We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

14

Cell Cycle and DNA Damage Response in Postmitotic Neurons

Inna I. Kruman
Texas Tech University Health Sciences Center
USA

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 (γH2AX) 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 γH2AX, 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 kineses 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 14-3-3δ 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 14-3-3δ 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 compexes 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 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 γH2AX 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 pro-apoptotic 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 irrepairable 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 14-3-3δ, 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 14-3-3δ 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. 14-3-3δ 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, 14-3-3δ 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 (Athanasiou 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-tertahydropyridine (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 (Athanasiou 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; Nouspikel, & Hanawalt, 2000, 2002). Indeed, following cellular differentiation, the levels of many repair factors are reduced (Bill et al., 1992; Nouspikel, & Hanawalt, 2000, 2002).

However, in contrast to global genomic repair (GGR), the repair of transcribed genes is more vigorous (Nouspikel, & 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 (Nouspikel, 2007; Nouspikel, & 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 irrepairable 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; Nouspikel, & 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; Nouspikel, & 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.

5. Acknowledgments

This work was supported by Texas Tech University Health Sciences Center grant.

6. References

Abbas, T. & Dutta, A. (2009). p21 in cancer: intricate networks and multiple activities. *Nat Rev Cancer*, Vol.9, No.6, (June 2009), pp.400-414, ISSN 1944-0234

Ahel, D.; Horejsí, Z.; Wiechens, N.; Polo, S.E.; Garcia-Wilson, E.; Ahel, I.; Flynn, H.; Skehel, M.; West, S.C.; Jackson S.P.; Owen-Hughes, T. & Boulton, S.J. (2009). Poly(ADP-ribose)-dependent regulation of DNA repair by the chromatin remodeling enzyme ALC1. *Science*, Vol.325, No.5945, (August 2010), pp.1240-1243, ISSN 1966-1379

Al-Hakim, A.; Escribano-Diaz, C.; Landry, M.C.; O'Donnell, L.; Panier, S.; Szilard, R.K. & Durocher, D. (2010). The ubiquitous role of ubiquitin in the DNA damage response. *DNA Repair (Amst),* Vol.9, No.12, (November 2010), pp.1229-1240, ISSN 2105-6014

Alvira, D.; Yeste-Velasco, M.; Folch, J.; Casadesús, G.; Smith, M.A.; Pallàs, M. & Camins, A. (2007). Neuroprotective effects of caffeine against complex I inhibition-induced apoptosis are mediated by inhibition of the Atm/p53/E2F-1 path in cerebellar granule neurons. *J Neurosci Res*, Vol.85, No.14, (November 2007), pp.3079-3088, ISSN 1763-8302

Amsel, A.D.; Rathaus, M.; Kronman, N. & Cohen, H.Y. (2008). Regulation of the proapoptotic factor Bax by Ku70-dependent deubiquitylation. *Proc Natl Acad Sci U S A*, Vol.105, No.13, (March 2008), pp. 5117-5122, ISSN 1836-2350

Antignani, A. & Youle, R.J. (2006). How do Bax and Bak lead to permeabilization of the outer mitochondrial membrane? *Curr Opin Cell Biol*, Vol.18, No.6, (October 2006), pp. 685-689, ISSN 1704-6225

Antoni, L.; Sodha, N.; Collins, I. & Garrett, M.D. (2007). CHK2 kinase: cancer susceptibility and cancer therapy-two sides of the same coin? *Nat Rev Cancer*, Vol.7, No.12, (December 2007), pp.925-936, ISSN 1800-4398

Aressy, B. & Ducommun, B. (2008) Cell cycle control by the CDC25 phosphatases. *Anticancer Agents Med Chem*, Vol.8, No.8, (December 2008), pp.818-824, ISSN 1907-5563

Athanasiou, M.C.; Yunis, W.; Coleman, N.; Ehlenfeldt, R.; Clark, H.B.; Orr, H.T. & Feddersen, R.M. (1998). The transcription factor E2F-1 in SV40 T antigen-induced cerebellar Purkinje cell degeneration. *Mol Cell Neurosci*, Vol.12, No.1-2, (September 1998), pp.16-28, ISSN 977-0337

Averbeck, N.B. & Durante, M. (2011). Protein acetylation within the cellular response to radiation. *J Cell Physiol*, Vol.226, No.4, (April 2011), pp.962-967, ISSN 2094-5393

Aylon, Y. & Oren, M. (2007). Living with p53, dying of p53. *Cell*, Vol.130, No.4, (August 2007), pp. 597-600, ISSN 1771-9538

Banin, S.; Moyal, L.; Shieh, S.; Taya, Y.; Anderson, C.W.; Chessa, L.; Smorodinsky, N.I.; Prives, C.; Reiss, Y.; Shiloh, Y.& Ziv, Y. (1998). Enhanced phosphorylation of p53 by ATM in response to DNA damage. *Science*, Vol.281, No.5383, (September 1998), pp. 1674–1677, ISSN 973-3514

Baptiste-Okoh, N.; Barsotti, A.M. & Prives, C. (2008). Caspase 2 is both required for p53-mediated apoptosis and downregulated by p53 in a p21-dependent manner. *Cell Cycle*, Vol.7, No.9, (February 2008), pp.1133-1138, ISSN 1841-8048

Bartek, J. & Lukas, J. (2001). Mammalian G1- and S-phase checkpoints in response to DNA damage. *Curr Opin Cell Biol*, Vol.13, No.6, (December 2001), pp.738-747, ISSN 1169-8191

Bartek, J.; Lukas, C. & Lukas, J. (2004). Checking on DNA damage in S phase. *Nat Rev Mol Cell Biol*, Vol.5, No.10, (October 2007), pp. 792-804, ISSN1545-9660

Bartek, J. & Lukas, J. (2007). DNA damage checkpoints: from initiation to recovery or adaptation. *Curr Opin Cell Biol*, Vol.19, No.2, (February 2007), pp.238-245. ISSN 1730-3408

Bartek, J.; Lukas, J. & Bartkova, J. (2007). DNA damage response as an anti-cancer barrier: damage threshold and the concept of 'conditional haploinsufficiency'. *Cell Cycle*, Vol.6, No.19, (July 2007), pp. 2344–2347, ISSN 1770-0066

Bartkova, J.; Horejsí, Z.; Koed, K.; Krämer, A.; Tort, F.; Zieger, K.; Guldberg, P.; Sehested, M.; Nesland, J.M.; Lukas, C.; Ørntoft, T.; Lukas, J. & Bartek, J. (2005). DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis. *Nature*, Vol.434, No.7035, (April 2005), pp. 864-870. ISSN 1582-9956

Barzilai, A.; Biton, S. & Shiloh, Y. (2008). The role of the DNA damage response in neuronal development, organization and maintenance. *DNA Repair (Amst),* Vol.7, No.7, (May 2008), pp. 1010-1027. ISSN 1845-8000

Barzilai A. (2010). DNA damage, neuronal and glial cell death and neurodegeneration. *Apoptosis*, Vol.15, No.11, (November 2010), pp.1371-1381. ISSN 2043-7103

Bazzi, M.; Mantiero, D.; Trovesi, C.; Lucchini, G. & Longhese, M.P. (2010). Dephosphorylation of gamma H2A by

Glc7/protein phosphatase 1 promotes recovery from inhibition of DNA replication. *Mol Cell Biol*, Vol.30, No.1, (January 2010), pp.131-145, ISSN 1988-4341

Becker, E.B. & Bonni, A. (2004). Cell cycle regulation of neuronal apoptosis in development and disease. *Prog Neurobiol*, Vol.72, No.1, (January 2004), pp.1-25, ISSN 1501-9174

Bekker-Jensen, S.; Lukas, C.; Melander, F.; Bartek, J. & Lukas, J. (2005). Dynamic assembly and sustained retention of 53BP1 at the sites of DNA damage are controlled by Mdc1/NFBD1. *J Cell Biol*, Vol.170, No.2, (July 2005), pp.201–211, ISSN 1600-9723

Bekker-Jensen, S.; Lukas, C.; Kitagawa, R.; Melander, F.; Kastan, M.B.; Bartek, J. & Lukas, J. (2006). Spatial organization of the mammalian genome surveillance machinery in response to DNA strand breaks. *J Cell Biol*, Vol.173, No.2, (April 2006), pp.195-206, ISSN 1661-8811

Bennett, C.B.; Lewis, A.L.; Baldwin, K.K. & Resnick, M.A. (1993). Lethality induced by a single site-specific double-strand break in a dispensable yeast plasmid. *Proc Natl Acad Sci U S A*, Vol.90, No.12, (June 1993), pp. 5613-5617, ISSN 851- 6308

Berkovich, E.; Monnat, R.J. Jr. & Kastan, M.B. (2007). Roles of ATM and NBS1 in chromatin structure modulation and DNA double-strand break repair. *Nat Cell Biol,* Vol.9, No.6, (May 2007), pp.683–690, ISSN 1748-6112

Bill, C.A.; Grochan, B.M.; Vrdoljak, E.; Mendoza, E.A. & Tofilon, P.J. (1992). Decreased repair of radiation-induced DNA double-strand breaks with cellular differentiation. *Radiat Res*, Vol.132, No.2, (November 1992), pp.254–258, ISSN 143- 8708

Bitomsky, N. & Hofmann, T.G. (2009). Apoptosis and autophagy: Regulation of apoptosis by DNA damage signalling - roles of p53, p73 and HIPK2. *FEBS J*, Vol.276, No.21, (September 2007), pp. 6074-6083, ISSN 1978-8416

Biton, S.; Dar, I.; Mittelman, L;. Pereg, Y.; Barzilai, A. & Shiloh, Y. (2006). Nuclear ataxia-telangiectasia mutated (ATM) mediates the cellular response to DNA double strand breaks in human neuron-like cells, *J Biol Chem*, Vol.281, No.25, (April 2006), pp.17482-17491, ISSN 1662-7474

Biton, S.; Gropp, M.; Itsykson, P.; Pereg, Y.; Mittelman, L.; Johe, K.; Reubinoff, B. & Shiloh, Y. (2007). ATM-mediated response to DNA double strand breaks in human neurons

derived from stem cells. *DNA Repair (Amst),* Vol.6, No.1, (December 2006), pp.128-134, ISSN 1717-8256

Biton, S.; Barzilai, A. & Shiloh, Y. (2008). The neurological phenotype of ataxia–telangiectasia: solving a persistent puzzle. *DNA Repair (Amst),* Vol.7, No.7, (May 2008), pp.1028-1038, ISSN 1845-6574

Blank, M. & Shiloh, Y. (2007). Programs for cell death: apoptosis is only one way to go. *Cell Cycle*, Vol.6, No.6, (March 2007), pp. 686-95, ISSN 1736-1099

Bonilla, C.Y.; Melo, J.A. & Toczyski, D.P. (2008). Colocalization of sensors is sufficient to activate the DNA damage checkpoint in the absence of damage. *Mol Cell*, Vol.30, No.3, (May 2008), pp.267–276, ISSN 1847-1973

Brady, C.A. & Attardi, L.D. (2010). p53 at a glance. *J Cell Sci*, Vol.123, Pt.15, (August 2010), pp.2527-2532, ISSN 2094-0128

Branzei, D. & Foiani, M. (2008). Regulation of DNA repair throughout the cell cycle. *Nat Rev Mol Cell Biol*, Vol.9, No.4, (February 2008), pp.297–308, ISSN 1828-5803

Brugarolas, J.; Moberg, K.; Boyd, S.D.; Taya, Y.; Jacks, T. & Lees, J.A. (1999). Inhibition of cyclindependent kinase 2 by p21 is necessary for retinoblastoma protein-mediated G1arrest after gamma-irradiation. *Proc Natl Acad Sci USA,* Vol.96, No.3, (February 1999), pp.1002–1007, ISSN 992-7683

