

Epigenetic markers shows promise in Alzheimer's disease

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Increasing evidence suggests that epigenetic regulation is associated with the pathogenesis of Alzheimer's disease (AD) and targeting it may one day lead to novel diagnostic and therapeutic strategies, research suggests.

Scientists at The School for Mental Health and Neuroscience at Maastricht University, the Netherlands, have been performing parallel studies in mice and men to investigate the role of epigenetic mechanisms in ageing and AD.

"We have shown that ageing in mice is associated with a variety of [epigenetic changes](#) in the brain," explained Dr van den Hove, who led the research. "Our data suggest that, from an epigenetic point of view, AD does not simply represent an accelerated form of ageing, which puts existing knowledge in a completely new perspective," he added.

In mice, the researchers found that ageing was associated with an increase in hippocampal DNA methyltransferase 3a, a novel DNA methyltransferase that was shown to play a role in cell proliferation and differentiation. Age-related increases of 5-methylcytosine (5-mC) and 5-hydroxymethylcytosine (5-hmC), markers of global DNA methylation and hydroxymethylation respectively, were also identified.

Histone deacetylase 2 (HDAC2), which forms a part of methyl-CpG-binding complexes and is crucially involved in memory formation and neurodegeneration-related cognitive impairment, was also shown to increase with age.

"Interestingly, caloric restriction, which has been suggested as an effective strategy to prevent or attenuate age-related processes in the brain, could prevent these epigenetic changes in ageing mice," noted Dr van den Hove.

The team also collaborated in a series of studies performed in human post-mortem brain tissue. Working with Professor Coleman and Dr Diego Mastroeni at the Banner Sun Health Research Institute (Sun City, AZ, US), the researchers found that AD pathology in humans was associated with different methylation and hydroxymethylation patterns in the hippocampus compared with those seen in normal ageing.

"We have found robust decrements of 5-mC and 5-hmC in the hippocampus of AD patients when compared to carefully-matched controls. Interestingly, this decrease correlated with hippocampal amyloid plaque load," explained Dr van den Hove.

Investigating whether these changes were linked with aberrant amyloid processing, the team looked at the same markers in the hippocampus of a mouse model of AD. They found that global methylation and hydroxymethylation increased with ageing in normal mice, while the onset of AD pathology in the AD [mice](#) corresponded with an [age](#)-related dis-balance of the DNA methylation and hydroxymethylation markers. Furthermore, they observed negative correlations between global DNA methylation levels and amyloid plaque load.

"Because epigenetic processes are known to be dynamic and reversible, future treatment strategies directly targeting epigenetic regulation may provide powerful means for pharmacological and/or behavioural intervention strategies in neurodegenerative disorders like AD," speculated Dr van den Hove. Nevertheless, specificity and safety issues warrant further research before epigenetics-based therapies for AD could be clinically applicable.

And the findings may also lead to novel diagnostic tests for AD. "The fact that the degree of between-individual variation in DNA methylation profiles is partially correlated across the brain and blood offers the possibility that diagnostic predictors of AD risk will be discovered in peripheral tissues."

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