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Cell Cycle and DNA Damage Response in Postmitotic Neurons

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1. Introduction

Cellular DNA copes with constant exposure to different hazards, environmental and intrinsic. This leads to DNA lesions which interfere with transcription and replication and if not repaired or repaired incorrectly, can produce mutations or large-scale genome aberrations that may lead to cell malfunction or cell death and contribute to different pathologies (Jackson, 2009; Sancar et al., 2004). For this reason, virtually every organism is equipped with highly conserved genome surveillance network known as the DNA damage response (DDR) whose function is to sense genome damage and activate several downstream pathways, including cell cycle checkpoints, DNA repair and apoptotic signaling (Rouse & Jackson, 2002; Zhou & Elledge., 2000). The DDR has been investigated mainly in mitotic cells, in which the cell cycle checkpoints are a major contributor to the DDR, required for DNA repair (Stracker et al., 2008). Not much is known about the DDR in postmitotic neurons. It is known, however, that all eukaryotic DNA repair systems operating in proliferating cells also operate in neurons (Fishel et al., 2007; Lee & McKinnon, 2007; Sharma, 2007; Weissman et al., 2007; Wilson, & McNeill, 2007) and that dysfunctional DDR plays an important role in neurodegeneration and is associated with syndromes (e.g. ataxia telangiectasia) characterized by neurological abnormalities (Barzilai, 2010; Rass et al., 2007; Shiloh, 2003, 2006). This suggests the importance of DDR for postmitotic neurons. While the cell cycle checkpoints are part of DDR involved in DNA repair, apoptotic signaling, and cell fate decisions in mitotic cells, their contribution to the DDR of postmitotic neurons remains unclear. Nonetheless, evidence accumulates that DNA damage-initiated apoptosis of postmitotic neurons is associated with cell cycle signaling. Recently, we have demonstrated the importance of the cell cycle activation for DNA repair in postmitotic neurons (Tomashevski et al., 2010). This suggests that the expression of cell-cycle markers (Schmetsdorf et al., 2007, 2009) and DNA repair activity (Sharma, 2007) observed in the brain under physiological conditions may contribute to DNA repair. The involvement of the cell cycle machinery to both DNA repair and DNA damage-initiated apoptosis in postmitotic neurons suggests a potential function of cell cycle checkpoints in the DDR of these postmitotic cells.

This review focuses on the DDR of postmitotic neurons in the context of what is known about the DDR of mitotic cells.

2. DNA damage response in mitotic cells

The genome of eukaryotic cells is continuously exposed to chemicals, ultraviolet (UV) or ionizing radiation (IR), as well as to by-products of intracellular metabolism (e.g.

oxyradicals). The resulting DNA lesions can block genome replication and transcription and result in loss or incorrect transmission of genetic information. If left unrepaired or are repaired incorrectly, DNA lesions lead to mutations or cell death resulting in different abnormalities, including tumorigenesis and neurodegeneration. To maintain genomic integrity during cell division, cells are equipped with highly efficient defense mechanism, the DDR (Reinhardt & Yaffe, 2009) which functions to recognize and remove DNA lesions by DNA repair and eliminate the irreparably damaged cells by apoptosis (Ciccia & Elledge, 2010; Jackson, 2009; Jackson & Bartek 2009). The DDR cascade senses genome damage and activates several pathways, including cell cycle checkpoints, DNA repair and apoptotic programs. Defects in DDR or DNA repair contribute to aging and various disorders, including neurodegenerative diseases and cancer (Jackson & Bartek 2009). This underlines the critical importance of DDR as a regulator of both cell death and survival processes.

2.1 Formation of DDR foci

The earliest events of the DDR involve alterations in chromatin structure (Berkovich et al., 2007; Downs et al., 2007; Smerdon et al., 1978) and the formation of DDR foci. The biochemical details of these processes are poorly understood. Since DDR foci are the sites where DDR signaling originates, the understanding of their formation and functioning is crucial to understanding how DDR activities are exerted. Among the first events of the DDR is recruitment of a mediator complex MRN consisting of Mre11, Rad50, and Nbs1, and phosphorylation of a variant H2A histone - H2AX - near the break, extending for distances up to several megabases (Fernandez-Capetillo et al., 2004). Working together, MRN and phosphorylated H2AX (γ H2AX) act as a signal amplifier that recruits additional signaling molecules to the DSB lesion. The MRN complex serves as an initial DSB sensor, at least one component of which (Nbs1) localizes to the break in an H2AX-independent manner (Celeste et al., 2002, 2003) and facilitates the recruitment and activation of the apical DDR phosphoinositide-3-kinase related kinase (PIKK) ataxia telangiectasia mutated (ATM) (Falck et al., 2005; Lee & Paull 2005; Uziel et al., 2003). This is an important step in the DDR. ATM phosphorylates a number of proteins essential in the control of cell-cycle checkpoints, DNA repair and, in the case of excessive DNA damage, cell death (Khanna et al., 2001; Shiloh, 2003). The widely accepted model of ATM activation is its autophosphorylation at Ser 1981 which releases it from the inhibitory homodimer structure, leading to its recruitment to sites of DNA double-strand breaks (DSBs) (Dupre et al., 2006; Lavin & Kozlov, 2007). Among the first proteins recruited to DNA breaks are direct sensors of DNA breaks such as PARP-1 and PARP-2 whose catalytic activity is triggered by their binding to single-strand breaks (SSBs) and DSBs (D'Amours et al. 1999; de Murcia & Ménissier de Murcia, 1994). The Ku70-Ku80 heterodimer and the MRN complex, DSB sensors, directly bind to DSBs (de Jager et al., 2001; Kim et al., 2005; Lisby et al., 2004; Mimori & Hardin, 1986). Ku heterodimer possibly competes with MRN and PARP-1 for binding to DSBs (Clerici et al., 2008; Wang et al., 2006; Zhang et al., 2007). The direct binding of DNA breaks by factors such as Ku and MRN is crucial for the DDR. The recruitment and activation of the apical DDR kinases ATM, ATM rad3-related (ATR), and DNA-dependent protein kinase (DNA-PK) have also well-known significance at sites of DNA breaks and in DDR foci formation (Polo & Jackson, 2011). The functional importance of downstream DDR factors is not well understood which can be explained by complexity and diversity of downstream DDR events, and the fact that multiple systems appear to cooperate to control the formation of DDR foci. However, it is clear the DDR foci formation is critical for the maintenance of genome integrity.

Downstream from direct sensors of DNA breaks, mediator of DNA damage checkpoint protein1 (MDC1) is recruited. This DDR component serves as a binding platform for DNA damage checkpoint and repair proteins (Jungmichel & Stucki, 2010). For example, ATM-dependent phosphorylation of MDC1 creates binding sites for the FHA domain of the ubiquitin E3 ligase RNF8, which in turn promotes the focal accumulation of another mediator of the DNA damage checkpoint, 53BP1 and breast cancer 1 (BRCA1) at DSB sites (Huen et al., 2008; Kolas et al., 2007; Mailand et al. 2006). Constitutive phosphorylation of MDC1 by casein kinase 2 (CK2) mediates DSB focus formation by MRN (Chapman & Jackson, 2008; Melander et al. 2008; Spycher et al., 2008).

The building of multiprotein DDR foci at DNA breaks is tightly controlled by posttranslational protein modifications, including phosphorylation, ubiquitylation, sumoylation, methylation, acetylation, and PARylation (Polo & Jackson, 2011).

