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# **COVID-19 and acute limb ischemia: latest hypotheses of pathophysiology and molecular mechanisms**

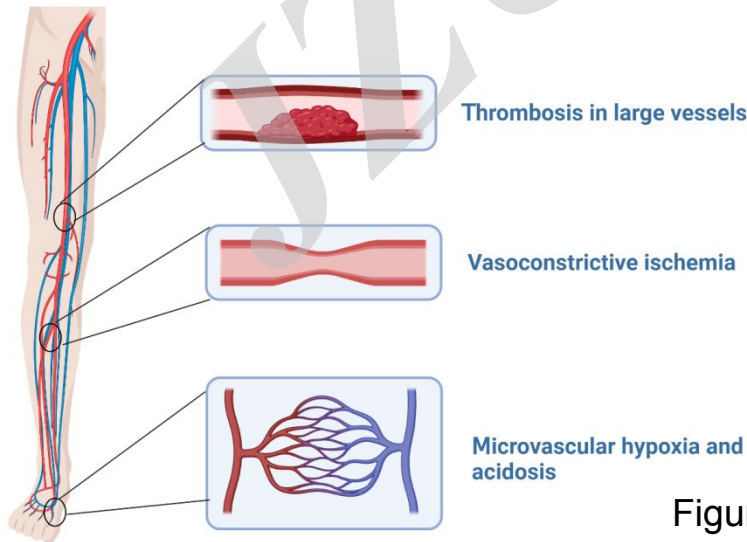
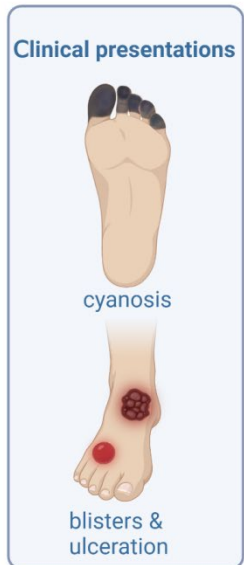
**Key words:** Acute limb ischemia, COVID-19 infection complication, Hypercoagulability, Thrombosis, Vasospasm, Hypoxia-inducible factor 1 $\alpha$ , ACE2, IFN-I, Tocilizumab

# Research Summary

Acute limb ischemia (ALI) has been increasingly recognized as a COVID-19-associated complication that often predicts a poor prognosis.



Figure 1



- The pathophysiological hypotheses involve hypercoagulability and thrombosis, vasoconstrictive ischemia, and microvascular hypoxia with acidosis, affecting different artery types.

Figure 2

# Research Summary

●The IL-6 and IFN-I balance significantly impacts the presentation of COVID-19-associated ALI.

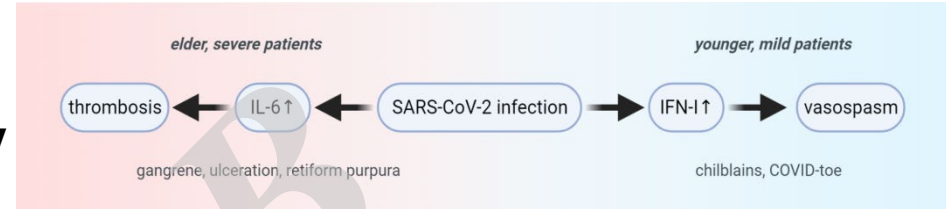


Figure 3

●The ACE2-Ang II mechanism altered following SARS-CoV-2 infection, contributing to the occurrence of ALI.

