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Involvement of Histone PTMs in DNA Repair Processes in Relation to Age-Associated Neurodegenerative Disease

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1. Introduction

Neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), are becoming common in the world with increasing number of aged people in the population. Many investigations have been performed in an attempt to elucidate the mechanisms of neurodegenerative diseases. However, no single etiopathological factor was found to be responsible for such diseases, and therefore no effective therapeutic strategy could be designed.

Aging is regarded as the greatest risk factor for the development of neurodegenerative diseases. Upon aging, reactive oxygen species (ROS) accumulation induces damage to DNA as well as protein and lipid, thus resulting in a progressive loss in the functional efficiency of the brain. Recently, it has been demonstrated that hundreds of proteins including KIN-19, a homolog of mammalian casein kinase 1 isoform alpha (CK1a), become more insoluble with age in *Caenorhabditis elegans* and its over-expression could enhance polyglutamine-repeat pathology (David et al., 2010). Such discovery indicated that aging process itself could be a causative factor for protein aggregation. Increasing aggregation of proteins, such as amyloid beta peptide, could also promote the generation of ROS, DNA damage and thus accelerate neurodegenerative events (Butterfield, 2002). In addition, redox-active metals Cu and Fe could also generate ROS. Normal aging resulted in an elevation of Cu and Fe in the brain, and further interruption of metal homeostasis was noted in AD (Tabner et al., 2010).

Oxidative DNA lesions, such as 8-oxoguanine (8-oxoG) and 8-hydroxyguanosine (8-OHG), were increased dramatically in patients with PD (Nakabeppu et al., 2007; Lovell et al., 1999). Statistically significant elevation of 8-hydroxy-2'-deoxyguanosine (8-OHdG) was detected on DNA of AD subjects, even at the early stage of AD (Lovell et al., 1999; Markesbery & Lovell, 2006). At the same time, DNA repair deficiency in aged or neurodegenerative brain was observed. Both base excision repair (BER) and non-homologous end joining (NHEJ) pathway were deficient in AD subjects (Shackelford, 2006; Weissman et al., 2007). The animals with deficiencies in DNA repair exhibited neurological abnormalities or severe postnatal neurodegeneration and shortened life span (Laposa & Cleaver, 2001; Best, 2009; Dollé et al., 2006), that proved the role of DNA repair deficiency in neurodegeneration. DNA damage combined with inefficient repair mechanism could induce the apoptosis of

brain cells, as well as transcriptional inhibition of the vulnerable genes involved in learning, memory and neuronal survival (Hetman et al., 2010). All these contribute to the pathogenesis of age related neurodegenerative diseases.

Now, histone posttranslational modifications (PTMs) have become an emerging discipline of research, exploring various physiological and pathological processes. Histone PTMs take part in diverse biological processes by inducing chromatin remodelling and regulating gene expression. Increasing evidence suggests that altered patterns of histone PTMs are central to many human diseases. The involvement of histone PTMs in normal nervous system development has been demonstrated and the aberrant PTMs patterns were detected in neurodegenerative disorders (Büttner et al., 2010; Mattson, 2001; Wang et al., 2010; Penner et al., 2010).

It has been widely accepted that histone modifications play important roles in response to DNA damage and in DNA repair (Méndez-Acuña et al., 2010). In the cellular repair machinery, these modified histone sites not only signal the presence of damage, but also provide a landing platform for necessary repair/signaling proteins. Moreover, different PTMs could work together during DNA damage response (Van Attikum & Gasser, 2009). Here, we summarize the abnormal histone PTMs patterns in nuclear DNA damage response (DDR). The role of abnormally expressed histone PTMs in age-associated neurodegenerative disease and their mechanisms are also proposed.

2. Histone PTMs in DNA damage and repair

The core unit of chromatin is the nucleosome which consists of 147 bp of DNA wrapped around histone octamer containing two of each of the core histone proteins H2A, H2B, H3 and H4. The residues at the histone N-terminal tails and globular domains are subjected to PTMs. There are at least nine different types of covalent modifications found in histone proteins, including acetylation, methylation, phosphorylation, deimination, ubiquitination, sumoylation, ADP-ribosylation, proline isomerization and O-linked β-N-acetylglucosamination. Méndez-Acuña has summarized four types of these histone PTMs related to DNA damage response (Méndez-Acuña et al., 2010). Here, we will focus on histone PTMs which are related to DNA damage response during aging and neurodegeneration.