ATM, ATR, and DNA-PK phosphorylate H2AX (Burma et al., 2001; Downs et al., 2000; Rogakou et al., 1998; Stiff et al. 2004; Ward & Chen 2001) which is followed by the recruitment of downstream DDR components, including checkpoint mediators such as MDC1 (Hammet et al., 2007; Nakamura et al., 2004; Sanders et al., 2010; Sofueva et al., 2010; Stucki et al., 2005). Phosphorylated H2AX also promotes the recruitment of chromatin modifying complexes, such as p400 (Downs et al., 2004; Kusch et al., 2004; van Attikum et al., 2004, 2007; Xu et al., 2010). In some cases, phosphorylation promotes the dissociation of proteins from sites of DNA breaks. For example, autophosphorylation of DNA-PK catalytic subunit (DNA-PKcs) induces its dissociation from Ku (Chan & Lees-Miller, 1996; Merkle et al., 2002). Recent studies have revealed the critical importance of ubiquitylation, the process whereby ubiquitin (monoubiquitylation) or polyubiquitin (polyubiquitylation) is covalently attached to proteins in the assembly of DDR proteins at DSB sites (Al-Hakim et al., 2010; Messick & Greenberg, 2009; Pickart, 2001). Another critical modification involved in control of DDR foci is histone acetylation near DSBs. Acetylation of histones H3 and H4 is essential for DNA repair (Averbeck & Durante, 2011). The importance of this modification is underlined by the recruitment of several histone acetyltransferases including Hat1, and NuA4 and deacetylases such as Sir2 and Hst1 in budding yeast (Downs et al., 2004; Qin & Parthun, 2006; Tamburini & Tyler 2005) and the Tip60 acetyltransferase and deacetylases (HDAC1, HDAC2, HDAC4, SIRT1 and SIRT6) in mammalian cells (Kaidi et al., 2010; Miller et al., 2010; Murr et al., 2006; O'Hagan et al., 2008; Oberdoerffer et al., 2008). SIRT1 binding in the DSB area has been found to promote the recruitment of NBS1 and RAD51 (Oberdoerffer et al., 2008). Histone H3K56 deacetylation by HDAC1 and HDAC2 regulates recruiting DNA repair factors of nonhomologous end-joining pathway to DSB regions (Miller et al., 2010). Additionally, MOF (males absent on the first)-dependent acetylation of histone H4K16 is important for IR-induced focus formation of MDC1, 53BP1, and BRCA1 in mammalian cells (Li et al., 2010; Sharma et al., 2010). H2AX acetylation by Tip60 promotes H2AX eviction from damaged chromatin, as shown in both *Drosophila* and mammalian cells (Ikura et al., 2007; Kusch et al., 2004). The acetylation of histone proteins in the DNA break area can regulate the assembly of DDR factors indirectly by modulating chromatin compaction (Lee et al., 2010).

The covalent protein modification process of binding with ADP-ribose polymers, known as PARylation, is one of the earliest events in the DDR. The PARylation is catalyzed by PARP enzymes (Hakme et al. 2008) comprising a large family of proteins, several members of which have clearly identified DDR functions (Citarelli et al., 2010). PARylation is quickly

suppressed by PARG (PARG) (Gagne et al., 2006; Hakme et al. 2008; Krishnakumar & Kraus, 2010). It is involved in buildup of the chromatin remodeling factors ALC1 and CHD4 (Ahel et al., 2009; Chou et al., 2010; Gottschalk et al., 2009; Polo et al., 2010), the Polycomb histone-modifying complex (Chou et al., 2010), and the histone variant macro H2A (Timinszky et al., 2009). A contribution of PARylation to the early recruitment of MRN has also been reported (Haince et al., 2008). PARylation can also promote protein dissociation from DNA damage, as shown for the histone chaperone FACT which facilitates chromatin transcription (Heo et al., 2008; Huang et al., 2006).

The mobilization of DDR factors to SSBs or DSBs is very rapid and transient (Gagne et al. 2006; Hakme et al., 2008; Lieber, 2010; Mahaney et al., 2009; Mortusewicz et al., 2007). Responses to DSBs can be markedly influenced by cell cycle status. While accumulation of DDR factors such as γ H2AX, MRN, and MDC1 occurs regardless of the cell cycle phase, others - including BRCA1 and RAD51 accumulate effectively only in S/G2 cells (Bekker-Jensen et al., 2006; Jazayeri et al., 2006; Lisby et al., 2004; Sartori et al., 2007). Studies in yeast and mammalian systems have demonstrated that colocalization of DDR proteins rather than DNA damage per se is critical for DNA damage signaling (Bonilla et al., 2008; Soutoglou & Misteli, 2008). One of important regulatory functions of DDR foci is to contribute to the proper coordination of DNA damage signaling and repair with other DNA metabolic activities by inhibiting replication and transcription. In this regard, DNA and histone modifications at sites of DNA breaks have been proposed to contribute to silencing of damaged chromatin (O'Hagan et al., 2008; Shanbhag et al., 2010).

It is now clear that chromatin modifications are an important component DDR network (van Attikum & Gasser, 2009). Recent electron microscopy studies revealed that generation of DSB leads to a rapid, ATP-dependent, local decondensation of chromatin that occurs in the absence of ATM activation. ATM activation itself leads to chromatin relaxation at DSB sites (Ziv et al., 2006). The local and global changes in chromatin organization facilitate recruitment of damage-response proteins and remodeling factors, which further modify chromatin in the vicinity of the DSB and propagate the DNA damage response, thereby providing functional crosstalk between chromatin modification and proteins involved in DDR (Peterson & Cote, 2004; van Attikum & Gasser, 2005).

2.2 DNA repair

DNA repair is essential for maintaining the integrity of the genome. The complicated network of DNA repair mechanisms functions to remove DNA damage by DNA repair pathways. This network include base excision repair (BER), mismatch repair (MMR) and nucleotide excision repair (NER) (Hakem, 2008). One of the most powerful activators of the DDR are DSBs, the most cytotoxic DNA lesions which potentially induce gross chromosomal aberrations, often linked to cell death or cancer (Hopfner, 2009). It has been estimated that a single unrepaired DSB is sufficient for cell lethality (Khanna & Jackson, 2001). DSBs in eukaryotic cells are repaired by two major mechanisms: nonhomologous end-joining (NHEJ), an error-prone ligation mechanism, and a high-fidelity process based on homologous recombination (HR) between sister chromatids that operate in the S and G2 phases of the cell cycle (Pardo et al., 2009; van Gent & der Burg, 2007). DNA damage-induced recruitment of the protein MDC1 dramatically enhances activation of ATM which in turn recruits 53BP1 and BRCA (Bekker-Jensen et al., 2005; Stewart et al., 2003; Stucki et al., 2005). 53BP1 facilitates DNA repair by NHEJ pathway, predominant in mammalian cells

(Moynahan et al., 1999). Several proteins are required for efficient repair of DSB by NHEJ. The core complex consists of the DNA-PK and the ligase IV/XRCC4/XLF complexes. NHEJ initiates upon the binding of two ring-shaped Ku70/Ku80 heterodimers to both DNA broken ends within seconds of the creation of the DNA damage (Lieber, 2010; Mahaney et al., 2009). DNA-PKcs is also recruited to this DNA-Ku scaffold and probably enables the formation of a synaptic complex. In the synaptic complex, the DNA broken ends are positioned next to each other. Depending on the properties of the lesion, some DNA ends must be processed before the final ligation step. For example, a damaged DNA end can contain an aberrant 5' hydroxyl group, aberrant 3' phosphate, damaged base and/or damaged backbone sugar residue. Several enzymes can process such lesions (Chappell et al., 2002; Koch et al., 2004). Werner helicase, associated with Ku70 and Artemis, a structure-specific nuclease, which can cleave DNA hairpin structures and remove 3' overhang DNA may prepare DNA ends (Perry et al., 2006). When the end processing has been accomplished, ligase IV/XRCC4 can catalyze the final ligation reaction. For NHEJ, the Ku70-Ku80 heterodimer plays a central role in recruiting other NHEJ components. In particular, Ku recruits the protein kinase DNA-PKcs (Dvir et al., 1992; Gottlieb & Jackson, 1993) via a specific interaction between DNA-PKcs and the Ku80 C terminus (Gell & Jackson, 1999; Singleton et al., 1999), as well as the downstream NHEJ complex XLF-XRCC4-LigaseIV and the nuclease Artemis (Calsou et al., 2003; Yano et al., 2008).

