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Thromboinflammation in therapeutic medicine

Bo Nilsson, Uppsala University, Sweden

Höstmöte KITM 30-31th of August, 2017, Uppsala

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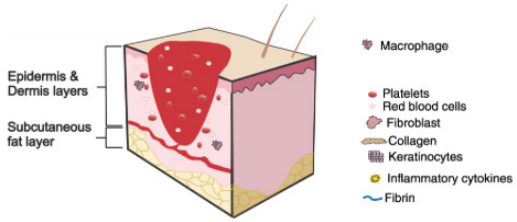
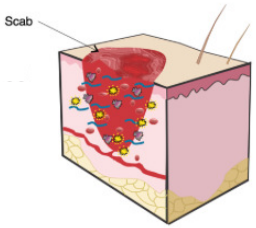
Thromboinflammation

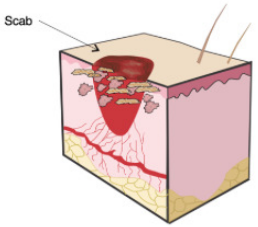
Clot



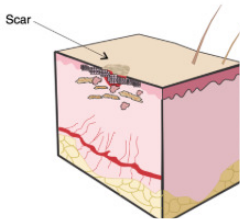
Inflammation



Proliferation



Remodelling



Sowa et al, J Biomed Opt, 2017

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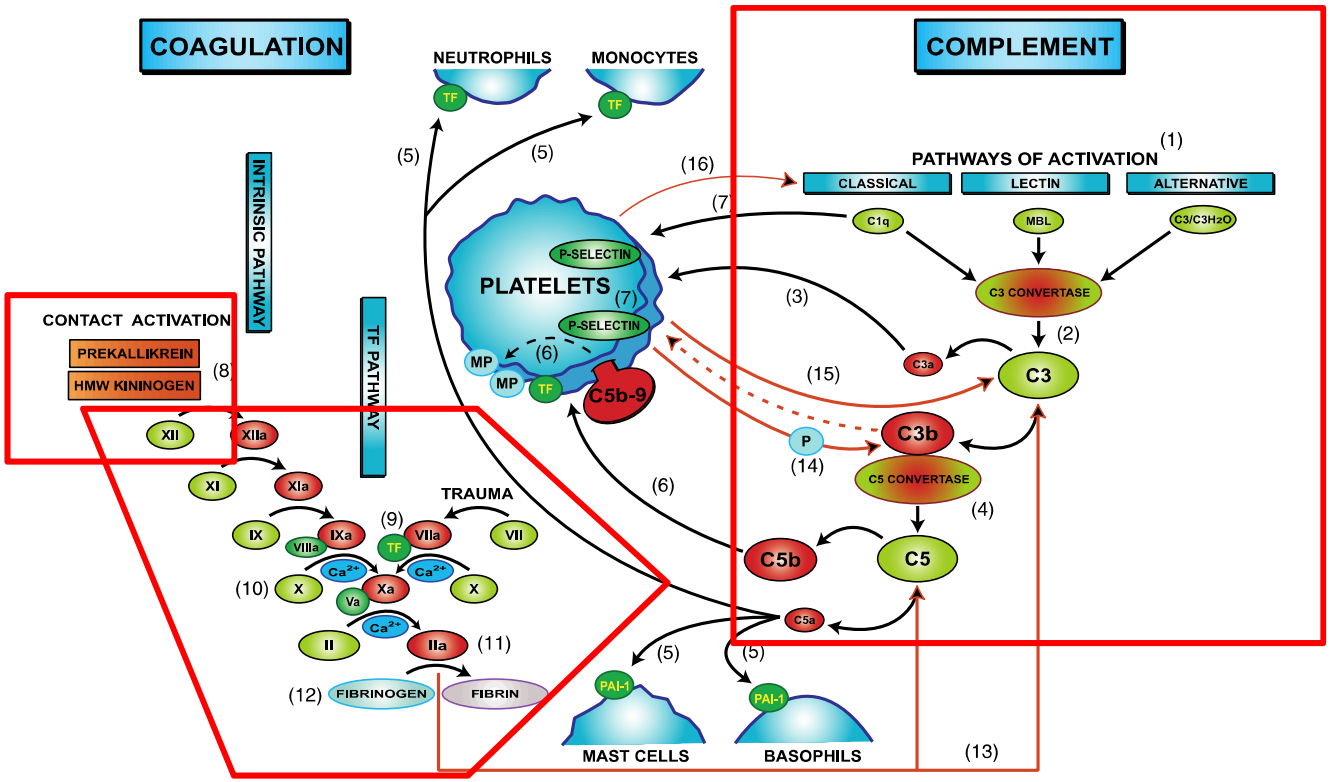
The cascade systems of the blood



Markiewski, Trends Immunol, 2007

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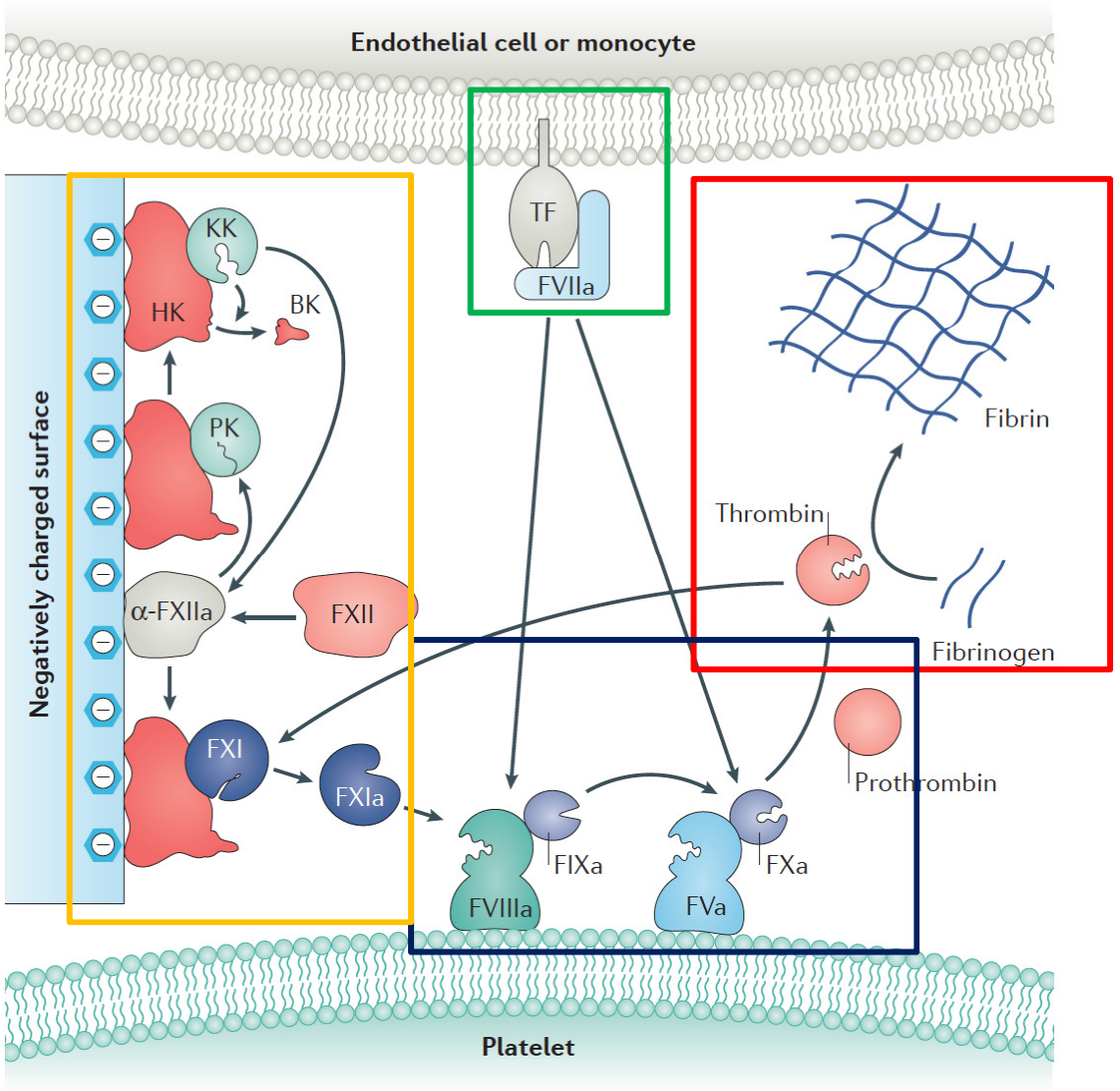
Coagulation



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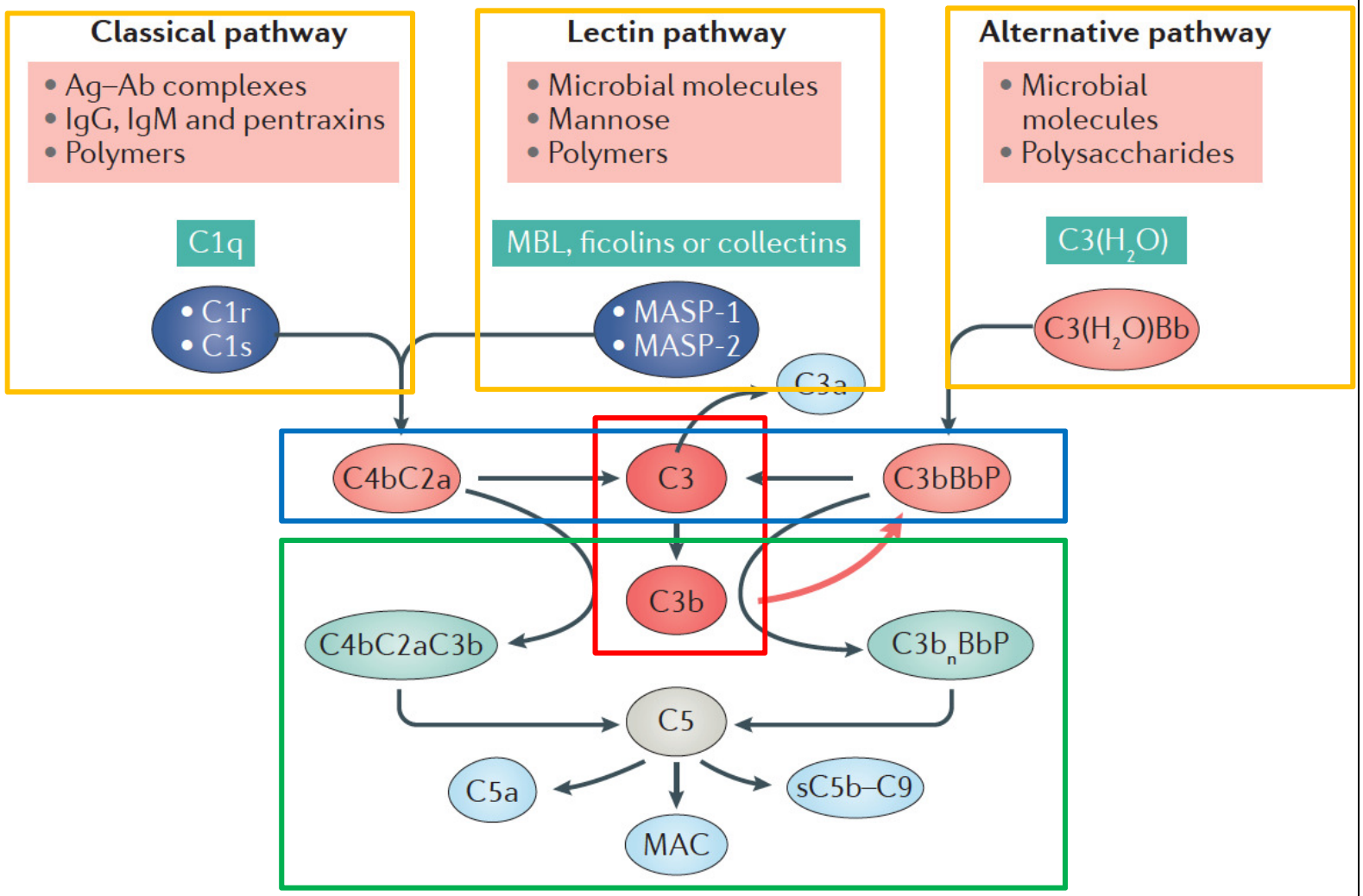
Complement



