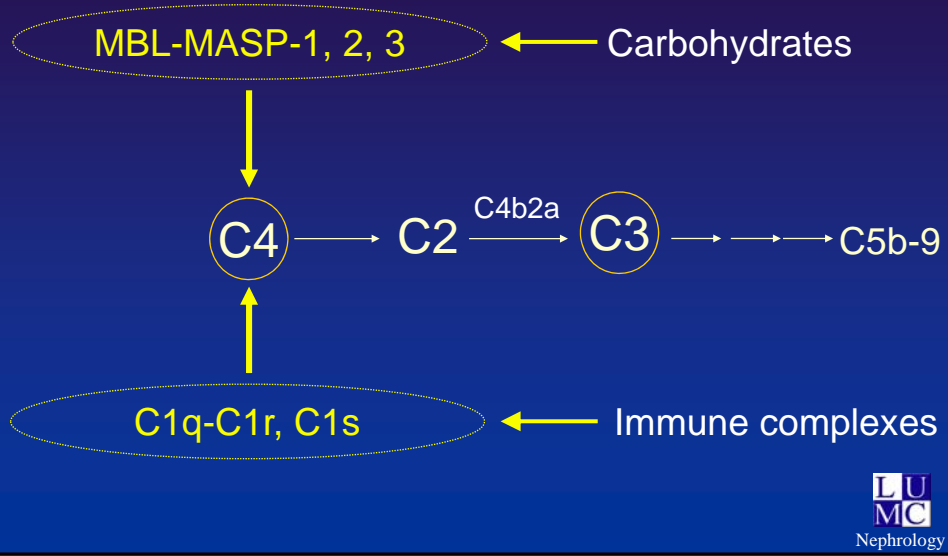
Collectin receptor

MASP-1, MASP-2,
MASP-3, sMAP

Carbohydrates:

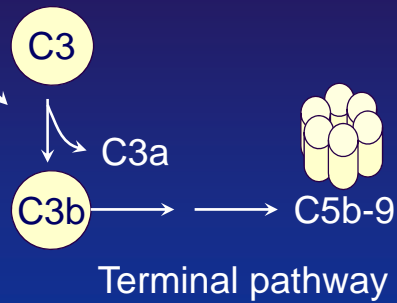
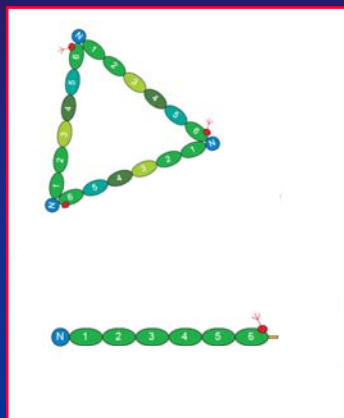
Mannose, Fucose,
GlcNAc, ManNAc