2.1 Phosphorylation

Histone H2A has four variants including H2A1, H2A2, H2AX, and H2AZ. Among them, H2AX is the histone guardian of the genome (Fernandez-Capetillo et al., 2004b). H2AX-/- mice showed the phenomena of radiation sensitivity, growth retardation and immune deficiency (Celeste et al., 2002). Phosphorylation of histone H2AX at serine 139, named gamma-H2AX, is the most characterized PTM at DNA double strand breaks (DSBs). It is catalyzed by the kinases of the PI3-family (ATM, ATR and DNA-PK), especially by ATM (Kinner et al., 2008). It appeared rapidly after the exposure to ionizing radiation and half-maximal amounts were reached by 1 min and maximal amounts by 10 min (Rogakou et al., 1998). Therefore, gamma-H2AX is the first step in recruiting and localizing DNA repair proteins after damage. Presently, gamma-H2AX is regarded as a novel biomarker for DNA breaks and for early stage of apoptosis. Moreover, its expression in a wide range of eukaryotic organisms has indicated its conserved function (Foster & Downs, 2005).

Gamma-H2AX was suggested as a molecular marker of aging and diseases (Mah et al., 2010). The level of H2AX in astrocytes and neurons was found to significantly decrease with the age of participants (Simpson et al., 2010). Meanwhile, the incidence of endogenous gamma-H2AX foci was increased with age (Sedelnikova et al., 2008). The number of gamma H2AX-immunopositive nuclei was significantly increased in the astrocytes of both gray and white matter, and consistently in the cornus ammonus (CA) regions of the hippocampus of AD patients compared to those of control cases (Myung et al., 2008). However, the rate of recruitment of DSB repair proteins to gamma-H2AX foci was correlated inversely with age for both normal and premature aging disease donors (Sedelnikova et al., 2008).

Nuclear localization of DNA repair enzyme DNA-PK and of damaged base 8-OHdG reflect different aspects of the cell response to DNA damage. DNA-PK is required for the NHEJ pathway of DNA repair, whereas, 8-OHdG indicates DNA lesion caused by oxidative damage. Simpson and his colleagues found that the localization of H2AX and DNA-PK demonstrated a good correlation, whereas 8-OHdG localization expression demonstrated a weak correlation with DNA-PK and no significant correlation with H2AX (Simpson et al., 2010). This indicates that H2AX preferentially detects DSBs and is involved in NHEJ repair.

Besides gamma-H2AX, other histone serine phosphorylation events also take place during DDR. Yeast H2A is phosphorylated at serine 122 (threonine 119 in higher eukaryotes) upon DNA damage. Such serine residue was essential for cell survival in the presence of DNA damaging agents (Harvey et al., 2005). The phosphorylation at serine 14 of histone H2B (H2BS14ph) and the phosphorylation at serine 1 of histone H4 (H4S1ph) also occurred in response to DNA damage, and H4S1ph has been shown to be required for an efficient DSB repair by NHEJ (Fernandez-Capetillo et al., 2004a; Cheung et al., 2005). However, the expression of all these PTM sites in aged or neurodegenerative brain has not been reported yet.

Recently, histone phosphorylation at tyrosine was found to be involved in aging, such as phosphorylation of histone H2AX on tyrosine 142 (H2AXY142ph) and histone H3 on tyrosine 99 (H2AXY99ph) (Singh & Gunjan, 2011). Histone H2AXY142 was phosphorylated by the WICH complex and dephosphorylated by the EYA1/3 phosphatases, determining the relative recruitment of either DNA repair or pro-apoptotic factors to DNA damage sites (Stucki, 2009). In contrast to H2AX serine 139 phosphorylation, tyrosine 142 appeared to be constitutively phosphorylated in undamaged cells, but was gradually dephosphorylated in chromatin bearing unrepaired DSBs (Stucki, 2009).

2.2 Methylation

Along the histone polypeptide chain, one, two, or three methyl groups could be added onto the lysine residues by histone methyltransferases (HMT) and could also be removed by histone demethyltransferase (HDMT). Histone methylation is generally associated with transcriptional repression with the exception that several methylation sites are involved in transcriptional activation.

