Nuclear factor erythroid 2-related factor 2 (Nrf2) as a promising target for neuroinflammation.

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Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that plays an important role in the cellular protection against free radical damage and reduces the incidence of radical-derived degenerative diseases. Nrf2 is referred to as the "master regulator" of the antioxidant response due to the fact that it modulates the expression of several genes including phase-2 and antioxidant enzymes playing a crucial role in detoxification of electrophiles and reactive oxygen species (ROS), including glutathione-S-transferase(GST), gamma-glutamyl cysteine ligase (γ-GCL), glutathione-S-reductase (GSR), NAD(P)H:quinoneoxidoreductase-1(NQO1), heme oxygenase-1(HO-1). Nrf2 remains sequestered in the cytosol of cells under basal conditions tightly bound to its repressor Keap1 and upon oxidative stress dissociates from Keap1 and translocates into the nucleus to stimulate transcription of antioxidant defense mechanisms.

Persistent inflammatory and oxidative stress is largely responsible for the progressive loss of non-neuronal and neuronal cells integrity and connectivity underlying the continuous decline of cognitive function associated with most chronic CNS disorders as well as normal aging. Because chronic neuroinflammation is a hallmark of neurodegenerative diseases and compromises cell viability, it is imperative to discover pharmacologic targets to modulate the activation of immune brain cells. For these reason, there is an increasing clinical interest in using NRF2 activators for therapeutic purposes. There is a desperate need of safe, potent, blood-brain barrier permeable displacement-type Nrf2 activators as therapeutic agents for chronic neurodegenerative diseases. Monomethylfumarate, which upon hydrolysis gives a natural metabolite – fumaric acid, has a low alkylating potency and thus, low toxicity, could be the best option to treat chronic neurodegenerative disease such as PD.