Burma, S.; Chen, B.P.; Murphy, M.; Kurimasa, A. & Chen, D.J. (2001). ATM phosphorylates histone H2AX in response to DNA double-strand breaks. *J Biol Chem*, Vol.276, No.45, (September 2001), pp.42462-42467, ISSN 1157-1274

Busino, L.; Chiesa, M.; Draetta, G.F. & Donzelli, M. (2004) Cdc25A phosphatase:combinatorial phosphorylation, ubiquitylation and proteolysis. *Oncogene*, Vol.23, No.11, (March 2004), pp. 2050-2056, ISSN 1502-1892

Caelles, C.; Helmberg, A. & Karin, M. (1994) p53-dependentapoptosis in the absence of transcriptional activation of p53- target genes. *Nature*, Vol.370, No.6486, (July 1994), pp. 220-223, ISSN 802-8670

Calsou, P.; Delteil, C.; Frit, P.; Drouet, J. & Salles, B. (2003). Coordinated assembly of Ku and p460 subunits of the DNA- dependent protein kinase on DNA ends is necessary for XRCC4-ligase IV recruitment. *J Mol Biol*, Vol.326, No.1, (February 2003), pp.93-103, ISSN 1254-7193

Castedo, M.; Perfettini, J.L.; Roumier, T.; Andreau, K.; Medema, R. & Kroemer, G. (2004). Cell death by mitotic catastrophe: a molecular definition. *Oncogene*, Vol.23, No.16, (April 2004), pp. 2825-2837, ISSN 1507-7146

Celeste, A.; Petersen, S.; Romanienko, P.J.; Fernandez-Capetillo, O.; Chen, H.T.; Sedelnikova, O.A.; Reina-San-Martin, B.; Coppola, V.; Meffre, E.; Difilippantonio, M.J.; Redon, C.; Pilch, D.R.; Olaru, A.; Eckhaus, M.; Camerini-Otero, R.D.; Tessarollo, L.; Livak, F.; Manova, K.; Bonner ,W.M.; Nussenzweig, M.C. & Nussenzweig, A. (2002). Genomic instability in mice lacking histone H2AX. *Science,* Vol.296, No.5569, (May 2002) pp.922–927, ISSN 1193-4988

Celeste, A.; Fernandez-Capetillo, O.; Kruhlak, M.J.; Pilch, D.R.; Staudt, D.W.; Lee, A.; Bonner, R.F.; Bonner,W.M. & Nussenzweig, A. (2003). Histone H2AX phosphorylation is dispensable for the initial recognition of DNA breaks. *Nat Cell Biol,* Vol.5, No7, (July 2003), pp.675–679, ISSN 1279-2649

Cha, H.; Lowe, J.M.; Li, H.; Lee, .;, Belova, G.;, Bulavin, D.V. & Fornace, A.J. Jr. (2010). Wip1 directly dephosphorylates gamma-H2AX and attenuates the DNA damage response. *Cancer Res*, Vol.70, No.10, (May 2010), pp.4112-2412, ISSN 204-60517

Chan, D.W. & Lees-Miller, S.P. (1996). The DNA-dependent protein kinase is inactivated by autophosphorylation of the catalytic subunit. *J Biol Chem*, Vol.271, No.15, (April 1996), pp.8936-8941, ISSN 86-21537

Chan, T.A.; Hermeking, H.; Lengauer, C.; Kinzler, K.W. & Vogelstein, B. (1999). 14-3-3Sigma is required to prevent mitotic catastrophe after DNA damage. *Nature*, Vol.401, No. 6753, (October 1999), pp. 616-620, ISSN 1052-4633

Chan, T.A.; Hwang, P.M.; Hermeking, H.; Kinzler, K.W. & Vogelstein, B. (2000). Cooperative effects of genes controlling the G(2)/M checkpoint. *Genes Dev*, Vol.14, No.13, (July 2000), pp.1584-1588, ISSN 1088-7152

Chao, C.; Wu, Z.; Mazur, S.J.; Borges, H.; Rossi, M.; Lin, T.; Wang, J.Y.; Anderson, C.W.; Appella, E. & Xu, Y. (2006). Acetylation of mouse p53 at lysine 317 negatively regulates p53 apoptotic activities after DNA damage. *Mol Cell Biol*, Vol.26, No.18, (September 2006), pp. 6859-6869, ISSN 1694-3427

Chapman, J.R. & Jackson, S.P. (2008). Phospho-dependent interactions between NBS1 and MDC1 mediate chromatin retention of the MRN complex at sites of DNA damage. *EMBO Rep*, Vol.9, No.8, (June 2008), pp.795-801, ISSN 1858- 3988

Chappell, C.; Hanakahi, L.A.; Karimi-Busheri, F.; Weinfeld, M. & West, S.C. (2002). Involvement of human polynucleotide kinase in double-strand break repair by non-homologous end joining. *EMBO J*, Vol.21, No.11, (June 2002), pp. 2827- 2832, ISSN 1203-2095

Chen, J.; Peters, R.; Saha, P.; Lee, P.; Theodoras, A.; Pagano, M.; Wagner, G. & Dutta, A. (1996). A 39 amino acid fragment of the cell cycle regulator p21 is sufficient to bind PCNA and partially inhibit DNA replication in vivo. *Nucleic Acids Res*, Vol.24, No.9, (May 1996), pp.1727–1733, ISSN 864-9992

Chou, D.M., Adamson, B, Dephoure, N.E., Tan, X., Nottke, A.C., Hurov, K.E., Gygi, S.P., Colaiácovo, M.P., Elledge, S.J. (2010). A chromatin localization screen reveals poly (ADP ribose)-regulated recruitment of the repressive polycomb and NuRD complexes to sites of DNA damage. *Proc Natl Acad Sci U S A*, Vol.107, No.43, (October 2010), pp. 18475- 18480, ISSN 2093-7877

Chowdhury, I.; Tharakan, B. & Bhat, G.K. (2006). Current concepts in apoptosis: The physiological suicide program revisited. *Cell Mol Biol Lett*, Vol.11, No.4, (September 2006), pp. 506-525, ISSN 1697-7376

Chowdhury, D.; Xu, X.; Zhong, X.; Ahmed, F.; Zhong, J.; Liao, J.; Dykxhoorn, D.M.; Weinstock, D.M.; Pfeifer, G.P. & Lieberman, J. (2008). A PP4-phosphatase complex dephosphorylates gamma-H2AX generated during DNA replication. *Mol Cell*, Vol.31, No.1, (July 2008), pp. 33-46, ISSN 1861-4045

Ciccia, A. & Elledge, S.J. (2010). The DNA damage response: making it safe to play with knives. *Mol Cell,* Vol.40, No.2, (October 2010), pp.179-204, ISSN 2096-5415

Citarelli, M.; Teotia, S. & Lamb, R.S. (2010). Evolutionary history of the poly(ADP-ribose) polymerase gene family in eukaryotes. *BMC Evol Biol*, Vol.10, (October 2010), pp.308-334, ISSN 2094-2953

Clerici, M.; Mantiero, D.; Guerini, I.; Lucchini, G. & Longhese, M.P. (2008). The Yku70-Yku80 complex contributes to regulate double-strand break processing and checkpoint

activation during the cell cycle. *EMBO Rep,* Vol.9, No.8, (July 2008), pp.810-818, ISSN 1860-0234

Cohen, H.Y.; Lavu, S.; Bitterman, K.J.; Hekking, B.; Imahiyerobo, T.A.; Miller, C.; Frye, R.; Ploegh, H.; Kessler, B.M. & Sinclair, D.A. (2004). Acetylation of the C terminus of Ku70 by CBP and PCAF controls Bax-mediated apoptosis. *Mol Cell*, Vol.13, No.5, (March 2004), pp. 627-638, ISSN 1502-3334

Copani, A.; Sortino, M.A.; Caricasole, A.; Chiechio, S.; Chisari, M.; Battaglia, G.; Giuffrida-Stella, A.M.; Vancheri, C. & Nicoletti, F. (2002). Erratic expression of DNA polymerases by beta-amyloid causes neuronal death. *FASEB J*, Vol.16, No.14, (October 2002), pp. 2006-2008, ISSN 1239-7084

Coppede, F & Migliore, L. (2010). DNA repair in premature aging disorders and neurodegeneration. *Curr Aging Sci*, Vol.3, No.1, (February 2010), pp.3-19, ISSN 2029-8165

Costanzo, A.; Merlo, P.; Pediconi, N.; Fulco, M.; Sartorelli, V.; Cole, P.A.; Fontemaggi, G.; Fanciulli, M.; Schiltz, L.;

Blandino, G.; Balsano, C. & Levrero, M. (2002). DNA damage-dependent acetylation of p73 dictates the selective activation of apoptotic target genes. *Mol Cell*, Vol.9, No.1, (January 2002), pp.175–186, ISSN 1180-4596

Elledge, S. J. (1996). Cell cycle checkpoints: preventing an identity crisis. *Science,* Vol.274, No.5293, (December 1996), pp. 1664-1672, ISSN 893-9848

D'Amours, D.; Desnoyers, S.; D'Silva, I. & Poirier, G.G. (1999). Poly(ADP-ribosyl)ation reactions in the regulation of nuclear functions. *Biochem J*, Vol.342, Pt. 2, (September 1999), pp.249-268, ISSN 1045-5009

Das, S.; Boswell, S.A.; Aaronson, S.A. & Lee, S.W. (2008). P53 promoter selection: choosing between life and death. *Cell Cycle*, Vol.7, No.2, (October 2007), pp.154-157, ISSN 1821-2532

Deckbar, D.; Birraux, J.; Krempler, A.; Tchouandong, L.; Beucher, A.; Walker, S.; Stiff, T.; Jeggo, P. & Löbrich, M. (2007). Chromosome breakage after G2 checkpoint release. *J Cell Biol*, Vol.176, No.6, (March 2007), pp.749-755, ISSN 1735- 3355

de Jager, M.; van Noort, J.; van Gent, D.C.; Dekker, C.; Kanaar, R. & Wyman, C. (2001). *Mol Cell,* 2001 Nov;Vol.8, No.5, (November 2001), pp.1129-1135, ISSN 1174-1547

de Murcia, G. & Ménissier de Murcia, J. (1994). Poly(ADP-ribose) polymerase: a molecular nick-sensor. *Trends Biochem Sci,* Vol.19, No.4 (April 1994), pp172-176, ISSN 8016-868

Demidenko, Z.N.; Korotchkina, L.G.; Gudkov, A.V. & Blagosklonny, M.V. (2010). Paradoxical suppression of cellular senescence by p53. *Proc Natl Acad Sci USA*, Vol.107, No.21 (May 2010), pp.9660-9664, ISSN 2045-7898

Deng, C.; Zhang, P.; Harper, J.; Elledge, S.J. & Leder, P. (1995). Mice lacking p21CIP1/WAF1 undergo normal development, but are defective in G1 checkpoint control. *Cell*, Vol.82, No.4 (August 1995), pp. 675-684, ISSN 766-4346

Ding, H.F.; McGill, G.; Rowan, S.; Schmaltz, C.; Shimamura, A. & Fisher, D.E. (1998). Oncogene-dependent regulation

of caspase activation by p53 protein in a cell-free system. *J Biol Chem*, Vol.273, No.43 (October 1998), pp.28378-28383, ISSN 977-4464

Dobbelstein, M.; Strano, S.; Roth, J. & Blandino, G. (2005). p73-induced apoptosis: a question of compartments and cooperation. *Biochem Biophys Res Commun*, Vol.331, No.3 (June 2005), pp. 688-693, ISSN 1586-5923

