34

EGFR activation correlates with intracranial pressure and survival in a mixed intracranial bleeding porcine model

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Background: The pig model is an advanced system for studying human brain trauma due to its anatomical similarities with the human brain, such as brain size, gyrencephalic structure and white-to-gray matter ratio. Ischemia, a common feature in fatal acute intracranial hemorrhage, occurs when brain tissue compression obstructs vasculature, reducing cerebral blood flow. This ischemia-driven injury is central to brain injury pathophysiology.

Objective: This study investigates the role of receptor tyrosine kinases (RTKs) in the injury response and clinical outcomes, focusing on their potential as therapeutic targets for edema and reperfusion control after injury.

Methods: We developed a sustained, resuscitated pig model of acute mixed intracranial hemorrhage with ICP, providing a robust system for in-depth examination of brain injury. Multimodal brain monitoring and neurological assessments offered valuable insights into the progression of the injury. Postmortem analysis, transcriptional evaluations combined with western blotting and protein arrays, allowed the assessment of RTK pathway activation.

Results: Our findings showed that 44-54 hours post-injury, animals exhibited signs of hypoxia, neuroinflammation, and extensive tissue damage. Elevated HIF1-α expression in the ipsilateral hemisphere confirmed local hypoperfusion. Inflammatory markers such as TNF-α, CD68, and MMP-9 were upregulated in both hemispheres, reflecting a generalized neuroinflammatory response. Gene expression analysis revealed increased markers of vascular, astrocytic, and neuroimmune activation, particularly related to endothelial integrity and astrocyte activation.

RTK expression analysis showed increased levels of VEGFR1, VEGFR2, Tie-2, EGFR, and Axl in the injured cortex, with activation of EGFR/ErbB4 and HGFR/Met pathways. Hierarchical clustering of intrand astrocytic markers revealed distinct patterns of activation, highlighting the relationship between ICP severity and astrocyte response. Elevated EGFR phosphorylation correlated with astrocyte activation and ICP severity, survival, and Glasgow Coma Scale outcomes.

Conclusions: These findings suggest that modulating EGFR signaling may offer a therapeutic approach for managing ICP and improving outcomes in traumatic brain injury.