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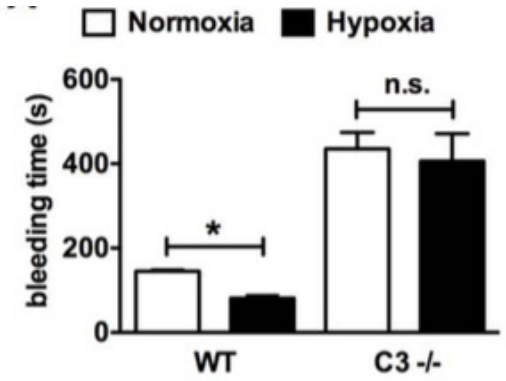
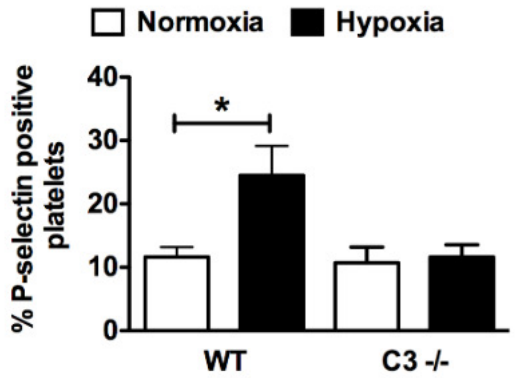
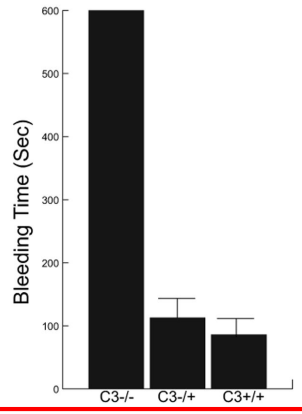
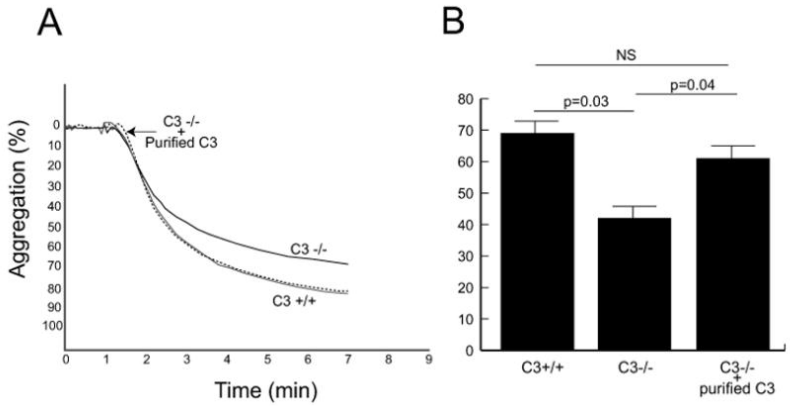
C3 deficiency leads to prolonged bleeding time





Bauer et al., PlosOne, 2011





Gushiken et al., J Thromb Haemost, 2009

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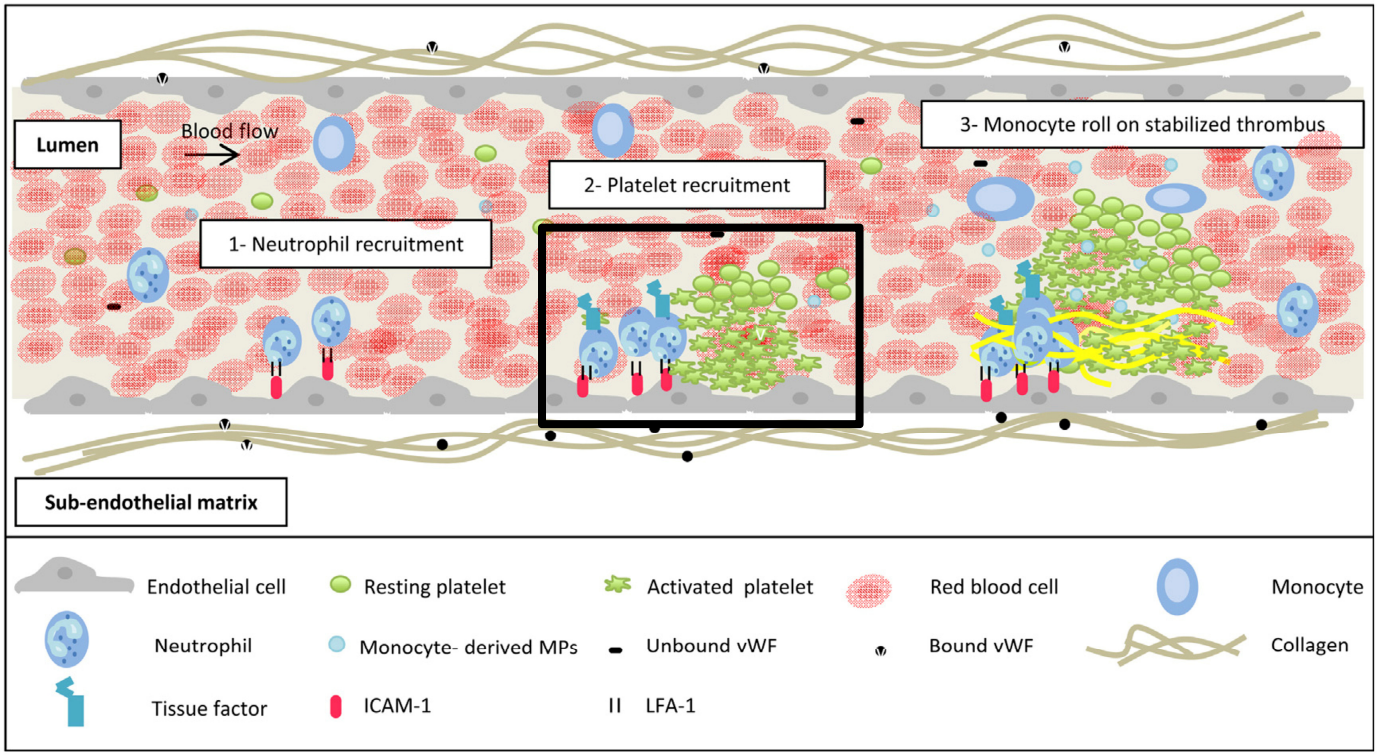
C3 KO mice have attenuated platelet aggregation and prolonged bleeding time



Darbousset R, Blood, 2012; 2014.

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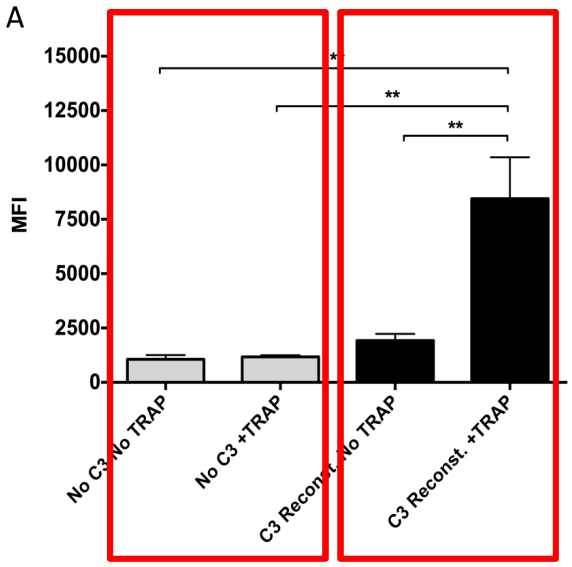
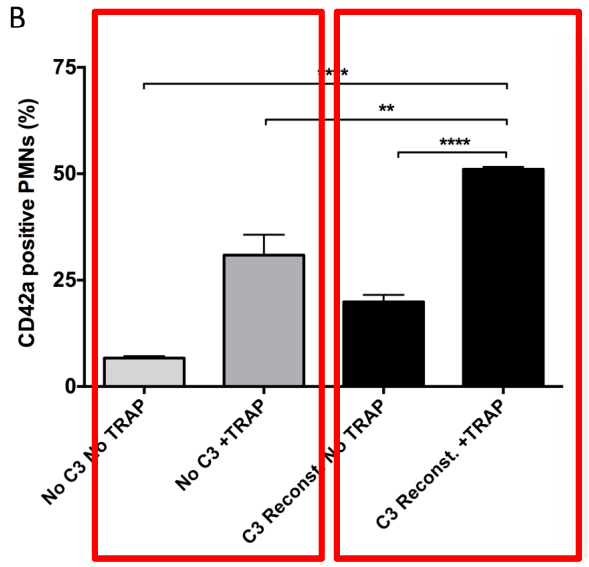
Formation of PMN (CD16+)-platelet (CD42a+) complexes in whole blood from a C3 deficient person

CD11b upregulation



CD16/CD42a complexes



Hamad, Thrombosis Haemostasis, 2015

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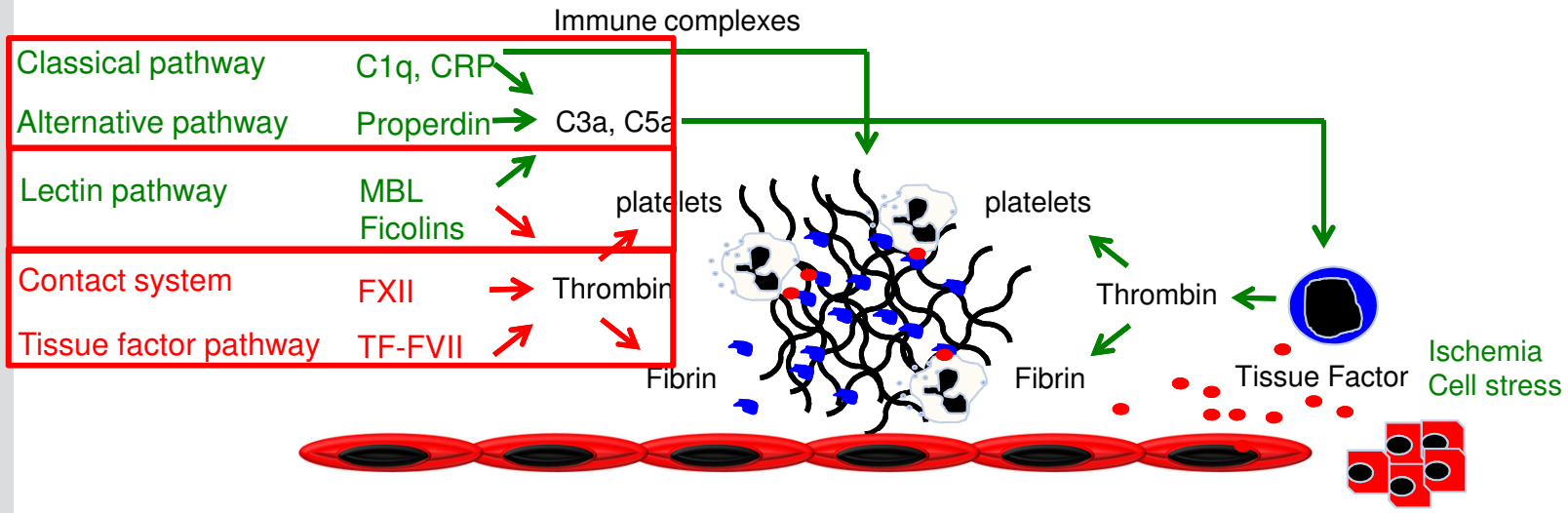
Thrombo-inflammation



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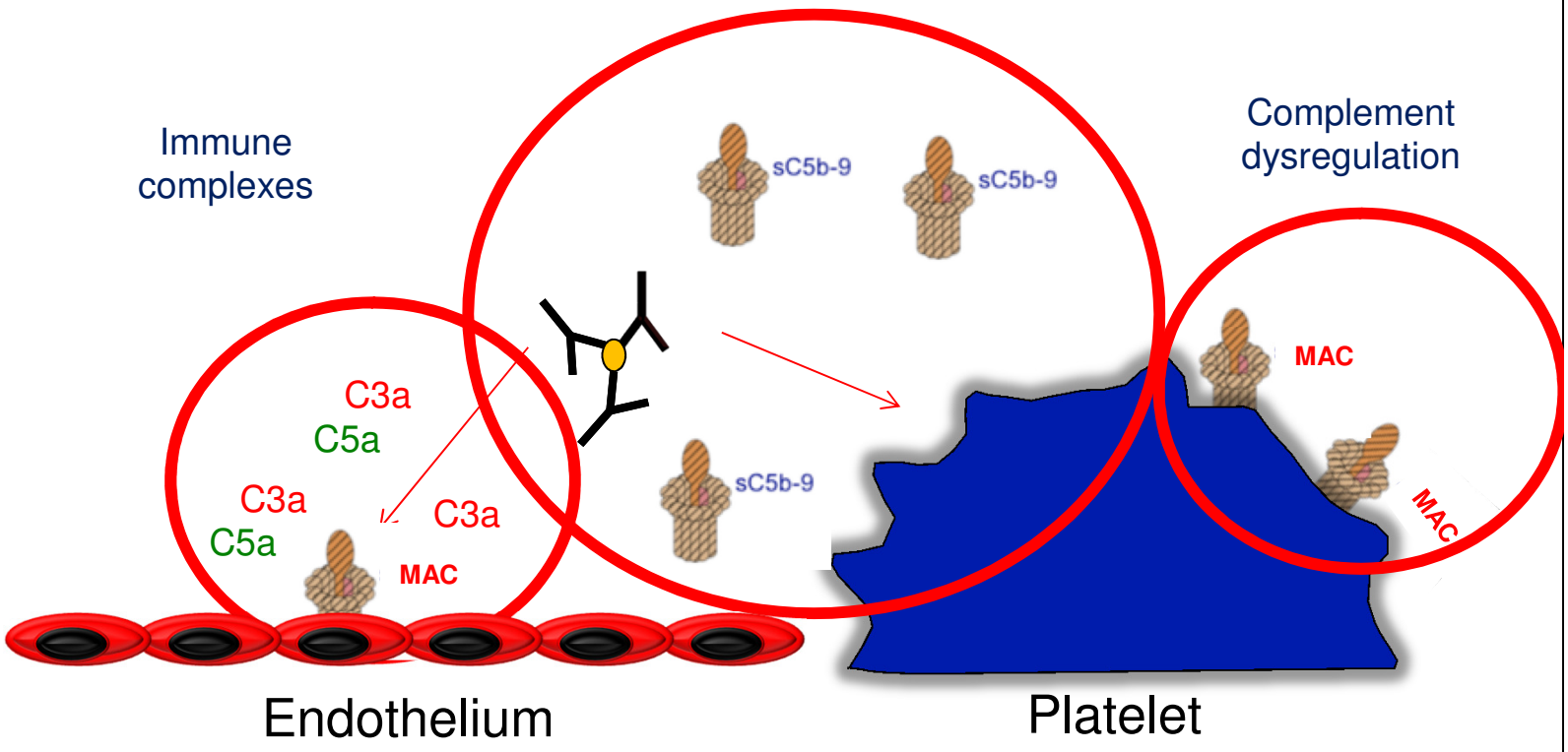
Thromboinflammation triggered by complement