Downs, J.A.; Lowndes, N.F. & Jackson, S.P. (2000). A role for Saccharomyces cerevisiae histone H2A in DNA repair. *Nature*, Vol.408, No.6815, (Decemeber 2000), pp.1001-1004, ISSN 1114-0636

Downs, J.A.; Allard, S.; Jobin-Robitaille, O.; Javaheri, A.; Auger, A.; Bouchard, N.; Kron, S.J.; Jackson, S.P. & Côté, J. (2004). *Mol Cell,* Vol.16, No.6, (December 2004), pp.979-990,ISSN 1561-0740

Downs, J.A.; Allard, S.; Jobin-Robitaille, O.; Javaheri, A.; Auger, A.; Bouchard, N.; Kron, S.J.; Jackson, S.P. & Côté J. (2004). Binding of chromatin-modifying activities to phosphorylated histone H2A at DNA damage sites. *Mol Cell*, 2004 Dec 22;Vol.16, No.6, (December 2004), pp.979-990, ISSN 15610740

Downs, J.A.; Nussenzweig, M.C. & Nussenzweig, A. (2007). Chromatin dynamics and the preservation of genetic information. *Nature,* Vol.447, No.7147, (June 2007), pp.951-958, ISSN 1758-1578

Dupre, A.; Boyer-Chatenet, L. & Gautier, J. (2006). Two-step activation of ATM by DNA and the Mre11-Rad50-Nbs1 complex. *Nature Struct Mol Biol,* Vol. 13, No.5, (May 2006), pp.451–457, ISSN 1662-2404

Durant S.T.; Cho, E.C. & La Thangue, N.B. (2009).p53 methylation—the argument is clear. *Cell Cycle*, Vol.8, No.6, (March 2009), pp. 801-802, ISSN 1922-1494

Dvir, A.; Peterson, S.R.; Knuth, M.W.; Lu, H. & Dynan, W.S. (1992). Ku autoantigen is the regulatory component of a template-associated protein kinase that phosphorylates RNA polymerase II. *Proc Natl Acad Sci U S A*, Vol.89, No.24, (December 1992), pp.11920-11924, ISSN 146-5419

el-Deiry, W.S.; Tokino, T.; Velculescu, V.E.; Levy, D.B.; Parsons, R.; Trent, J.M.; Lin, D.; Mercer, W.E.; Kinzler, K.W. & Vogelstein, B. (1993). WAF1, a potential mediator of p53 tumor suppression. *Cell*, Vol.75, No.4, (September 1993), pp.817-825, ISSN 824-2752

Ewen, M.E.; Sluss, H.K.; Sherr, C.J.; Matsushime, H.; Kato, J. & Livingston, D.M. (1993). Functional interactions of the retinoblastoma protein with mammalian D-type cyclins. *Cell*, Vol.73, No.3, (May 1993), pp. 487–497, ISSN 834-3202

Falck, J.; Lukas, C.; Protopopova, M.; Lukas, J.; Selivanova, G. & Bartek, J. (2001). Functional impact of concomitant versus alternative defects in the Chk2–p53 tumour suppressor pathway. *Oncogene*, Vol.20, No.39, (September 2001), pp.5503- 5510, ISSN 1157-1648.

Falck, J.; Coates, J. & Jackson, S.P. (2005). Conserved modes of recruitment of ATM, ATR and DNA-PKcs to sites of DNA damage. *Nature*, Vol.434, No.7033, (March 2005), pp.605–611, ISSN 1575-8953

Feddersen, R.M.; Ehlenfeldt, R.; Yunis, W.S.; Clark, H.B. & Orr, H.T. (1992). Disrupted cerebellar cortical development and progressive degeneration of Purkinje cells in SV40 T antigen transgenic mice. *Neuron*, Vol.9, No.5, (November 1992),

Feddersen, R.M.; Clark, H.B.; Yunis, W.S. & Orr, H.T. (1995). In vivo viability of postmitotic Purkinje neurons requires pRb family member function. *Mol Cell Neurosci*. Vol.6, No.2, (April 1995), pp.153-167, ISSN 755-1567

Ferguson, A.T.; Evron, E.; Umbricht, C.B.; Pandita, T.; Chan, T.A.; Hermeking, H.; Marks, J.R.; Lambers, A.R.; Futreal, P.A.; Stampfer, M.R. & Sukumar, S. (2000). High frequency of hypermethylation at the 14-3-3sigma locus leads to gene silencing in

breast cancer. *Proc Natl Acad Sci USA*, Vol.97, No.22, (May 2000), pp. 6049-6054, ISSN 1081-1911

Fernandez-Capetillo, O.; Lee, A.; Nussenzweig, M.; & Nussenzweig, A. (2004). H2AX: the histone guardian of the genome. *DNA Repair (Amst)*, Vol.3, No.8-9, (Aug-Sep 2004), pp.959–967, ISSN 1527-9782

Field, S.J.; Tsai, F.; Kuo, F.; Zubiaga, A.M.; Kaelin, Jr. W.G.; Livingston, D.M.; Orkin, S.H. & Greenberg, M.E. (1996). E2F-1 functions in mice to promote apoptosis and suppress proliferation. *Cell*, Vol.85, No.4, (May 1996), pp. 549–561, ISSN 865-3790

Fishel, M.L.; Vasko, M.R. & Kelley, M.R. (2007). DNA repair in neurons: so if they don't divide what's to repair? *Mutat Res,* Vol.614, No.1-2, (August 2006), pp.24–36, ISSN 1687-9837

Gagné, J.P.; Hendzel, M.J.; Droit, A. & Poirier, G.G. (2006). The expanding role of poly(ADP-ribose) metabolism: current challenges and new perspectives. *Curr Opin Cell Biol*, Vol.18, No.2, (April 2006), pp.145-151, ISSN 1651-6457

Garner, E. & Raj, K. (2008). Protective mechanisms of p53–p21–pRb proteins against DNA damage-induced cell death. *Cell Cycle*, Vol.7, No.3, (November 2008), pp.277–282, ISSN 1823-5223

Gell, D. & Jackson SP. (1999). Mapping of protein-protein interactions within the DNA-dependent protein kinase complex. *Nucleic Acids Res*, Vol.27, No.17, (September 1999), pp. 3494-3502, ISSN 1044-6239

Gobbel, G.T.; Bellinzona, M.; Vogt, A.R.; Gupta, N.; Fike, J.R. & Chan, P.H. (1998). Response of postmitotic neurons to X- irradiation: implications for the role of DNA damage in neuronal apoptosis. *J Neurosci*, Vol.18, No.1, (January 1998), pp.147–155, ISSN, 941-2495

Gorgoulis, V.; Vassiliou, L.V.; Karakaidos, P.; Zacharatos, P.; Kotsinas, A.; Liloglou, T.; Venere, M.; Ditullio, R.A. Jr.; Kastrinakis, N.G.; Levy, B.; Kletsas, D.; Yoneta, A.; Herlyn, M.; Kittas, C. & Halazonetis, T.D. (2005). Activation of the DNA damage checkpoint and genomic instability in human precancerous lesions. *Nature*, Vol.434, No.7035, (April 2005), pp. 907-913, ISSN 1582-9965

Gorodetsky, E.; Calkins, S.; Ahn, J. & Brooks, P.J. (2007). ATM, the Mre11/Rad50/Nbs1 complex, and topoisomerase I are concentrated in the nucleus of Purkinje neurons in the juvenile human brain. *DNA Repair (Amst)*, Vol.6, No.11, (August 2007), pp.1698-1707, ISSN 1770-6468

Gottlieb, T.M. & Jackson, S.P. (1993). The DNA-dependent protein kinase: requirement for DNA ends and association with Ku antigen. *Cell*, Vol.72, No.1, (January 1993), pp. 131-142, ISSN 842-2676

Gottschalk, A.J.; Timinszky, G.; Kong, S.E.; Jin, J.; Cai, Y.; Swanson, S.K.; Washburn, M.P.; Florens, L.; Ladurner, A.G.; Conaway, J.W. & Conaway, R.C. (2009). Poly(ADP-ribosyl)ation directs recruitment and activation of an ATP- dependent chromatin remodeler. *Proc Natl Acad Sci U S A*, Vol.106, No.33, (August 2009), pp. 13770-13774, ISSN 1966- 6485

Gottifredi, V.; Shieh, S.Y.; Taya, Y. & Prives, C. (2001). p53 accumulates but is functionally impaired when DNA synthesis is blocked. *Proc Natl Acad Sci USA,* Vol.98, No.3, (January 2001), pp.1036-1041, ISSN 1115-8590

Green, D.R. & Kroemer, G. (2009). Cytoplasmic functions of the tumour suppressor p53. *Nature*, Vol.458, No.7242, (April 2009), pp.1127-1130, ISSN 1940-7794

Groth, A.; Rocha, W.; Verreault, A. & Almouzni, G. (2007). Chromatin challenges during DNA replication and repair. *Cell,* Vol.128, (February 2007), pp. 721-733, ISSN 173-20509

Gu, Y.; Turck, C.W. & Morgan, D.O. (1993). Inhibition of CDK2 activity in vivo by an associated 20K regulatory subunit. *Nature*, Vol.366, No.6456, (December 1993), pp.707–710, ISSN 825-9216

Haince, J.F.; McDonald, D.; Rodrigue, A.; Déry, U.; Masson, J.Y.; Hendzel, M.J. & Poirier, G.G. (2008). PARP1-dependent kinetics of recruitment of MRE11 and NBS1 proteins to multiple DNA damage sites. *J Biol Chem*, Vol.283, No.21, (November 2008), pp.1197-1208, ISSN 1802-5084

Hakem, R. (2008). DNA-damage repair; the good, the bad, and the ugly. *EMBO J*, Vol.27, No.4, (February 2008), pp.589-605, ISSN 1828-5820

Hakmé, A.; Wong, H.K.; Dantzer, F. & Schreiber, V. (2008). The expanding field of poly(ADP-ribosyl)ation reactions. 'Protein Modifications: Beyond the Usual Suspects' Review Series. *EMBO Rep*, Vol.9, No.11, (October 2008), pp.1094-100, ISSN 1892-7583

Hammel, M.; Yu, Y.; Mahaney, B.L.; Cai, B.; Ye, R.; Phipps, B.M.; Rambo, R.P.; Hura, G.L.; Pelikan, M.; So, S.; Abolfath, R.M.; Chen, D.J.; Lees-Miller, S.P. & Tainer, J.A. (2009). Ku and DNA-dependent protein kinase dynamic conformations and assembly regulate DNA binding and the initial non-homologous end joining complex. *J Biol Chem*, Vol.285, No.2, (November 2009), pp.1414-1423, ISSN 1989-3054

Hammet, A.; Magill, C.; Heierhorst, J. & Jackson, S.P. (2007). Rad9 BRCT domain interaction with phosphorylated H2AX regulates the G1 checkpoint in budding yeast. *EMBO Rep*, Vol.8, No.9, (August 2007), pp.851-857, ISSN 1772-1446

Hammond, E.M.; Denko, N.C.; Dorie, M.J.; Abraham, R.T. & Giaccia, A.J. (2002). Hypoxia links ATR and p53 through replication arrest. *Mol Cell Biol*, Vol.22, No.6, (March 2002), pp.1834-1843, ISSN 1186-5061

Harper, J.W.; Adami, G.R.; Wei, N.; Keyomarsi, K. & Elledge, S.J. (1993). The p21 Cdk-interacting protein Cip1 is a potent inhibitor of G1 cyclin-dependent kinases. *Cell*, Vol.75, No.4, (November 1993), pp.805-816, ISSN 824-2751

