Title: **MicroRNA-451 regulates angiogenesis and neurological recovery after intracerebral hemorrhage by targeting macrophage migration inhibitory factor.**

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Abstract Angiogenesis exists in peripheral hematoma tissue after intracerebral hemorrhage (ICH) and acts as an important role in nerve repair. MicroRNA-451 (miR-451) is a kind of microRNA that plays an important role in the proliferation and migration in cells, such as carcinoma cells and vascular endothelial cells. Research has shown that miR-451 could act on macrophage migration inhibitory factor (MIF), a proinflammatory factor playing an important role in regulating vascular function. Currently, there are few studies on the role of miR-451 in ICH. This study aims to evaluate the role of miR-451 on angiogenesis after ICH and explore the involved mechanisms. Male, adult wild-type (WT)/miR-451 knock-out (miR-451 KO) mice were subjected to intrastriatal injection of collagenase to induce ICH. Levels of miR-451 in the peripheral hematoma tissues after ICH were detected by quantitative real-time PCR (qPCR). After miR-451 overexpression, KO or application of MIF inhibitor, angiogenesis in the peripheral hematoma tissues after ICH was detected by immuno-fluorescence staining and FITC perfusion and neurological deficits were assessed by modified neurological score, forelimb placement test, and corner test. In vitro, ICH condition of human brain microvascular endothelial cells (hBMECs) were stimulated by hemin. The proliferation, migration, angiogenesis of HBMECs was respectively detected by CCK-8 assay, wound healing assay, transwell migration assay and matrigel tube formation assay. In addition, dual-luciferase reporter assay, qPCR and Western blots were conducted to explore the molecule mechanisms. We detected decreased miR-451 levels in perihematomal tissues after ICH. MiR-451 overexpression inhibited angiogenesis and aggravated neurological deficits in mice, while miR-451 KO promoted angiogenesis and alleviated neurological deficits. In vitro, decreased miR-451 levels were also detected in HBMECs exposed to hemin. MiR-451 overexpression significantly decreased proliferation, migration, angiogenesis of HBMECs, while miR-451 KO significantly increased its proliferation, migration, angiogenesis. Furthermore, dual-luciferase reporter assay showed that miR-451 directly targeted the 3'-UTR region of MIF mRNA and negatively regulated its expression. After miR-451 overexpression or KO in ICH mice, we detected opposite changes between miR-451 and MIF protein levels in perihematomal tissues. In addition, hosphorylation levels of ERK1/2 and Akt were significantly increased after ICH and got a further incease after miR-451 KO, while the increase could be offset by MIF inhibitor. Collectively, level of miR-451 was decreased after ICH. Decreased miR-451 promoted angiogenesis and neurological recovery after ICH by negatively regulating MIF through ERK1/2 and Akt pathways. MiR-451/MIF axis may be a potential target for ICH treatment.