Similarity between the MBL pathway and the classical pathway of complement

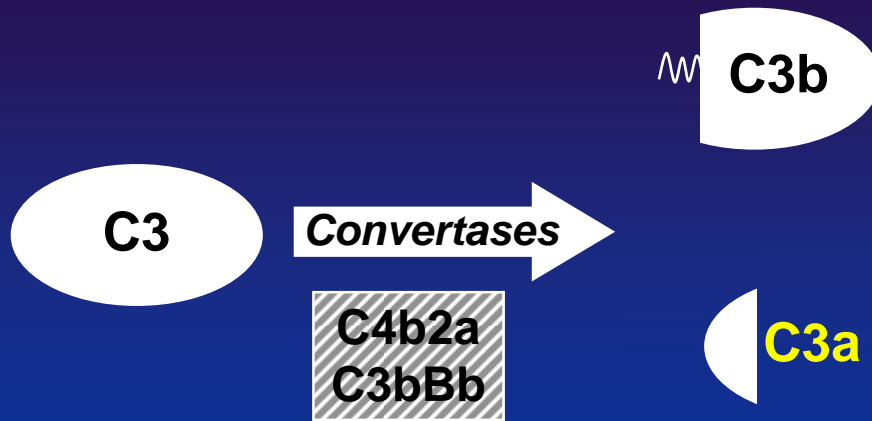


Sensors of the Complement System: Properdin comes in two flavors

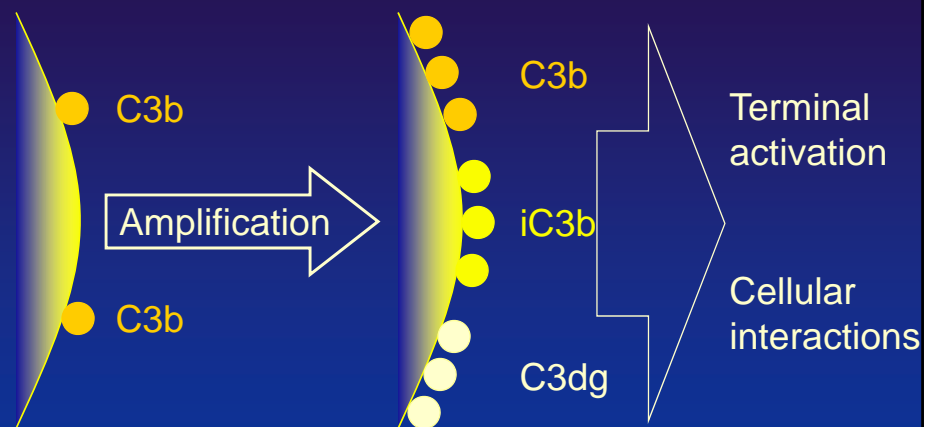
Alternative pathway
