DNA Double-Strand breaks in Alzheimer's disease: Evidence from experimental models and post-mortem human brain.

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Alzheimer's disease (AD) accounts for the majority of dementia cases and are a pressing problem and growing challenge for modern societies with aging populations. Several hypotheses have been proposed to explain the pathogenesis of AD, including neuronal loss, amyloid deposition, synaptic dysfunction, hyperphosphorylated tau, oxidative stress, and inflammation. However, despite extensive investigation using several different approaches, the exact causes of AD are still unclear. Knowledge of the precise molecular mechanisms underlying AD/ADRD remains incomplete and these gaps in our knowledge about fundamental neurobiology are a major barrier to therapeutic discovery. Failure in clinical trials of drugs targeting the amyloid pathway have led to a surge in targeting alternative mechanisms. Recent studies have highlighted the role of DNA damage, particularly, DNA double-strand breaks (DSBs), in the progression of neuronal loss in a broad spectrum of neurodegenerative diseases including AD. Here, we found increased expression of DSBs in the brains of AD patients and 5xFAD transgenic mice using immunohistochemistry and Comet assay. To identify the cell types in which DSBs occurs, we will utilize double-antibody immunohistochemistry of tissue sections using cell-specific markers (GFAP, Iba1, NeuN, and CD31) and specific DNA damage markers [53BP1 and -H2A.X (ser139)]. Our findings suggest that accumulation of DSBs in the brain make an important early part of the pathway toward neural damage and memory loss in AD.