Henrique, R.; Jeronimo, C.; Hoque, M.O.; Carvalho, A.L.; Oliveira, J.; Teixeira, M.R.; Lopes, C. & Sidransky, D. (2005). Frequent 14-3-3sigma promoter methylation in benign and malignant prostate lesions. *DNA Cell Biol*, Vol.24, No.4, (April 2005), pp.264-269, ISSN 1581-2243

Heo, K.; Kim, H.; Choi, S.H.; Choi, J.; Kim, K.; Gu, J.; Lieber, M.R.; Yang, A.S. & An, W. (2008). FACT-mediated exchange of histone variant H2AX regulated by phosphorylation of H2AX and ADP-ribosylation of Spt16. *Mol Cell*, Vol.30, No.1, (April 2008), pp.86-97, ISSN 1840-6329

Herrup, K.; Neve, R.; Ackerman, S.L. & Copani, A. (2004). Divide and die: cell cycle events as triggers of nerve cell death. *J Neurosci*, Vol.24, No.42, (October 2004), pp.9232-9239, ISSN 1549-6657

Herzog, K.H.; Chong, M.J.; Kapsetaki, M.; Morgan, J.I. & McKinnon, P.J. (1998). Requirement for Atm in ionizing radiation- induced cell death in the developing central nervous system. *Science*, Vol.280, No.55366, (May 1998), pp.1089–1091, ISSN 9582124

Hirao, A.; Kong, Y.Y.; Matsuoka, S.; Wakeham, A.; Ruland, J.; Yoshida, H.; Liu, D.; Elledge, S.J. & Mak, T.W. (2000). DNA damage-induced activation of p53 by the checkpoint kinase Chk2. *Science*, Vol.287, No.5459, (March 2000), pp.1824- 1827, ISSN 1071-0310

Hoffmann, I.; Clarke, P.R.; Marcote, M.J.; Karsenti, E. & Draetta, G. (1993). Phosphorylation and activation of human cdc25-C by cdc2–cyclin B and its involvement in the self-amplification ofMPFatmitosis. *EMBOJ*, Vol.12, No.1, (January 1993), pp.53-63, ISSN 842-8594

Höglinger, G.U.; Breunig, J.J.; Depboylu, C.; Rouaux, C.; Michel, P.P.; Alvarez-Fischer, D.; Boutillier, A.L.; Degregori, J.; Oertel, W.H.; Rakic, P.; Hirsch, E.C. & Hunot, S. (2007). The pRb/E2F cell-cycle pathway mediates cell death in Parkinson's disease. *Proc Natl Acad Sci USA*, Vol.104, No.9, (February 2007), pp.25-27, ISSN 1736-0686

Hopfner, K.P. (2009). DNA double-strand breaks come into focus. *Cell*, Vol.139, No.1, (October 2009), pp.25-27, ISSN 1980- 4750

Houtgraaf, J.H.; Versmissen, J. & van der Giessen, W.J. (2006). A concise review of DNA damage checkpoints and repair in mammalian cells. *Cardiovasc Revasc Med*, Vol.7, No.3, (July-September 2006), pp.165-172, ISSN 1694-5824

Huang, J.Y.; Chen, W.H.; Chang, Y.L.; Wang, H.T.; Chuang, W.T & Lee SC. (2006). Modulation of nucleosome-binding activity of FACT by poly(ADP-ribosyl)ation. *Nucleic Acids Res*, Vol.34, No.8, (May 2006), pp.2398-2407, ISSN 1668- 2447

Huen, M.S. & Chen, J. (2008). The DNA damage response pathways: at the crossroad of protein modifications. *Cell Res,* Vol.18, No.1, (January 2008), pp.8-16, ISSN 1808-7291

Husseman, J.W.; D. Nochlin, D. & Vincent, I. (2000). Mitotic activation: a convergent mechanism for a cohort of neurodegenerative diseases. *Neurobiol Aging,* Vol.21, No.6, (November 2000), pp.815-828, ISSN 1112-4425

Iaquinta, P.J. & Lees, J.A. (2007). Life and death decisions by the E2F transcription factors. *Curr Opin Cell Biol*, Vol.19, No.6, (November 2007), pp. 649–657, ISSN 1803-2011

Ikura, T.; Tashiro, S.; Kakino, A.; Shima, H.; Jacob, N.; Amunugama, R.; Yoder, K.; Izumi, S.; Kuraoka, I.; Tanaka, K.; Kimura, H.; Ikura, M.; Nishikubo, S.; Ito, T.; Muto, A.; Miyagawa, K.; Takeda, S.; Fishel, R.; Igarashi, K. & Kamiya, K. (2007). DNA damage-dependent acetylation and ubiquitination of H2AX enhances chromatin dynamics. *Mol Cell Biol*, Vol.27, No.20, August 2007), pp.7028-7040, ISSN 1770-9392

Jackson, S.P. (2009). The DNA-damage response: new molecular insights and new approaches to cancer therapy. *Biochem Soc Trans,* Vol.37, Pt.3, (June 2009), pp. 483–494, ISSN 1984-7258

Jackson, S.P. & Bartek, J. (2009). The DNA-damage response in human biology and disease. *Nature,* Vol.461, No.7267, (October 2009), pp.1071-1078, ISSN 1984-7258

Jansson, M.; Durant, S.T.; Cho, E.C.; Sheahan, S.; Edelmann, M.; Kessler, B. & La Thangue, N.B. (2008). Arginine methylation regulates the p53 response. *Nat Cell Biol*, Vol.10, No.12, (November 2008), pp. 1431-1439, ISSN 1901-1621

Jazayeri, A.; Falck, J.; Lukas, C.; Bartek, J.; Smith, G.C.; Lukas, J. & Jackson, S.P. (2006). ATM- and cell cycle-dependent regulation of ATR in response to DNA double-strand breaks *Nat Cell Biol*, Vol.8, No.1, (December 2005), pp.37-45, ISSN 1632-7781

Jeong, J.; Juhn, K.; Lee, H.; Kim, S.H.; Min, B.H.; Lee, K.M.; Cho, M.H.; Park, G.H. & Lee, K.H. (2007). SIRT1 promotes DNA repair activity and deacetylation of Ku70. *Exp Mol Med*, Vol.39, No.1, (February 2007), pp.8-13, ISSN 1733-4224

Jha, S.; Shibata, E. & Dutta, A. (2008). Human Rvb1/Tip49 is required for the histone acetyltransferase activity of Tip60/NuA4 and for the downregulation of phosphorylation on H2AX after DNA damage. *Mol Cell Biol*, Vol.28, No.8, (February 2008), pp. 2690-2700, ISSN 1828-5460

Jin, Y.H.; Yoo, K.J.; Lee, Y.H. & Lee SK. (2000). Caspase 3-mediated cleavage of p21WAF1/CIP1 associated with the cyclin A- cyclin-dependent kinase 2 complex is a prerequisite for apoptosis in SK-HEP-1 cells. *J Biol Chem*, Vol.275, No.39, (September 2000), pp.30256–30263, ISSN 1088-4382

Johnson, D.G.; Schwarz, J.K.; Cress, W.D. & Nevins, J.R. (1993). Expression of transcription factor E2F1 induces quiescent cells to enter S phase. *Nature*, Vol.365, No.6444, (September, 1993), pp.349-352. ISSN 837-7827

Jungmichel, S. & Stucki, M. (2010). MDC1: The art of keeping things in focus. *Chromosoma,* Vol.119, No.4, (March, 2010), pp.337-349. ISSN 2022-4865

Kaidi, A.; Weinert, B.T.; Choudhary, C. & Jackson, S.P. (2010). Human SIRT6 promotes DNA end resection through CtIP deacetylation. *Science*, Vol.329, No.5997, (September 2010), pp.1348-1353, ISSN 2082-9486

Karagiannis, T. C. & El-Osta, A. (2007). Chromatin modifications and DNA double-strand breaks: the current state of play. *Leukemia,* Vol.21, No.2, (December 2006), pp.195–200, ISSN 1715-1702

Kastan, M.B. & Bartek, J. (2004). Cell-cycle checkpoints and cancer. *Nature*, Vol. 432, No. 7015, (November 2004), pp.316– 323, ISSN 1554-9093

Khanna, K.K. & Jackson, S.P. (2001). DNA double-strand breaks: signaling, repair and the cancer connection. *Nat Genet*, Vol. 27, No.3, (March 2001), pp.247–254, ISSN 1124-2102

Khanna, K. K.; Lavin, M. F., Jackson, S. P. & Mulhern, T. D. (2001). ATM, a central controller of cellular responses to DNA damage. *Cell Death Differ,* Vol. 8, No. 11, (November 2001), pp.1052–1065, ISSN 1168-7884

Kim, D. & Tsai, L.H. (2009). Linking cell cycle reentry and DNA damage in neurodegeneration. *Ann N Y Acad Sci*, Vol. 1170, (July 2009), pp. 674-679, ISSN 1968-6210

Kim, M.Y.; Zhang, T. & Kraus, W.L. (2005). Poly(ADP-ribosyl)ation by PARP-1: 'PAR-laying' NAD+ into a nuclear signal. *Genes Dev*, Vol.19, No.17, (September 2005), pp.1951-1967, ISSN 1614-0981

Knights, C.D.; Catania, J.; Di Giovanni, S.; Muratoglu, S.; Perez, R.; Swartzbeck, A.; Quong, A.A.; Zhang, X.; Beerman, T.; Pestell, R.G. & Avantaggiati, M.L. (2006). Distinct p53 acetylation cassettes differentially influence gene-expression patterns and cell fate. *J Cell Biol*, Vol.173, No.4, (May 2006), pp.533-544, ISSN 1671-7128

Koch, C.A.; Agyei, R.; Galicia, S.; Metalnikov, P.; O'Donnell, P.; Starostine, A.; Weinfeld, M. & Durocher, D. (2004).Xrcc4 physically links DNA end processing by polynucleotide kinase to DNA ligation by DNA ligase IV. *EMBO J*, Vol. 23, No.19, (September 2004), pp. 3874–3885, ISSN 1538-5968

Kolas, N.K.; Chapman, J.R.; Nakada, S.; Ylanko, J.; Chahwan, R.; Sweeney, F.D.; Panier, S.; Mendez, M.; Wildenhain, J.; Thomson, T.M.; Pelletier, L.; Jackson, S.P. & Durocher, D. (2007). Orchestration of the DNA-damage response by the RNF8 ubiquitin ligase. *Science,* Vol.318, No.5856, (November 2007), pp.1637-1640, ISSN 1800-6705

Korotchkina, L.G.; Leontieva, O.V.; Bukreeva, E.I.; Demidenko, Z.N.; Gudkov, A.V. & Blagosklonny, M.V. (2010).The choice between p53-induced senescence and quiescence is determined in part by the mTOR pathway. *Aging (Albany NY)*, Vol.2, No.6, (June 2010), pp. 344-352, ISSN 2060-6252

Kraemer, K.H.; Sander, M. & Bohr, V.A. (2007). New areas of focus at workshop on human diseases involving DNA repair deficiency and premature aging. *Mech Ageing Dev*, Vol.128, No.2, (February 2007), pp.229-235, ISSN 1736-1460

Kraljevic Pavelic, S.; Cacev, T. & Kralj, M. (2008). A dual role of p21waf1/cip1 gene in apoptosis of HEp-2 treated with cisplatin or methotrexate. *Cancer Gene Ther*, Vol.15, No.9, (May 2008), pp. 576-590, ISSN 1848-3502

Krishnakumar, R. & Kraus, W.L. (2010). The PARP side of the nucleus: molecular actions, physiological outcomes, and clinical targets. *Mol Cell*, Vol.39, No.1, (July 2010), pp.8-24, ISSN 2060-3072

Kouzarides, T. (2007).Chromatin modifications and their function. *Cell,* Vol.128, No.4, (February 2007), pp.693–705, ISSN 1732-0507

