NOX2

Cytochrome b-245 heavy chain also known as cytochrome b(558) subunit beta or NADPH oxidase 2 or Nox2 is a protein that in humans is encoded by the CYBB gene.

The protein is a super-oxide-generating enzyme that forms reactive oxygen species (ROS).

Yingze et al. tested the hypothesis that ROS activity mediated by NADPH oxidase 2 (NOX2) contributes to acute brain injury but promotes functional recovery during the delayed phase, which is linked with neuroinflammation, autophagy, angiogenesis, and the PI3K/Akt signaling pathway.

They used the NOX2 inhibitor apocynin to study the role of NOX2 in brain injury and functional recovery in a middle cerebral artery occlusion (MCAO) stroke mouse model. Infarct size, neurological deficits and behavior were evaluated on days 3, 7, 10, and 14 after reperfusion. In addition, dynamic NOX2-induced ROS levels were measured by dihydroethidium (DHE) staining. Autophagy, inflammasomes, and angiogenesis were measured by immunofluorescence staining and western blotting. RNA sequencing was performed, and bioinformatics technology was used to analyze differentially expressed genes (DEGs), as well as the enrichment of biological functions and signaling pathways in ischemia penumbra at 7 days after reperfusion. Then, Akt pathway-related proteins were further evaluated by western blotting.

The results showed that apocynin injection attenuated infarct size and mortality 3 days after stroke but promoted mortality and blocked functional recovery from 5 to 14 days after stroke. DHE staining showed that ROS levels were increased at 3 days after reperfusion and then gradually declined in WT mice, and these levels were significantly reduced by the NOX2 inhibitor apocynin. RNA-Seq analysis indicated that apocynin activated the immune response under hypoxic conditions. The immunofluorescence and western blot results demonstrated that apocynin inhibited the NLRP3 inflammasome and promoted angiogenesis at 3 days but promoted the NLRP3 inflammasome and inhibited angiogenesis at 7 and 14 days after stroke, which was mediated by regulating autophagy activation. Furthermore, RNA-Seq and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis indicated that apocynin injection resulted in PI3K-Akt signaling pathway enrichment after 7 days of MCAO. We then used an animal model to show that apocynin decreased the protein levels of phosphorylated PI3K and Akt and NF-κB p65, confirming that the PI3K-Akt-NF-κB pathway is involved in apocynin-mediated activation of inflammation and inhibition of angiogenesis.

NOX2-induced ROS production is a double-edged sword that exacerbates brain injury in the acute phase but promotes functional recovery. This effect appears to be achieved by inhibiting NLRP3 inflammasome activation and promoting angiogenesis via autophagy activation [1)].

In a study, Wang et al., found that deletion of NOX2 (NOX2-KO) significantly decreases the population of radial glia-like NSCs and neuroblasts but maintains the population of non-radial Sox2 expressing stem cells under physiological (non-injury) conditions. Surprisingly, the brains of NOX2-KO mice demonstrated a robust increase in the number of neuroblasts during the first week after TBI, as compared to the wild-type group. This increase may result from an enhanced proliferation of NPCs in a lower ROS environment after brain injury, as further examination revealed a significant increase of dividing neuroblasts in both NOX2-KO and NOX inhibitor-treated mouse brain during the first week

following TBI. Finally, 5-Bromo-2'-deoxyuridine (BrdU) lineage tracing demonstrated a significantly increased number of newborn neurons were present in the perilesional cortex of NOX2-KO mice at 5 weeks post TBI, indicating that deletion of NOX2 promotes long-term neurogenesis in the injured brain following TBI. Altogether, these findings suggest that targeting NOX through genetic deletion or inhibition enhances post-injury neurogenesis, which may be beneficial for recovery following TBI [2].

1)
Yingze Y, Zhihong J, Tong J, Yina L, Zhi Z, Xu Z, Xiaoxing X, Lijuan G. NOX2-mediated reactive oxygen species are double-edged swords in focal cerebral ischemia in mice. J Neuroinflammation. 2022 Jul 14;19(1):184. doi: 10.1186/s12974-022-02551-6. PMID: 35836200.
2)
Wang J, Ma MW, Dhandapani KM, Brann DW. NADPH Oxidase 2 Deletion Enhances Neurogenesis Following Traumatic Brain Injury. Free Radic Biol Med. 2018 May 18. pii: S0891-5849(18)30893-1. doi: 10.1016/j.freeradbiomed.2018.05.069. [Epub ahead of print] PubMed PMID: 29782989.