Lysosomal-associated transmembrane protein 5 (LAPTM5) has been demonstrated to be involved in regulating immunity, inflammation, cell death, and autophagy in the pathophysiological processes of many diseases. However, the function of LAPTM5 in cerebral ischemia-reperfusion (I/R) injury has not yet been reported. In this study, we found that LAPTM5 expression was dramatically decreased during cerebral I/R injury both in vivo and in vitro. LAPTM5 knockout (KO) mice were compared with a control, and they showed a larger infarct size and more serious neurological dysfunction after transient middle cerebral artery occlusion (tMCAO) treatment. In addition, inflammatory response and apoptosis were exacerbated in these processes. Furthermore, gain- and loss-of-function investigations in an in vitro model revealed that neuronal inflammation and apoptosis were aggravated by LAPTM5 knockdown but mitigated by its overexpression. Mechanistically, combined RNA sequencing and experimental verification showed that the apoptosis signal-regulating kinase 1 (ASK1)-c-Jun N-terminal kinase (JNK)/p38 pathway was mainly involved in the detrimental effects of LAPTM5 deficiency following I/R injury. Specifically, LAPTM5 directly interacts with ASK1, leading to decreased ASK1 N-terminal dimerization and the subsequently reduced activation of downstream JNK/p38 signaling. In conclusion, LAPTM5 was demonstrated to be a novel modulator in the pathophysiology of brain I/R injury, and targeting LAPTM5 may be feasible as a stroke treatment [1].

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