see Nrf2 signaling pathway.

Nuclear factor (erythroid-derived 2)-like 2, also known as NFE2L2 or Nrf2, is a transcription factor that in humans is encoded by the NFE2L2 gene, which protects cells from the oxidative damage caused by reactive oxygen species and, on the other hand, are associated with resistance to cancer treatments.

Several drugs that stimulate the NFE2L2 pathway are being studied for the treatment of diseases that are caused by oxidative stress.

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In glioma, temozolomide resistance is due to overexpression of CD147 protein and induction of Nuclear factor-erythroid 2 related factor 2 [1].

Inhibition of Nrf2 expression might enhance the effect of TMZ on the treatment of Glioblastoma and might be a new therapeutic strategy [2].

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NFE2L2 SNP, rs10183914, is significantly associated with aneurysmal subarachnoid hemorrhage outcome. This is consistent with a clinically relevant pathophysiological role for oxidative and inflammatory brain injury due to blood and its breakdown products in aSAH. Furthermore, the findings support NRF2 as a potential therapeutic target following aSAH and other forms of intracranial hemorrhage [3]

# Protective Role of NRF2 in Macrovascular Complications of Diabetes

Macrovascular complications develop in over a half of the diabetic individuals, resulting in high morbidity and mortality. This poses a severe threat to public health and a heavy burden to social economy. It is therefore important to develop effective approaches to prevent or slow down the pathogenesis and progression of macrovascular complications of diabetes (MCD). Oxidative stress is a major contributor to MCD. Nuclear factor (erythroid-derived 2)-like 2 (NRF2) governs cellular antioxidant defence system by activating the transcription of various antioxidant genes, combating diabetes-induced oxidative stress. Accumulating experimental evidence has demonstrated that NRF2 activation protects against MCD. Structural inhibition of Kelch-like ECH-associated protein 1 (KEAP1) is a canonical way to activate NRF2. More recently, novel approaches, such as activation of the Nfe2l2 gene transcription, decreasing KEAP1 protein level by microRNA-induced degradation of Keap1 mRNA, prevention of proteasomal degradation of NRF2 protein and modulation of other upstream regulators of NRF2, have emerged in prevention of MCD. This review provides a brief introduction of the pathophysiology of MCD and the role of oxidative stress in the pathogenesis of MCD. By reviewing previous work on the activation of NRF2 in MCD, we summarize strategies to activate NRF2, providing clues for future intervention of MCD. Controversies over NRF2 activation and future perspectives are also provided in this review [4].

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Accumulating evidence suggests that nuclear factor erythroid 2-related factor 2 (Nrf2) could play a neuroprotective role in experimental TBI models by regulating the expression of numerous antioxidant, anti-inflammatory, and neuroprotective proteins. However, whether Nrf2 is activated in

patients following TBI is still unknown.

In a study, human brain tissues were obtained during surgery from patients suffering from TBI. The purpose of this study was to investigate the expression of Nrf2 and Nrf2-regulated gene products, NAD(P)H quinine oxidoreductase 1, and glutathione S-transferase in human injured brain tissue after TBI.

The results revealed that the nuclear level of Nrf2 was significantly increased in injured brain tissues, whereas the cytoplasmic level of Nrf2 was markedly decreased. In addition, the expression of NAD(P)H quinine oxidoreductase 1 and glutathione S-transferase was significantly upregulated. Nrf2 may be activated and confer neuroprotection against secondary brain injury following TBI. Therefore, Nrf2 could serve as a promising molecular target for the treatment of TBI [5)].

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The cytoplasmic NRF2 expression was higher in tumors with a higher malignancy grade, whereas the nuclear and cytoplasmic DJ1 expression was associated with a lower grade. The presence of the isocitrate dehyrdogenase 1 mutation (IDH1) was associated with an increasing cytoplasmic and nuclear expression of NRF2 and a nuclear DJ1 expression. When primary grade IV astrocytomas were compared to secondary glioblastomas, nuclear DJ1 was associated with secondary tumors. In grade II-IV tumors, the cytoplasmic NRF2 expression was associated with a poor prognosis, whereas nuclear NRF2 and both cytoplasmic and nuclear DJ1 were associated with a better patient prognosis. Recurrent homozygous deletions of DJ1 were observed, especially in the IDH-wildtype samples. When only the glioblastomas were evaluated, nuclear NRF2 and SRNX1 predicted better survival. As a conclusion, NRF2, DJ1 and SNXR1 can be used as prognosticators in gliomas [6)].

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Nrf2 is a basic leucine zipper (bZIP) protein that regulates the expression of antioxidant proteins that protect against oxidative damage triggered by injury and inflammation and is a key regulator in these redox-dependent events and operates in cytoprotection, drug metabolism and malignant progression in cancer cells.

Fan et al. show that patients with primary malignant brain tumors (glioblastomas, WHO °IV gliomas, Glioblastoma) have a devastating outcome and overall reduced survival when Nrf2 levels are upregulated. Nrf2 overexpression or Keap1 knockdown in glioma cells accelerate proliferation and oncogenic transformation. Further, activation of the Nrf2-Keap1 signaling upregulates xCT (aka SLC7A11 or system Xc-) and amplifies glutamate secretion thereby impacting on the tumor microenvironment. Moreover, both fostered Nrf2 expression and conversely Keap1 inhibition promote resistance to ferroptosis. Altogether, the Nrf2-Keap1 pathway operates as a switch for malignancy in gliomas promoting cell proliferation and resistance to cell death processes such as ferroptosis. Our data demonstrate that the Nrf2-Keap1 pathway is critical for cancer cell growth and operates on xCT. Nrf2 presents the Achilles' heel of cancer cells and thus provides a valid therapeutic target for sensitizing cancer for chemotherapeutics [7)].

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