



BRIDGE/HSS 2021: Heparin: Beyond Anticoagulation

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Abstract

- COVID-19 is associated with a hypercoagulable and inflammatory state predisposing patients to thrombosis. Reports suggest that heparin, a common anticoagulant, has effects beyond anticoagulation that will benefit the patient. This article will summarize non-anticoagulant effects of heparin including neutralization of chemokines and cytokines, reducing viral cellular entry, as well as neutralization of extracellular cytotoxic histones which in effect reduces the risk of a cytokine storm. Considering the pro-inflammatory nature of COVID-19, these anti-inflammatory effects targeted by heparin should be further studied.

Introduction

- ① COVID-19 induces hypercoagulable state→ results in potential thrombotic complications.
 - ① pro-inflammatory condition that triggers a cytokine storm.
- ① Heparin (anticoagulant with anti-inflammatory effects) used prophylactically and therapeutically to treat this.
- ① Let's explore the potential therapeutic benefits of heparin beyond anticoagulation in COVID-19 patients.

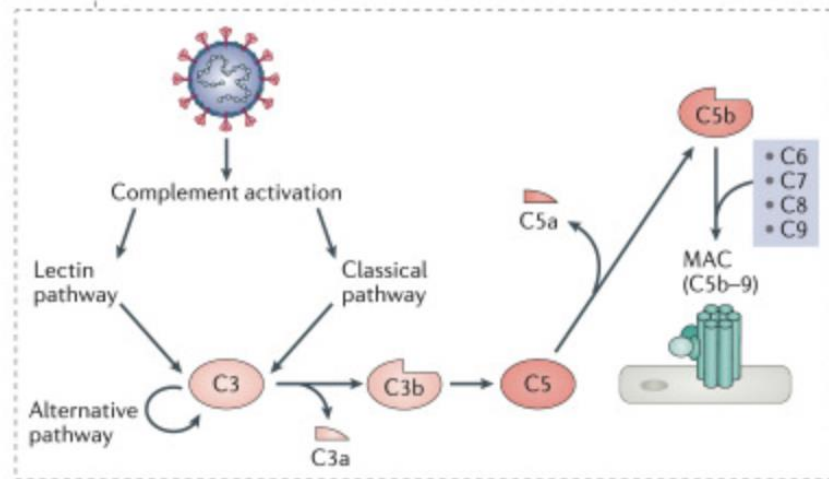
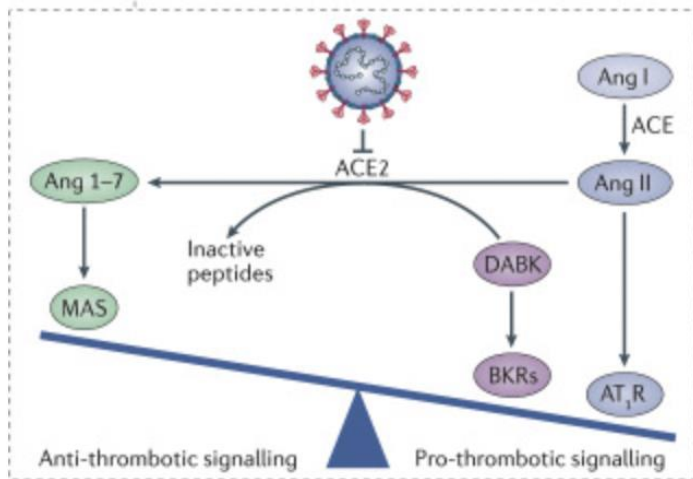
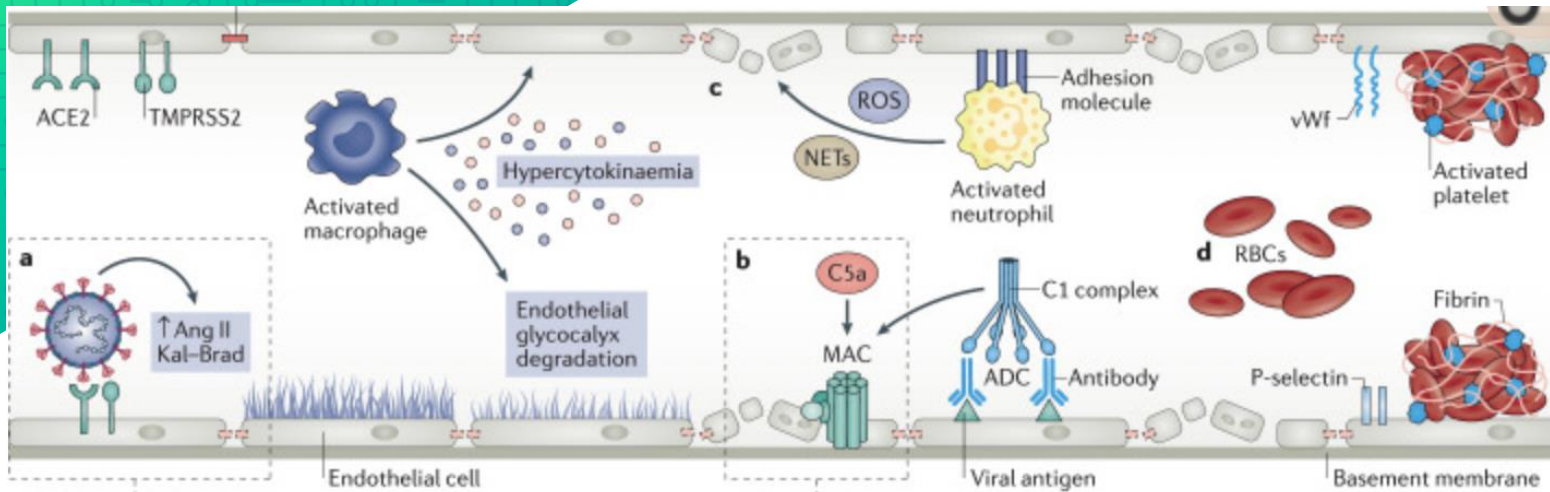
COVID-19: Hypercoagulable State