Properdin



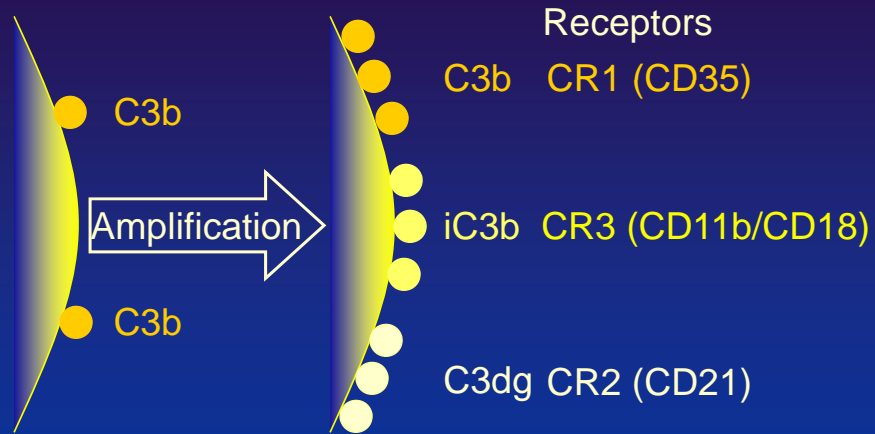
Activation of C3



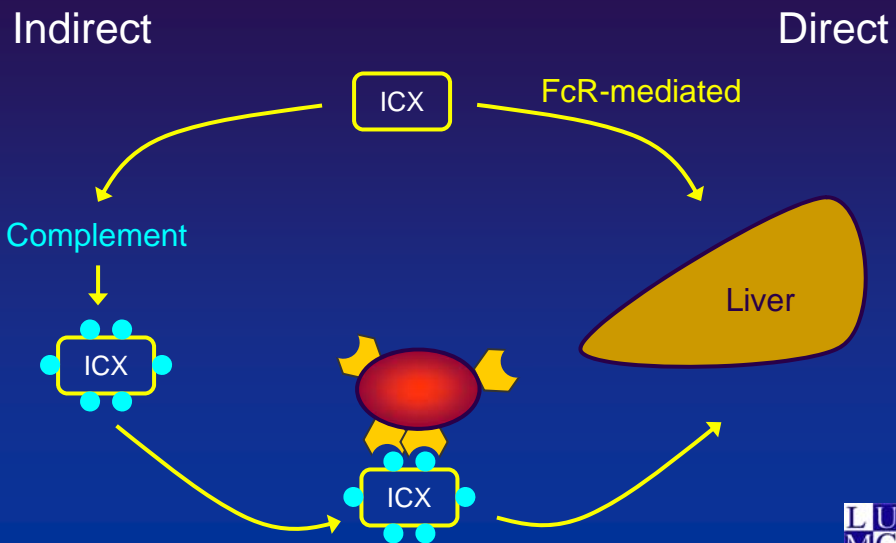
C3 deposition



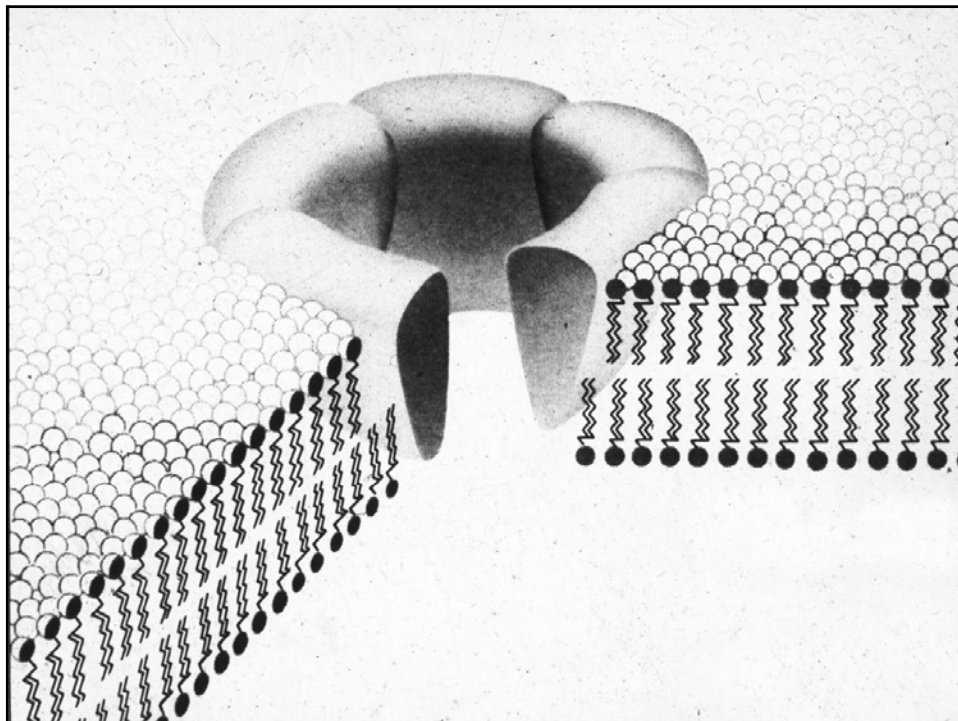
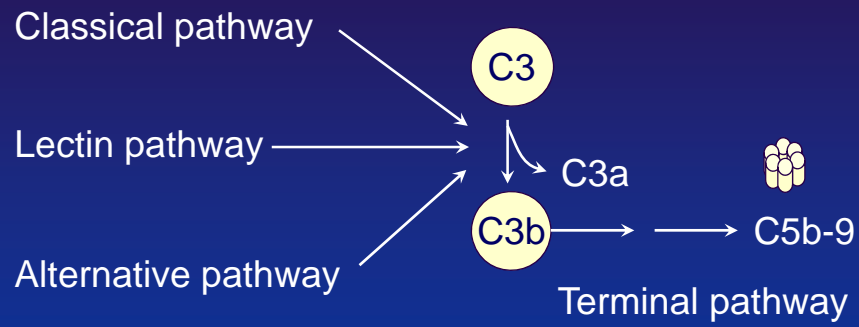
C3 deposition and receptor interactions



