ERBB4

Receptor tyrosine protein kinase erbB-4 is an enzyme that in humans is encoded by the ERBB4 gene. Alternatively spliced variants that encode different protein isoforms have been described; however, not all variants have been fully characterized.

Specifically, proteomics and phosphoproteomic analyses identify aberrant ERBB4-SRC signaling in group 4 medulloblastoma. Hence, enforced expression of an activated SRC combined with p53 inactivation induces murine tumors that resemble group 4 medulloblastoma. Therefore, the integrative proteogenomics approach of Forget et al. unveils an oncogenic pathway and potential therapeutic vulnerability in the most common medulloblastoma subgroup [1)].

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investigated ERBB4 as a prognostic marker and therapeutic target in GBM. Using RT-qPCR, we quantified mRNA encoding total ERBB4 and known ERBB4 variants in GBM and non-neoplastic normal brain (NNB) samples. Using immunohistochemistry, we characterized the localization of total and phosphorylated ERBB4 (p-ERBB4) and EGFR protein in archived GBM samples and assessed their association with patient survival. Furthermore, we evaluated the effect of ERBB4 phosphorylation on angiogenesis and tumorigenicity in GBM xenograft models. Total ERBB4 mRNA was significantly lower in GBM than NNB samples, with the juxtamembrane JM-a and cytoplasmic CYT-2 variants predominating. ERBB4 protein was ubiquitously expressed in GBM but was not associated with patient survival. However, high p-ERBB4 in 11% of archived GBM samples, independent of p-EGFR, was associated with shorter patient survival (12.0 ± 3.2 months) than was no p-ERBB4 (22.5 ± 9.5 months). Increased ERBB4 activation was also associated with increased proliferation, angiogenesis, tumorigenicity and reduced sensitivity to anti-EGFR treatment in xenograft models. Despite low ERBB4 mRNA in GBM, the functional effects of increased ERBB4 activation identify ERBB4 as a potential prognostic and therapeutic target [2)].

Activation of the receptor tyrosine kinase ErbB4 can cause intramembrane proteolysis and release a soluble intracellular domain (ICD) that modulates transcription in the nucleus.

A study was carried out to investigate the potential roles of ErbB4 in preserving BBB integrity after experimental SAH, as well as the underlying mechanisms of its protective effects. Endovascular perforation was used to prepare a rat SAH model. The SAH grade, neurological score, brain edema and BBB permeability were evaluated after surgery. Immunohistochemistry was used to determine the localization of ErbB4 and yes-associated protein (YAP). ErbB4 activator Nrg1 isoform β1 (Nrg1β1), Specific ErbB4 siRNA, YAP siRNA and PIK3CB specific inhibitor TGX 221 were used to manipulate the proposed pathway. The expression levels of ErbB4 ICD and YAP were markly increased after SAH. Double immunohistochemistry labeling showed that ErbB4 and YAP were expressed in endothelial cells and neurons. Activation of ErbB4 by Nrg1β1 (dosage 150 ng/kg) treatment promoted the neurobehavioral deficit, alleviated the brain water content and reduced albumin leakage 24 and 72 h after SAH. ErbB4 activation significantly promoted YAP and PIK3CB activity and increased the expression of tight junction proteins Occludin and Claudin-5. Depletion of ErbB4 aggravated neurological impairment and BBB disruption after SAH. The beneficial effects of ErbB4 activation were abolished by YAP small-interfering RNA and specific PIK3CB inhibitor. Activation of ErbB4 improved neurological performance after SAH through the YAP/PIK3CB signaling pathway, this neuroprotective

effects may associated with BBB maintenance [3].

Previous studies suggested that disturbance of Neuregulin1 (NRG1)/ErbB4 signaling is associated with cognitive impairments, as well as neuronal apoptosis and neuroinflammation in CNS. However, the expression pattern of hippocampal NRG1/ErbB4 has not been systematically investigated during CCH. Here, we aim to investigate the temporal changes of hippocampal NRG1/ErbB4 during CCH and their possible relationship with neuronal apoptosis and glial activation. Morris water maze (MWM) and Radial arm water maze (RAWM) tests were used to analyze cognitive impairment in 2VO rats at 28 days post-surgery, and Enzyme-Linked Immunosorbent Assay (ELISA), western blotting and immunostaining were performed at different time points (24 h, 7 days, 14 days, 28 days) to detect the expression pattern of NRG1/ErbB4 and the distribution of ErbB4. Neuronal nuclei (NeuN), NeuN/TUNEL, Iba1 and GFAP immunostaining and caspase activity in hippocampal CA1 subarea were assessed during CCH as well. We found that the expression of NRG1 and phosphorylated ErbB4 (pErbB4)/ErbB4 changed in a time-dependent manner (up-regulated in the acute phase and then decreased in the chronic phase of CCH). Besides, ErbB4-expressed neurons and selective types of GABAergic cells decreased after CCH, but the distribution pattern of ErbB4 remained unchanged. In addition, the expression of hippocampal NRG1/ErbB4 positively correlated with the level of neuronal apoptosis (both NeuN/TUNEL immunostaining and caspase-3 activity), but not with glial activation according to Pearson's correlation. These findings indicated that hippocampal NRG1/ErbB4 may be involved in the pathogenesis of CCH, especially neuronal apoptosis during CCH [4].

1)
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