Kruman, I.I. (2004). Why do neurons enter the cell cycle? *Cell Cycle*, Vol.3, No.6, (June 2004), pp. 769-773, ISSN 1513-6759

Kruman, I.I., Wersto, R.P.; Cardozo-Pelaez, F.; Smilenov, L.; Chan, S.; Chrest, F.; Emokpae, R. Jr.; Gorospe, M. & Mattson, M.P. (2004). Cell cycle activation linked to neuronal cell death initiated by DNA damage. *Neuron*, Vol.41, No.4, (February 2004), pp.549–561, ISSN 1498-0204

Kuan, C.Y.; Schloemer, A.J.; Lu, A.; Burns, K.A.; Weng, W.L.; Williams, M.T.; Strauss, K.I.; Vorhees, C.V.; Flavell, R.A.; Davis, R.J.; Sharp, F.R. & Rakic, P. (2004). Hypoxia-ischemia induces DNA synthesis without cell proliferation in dying neurons in adult rodent brain. *J Neurosci*, Vol.24, No.47, (November 2004), pp. 10763-10772, ISSN 1556-4594

Kumagai, A. & Dunphy, W.G. (2006) How cells activate ATR. *Cell Cycle*, Vol.5, No.12, (June 2006), pp. 1265-1268, ISSN 1676- 0665

Kuroda, Y.; Aishima, S.; Taketomi, A.; Nishihara, Y.; Iguchi, T.; Taguchi, K.; Maehara, Y. & Tsuneyoshi, M. (2007). 14-3- 3sigma negatively regulates the cell cycle, and its downregulation is associated with poor outcome in intrahepatic cholangiocarcinoma. *Hum Pathol,* Vol.38, No.7, (March 2007), pp. 1014-1022, ISSN 1739-1729

Kusch, T.; Florens, L.; Macdonald, W.H.; Swanson, S.K.; Glaser, R.L.; Yates, J.R. 3rd.; Abmayr, S.M.; Washburn, M.P. & Workman, J.L. (2004). Acetylation by Tip60 is required for selective histone variant exchange at DNA lesions. *Science*, Vol.306, No.5704, (November 2004), pp.2084-2087, ISSN 1552-8408

Lal, A.; Abdelmohsen, K.; Pullmann, R.; Kawai, T.; Galban, S.; Yang, X.; Brewer, G. & Gorospe, M. (2006). Posttranscriptional derepression of GADD45alpha by genotoxic stress. *Mol Cell*, Vol.22, No.1, (April 2006), pp.117-128, ISSN 1660-0875

Laronga, C.; Yang, H.Y.; Neal, C. & Lee, M.H. (2000). Association of the cyclin-dependent kinases and 14-3-3sigma negatively regulates cell cycle progression. *J Biol Chem*, Vol. 275, No.30, (July 2000), pp. 23106-23112, ISSN 1076-7298

Lavin, M.F. & Kozlov, S. (2007). DNA damage-induced signalling in ataxia–telangiectasia and related syndromes. *Radiother Oncol,* Vol. 83, No.3, (May 2007), pp.231–237, ISSN 1751-2070

Le Cam, L.; Linares, L.K.; Paul, C.; Julien, E.; Lacroix, M.; Hatchi, E.; Triboulet, R.; Bossis, G.; Shmueli, A.; Rodriguez, M.S.; Coux, O. & Sardet, C. (2006). E4F1 is an atypical ubiquitin ligase that modulates p53 effector functions independently of degradation. *Cell*, Vol.127, No.4, (November 2006), pp. 775-788, ISSN 1711-0336

Lee, E.W.; Lee, M.S.; Camus, S.; Ghim, J.; Yang, M.R.; Oh, W.; Ha, N.C.; Lane, D.P. & Song, J. (2009).Differential regulation of p53 and p21 by MKRN1 E3 ligase controls cell cyclearrest and apoptosis, *EMBO J,*. Vol.28, No.14, (June 2009), pp.2100–2113, ISSN 1953-6131

Lee, J.H. & Paull, T.T. (2005). ATM activation by DNA double-strand breaks through the Mre11-Rad50-Nbs1 complex. *Science*, Vol.308, No. 5721, (March 2005), pp.551-554, ISSN 1579-0808

Lee, J.H., Choy, M.L., Ngo, L., Foster, S.S., Marks, P.A. (2010). Histone deacetylase inhibitor induces DNA damage, which normal but not transformed cells can repair. *Proc Natl Acad Sci U S A*, Vol.107, No.33, (August 2010), pp.14639-14644, ISSN 2067-9231

Lee, S.M.; Bae, J.H.; Kim, M.J.; Lee, H.S.; Lee, M.K.;Chung, B.S.; Kim, D.W.; Kang, C.D. & Kim, S.H. (2007). Bcr-Abl- independent imatinib-resistant K562 cells show aberrant protein acetylation and increased sensitivity to histone deacetylase inhibitors. *J Pharmacol Exp Ther*, Vol.322, No.3, (June 2007), pp.1084-1092, ISSN 1756-9822

Lee, Y. & McKinnon, P.J. (2000). ATM dependent apoptosis in the nervous system. *Apoptosis* Vol.5, No.6, (December 2000), pp.523–529, ISSN 1130-3911

Lee, Y.; Chong, M.J. & McKinnon PJ. (2001). Ataxia telangiectasia mutated–dependent apoptosis after genotoxic stress in the developing nervous system is determined by cellular differentiation status. *J Neurosci*, Vol.21, No.17, (September 2001), pp.6687–6693, ISSN 1151-7258

Lee, Y. & McKinnon, P.J. (2007). Responding to DNA double strand breaks in the nervous system. *Neuroscience*, Vol.145, No.4, (April 2007), pp.1365-1374, ISSN 16934412

Leroy, C.; Lee, S.E.; Vaze, M.B.; Ochsenbien, F.; Guerois, R.; Haber, J.E. & Marsolier-Kergoat, M.C. (2003). PP2C phosphatases Ptc2 and Ptc3 are required for DNA checkpoint inactivation after a double-strand break. *Mol Cell*, Vol.285, No.2, (November 2003), pp.1414-1423, ISSN 1989-3054

Levine, A.J. & Oren, M. (2009). The first 30 years of p53: growing ever more complex. *Nat Rev Cancer*, Vol.9, No.10, (October 2009), pp.749-758, ISSN 1977-6744

Levkau, B.; Koyama, H.; Raines, E.W.; Clurman, B.; Herren, B.; Orth, K.; Roberts, J.M. & Ross, R. (1998). Cleavage of p21Cip1/Waf1 and p27Kip1 mediates apoptosis in endothelial cells through activation of Cdk2: role of a caspase cascade. *Mol Cell*, Vol.1, No.4, (March 1998), pp.553-563, ISSN 966-0939

Li, X.; Corsa, C.A.; Pan, P.W.; Wu, L.; Ferguson, D.; Yu, X.; Min, J. & Dou, Y. (2010). MOF and H4 K16 acetylation play important roles in DNA damage repair by modulating recruitment of DNA damage repair protein Mdc1. *Mol Cell Biol*, Vol.30, No.22, (September 2010), pp.5335-5347, ISSN 2083-7706

Lieber MR. (2010). The mechanism of double-strand DNA break repair by the nonhomologous DNA end-joining pathway. *Annu Rev Biochem*, Vol.79, pp. 181-211, ISSN 2019-2759

Lisby, M; Barlow, J.H.; Burgess, R.C. & Rothstein, R. (2004). *Cell,* Vol.118, No.6, (September 2004), pp.699-713, ISSN 1536- 9670

Liu, Z.M.; Chen, G.G.; Ng, E.K.; Leung, W.K.; Sung, J.J. & Chung, S.C. (2004). Upregulation of heme oxygenase-1 and p21 confers resistance to apoptosis in human gastric cancer cells. *Oncogene*, Vol.23, No.2, (January 2004), pp.503-13, ISSN 1464-7439

Lobrich, M. & Jeggo, P.A. (2007). The impact of a negligent G2/M checkpoint on genomic instability and cancer induction. *Nat Rev Cancer*, Vol. 7, No.11, (November 2007), pp.861–869, ISSN 1794-3134

Lu, T.; Pan, Y.; Kao, S.Y.; Li, C.; Kohane, I.; Chan, J. & Yankner, B.A. (2004). Gene regulation and DNA damage in the ageing human brain. *Nature*, Vol.429, No.6994, (June 2004), pp.883-891, ISSN 1519-0254

Lukas, C.; Bartkova, J.; Latella, L.; Falck, J.; Mailand, N.; Schroeder, T.; Sehested, M.; Lukas, J. & Bartek, J. (2001). DNA damage-activated kinase Chk2 is independent of proliferation or differentiation yet correlates with tissue biology. *Cancer Res*, Vol.61, No.13, (July 2001), pp.4990-4903, ISSN 1143-1331

Luo, J.; Nikolaev, A.Y.; Imai, S.; Chen, D.; Su, F.; Shiloh, A.; Guarente, L. & Gu, W. (2001). Negative control of p53 by Sir2alpha promotes cell survival under stress. *Cell*, Vol.107, No.2, (October 2001), pp. 137-148, ISSN 1167-2522

Macůrek, L.; Lindqvist, A.; Voets, O.; Kool, J.; Vos, H.R. & Medema, R.H. (2010). Wip1 phosphatase is associated with chromatin and dephosphorylates gammaH2AX to promote checkpoint inhibition. *Oncogene*, Vol.29, No.15, (January 2010), pp.2281-2291, ISSN 2010-1220

Mahaney, B.L.; Meek, K. & Lees-Miller, S.P. (2009). Repair of ionizing radiation-induced DNA double-strand breaks by non- homologous end-joining. *Biochem,* Vol.417, No.3, (February 2009), pp.639–650, ISSN 1913-3841

Mailand, N.; Bekker-Jensen,S.; Bartek, J. & Lukas, J. (2006). Destruction of Claspin by SCFbetaTrCP restrains Chk1 activation and facilitates recovery from genotoxic stress. *Mol Cell,* Vol.23, No.3, (August 2006), pp.307–318, ISSN 1688-5021

Mamely, I., van Vugt, M.A., Smits, V.A., Semple, J.I., Lemmens, B., Perrakis, A., Medema, R.H, & Freire, R. (2006). Pololike kinase-1 controls proteasome-dependent degradation of claspin during checkpoint recovery. *Curr Biol*, Vol.16, No.19, (August 2006), pp. 1950-1955, ISSN 1693-4469

Marchenko. N.D.; Zaika, A. & Moll, U.M. (2000) Death signal-induced localization of p53 protein to mitochondria. A potential role in apoptotic signaling. *J Biol Chem*, Vol.275, No.21, (May 2000), pp.16202–16212, ISSN 1082-1866

Martin, L.J. (2008). DNA damage and repair: relevance to mechanisms of neurodegeneration. *J Neuropathol Exp Neurol*, Vol.67, No.5, (May 2008), pp.377-387, ISSN 1843-1258

Martin, L.J.; Liu, Z.; Pipino, J.; Chestnut, B. & Landek, M.A. (2009). Molecular regulation of DNA damage-induced apoptosis of neurons in cerebral cortex. *Cerebral Cortex*, Vol.19, No.6, (September 2008), pp. 1273-1293, ISSN 1882-0287

Martinez, L.A.; Yang, J.; Vazquez, E.S.; Rodriguez-Vargas Mdel, C.; Olive, M.; Hsieh, J.T.; Logothetis, C.J. & Navone, N.M. (2002).p21 modulates threshold of apoptosis induced by DNA-damage and growth factor withdrawal in prostate cancer cells. *Carcinogenesis*, Vol.23, No.8, (August 2002), pp.1289–1296, ISSN 1215-1346