2.3 Cell cycle checkpoints

Checkpoints are complex kinase signaling pathways that prevent further progression through the cell cycle and coordinate DNA repair with chromosome metabolism and cell-cycle transitions (Houtgraaf et al., 2006; Poehlmann & Roessner, 2010). In response to DNA damage, the checkpoints delay or stop the cell cycle at critical points before or during DNA replication (G1/S and intra-S checkpoints) and before cell division (G2/M checkpoint), thereby preventing replication and segregation of damaged DNA. The critical importance of the cell cycle checkpoint pathways in maintaining genomic integrity is highlighted by the observation that loss or mutation of checkpoint genes is frequently observed in cancer (Kastan & Bartek, 2004). Recent evidence suggests mutually integrated roles of the checkpoint machinery in the activation of DNA repair, chromatin remodelling, modulation of transcriptional programmes and the optional triggering of permanent cell cycle withdrawal by cellular senescence or apoptosis (Bartek & Lukas, 2001; Shiloh, 2003; Zhou & Elledge, 2000). The canonical DDR network has traditionally been divided into two major kinase signaling branches utilizing the upstream kinases ATM and ATR. These kinases control the G1/S, intra-S, and G2/M checkpoints through activating their downstream effector kinases Chk2 and Chk1, respectively (Reinhardt & Yaffe, 2009). The ATM/Chk2 module is activated after DNA DSBs and the ATR/Chk1 pathway responds primarily to DNA SSBs or bulky lesions. Both pathways converge on cell division cycle 25 homolog A (Cdc25A), a positive regulator of cell cycle progression, which is inhibited by Chk1- or Chk2-mediated phosphorylation (Poehlmann & Roessner, 2010). Post-translational modifications, such as checkpoint- and cyclin-dependent kinase (CDK)-dependent phosphorylation, ubiquitylation and sumoylation were shown to be crucial for regulation of stability and activity of important components of the checkpoint machinery, thereby regulating important cell cycle events. These post-translational modifications may affect the recruitment of repair proteins to damaged DNA or tune the efficiency or the specificity of

the repair machinery towards a certain type of DNA damage and facilitate repair in a specific cell-cycle phase (Branzei & Foiani, 2008). Chromatin structure and compaction is also regulated throughout the cell cycle, and can be influenced by checkpoints and post-translational modifications (Groth et al., 2007; Karagiannis & El-Osta, 2007; Kouzarides, 2007). Thus, cell cycle checkpoints induce G1, S, and G2 cell cycle arrest, recruit repair machinery to the sites of damage, and target irreversibly damaged cells for apoptosis (Kastan & Bartek, 2004; Reinhardt & Yaffe, 2009). ATM and DNA-PK respond mainly to DSBs, whereas ATR is activated in response to incomplete DNA replication due to stalled replication forks (Bartek, & Lukas, 2007; Reinhardt & Yaffe, 2009). During replication, single-stranded DNA becomes opsonized by the replication protein A, which recruits ATR via the ATR-interacting protein to the DNA lesions exposed by stalled forks and orchestrates DNA-topoisomerase II beta-binding protein (TopBP1)-dependent ATR- (Kumagai & Dunphy, 2006) and checkpoint activation (Elledge, 1996). Following activation, the checkpoint transducers transmit and amplify the checkpoint signal to downstream targets such as the DNA-repair apparatus and the cell-cycle machinery (Branzei & Foiani, 2008). DNA synthesis is frequently associated with nucleotide misincorporation, accumulation of nicks and gaps, slippage at repetitive sequences, fork collapse at DNA breaks and aberrant transitions at collapsed forks that cause reversed and/or resected forks. Replication-fork collapse during S phase can often induce DSBs (Branzei & Foiani, 2008). ATR activation by DSBs requires ATM and MRN (Jazayeri et al., 2006; Sartori et al., 2007). It is possible that activation of the tumor suppressor protein, p53, following this replication fork collapse could be detrimental per se, taking into account its implication in apoptosis (Brady & Attardi, 2010). However, there are mechanisms that operate in the S phase to prevent p53 from a death-related activation of p53 transcription programme. It has been speculated that induction of such program within S phase, when the E2F-1 transcription factor (known to cooperate with p53 to induce apoptosis) is highly active, could promote unwanted cell death (Gottifredi et al., 2001).

A major target of ATM in checkpoint pathways is the effector kinase Chk2 that functions to arrest the cell cycle after DSBs by inactivating phosphatases of the Cdc25 family through catalytic inactivation, nuclear exclusion, and/or proteasomal degradation (Aressy & Ducommun, 2008; Busino et al., 2004). This, in turn, prevents Cdc25 family members from dephosphorylating and activating cyclin-CDK complexes, thereby initiating G1/S and G2/M cell cycle checkpoints. In contrast to G1/S or G2/M arrest, cells that experience genotoxic stress during DNA replication only delay their progression through S phase in a transient manner, and if damage is not repaired during this delay they exit S phase and are arrested later when reaching the G2 checkpoint (Bartek et al., 2004).

Following DNA repair, cells must extinguish the DNA damage signal to allow the cells to reenter the cell cycle, but the mechanisms through which this occurs, particularly with respect to the ATM-Chk2 pathway, are poorly understood. Since DNA damage checkpoints respond to as little as a single DNA DSB (Lobrich & Jeggo, 2007), it has long been assumed that human cells also maintain the G2/M checkpoint until all of the breaks are repaired. Recent evidence, however, shows that the G2 checkpoint in immortalized human cells in culture displays a defined threshold of approximately 10–20 DSBs (Deckbar et al., 2007). Limited checkpoint control was not only apparent in response to IR doses that cause very few DNA DSBs, but also in response to more extensive amounts of DNA damage where checkpoint release occurred at fewer than 10–20 unrepaired DSBs (Deckbar et al., 2007).

Although the fate of cells that continue proliferating in the presence of unrepaired DNA breaks is unclear, and the identity of the rate-limiting DNA damage checkpoint components has yet to be revealed, accumulating evidence suggests that the DNA damage checkpoint machinery can be overridden. G2 checkpoint escape in the presence of unrepaired DNA damage may be particularly common during the evolution of cancer cells (Bartek & Lukas, 2007; Bartkova et al., 2005; Gorgoulis et al., 2005; Kastan & Bartek 2004; Shiloh, 2003).

In mammalian cells, p53 is an important player of the cell cycle checkpoint machinery (Polager & Ginsberg, 2009). During checkpoint control following DNA damage, p53 can either be phosphorylated directly by ATM or ATR (Banin et al., 1998; Hammond et al., 2002; Tibbetts et al., 1999), or indirectly via Chk1 and Chk2 (Hirao et al., 2000; Shieh et al., 2000). Certain cancer-related mutations in the *Chk2* gene can prevent phosphorylation of p53 (Falck et al., 2001; Jazayeri et al., 2006). The effects of Chk1 and Chk2 in the regulation of p53 also depend on the site where p53 is phosphorylated (Polo & Jackson, 2011). A target of p53 in cell cycle checkpoints is the CDK inhibitor p21 (Deng et al., 1995; el-Deiry et al., 1993; Gu et al., 1993; Xiong et al., 1993). P21 functions by inhibiting several CDKs, including CDK4/6, and CDK2 (Harper et al., 1993; Xiong et al., 1993). The silencing of cyclin E - CDK2 activity in late G1 occurs even in cells lacking p53 or p21 (Bartek & Lukas, 2001). These facts argue for a two-wave model of the G1 checkpoint response in mammalian cells, in which the initial, rapid, transient and p53-independent response (Chk2 - Cdc25A - CDK2 axis) is followed by the delayed but more sustained G1 arrest imposed by the Chk1/Chk2-p53-p21-CDK pathway centered on p53 (Bartek & Lukas, 2001; Polager & Ginsberg, 2009). G2 arrest following DNA damage is dependent on the actions of several proteins such as 14-3-3 δ which is strongly induced by DNA damage (Chan et al., 1999; Laronga et al., 2000). It acts by sequestering CDK1 -cyclin B complex to prevent entry into mitosis and by modulating the p53-Mdm2 axis (Chan et al., 1999; Yang et al., 2008). 14-3-3 δ is a valid tumor suppressor gene that is frequently inactivated in a number of human malignancies (Ferguson et al., 2000; Henrique et al., 2005; Kuroda et al., 2007). P21 and 14-3-3 δ cooperate to maintain G2 arrest following DNA damage. CDK1-cyclin B is subsequently inactivated by p21 in the nucleus (Chan et al., 2000).