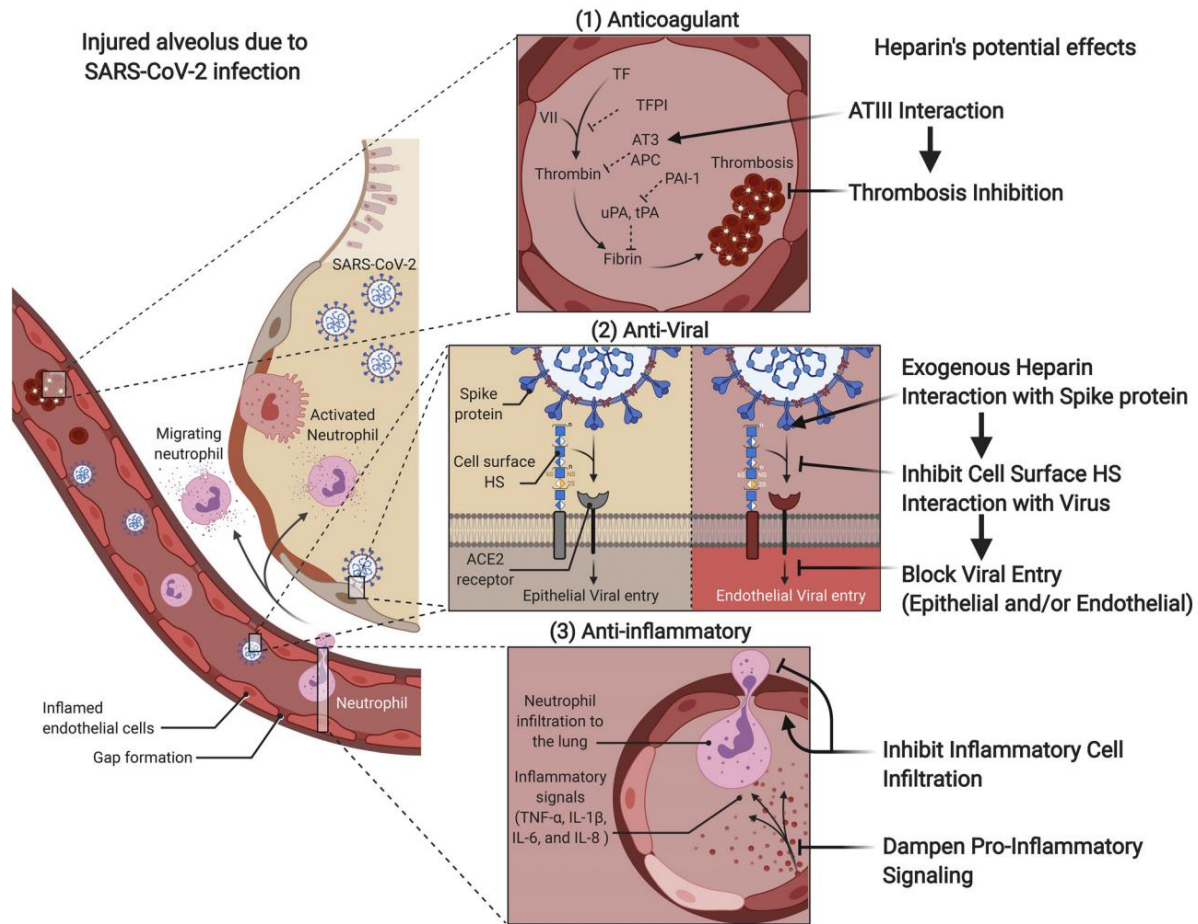
- ① COVID-19 infection induces hypercoagulable state
- ① Predisposes potential thrombotic complications.
 - ① Involves a host immune response that contributes to vascular endothelial cell injury, inflammation, activation of the coagulation cascade via tissue factor expression, and shutdown of fibrinolysis.
 - Occur more frequently in patients with more severe infection