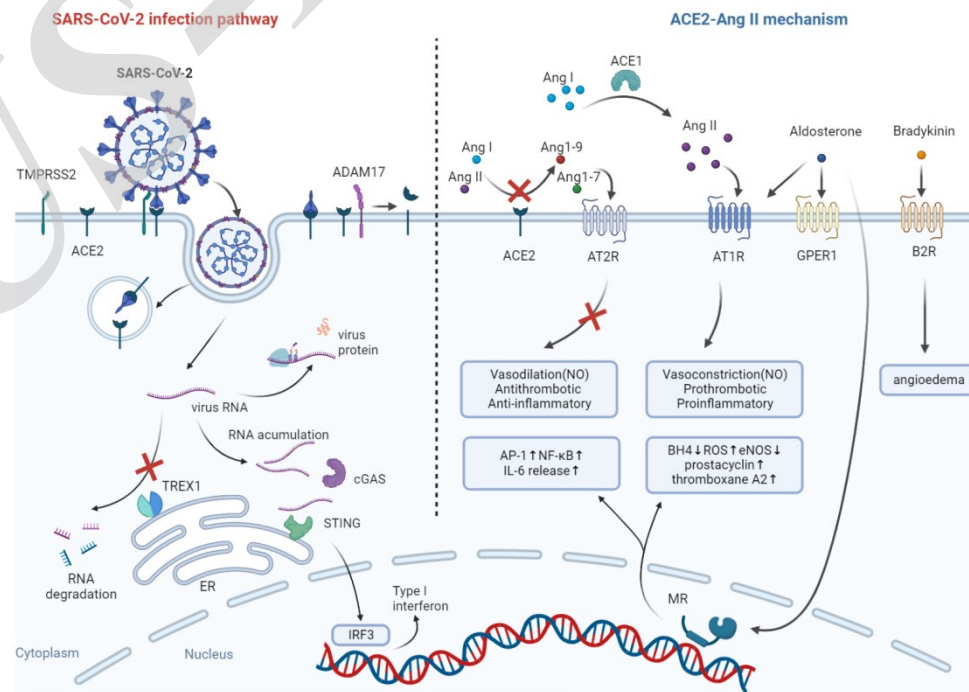


Figure 4

# Research Summary

Figure 4

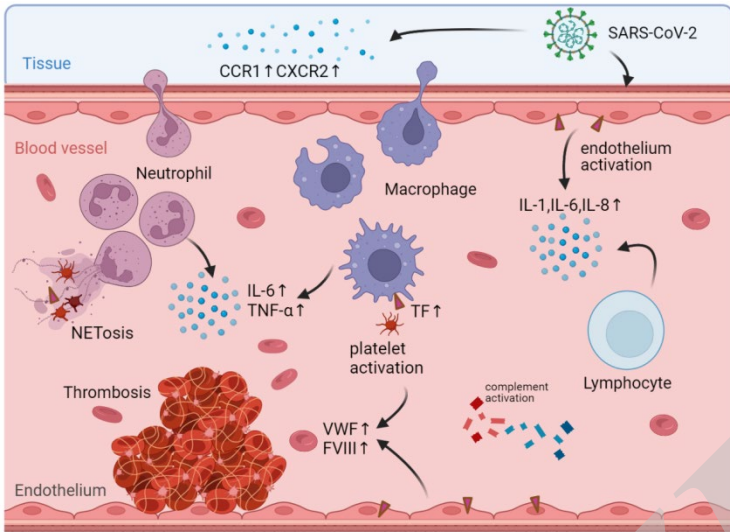


Figure 5

●The IL-6 primary cytokine plays a crucial role in regulating vascular endothelial function.

●Post COVID-19 infection, various inflammatory cells interact with vascular endothelium, mutually promoting thrombus formation through inflammatory factors and complement, etc.

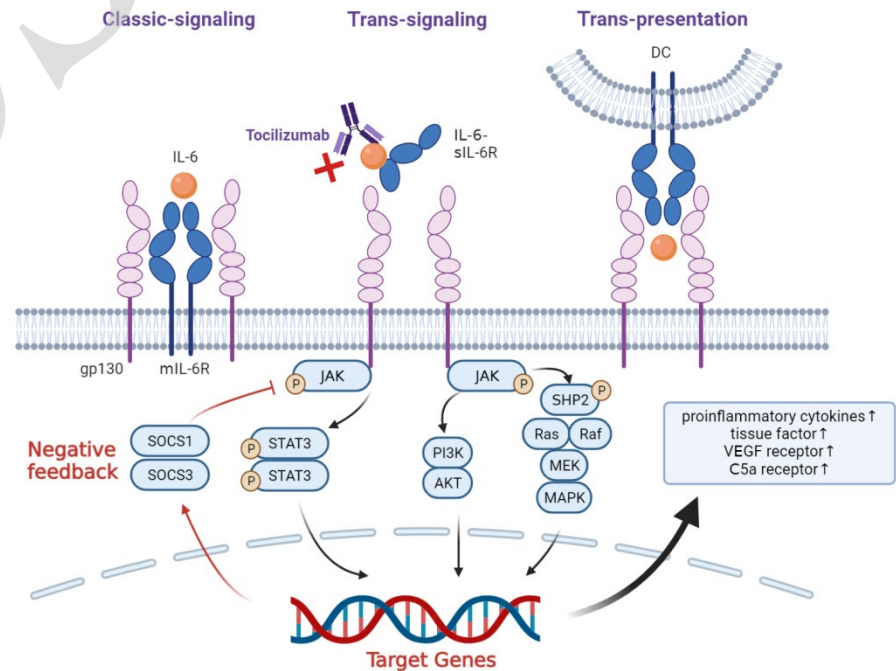


Figure 6

# Research Summary

| Risk Factors | Hypotheses  |
|--------------|---|
| Genetics     | TREX1 inactivation  |
|              | ACE2 polymorphism   |
|              | Recombination of chromosome structure and epigenetic change induced by SARS-Cov-2 |
| Age>65       | Lack of ACE2 expression   |
|              | IFN-I and IL-6 levels   |
|              | Comorbidity impact  |
| Male         | ACE2 gene location  |
|              | TLR7 gene and IFN-I   |
|              | Estrogen protection   |

•The hypotheses of COVID-19 severe complications involving genetics, age, gender, etc.

•Novel treatment strategies for COVID-19 associated ALI encompass a comprehensive approach, including anticoagulants, tocilizumab, and vasodilators.

# ***Innovation points***

**This article summarized the latest pathophysiological processes and molecular mechanism hypotheses related to the occurrence of COVID-19-associated ALI.**

- Discussed three distinct pathophysiological processes affecting different types of vessels
- Comprehensively analyzed the IL-6 and IFN-I balance hypothesis, explaining the occurrence of two different types of ALI manifestations.
- Specifically summarized the molecular mechanisms and effects of SARS-CoV-2 virus on the regulation of ACE2-Ang II
- Summarized the regulatory mechanisms of vascular inflammatory thrombosis post COVID-19.
- Proposed are potential risk factors and innovative treatment hypotheses based on these mechanism hypotheses.