The G1/S checkpoint generated through the Chk1/Chk2 - Cdc25A - CDK2 pathway is executed by the active unphosphorylated Cdc25A phosphatase through dephosphorylation of the CDK2-cyclin E complex (Poehlmann & Roessner, 2010). As a consequence, the CDK2 - cyclin E complex is kept in its active form, which causes G1-S transition. Following DNA damage, Chk1 and Chk2 phosphorylate Cdc25A, inducing its degradation. Due to the degradation of the Cdc25A phosphatase, the CDK2-Cyclin E complex remains in its hyperphosphorylated inactive form, culminating in G1/S arrest. P21 potentially participates in the G1/S checkpoint by blocking directly DNA synthesis due to its ability to bind the central region of proliferating cell nuclear antigen (PCNA), a protein that acts as a processivity factor for DNA synthesis in eukaryotic cells (Oku et al., 1998). *In vitro* studies showed that the C-terminal domain of p21 is sufficient to displace DNA replication enzymes from PCNA, thereby blocking DNA synthesis (Chen et al., 1996; Warbrick et al., 1995). The main role of p21 in the G1 checkpoint lies in its ability to inhibit the activity of cyclin E- and cyclin A-CDK2 complexes required for the G1-S transition (Brugarolas et al., 1999). Consequently, pRb remains hypophosphorylated thereby sequestering the transcription factor E2F, whose activity is required for S-phase entry (Ewen et al., 1993).

The G2/M checkpoint generated through the Chk1/Chk2 - Cdc25C - CDK1 pathway is executed by Cdc25C through dephosphorylation of CDK1-Cyclin B1 complex (Reagan-Shaw et al., 2005; Roshak et al., 2000). Since activating dephosphorylation of only a small amount of CDK1-Cyclin B1 complex is the initiating step for mitotic entry (Hoffmann et al., 1993), and the maintenance of the Cdk1-Cyclin B1 complex in its inactive state blocks entry into mitosis (Poehlmann and Roessner, 2010), CDK1 is the ultimate target of the G2 checkpoint regulation. CDK1 is phosphorylated at two positions by protein kinases Wee1 and Myt1, and is dephosphorylated by Cdc25C phosphatase. G2/M DNA damage checkpoint arrest may be induced by increased phosphorylation of CDK1 by Wee1/Myt1 or by preventing CDK1 dephosphorylation by Cdc25C phosphatase triggered by activated Chk1.

In response to DNA damage, p53 can be phosphorylated at multiple sites by several different protein kinases such as ATM, ATR, DNA-PK, and Chk1/Chk2 (Meek et al., 1994; Milczarek et al., 1997). Phosphorylation impairs the ability of Mdm2 to bind p53, promoting p53 accumulation and activation (Shieh et al., 1997; Tibbetts et al., 1999). Activated p53 upregulates a number of target genes, such as Gadd45 and p21. The accumulation of p21 inhibits CDK2-cyclin E kinase activity, which results in G1 arrest (Bartek et al., 2007). Thus, G1 arrest is a consequence of preventing pRb phosphorylation via inhibition of CDK2. P53 also has functions in the G2/M checkpoint via activating by Chk1/Chk2 which may trigger induction of p21 and by blocking the activity of the mitotic CDK1-Cyclin B1 complex (Stark & Taylor, 2006; Stewart et al., 1995; Taylor & Stark, 2001). In general, one key function of Chk1 and Chk2 activated by ATR and ATM, respectively, manifests in the inactivation of different members of the Cdc25 family by phosphorylation, resulting in a stop of cell cycle progression after DNA damage in the G1/S - or G2/M phases of the cell cycle.

In order for cells to survive following DNA damage, it is important that cell cycle arrest is not only initiated but also maintained for the duration of time necessary for DNA repair (Van Vugt et al., 2010). Mechanisms governing checkpoint initiation versus maintenance appear to be molecularly distinct. This was initially demonstrated by the observation that interference with specific checkpoint components can leave checkpoint initiation intact but disrupt checkpoint maintenance, leading to premature cell cycle reentry accompanied by death by mitotic catastrophe (Bekker-Jensen et al., 2005; Castedo et al., 2004; Deckbar et al., 2007; Lal et al., 2006; Lobrich & Jeggo, 2007). Although the process of checkpoint termination and cell cycle reentry has not been studied extensively, the existing data suggest that inactivation of a checkpoint response is an active process that requires dedicated signaling pathways, such as the polo-like kinase 1 (Plk1) pathway (Bartek & Lukas, 2007; van Vugt & Medema, 2004). Interestingly, a number of proteins involved in terminating the maintenance phase of a DNA damage checkpoint also play critical roles in later mitotic events, suggesting the existence of a positive feedback in which the earliest events of mitosis involve the DNA damage checkpoint through unclear mechanism(s). Resumption of cell cycle progression following DNA repair involves switching off the DDR, including disassembly of DDR foci (Bartek & Lukas, 2007). This occurs mainly by reversing the posttranslational modifications associated with focal DDR protein assembly such as PARG-induced erasing PARylation (Gagne et al., 2006) or γ H2AX dephosphorylation which plays an important role in terminating checkpoint signaling (Bazzi et al. 2010; Cha et al. 2010; Chowdhury et al., 2008; Macurek et al. 2010; Nakada et al. 2008). Deubiquitylating enzymes have also been implicated in terminating DDR processes (Nicassio et al., 2007; Shao et al. 2009). Deubiquitylation of histone H2A was shown to relieve the inhibition of RNA

polymerase II transcription at DSBs (Shanbhag et al., 2010). Automodification is coupled to its dissociation from DNA damage sites, such as DNA-PKcs autophosphorylation and its dissociation from Ku (Chan & Lees-Miller 1996; Hammel et al. 2010; Merkle et al., 2002) and auto-PARYlation of PARP-1 and its dissociation from DNA damage sites (Mortusewicz et al. 2007). Checkpoint silencing has been best studied in the budding yeast *S. cerevisiae* (Leroy et al., 2003; Toczyski et al., 1997; Vaze et al., 2002). The Plk Cdc5 is required for silencing checkpoint signaling, and this requirement appears to be widely conserved, since *S. cerevisiae*, and human cells all depend on Plks for silencing of the S- or G2 checkpoints, respectively (Syljuasen et al., 2006; Toczyski et al., 1997; van Vugt et al., 2004; Yoo et al., 2004). The activity of Plks has been shown to be required for inactivation of the ATR-Chk1 pathway and the Wee1 axis of checkpoint signaling (Mailand et al., 2006; Mamely et al., 2006; van Vugt et al., 2004; Yoo et al., 2004). DSBs primarily trigger a checkpoint arrest through the ATM-Chk2 signaling pathway. The CDK- and Plk1-dependent phosphorylation of 53BP1 and Chk2 are critical checkpoint-inactivating events in the sensor and effector arms of the G2/M checkpoint pathway, important for checkpoint termination and cell cycle reentry (Van Vugt et al., 2010). This inactivation can take place on chromatin, as reported in human cells (Chowdhury et al., 2008; Nakada et al., 2008). The reversal of H2AX phosphorylation also involves Tip60-dependent histone acetylation and subsequent histone eviction from damaged chromatin in *Drosophila* and human cells (Jha et al., 2008; Kusch et al. 2004). This is particularly relevant if one considers that DNA damage checkpoints are to respond to very small numbers of DSBs, with some experimental data indicating that 10 -20 DSBs are enough to elicit G2 arrest in human cells (Deckbar et al., 2007), while very few or even a single unrepaired DSB can be sufficient to trigger p53-dependent G1 arrest in human cells (Huang et al., 1996) or cell death in yeast (Bennett et al., 1993).