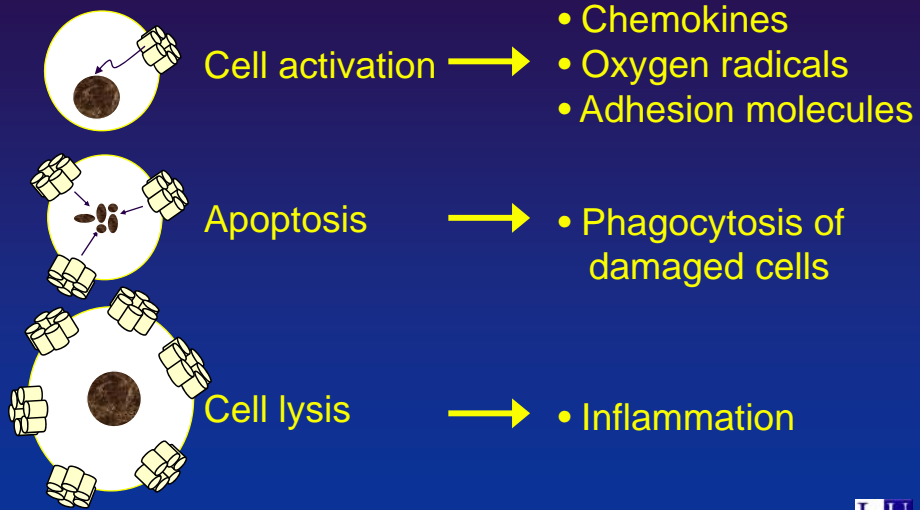
Immune complex clearance in humans



The terminal pathway of complement

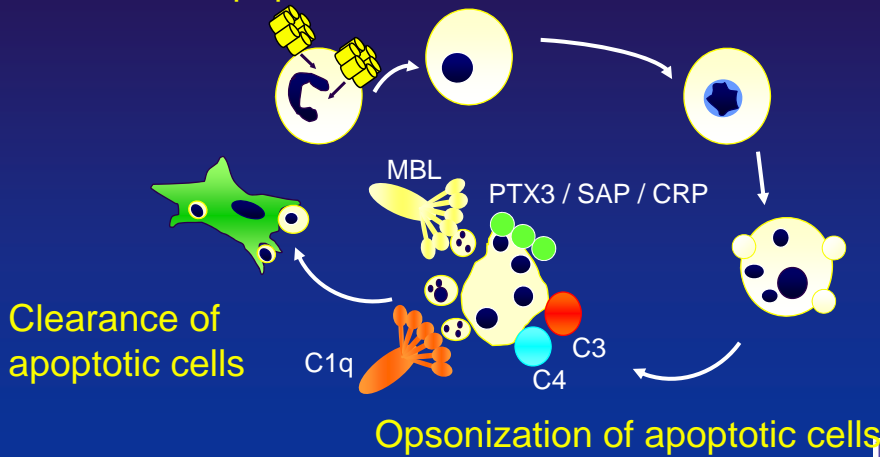


Dose-dependent effects of terminal complement complexes



Membrane Flip-flop and Loss of Complement Control

Induction of apoptosis



Regulation of Complement activation

Regulation of Complement activation occurs at least at three levels:

In the fluid Phase

At the tissue level

And is also determined by the integrity of the tissue itself(apoptosis or necrosis)

