Letter by Zuo and Xu Regarding Article, “Norrin Protected Blood–Brain Barrier via Frizzled-4/β-Catenin Pathway After Subarachnoid Hemorrhage in Rats”

To the Editor:

We read with great interest the article by Chen et al,1 titled “Norrin protected blood–brain barrier via frizzled-4/β-catenin pathway after subarachnoid hemorrhage in rats,” published online in December 30, 2014, in Stroke. The authors performed a study to investigate a potential role and mechanism of norrin/frizzled-4 on protecting blood–brain barrier (BBB) integrity after subarachnoid hemorrhage (SAH), which could provide treatment option to protect BBB after SAH. Based on the authors’ results, we wish to communicate to the authors.

1. No small interfering RNA efficacy measurement data are provided. The magnitude of suppression of frizzled-4 small interfering RNA in vivo was less than that achieved in vitro. The estimation of frizzled-4 small interfering RNA efficacy, protein level of frizzled, and norrin after intracerebroventricular injection would strongly support the authors’ results.

2. Norrin was thought to be secreted by perivascular astrocyte, affecting β-catenin translocation from cytoplasmic into nuclear and an increase of occludin, vascular endothelial-cadherin, and zona occludens (ZO)-1 protein expressions.1 But, other molecular mechanisms of norrin were unclear. The gap junction protein connexin 43 (Cx43) is widely expressed in mammalian cells. Some research demonstrated that mice lacking Cx43 in glial fibrillary acidic protein–positive cells display astrocyte endfoot edema and weaken the BBB.3 Nagasawa et al3 reported that Cx43 are colocalized and coprecipitated with occludin, claudin-5, and ZO-1 in porcine BBB endothelial cells. These findings showed that Cx43-based gap junctions might be required to maintain the endothelial barrier function.1 Furthermore, knockdown of β-catenin expression resulted in a reduction in Cx43 protein. It suggests that β-catenin could regulate Cx43 expression.4

Based on the results of these studies, Cx43 signaling pathways may be mediated by norrin via frizzled-4/β-catenin pathway after SAH. So, we hypothesize that norrin may play a role in regulation of Cx43 and brain water content, resulting in protection of BBB after SAH? Thanks go to the authors for their contribution to investigate a potential role and mechanism of norrin/frizzled-4 on protecting BBB integrity after SAH. It will be interesting to explore the relationships between norrin and Cx43 after SAH that may be is one of the mechanisms of norrin to protect BBB after SAH.

Disclosures

None.

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