Mazumder, S.; Plesca, D.; Kinter, M. & Almasan, A. (2007). Interaction of a cyclin e fragment with Ku70 regulates bax- mediated apoptosis. *Mol Cell Biol*, Vol.27, No.9, (February 2007), pp.3511-3520, ISSN 1732-5036

McKinnon, P.J. (2001). Ataxia telangiectasia: new neurons and ATM. *Trends Mol Med*, Vol.7, No.6, (June 2001), pp.233-234, ISSN 1137-8498

McMurray, C.T. (2005). To die or not to die: DNA repair in neurons. *Mutat Res*, Vol.577, No.1-2, (September 2005), pp.260– 274, ISSN 1592-1706

McShea, A.; Wahl, A.F. & Smith, M.A. (1999). Re-entry into the cell cycle: a mechanism for neurodegeneration in Alzheimer disease. *Med Hypotheses*, Vol.52, No.6, (June 1999), pp. 525–527, ISSN 1045-9833

Meek, D.W. (1994). Post-translational modification of p53. *Semin Cancer Biol*, Vol.5, No.3, (June 1994), pp.203-210, ISSN 794- 8948

Melander, F.; Bekker-Jensen, S.; Falck, J.; Bartek, J.; Mailand, N. & Lukas, J. (2008). Phosphorylation of SDT repeats in the MDC1 N terminus triggers retention of NBS1 at the DNA damage-modified chromatin. *J Cell Biol,* Vol.181, No.2, (April 2008), pp.213-226, ISSN 1841-1307

Melino, G. (2003) p73, the ''assistant'' guardian of the genome? *Ann N Y Acad Sci*, Vol.1010, pp.9-15, ISSN 1503-3688

Meng, S.; Arbit, T.; Veeriah, S.; Mellinghoff, I.K.; Fang, F.; Vivanco, I.; Rohle, D. & Chan, T.A. (2009). 14-3-3sigma and p21 synergize to determine DNA damage response following Chk2 inhibition. *Cell Cycle*, Vol.8, No.14, (July 2009), pp. 2238- 2246, ISSN 1950-2805

Merkle, D.; Douglas, P.; Moorhead, G.B.; Leonenko, Z.; Yu, Y.; Cramb, D.; Bazett-Jones, D.P. & Lees-Miller, S.P. (2002). The DNA-dependent protein kinase interacts with DNA to form a protein-DNA complex that is disrupted by phosphorylation. *Biochemistry*, Vol.41, No.42, (October 2002), pp.12706-12714, ISSN 1237-9113

Milczarek, G.J.; Martinez, J. & Bowden, G.T. (1997). p53 Phosphorylation: biochemical and functional consequences. *Life Sci*, Vol.60, No.1, pp.1-11, ISSN 899-5526

Messick TE, Greenberg RA. (2009). The ubiquitin landscape at DNA double-strand breaks. *J Cell Biol*, Vol.187, No.3, (November 2009), pp.319-326. ISSN 1994-8475

Mihara, M.; Erster, S.; Zaika, A.; Petrenko, O.; Chittenden, T.; Pancoska, P. & Moll, U.M. (2003) p53 has a direct apoptogenic role at the mitochondria. *Mol Cell*, Vol.11, No.3, (March 2003), pp. 577-590. ISSN 1266-7443

Miller, S.A.; Mohn, S.E. & Weinmann, A.S. (2010). Jmjd3 and UTX play a demethylase-independent role in chromatin remodeling to regulate T-box family member-dependent gene expression. *Mol Cell*, Vol.40, No.4, (November 2010), pp.594-605, ISSN 2109-5589

Mimori, T. & Hardin, J.A.(1986). Mechanism of interaction between Ku protein and DNA. *J Biol Chem,* Vol.261, No,22, (August 1986), pp.10375-10379, ISSN 301-5926

Morselli, E.; Galluzzi, L.; Kepp, O. & Kroemer, G. (2009). Nutlin kills cancer cells via mitochondrial p53. *Cell Cycle*, Vol.8, No.11, (June 2009), pp. 1647-1648, ISSN 1944-8434

Mortusewicz, O.; Amé, J.C.; Schreiber, V. & Leonhardt, H. (2007). Feedback-regulated poly(ADP-ribosyl)ation by PARP-1 is required for rapid response to DNA damage in living cells. *Nucleic Acids Res*, Vol.35, No.22, (November 2007), pp.7665- 7675, ISSN 1798-2172

Moynahan, M.E.; Chiu, J.W.; Koller, B.H. & Jasin, M. (1999). Brca1 controls homology-directed DNA repair. *Mol Cell*, Vol. 4, No.4, (October 1999), pp.511-518, ISSN 1054-9283

Murr, R.; Loizou, J.I.; Yang, Y.G.; Cuenin, C.; Li, H.; Wang, Z.Q. & Herceg, Z. (2006). Histone acetylation by Trrap-Tip60 modulates loading of repair proteins and repair of DNA double-strand breaks. *Nat Cell Biol,* Vol.8, No.1, (Dec 2006), pp.91–99, ISSN 1634-1205

Nagayama, T.; Lan, J.; Henshall, D.C.; Chen, D.; O'Horo, C.; Simon, R.P. & Chen, J. (2000). Induction of oxidative DNA damage in the peri-infarct region after permanent focal cerebral ischemia. *J Neurochem*, Vol.75, No.4, (October 2000), pp.1716-1728, ISSN 1098-7855

Nakada, S.; Chen, G.I.; Gingras, A.C. & Durocher, D. (2008). PP4 is a gamma H2AX phosphatase required for recovery from the DNA damage checkpoint. *EMBO Rep*, Vol.9, No.10, (August 2008), pp.1019-1026, ISSN 1875-8438

Nakamura, T.M.; Du, L.L.; Redon, C. & Russell, P. (2004). Histone H2A phosphorylation controls Crb2 recruitment at DNA breaks, maintains checkpoint arrest, and influences DNA repair in fission yeast. *Mol Cell Biol*, Vol.24, No.1,14, (July 2004), pp.6215-6230, ISSN 1522-6425

Narciso, L.; Fortini, P.; Pajalunga, D.; Franchitto, A.; Liu, P.; Degan, P.; Frechet, M.; Demple, B.; Crescenzi, M. & Dogliotti, E. (2007). Terminally differentiated muscle cells are defective in base excision DNA repair and hypersensitive to oxygen injury. *Proc Natl Acad Sci U S A*, Vol.104, No.43, (October 2007), pp.17010-17015, ISSN 1794-0040

Nicassio, F.; Corrado, N.; Vissers, J.H.; Areces, L.B.; Bergink, S.; Marteijn, J.A.; Geverts, B.; Houtsmuller, A.B.; Vermeulen, W.; Di Fiore, P.P. & Citterio, E. (2007). Human USP3 is a chromatin modifier required for S phase progression and genome stability. *Curr Biol*, Vol.17, No.22, (November 2007), pp.1972-1977, ISSN 1798-0597

Nouspikel, T. & Hanawalt, P.C. (2000). Terminally differentiatedhuman neurons repair transcribed genes but display attenuated global DNA repair and modulation of repair gene expression.*Mol Cell Biol*, Vol.20, No.5, (March 2000), pp.1562–1570, ISSN 1066-9734

Nouspikel, T. & Hanawalt, P.C. (2002). DNA repair in terminally differentiated cells. *DNA Repair (Amst),* Vol.1, No.1, (January 2002), pp.59-75, ISSN 1250-9297

Nouspikel, T. (2007). DNA repair in differentiated cells: some new answers to old questions. *Neuroscience,* Vol.145, No.4, (August 2006), pp.1213-1221, ISSN 1692-0273

Oberdoerffer, P.; Michan, S.; McVay, M.; Mostoslavsky, R.; Vann, J.; Park, S.K.; Hartlerode, A.; Stegmuller, J.; Hafner, A.; Loerch, P.; Wright, S.M.; Mills, K.D.; Bonni, A.; Yankner, B.A.; Scully, R.; Prolla, T.A.; Alt, F.W. & Sinclair, D.A. (2008). SIRT1 redistribution on chromatin promotes genomic stability but alters gene expression during aging. *Cell*, Vol.135, No.5, (November 2008), pp.907-918, ISSN 1904-1753

O'Hagan, H.M.; Mohammad, H.P. & Baylin, S.B. (2008). Double strand breaks can initiate gene silencing and SIRT1- dependent onset of DNA methylation in an exogenous promoter CpG island. *PLoS Genet*, Vol.4, No.8, (August 2008), pp.e1000155, ISSN 1870-4159

O'Hare, M.J.; Hou, S.T.; Morris, E.J.; Cregan, S.P.; Xu, Q.; Slack, R.S. & Park, D.S. (2000). Induction and modulation of cerebellar granule neuron death by E2F-1. *J Biol Chem*, Vol.275, No.33, (August 2000), pp. 25358–25364, ISSN 1085- 1232

Okoshi, R.; Ozaki, T.; Yamamoto, H.; Ando, K.; Koida, N.; Ono, S.; Koda, T.; Kamijo, T.; Nakagawara, A. & Kizaki, H. (2008). Activation of AMP-activated protein kinase induces p53-dependent apoptotic cell death in response to energetic stress. *J Biol Chem*, Vol.283, No.7, (December 2007), pp. 3979-3987, ISSN 1805-6705

Oku, T.; Ikeda, S.; Sasaki, H.; Fukuda, K.; Morioka, H.; Ohtsuka, E.; Yoshikawa, H. & Tsurimoto, T. (1998). Functional sites of human PCNA which interact with p21 (Cip1/Waf1), DNA polymerase delta and replication factor C. *Gene Cells*, Vol.3, No.6, (June 1998), pp. 357-369, ISSN 973-4782

Otsuka, Y.; Tanaka, T.; Uchida, D.; Noguchi, Y.; Saeki, N.; Saito, Y. & Tatsuno, I. (2004). Roles of cyclin-dependent kinase 4 and p53 in neuronal cell death induced by doxorubicin on cerebellar granule neurons in mouse. *Neurosci Lett*, Vol.365, No.3, (July 2004), pp. 180-185, ISSN 1524-6544

Pajalunga, D.; Mazzola, A.; Salzano, A.M.; Biferi, M.G.; De Luca, G. & Crescenzi, M. (2007). Critical requirement for cell cycle inhibitors in sustaining nonproliferative states. *J Cell Biol*, Vol.176, No.6, (March 2007), pp.1039-1056, ISSN 1735-3358

Pardo, B.; Gómez-González, B. & Aguilera, A. (2009). DNA repair in mammalian cells: DNA double-strand break repair: how to fix a broken relationship. *Cell Mol Life Sci*, Vol.66, No.6, (March 2009), pp.1039-1056, ISSN 1915-3654

Park, D.S.; Morris, E.J.; Greene, L.A. & Geller, H.M. (1997). G1/S cell cycle blockers and inhibitors of cyclin-dependent kinases suppress camptothecin-induced neuronal apoptosis. *J Neurosci*, Vol.17, No.4, (February 1997), pp. 1256–1270, ISSN 900- 6970

Park, D.S.; Morris, E.J.; Padmanabhan, J.; Shelanski, M.L.; Geller, H.M. & Greene, L.A. (1998). Cyclin-dependent kinases participate in death of neurons evoked by DNA-damaging agents. *J Cell Biol*, Vol.143, No.2, (October 1998), pp.457–467, ISSN 978-6955

Perry, J.J.; Yannone, S.M.; Holden, L.G.; Hitomi, C.; Asaithamby, A.; Han, S.; Cooper, P.K.; Chen, D.J. & Tainer, J.A. (2006). WRN exonuclease structure and molecular mechanism imply an editing role in DNA end processing. *Nat Struct Mol Biol*, Vol.13, No.5, (April 2006), pp.414-422. ISSN 1662-2405