Tri-methylated histone H3 at position lysine 4 (H3K4me3), an important modification associated with transcriptional regulation, showed different epigenome in neuron cells comparing with non-neuronal cells (Cheung et al., 2010). During aging, a significant decrease in H3K4me3 was observed at migrated neural progenitor double cortin gene promoters, indicating the possibility of H3K4me3 in the mechanism of aging-dependent hippocampal dysfunction (Kuzumaki et al., 2010). Other investigation also found that H3K4me3 was related to DDR and could be detected at newly created DSB. In budding

yeast cells, H3K4me3 was important for a proper response to DNA damaging agents, and the cells that cannot methylate H3K4 displayed a defect in DSB repair by NHEJ (Faucher & Wellinger, 2010). During meiosis, H3K4me3 was critical for the formation of the programmed DSB that initiated homologous recombination (Kniewel & Keeney, 2009).

Histone H3 is constitutively methylated at lysine 79 (H3K79me) in both mammalian and yeast cells. In yeast, H3K79 methylation played an important role in the activation of the G1 and intra S-phase DNA damage checkpoint (Wysocki et al., 2005). It was also detected in the brains of senescence-accelerated prone 8 mice and increased with aging (Wang et al., 2010). Lysine 79 locates in a loop connecting the first and the second α helixes in H3 structure (Luger et al., 1997). This region is exposed and adjacent to the interface between H3/H4 tetramer and H2A/H2B dimer, which could influence the access of molecules to the interface. Therefore, the added methyl group on H3K79 might alter the properties of the nucleosome and play an important role in regulating the access of other DNA binding factors to chromatin (Feng et al., 2002). However, the expression level of H3K79 methylation was found unchanged in response to DNA damage. Therefore, methylated H3K79 site might change the higher-order chromatin structure and expose the binding site to DNA damage and repair factors, e.g. the exposure of 53BP1 binding site (Huyen et al., 2004). In addition, H3K79me worked together with phosphorylated H2A serine 129 for the recruitment of budding yeast homolog Rad9 to the DNA damage sites (Huyen et al., 2004; Toh et al. 2006).

Previous investigation has shown that methylated histone H4 at lysine 20 (H4K20me) increased in kidneys and liver of the old-aged rat (Sarg et al., 2002). Except for transcriptional regulation, H4K20me is another reported methylation site that related to DDR. DNA breakage might cause exposure of methylated H4K20 previously buried within the chromosome. At the same time, the level of H4K20 methylation increased locally upon the induction of DSBs by the enzyme named histone methyltransferase MMSET (also known as NSD2 or WHSC1) in mammals (Pei et al., 2011).

2.3 Acetylation

During neurodegeneration, the degree of acetylation balance in brain was greatly impaired (Saha & Pahan, 2006). The inhibition of histone deacetylation induced the sprouting of dendrites, an increased number of synapses, learning behavior reinstatement and long-term memories in bi-transgenic CK-p25 Tg mice (Fischer et al., 2007). All these changes are mainly caused by transcriptional regulation of histone acetylation and/or deacetylation. Actually, DNA damage response regulated by histone acetylation and deacetylation state is also important in neurodegenerative diseases. Moreover, histone deacetylases (HDAC) 1- and 2-depleted cells were hypersensitive to DNA-damaging agents and showed defective DSB repair, particularly NHEJ repair pathway (Miller et al., 2010).

It was found that the acetylation of histone H3 lysine 56 (H3K56ac) was involved in DDR. Mutation of K56 site made the cells sensitive to genotoxic agents (Masumoto et al., 2005). After DNA damage, H3K56ac co-localized with gama-H2AX and other proteins, involved in DNA damage signaling pathways, such as phospho-ATM, CHK2, and p53, at the sites of DNA repair (Vempati et al., 2010). Furthermore, GCN5, histone acetyltransferase (HAT) for H3K56 was shown to have an important role in maintaining genome stability (Burgess & Zhang, 2010). Knocking down of GCN5 resulted in impaired recruitment of NER factors to sites of damage and inefficient DNA repair (Guo et al., 2011). Histone deacetylases HDAC1 and HDAC2 could be rapidly recruited to DNA-damage sites and promote hypoacetylation

of H3K56. However, HDAC1/2 depletion or inhibition did not affect the amount of DNA damage produced by DSB-inducing agents but impaired DNA repair particularly through NHEJ (Miller et al., 2010)

