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DNA damage responses in central nervous system and age-associated neurodegeneration

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Despite a colossal upsurge in our understanding of the cellular and molecular changes in the nervous system during aging and age-associated neurodegeneration, there is no cure or effective disease-management therapies at present for most debilitating brain diseases. Current treatment modalities may only temporarily slow down the symptoms, but cannot stop inevitable disease progression.

The fidelity of the genomes in all aerobic cells is continuously challenged by reactive oxygen species (ROS) generated as byproducts of respiratory metabolism, in addition to the general genotoxic stress from other endogenous and exogenous sources (Lindahl, 1993). Post-mitotic neurons in the central nervous system (CNS) may be particularly vulnerable due to higher rate of O_2 consumption, strong metabolic activity associated with high transcriptional levels [reviewed in (Hegde et al., 2012)]. As most adult neurons are generated within three years of development, it is important to note that a typical neuron must survive for ~80 years in a long-lived species such as humans. Consistently, the extent of DNA damage was correlated with but also proposed to drive the aging process [(Hart and Setlow, 1974); reviewed in (Chow and Herrup, 2015)]. Following the first suggested link between genetic mutations and other DNA alterations and aging in 1959 (Szilard, 1959), subsequent studies endorsed the genome instability and aging theory by demonstrating increased mutation rate (Bohr and Anson, 1995; Suh and Vijg, 2006) and rate of DNA damage accumulation with age and age-associated neurodegeneration (Niedernhofer et al., 2006). Progressive damage accumulation in the affected neuronal genomes also routinely correlates with the symptomatic severity in many neurodegenerative and neuropsychiatric diseases with diverse pathology. While the most common threat to neuronal genomes comes from

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ROS which contributes oxidative DNA lesions including single-strand breaks (SSBs), recent studies reveal that DNA double strand breaks (DSBs) also are routinely formed during normal physiological/metabolic processes involving gene expression and chromosome remodeling associated with learning and memory (Suberbielle et al., 2013).

Thus, faced with the constant challenge of maintaining DNA fidelity during the life span, all cells including neurons have evolved a robust array of DNA damage response processes with overlapping networks of independent DNA repair pathways. While an efficient repair of DNA damage is crucial for maintaining genomic integrity in dividing neural progenitors during development, the post-mitotic, mature neurons lack DNA replication- dependent DNA repair processes such as homologous recombination (HR).

The relationship between compromised DNA repair and neurodegeneration was first suggested after the discovery of premature neuronal death in patients with xeroderma pigmentosum [XP; (Cleaver, 1968)]. This was further reinforced when several mutations implicated neurodegenerative disorders were found to involve DNA damage-response proteins [reviewed in (McKinnon, 2009)]. A number of later studies in Alzheimer's disease (AD), Parkinson's disease (PD) amyotrophic lateral sclerosis (ALS), Huntington disease (HD), ataxia and stroke demonstrated that inadequate DNA repair both in nuclear and mitochondria genomes as well as persistent/aberrant damage signaling (DDR) are strongly associated with both inherited and sporadic neurodegeneration (Caldecott, 2008; McKinnon, 2009). For example, base excision repair (BER) deficiencies in the brains from AD patients (Weissman et al., 2007) and in fibroblasts from Cockayne syndrome (CS) patients (Tuo et al., 2003), defective nucleotide excision repair (NER) in XP (Cleaver, 1968) and CS (Venema et al., 1990), reduced DNA mismatch repair (MMR) in HD (Manley et al., 1999), inefficient SSBR in ataxia syndromes AOA1 and SCAN1 (Ahel et al., 2006; El-Khamisy et al., 2005), and DSBR deficiencies in AD (Shackelford, 2006), ataxia telangiectasia (A-T) and ALS (Maser et al., 2001; McKinnon, 2004; Taylor et al., 1975) were reported. These studies not only support the involvement of DDR defects in brain aging and age-associated decline in brain functions, but also underscore the unique vulnerability of CNS for genome repair defects. Some of the deleterious CNS response to persistent DDR include transcriptional arrest at the damage sites, formation of RNA-DNA hybrids or R-loops at the stalled transcriptional sites, DDR-mediated activation of neuro-inflammatory signaling, possible damage-induced deregulation of the cell cycle machinery and abortive cell cycle-mediated cell death initiation and brain atrophy (Herrup et al., 2004; Jaarsma et al., 2011). Furthermore, alterations in mitochondrial genome fidelity could impact nuclear-mitochondria functional homeostasis in CNS, and contribute to neuronal death in some brain diseases (Fang et al., 2016).