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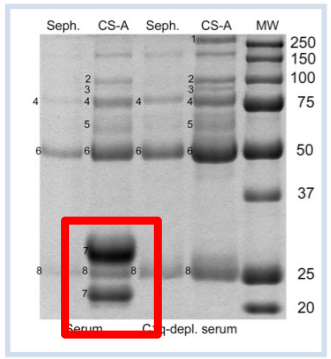
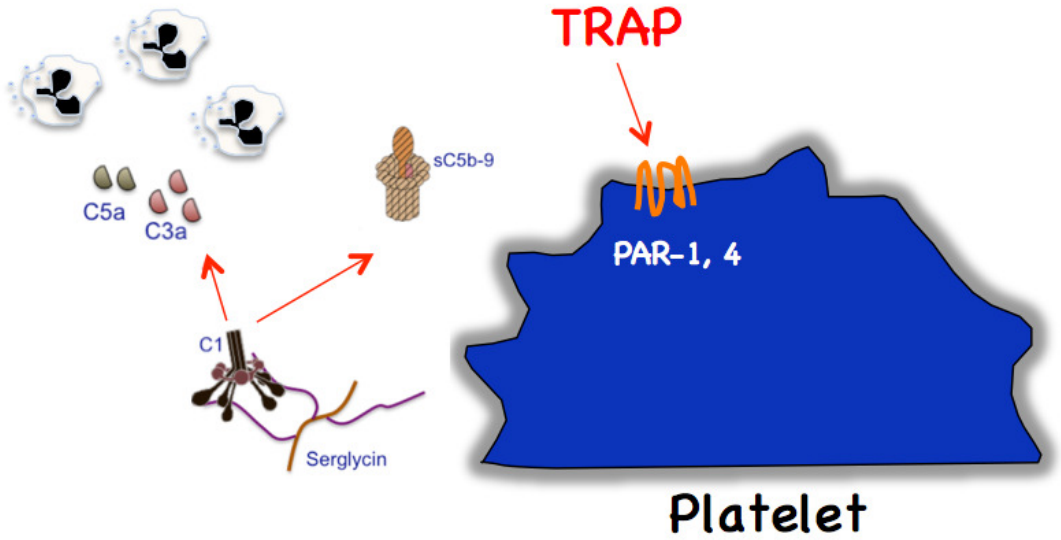
1. Complement activation triggered by C1q



C1q is the main ligand for CS-A



Hamad et al., JTH, 2009

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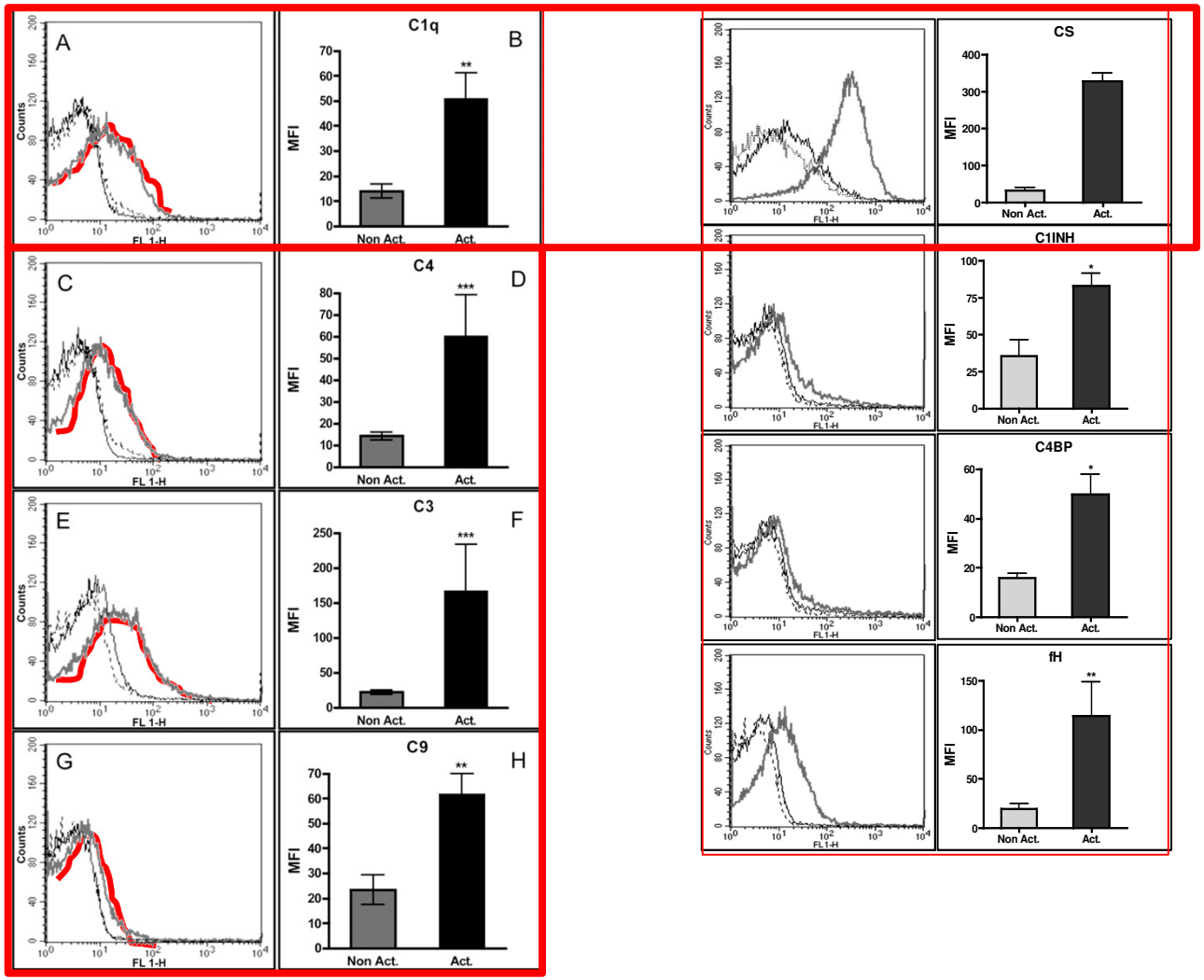
Binding of complement components to activated platelets



Hamad et a., J Immunol, 2010

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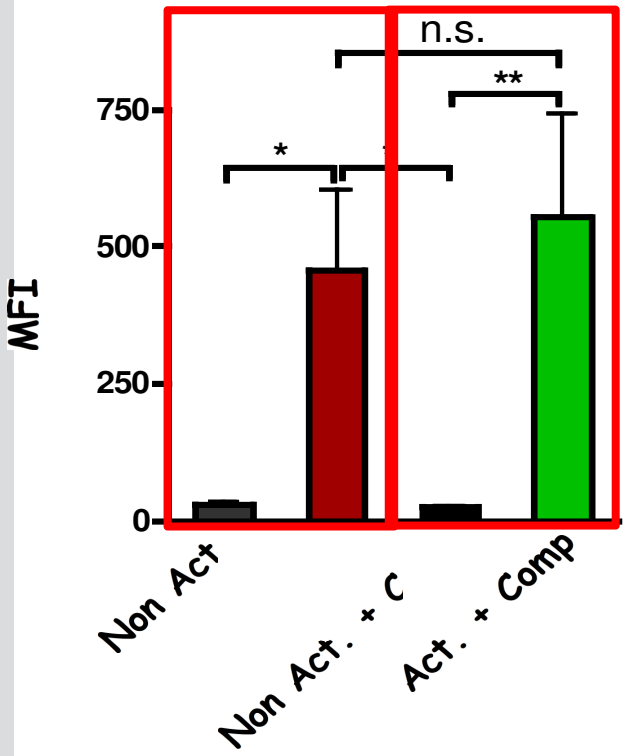
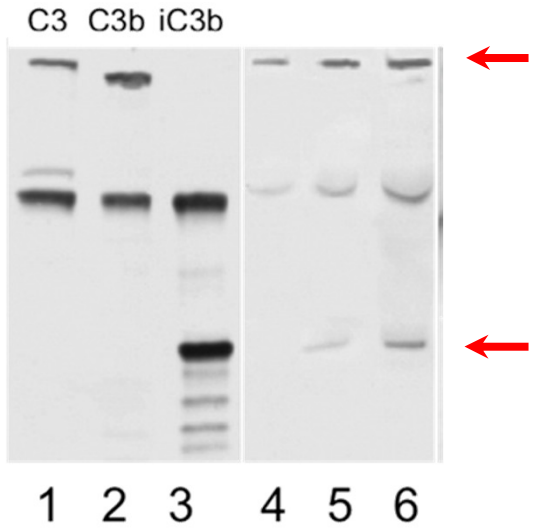
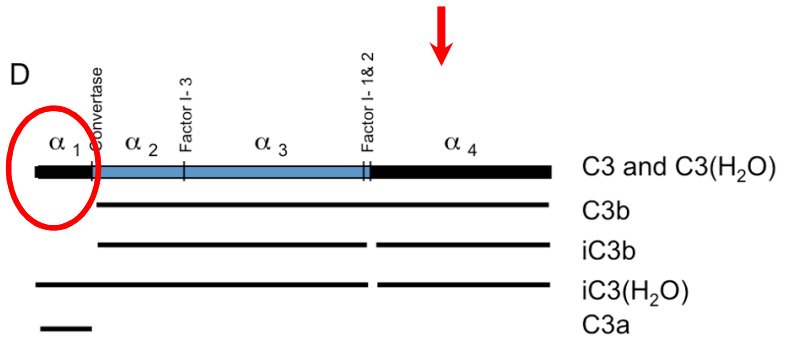
Blocking Complement Activation







Blocking at the C1q and C3 levels or activation in the presence of EDTA, EGTA did not affect the binding.

Hamad, J Immunol, 2010

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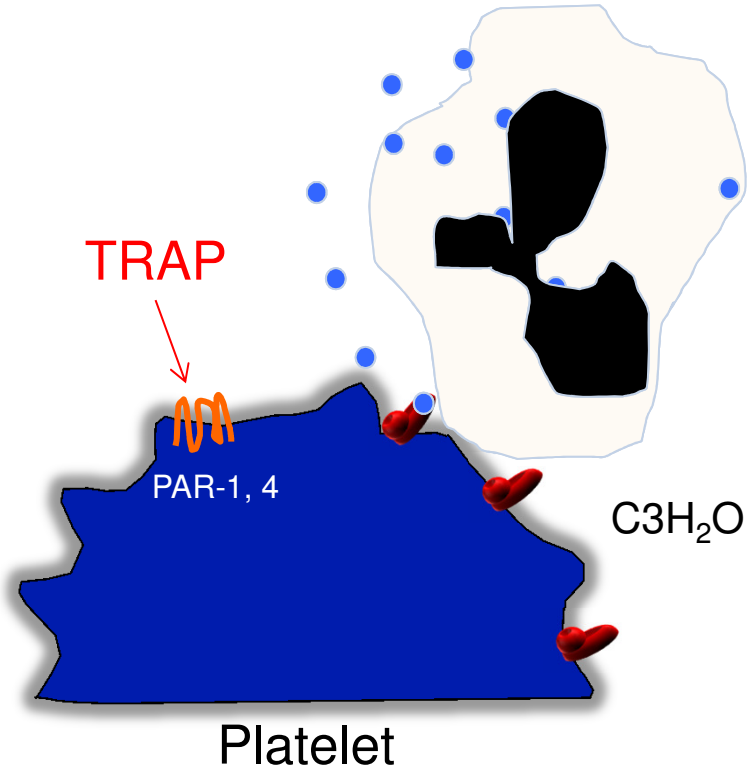
2. $C3H_2O$ acts as a ligand for leukocyte receptors CR1 and CR3

$C3H_2O$ acts as a ligand for:

