Title: **Inhibition of autophagy accelerates hematoma clearance via activating SQSTM1/Keap1/Nrf2 signaling pathway after experimental intracerebral hemorrhage**

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Abstract Effective hematoma clearance and/or facilitating phagocytosis of microglia/microphages (MMΦ) is a promising therapeutic strategy to improve functional recovery after intracerebral haemorrhage (ICH). Autophagy and phagocytosis are lysosomal clearance pathways that share mechanistic and functional similarities. Accumulating evidence suggests that there exist some interactions between these two processes. However, how autophagy influences erythrophagocytosis in hematoma post-ICH remains unknown. It has been shown that inhibiting excessive microglial autophagy can be regarded as a method to ameliorate inflammatory injury after ICH. Sequestosome 1 (SQSTM1) is the adaptor protein responsible for recognition and loading of cargo in to the autophagosomes for clearance, and inhibition of autophagy will lead to an increased level of SQSTM1. It has been found that SQSTM1 could activate transcription factor Nrf2 through inactivation of Keap1, thus upregulating scavenger receptors and driving microglia/macrophages (MMΦ) transition to M2 phenotype. The aim of this research is to evaluate the role of autophagy on the erythrophagocytosis activity and explore the involved molecular mechanisms during hematoma resolution in experimental ICH. Male, adult CD1 mice were subjected to intrastriatal injection of collagenase to induce ICH and randomly assigned to receive autophagy inhibitor (3-MA), autophagy activator (rapamycin) or vehicle which was administered intracerebroventricular at 1 h after ICH. To elucidate the underlying mechanism, SQSTM1 KO CRISPR plasmid was administered 48 h prior to ICH induction. Brain edema, short- and long-term neurobehavior evaluation, hematoma volume, hemoglobin levels, and iron staining were performed to evaluate the role of autophagy in hematoma resolution. In addition, western blot, immunoprecipitation and immunofluorescence staining were conducted to explore the molecule mechanisms. We found that inhibiting autophagy with 3-MA enhanced the process of hematoma clearance after ICH, attenuated brain edema and improved short-term and long-term neurobehavior function. Autophagy inhibitor 3-MA increased the expression of scavenger receptor CD36 and CD163, and promoted M2 MMΦ polarization. In addition, iron deposition in perihematomal region and neurodegeneration in hippocampus were attenuated after inhibition of microglial autophagy. Potential underlying mechanism by which autophagy modulated phagocytosis is activation of SQSTM1/Keap1/Nrf2 pathway after administration with 3-MA. And the protection effects can be partially reversed after in vivo CRISPR knock down SQSTM1. Therefore, inhibition of excessive autophagy in microglia might be taken as a target to accelerate hematoma clearance in the future.