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DNA-PK Deficiency in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is characterized by neuronal death with an accumulation of intra-cellular neurofibrillary tangles (NFT) and extracellular amyloid plaques. Reduced DNA repair ability has been reported in AD brains. In neurons, the predominant mechanism to repair double-strand DNA breaks (DSB) is non-homologous end joining (NHEJ) that requires DNA-dependent protein kinase (DNA-PK) activity. DNA-PK is a holoenzyme comprising the p460 kD DNA-PK catalytic subunit (DNA-PKcs) and its activator Ku, a heterodimer of p86 (Ku80) and p70 (Ku70) subunits. Upon binding to double-stranded DNA ends, Ku recruits DNA-PKcs to process NHEJ. In AD brains, reduced NHEJ activity as well as DNA-PKcs and Ku protein levels have been shown. Normal aging brains also show a reduction in both DNA-PKcs and Ku levels questioning a direct link between NHEJ ability and AD, and suggesting additional players/events in AD pathogenesis. Deficiency of Ku80, a somatostatin receptor, can disrupt somatostatin signaling thus inducing amyloid beta (Aβ) generation, which in turn can potentiate DNA-PKcs degradation and consequently loss of NHEJ activity, an additional step negatively affecting DSB repair. Trigger of these two different pathways culminating in genome instability may differentiate the outcomes between AD and normal aging.

Alzheimer's disease (AD) is a CNS neurodegenerative disease, characterized by specific neuronal death with accumulated neurofibrillary tangles (NFT) and extracellular amyloid beta (Aβ) deposits[1]. Aβ directly injures neocortical and limbic system neurons[2]. It also indirectly activates the microglia that release pro-inflammatory cytokines and reactive oxygen species (ROS), both events being neurotoxic[3,4]. Other factors linked to the development of AD include apolipoprotein E genotype[5]; hyperphosphorylation of cytoskeletal proteins (neurofilaments and Tau)[6], and Aβ metabolism[7]. As diverse as the pathological and biochemical presentations of AD are[8], no single factor has been confirmed as the sole cause of this complex disease[9-12]. Studies have shown a link between oxidative stress (e.g., ROS) and AD pathogenesis[11,13,14]. Since oxidative stress can cause DNA lesions, changes in the levels and activity of DNA-repair proteins have garnered special interest of study of AD patients or patients with mild cognitive impairment[15,16].

Cellular damage by oxidative stress caused by the generation of ROS has been implicated in pathophysiology of AD as well as normal aging and elevated levels of oxidative damage in DNA, both nuclear and mitochondrial, have been observed in AD brains[17]. As DNA damage accumulates and DNA repair process lags or goes awry, a potentially adverse scenario can set in contributing to AD[18,19].

Some human hereditary genetic defects in the DNA repair system also manifest in early onset of developmental and progressive neurodegeneration[20,21]. Cells use several types of DNA repair systems such as base excision repair (BER), nucleotide excision repair (NER), single strand break repair (SSBR), and double strand break repair (DSBR). Of all these various DNA damages, double strand break (DSB) happens to be the most lethal. There are two major DSB repair pathways in the eukaryotes; non-homologous end joining (NHEJ) and homologous recombination (HR). NHEJ, the predominant pathway for DSBR in higher order organisms, functions throughout the cell cycle[22-24], whereas HR functions are confined to the S and G2 stages of the cell cycle[25]. DNA-PK plays an essential role in accessing the DNA ends during NHEJ[26,27].

