Trisomy21 and aberrant BACH1/Nrf-2 axis: implications for neurodegeneration

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Several studies support the implication of oxidative stress (OS) in phenotypic changes in Down syndrome (DS) subjects. Mapping of Human Chromosome 21 (HSA21) has shown the involvement of several genes, such as SOD-1, BACH1, APP, CBR, and S100B, in reactive oxygen species (ROS) overproduction in DS subjects and in animal models. We focused our attention on BACH1, a transcription repressor that competes with the Keap1Nrf2ARE complex and negatively regulates the Nrf-2-mediated antioxidant response. For this reason, we studied the role of BACH1 in the brain and its implication in the failure of antioxidant response in DS.

In this scenario, we investigated the BACH1/Nrf-2 dysregulation in human DS cells and animal models of the disorder: for human studies we analyzed lymphoblastoid cell lines (LCLs), whereas for animal studies we isolated hippocampal astrocytes and neurons from Ts2cje mice. Our results revealed that overexpression of BACH1 alters the BACH1/Nrf-2 ratio in the nucleus and impaired the transcriptional activation of antioxidant response genes, ultimately leading to the accumulation of oxidative damage. Overall, our study supports the hypothesis that BACH1 triplication in DS subjects plays a critical role in the alteration of redox homeostasis; therapeutic strategies able to restore Bach1/Nrf2 axis are currently under investigation in our laboratory.