The Role of Nrf2 in Mutant FUS mediated neurodegeneration

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Mutations in FUS, a protein critically implicated in familial amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), are central to the complex pathogenesis of a spectrum of neurodegenerative diseases that collectively represent a significant global health burden. These diseases, while exhibiting distinct clinical phenotypes, share common disruptions in fundamental cellular processes, notably the oxidative stress response and cell death pathways. This study endeavors to elucidate the mechanisms by which FUS mutations modulate Nrf2, a pivotal regulator of antioxidant defenses, and its intricate relationship with antioxidant. In cellular models, we observed that FUS mutations reduced Nrf2 protein levels, partly through post-transcriptional regulatory mechanisms. We also found that FUS mutants influenced the expression of proteins integral to Nrf2-dependent antioxidant regulation. These findings indicate that FUS is involved in maintaining the antioxidant system against oxidative stress. Consequently, its dysregulation due to mutation may significantly contribute to the pathogenesis of neurodegenerative disease. This highlights its importance as a key factor in the underlying mechanisms of disease. The observations provide a novel mechanistic insight into FUS-related neurodegeneration.

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