COVID-19: Hypercoagulable State

Vascular endothelial cell injury

- ◎ Covid-19 spike protein binds to angiotensin converting enzyme 2 (ACE2) receptors
 - highly expressed in the lungs, heart, and vascular endothelial cells.
- ◎ Primary clot formation occurs directly in the lungs
- ◎ Capillary microthrombi leads to DIC (disseminated intravascular coagulopathy)
- ◎ Microvascular microthrombi triggers expression of tissue factor.
 - Increased tissue factor, in combination with local hypoxia from COVID-19 induced ARDS, creates a positive thrombo-inflammatory feedback loop, AKA a cytokine storm.





Hypercoagulability Management

- ① Heparin has suppressive effects against IL-6 and IL-8 expression from pulmonary epithelial cells
 - ① Helps to reduce thrombotic complications associated with cytokine storm in COVID-19 pneumonia.
 - ① Shown to have competitive binding activity to previous strains of coronavirus
 - Leads to reduced pathogenic activity of SARS-CoV-2

Anti-Inflammatory Effects of Heparin

- ① COVID-19 is associated with production of high levels of pro-inflammatory cytokines
- ① Heparin/LMWH are able to bind to the vast majority of chemokines and cytokines including IL-8
 - ① may neutralise their biological effect

Heparin Binding Peptides: A Novel Therapy

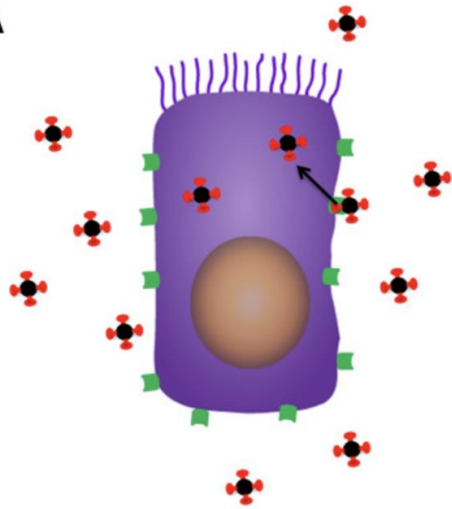
Heparan sulfate proteoglycans (HSPGs) are cell surface receptors that are involved in the uptake of viral pathogens

- ⊙ Heparin and heparan sulfate antagonize binding of pathogen to the HSPGs to prevent its cellular internalization.
 - Anticoagulant effect limits therapeutic use
- ⊙ Heparin-binding peptides (HBPs) are non-anticoagulant agents that antagonize binding of pathogens to HSPGs.
 - S1 subunit of spike glycoprotein of the virus binds to heparin
- ⊙ Sepsis in severe cases of COVID-19 induced coagulopathy
 - Increased risk of bleeding and clot formation
- ⊙ Heparin only beneficial with severe sepsis
 - ⊙ not recommended for mild cases (almost 70% of reported patients with COVID-19)

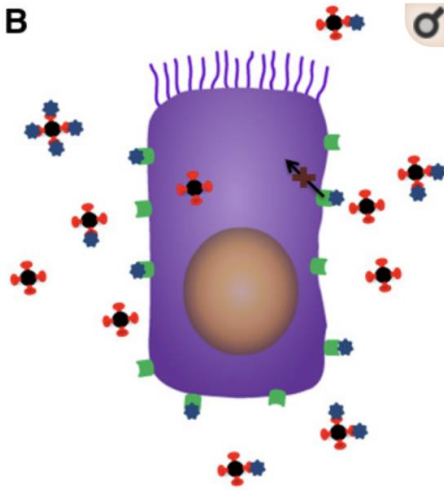
Heparin Binding Peptides (HBPs)

- Synthetic HBPs are effective in lab setting but not in animal cells
 - Upon infection induction, viruses enter the cytoplasm of cells (HBPs cannot reach to neutralize them).
 - Viruses hijack cellular endocytosis pathways to enter cells and travel through the cytoplasm
 - initiate replication and infection at nucleus
- HBPs cannot escape the endosomal/lysosomal system and are destroyed.
 - Ineffective to suppress cytoplasmic viral particles
- HBPs did not show strong antiviral activity to prevent infection
 - Only target the first stage of infection (on cell membrane)
 - unable to prevent cell-cell transmission

A



B



 HSPG

 HBPs

 Virus

Conclusion

- COVID-19 induces a hypercoagulable state in patients, causing them to be at higher risk of thrombosis including DVT and PE. There are several effects of heparin besides anticoagulation that could benefit patients with COVID-19. Further studies are needed to confirm these benefits, however, DOACs, due to their ease of administration, could also possibly be considered in the future for their wide ranging effects aside from anticoagulation.

Acknowledgments

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