THE PROTECTIVE ROLE OF NRF2/KEAP1 IN NEUROLOGICAL DISEASE AND OXIDATIVE STRESS-INDUCED CELL DAMAGE

Akademisk avhandling

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av

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1Dessa författare bidrog likvärdigt till artikeln.
THE PROTECTIVE ROLE OF NRF2/KEAP1 IN NEUROLOGICAL DISEASE AND OXIDATIVE STRESS-INDUCED CELL DAMAGE

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ABSTRACT

Oxidative stress is a common feature in the pathogenesis of many diseases, including neurodegenerative diseases like Parkinson’s disease (PD) and amyotrophic lateral sclerosis (ALS). Nrf2 and Keap1 regulate an inducible defense system against oxidative stress. In addition to oxidative stress, the Nrf2-dependent defense system is also triggered by reactive substances in our diet, such as the isothiocyanate sulforaphane from broccoli, and both broccoli and sulforaphane have been shown to protect from disease in a number of studies. The aim of this thesis has been to investigate the Nrf2 response after repeated, short stimulations with sulforaphane, simulating the brief Nrf2 stimulation expected after regular broccoli intake. Furthermore, genetic variation in the Nrf2- and Keap1-encoding genes NFE2L2 and KEAP1 were investigated for associations with PD and ALS. In paper I, we found that brief stimulation of Nrf2 with sulforaphane was enough to induce a prolonged Nrf2 response in astrocytes. We also found that repeated four-hour stimulations for several days resulted in sustained increase in the resistance to superoxide-induced cell death and an accumulation of one of the protective enzymes induced by Nrf2. The results of paper II indicate that brief sulforaphane treatment repeated for three consecutive days increased radioresistance in an Nrf2-dependent manner, suggesting that the Nrf2 system can be trained. In paper III and IV, we found that genetic variants of the NFE2L2 gene may affect risk and phenotype of both PD and ALS. We also found that a genetic variant of the KEAP1 gene may affect the phenotype of ALS. In conclusion, data presented in this thesis indicate that Nrf2 can be activated by brief, repeated stimulations to protect from oxidative stress-induced damage. In addition, NFE2L2 may be a risk gene for both PD and ALS, while KEAP1 may affect the phenotype of ALS.

Keywords: ALS, amyotrophic lateral sclerosis, astrocytes, haplotype, Keap1, KEAP1, neuroprotection, NFE2L2, Nrf2, oxidative stress, Parkinson’s disease, risk factor, SNP, sulforaphane, genetic variation