Histone H4 is acetylated at lysine 16 (H4K16ac) by a human MOF gene encoded protein. Reduced level of H4K16ac correlated with a defective DDR and DSB repair after exposure to ionizing radiation (IR). MOF depletion greatly decreased DSB repair by both NHEJ and homologous recombination (HR) (Sharma et al., 2010). Its specific deacetylase Sir2 was recruited to the HO lesion during HR repair process in budding yeast cells (Tamburini & Tyler, 2005). In response to DNA damage, SIRT1, a mammalian homologue of yeast Sir2, re-localized to DNA breaks to promote repair, resulting in transcriptional changes that parallel those in the aging mouse brain (Oberdoerffer et al., 2008).

Acetylation of H2AX on lysine 36 (H2AXK36Ac) also plays a key role in DSB repair pathway. This modification site is constitutively acetylated by the CBP/p300 acetyltransferase. Though its level was not increased by DNA damage, this modification was required for cells to survive in IR exposure. However, H2AXK36Ac did not affect phosphorylation of H2AX or the formation of DNA damage foci, indicating that H2AXK36Ac was a novel, constitutive histone modification regulating radiation sensitivity independently of H2AX phosphorylation (Jiang et al., 2010).

2.4 Ubiquitination

Increased level of monoubiquitinated histone H2A and decreased level of monoubiquitinated H2B were found to be involved in transcriptional repression during HD, and these two ubiquitylation states inhibited methylation of histone H3K9 and histone H3K4, respectively (Kim et al., 2008). Interestingly, histone acetylation could affect monoubiquitination of histone H2A (Sadri-Vakili et al., 2007), whereas monoubiquitinated histone H2B controlled histone methylation (Sun and Allis, 2002). Thus, histone monoubiquitylation provided a potential bridge between histone acetylation and methylation, which leaded to the change of gene expression in neurodegenerative diseases (Kim et al., 2008).

Same as other modifications, histone ubiquitination is also involved in DNA damage response. Monoubiquitination of histone H2B, known for its involvement in transcription, was also important for a proper response of budding yeast cells to DNA damaging agents (Faucher & Wellinger, 2010). In human cells, DSBs induced monoubiquitination of histone H2B on lysine 120, and this monoubiquitination was required for timely repair of DSBs (Moyal et al., 2011).

2.5 Poly ADP-ribosylation

Poly ADP-ribosylation of histones is carried out by poly ADP-ribose polymerases (PARPs). Poly ADP-ribosylated histones could stimulate local chromatin relaxation to facilitate the repair process (Monks et al., 2006). Poly (ADP-ribose) polymerase-1 (PARP-1) is a nuclear enzyme that contributed to both neuronal death and survival under stress conditions (Kauppinen & Swanson, 2007). PARPs were activated in AD in response to oxidative damage to DNA (Love et al., 1999). PARP-1 activation enhanced core histone acetylation, and the acetylated histone H4 facilitated ADP-ribosylation of histones (Cohen-Armon et al., 2007; Boulikas, 1990). 3-aminobenzamide was found to inhibit poly (ADP-ribose) polymerase as well as histone H3 phosphorylation (Tikoo et al., 2001). Therefore, histone H3

phosphorylation was often coupled to poly-(ADP-ribosylation) during ROS-induced cell death. However, the appearance of histone ADP-ribosylation preceded histone H3 phosphorylation after DNA damage (Monks et al., 2006).

3. How are PTMs involved in DNA damage response and repair?

Several histone modifications are associated with DNA damage and repair by directly regulating activation or repression of DNA repair genes. For example, the expression of manganese-dependent superoxide dismutase (Mn-SOD) was regulated by the acetylation of histones H3 and H4 at Mn-SOD proximal promoter (Maehara et al., 2002). In addition, decreased level of dimethyl H3K4 and acetylated H3K9 also regulated the expression of SOD2 gene (Hitchler et al., 2008). SODs are a group of critical enzymes in counteracting the superoxide toxicity. Altered expression and activity of SOD are all associated with oxidative DNA damage. It was found that *SOD1* mutation could cause familial amyotrophic lateral sclerosis (ALS) (Li et al., 2010). High level of MnSOD was detected in hippocampus of AD patients (Marcus et al., 2005).

