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LETTER TO THE EDITOR

Letter to "AAV/BBB-Mediated Gene Transfer of CHIP Attenuates Brain Injury Following Experimental Intracerebral Hemorrhage"

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Dear editor,

We read with great interest the article by Shuo Zhang et al. regarding the "AAV/BBB-Mediated Gene Transfer of CHIP Attenuates Brain Injury Following Experimental Intracerebral Hemorrhage" [1]. The authors reported that CHIP expression was increased in the peri-hematomal area in ICH rats. Furthermore, overexpression of CHIP by AAV/BBB viral platform ameliorated brain injury and inhibited neuronal necroptosis and inflammation in wild-type rats following ICH. Additionally, rats with CHIP deficiency ($CHIP^{M/M}$) experienced severe brain injury and increased levels of neuronal necroptosis and inflammation compared with the wild-type rats after ICH. The authors concluded that overexpression of CHIP may represent a therapeutic intervention for ICH. We really appreciate the interesting observation for their conclusion. However, after reading this article, we would like to highlight 2 important questions that it raises.

Firstly, the authors have used propidium iodide (PI) staining and protein levels of the necroptosis markers (RIPK1, RIPK3, and MLKL) to detect necroptosis in this study. It is worth noting that PI will stain all non-viable cells including apoptotic (at least in some setting) and necrotic cells. Additionally, based on the Recommendations of the Nomenclature Committee on Cell Death 2018 [2], necroptosis was critically depended on the sequential activation of RIPK3 and MLKL, but not only their increased protein levels. So, the sensitivity and specificity of this test should be stated. Alternatively, some additional evaluation for necroptosis can be done because this is the most important mechanism measure in this study.

Meanwhile, in this study, the injection of bacterial collagenase type VII into the right striatum was used to induce ICH model in rat. The collagenase could induce potential neuroinflammatory reactions in ICH modeling. As the TNF-α is a key activator of necroptosis, potential neuroinflammatory properties induced by collagenase may affect the actual extent of necroptosis [2, 3]. How to evaluate the side effects of collagenase on inflammatory response and necroptosis in this study? The authors also declared that CHIP overexpression ameliorated inflammation through inhibiting necroptosis in rats with collagenase-induced ICH in this study; we believe that the relationship of inflammation and necroptosis should be considered very carefully in the model selection.

Declarations

Ethics Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

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