As a response to DNA damage, expression and activity of many kinases including members of the PI3 kinase family are altered[28]. One of these kinases, the DNA-dependent protein kinase (DNA-PK) preferentially phosphorylates the serines (S) and threonines (T) of its targets although it can also phosphorylate other S-T/hydrophobic residues[29]. DNA-PK holoenzyme consists of a catalytic subunit ($DNA\text{-}PK_{cs}$), p460 and a regulatory subunit (Ku). The Ku protein is a heterodimer composed of 70 kD (Ku70) and 80 kD (Ku80) subunits; and possesses the ability to bind to DNA ends[30,31]. DNA-PK is conserved across species[32,33] and participates in transcription, DNA recombination and repair[34-38]. In the absence of $DNA\text{-}PK_{cs}$, Ku binds DNA ends in a sequence-independent manner[39], however, Ku is required for targeting $DNA\text{-}PK_{cs}$ to damaged DNA ends in physiologic conditions *in vitro* and in living cells[40]. DSB can activate DNA-PK both in *trans* (occurs via kinase autophosphrylation) or *cis* (occurs via specific DNA strand orientation and sequence bias) modes[41-43].

Post-mitotic neurons are mature, do not proliferate[44,45] and are also one of the most metabolically and transcriptionally active cells (review[46]). Therefore, these neurons are more susceptible to suffer from risks involving DNA damage. NHEJ, unlike HR, is error-prone since it acts at the DNA break points and the repair process can cause loss of one or more nucleotides. However, since most of the higher eukaryote genome is non-coding, errors occurred during DSBR by NHEJ rarely translate into any deleterious effects. Unfortunately, as people age, accumulation of these non-obvious errors eventually can lead to genome instability, thereby causing cellular death or dysfunction. For example, 10% of p53 mutations in human cancers could be attributed to deletions arising from NHEJ sites[47]. NHEJ being the predominant form of DSBR pathway in post-mitotic neurons[48], mouse neurons deficient in components of NHEJ, such as XLF, DNA Ligase IV, XRCC4, Ku70 and Ku80 (Figure 1), undergo excessive apoptosis[49,50]. Mice with defective NHEJ show accelerated aging[51,52]. Loss of NHEJ activity in the developing brain causes prenatal lethality and can lead to neurodegenerative diseases in adults[49,53,54].

Terminally differentiated post-mitotic neurons triggered to re-enter cell cycle following stimuli associated with DNA damage and oxidative stress undergo apoptosis[55,56]. Neuronal DNA damage is linked to neurons re-entering cell cycle[56,57]. To this end, DNA replication may be a consequence of cell cycle re-entry preceding neurodegeneration in AD brains[58]. Moreover, reactive oxygen/nitrogen species reportedly cause deregulated and inefficient DNA replication known as 'replication stress'[59]. It is possible that "replication stress" in AD pathogenesis can lead to genomic instability potentially resulting in Aβ accumulation and deregulated cell cycles[60]. Adding to this scenario, existence of defective DNA repair systems in post-mitotic neurons would lead to accumulation of further DNA damages and genomic instabilities[61,62] (Figure 1). It has been suggested that accumulated single-stranded DNA (ssDNA) at replication forks may give rise to aberrant DNA structures resulting in DSBs that activate DNA-PK[63]. With this scenario, in AD, reduced DNA-PK as such would further enhance DSB accumulation. Intracellular increase in DNA content observed in AD brains[58,64] may also result from these combined events. Indeed, it has been reported that $DNA\text{-}PK_{cs}$ mutant cells under stress fail to arrest replication[65]. Thus, neurons deficient in DNA-PK activity could uninterruptedly undergo replication stress ending with genome instability (Figure 1).

DNA-PK plays a critical role, first, by sensing DNA damage and then, inducing signaling pathways including programmed cell death[51]. $Ku80^{-/-}$ mice are defective in NHEJ, telomere maintenance and show premature aging[52,66]. Ku80 and $DNA\text{-}PK_{cs}$ protein levels as well as Ku80's DNA-binding ability are reduced following severe ischemic injury leading to neuronal death in rabbit[67]. Furthermore, although not significantly different from the age-matched controls, Ku-DNA binding is reduced in extracts of post-mortem AD mid-frontal cortex that may be linked to reduced levels of Ku and $DNA\text{-}PK_{cs}$ proteins[68]. Reduced NHEJ activity in extracts of the cortices of AD brains compared to the normal subjects and significantly lower levels of $DNA\text{-}PK_{cs}$ in the AD brain extracts have also been reported[69]. Since DNA-PK is a critical player in cell survival/death and gene transcription, it is tempting to directly link reduced levels of DNA-PK subunits to less proficient NHEJ in AD brains and neurodegeneration. It is likely that DNA damage (e.g., induced by ROS) in neurons that are already challenged with reduced NHEJ activity, may trigger them to re-enter cell cycle albeit unsuccessfully, resulting in accumulation of excessive genomic damage leading to neuronal death. Therefore, reduced levels of $DNA\text{-}PK_{cs}$ and Ku80/Ku70 subunits in post-mortem AD brains may be an important upstream event that predisposes the neurons to AD.