1. CR1 (CD35)
2. CR3 (CD11b/CD18)

on PMNs and monocytes



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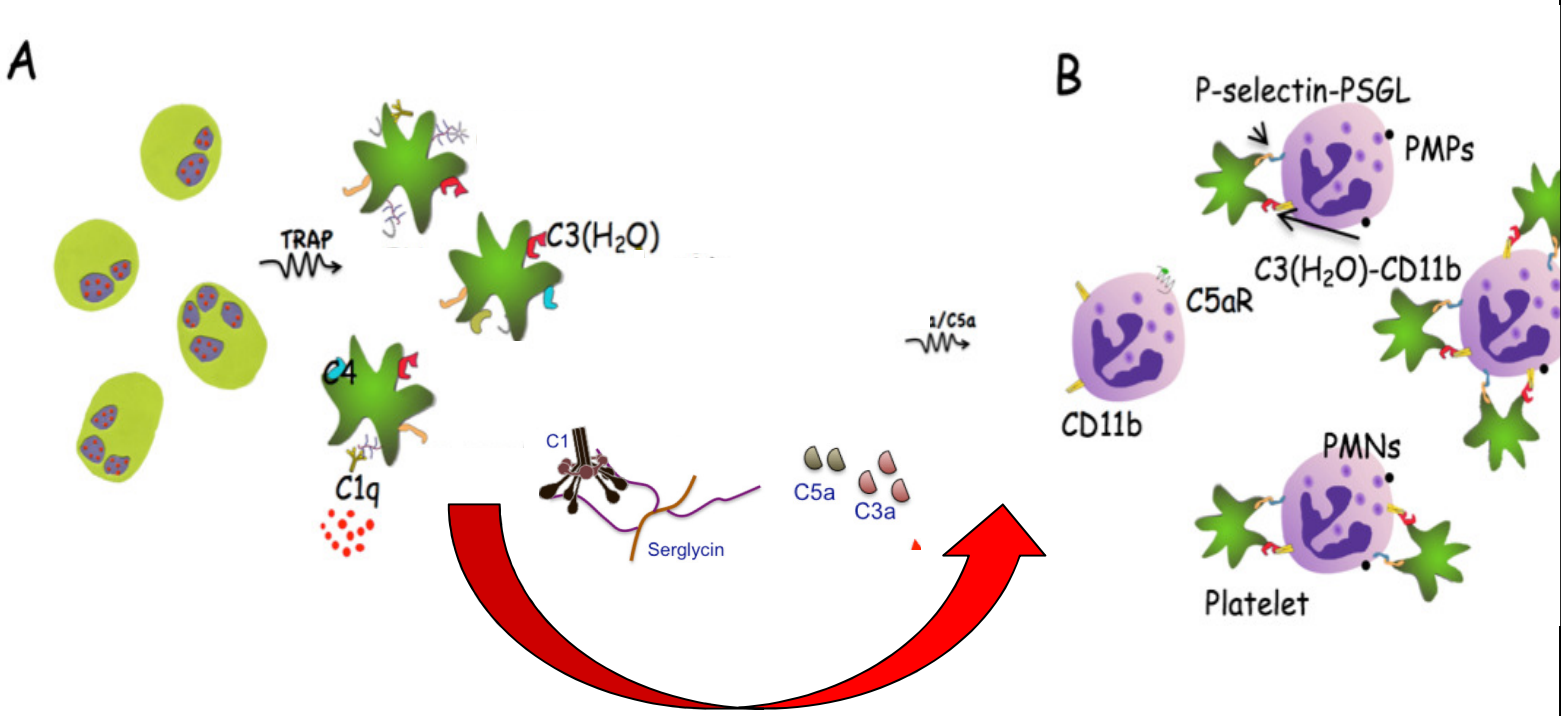
Summary



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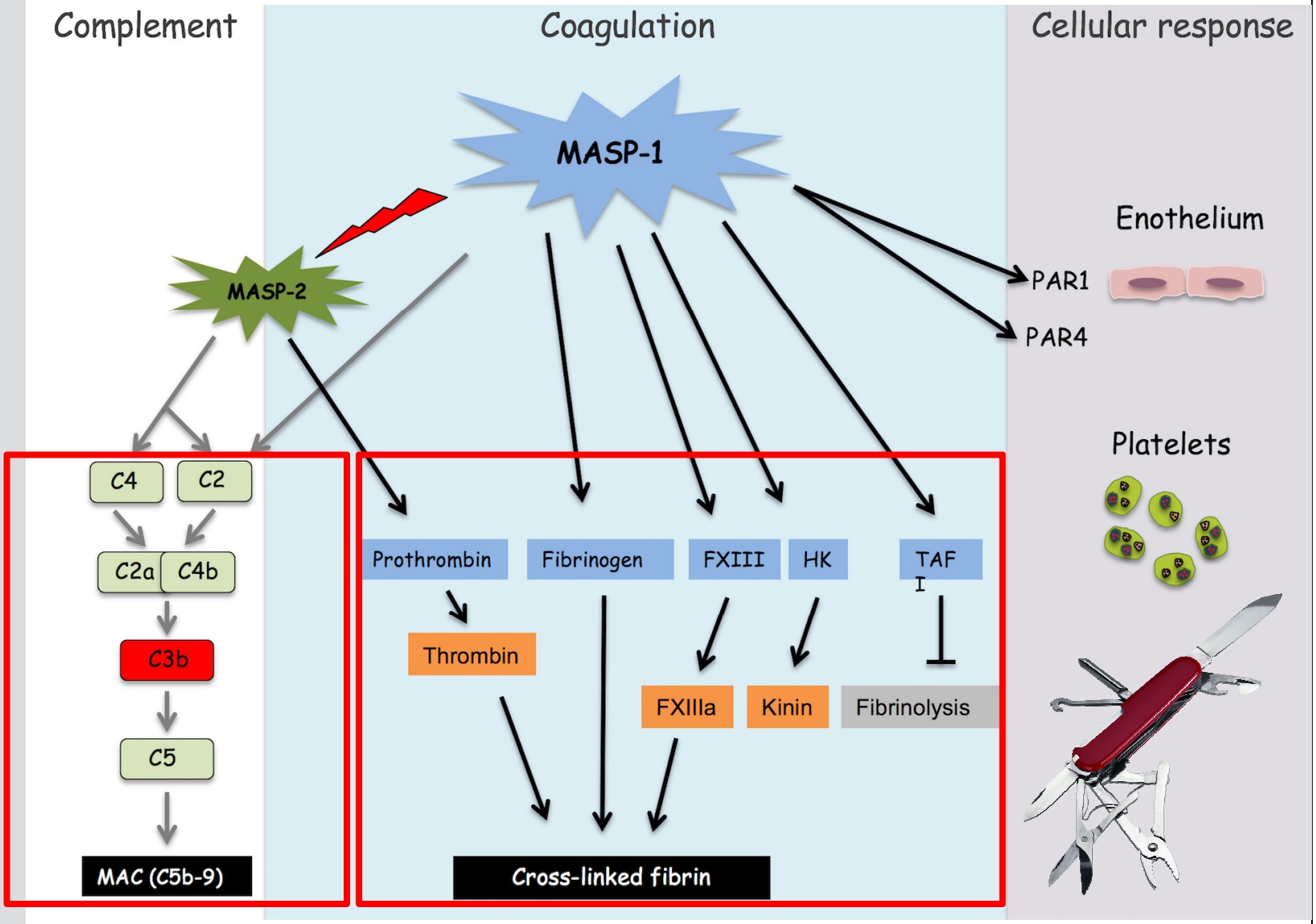
The specificity of MASP-1 and -2



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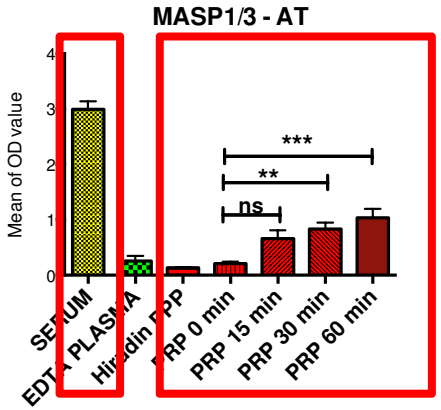
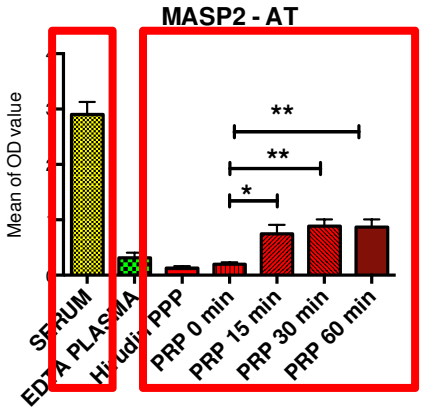
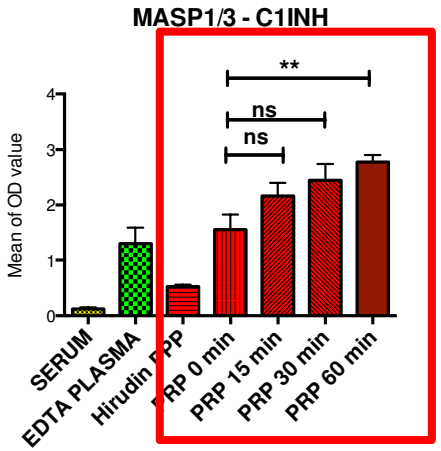
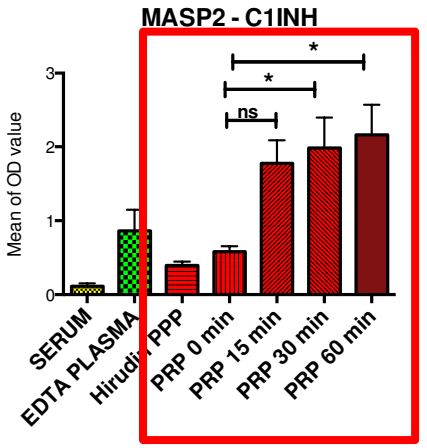
Generation of MASP-AT/C1INH Complexes by TRAP activated platelets









Kozarcanin et al., JTH, 2016

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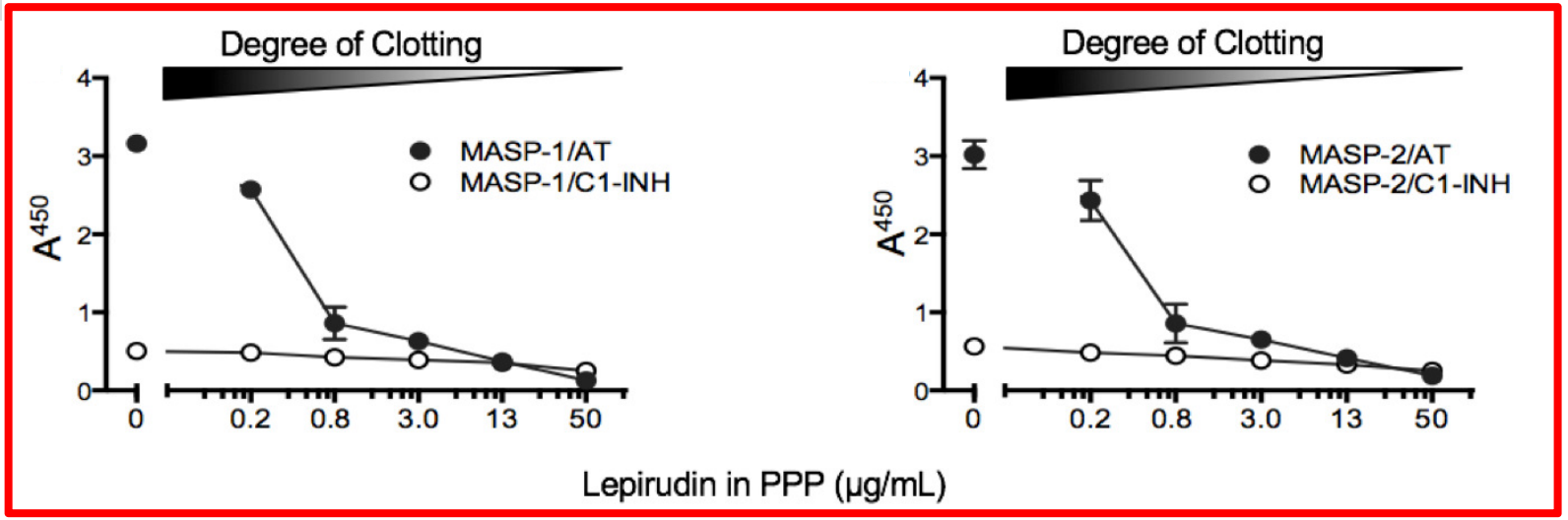
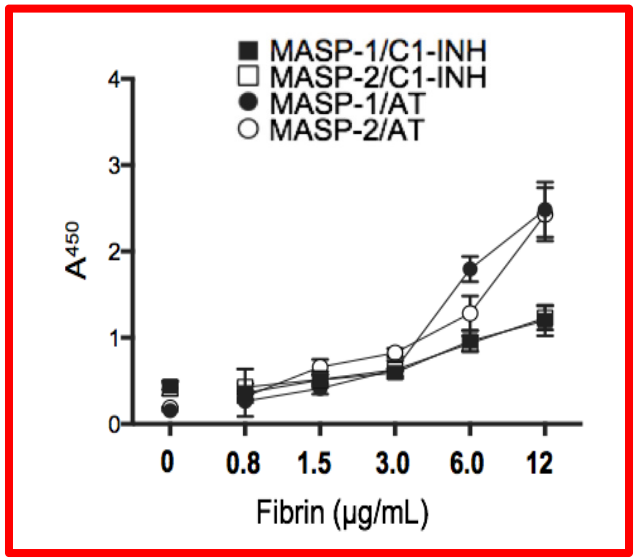
MASP-1,-2/serpin complexes

