Contribution of DNA Repair Deficits to Alzheimer Pathogenesis

https://neurodegenerationresearch.eu/survey/contribution-of-dna-repair-deficits-to-alzheimer-pathogenesis/

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Country

USA

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Contribution of DNA Repair Deficits to Alzheimer Pathogenesis

Source of funding information

NIH (NIA)

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Cancer... Dementia... Genetics... Neurodegenerative... Neurosciences... Women's Health for IC Use

Research Abstract

The increased life expectancy of populations around the world has led to a striking increase in

the prevalence of Alzheimer’s disease (AD), the most common and costly among neurodegenerative disease. It has become increasingly evident that DNA damage is exacerbated in neurons of AD patients, which may lead to neuronal dysfunction and contribute to disease development and progression. In recent studies, we demonstrated an increase in DNA double-strand breaks (DSBs), the most severe form of DNA damage, in neurons of human amyloid precursor protein (hAPP) transgenic mice, which simulate several aspects of AD. Interestingly, we also discovered that hAPP mice showed a delay in the repair of activity-induced DSBs, when compared to wildtype mice, suggesting deficits in their neuronal DNA repair machinery. We subsequently discovered that breast cancer factor 1 (BRCA1), a well-described DSB repair factor and tumor suppressor, was depleted by approximately 50% in brains of hAPP mice and of patients with AD. Reducing BRCA1 levels in the dentate gyrus of wildtype mice to a similar extent by lentiviral expression of anti-BRCA1 shRNA increased the number of neuronal DSBs in this region and led to cognitive impairments. It is also possible that alterations in other DSB repair factors contribute to AD pathogenesis also. We hypothesize that efficient repair of DSBs is essential for proper neuronal function. We further hypothesize that deficits in neuronal DSB repair critically contribute to the accumulation of neuronal DNA damage in AD and that this process contributes to morphological and functional neuronal alterations that underlie the inexorable cognitive decline this disease causes. To test these hypotheses, we will determine which DSB repair factors are altered in postmortem MCI/AD tissue, examine the pathogenic mechanisms by which DSB repair factors are altered, investigate how DSB repair factors are regulated in neurons, and test whether elevating BRCA1 levels is of therapeutic benefit in AD-related models. Protecting the neuronal genome by increasing DNA repair is a novel strategy that might help prevent or slow the progression of AD and related disorders.

Lay Summary

Neuronal DNA damage likely contributes to the neurological manifestations and progression of neurodegenerative diseases. Counteracting defective DNA repair mechanisms represents a novel and largely unexplored strategy that might improve our ability to prevent or stall these conditions. The current proposal aims to determine which neuronal double-strand break (DSB) repair factors are altered in Alzheimer’s disease, the mechanisms by which DSB factors are altered, and whether increasing DSB factor levels might be therapeutically beneficial in this devastating condition. !

Further information available at:

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Investments > €500k

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United States of America

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