In NGF-differentiated PC12 cells, sub-lethal levels of aggregated $A\beta^{25-35}$ have been shown to inhibit DNA-PK activity as does hydrogen peroxide[70]. One of its potential mechanisms may be Aβ-induced ROS-mediated DNA-PK_{cs} degradation via carbonylation, an irreversible oxidative protein modification[71,72]. A decrease in DNA-PK_{cs} expression in neurons and astrocytes of AD brains[73], although not significant compared to age-matched controls, has been reported[74]. Whether Aβ-induced attenuation of DNA-PK activity and reduced NHEJ activity (Figure 1) leading to neurotoxicity is linked to the development of AD awaits careful scrutiny.

Ku80 has been shown to be a specific receptor for somatostatin[75] and can regulate DNA-PK activity through somatostatin signaling pathways[76]. Somatostatin modulates both motor activity and cognition[77]. Somatostatinergic neurons exist in the CNS including the cerebral cortex, hippocampus, hypothalamus, and spinal cord[78]. Along with various other neuropeptides, somatostatin levels are significantly reduced in AD brains[79] and cerebrospinal fluid[80]. Somatostatin receptors are also reduced in the cortical areas of the AD brain[81]. Loss of somatostatinergic neurons along with reduction in somatostatin transcripts in a transgenic mouse model of AD, and somatostatin deficiency potentially triggering Aβ generation have been reported[82]. It is possible that Ku80 deficiency can negatively affect somatostatin signaling leading to Aβ generation, thereby contributing to AD pathogenesis, a process independent of the involvement of DSB (Figure 1).

