Monocytes and Macrophages Promote Increased Tissue Factor-Factor VIIa-Dependent Procoagulant Activity in Response to the SARS-CoV-2 Spike Protein

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Background
Venous thromboembolism (VTE) is a high-incidence complication of severe SARS-CoV-2-associated COVID-19. Recently, abnormal tissue factor expression has been linked to thromboembolic events in patients with COVID-19. Monocytes and macrophages are the predominant source of tissue factor in peripheral circulation, which suggests a potential pathomechanistic interplay between SARS-CoV-2 and the monocyte-macrophage axis. However, the link between monocytes and macrophages and the thromboembolic risk associated with COVID-19 is largely unaddressed.

Aims
In this study, we investigated changes in monocyte/macrophage procoagulant activity in response to the SARS-CoV-2 spike protein.

Methods
Immortalised human-derived monocytes and differentiated macrophages were treated with the SARS-CoV-2 spike protein, and changes in monocyte/macrophage procoagulant activity were assessed using biochemical and haematological assays.

Results
The ancestral Wuhan-Hu-1 SARS-CoV-2 spike protein induced time- and concentration-dependent increases in monocyte/macrophage procoagulant activity, characterised by a significant reduction in the recalcified clotting time of human plasma. Moreover, monocyte/macrophage procoagulant activity correlated with the severity of the SARS-CoV-2 variant of concern. The resulting clots possessed features consistent with the prothrombotic phenotype: decreased permeability. increased fibrin inclusion, and increased resistance to fibrinolysis. Furthermore, spike protein-induced procoagulant activity was shown to require extrinsic coagulation factors; in particular, recalcified clotting times were significantly affected by deficiencies in tissue factor-factor VIIa complexes.

Conclusion
Collectively, our data suggests that the SARS-CoV-2 spike protein promotes tissue factor/factor VIIa-dependent procoagulant activity in monocytes and macrophages as a pathocontributor to the COVID-19-associated coagulopathy. Investigations are on-going to further understand the pathophysiological interplay between SARS-CoV-2 and the monocyte-macrophage axis in patients with COVID-19.