Maria De Sousa

Bio 294

Genetics topic assignment

Dec 9, 2022

The Epigenetic Connection to Alzheimer’s Disease

To this day, Alzheimer’s Disease pathology remains a mystery in the field of medicine and research. This neurodegenerative disease is considered the most common cause of dementia and affects millions worldwide. It is characterized by aggregation of beta-amyloid plaques and neurofibrillary tangles, which causes progressive loss of memory and cognitive functions. There are currently no effective biomarkers to diagnose the disease or differentiate the causing neuropathologies. Furthermore, current treatments such as acetylcholinesterase inhibitors only improve short-term cognitive function and potentially better quality of life. The reality is that no treatments have been able to significantly delay or stop disease progression. In searching for a cure for AD, researchers have explored different possible therapeutic methods. One of the promising areas has been epigenetics.

The field of epigenetics studies factors beyond genetics that play a role in an organism’s gene activity. It is commonly known that an individual’s characteristics are not solely dependent on their genetic makeup, but also on external factors such as stress, diet, exposure to harmful agents, etc. Epigenetics utilizes that knowledge by applying different methods and making structural changes that modify an organism’s phenotype without changing the genotype. These methods include DNA methylation, noncoding RNA molecules, and histone modification.

First, DNA methylation involves the addition of a methyl group to a DNA molecule with the use of an enzyme known as DNA methyltransferase. This enzyme can methylate different sites of the chain, which may result in the repression or expression of a gene. Evidence of an association between DNA methylation and AD was first found in 1995 when researchers found significantly low methylation levels in a person with a neurodegenerative disease. Other findings showed that exposure to heavy metals such as lead, and certain vitamin deficiencies caused genes associated with AB peptide to be methylated. This peptide is directly connected to Alzheimer’s as it triggers beta-amyloid accumulation, and consequentially progression of AD. Furthermore, it has also been shown that epigenetic methylation of the ADARB2 gene in the hippocampus further impaired the brain’s plasticity and memory.

Another epigenetics method used to analyze the association with Alzheimer’s Disease is histone modification. Histone proteins are directly associated with DNA, as they wrap around the strands to provide stability and compactness. Like in DNA methylation, enzymes are used to modify histones and bring upon activation or deactivation of gene expression. These enzymes include histone demethylases, methyltransferases, deacetylases, and acetyltransferases. One of the ways the modification occurs is through acetylation, which relaxes the chromatin structure and allows transcription mechanisms to access the DNA. Alzheimer’s studies focused on this specific modification and it was observed that enhanced acetylation of the histone H4 at a specific lysine 12 residue was present in the early aggregation of beta-amyloid in the brain. Further conducted studies ultimately supported this when they began treating specimens with histone deacetylase inhibitors, which in turn showed decreased levels of beta-amyloid in the brain.

Like DNA methylation, and histone modification, non-protein coding RNAs (ncRNA) have also been studied as a potential epigenetics regulator for AD. mRNAs play a significant role in numerous cellular and neural processes associated with Alzheimer’s Disease. For instance, BACE1 is a miRNA responsible for the formation of AB peptides in the brain, but others are also involved in neuroinflammation. Neuroinflammation is considered to promote AD by increasing the death of healthy neurons, production of amyloid, and reducing cells’ ability to remove amyloid plaques.

Overall, Alzheimer’s research with epigenetic applications has brought forward crucial results that support a direct association between epigenetic modifications and AD pathology. More specifically, these studies have shown that targeting certain epigenetic markers can be used as a therapeutic strategy for neurodegenerative disorders. Although epigenetic therapies for AD have shown to be promising, there are factors researchers should bear in mind as they continue this exploration. Not only are epigenetic changes difficult to control, but regions of the same genes can be unpredictable, and may potentially cause unwanted side effects. In conclusion, Alzheimer’s is a detrimental neurodegenerative disease that remains with no effective treatment or cure. Throughout this essay, studies and potential applications of epigenetic changes are discussed in order to highlight the evident association of epigenetic changes to the pathogenesis of AD. Given this connection, promising treatments and therapies targeting these epigenetic changes should lie ahead in future research, and hopefully pave the way for an effective treatment for this disease.

Works Cited

Alzheimer's disease facts and figures. *Alzheimer's Disease and Dementia* Available at: https://www.alz.org/alzheimers-dementia/facts-figures?utm\_source=google&utm\_medium=paidsearch&utm\_campaign=google\_grants&utm\_content=alzheimers&gclid=Cj0KCQiA1sucBhDgARIsAFoytUs1IZg1SqkFUQJHkSPRMh5XwHM8KmUEqiDHMYhu2Mg-w\_3aqNYDg98aAob4EALw\_wcB. (Accessed: 9th December 2022)

Nikolac Perkovic, M. *et al.* Epigenetics of Alzheimer's disease. *Biomolecules* (2021). Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7911414/. (Accessed: 9th December 2022)

Home - books - NCBI. *National Center for Biotechnology Information* Available at: https://www.ncbi.nlm.nih.gov/books. (Accessed: 9th December 2022)