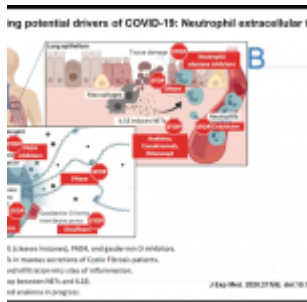
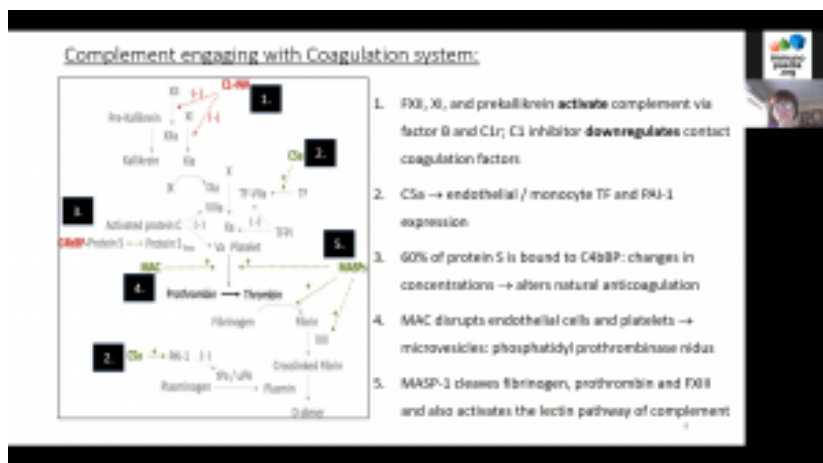


SAIS/Immunopaedia Webinar: Immunothrombosis & COVID-19



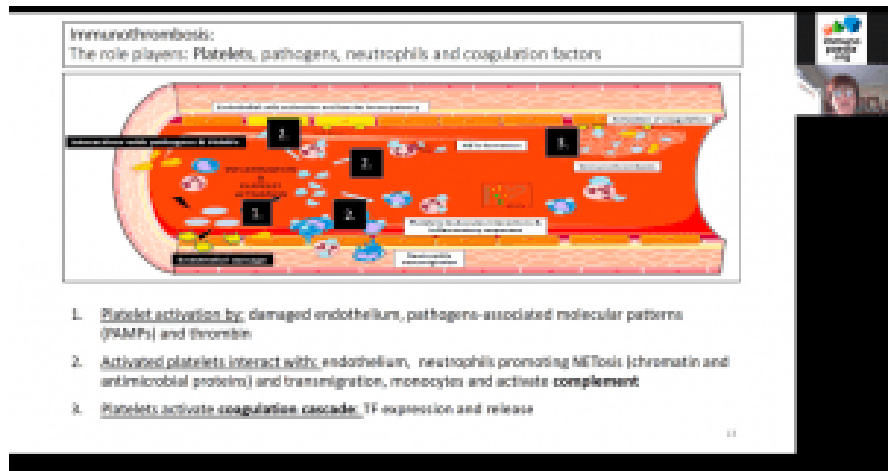
This week we highlight SAIS/Immunopaedia COVID-19 Webinar featuring talks by haematopathologists Dr Susan Louw and A/Prof Jessica Olpie on immunothrombosis & COVID-19. Immunothrombosis is the direct interaction of activated leukocytes with platelets and coagulation function, this interaction usually involves dysregulation of neutrophil extracellular trap formation.



Dr Susan Louw began her talk titled “Immunothrombosis: lessons from other conditions” with a brief background on Thrombosis and how physiological process if left unchecked can lead to pathology. She

discussed how cross-talk between the immune system (macrophages, complement proteins, neutrophils) and coagulation cascade (platelets and tissue factors) can cause

to immunothrombosis. She then gave an in-depth yet brief overview of how coagulation proteins engage with the complement cascade (see image below) and the role of innate cells (macrophages and neutrophils) and cytokines in immunothrombosis. Further, she then highlighted that platelets, well known for their role in blood-clotting, have immunomodulatory properties. Dr Low concluded her talk describing clinical conditions associated with immunothrombosis (see below).