Activation of PPP by glas





Kozarcanin et al., JTH, 2016

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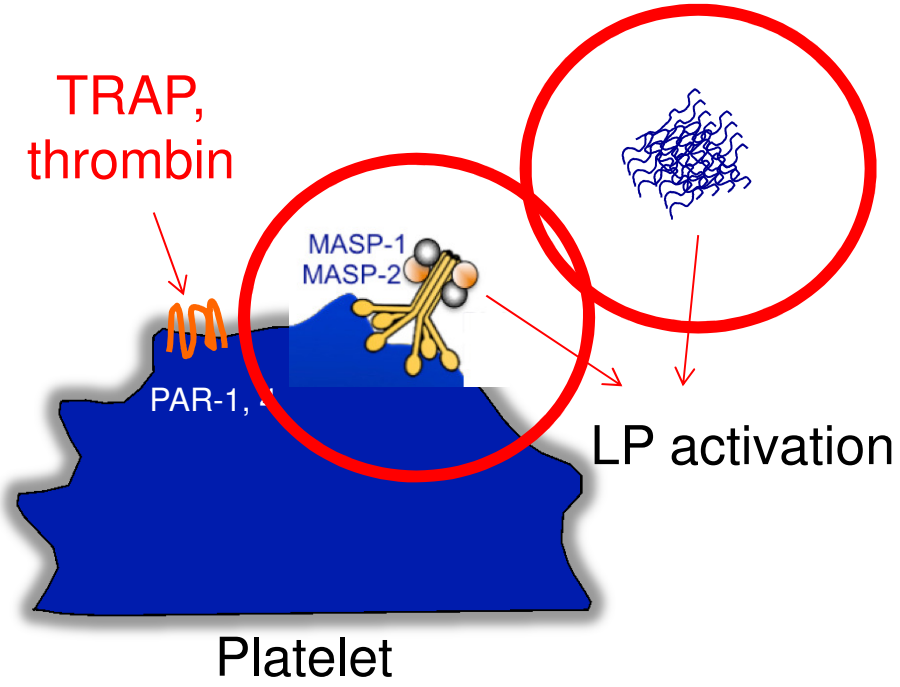
3. Platelet- and fibrin-mediated lectin pathway activation



Kozarcanin et al., JTH, 2016

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Thromboinflammation is an important pathophysiological mechanism in several clinical conditions and treatments

1. DIC
2. Thrombotic events such as cardiac infarction, stroke and other cardiovascular conditions
3. Biomaterials implants (joint replacements, scaffolds for tissue engineering etc), extracorporeal treatments (hemodialysis, cardiopulmonary bypass)
4. Pharmacological delivery systems e.g. lipid micelles, polymers, virus vectors etc.
5. Microangiopathies- dysregulation (aHUS)
6. Cell and cell cluster transplantation and therapies.
7. Whole organ transplantation
1. Rheumatic disease (scleroderma, SLE, antiphospholipid syndrome).

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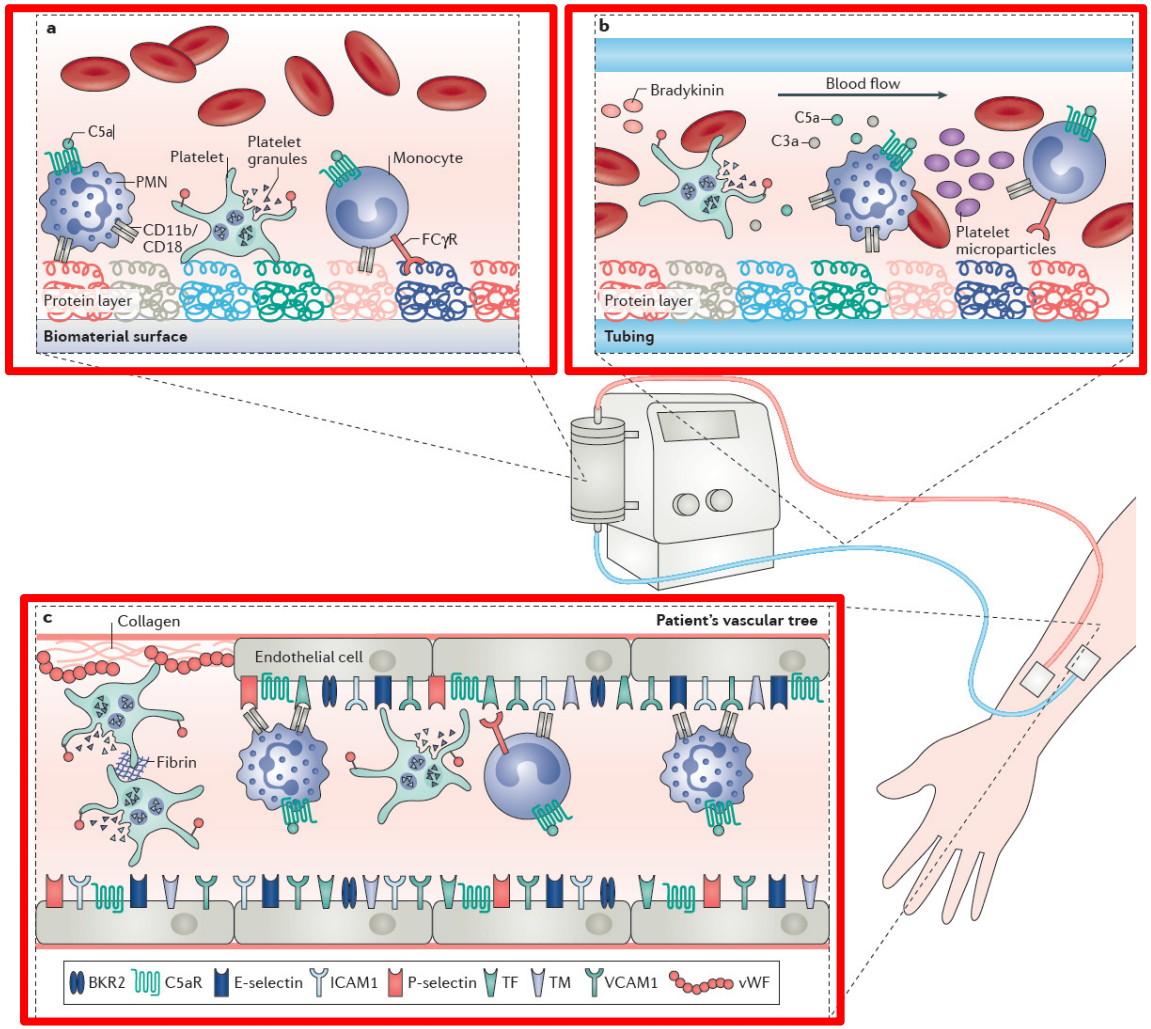
1. Thromboinflammation in hemodialysis



Ekdahl et al., Nature Rev Neph, 2017

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2. Thromboinflammation in transplantation

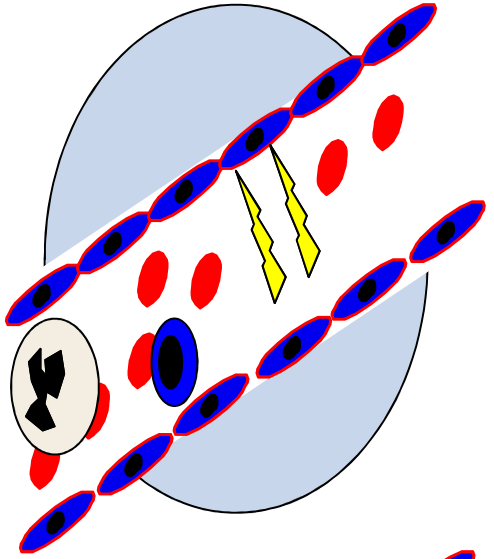
Mechanism:

- Antibodies and lectins
- Lack of cell associated regulators e.g. DAF, MCP, AT, C1-INH
- Cell stress- cyto/chemokines, TF expression

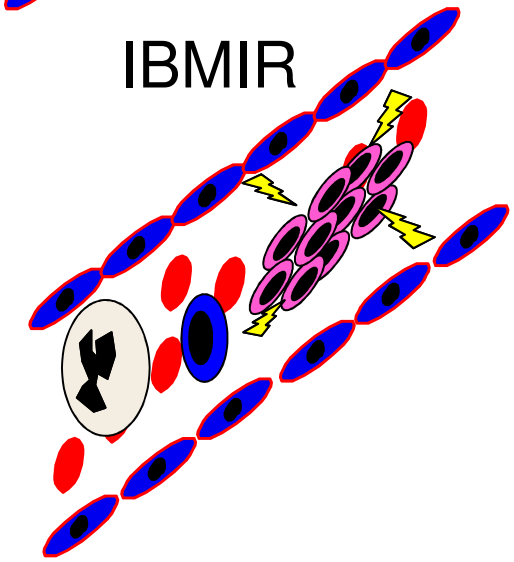
Characterized by:

- Coagulation and complement activation
- Platelet consumption
- Leukocyte activation and infiltration
- Cytokine generation
- Cell death
- Graft loss / delayed graft function

I/R injury



IBMIR



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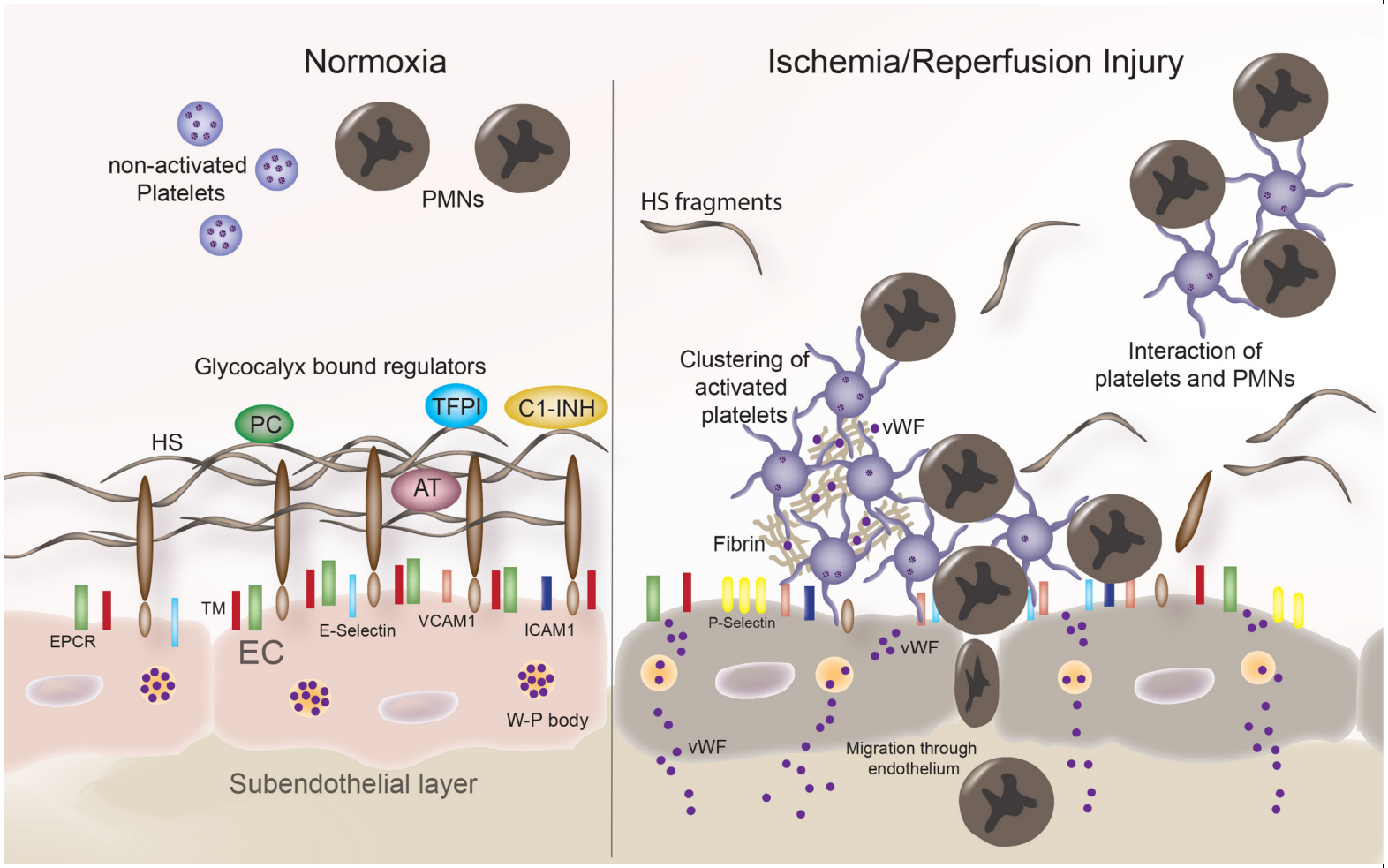
Ischemia/reperfusion injury



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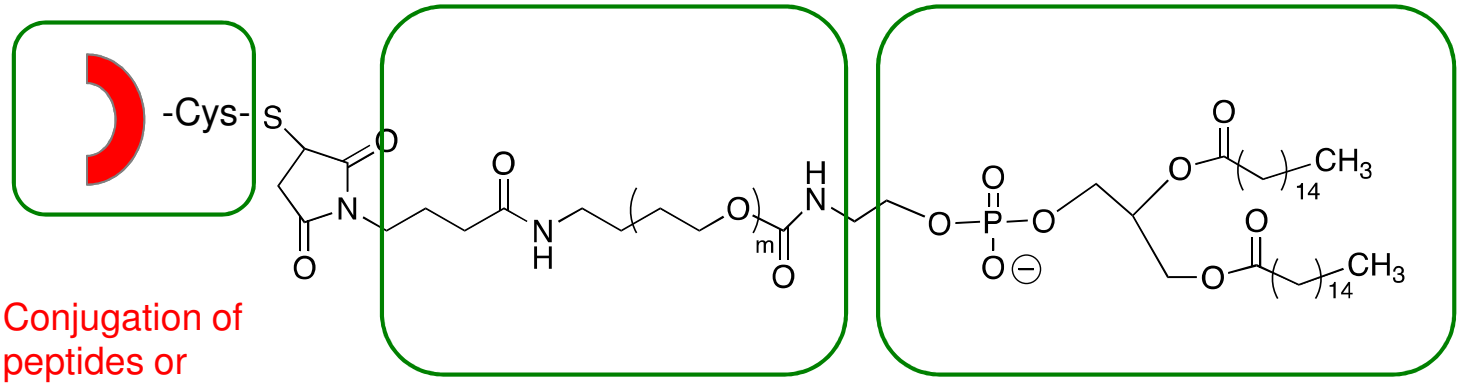
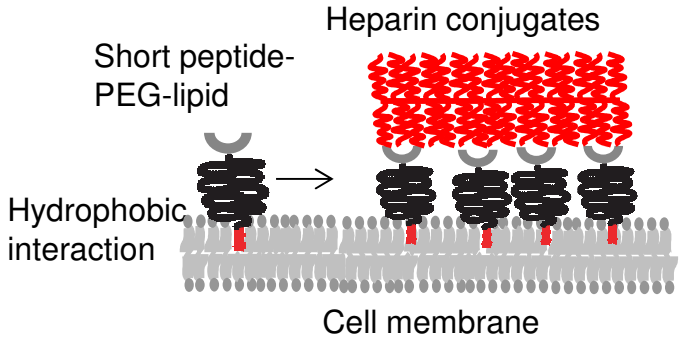
PEG-phospholipid linker



