学位論文の要約

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主論文の題名

Role of Periostin in Early Brain Injury After Subarachnoid Hemorrhage in Mice
（マウスくも膜下出血後の早期脳損傷におけるペリオスチンの役割）

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主論文の要約

Introduction

Accumulating evidences suggest that early brain injury (EBI) is the primary cause of poor outcome after aneurysmal subarachnoid hemorrhage (SAH). One of the most important pathological manifestations of EBI is the blood-brain barrier (BBB) disruption, and therefore elucidation of the pathogenesis is crucial to develop new therapies against EBI and to improve outcomes after SAH. Periostin is a matricellular protein (MCP) and activates many signaling pathways including mitogen-activated protein kinase (MAPK) through integrins. Periostin also directly interacts with another MCP tenascin-C (TNC), which was reported to cause post-SAH EBI via MAPK activation. However, the role of periostin has never been studied in the context of SAH. The aim of this study was to evaluate the role of periostin and the relationships with TNC in post-SAH EBI by focusing on BBB disruption.

Background

Periostin is a secreted extracellular matrix protein that has been reported to be a critical

factor in tumorigenesis, fibrosis, arthritis, atherosclerosis and inflammatory diseases. However, the effects of periostin on EBI have not been investigated in SAH.

Objectives

The aim of this study was to evaluate the role of periostin in EBI after SAH in a mice model.

Methods

Wild-type (n=226) and TNC knockout (n=9) C57BL/6 male adult mice underwent sham or filament perforation SAH modeling. Vehicle, anti-periostin antibody or recombinant periostin was randomly administrated by an intracerebroventricular injection at 30 minutes post-modeling. Neuroscores, SAH grading, brain water content, immunostaining and Western blotting were blindly evaluated at 24-48 hours post-SAH.

Results

Periostin was induced in capillary endothelial cells and neurons at 24 hours post-SAH. Anti-periostin antibody improved post-SAH neurobehavior, brain edema and BBB disruption associated with downregulation of TNC, inactivation of p38, extracellular signal-related kinase (ERK) 1/2 and matrix metalloproteinase (MMP)-9, and subsequent preservation of zona occludens-1. Recombinant periostin aggravated post-SAH brain edema and TNC induction. TNC knockout prevented post-SAH neurobehavioral impairments and periostin induction.

Consideration

This study first demonstrated that periostin was upregulated in cerebral cortex after experimental SAH and was responsible for EBI, which was mediated possibly by p38/ERK/MMP-9 signaling pathways. Anti-periostin antibody suppressed periostin expression in brain capillary endothelial cells and EBI as evaluated by neuroscore, brain edema and BBB permeability. Meanwhile, we found the interaction of periostin with TNC, which is another mediator of BBB disruption after SAH.

Conclusion

Periostin may cause post-SAH EBI through activating downstream signaling pathways and interacting with TNC, providing a novel approach for the treatment of EBI.