Fluid phase complement regulators

Molecules

- C1 inhibitor
- C4 binding protein
- Factor H
- Factor I

Level of inhibition

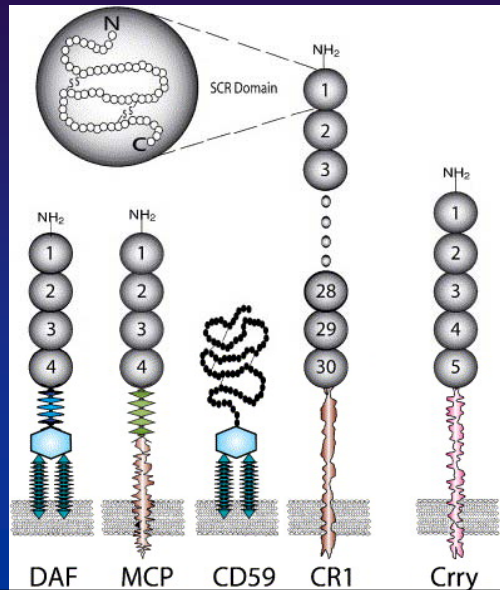
C1r, C1s, MASP's
C4b, C4b2a
C3b, C3bBb
C4b, C3b

Fluid Phase Regulators of C3 convertase activity

Dissociation of C3 convertases **Cofactor for factor I-mediated proteolysis**

protein	C4b2a	C3bBb	C4b	C3b
Factor H	-	+	-	+
C4bp	+	-	+	-
DAF	+	+	-	-
MCP	-	-	+	+
CR1	+	+	+	+

Membrane-bound regulators of complement



From: Kim et al,
Clinical Immunology

Membrane-bound complement regulators

Molecules

- Membrane cofactor protein (MCP, CD46)
- Decay acceleration factor (DAF, CD55)
- CR1
- CD59

Level of inhibition

C3b, C4b

C3bBb, C4b2b

C3b, C4b, C3bBb, C4b2b

C8

Properdin

*A Positive Regulator
of Complement Function*

Functions of Properdin

- Recognition of foreign pathogens and altered self
- Binding of C3(H₂O) and C3b
- Stabilisation of C3bBb

Stability of the Amplification Convertase

<i>Convertase</i>	<i>T</i> ½ (minutes)
C3bBb	1-2
C3bBbP	30-60
C3bBbNeF	90-120

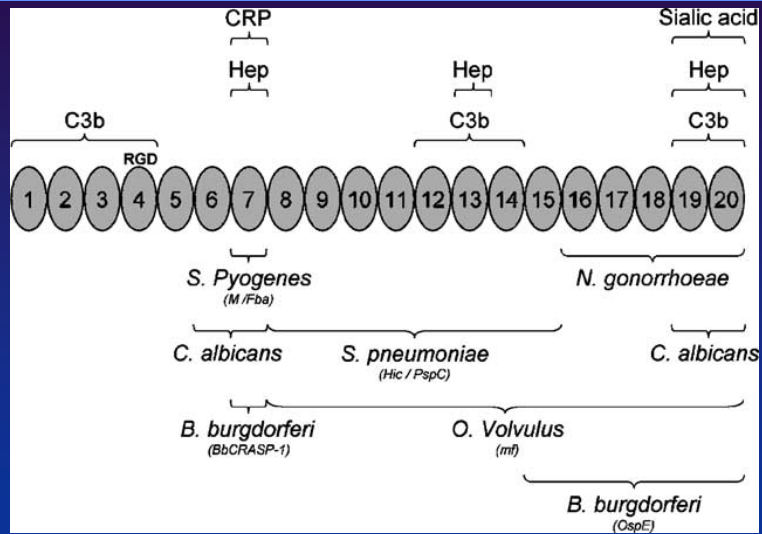
Deregulation of complement and disease

- Age related macular degeneration
- Atypical hemolytic uremic syndrome
- Membrane proliferative glomerulonephritis
- Paroxysmal Nocturnal Hemoglobinuria(PNH)