2.4 DNA damage-induced apoptosis

Programmed cell death, or apoptosis, is a natural process of removing unnecessary or damaged cells, and is required for the proper execution of the organism's life cycle (Chowdhury et al., 2006; Zimmermann et al., 2001). Apoptosis was shown to be involved in numerous processes including embryonic development, response to cellular damage, aging and as a mechanism of tumor suppression (Blank & Shiloh, 2007; Cohen et al., 2004; Lee et al., 2007; Mazumder et al., 2007; Rich et al., 2000; Subramanian et al., 2005). Two pathways were shown to induce apoptosis: an extrinsic and an intrinsic pathways. The difference between these two pathways is the mechanism by which the death signal is transduced (Chowdhury et al., 2006). Whereas the extrinsic pathway is activated by binding of ligands to a death receptor, the intrinsic pathway is activated by cellular stress, for example DNA damage. The intrinsic pathway involves the release of cytochrome *c* from the intermembrane space of the mitochondria. Together with apoptotic protease activating factor 1 (APAF1), cytochrome *c* activates caspase 9, leading to activation of downstream caspases and the induction of the death response (Bitomsky & Hofmann, 2009). Key players in the regulation of the intrinsic pathway include the Bcl2 protein family, which can influence the permeability of the outer mitochondrial membrane (Reed, 2006). Members of the Bcl2 protein family are divided into proapoptotic proteins such as Bax, Bak and Bok, and antiapoptotic ones including Bcl2, Bcl-X, Bcl-w and Mcl-1. Proteins of a third subfamily, known as the BH3-only proteins, are thought to be initiators of apoptosis, and probably function by regulating Bcl2-like proteins from the other two subfamilies. In healthy cells,

Bax exists as a monomer, either in the cytosol or weakly bound to the outer mitochondrial membrane. Upon stimulation of apoptosis, Bax translocates to the mitochondria, where it becomes anchored into the mitochondrial membrane. Following its translocation, Bax oligomerizes into large complexes, which are essential for the permeabilization of the mitochondrial membrane (Antignani & Youle, 2006; Bitomsky & Hofmann, 2009; Reed, 2006). Given its central role in mediating apoptosis, several mechanisms have been proposed for Bax regulation and retention in the cytosol, both by binding to other proteins and through posttranslational modifications. One of the first proteins that were shown to sequester Bax away from the mitochondria was Ku70 (Cohen et al., 2004; Lee et al., 2007; Mazumder et al., 2007; Subramanian et al., 2005). Thus, in addition to its role in regulating NHEJ DNA-repair, Ku70 functions in regulating Bax-mediated apoptosis. Overexpression of Ku70 lowered levels of cell death after apoptotic stimuli, while reducing Ku70 levels increased sensitivity to Bax-mediated apoptosis (Amsel et al., 2008). Taken together, these results suggest that Ku70 has anti-apoptotic activity. Such activity is associated with its ability to be acetylated (Cohen et al., 2004). Apoptotic stimuli lead to dissociation of the Ku70-Bax complex, resulting in cell death following Bax translocation to the mitochondria. It was suggested that under normal conditions, Bax undergoes ubiquitylation, which negatively regulates its proapoptotic function by labeling it for proteasomal degradation. The association with Ku70 mediates and promotes Bax deubiquitylation. Upon apoptotic stimulus, Ku70 is acetylated and releases Bax which translocates to the mitochondria where induces apoptosis. These findings suggest a complex role for Ku70 with both pro-apoptotic (maintaining an active pool of Bax) and anti-apoptotic (sequestering Bax away from the mitochondria) elements.

In response to DNA damage, deacetylase SIRT1 binds to and deacetylates specific lysine residue of substrate proteins, the modification of which leads to the repression of their transcriptional activities (Luo et al., 2001; Picard et al., 2004; Vaziri et al., 2001). SIRT1 has been suggested to suppress apoptotic responses (Luo et al., 2001; Vaziri et al., 2001). It has been demonstrated that, when exposed to IR, SIRT1 enhances DNA repair activity by binding to Ku70 and subsequently deacetylating this protein. This could facilitate one possible mechanism of cell survival (Jeong et al., 2007).

Another mechanism of cell fate regulation involves p21 (Abbas & Dutta, 2009; Garner & Raj, 2008; Liu et al., 2003). Under some circumstances (i.e., enforced overexpression), p21 may promote apoptotic signaling that ultimately leads to cell death (Liu et al., 2003). However, DNA-damaged cells can undergo cell cycle arrest followed by apoptosis in the absence of p21 (Waldman et al., 1996, 1997). The mechanism by which p21 negatively regulates DNA damage-induced death machinery relies on its binding to key apoptotic regulatory proteins (Liu et al., 2003). P21 physically interacts, through its first N-terminal 33 aminoacids, with procaspase-3, i.e. the inactive precursor of the apoptotic executioner caspase-3 (Suzuki et al., 1998, 1999). When bound to p21, the inactive pro-caspase cannot be converted into the active protease, and apoptosis is impeded (Suzuki et al., 1999). Caspase 2, which acts upstream of caspase 3, is also kept in a repressed status by p21 (Baptiste-Okoh et al., 2008). The strict interaction between p21 and caspases is supported also by the observation that p21 itself is cleaved by caspases early during DNA damage- induced apoptosis (Jin et al., 2000; Levkau et al., 1998). The anti- or pro-apoptotic role of p21 could depend on the nature of the apoptotic stimulus. For example, apoptosis was enhanced or inhibited by p21, according to whether cells were treated with cisplatin, or methotrexate (Kraljevic Pavelic et al., 2008).

Functions of p21 in response to DNA damage could be also modulated by the extent of genotoxic lesions, through either stabilization or degradation of the protein. Low levels of DNA lesions will allow p21 stabilization and induce cell cycle arrest (thus having anti-apoptotic activity). In contrast, after extensive DNA damage, p21 down-modulation will allow cells to go to apoptosis (Lee et al., 2009; Martinez et al., 2002).

It is well established that p53 is capable of inducing apoptosis by transcription-dependent and transcription-independent mechanisms (Caelles et al., 1994). It has been demonstrated that recombinant p53 is capable of triggering mitochondrial membrane permeabilization in cell-free systems (Ding et al., 1998; Schuler et al., 2000). Later on, p53 has been reported to translocate to the cytoplasm in response to numerous stress signals, including DNA damage, where it drives mitochondrial outer membrane permeabilization and caspase activation (Marchenko et al., 2000; Mihara et al., 2003). Modifications of p53 may affect its transcriptional activity. For example, acetylation at p53 carboxyl-terminal lysine residues enhances its transcriptional activity associated with cell cycle arrest and apoptosis (Yamaguchi et al., 2009). The interaction between p53 and Ku70 is independent of p53 acetylation. However, p53 acetylation at its carboxyl terminus is required for p53 to prevent and/or displace Bax from its inhibitory interaction with Ku70, thus allowing this key proapoptotic protein to target mitochondria and initiate apoptosis (Yamaguchi et al., 2009). P53 has powerful apoptotic effects, and consequently is a subject to tight regulatory control. Normally, p53 protein is maintained at a low level through the Mdm2-mediated ubiquitination and degradation pathway. However, when cells are exposed to stress including genotoxic one, p53 protein is rapidly accumulated and activated for downstream biological functions. The regulatory events that affect the amount, stability and activity of p53 are in part associated with a variety of post-translational modifications, including phosphorylation, ubiquitination and acetylation. In fact, p53 is the first functional non-histone substrate identified for the histone acetyltransferases (HATs) (Yi & Luo, 2010).