On the other hand, these PTM signals are directly read to initiate DNA repair process. 53BP1 is found as one key point protein connecting the PTM signals with other repair molecules. It is a conserved checkpoint protein with properties of a DSB sensor. DNA damage-induced PTMs could change higher-order structure of chromatin and then expose the 53BP1-binding site. In response to DNA damage, 53BP1 is recruited to DSBs sites by binding to gamma-H2AX. A region of 53BP1 upstream of tandem tudor domains bound gamma-H2AX in vitro (Ward et al., 2003). Moreover, 53BP1 was recruited to the sites of DSBs by binding of its tandem tudor domain to methylated histones, such as H4K20me1/2, H3K79me1/2 (Huyen et al., 2004; Pei et al., 2011).

However, the binding of 53BP1 to DNA damage sites is not the first step in DDR. The upstream molecules could regulate such binding activity, such as mediator of DNA damage checkpoint protein 1 (MDC1) and E3 ubiquitin-protein ligase RNF8. MDC1 is a cell cycle checkpoint protein, activated in response to DNA damage. Through its BRCT motifs, MDC1 interacted with gamma-H2AX at sites near DDR within minutes after exposure to ionizing radiation, which facilitated the recruitment of ATM kinase to DNA damage foci (Stewart et al., 2003). Then RNF8 was rapidly assembled at DSBs via interaction of its FHA domain with the phosphorylated adaptor protein MDC1 (Mailand et al., 2007). After that, ubiquitinated H2A and H2AX by RNF8 made the translocation of 53BP1 to the sites of DNA damage (Yan & Jetten, 2008). At the same time, phosphorylated histone methyltransferase MMSET (at Ser 102 site) was also recruited with the interaction to MDC1 BRCT domain, which induced H4K20 methylation around DSBs and also facilitates 53BP1 recruitment (Pei et al., 2011).

What about the mechanism of histone acetylation in DDR? Evidence has indicated that acetylated histones and histone acetyltransferases were involved in DDR by recruiting DNA repair proteins as well as chromatin remodeling factors to DSB sites (Tamburini & Tyler, 2005; Ogiwara et al., 2011). For example, the recruitment of CBP and p300 to the DSB sites induced the acetylation of lysine 18 within histone H3, and lysines 5, 8, 12, and 16 within histone H4, which facilitated the recruitment of KU70 and KU80 for NHEJ. At the same time, BRM, a catalytic subunit of the SWI/SNF complex, was also recruited at DSB sites to establish a relaxed chromatin environment for DNA damage repair. During homologous recombinational repair, histone acetyltransferases GCN5 and Esa1 and histone deacetylases Rpd3, Sir2 and Hst1 were recruited to the HO lesion (Tamburini & Tyler, 2005). Dynamic

changes in histone acetylation were detectable at DSB sites, which might represent important signal for cells indicating that chromosomal repair was complete and might be required to turn off the DNA damage or chromatin structure checkpoint (Tamburini & Tyler, 2005).

Recently, researchers explained the mechanism of ubiquitination of histone H2A at lysine 119 (H2AK119ub) in DDR (Ginjala et al., 2011). ATM, phosphorylated H2AX and RNF8 firstly recruited polycomb protein BMI1 to sites of DNA damage. BMI1 then catalyzed ubiquitination of histone H2AK119 and activated homologous recombination.

Kauppinen and Swanson have described the possible mechanism of poly ADP-ribosylation in DDR (Kauppinen & Swanson, 2007). Poly ADP-ribosylation of histones induced local relaxation of the chromatin structure, which in turn facilitated access of repair proteins to damaged DNA. In addition, the binding of PARP induced the synthesis of a poly ADP-ribose chain (PAR), which worked as a signal for the other DNA repair enzymes, such as DNA ligase III (LigIII) and DNA polymerase beta (polβ), which were necessary for BER process. Regretfully, over-activation of PARP might induce a progressive ATP depletion and finally result in cell death.

