Kanungo, Cell Dev Biol 2012, 1:2
DOI: 10.4172/2168-9296.1000e105

Cell & Developmental Biology
ISSN: 2168-9296

Editorial Open Access

# DNA Repair Defects and DNA-PK in Neurodegeneration

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**Keywords:** Ku; DNA-PK; Alzheimer's disease; p53; DNA repair

Mammalian brain consists of two major types of cells, the neurons and glia. Mature neurons are essentially post-mitotic and do not proliferate whereas some glial cells can undergo replication especially as a response to stress or damage [1,2]. Nervous system is one of the earliest systems to develop and differentiate in almost all the species. Therefore, literally, neurons in the brain are one of the oldest cell populations in the organism. Neurons are also one of the most metabolically active cells and gene expression is two- to three-fold higher in neurons than in any other cell [3]. These non-dividing, metabolically hyperactive cells are, therefore, vulnerable to risks that involve DNA damage.

DNA repair pathways in brain have been studied extensively over the last two decades (reviews [4,5]). In mammals, DNA double-strand break (DSB) repair uses two mechanisms, homologous recombination (HR) and non-homologous DNA end joining (NHEJ). NHEJ is the predominant double-stranded DNA repair pathway in mammalian cells [6]. NHEJ is among the most recently defined repair pathways with substantial importance in cancer, aging and immune system development. Compared to the HR, NHEJ is considered error-prone and imprecise since it acts at the DNA break sites to restore the chromosomal structural integrity which could come at the expense of one or few nucleotides. Over time, as in aging, these small errors can accumulate resulting in genome instability leading to cellular dysfunction or death. Interestingly, it has been reported that 10% of p53 mutations in human cancers could be attributed to deletions arising from NHEJ sites [7].

NHEJ is also the predominant form of double-stranded DNA repair pathway in post-mitotic neurons [8]. DNA-dependent protein kinase, a complex of the DNA-dependent protein kinase catalytic subunit (DNA-$PK_{cs}$) and a heterodimer of Ku70 and Ku80, plays a principal role in NHEJ [9]. NHEJ is critical in the nervous system development since mice deficient in DNA Ligase IV, XRCC4, Ku70 and Ku 80 that are participants in the NHEJ event, show massive apoptosis in post-mitotic neurons [4,10]. When a DSB occurs, the Ku heterodimer (Ku80/Ku70) binds to the broken ends first using Ku80 and then recruits the DNA-$PK_{cs}$ which is activated upon binding to Artemis nuclease and the repair process is completed by XRCC4-DNA ligase IV [11,12].

Loss of NHEJ activity in the developing brain can be prenatally lethal and in adults, can lead to neurodegenerative diseases [4,13,14]. The type of DNA damage most likely occurring in neurons is oxidative damage. High metabolic rate of neurons can generate excessive oxygen radicals and neurodegenerative diseases like Alzheimer's disease (AD) have been linked to oxidative stress (reviews [4,15]). The other aspect contributing to neuronal DNA damage is linked to neurons re-entering cell cycle [16,17]. When post-mitotic neurons try to re-enter the cell cycle, the very attempt to transcribe a subset of cell cycle-related genes that have not been transcribed for years in a mature neuron's lifetime may accumulate damaged DNA that could trigger neuronal apoptosis [18]. In neurodegenerative diseases like AD, the types of DNA damages are likely induced by reactive oxygen species (ROS) [19]. With aging, NHEJ activity gradually decreases as the neurons become terminally differentiated. However, in mature rats, the NHEJ activity in the brain is comparable to the level observed in the testes [20]. When a declining activity in the nervous system matches with the normal activity in another tissue (testis), it is conceivable that NHEJ activity during nervous system development could, in fact, be robust.

