Medicine, Drug discovery

R-spondin 3/LGR4 (Leucine-rich repeat-containing G protein-coupled receptor 4) axis is a novel inflammatory and neurite outgrowth signaling system in the ischemic brain in mice

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Researchmap https://researchmap.jp/read8359?lang=en

Abstract

Existing treatments for ischemic stroke include a therapy that dissolves thrombi (t-PA), endovascular therapy that removes thrombi, and a therapeutic agent that inhibits the effects of reactive oxygen species (edaravone) produced after stroke. In this study, we found the possibility of developing novel therapeutic agents based on mechanisms that differ from those of these therapies. Recovery from neurological dysfunction after stroke requires the suppression of neuronal cell death caused by excessive inflammation from activated microglia/microphages in the brain and promotion of neurite outgrowth to reconstruct neuronal circuits. We have elucidated that RSPO3, a secreted protein, is a novel molecule that inhibits inflammation-mediated neuronal cell death and promotes neurite outgrowth by binding to the LGR4 receptor on microglia/macrophages/neurons, thereby restoring neuronal dysfunction after stroke.

Background & Results

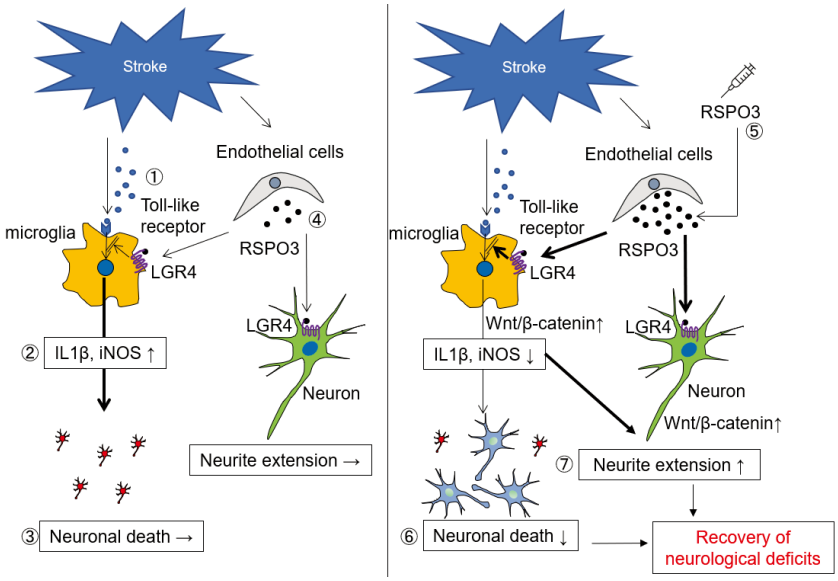
Since ischemic stroke is the second most common causative disease requiring long-term care after dementia, it is desirable to develop treatments that can prevent the deterioration of ischemic stroke and restore neurological dysfunction. Inflammation after stroke promotes such deterioration, and thus controlling inflammation is important to prevent the deterioration. In addition, recovery from neurological dysfunction requires reconstruction of the remaining neuronal circuitry, which in turn requires stimulation of neurite outgrowth.

RSPO3, a member of the secreted glycoprotein family (RSPO1-4), enhances the Wnt/β-catenin signaling pathway via the leucine-rich repeat-containing G protein-coupled receptor (LGR) 4/5/6 complex. Recently, it has been reported that LGR4 is expressed on lung macrophages in septic lung injury, and that the binding of RSPO3 and LGR4 also suppresses macrophage-mediated inflammation. We hypothesized that RSPO3/LGR4 signaling may regulate inflammation and promote neurite outgrowth after stroke.

In this study, we found that the receptor LGR4 is expressed in microglia, macrophages, and neurons, and RSPO3 is expressed in vascular endothelial cells in infarcted mice. RSPO3 inhibits neuronal cell death by suppressing the expression of inflammatory cytokines from microglia via TLR2, TLR4, and TLR9, and promotes neurite outgrowth in neurons. In addition, it also promotes neurite outgrowth in neurons. Taken together, these findings demonstrate that RSPO3/LGR4 signaling is a novel molecular mechanism that can ameliorate neuronal dysfunction after cerebral infarction by regulating inflammation and promoting neurite outgrowth.

Significance of the research and Future perspective

The discovery of this mechanism is expected to lead to a novel therapeutic concept, as the current situation targeting known molecules has not yet achieved sufficient therapeutic effects. In addition, RSPO3/LGR4 signaling has the ability to both suppress the expression of inflammatory cytokines from microglia and promote neurite outgrowth. This novel signal may be a promising target for therapeutic agents in ischemic stroke.



①In ischemic stroke, signals that induce inflammation from the damaged cells stimulates microglia(①), resulting in producing inflammatory cytokines(②)and induce neuronal death(③). RSPO3 is secreted from endothelial cells in the ischemic brain(④), but its effectiveness is not enough. When recombinant RSPO3 was administered (i.c.v.)(⑤). RSPO3 binds to receptor LGR4 exressed in microglia and neurons, promoting nuclear translocation of β-catenin, inhibiting neuronal cell death by suppressing the production of inflammatory cytokines (⑥) and promoting neurite outgrowth (⑦), thus improving neurological deficits after ischemic stroke.

Patent
Treatise Shimamura, Munehisa; Hayashi, Hiroki; Ju, Nan et al. R-spondin 3/LGR4 axis is a novel inflammatory and neurite outgrowth signaling system in the ischemic brain in mice. Stroke. 2023, 54(6), 1606-1615. doi: 10.1161/STROKEAHA.122.041970
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URL https://www.genestemcell.com/english/
Keyword ischemic stroke, inflammation, neurite, R-spondin