POTENTIAL TARGETS FOR NEUROPROTECTIVE AGENTS IN HUNTINGTON'S DISEASE

Letizia Pruccoli[1], Gabriella Teti[2], Mirella Falconi[2], Andrea Tarozzi[1]

[1]Department for Life Quality Studies, University of Bologna, Rimini - Italy, [2]Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna - Italy

Introduction: Huntington's disease (HD) is a progressive neurodegenerative disorder caused by an expansion of CAG (glutamine) repeats in the coding region of the Huntingtin (Htt) gene. Proteolytic cleavage of mutant Htt (mHtt) protein with an expanded polyglutamine (polyQ) stretch results in production of Htt fragments that aggregate and induce neuronal dysfunction and death through different mechanisms including impairment of proteostasis, transcription and mitochondrial function as well as cellular redox status. Knowledge of the causal relationship between mHtt protein aggregation and pathogenic changes provides important information to find potential targets for neuroprotective agents.

Methods: We used rat pheochromocytoma PC12cells containing a stably integrated, doxycycline-inducible, eGFP-tagged N-terminal human Htt fragment with an expanded polyQ domain to evaluate gene expression changes, mitochondrial function, redox status and cell death at different stages of mHtt aggregation. In parallel, we also evaluated the neuroprotective of isothiocyanates and phenolic compounds with antioxidant properties.

Results: mHtt aggregate formation and subsequent accumulation of aggregates matched with a rapid increase in the number of differentially expressed genes. In particular, we recorded a down-regulation of dopamine biosynthesis genes and an up-regulation of Nrf2-ARE pathway genes as well as oxidative stress related genes, probably as a protective adaptive response. In parallel, we detected several morphological and functional alterations of mitochondria that may be related to oxidative stress and neuronal death elicited by mHtt aggregate. Among the compounds evaluated, the isothiocyanates restored the normal mitochondrial functions and decreased the neuronal death in presence of mHtt protein through their ability to reinforce the Nrf2-ARE signaling pathway.

Conclusion: Our results show the pathogenic impact of mHtt on expression of antioxidant genes and neuronal redox status implying cellular homeostasis defects in HD. In particular, the Nrf2-ARE pathway genes could be a new attractive therapeutic target for HD.