Another key molecule critically involved in DNA damage-induced cell death signaling is the p53-related tumour suppressor and transcription factor p73 (Melino et al., 2003). In unstressed cells, p73 forms a complex with the E3 ubiquitin ligase Itch, which marks it for degradation by the ubiquitin-proteasome system. Upon DNA damage, the levels of Itch become reduced and allow the accumulation of p73 (Rossi et al., 2005). Many of p73 proapoptotic target genes such as Puma, caspase-6 or CD95, overlap with those of p53 (Dobbelstein et al., 2005). Post-translational modifications of p73 by acetylation through p300 and by phosphorylation by the DNA damage-activated, nonreceptor tyrosine kinase c-Abl were found to be crucial for transactivation of its pro-apoptotic target genes (Costanzo et al., 2002).

The E2F1 transcription factor, which was originally identified as a cell-cycle initiator, mediates apoptosis in response to DNA damage (Iaquinta & Lees, 2007; Polager & Ginsberg, 2008; Yamasaki et al., 1996). Under certain conditions, deregulated E2F1 triggers apoptosis via both p53-dependent and p53-independent mechanisms. To induce p53-dependent apoptosis, E2F1 activates the expression of p14/p19ARF tumor suppressor gene to stabilize p53 (Phillips & Vousden, 2001). Alternatively, E2F1 directly activates various proapoptotic genes or inactivates several antiapoptotic genes (Iaquinta & Lees, 2007; Polager & Ginsberg, 2008). In support of the importance of E2F1 for apoptotic signaling, germline deletion of E2F1 in mice leads to the formation of various tumors, presumably resulting from the lack of E2F1-induced apoptosis (Field et al., 1996; Yamasaki et al., 1996).

2.5 Cell fate decision

Depending on the amount of damage, the DDR activates one of two alternatives: a prosurvival network that includes the damage-induced cell cycle checkpoints and DNA repair or programmed cell death (Barzilai et al., 2008). The mechanistic aspects of this critical choice remain unclear. Activation of p53 in response to DNA damage results in either cell cycle arrest or apoptosis. Although genes that regulate these cellular processes are essentially p53 targets, activation of p53 always results in specific and selective transcription of p53-regulated genes (Riley et al, 2008). Thus, it is likely that unique sets of p53-regulated genes operate in tandem to bring about a desired outcome in response to specific stimuli. How p53 executes these two distinct functions remains largely unclear. Recent reports suggest that activation of specific promoters by p53 is achieved through its interaction with heterologous transcription factors such as Hzf and ASPP family proteins (Das et al, 2007; Tanaka et al, 2007). P53 modifications following stress such as phosphorylation and acetylation stabilize p53, enhancing its sequence-specific DNA binding and transcriptional activity (Sakaguchi et al, 1998). The phosphorylation at amino-terminus is required for p53 stability, while acetylation at carboxyl-terminus is indispensable for p53 transcriptional activation (Tang et al., 2008). The p53 target gene SMAR1 modulates the cellular response to genotoxic stress by a dual mechanism. First, SMAR1 interacts with p53 and facilitates p53 deacetylation through recruitment of deacetylase HDAC1. Then SMAR1 represses the transcription of Bax and Puma by binding to an identical 25 bp MAR element in their promoters (Sinha et al., 2010). A mild DNA damage induces SMAR1-generated anti-apoptotic response by promoting p53 deacetylation and specifically repressing Bax and Puma expression. Reducing the expression of SMAR1 by shRNA leads to significant increase in p53-dependent apoptosis (Sinha et al., 2010). Severe DNA damage results in sequestration of SMAR1, p53 acetylation and transactivation of Bax and Puma leading to apoptosis. Thus, sequestration of SMAR1 into the PML-NBs acts as a molecular switch to p53-dependent cell arrest and apoptosis in response to DNA damage (Sinha et al., 2010). The mechanisms by which moderate damage resulting from mild stress leads to repair, while severe damage results in the 'decision' to kill a cell, remains unclear. Every single cell is therefore continuously confronted with the choice: repair and live or die. Irreparable damage triggers p53's killer functions to eliminate genetically-altered cells. The killer functions of p53 are tightly regulated and balanced against protector functions that promote damage repair and support survival in response to mild damage (Schlereth et al., 2010). In molecular terms, these p53-based cell fate decisions involve protein interactions with factors, which modulate the activation of distinct sets of p53 target genes. The induction of a transient cell cycle arrest that allows for damage repair depends critically on the genes *p21*, *14-3-3 σ* and *GADD45A*, with *p21* being crucial for cell cycle arrest in the G1 phase, while *14-3-3 σ* and *GADD45A* - for arrest in G2 (Levine & Oren, 2009). In the case of prolonged damage, p53-mediated transactivation of the sestrins (*SESN1* and *SESN2*) causes inhibition of the mammalian target of rapamycin (mTOR) signaling and helps to maintain the arrest reversible, while activation of mTOR under these conditions triggers a shift to irreversible cell cycle exit (senescence) (Demidenko et al., 2010; Korotchkina et al., 2010; Steelman & McCubrey, 2009). Another way for p53 to permanently stop cell proliferation without compromising cell viability is induction of differentiation (Schlereth, 2010). Only when cells have irreparable DNA damage that is incompatible with further survival, p53 shifts

to the most extreme and irrevocable antiproliferative response - apoptosis (Aylon & Oren, 2007). p53-induced apoptosis does not only require activation of proapoptotic target genes such as *Bax* and *Noxa* but may also involve transcription-independent functions of p53 in the cytoplasm (Green & Kroemer, 2009; Morselli et al., 2009; Vaseva et al., 2009). Discriminatory effects on target can also be exerted by interacting proteins that modulate p53's DNA binding properties via covalent post-translational modifications including phosphorylation, acetylation, methylation, ubiquitylation, and sumoylation. Among the phosphorylation sites, serine 46 (S46) has clear discriminatory function for p53 as a transcriptional activator (Okoshi et al., 2008; Rinaldo et al., 2007). P53 is phosphorylated at this residue by homeodomain interacting protein kinase 2 (HIPK2), dual-specificity tyrosine-phosphorylation-regulated kinase 2 (DYRK2), AMPK, protein kinase C delta or p38 mitogen activated protein kinase in response to severe cellular damage (Okoshi et al., 2008; Rinaldo et al., 2007). While numerous studies have implicated acetylation of lysine residues in the C-terminus of p53 as being important for p53's transcriptional activity in general, acetylation of lysine 120 (K120) in the DNA binding domain by the MYST family histone acetyl transferases, hMOF and Tip60 specifically results in increased binding to proapoptotic targets like *Bax* and *Puma*, while the nonapoptotic targets *p21* and *Mdm2* remain unaffected (Sykes et al., 2006; Tang et al., 2006). On the other hand, acetylation of lysine 320 (K320) by the transcriptional coactivator p300/CBP-associated factor (PCAF) predisposes p53 to activate *p21* and decreases its ability to induce proapoptotic genes. Cells ectopically expressing a mutant p53 where K320 is mutated to glutamine (K320Q) to mimic acetylation, display reduced apoptosis after some forms of DNA damage (Knights et al., 2006). In contrast, K317R knockin mice, where K317 acetylation is missing, consistently display increased apoptosis and higher expression of relevant target genes in several cell types (Chao et al., 2006). However, K320 is not only a target for acetylation but it is also ubiquitylated by the zincfinger protein E4F1 (Le Cam et al., 2006). This modification facilitates p53-dependent activation of *p21* and *Cyclin G1* expression without affecting the expression of the proapoptotic gene *Noxa*, overall resulting in reduced p53-mediated cell death in response to UV. P53-mediated cell cycle arrest is also favored following methylation of at least two arginine residues (R333 and R335) by the arginine methyltransferase PRMT5. Consistently, depletion of PRMT5 by siRNA leads to increased apoptosis following p53 activation (Durant et al., 2009; Jansson et al., 2008).