4. Specificity of DNA damage and repair in age-associated neurodegenerative diseases

DNA damage could be caused by both exogenous and endogenous damaging agents. However, some external agents, such as UV light, are unlikely to affect neuronal cells because they are never exposed to sunlight. Endogenous DNA damaging agents, such as ROSs, is the predominant DNA damaging agent in age-associated neurodegenerative diseases. The DNA damage and repair occurring in neurodegenerative diseases have been summarized in a number of reviews (Fishel et al., 2007; Martin, 2008). The main forms of damage detected in AD brains as well as in other neurodegenerative diseases are DNA single-strand breaks (SSBs) and DSBs, which are intermediates in repair of oxidative DNA damage. SSBs are primarily removed by BER pathway and nucleotide excision repair (NER) pathway. Neuronal cells also have the capacity to repair DNA lesions by direct repair and mismatch repair (MMR) and have the ability to repair DSBs through homologous recombination (HR) and NHEJ mode. However, the cohesive end joining activity decreased with age of the animal (Vyjayanti & Rao, 2006).

Interestingly, different types of DNA damage had different distribution patterns in neurodegenerative brain, and different cells showed various fates (Barzilai et al., 2008). Most of DNA damage was found in the hippocampus and cortex during aging, which was consistent with the decline in memory and cognitive capacity as the early features of neurodegenerative disease. Astrocytes and neurons, but not microglia, were associated with the presence of DNA damage-associated molecules (H2AX, DNA-PK and 8-OHdG). PARP protein recognizes SSBs sites. Most of the cells containing poly (ADP-ribose), end-product of PARP, were neurons, such as small pyramidal neurons in cortex and some astrocytes, but not microglia (Love et al., 1999). Interestingly, accumulation of poly (ADP-ribose) was not detectable in the cells containing tangles and relatively low accumulation occurred within plaques, which were caused by tau or amyloid beta protein (Love et al., 1999). This might imply that the damage form caused by tau or amyloid beta protein might be DSBs rather than SSBs.

The destiny of different brain cells in response to the same type of DNA damage was diverse, which leaded researchers to propose that brain cells had different thresholds to

DNA damage (Barzilai et al., 2008). Certain types of neurons, such as hippocampal, pyramidal and granule cells as well as cerebellar granule cells, suffer from an age-associated accumulation of DNA damage but do not reduce in number during aging. Other types of neurons, such as cerebellar Purkinje cells, reduce cell number during aging, but remaining cells show no age-associated accumulation of DNA damage.

In conclusion, DDR differs between various neuronal cells. Therefore certain histone PTM types and their role in repair pathways might be specific to certain age-associated neurodegenerative diseases. However, we should note that some conclusions on histone PTMs involving in DDR came from the investigations on budding yeast cells or non- human mammalian cells. Therefore, further work focusing on human neuronal cells is needed.

5. PTMs in cell cycle re-entry

It is commonly believed that neurons are postmitotic cells, which remains in G0 phase of the cell cycle indefinitely. Actually, neurons in the adult human brain are able to re-enter the cell-division cycle. Schwartz and colleagues have demonstrated cell cycle re-entry phenomenon in neurons (Schwartz et al., 2007). They found that subtoxic concentrations of H_2O_2 induced the formation of repairable DSBs associated with the activation of cyclin D1, G1 cell cycle component, and the phosphorylation of retinoblastoma tumor suppressor protein (pRB) at serine 795, a marker of G0-G1 transition, was also significantly elevated. In addition, DNA helicase subunit minichromosome maintenance (Mcm) protein 2, which is strongly down regulated in quiescent, terminally differentiated or senescent cells, was higher in H_2O_2 -treated cells. Nuclear antigen Ki-67 positive neurons, a marker of cells in G1, S, G2 and mitosis, were also increased after treatment. Except for the expression of several cell cycle proteins (Nagy et al., 1997), H3 phosphorylation at serine 10, as a marker for mitosis and transcriptional activation, was also significantly increased in the cytoplasm of neurons in the hippocampus of AD cases (Ogawa et al., 2003).

