Epigenetics and Aging: An Exploration of Alzheimer’s Disease

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Epigenetics, in general terms, is a heritable change in gene expression and stability that are not due to alterations in DNA sequence. Epigenetic modifications responsible for differential gene expression include DNA methylation, histone modification/nucleosome positioning and in some cases non-coding RNAs (1). Environment and life style are two important factors that are known to modify the epigenome and are thus responsible for a person aging with or without “grace” (2). Epigenetic modifications are also widely debated between being a pre-programmed part of aging versus a consequence of the aging process (3). With this debate in mind, one way to determine the impact of epigenetics on aging, is to evaluate epigenetic modifications through the lens of an old-age disease, in this case Alzheimer’s disease (AD). AD can be sporadic or heritable developing in persons over the age of 60 (4). The disease is caused by the accumulation of amyloid beta (Aβ) protein plaques in the brain resulting in gene expression alterations, cognitive impairment and eventually death. Both environmental and epigenetic factors have been associated with the pathogenesis of AD through the hypomethylation of amyloid precursor protein gene, hippocampus and cortex DNA methylation and DNA methylation, all of which play a role in Aβ plaque formation and nerve inflammation (5). This study aims to evaluate a mouse model of AD to determine a link between Aβ accumulation, oxidative stress and epigenetic enzymes that result in AD pathogenesis. Wild type (WT) and familial (heritable) AD mice (5XFAD) were evaluated for hallmarks of AD, oxidative stress and expression of epigenetic machinery at two (new onset AD) and eight (fully progressed AD) months of age. 5XFAD mice exhibited cognitive and locomotor impairment along with fearful behavior at eight months of age compared to WT counterparts. 5XFAD mice were also more prone to oxidative stress and had elevated expression of genes involved in the Aβ production pathway (production of AD), inflammation and markers of neuronal loss. Many of the AD hallmarks appeared in the hippocampus suggesting this region is the most affected portion of the brain in 5XFAD mice. Epigenetic measurements indicated that 5XFAD mice demonstrated differential expression of methyl cytosine, DNA methyltransferases, histone methyltransferases and histone deacetylases. Further correlation coefficient revealed that 5XFAD mice AD pathology correlated with cognitive ability, oxidative stress and epigenetic machinery expression. Together this data demonstrated that epigenetic changes correlate with AD hallmarks and oxidative stress in 5XFAD mice providing a useful link for epigenetics in AD and aging studies and potential treatment.