

# 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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Avhandlingen baseras på följande arbeten:

- I. **Petra Bergström**<sup>1</sup>, Heléne C. Andersson<sup>1</sup>, Yue Gao, Jan-Olof Karlsson, Christina Nodin, Michelle F. Anderson, Michael Nilsson, Ola Hammarsten. *Repeated transient sulforaphane stimulation in astrocytes leads to prolonged Nrf2-mediated gene expression and protection from superoxide-induced damage*. *Neuropharmacology*. 2011; 60: 343-353.
- II. Sherin T Mathew<sup>1</sup>, **Petra Bergström**<sup>1</sup>, Ola Hammarsten. *Repeated transient Nrf2 stimulation protects primary human fibroblasts from radiation-induced damage*. Manuscript in preparation.
- III. Malin von Otter<sup>1</sup>, Sara Landgren<sup>1</sup>, Staffan Nilsson, Dragana Celojevic, **Petra Bergström**, Anna Håkansson, Hans Nissbrandt, Marek Drozdziak, Monika Bialecka, Mateusz Kurzawski, Kaj Blennow, Michael Nilsson, Ola Hammarsten, Henrik Zetterberg. *Association of Nrf2-encoding NFE2L2 haplotypes with Parkinson's disease*. *BMC Medical Genetics*. 2010; 11:36:1471-2350.
- IV. **Petra Bergström**<sup>1</sup>, Malin von Otter<sup>1</sup>, Staffan Nilsson, Ann-Charloth Nilsson, Michael Nilsson, Peter M. Andersen, Ola Hammarsten, Henrik Zetterberg. *Association of NFE2L2 and KEAP1 haplotypes with amyotrophic lateral sclerosis*. Submitted manuscript, April 2013.

<sup>1</sup>Dessa 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

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