Another factor which can impact cell fate decision is Chk2. Following DNA damage, Chk2 functions by suppressing apoptosis. In cells that express cell cycle inhibitors such as p21 and 14-3-3 δ , cell cycle arrest appears to prevent or slow the onset of cell death. Without these proteins, Chk2-regulated apoptosis is much more apparent. Thus, it seems that the balance between cell cycle inhibitors and Chk2 dictates the outcome following DNA damage (Antoni et al., 2007). The finding that loss of both p21 and 14-3-3 δ but not each alone is required to unmask the effect of Chk2 can be understood in the context of how each functions to effect cell cycle arrest. 14-3-3 δ is a cytoplasmic protein which in response to DNA damage accumulates and acts by sequestering CDK1 and CDK2 in the cytoplasm and preventing cytokinesis (Chan et al., 1999; Laronga et al., 2000; Wilker et al., 2007). P21 is a nuclear cyclin-dependent kinase inhibitor that directly binds and inactivates cyclin-CDK complexes (el-Deiry et al., 1993; Harper et al., 1993; Xiong et al., 1993). Cooperative effects between these two factors have been shown to dictate the biological response to apoptotic stimuli (Jazayeri et al., 2006; Meng et al., 2009). This implies that the ultimate outcome of

Chk2 activation may depend on the particular cellular context and on molecular determinants of Chk2 function, 14-3-3 δ and p21.

3. DNA damage response in postmitotic neurons

Neurons are extremely active cells (Barzilai, 2010; Fishel et al., 2007) and generally exhibit high mitochondrial respiration and production of reactive oxygen species (ROS) that can damage mitochondrial and nuclear DNA (Weissman et al., 2007). For this reason, neurons are particularly susceptible to genotoxic effects generated by ROS (Barzilai et al., 2008). ROS induce the formation of various DNA lesions including oxidative DNA base modifications, SSBs and DSBs (Martin, 2008). DNA damage plays an important role in brain damage (Nagayama et al., 2000). This damage is a common feature of neurodegenerative diseases (Kraemer et al., 2007; Trushina, & McMurray, 2007). The importance of DNA damage in pathogenesis of neurodegenerative diseases is illustrated by the observation that defective DNA repair in various human syndromes such as ataxia telangiectasia is accompanied by neurological abnormalities (Rolig, & McKinnon, 2000). There is a growing interest in the role of DNA damage in neurological dysfunctions associated with cancer treatments (Wefel et al., 2004). Significant evidence points to the critical role of cumulative DNA damage in the aging process of neurons in the central nervous system (CNS) (Coppede & Migliore, 2010; Fishel et al., 2007; Weissman et al., 2007).

3.1 Cell cycle and neuronal apoptosis

Although accumulating evidence suggests the importance of proper DDR for the nervous system, most of the work to elucidate DDR components has been carried out in proliferating cells. The signal transduction mechanisms in neurons that link DNA damage to apoptosis are not well characterized, and the sensors of DNA damage in neurons are largely unknown (Martin et al., 2009). However, some observations suggest that DDR in postmitotic neurons may have survival checkpoint that serves to eliminate neurons with excessive DNA damage. A loss of function of DDR proteins such as ATM leads to genomic instability and human hereditary diseases, characterized by neurodegeneration (Rass et al., 2007). ATM has a pro-apoptotic function in the developing mouse CNS (Herzog et al., 1998; Lee et al., 2001) and operates similarly to how it operates in proliferating cells (Biton et al., 2006, 2007; Gorodetsky et al., 2007). In addition, neurons in ATM^{-/-} mice are resistant to DNA damage-induced apoptosis (Herzog et al., 1998; Kruman et al., 2004; Lee & McKinnon, 2000; McKinnon, 2001). However, ascribing to ATM and cell cycle checkpoints in neurons the same functions they have in proliferating cells poses certain conceptual difficulties, given the postmitotic nature of these cells.

Another indication of possible cell cycle checkpoint functioning in neurons is extensively documented cell cycle reentry of these postmitotic cells following genotoxic stress. The neurons undergo full or partial DNA replication, showing that they reenter the S phase (Kruman et al., 2004; Yang et al., 2001). This attempt to enter the cell cycle is abortive and does not result in actual division (Athanasίου et al., 1998; Becker & Bonni, 2004; Feddersen et al., 1992) but culminates in apoptotic cell death (Becker & Bonni, 2004; Kruman, 2004; Yang & Herrup, 2001). Cell cycle activation is a common feature of neuronal apoptosis during development and in neurodegenerative disorders (Becker & Bonni, 2004; Herrup et al., 2004; Kruman, 2004; Kruman et al., 2004; Park et al., 1997, 1998). On the other hand, forced cell cycle entry mediated by targeted disruption of the pRb or ectopic E2F1

expression also results in apoptosis of postmitotic neurons (Becker & Bonni, 2004; Feddersen et al., 1995; Johnson et al., 1993; Smith et al., 2000), while preventing cell cycle entry is protective against neurotoxic insults, such as ischemia and kainate-induced excitotoxicity (Kim & Tsai, 2009; Kruman et al., 2004; Zhang et al., 2006). Exposure of mice or mesencephalic neuronal cultures to the dopaminergic cell neurotoxins 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) results in cell cycle activation in post-mitotic neurons prior to their subsequent death, while E2F1 deficiency leads to a significant resistance to MPTP-induced dopaminergic cell death (Hoglinger et al., 2007).

Our recent findings demonstrate the particular role of S phase entry and DNA replication in DNA damage-induced neuronal apoptosis (Kruman et al., 2004; Tomashevski et al., 2010). Expression of S-phase markers was reported in post-mitotic neurons following hypoxia-ischemia (Kuan et al., 2004), in neurons in Alzheimer's disease (Yang et al., 2001) and in neurons ectopically expressing E2F1 (Smith et al., 2000). The special role of S phase might be linked to DNA replication errors which are usually accompanied by DNA damage and activation of cell cycle checkpoints (Elledge, 1996; Kumagai & Dunphy, 2006). Activation of Chk2 following DSB formation was observed in primary neurons exposed to DSB inducer producing repairable DSBs (Sordet et al., 2009). This is consistent with previous finding demonstrating that Chk2, in contrast to Chk1, is expressed and activatable in quiescent cells. This may suggest the survival mechanism by which S phase entry is prevented in postmitotic cells. Since differentiated neurons which enter S phase prior apoptosis predominantly express a highly error prone DNA polymerase β (Copani et al., 2002), the DNA replication might produce additional DNA damage. This may amplify DNA damage and generate apoptotic signaling. The functional link between neuronal cell cycle reentry, DDR, cell cycle checkpoints and apoptosis is supported by data demonstrating that both cell cycle activation and apoptosis in postmitotic neurons exposed to DSB-inducing agents are ATM-dependent (Alvira et al., 2007; Kruman et al., 2004; Otsuka et al., 2004). There is no evidence of entry of neurons under conditions of DNA damage-induced apoptosis into mitosis, although they may progress through DNA synthesis and G2 (Athanasίου et al., 1998; Becker & Bonni, 2004; Feddersen et al., 1992; Yang et al., 2001). This may be explained by activation of G2/M checkpoint induced by replication stress which prevents entry into mitosis. Indeed, expression of G2/M checkpoint markers has been reported in vascular dementia (McShea et al., 1999), and several other neurodegenerative diseases (Husseman et al., 2000).

3.2 Cell cycle and DNA repair in neurons

Terminally differentiated neurons are highly susceptible to oxidative DNA damage (Fishel et al., 2007), and DNA repair is very important for these cells (Biton et al., 2008; Fishel et al., 2007; Lavin & Kozlov, 2007). All eukaryotic DNA repair systems operating in proliferating cells also operate in neurons (Fishel et al., 2007; Lee, & McKinnon, 2007; Sharma, 2007; Weissman et al., 2007; Wilson, & McNeill, 2007). It is believed that most of the lesions inflicted in neuronal genomic and mitochondrial DNA are produced by ROS. These lesions are repaired mainly via the BER pathway, although other types of DNA repair are involved (Fishel et al., 2007; Weissman et al., 2007; Wilson & McNeill, 2007). Although DNA repair activity exists in neurons, it was found that this repair is not as effective as in dividing cells, suggesting that lesions are likely to accumulate (Gobbel et al., 1998; McMurray, 2005; Nospikel, & Hanawalt, 2000, 2002). Indeed, following cellular differentiation, the levels of many repair factors are reduced (Bill et al., 1992; Nospikel, & Hanawalt, 2000, 2002).

