A Study of the Relationship between Aging, Maturity, and Oxidative Stress on Huntington Disease Neurons

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Huntington’s disease (HD) is a fatal neurodegenerative disorder caused by an expansion of the CAG tract in the huntingtin (HTT) gene. Oxidative stress (OS), or an abundance of oxidants in the brain, causes neurodegeneration. Although a relationship has been suggested, whether OS is an HD onset driver or bystander is yet to be known. To investigate this, immature and mature wild type (WT) and mutant HTT primary neurons were cultured and treated with hydrogen peroxide (H202) to induce OS. In previous experimentation, it was shown that unlike immature HD neurons, WT neurons responded to H202-induced OS by increasing damage and other cellular responses. Although basally, immature HD and WT neurons had similar damage, mature HD neurons had increased ROS production and oxidative damage compared to WT neurons. Oxidative stress responses were decreased in mature HD neurons. Since HD is neurodegenerative and characterized by cell death and damage, this suggests that a mature neuronal model should be used. To further simulate the adult onset disease, neurons were aged with progerin (protein that causes accelerated aging in the disease Progeria). Progerin treatment induced Huntingtin oligomerization and increased age markers in primary neurons. When mature HD neurons were aged with progerin and stressed with H202, oxidative DNA damage was selectively increased, implying an oxidative stress role in the onset and progression of HD. Using an aged mature neuron model can uncover HD related phenotypes. Treatment with an Antisense Oligonucleotide (ASO) showed qualitative reversal of damaged nuclear integrity seen with H202 treatment.

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