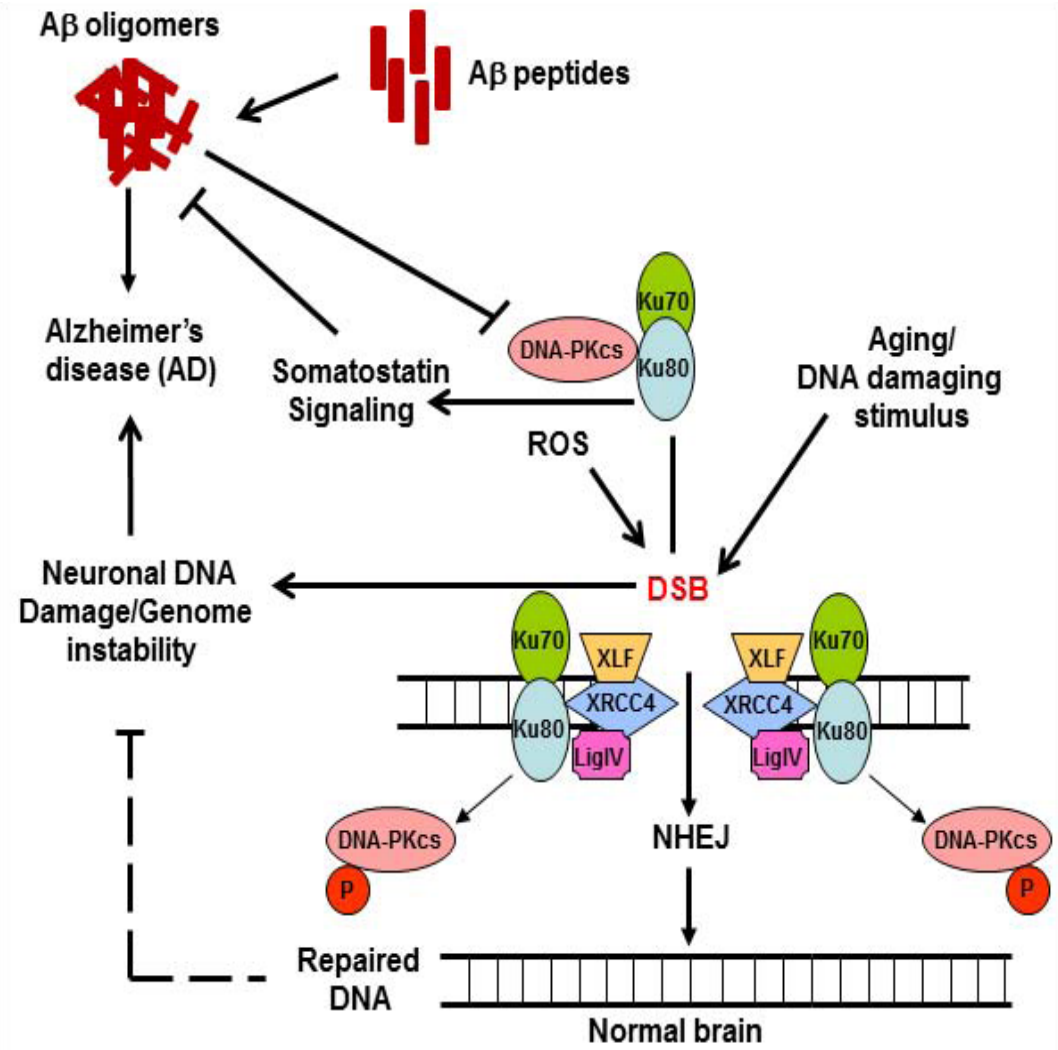

Figure 1: Schematic presentation of a potential link of DSB, DNA-PK and Aβ in AD brains. Upon induction of DSB either by normal aging/ ROS or other DNA damaging agents, Ku80/Ku70 and DNA-PKcs are rapidly recruited to DNA ends, and DNA repair occurs as it would in normal cases. However, in AD brains, in addition to formation of Aβ oligomers from Aβ peptides, sustained DSB in the genome would cause genome instability leading to the loss of normal neuronal activity. Additionally, with depleted Ku80, a somatostatin receptor, disruption of somatostatin signaling could potentially induce Aβ generation thus accelerating AD pathology.
DSB: DNA double strand break; DNA-PK: DNA-dependent protein kinase; ROS: Reactive oxygen species; Aβ Amyloid beta

DNA-PK$_{cs}$, Ku80 and Ku70 are exceptionally abundant proteins in human cells[83]. Reduced level of DNA-PK$_{cs}$ in AD brains has been attributed to Aβ-induced proteasome-mediated degradation of DNA-PK$_{cs}$[71,72]. Whether disruption of the somatostatin signaling due to Ku80 deficiency inducing Aβ generation precedes DNA-PK$_{cs}$ degradation is not known. If true, it would highlight Ku80 as a dual player in AD pathogenesis; when deficient, by indirectly promoting Aβ generation and directly causing NHEJ deficiency.

Abbreviations

AD: Alzheimer's disease; ATM: Ataxia telangiectasia mutated protein; BER: base excision repair; DNA-PK: DNA-dependent protein kinase; DSB: double strand breaks; DSBR: Double strand break repair; HR: Homologous recombination; NER: Nucleotide excision repair; NGF: Nerve growth factor; Lig IV: Ligase IV; NHEJ: Non-homologous end-joining; NFT: Neurofibrillary tangle; SSBR: Single strand break repair; XLF: XRCC4-like factor; XRCC4: X-ray repair cross-complementing protein 4

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