Medical & healthcare, Drug discovery

Development of drugs for severe infectious diseases by targeting vascular permeability

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Abstract

In recent years, infectious diseases, including COVID-19, have posed a significant threat to public health. Although effective drugs targeting pathogens, immune cells, and inflammatory cytokines have been developed, fully controlling infectious diseases remains challenging. In this study, we focused on an underexplored process in severe infectious diseases—the increase in vascular permeability—and developed a novel therapeutic strategy to suppress it. By increasing the expression of Robo4, an endothelial cell-specific vascular stabilizing molecule, vascular permeability and mortality in a mouse sepsis model were reduced. Furthermore, we elucidated the regulatory mechanism of Robo4 expression and identified a small molecule that enhances Robo4 expression. Finally, we demonstrated that the small molecule reduced vascular permeability and mortality in sepsis and COVID-19 mouse models. These findings revealed the potential of Robo4-targeted therapies to alleviate severe infectious diseases by suppressing vascular permeability.

Background & Results

Vascular permeability is controlled by the adhesion between endothelial cells, which cover the inner surface of blood vessels. Robo4, a protein specifically expressed in endothelial cells, has been shown to stabilize cell adhesion and suppress vascular permeability. In this study, we investigated whether Robo4 overexpression in endothelial cells could suppress vascular permeability and alleviate the pathological conditions associated with severe infectious diseases. We generated endothelial cell-specific Robo4 overexpression mice and administered lipopolysaccharide, a bacterial membrane component, to the mice. Compared to wild-type mice, Robo4 overexpression mice exhibited reduced vascular permeability and lower mortality rates, indicating that endothelial Robo4 overexpression mitigates sepsis.

To develop drugs enhancing Robo4 expression, the signaling pathways that regulate Robo4 expression were investigated. We generated cell lines with the Robo4 promoter and screened for compounds that affect the promoter activity. Through the screening, an inhibitor for a receptor, ALK5, was identified as a Robo4 decreasing molecule. Further analysis of the signaling pathway revealed that ALK5-SMAD2/3 signaling enhances Robo4 expression, while ALK1-SMAD1/5 signaling, which was known to compete with ALK5-SMAD2/3 signaling, suppresses Robo4 expression. Based on the findings, we revealed that an ALK1 inhibitor increases Robo4 expression. Finally, we demonstrated that injection of the ALK1 inhibitor suppressed vascular permeability in the lungs and mortality in sepsis and COVID-19 model mice. These results indicated that drugs enhancing Robo4 expression alleviate severe infectious diseases by reducing vascular permeability.

Significance of the research and Future perspective

Our research highlights that drugs targeting vascular permeability could serve as new therapeutic agents for severe infectious diseases. This drug is expected to be effective against various pathogens because of its mechanism of action to inhibit vascular permeability. As a result, these drugs are expected to play a key role in treating future severe infectious diseases for which no pathogen-specific drugs or vaccines are available.

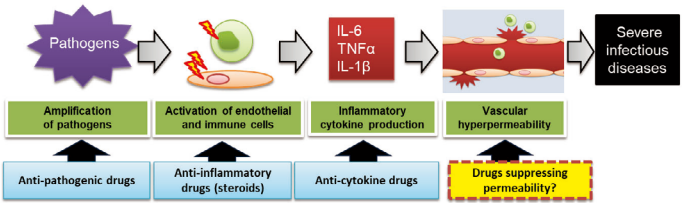

Fig. 1 Processes of severe infectious diseases and therapeutic drugs

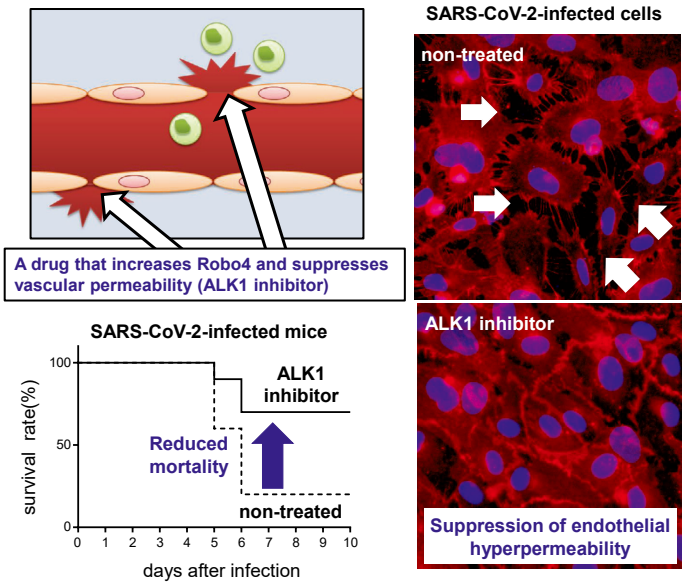

Fig. 2 Effects of the ALK1 inhibitor that promote Robo4 expression on COVID-19 models

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Keyword vascular permeability, severe infectious disease, COVID-19, sepsis, endothelial cells