

RUNX3 Influences Edema After Intracerebral Hemorrhage via TIMP1-mediated Regulation of the PI3K/AKT Pathway

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Abstract

Intracerebral hemorrhage (ICH) accounts for 20%–30% of acute cerebrovascular diseases in China, and perihematomal brain edema (PHE) secondary to ICH is a critical factor contributing to high mortality and disability rates during the acute phase. Although immune-inflammatory responses play an important role in the development of PHE, the underlying molecular mechanisms remain poorly understood. This study aimed to explore the role of RUNX3 in brain edema formation after ICH and its association with TIMP1 and the PI3K/AKT signaling pathway. Transcriptome sequencing was performed on perihematomal brain tissues from clinical ICH patients and normal brain tissues. Weighted gene co-expression network analysis (WGCNA), combined with three machine learning algorithms—Lasso regression, support vector machine (SVM), and random forest (RF)—was applied to screen key immune-related gene biomarkers. Receiver operating characteristic (ROC) curves were used to evaluate diagnostic performance, while Gene Set Enrichment Analysis (GSEA) was employed to identify associated signaling pathways. Immune infiltration analysis was conducted to assess the correlation between gene expression and immune cell infiltration, and the GEO external dataset (GSE24265) was utilized to validate downstream target genes. A total of 163 co-expressed differentially expressed genes were identified, and RUNX3 was determined as the key immune-related gene biomarker through cross-validation across the three machine learning algorithms. ROC analysis demonstrated that RUNX3 distinguished ICH patients from normal controls with an AUC > 0.90 (95% CI: 0.89–0.95), indicating its potential diagnostic value. GSEA revealed that gene sets associated with the PI3K/AKT signaling pathway were significantly enriched in samples with high RUNX3 expression. Immune infiltration analysis further showed that RUNX3 expression was significantly correlated with the infiltration abundance of multiple immune cell types, including microglia and macrophages. Through TRRUST database prediction and cross-validation with the GEO dataset (GSE24265), TIMP1 was identified as a potential downstream target gene of RUNX3. In conclusion, RUNX3 serves as a key immune-related gene biomarker associated with brain edema following ICH, potentially participating in neuroinflammation and brain edema progression through the regulation of TIMP1 and involvement in PI3K/AKT signaling-associated processes. This study provides a theoretical basis for understanding the mechanisms of secondary brain injury after ICH and suggests potential molecular targets for future functional validation.

Keywords

Intracerebral Hemorrhage, Perihematomal Edema, RUNX3, TIMP1, PI3K/AKT Signaling Pathway