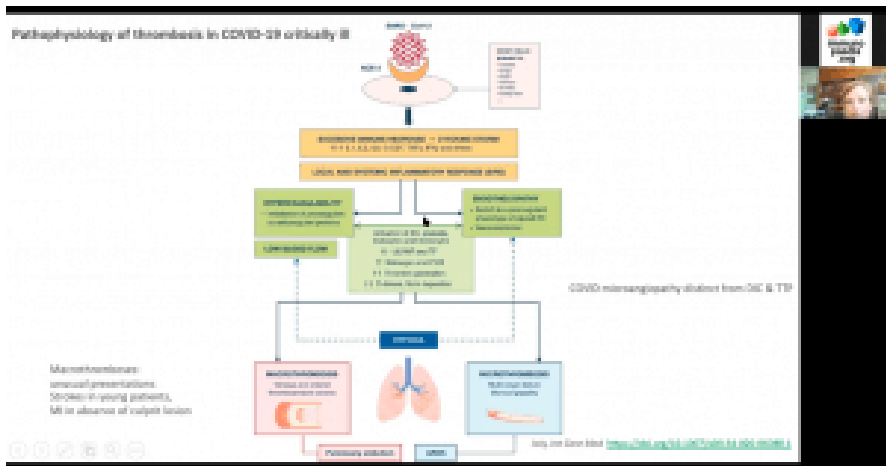


Clinical condition	Coagulation dysfunction	Complement dysfunction
Septis	Potent activator of coagulation via tissue factor with endothelial dysfunction	Activation of multiple complement pathways
Trauma related microangiopathy	Potent activator of coagulation , hyperfibrinolysis and DIC	Increased C3a and C4d on surface of platelets
Systemic lupus erythematosus (SLE)	Complement promotes platelet activation and thrombosis; APLAs extreme complement and coagulation cascade	Complement activation by nuclear autoantibodies; Deficiencies and mutations in other classical pathway proteins; Reduced expression of complement inhibitors
Antiphospholipid Syndrome	C3a upregulates TF on neutrophils which then activates coagulation with inflammation, trophoblast injury and foetal death	APLAs activate complement on trophoblasts leading to C3a generation
Auto- and alloimmune haemolytic anaemia	Complement-mediated RBC lysis causes activation of coagulation via - Exposure of procoagulant surface - Release of tissue factor bearing microparticles - Endothelial cell injury - Altered vasodynamics - Release of reactive oxygen species	Activation of the classical complement pathway by IgM antibody bound agglutinated RBCs bind C1; Extravascular haemolysis of C3b-coated erythrocytes; Activation of complement by circulating free haem

Clinical condition	Coagulation dysfunction	Complement dysfunction
Paroxysmal nocturnal haemoglobinuria	Platelet activation ; Absence of GPIIb/IIIa (P2Y1) receptor with impaired fibrinolysis ; Endothelial dysfunction from free haemoglobin and nitric oxide depletion; MAC and C3a generation promote thrombosis; IL6 promotes thrombin generation and inhibits ADAMTS13	Complement-mediated haemolysis by unregulated production of MAC on cell surfaces; C3a upregulates IL6, IL8, TNF- α
Atypical haemolytic uremic syndrome	Endothelial cell damage and disruption of microvasculature with thrombosis ; Platelets are activated by MAC or C3a Unopposed complement-mediated destruction of platelets (due to lack of Factor III and other membrane regulators)	Dysregulation of alternate CP and C3 convertase activity due to loss of inhibitory complement
Hereditary angioedema	Unregulated activation of prokallikrein-kinin-kinin-kinin (trypsin-like) due to C1-INH deficiency or dysfunction	Deficiency/dysfunction of C1-inhibitor results in loss of neutralising C1s, C1r and MACs that dysregulating CP and LP

HIT associated TTP-like syndrome: endothelial injury by HIT itself / damage by opportunistic infections / endothelial activation by HIT-associated **chronic inflammation** → local activation of **coagulation** (isolated, elevated D-dimers)
→ release of **VWF**: overwhelming ADAMTS-13 capacity
→ **microangiopathic thrombosis**

Role of complement and endothelial dysfunction must be delineated



Jessica Opie's talk focused on "Thrombosis in COVID-19". A/Prof Opie gave an overview of homeostatic properties [coagulation factors (clot

formation), coagulation inhibitors (clot controlling) and fibrinolysis (clot-dissolving)] associated with blood vessel injury. She then provided evidence which demonstrated that severe COVID-19 pathology is associated with dysregulation of tissue repair and blood vessel formation of the lung endothelial membrane. She also discussed how cytokine storm and dysregulation of the complement pathway contributes to excessive NETosis and is associated with severe COVID-19 pathologies (such as hypercoagulability, endotheliopathy, macrothrombosis and microthrombosis). She ended her talk describing how targeting either NETosis (using NET inhibitors) and the complement cascade could be potential therapies for severe COVID-19.

Targeting potential drivers of COVID-19: Neutrophil extracellular traps

NETs can be targeted by existing drugs: NE cleaves fibrinogen, PAR-1, and gelatinase zymogens.

Colchicine has been used safely to target NETs in mouse variations of Cystic Fibrosis patients.

Colchicine inhibits neutrophil migration and infiltration into sites of inflammation.

RUC-28 blocks prevent an inflammatory loop between NETs and TLRs.

Targeting COVID-19 with inhibitors and antibodies in progress.

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Summary by Cheleka Mpande