Peterson, C.L. & Cote, J. (2004) Cellular machineries for chromosomal DNA repair. *Genes Dev*, Vol.18, No.6, (March 2004), pp.602-616. ISSN 1507-5289

Phillips, A.C. & Vousden, K.H. (2001). E2F-1 induced apoptosis. *Apoptosis*, Vol.6, No.3, (June 2001), pp.173–182. ISSN 1138- 8666

Pickart, C.M. (2001). Ubiquitin enters the new millennium. *Mol Cell*, Vol.8, No.3, (September 2001), pp.499-504. ISSN 1158- 3613

Picard, F.; Kurtev, M.; Chung, N.; Topark-Ngarm, A.; Senawong, T.; Machado De Oliveira, R.; Leid, M.; McBurney, M.W. & Guarente, L. (2004). Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. *Nature,* Vol.429, No.6993, (June 2004), pp. 771-776, ISSN 1517-5761

Poehlmann, A. & Roessner, A. (2010). Importance of DNA damage checkpoints in the pathogenesis of human cancers. *Pathol Res Pract*, Vol.206, No.9, (August 2010), pp. 591-601, ISSN 2067-4189

Polager, S. & Ginsberg, D. (2008). E2F – at the crossroads of life and death. *Trends Cell Biol*, Vol.18, No.11, (September 2008), pp. 528-535, ISSN 1880-5009

Polager, S. & Ginsberg, D. (2009). p53 and E2f: partners in life and death. *Nat Rev Cancer*, Vol.9, No.10, (October 2009), pp.738-748, ISSN 1977-6743

Polo, S.E.; Kaidi, A.; Baskcomb, L.; Galanty, Y.& Jackson, S.P. (2010). Regulation of DNA-damage responses and cell-cycle progression by the chromatin remodelling factor CHD4. *EMBO J*, Vol.29, No.18, (August 2010), pp.3130-3139, ISSN 2069-3977

Polo, S.E. & Jackson, S.P. (2011). Dynamics of DNA damage response proteins at DNA breaks: a focus on protein modifications. *Genes Dev*, Vol.25, No.5, (March, 2011), pp.409-33, ISSN 2136-3960

Qin, S. & Parthun, M.R. (2006). Recruitment of the type B histone acetyltransferase Hat1p to chromatin is linked to DNA double-strand breaks. *Mol Cell Biol*, Vol.26, No.9, (May 2006), pp.3649-3658, ISSN 1661-2003

Rass, U.; Ahel, I. & West, S.C. (2007). Defective DNA repair and neurodegenerative disease. *Cell,* Vol.130, No.6, (September 2007), pp.991-1004, ISSN 1788-9645

Reagan-Shaw, S. & Ahmad, N. (2005). Silencing of polo-like kinase (Plk) 1 via siRNA causes induction of apoptosis and impairment of mitosis machinery in human prostate cancer cells: implications for the treatment of prostate cancer. *FASEB J*, Vol.19, No.6, (January 2005), pp.611-613, ISSN 1566-1849

Reed, J.C. (2006). Proapoptotic multidomain Bcl-2/Bax-family proteins: mechanisms, physiological roles and therapeutic opportunities. *Cell Death Differ*, Vol.13, No.8, (June 2006), pp.1378-1386, ISSN 1672-9025

Reinhardt, H.C. & Yaffe, M.B. (2009). Kinases that control the cell cycle in response to DNA damage: Chk1, Chk2, and MK2. *Curr Opin Cell Biol,* Vol.21, No.2, (February 2009), pp.245–255, ISSN 1923-0643

Rich, T.; Allen, R.L. & Wyllie, A.H. (2000). Defying death after DNA damage. *Nature*, Vol.407, No.6805, (October 2000), pp.777–783, ISSN 1104-8728

Riley, T.; Sontag, E.; Chen, P. & Levine, A. (2008). Transcriptional control of human p53-regulated genes. *Nat Rev Mol Cell Biol*, Vol.9, No.5, (May 2008), pp.402-412, ISSN 1843-1400

Rinaldo, C.; Prodosmo, A.; Mancini, F.; Iacovelli, S.; Sacchi, A.; Moretti, F. & Soddu, S. (2007). MDM2-regulated degradation of HIPK2 prevents p53Ser46 phosphorylation and DNA damage-induced apoptosis. *Mol Cell*, Vol.25, No.5, (March 2007), pp.739-750, ISSN 1734-9959

Rogakou, E.P.; Pilch, D.R.; Orr, A.H.; Ivanova, V.S. & Bonner, W.M. (1998). DNA double-stranded breaks induce histone H2AX phosphorylation on serine 139. *J Biol Chem*, 1998 Mar 6;Vol.273, No.10, (March 1998), pp.5858-5868, ISSN 9488723

Rogoff, H.A. & Kowalik, T.F. (2004). Life, death and E2F: linking proliferation control and DNA damage signaling via E2F1. *Cell Cycle*, Vol.3, No.7, (July 2004), pp. 845–846, ISSN 1519-0206

Rolig, R.L. & McKinnon, P.J. (2000). Linking DNA damage and neurodegeneration. *Trends Neuroscie*, Vol.23, No.9, (September 2000), pp. 417-424, ISSN 1094-1191

Roshak, A.K.; Capper, E.A.; Imburgia, C.; Fornwald, J.; Scott, G. & Marshall, L.A. (2000). The human polo-like kinase PLK, regulates cdc2/cyclin B through phosphorylation and activation of the cdc25C phosphatase, *Cell Signal*, Vol.12, No.6, (June 2000), pp. 405–411, ISSN 1120-2906

Rossi, M.; De Laurenzi, V.; Munarriz, E.; Green, D.R.; Liu, Y.C.; Vousden, K.H.; Cesareni, G. & Melino, G. (2005) The ubiquitin-protein ligase Itch regulates p73 stability. *EMBO J*, Vol.24, No.4, (February 2005), pp. 836–848, ISSN 1567- 8106

Rouse, J. & Jackson SP. (2002). Interfaces between the detection, signaling, and repair of DNA damage. *Science,* Vol.297, No.5581, (July, 2002), pp. 547–551, ISSN 1214-2523]

Sakaguchi, K.; Herrera, J.E.; Saito, S.; Miki, T.; Bustin, M.; Vassilev, A.; Anderson, C.W. & Appella, E. (1998). DNA damage activates p53 through a phosphorylation-

acetylation cascade. *Genes Dev*, Vol.12, N0.18, (September 1998), pp.2831-2841, ISSN 9744-860

Sancar, A.; Lindsey-Boltz, L.A.; Unsal-Kacmaz, K. & Linn, S. (July 2004). Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. *Annu Rev Biochem, Vol*. 73, No. , (January, 2004), pp.39–85, ISSN 1518-9136

Sanders, S.L.; Arida, A.R. & Phan, F.P. (2010). Requirement for the phospho-H2AX binding module of Crb2 in double-strand break targeting and checkpoint activation. *Mol Cell Biol*, Vol.30, N0.19, (August 2010), pp.4722-4731, ISSN 2067-9488

Sartori, A.A.; Lukas, C.; Coates, J.; Mistrik, M.; Fu, S.; Bartek, J.; Baer, R.; Lukas, J. & Jackson, S.P. (2007). Human CtIP promotes DNA end resection. Nature, Vol.450, No.7169, (October 2007), pp.509–514, ISSN 1796-5729

Schlereth, K.; Beinoraviciute-Kellner, R.; Zeitlinger, M.K.; Bretz, A.C.; Sauer, M.; Charles, J.P.; Vogiatzi, F.; Leich, E.; Samans, B.; Eilers, M.; Kisker, C.; Rosenwald, A. & Stiewe, T. (2010). DNA binding cooperativity of p53 modulates the decision between cell cycle arrest and apoptosis. *Mol Cell*, Vol.38, No.3, (May 2010), pp.356-368, ISSN 2047-1942

Schmetsdorf, S.; Gartner, U. & Arendt, T. (2007). Constitutive expression of functionally active cyclin dependent kinases and their binding partners suggests noncanonical functions of cell cycle regulators in differentiated neurons. *Cereb Cortex,* Vol.17, No.8, (October 2006), pp.1821–1829, ISSN 1705-0646

Schmetsdorf, S.; Arnold, E.; Holzer, M.; Arendt, T.& Gartner, U. (2009). A putative role for cell cycle-related proteins in microtubule-based neuroplasticity. *Eur J Neurosci* , Vol.29, No.6, (March 2009), pp.1096–10107, ISSN 1930-2146

Schuler, M.; Bossy-Wetzel, E.; Goldstein, J.C.; Fitzgerald, P. & Green, D,R. (2000) p53 induces apoptosis by caspase activation through mitochondrial cytochrome c release. *J Biol Chem*, Vol.275, No.10, (March 2000), pp. 7337-7342, ISSN 1070-2305

Shanbhag, N.M.; Rafalska-Metcalf, I.U.; Balane-Bolivar, C.; Janicki, S.M. & Greenberg, R.A. (2010). ATM-dependent chromatin changes silence transcription in cis to DNA double-strand breaks. *Cell*, Vol.1413, No.6, (June 2010), pp.970– 981. ISSN 2055-0933

Shao, G.; Lilli, D.R.; Patterson-Fortin, J.; Coleman, K.A.; Morrissey, D.E. & Greenberg, R.A. (2009). The Rap80-BRCC36 de- ubiquitinating enzyme complex antagonizes RNF8-Ubc13-dependent ubiquitination events at DNA double strand breaks. *Proc Natl Acad Sci U S A*, Vol.106, No.9, (February 2009), pp. 3166-3171, ISSN 1920-2061

Sharma, S. (2007). Age-related nonhomologous end joining activity in rat neurons. *Brain Res Bull,* Vol.73, No1-3, (June 2007), pp.48–54. ISSN 1749-9636

Sharma, G.; Mirza, S.; Parshad, R.; Srivastava, A.; Gupta, S.D.; Pandya, P. & Ralhan, R. (2010). Clinical significance of promoter hypermethylation of DNA repair genes in tumor and serum DNA in invasive ductal breast carcinoma patients. *Life Sci*, Vol.87, No.3-4, (May 2010), pp.83-91, ISSN 2047-0789

Shieh, S-Y.; Ikeda, M.; Taya, Y. & Prives, C. (1997). DNA damage-induced phosphorylation of p53 alleviates inhibition by MDM2. *Cell*, Vol.91, No.3, (October, 2003), pp. 325-334, ISSN 936-3941

Shieh, S.Y.; Ahn, J.; Tamai, K.; Taya, Y. & Prives, C. (2000). The human homologs of checkpoint kinases Chk1 and Cds1 (Chk2) phosphorylate p53 at multiple DNA damage-inducible sites. *Genes Dev*, Vol.14, No.3, (February, 2000), pp. 289- 300, ISSN 1067-3501

Shiloh, Y. (2003). ATM and related protein kinases: safeguarding genome integrity. *Nat Rev Cancer,* 2003; Vol.3, No.3, (March, 2003), pp.155-168, ISSN 1261-2651

Shiloh, Y. (2006). The ATM-mediated DNA-damage response: taking shape. *Trends Biochem Sci,* Vol.31, No.7 (June 2006), pp.402-10. ISSN 1677-4833

Singleton, B.K.; Torres-Arzayus, M.I.; Rottinghaus, S.T.; Taccioli, G.E. & Jeggo, P.A. (1999). The C terminus of Ku80 activates the DNA-dependent protein kinase catalytic subunit. *Mol Cell Biol*, Vol.19, No.15, (May 1999), pp. 3267-3277, ISSN1020- 7052