However, in contrast to global genomic repair (GGR), the repair of transcribed genes is more vigorous (Nospikel, & Hanawalt, 2000). Thus, DNA repair in the nonessential bulk of the genome of postmitotic neurons is dispensable, and they repair only DNA needed for neuronal functioning (Nospikel, 2007; Nospikel, & Hanawalt, 2002). Since neurons are very active and the repair process carries a high energy cost, it is reasonable that these cells preferentially repair transcribed genes. This is important to avoid harming the fidelity of information transcribed to proteins (Fishel et al., 2007; Lu et al., 2004).

It is commonly believed that neurons remain in G0 phase of the cell cycle indefinitely. Cell-cycle reentry, however, is coupled with DNA damage-induced apoptosis of postmitotic neurons (Becker & Bonni, 2004; Herrup et al., 2004; Kruman, 2004; Kruman et al., 2004; Park et al., 1997, 1998). Moreover, recent evidence demonstrates the expression of cell-cycle proteins in differentiated neurons at physiological conditions (Schmetsdorf et al., 2007, 2009). The functional roles of such expression remain unclear. Since DNA repair is generally attenuated by differentiation in most cell types (McMurray, 2005; Narciso et al., 2007), the cell-cycle-associated events in postmitotic cells may reflect the need to reenter the cell cycle to activate DNA repair. Recently, we have demonstrated that the NHEJ activation in postmitotic neurons is associated with G0-G1 transition, driven by cyclin-C-associated pRb-kinase activity, while preventing cell cycle entry attenuated DNA repair (Tomashevski et al., 2010). This suggests the importance of cell cycle entry for DNA repair in postmitotic cells. Previously, quiescent cells, including differentiated cells, were shown to be able to reenter the cell cycle simply by removing appropriate cell cycle inhibitors such as p21. Interference with p21 was sufficient to reactivate the cell cycle and DNA synthesis in terminally differentiated skeletal muscle cells, quiescent fibroblasts and primary cortical neurons (Pajalunga et al., 2007; Tomashevski et al., 2010). Reactivation of cell cycle and DNA replication has also been documented in quiescent cells overexpressing E2F1 and Cdc25A (Pajalunga et al., 2007; Rogoff & Kowalik, 2004; Smith et al., 2000; Zhang et al., 2006). Such reactivation of cell cycle and DNA replication were sufficient to promote neuronal death even in the absence of DNA damage (O'Hare et al., 2000). However, preventing S phase entry, attenuated apoptotic signaling (Tomashevski et al., 2010), suggesting a decisive role of G1-S transition for activation of the apoptotic machinery. Thus, cell cycle activation occurs in response to DNA damage and is involved in both DNA repair and apoptosis in postmitotic neurons. These findings may imply that cell cycle checkpoints may orchestrate both DNA repair and apoptosis of postmitotic neurons, as it occurs in proliferating cells (Bartek & Lukas, 2001; Shiloh, 2003; Zhou & Elledge, 2000).

4. Conclusion and future perspectives

The way that cells react to DNA damage constantly produced by exogenous and endogenous factors is to trigger a complex and coordinated set of events termed the DDR (Reinhardt & Yaffe, 2009). The function of such response is to sense genome damage and activate several downstream pathways, including cell cycle checkpoints, DNA repair and apoptotic programs (Jackson, 2009; Zhou & Elledge, 2000). The earliest events of the DDR are associated with alterations in chromatin structure and the formation of DDR foci facilitating recruitment of proteins involved in DDR propagation (Berkovich et al., 2007; Downs et al., 2007; Smerdon et al., 1978). The biochemical details of these processes are poorly understood. However, studies in yeast and mammalian systems have demonstrated that colocalization of DDR proteins rather than DNA damage per se is

critical for DNA damage signaling (Bonilla et al., 2008; Soutoglou & Misteli, 2008). Another important component of DDR network is the cell cycle checkpoint pathway which plays roles in the activation of DNA repair, modulation of transcriptional programmes and the optional triggering apoptosis (Bartek & Lukas, 2001; Shiloh, 2003; Zhou & Elledge, 2000). In response to DNA damage, the checkpoints delay or stop the cell cycle at critical points before or during DNA replication (G1/S and intra-S checkpoints) and before cell division (G2/M checkpoint). This prevents replication and segregation of damaged DNA (Houtgraaf et al., 2006; Poehlmann & Roessner, 2010). DDR is involved in two alternatives: activation of a prosurvival network associated with DNA repair or initiation of programmed cell death removing cells with irreparable DNA (Barzilai et al., 2008; Kruman, 2004). The checkpoints play important roles in both processes (Bartek & Lukas, 2001; Shiloh, 2003; Zhou & Elledge, 2000). The importance of DDR is illustrated by various pathologies associated with defects in DDR proteins. Mutations in key DDR regulators such as ATM, ATR, MRE11, NBS1 are associated with severe genome instability disorders (Ciccia & Elledge, 2010; Jackson & Bartek 2009).

Due to a high rate of oxygen metabolism and the low levels of antioxidant enzymes compared to other cells, the DNA of postmitotic neurons is under increased risk of damage from free radicals. (Barzilai, 2010; Kruman, 2004). For this reason, DNA repair is critical for the nervous system. While all eukaryotic DNA repair systems operating in proliferating cells also operate in neurons (Fishel et al., 2007; Lee, & McKinnon, 2007; Sharma, 2007; Weissman et al., 2007; Wilson, & McNeill, 2007), differentiation is associated with a decrease in levels of many repair enzymes (Bill et al., 1992; Nospikel, & Hanawalt, 2000, 2002; Tofilon & Meyn, 1988), and DNA repair in neurons, is not as effective as in dividing cells (Gobbel et al., 1998; McMurray, 2005; Nospikel, & Hanawalt, 2000, 2002). It raises the question whether DDR in postmitotic neurons is similar to the DDR of mitotic cells. Some evidence such as a contribution of ATM to apoptosis of postmitotic neurons (Herzog et al., 1998; Kruman et al., 2004; Lee & McKinnon, 2000; McKinnon, 2001) points to such similarity. Although postmitotic neurons are quiescent cells, they are capable to reenter the cell cycle before apoptosis induced by genotoxic stress, as was extensively documented (Barzilai, 2010; Kim & Tsai, 2009; Kruman et al., 2004; Yang et al., 2001). Moreover, we recently demonstrated that DNA repair is also depends on cell cycle activation, driven by cyclin-C-associated pRb-kinase activity (Tomashevski et al., 2010). These findings together with observation that Chk2 is expressed and activated in postmitotic neurons and other postmitotic cells following genotoxic stress (Lukas et al., 2001; Sordet et al., 2009), are indications of cell cycle checkpoint functioning in neurons.

Compelling evidence points to similarities in the DDR of proliferating cells and postmitotic neurons. However, neurons are quiescent cells which requires adaptation of the DDR. The major future challenge is to understand the mechanisms by which cell cycle checkpoint machinery operates in postmitotic neurons and involves in DNA repair, apoptosis and cell fate decisions. Further investigation of the DDR in human genomic instability syndromes, neurodegenerative pathologies, and animal models of these conditions, will help to disclose these mechanisms. Clarification of the mechanisms at work will help guide the search for novel treatment modalities for a variety of neurodegenerative conditions.

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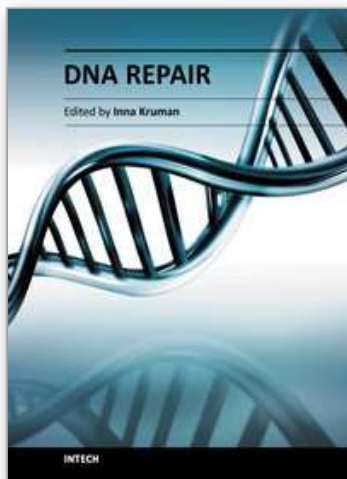
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