Strong evidence has accumulated linking oxidative stress causing genome damage and persistent DDR signaling to neuronal dysfunction. However, specific questions remain regarding, (a) selective vulnerability of selective neurons in various CNS diseases, (b) DDR dynamics in specific CNS cell types to ensure homeostasis, and (c) contribution of diverse cellular changes including protein aggregation, oxidative stress and transition metal toxicity and genome damage repair deficiency to disease initiation, progression and severity. The importance of a fundamental understanding of DDR processes to human health was

endorsed by the Royal Swedish Academy of Sciences when it awarded the 2015 Nobel Prize in Chemistry to the discoveries of the molecular bases of how cells repair the genomic DNA damage induced under diverse circumstances.

The aim of this special issue of MAD to summarize our comprehensive understanding of the link between etiologies and genomic instability in various CNS diseases and also aging and to explore possible preventive/therapeutic strategies for these. The contributors of this volume include renowned scientists who made seminal contribution to the unraveling of the role of genome damage and repair responses in aging and neurodegenerative pathologies as well as innovative young investigators in the field. A total of sixteen articles, both original research and reviews covered the broad topic of 'DNA Damage Responses in Central Nervous System and Age Associated Neurodegeneration' including a discussion of DDR-based therapeutics for neurodegeneration. Five articles focused on linkage of genome instability in aging, three articles on AD, one on PD, and six articles discussed specific DNA repair defects in nucleus or mitochondria in neurodegeneration.

In the opening article, Shiloh and colleagues highlight the role of genomic stability as a determinant of the pace of aging and glia/microglia specific responses to genome modifications. Karl Herrup and Kai-Hei Tse follow up with a critical discussion on the role of damage response in oligodendrocyte lineage via loss of myelin in brain aging. Boldogh and colleagues present new data on a paradoxical role of OGG1 mediated oxidized DNA repair signaling in cellular senescence as well as in lung aging. Mukunda and colleagues characterize age-dependent molecular/architectural changes in mouse striatum exposed to mitochondrial toxin 3-nitropropionic acid (3-NPA), further implicating diverse DDR responses in aging. Vijg and colleagues discuss the presence of enhanced somatic aneuploidy and other chromosome instabilities during brain aging and their chronic adverse consequences. Pandita and co-authors describe their recent studies on multifaceted role of a chromatin factor MOF in genome maintenance in Purkinje cells.

Bohr and colleagues highlight the phenomenon and implications of genome instability/DNA repair defects in AD and discuss the potential for DDR to be a component of a treatment strategy. Nakabeppu and colleagues describe a new connection between impaired glucose metabolism, mitochondrial dysfunction and oxidative genome damage in AD cognitive impairment. Migliore and co-authors revisit the controversial issue of promoter methylation status of DNA repair genes in blood DNA and their correlation to AD. Buhlman discuss the contribution of functional loss of Parkin to ROS-induced selective, premature senescence of dopaminergic neurons in PD.

While a focused commentary by McKinnon highlights the specific manifestation of polynucleotide kinase-phosphatase (PNKP) mutations in neurological disease phenotype associated with microcephaly with seizures (MCSZ) and ataxia with oculomotor apraxia 4 (AOA4), Weinfeld provides a broad overview of diverse neurological disorders associated with DNA single strand break repair machinery including TDP1, aprataxin and PNKP. He also discusses the molecular bases of how their impairment may give rise to respective disorders. El-Khamisy et al., present original research on ways to suppress the side effects on the drug doxorubicin in causing age-dependent cardiotoxicity using a natural compound

b-carboline alkaloid harmine, an inhibitor of DYRK1A kinase. Martin describes how forced ectopic expression of DNA repair enzymes OGG1 and APE1 rescues degenerating thalamic and motor neurons in mouse model of target deprivation and axotomy. Hegde, Mitra and co-authors review how the double whammy of chronic oxidative damage to DNA and its repair deficiency induced by neurodegeneration-linked etiological factors can provide a common basis for diverse neurodegenerative phenotypes, and discuss the potential of DDR signaling modulation in disease amelioration. In the final article, McMurray critically evaluate the involvement of mitochondrial dysfunction both as a cause and consequence of Huntington's disease.

We believe that the compendium of sixteen scholarly articles in this special issue will stimulate in-depth debate and push the current boundary of our understanding of the etiology of aging and neurodegenerative diseases.

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