Deregulation of complement

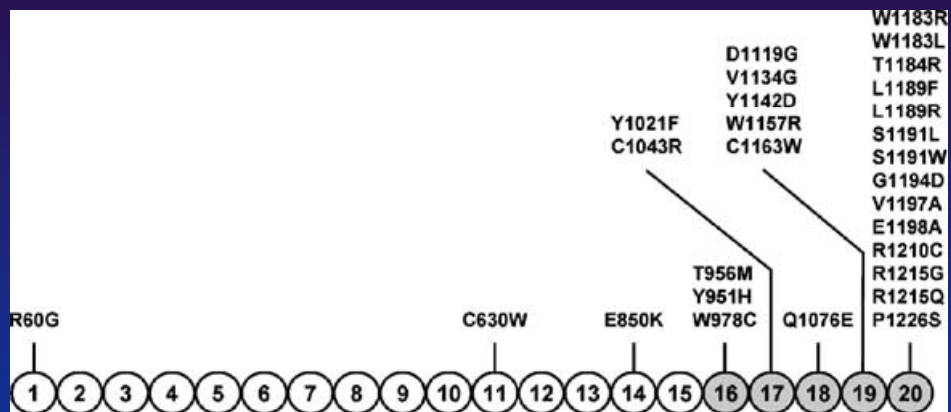
- Mutation in fH, fI, CD46, D55, (C1INH)
- Gain of function: C3, fB
- (Deregulation of properdin?)

Functional domains in factor H



From: Rodriguez de Córdoba, 2004

Factor H missense mutations associated with atypical hemolytic uremic syndrome



From: Rodriguez de Córdoba, 2004

Regulation of Complement activation

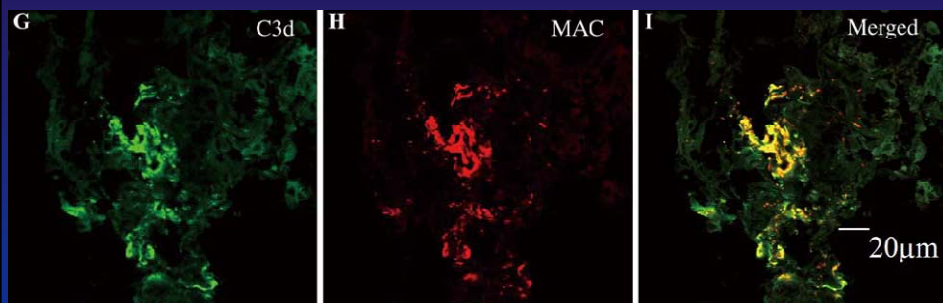
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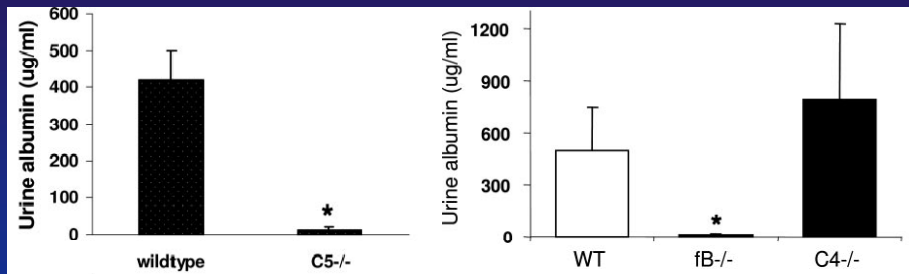
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Alternative Pathway Activation in MPO Vasculitis?