Once the neuron stops dividing, the need for DNA repair may be reduced and the necessity to maintain active NHEJ machinery may, as well, become obsolete. However, under oxidative stress or other endogenous or exogenous insults, when the neuronal DNA is damaged, due to a pre-existing reduced NHEJ activity, the neurons may undergo apoptosis or should they re-enter cell cycle, the damaged DNA could replicate thus compounding genomic aberration. Thus, in aging, the brain could harbor post-mitotic neurons with reduced NHEJ potential, but if not challenged with an insult, the neuron could die a normal death; whereas in neurodegenerative diseases like AD, factors, such as ROS, could trigger DNA damage and lacking its repair, neurons could degenerate prematurely. Because of a fine line between neurons in a normal aging brain and neurons in distress because of disposition to the neurodegenerative diseases, the proteins and enzymes involved in the NHEJ are worthy candidates for investigation.

DNA-PK plays a role in detecting DNA damage and triggering signaling pathways including programmed cell death [21]. $Ku80^{-/-}$ mice are defective in the NHEJ and telomere maintenance and show premature aging, but surprisingly no human disorder caused by Ku80 deficiency or mutation has been reported [22,23]. Interestingly, Ku80 and DNA-$PK_{cs}$ protein levels as well as Ku80's DNA-binding ability are reduced following severe ischemic injury that causes extensive neuronal death in rabbit [24]. Furthermore, although not significantly different from the age-matched controls, Ku-DNA binding is reduced in extracts of post-mortem AD mid-frontal cortex, which could be attributed to reduced levels of Ku subunits and DNA-$PK_{cs}$ [25]. However, another report from the same laboratory demonstrated that NHEJ is reduced in cortical extracts from brains of AD versus normal subjects and DNA-$PK_{cs}$ level was significantly lower in the AD brain extracts [24].

In order to make sense of the complexity of AD, a 'two-hit hypothesis' for AD development has been reported, which states that the first hit makes neurons vulnerable and the second hit triggers the neurodegenerative process [26]. The first hit may constitute abnormalities when neurons try to re-enter cell cycle or oxidative stress, which, if persistent, can create a pro-oxidant environment as encountered in pre-AD and AD cases. In this environment, proteins highly sensitive to redox modulation, including p53, can be compromised [27]. A number of postmortem studies suggest an

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**Received** May 23, 2012; **Accepted** May 24, 2012; **Published** May 25, 2012

**Citation:** Kanungo J (2012) DNA Repair Defects and DNA-PK in Neurodegeneration. Cell Dev Biol 1:e105. doi:10.4172/2168-9296.1000e105

involvement of p53 in AD and high levels of p53 in certain neurons in postmortem samples from AD patients have been reported (review [28]). DNA-PK activates p53 by phosphorylating the amino-terminal site [29] and p53 can induce Bax, a pro-apoptotic protein that translocates to the mitochondria and initiates the intrinsic death pathway [30]. Regulation of Bax-mediated neuronal death also reportedly involves Ku70 phosphorylation by DNA-PK [31]. In this regard, reduction in DNA-PK$_{cs}$ levels in AD brains does not seem to fit in to the concept of it being the trigger for p53-mediated neurodegeneration.

Considered indispensable for V (D) J recombination in immune response cells utilizing NHEJ, DNA-PK is believed to have little or no effect in p53-dependent cell cycle arrest. In contrast, there are reports linking p53 phosphorylation by DNA-PK to cellular death machinery (review [32]). DNA-PK is also involved in regulating the activities of RNA Polymerase I and II via phosphorylation (review [32]). Given these important substrates of DNA-PK that are critical players in cell death and gene transcription, it is difficult to pinpoint the exact role(s) of DNA-PK$_{cs}$ and its cofactor (Ku80/Ku70) in AD. Likewise, it would be simplistic to directly link reduced levels of DNA-PK subunits and consequently less proficient NHEJ in AD brains to neurodegeneration. On the other hand, it is attractive to speculate that DNA damage (e.g., induced by ROS downstream of Aβ) in neurons with reduced NHEJ activity, triggering them to re-enter cell cycle unsuccessfully, could lead to the accumulation of excessive genomic damage eventually causing neuron death. In either pathway, NHEJ being the process involved, the importance of DNA-PK$_{cs}$/Kυ complex in the development of neurodegenerative pathology may be considerable. The reduced levels of DNA-PK$_{cs}$ and Ku80/Ku70 subunits in postmortem AD brains may be perceived as upstream events of neuron loss in AD, although further studies are warranted to differentiate between cause and consequence.

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