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Susceptibility and Resilience Factors for Chronic Pain Development in Experimental Models and Human Pain Conditions

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Susceptibility to develop chronic pain varies substantially across individuals. Evidence suggests that basal immune state is a key determinant of progression. The general aim of this thesis is to identify susceptibility/resilience factors for the development of chronic pain and associated comorbidities. Nrf2, a master regulator of both anti-inflammatory and antioxidant pathways, will be central to the analysis.
In the rat spared nerve injury (SNI) model of chronic neuropathy, we used dimethyl fumarate (DMF) to activate Nrf2 around pain onset. DMF treatment decreased mechanical and cold allodynia and attenuated associated anxiety, depression, and cognitive dysfunction-like behaviors. The treatment altered the immune profile, increasing serum protein levels of anti-inflammatory and pleiotropic cytokines, and reducing pro-inflammatory adipokine leptin. The neuronal injury marker ATF-3 was also reduced by DMF, even on day 49 post-SNI. Nrf2 inhibition with trigonelline abolished DMF's protective effects. In humans, we examined the influence of *NRF2* genetic variations in a longitudinal adolescent cohort. Carriers of the GG allele of rs6721961 *NRF2* showed a higher anxiety score at age 14 and more pain complaints at age 16 than TG/TT carriers. Individuals with anxiety only presented a higher risk of developing future pain if they carried the GG allele. Meanwhile, pain complaints were predicted by anxiety and depression, regardless of the polymorphisms.
In conclusion, this thesis suggests the involvement of transcriptional factor Nrf2 in determining susceptibility and resilience to chronic pain (and related comorbidities) development in both a preclinical model and in humans. These findings are not only essential for the development of preventive strategies but also critical for our understanding of the mechanisms underlying chronic pain.