

# Antioxidant responsive element

Transcriptional activation of protective genes is mediated by a cis-acting element called the antioxidant responsive element (ARE). The transcription factor Nrf2 (NF-E2-related factor 2) binds to the ARE. Activation of this pathway protects cells from oxidative stress-induced cell death. Increased oxidative stress is associated with neuronal cell death during the pathogenesis of multiple chronic neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. We hypothesize that Nrf2-ARE activation is a novel neuroprotective pathway that confers resistance to a variety of oxidative, stress-related, neurodegenerative insults. In recent studies, primary neuronal cultures treated with chemical activators of the Nrf2-ARE pathway displayed significantly greater resistance to oxidative stress-induced neurotoxicity. Similar cultures generated from ARE-hPAP reporter mice demonstrated selective activation of the Nrf2-ARE pathway in astrocytes, suggesting that Nrf2 activation in astrocytes somehow confers resistance to naive neurons. Further, in chemical models of neurodegeneration, Nrf2 knockout mice are significantly more sensitive to mitochondrial complex I and II inhibitors. Combining these observations with the results implying that the astrocyte is central to Nrf2-ARE-mediated neuroprotection, we transplanted Nrf2-overexpressing astrocytes into the mouse striatum prior to lesioning with malonate. This procedure led to dramatic protection against malonate-induced neurotoxicity. Translating this to other chemical and genetic models of neurodegeneration will be discussed <sup>1)</sup>.

<sup>1)</sup>

Johnson JA, Johnson DA, Kraft AD, Calkins MJ, Jakel RJ, Vargas MR, Chen PC. The Nrf2-ARE pathway: an indicator and modulator of oxidative stress in neurodegeneration. *Ann N Y Acad Sci.* 2008 Dec;1147:61-9. doi: 10.1196/annals.1427.036. Review. PubMed PMID: 19076431; PubMed Central PMCID: PMC2605641.

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