Ming-hui Zhao's Group(Beijing, 2009)

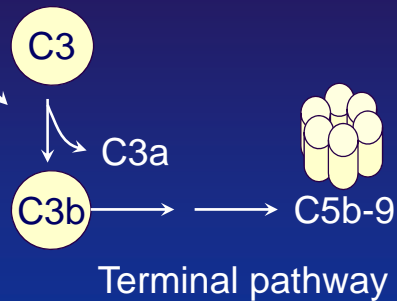
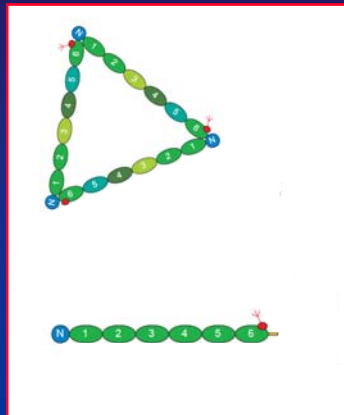
Alternative Pathway Involvement in Experimental MPO model in Mice



Hong Xiao et al, 2007

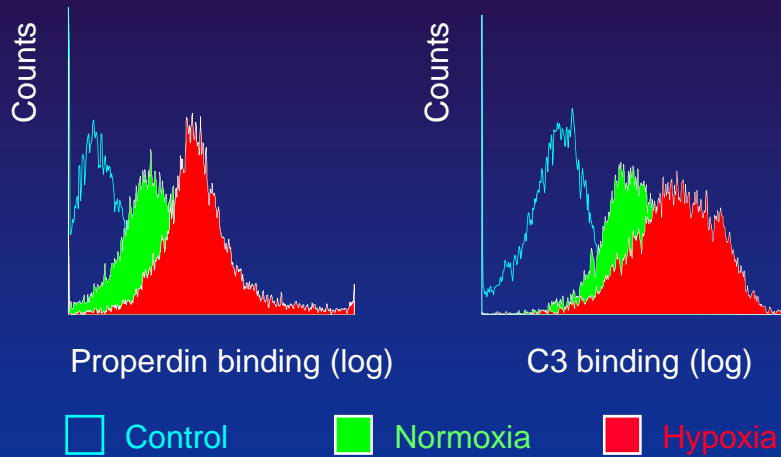
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Alternative pathway
Properdin

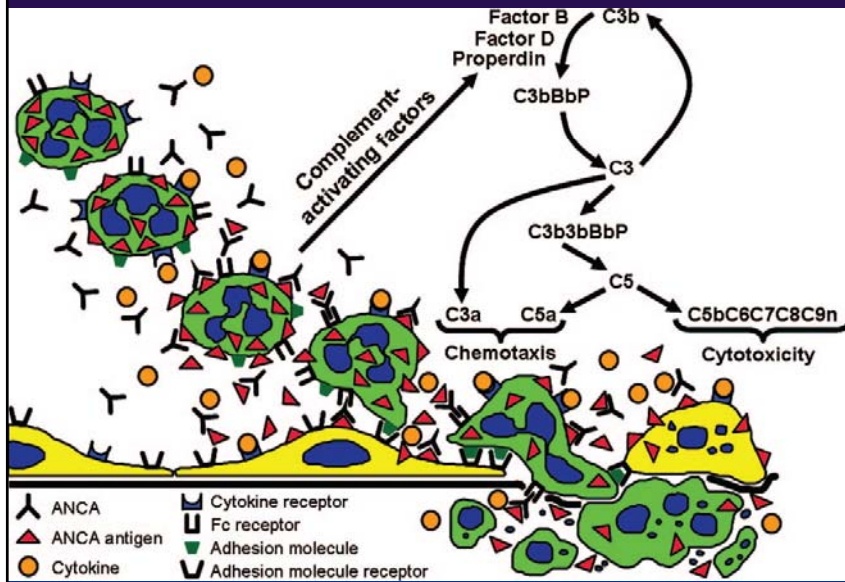


Properdin plays both a role in initiation of complement activation and in stabilization of C3bBb

Properdin displays increased binding to Ischemic Tubular Epithelial Cells and Induces Complement Activation



Role of Complement in Vasculitis: is this model complete or do we need more arrows?



From: Hong Xiao, 2007

Aknowledgements

Cees van Kooten	Wei Xu
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Stefan Berger	