Conjugation of peptides or macromolecules

PEG

phospholipid



Engberg, Biomaterials, 2009, Nilsson Biomaterials, 2012; Asif, Acta Biomaterialia, 2015

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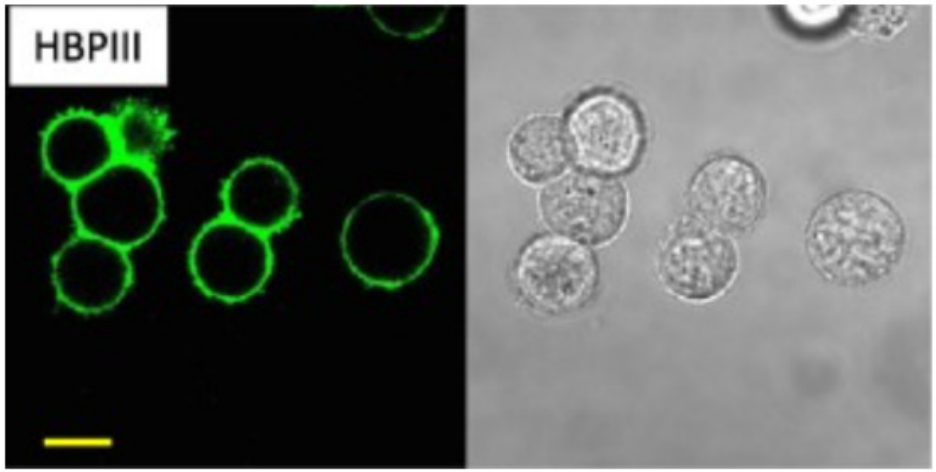
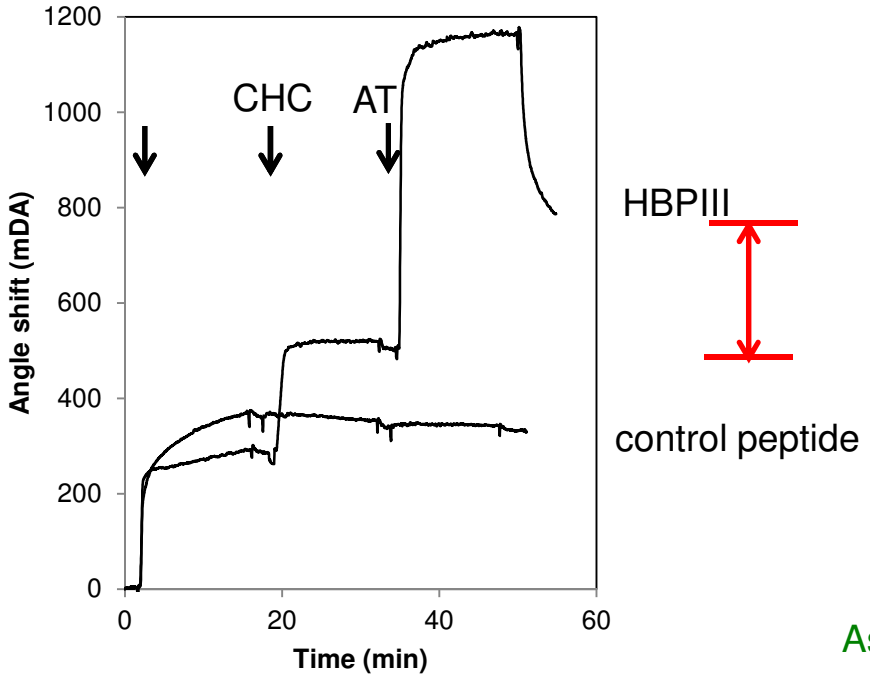
Heparin-coating





Asif, Acta Biomaterialia, 2015

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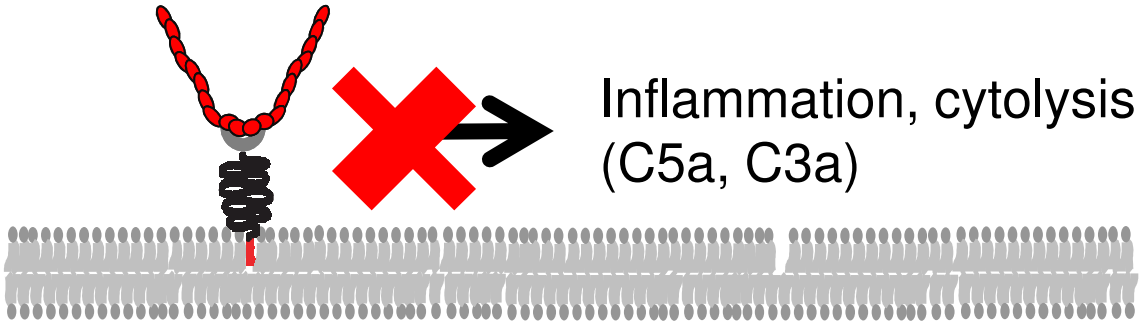
Regulation of the complement and coagulation system by autoregulation

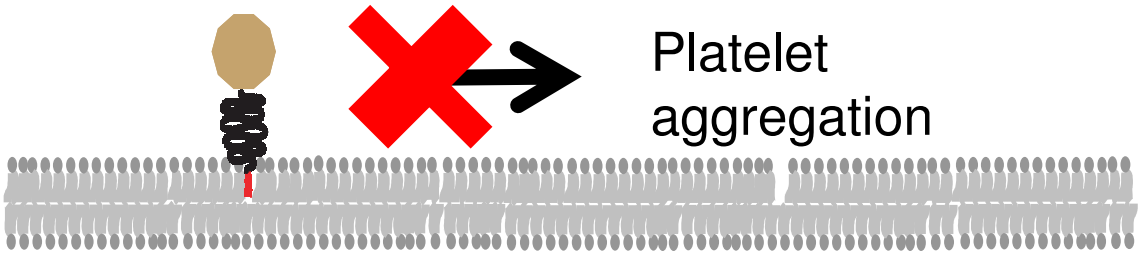
A. Regulation of the complement system

Recruited factor H



B. Regulation of platelet activation (and coagulation system)

Immobilized apyrase
(CD39)



Teramura, Biomaterials, 2013

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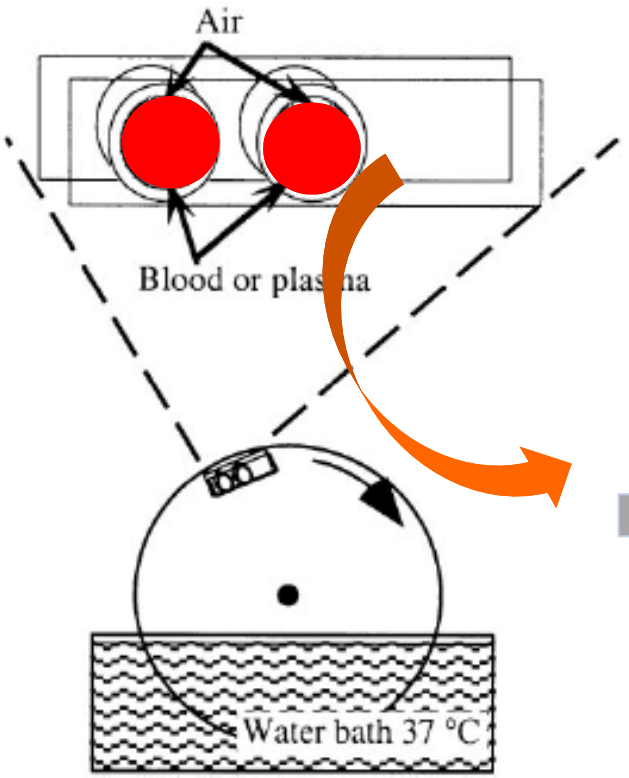
Slide chamber model experiment



Porcine aortic endothelial cells

Microscope slide glass

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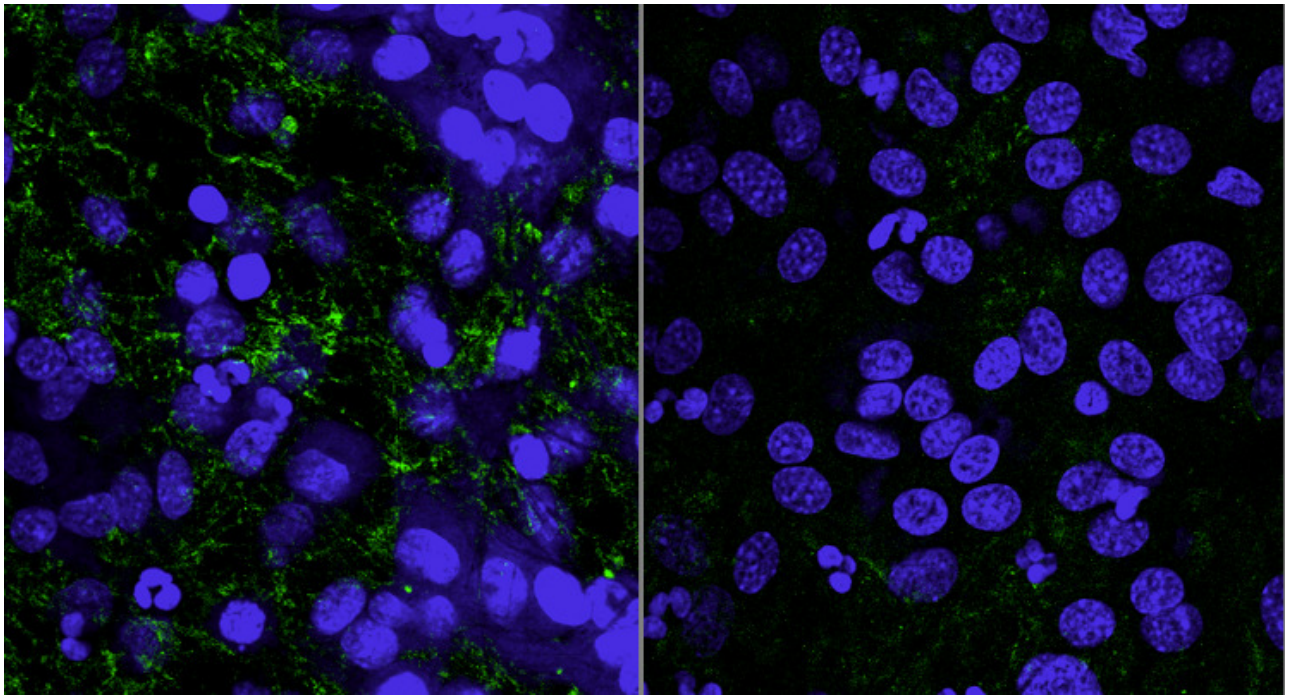
Factor H on PAEC after exposure with whole blood