It seemed that neuronal cells also need to re-enter the cell cycle to activate DNA repair and/or contribute to apoptosis, which shared the same function with proliferating cells (Kruman, 2004). The transition from G0 to G1 was required for NHEJ repair in neurons (Tomashevski et al., 2010). In the brains of AD patients, the cell cycle of neurons could progress as far as the G2 phase, which was also required for repairing DNA lesions (Obulesu & Rao, 2010).

Dynamic change of histone PTMs during cell cycle has been analyzed in HeLa cells (Bonenfant et al., 2007). For example, phosphorylated histone H3 at serine 10 and threonine 3 was only detected in G2/M phase and acetylation on histone H2A and H2B was reduced in G2/M phase, while histone H3K79me showed no change during the cell cycle. Such studies provide us with valuable information for understanding the roles of histone PTMs in cell cycle regulation. However, several recent investigations have reported the roles of histone PTMs in cell cycle re-entry under DNA damage stress (see above), which may be more important in terminally differentiated neurons and likely represent a new research area in the future.

6. Conclusions

Oxidative stress-induced DNA damage has been proposed as pathological mechanism contributing to age-associated neurodegenerative diseases. The modified histone sites not

only signal the presence of damage, but also provide a landing platform for necessary repair/signaling proteins in cellular repair machinery. Moreover, histone residues covalently modified alone or in combination could provide distinct docking sites for multiple nuclear proteins, and thus regulate the expression of genes in response to oxidative stress or other extracellular signals. Therefore, both direct and indirect participation of histone PTMs in DNA damage recognition and repair might play a critical role in the pathological process of age-related neurodegenerative diseases.

Except for nuclear DNA damage, mitochondrial DNA (mtDNA) damage is also proposed to play a critical role in aging and in the pathogenesis of several neurological disorders (Yang et al., 2008). According to previous studies, no histone proteins were found in mitochondria. DNA damage detection and DNA repair processes that involve histone PTMs might not be suitable for mtDNA damage. However, Katherine and her group recently found the positive signal of histone H3 in mitochondrial extracts from Brassica oleracea by western blot (Katherine et al., 2010). Regretfully, the function of mitochondrial H3 has not been demonstrated by experimental data. More evidence in other species had not been reported. The question whether there is a relationship between PTMs and mtDNA damage or not needs more hard experimental work to be answered.

In summary, studies of the mechanisms involving histone PTMs will enrich our basic knowledge of the role of histone PTMs in DNA damage response and thus will benefit the strategies for clinical interventions in age-related neurodegenerative diseases in the future.

7. Abbreviations

8-oxoG, 8-oxoguanine; 8-OHG, 8-hydroxyguanosine; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; BER, base excision repair; DDR, DNA damage response; DSBs, DNA double strand breaks; HMT, histone methyltransferases; HDMT, histone demethyltransferase; HDAC, histone deacetylases; HAT, histone acetyltransferase; HR, homologous recombination; IR, ionizing radiation; NER, nucleotide excision repair; NHEJ, non-homologous end joining; PARPs, poly ADP-ribose polymeras; PTMs, histone post translational modifications; ROS, reactive oxygen species; SSBs, single-strand breaks.

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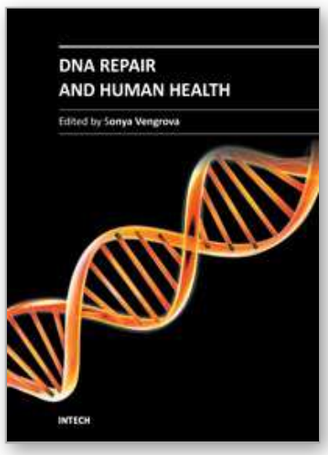

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Over the past decades, great advances have been made in understanding the cellular DNA repair pathways. At the same time, a wealth of descriptive knowledge of human diseases has been accumulated. Now, the basic research of the mechanisms of DNA repair is merging with clinical research, placing the action of the DNA repair pathways in the context of the whole organism. Such integrative approach enables understanding of the disease mechanisms and is invaluable in improving diagnostics and prevention, as well as designing better therapies. This book highlights the central role of DNA repair in human health and well-being. The reviews presented here, contain detailed descriptions of DNA repair pathways, as well as analysis of a large body of evidence addressing links between DNA damage repair and human health. They will be of interest to a broad audience, from molecular biologists working on DNA repair in any model system, to medical researchers.

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