Heme oxygenase-1

Heme oxygenase mediates the first step of heme catabolism, it cleaves heme to form biliverdin.

Heme oxygenase, an essential enzyme in heme catabolism, cleaves heme to form biliverdin, carbon monoxide, and ferrous iron.

The biliverdin is subsequently converted to bilirubin by biliverdin reductase. Heme oxygenase activity is induced by its substrate heme and by various nonheme substances. Heme oxygenase occurs as 2 isozymes, an inducible heme oxygenase-1 and a constitutive heme oxygenase-2. HMOX1 and HMOX2 belong to the heme oxygenase family.

The HMOX gene is located on the long (q) arm of chromosome 22 at position 12.3, from base pair 34,101,636 to base pair 34,114,748.

Heme oxygenase-1 plays a critical anti-inflammatory role and is essential for regulating cellular redox homeostasis. Metformin is a classic drug used to treat type 2 diabetes that can inhibit ferroptosis. Previous studies have shown that, when used to treat cardiovascular and digestive system diseases, metformin can also upregulate heme oxygenase-1 expression. Therefore, we hypothesized that heme oxygenase-1 plays a significant role in mediating the beneficial effects of metformin on neuronal ferroptosis after spinal cord injury. To test this, we first performed a bioinformatics analysis based on the GEO database and found that heme oxygenase-1 was upregulated in the lesion of rats with spinal cord injury. Next, we confirmed this finding in a rat model of T9 spinal cord compression injury that exhibited spinal cord nerve cell ferroptosis. Continuous intraperitoneal injection of metformin for 14 days was found to both upregulate heme oxygenase-1 expression and reduce neuronal ferroptosis in rats with spinal cord injury. Subsequently, we used a lentivirus vector to knock down heme oxygenase-1 expression in the spinal cord and found that this significantly reduced the effect of metformin on ferroptosis after spinal cord injury. Taken together, these findings suggest that metformin inhibits neuronal ferroptosis after spinal cord injury and that this effect is partially dependent on the upregulation of heme oxygenase-1 [1)]

Pearson correlation analysis revealed that CSDH thickness was positively correlated with midline shift distance ($r = 0.218$, $p < 0.05$) but negatively correlated with HO-1 concentration ($r = -0.364$, $p < 0.01$) and ferritin level ($r = -0.222$, $p < 0.05$). Multivariate linear regression analysis revealed that HO-1 was an independent predictor of CSDH thickness ($\beta = -0.084$, $p = 0.006$). The angiogenic potency of HO-1 in hematoma fluid was tested with the chick CAM assay; topical addition of CSDH fluid with low HO-1 levels promoted neovascularization and microvascular leakage. Addition of HO-1 in a rescue experiment inhibited CSDH fluid-mediated angiogenesis and microvascular leakage.

HO-1 is an independent risk factor in CSDH hematomas and is negatively correlated with CSDH thickness. HO-1 may play a role in the pathophysiology and development of CSDH, possibly by preventing neovascularization and reducing capillary fragility and hyperpermeability [2)]

Song et al. showed that selective overexpression of the stress protein, heme oxygenase-1 (HO-1) in

astrocytes of GFAP.HMOX1 transgenic mice between 8.5 and 19 months of age results in nigrostriatal hypodopaminergia associated with locomotor incoordination and stereotypy; downregulation of tyrosine hydroxylase, DAT, LMX1B, Nurr1, Pitx3 and DJ-1 mRNA and/or protein; overproduction of α-synuclein and ubiquitin; oxidative stress; basal ganglia siderosis; mitochondrial damage/mitophagy; and augmented GABAergic systems (increased GABA, GAD67 and reelin). The neurophenotype of these GFAP.HMOX18.5-19m mice is highly consistent with parkinsonism and differs dramatically from the schizophrenia-like features previously documented in younger GFAP.HMOX10-12m mice. Common stressors may elicit either early-onset developmental (schizophrenia) or later-life degenerative (PD) brain disorders depending on whether the glial HO-1 response is engaged prior to or following the maturation of dopaminergic circuitry. Curtailment of glial HO-1 transduction at strategic points of the life course may confer neuroprotection in human degenerative and developmental central nervous system disorders [3].

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2)
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3)
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