5% fH-bp-PEG-lipid/PAEC

Control PAEC



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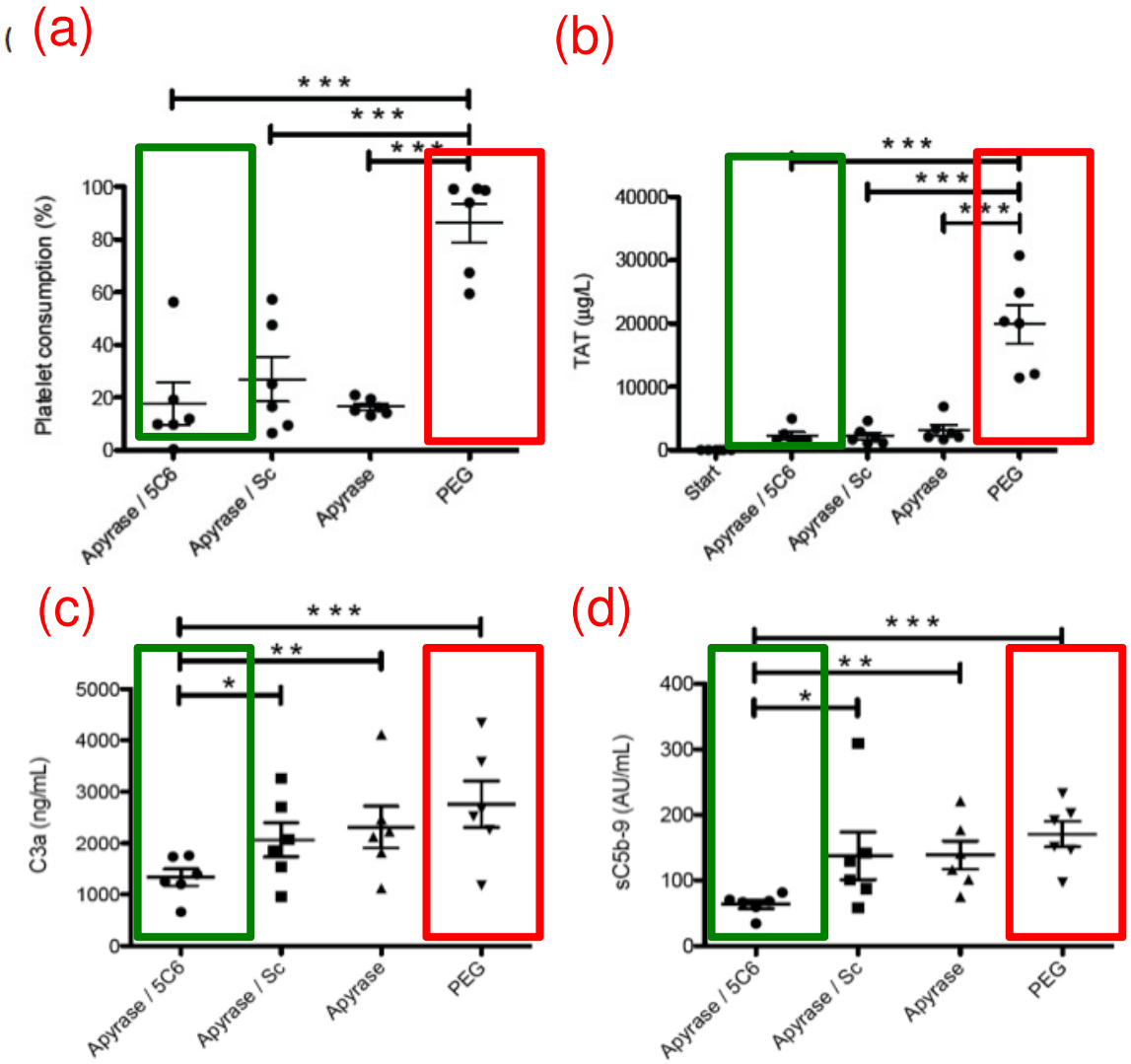
Whole blood experiment on Apyrase/5C6-immobilized surface



Nilsson, Biomaterials, 2013

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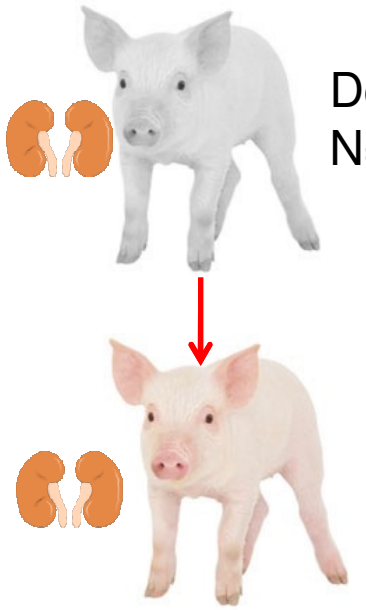
Protection of transplanted kidneys against I/R in two models

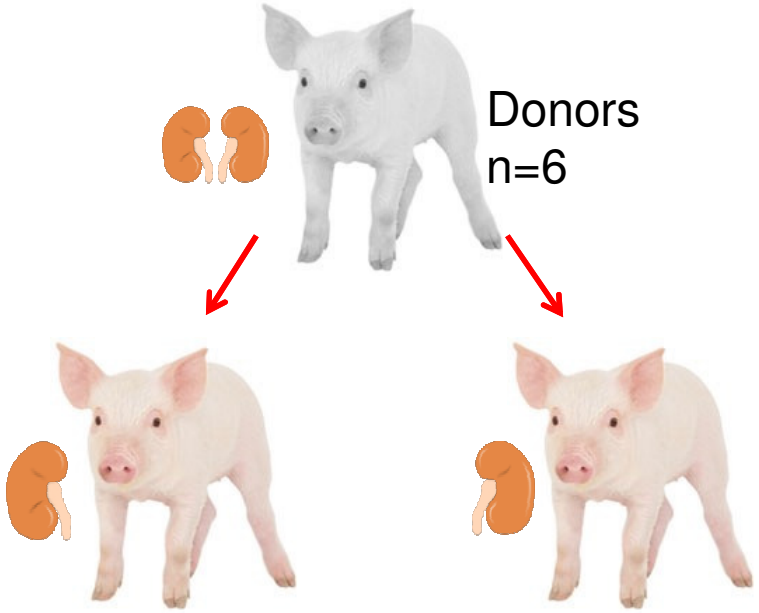
En bloc, short-term



Donors
N=7

Recipient, not related to donor (n=7)

Long-term, allogeneic



Donors
n=6

Recipient A, not related to donor (n=6)

Recipient B, not related to donor (n=6)

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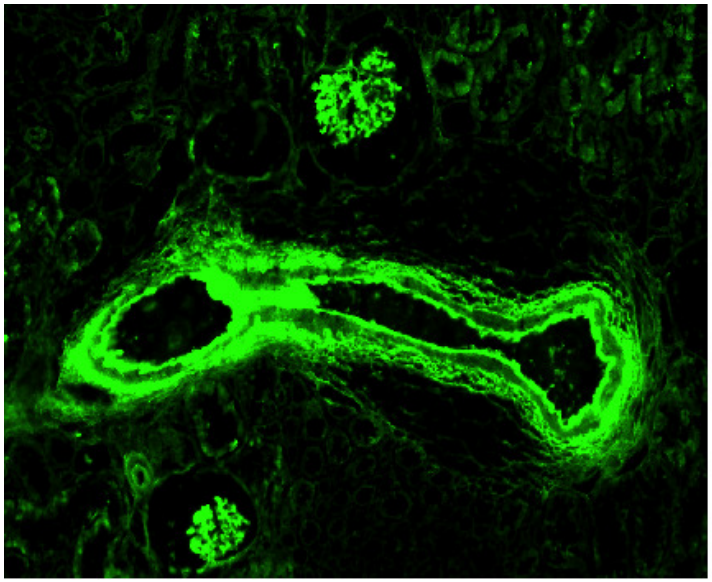
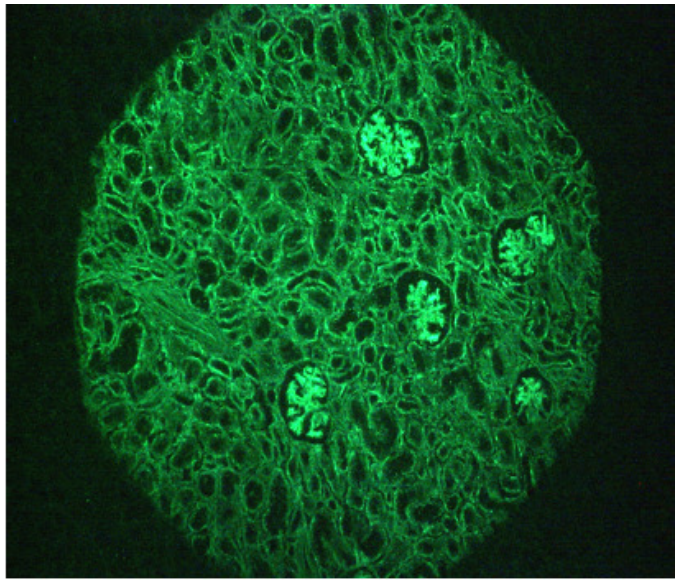
Binding of PEG-phospholipid





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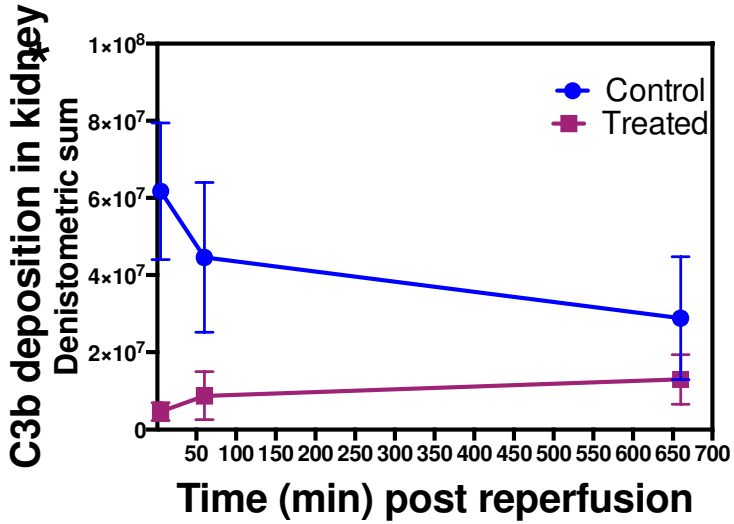
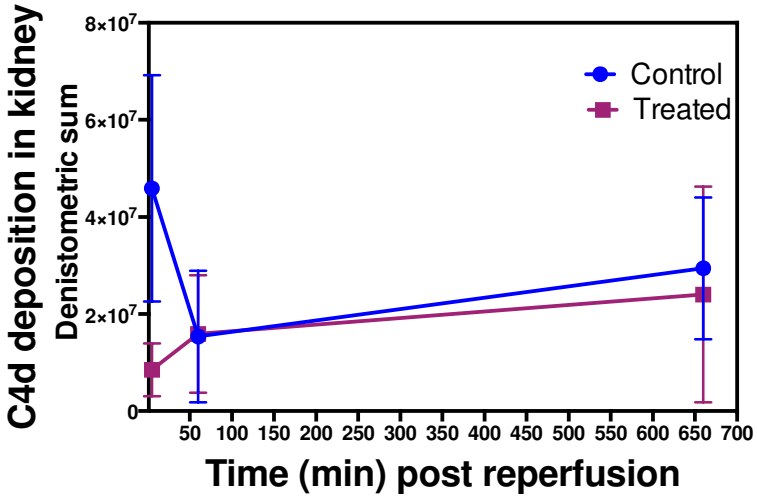
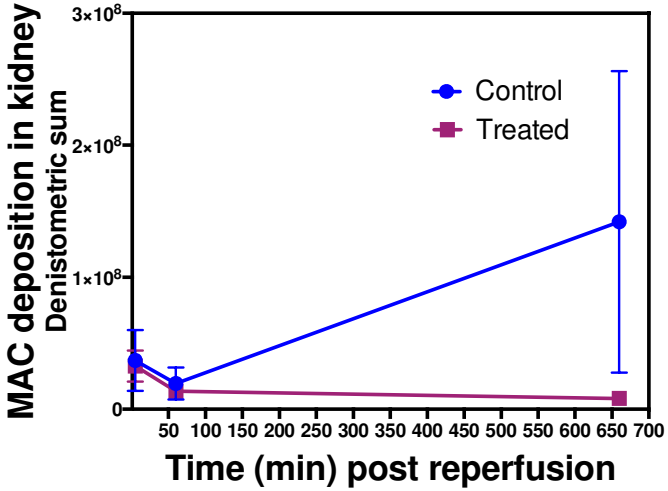
Complement deposition







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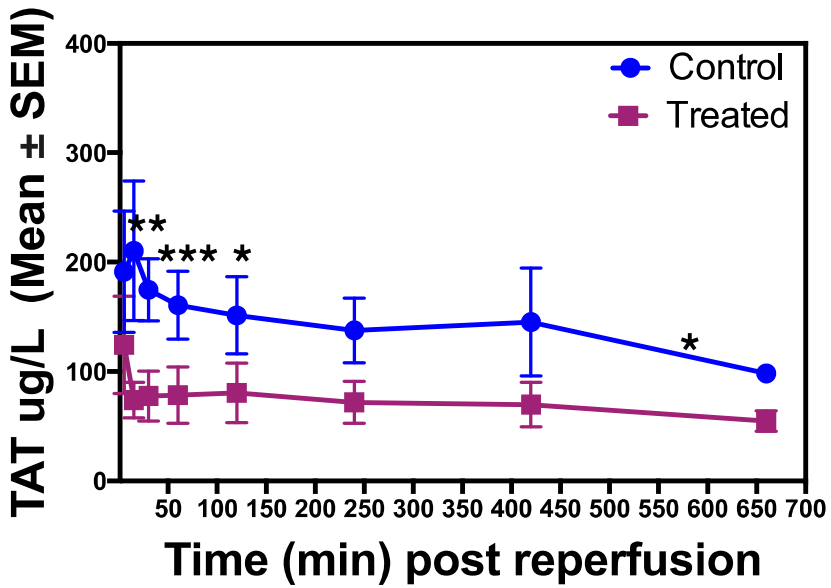
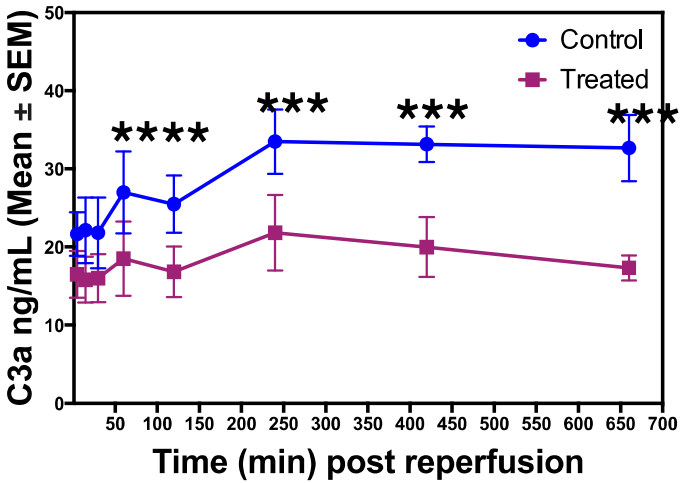
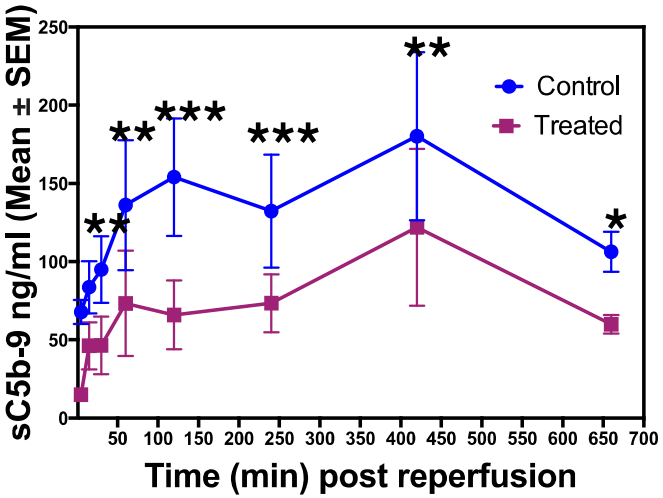
Coagulation and Complement activation







