DNA repair dysfunction in neurodegeneration

https://www.neurodegenerationresearch.eu/survey/dna-repair-dysfunction-in-neurodegeneration/

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Research Abstract

Our goal here is to determine whether changes in the formation or processing of oxidative DNA damage are associated with neurodegeneration. It is our hypothesis that DNA repair systems play critical roles in responding to multiple types of acute and chronic cellular stress. We found that mice carrying defects in base excision repair enzymes, Ogg1, Xrcc1, or Neil1, are compromised in their ability to recover from stroke. Curiously, Neil1 expression is substantially higher than other DNA repair enzymes in the brain. Upon further investigation into the function of Neil1 in the brain we reported that unstressed Neil1-/- mice display olfactory and memory deficits, two cognitive functions that are especially sensitive to defects in neurogenesis. Thus, we are continuing to characterize the role of Neil1 neurogenesis. The loss of smelling is a

common symptom reported in the elderly which also occurs as a consequence of neurodegeneration. Alzheimer's disease patients, even in early stages, report olfactory deficits. There are multiple reasons why individuals lose their sense of smell with age and we are investigating how DNA repair impacts neurodegeneration as it relates to the olfaction and Alzheimer's disease. One of the most heavily-studied animal models for human AD is a triple transgenic mouse, called 3xTgAD which carries three mutant human genes: PS1M16V, beta-APPSWE and tauP301L, all thought to be strong risk factors for AD in humans. Therefore, we crossed the 3xTgAD mouse with a DNA PolB heterozygous mouse (HT), which generated our novel 3xTgAD_PolB HT (3xTgAD_PolB) mice. This mouse was characterized by high levels of DNA damage, defects in neurogenesis, mitochondria, memory, long term potentiation, increased neuronal cell death and high intracellular amyloid beta (AB), recapitulating features of AD in humans. Because DNA base excision repair (BER) is reduced in brain cells during normal aging and AD, we determined whether inefficient BER due to reduced DNA PolB levels rendered olfactory bulb (OB) neurons vulnerable to degeneration in the 3xTgAD mouse model of AD. In particular, when compared with PolB heterozygous (PolB+/-) and 3xTgAD mice, 3xTgAD_PolB mice performed significantly less well than wild type control mice in finding buried food. The PolB deficiency did not affect the proliferation of OB neural progenitor cells in the subventricular zone however; the numbers of newly generated neurons were reduced over 60% in the 3xTgAD/PolB+/- mice compared to wild type control mice. Additionally, analyses of DNA damage and apoptosis revealed significantly greater degeneration of OB neurons in 3xTgAD/PolB+/- mice compared to 3xTgAD mice. Olfactory deficits are an early sign in human AD, but the mechanism is not yet understood. Our findings in our new AD mouse model demonstrate that diminution of BER can endanger OB neurons, and suggest a mechanism underlying early olfactory impairment in AD.

Further information available at:

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