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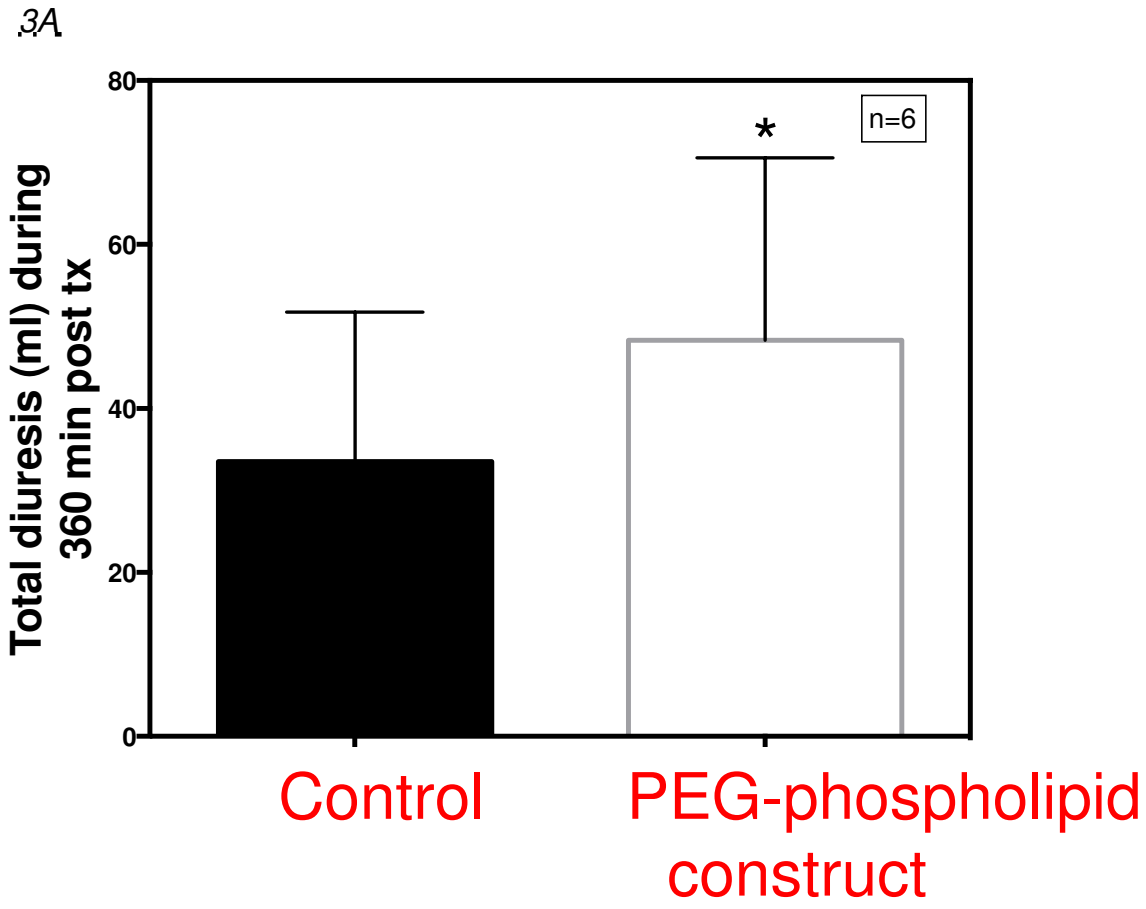
Diuresis



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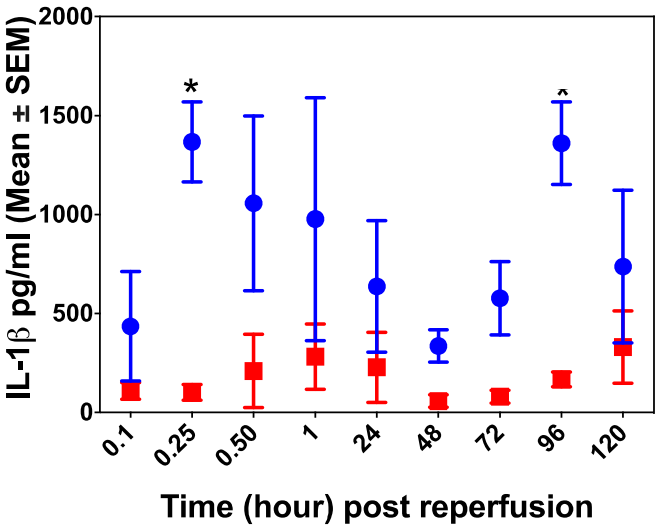
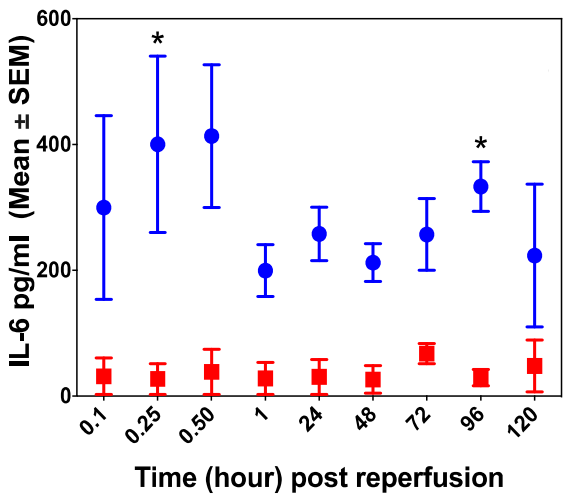
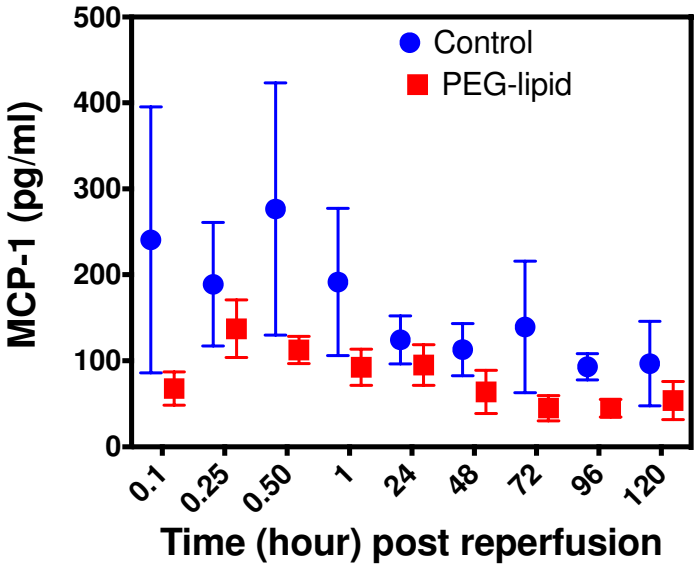
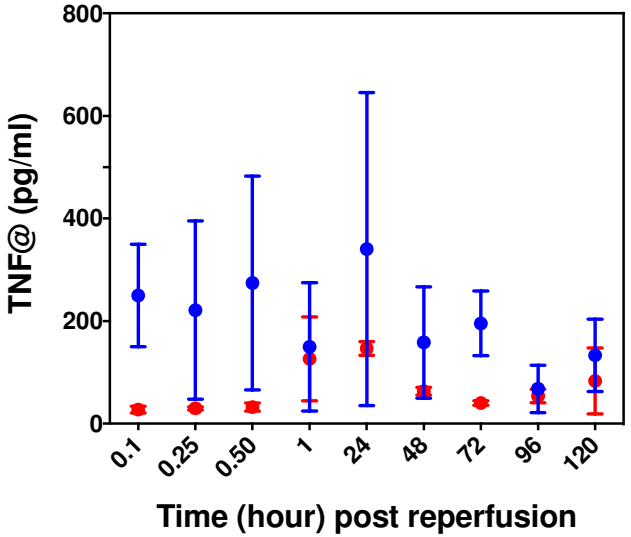
Cytokines
Inflammatory markers









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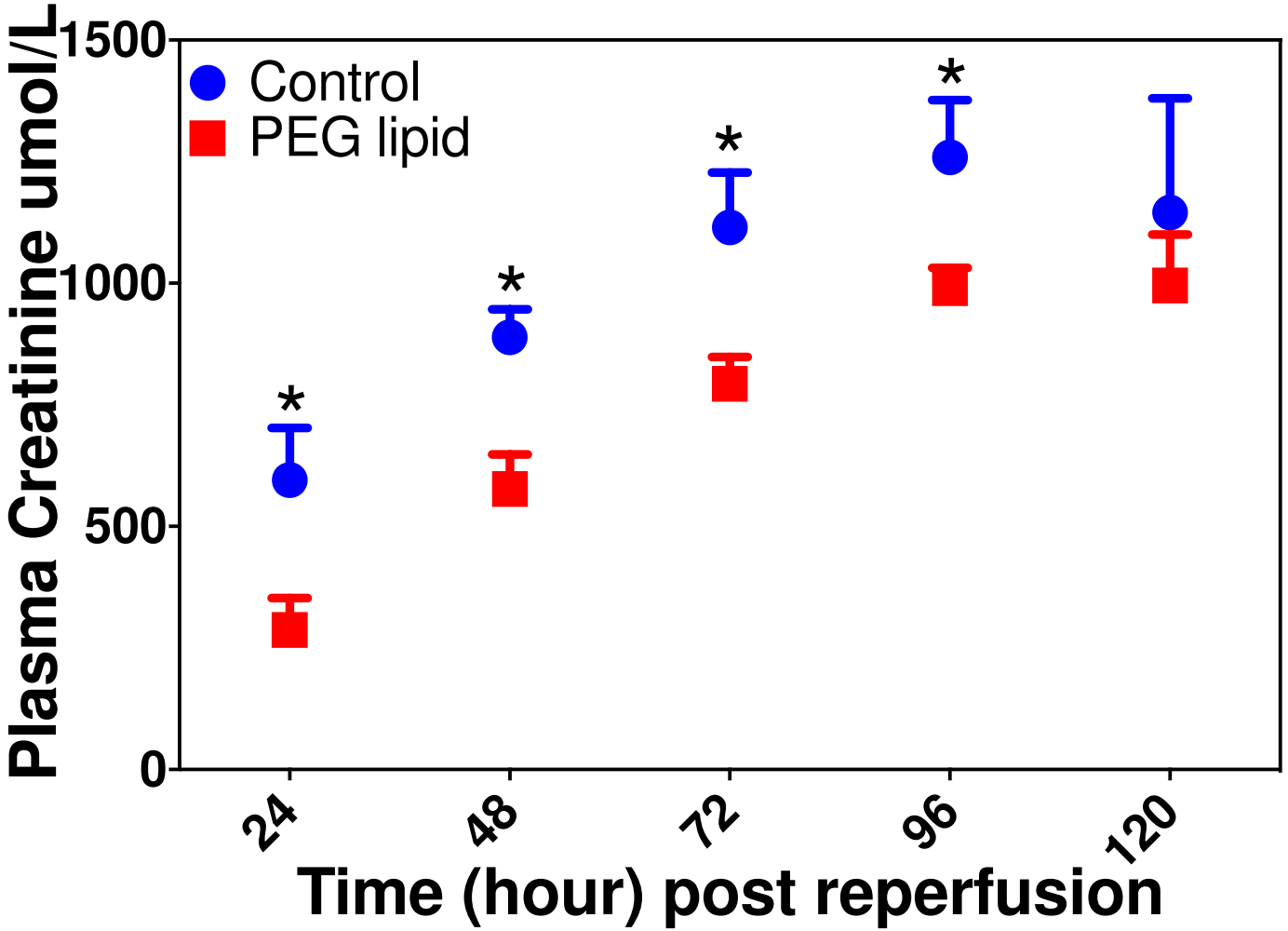
Plasma Creatinine
Kidney function marker



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Summary

1. PEG/phospholipid-linked regulators are efficient regulators of these reactions *in vitro*

2. Also the PEG/phospholipid linker alone has a significant effect on I/R injury *in vivo*

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Tack!