Sinha, S.; Malonia, S.K.; Mittal, S.P.; Singh, K.; Kadreppa, S.; Kamat, R.; Mukhopadhyaya, R.; Pal, J.K. & Chattopadhyay, S. (2010). Coordinated regulation of p53 apoptotic targets Bax and Puma by SMAR1 through an identical MAR element. *EMBO J*, Vol.29, No.4, (January 2010), pp.830-842, ISSN 2007-5864

Smerdon MJ, Tlsty TD, Lieberman MW. (1978). Distribution of ultraviolet-induced DNA repair synthesis in nuclease sensitive and resistant regions of human chromatin. *Biochemistry*, Vol.17, No.12, (June 1978), pp.2377–2386, ISSN 678515

Smith, D.S.; Leone, G.; DeGregori, J.; Ahmed, M.N.; Qumsiyeh, M.B. & Nevins, J.R. (2000). Induction of DNA replication in adult rat neurons by deregulation of the retinoblastoma/E2F G1 cell cycle pathway. *Cell Growth Differ*, Vol.11, No.12, (December 2000), pp. 625-633, ISSN 1114-9597

Sofueva S, Du LL, Limbo O, Williams JS, Russell P. (2010). BRCT domain interactions with phospho-histone H2A target Crb2 to chromatin at double-strand breaks and maintain the DNA damage checkpoint. *Mol Cell Biol*, Vol.30, No.19, (August 2010), pp.4732-4743, ISSN 2067-9485

Sordet, O.; Redon, C.E.; Guirouilh-Barbat, J.; Smith, S.; Solier, S.; Douarre, C.; Conti, C.; Nakamura, A.J.; Das, B.B.; Nicolas, E.; Kohn, K.; Bonner, W.M. & Pommier, Y. (2009). Ataxia telangiectasia mutated activation by transcription- and topoisomerase I-induced DNA double-strand breaks. *EMBO Rep*, Vol.10, No.8, (June 2009), pp.887-893, ISSN 1955-7000

Soutoglou, E. & Misteli, T. (2008). Activation of the cellular DNA damage response in the absence of DNA lesions. *Science*, Vol.320, No.5882, (May 2008), pp.1507-1510, ISSN 1848-3401

Spycher, C.; Miller, E.S.; Townsend, K.; Pavic, L.; Morrice, N.A.; Janscak, P.; Stewart, G.S. & Stucki, M. (2008). Constitutive phosphorylation of MDC1 physically links the MRE11-RAD50-NBS1 complex to damaged chromatin. *J Cell Biol*, Vol.181, No.2, (April 2008), pp.227-240, ISSN 1841-1308

Stark, G.R. & Taylor, W.R. (2006). Control of the G2/M transition. *Mol. Biotechnol*, Vol.32, No.3, (March 2006), pp.227-248, ISSN 1663-2889

Steelman, L.S. & McCubrey, J.A. (2010). Intriguing novel abilities of Nutlin-3A: induction of cellular quiescence as opposed to cellular senescence - implications for chemotherapy. *Cell Cycle*, Vol.8, No.22, (November 2010), pp. 3634-3635, ISSN 1987-5921

Stewart, G.S.; Wang, B.; Bignell, C.R.; Taylor, A.M. & Elledge, S.J. (2003). MDC1 is a mediator of the mammalian DNA damage checkpoint. *Nature*, Vol.421, No.6926, (February 2003), pp. 961–966, ISSN1260-7005

Stewart, N.; Hicks, G.G.; Paraskevas, F. & Mowat, M. (1995). Evidence for a second cell cycle block at G2/M by p53. *Oncogene*, Vol. 10, No.1, (January 1995), pp. 109-115, ISSN 7529-916

Stiff, T.; O'Driscoll, M.; Rief, N.; Iwabuchi, K.; Löbrich, M. & Jeggo, P.A. (2004). ATM and DNA-PK function redundantly to phosphorylate H2AX after exposure to ionizing radiation. *Cancer Res*, Vol.64, No.7, (April 2004), pp.2390-2396, ISSN 1505-9890

Stracker, T.H.; Couto, S.S.; Cordon-Cardo, C.; Matos, T. & Petrini, J.H. (2008). Chk2 suppresses the oncogenic potential of DNA replication-associated DNA damage. *Mol Cell* Vol.31, No.1, (July 2008), pp.21-32, ISSN 1861-4044

Stucki, M.; Clapperton, J.A.; Mohammad, D.; Yaffe, M.B.; Smerdon, S.J. & Jackson SP. (2005). MDC1 directly binds phosphorylated histone H2AX to regulate cellular responses to DNA double-strand breaks. *Cell*, Vol.123, No.7, (December 2005), pp.1213–1226, ISSN 1637-7563

Subramanian, C.; Opipari, A.W. Jr.; Bian, X.; Castle, V.P. & Kwok, R.P. (2005). Ku70 acetylation mediates neuroblastoma cell death induced by histone deacetylase inhibitors. *Proc Natl Acad SciUSA*, Vol.102, No.13, (March 2005), pp. 4842-4847, ISSN 1577-8293

Suzuki, A.; Tsutomi, Y.; Akahane, K.; Araki, T. & Miura, M. (1998). Resistance to Fas-mediated apoptosis: activation of caspase 3 is regulated by cell cycle regulator p21WAF1 and IAP gene family ILP. *Oncogene*, Vol.17, No.8, (August 1998), pp. 931-939, ISSN 974-7872

Suzuki, A.; Tsutomi, Y.; Miura, M. & Akahane, K. (1999). Caspase 3 inactivation to suppress Fas-mediated apoptosis: identification of binding domain with p21 and ILP and inactivation machinery by p21. *Oncogene*, Vol.18, No.5, (February 1999), pp. 1239-1244, ISSN 1002-2130

Sykes, S.M.; Mellert, H.S.; Holbert, M.A.; Li, K.; Marmorstein, R.; Lane, W.S. & McMahon, S.B. (2006). Acetylation of the p53 DNA-binding domain regulates apoptosis induction. *Mol Cell*, Vol.24, No.6, (December 2006), pp.841-851, ISSN 1718- 9187

Syljuasen, R.G.; Jensen, S.; Bartek, J. & Lukas, J. (2006) Adaptation to the ionizing radiation-induced G2 checkpoint occurs in human cells and depends on checkpoint kinase 1 and Polo-like kinase 1 kinases. *Cancer Res*, Vol.66, No.21, (November 2006), pp.10253–10257, ISSN 1707-9442

Tanaka, T.; Ohkubo, S.; Tatsuno, I. & Prives, C. (2007). hCAS/CSE1L associates with chromatin and regulates expression of select p53 target genes. *Cell*, Vol.130, No.4, (August 2007), pp.638-650, ISSN 1771-9542

Tang, Y.; Luo, J.; Zhang, W. & Gu, W. (2006). Tip60-dependent acetylation of p53 modulates the decision between cell cycle arrest and apoptosis. *Mol Cell*, Vol.24, No.6, (December 2006), pp.827-839, ISSN 1718-9186

Tamburini, B.A. & Tyler, J.K. (2005). Localized histone acetylation and deacetylation triggered by the homologous recombination pathway of double-strand DNA repair. *Mol Cell Biol*, 2005 Jun;Vol.25, No.12, (June 2005), pp.4903-4913, ISSN 1592-3609

Taylor, W.R. & Stark, G.R. (2001). Regulation of the G2/M transition by p53. *Oncogene*, Vol.20, No.15, (April 2001), pp.1803– 1815, ISSN1131-3928

Tibbetts, R.S.; Brumbaugh, K.M.; Williams, J.M.; Sarkaria, J.N.; Cliby, W.A.; Shieh, S.Y.; Taya, Y.; Prives, C. & Abraham, R.T. (1999). A role for ATR in the DNA damageinduced phosphorylation of p53. *Genes Dev*, Vol.13, No.2, (January 1999), pp. 152-157, ISSN 992-5639

Timinszky, G.; Till, S.; Hassa, P.O.; Hothorn, M.; Kustatscher, G.; Nijmeijer, B.; Colombelli, J.; Altmeyer, M.; Stelzer, E.H.; Scheffzek, K.; Hottiger, M.O. & Ladurner, A.G.

(2009). A macrodomain-containing histone rearranges chromatin upon sensing PARP1 activation. *Nat Struct Mol Biol*, Vol.16, No.9, (August 2009), pp.923-929, ISSN 1968-0243

Toczyski, D.P.; Galgoczy, D.J. & Hartwell, L.H. (1997) CDC5 and CKII control adaptation to the yeast DNA damage checkpoint. *Cell*, Vol.90, No.6, (September 1997), pp.1097-10106, ISSN 932-3137

Tofilon, P.J. & Meyn, E. (1988). Reduction in DNA repair capacity following differentiation of murine proadipocytes. *Exp. Cell Res*, Vol.174, No.2, (February 1988), pp.502–510, ISSN 333-8499

Tomashevski, A.; Webster, D.R.; Grammas, P.; Gorospe, M. & Kruman, I.I. (2010). Cyclin-C-dependent cell-cycle entry is required for activation of non-homologous end joining DNA repair in postmitotic neurons. *Cell Death Differ*. Vol.17, No.7 (January 2010), pp.1189-1198, ISSN 2011-1042

Trushina, E. &C McMurray, C.T. (2007). Oxidative stress and mitochondrial dysfunction in neurodegenerative diseases. *Neuroscience*, Vol.145, No.4 (February 2007), pp.1233–1248, ISSN 1730-3344

Uziel T, Lerenthal Y, Moyal L, Andegeko Y, Mittelman L, Shiloh Y. (2003). Requirement of the MRN complex for ATM activation by DNA damage. *EMBO J,* Vol.22, No20, (October 2003), pp.5612-5621, ISSN 1453-2133

van Attikum, H.; Fritsch, O.; Hohn, B. & Gasser, S.M.(2004). Recruitment of the INO80 complex by H2A phosphorylation links ATP-dependent chromatin remodeling with DNA double-strand break repair. *Cell*, Vol.119, No.6,(December 2004), pp.777-788, ISSN 1560-7975

van Attikum, H.; Fritsch, O. & Gasser, S.M. (2007). Distinct roles for SWR1 and INO80 chromatin remodeling complexes at chromosomal double-strand breaks. *EMBO J*, Vol.26, No.18, (August 2007), pp.4113-4125. ISSN 1776-2868

Van Attikum, H. & Gasser, S.M. (2005) The histone code at DNA breaks: a guide to repair? *Nat Rev Mol Cell Biol*, Vol. 6, No.10, (October 2005), pp.757-765, ISSN 1616-7054

van Attikum, H. & Gasser, S.M. (2009). Crosstalk between histone modifications during the DNA damage response. *Trends Cell Biol*, Vol.19, No.5, (April 2009), pp.207-217, ISSN 1934-2239

van Gent, D.C. & van der Burg, M. (2007). Non-homologous end-joining, a sticky affair. *Oncogene*, Vol. 26, No.56, (December 2007), pp. 7731–7740, ISSN 1806-6085

van Vugt, M.A. & Medema, R.H. (2004). Checkpoint adaptation and recovery: back with Polo after the break. *Cell Cycle*, Vol.3, No.11, (November 2004), pp. 1383-1386, ISSN 1549-2511

van Vugt, M.A.; Bras, A. & Medema, R.H. (2004). Polo-like kinase-1 controls recovery from a G2 DNA damage-induced arrest in mammalian cells. *Mol Cell*, Vol. 15, No.5, (September 2004), pp.799-811, ISSN 1535-0223

van Vugt, M.A.; Gardino, A.K.; Linding, R.; Ostheimer, G.J.; Reinhardt, H.C.; Ong, S.E.; Tan, C.S.; Miao, H.; Keezer, S.M.; Li, J.; Pawson, T.; Lewis, T.A.; Carr, S.A.; Smerdon, S.J.; Brummelkamp, T.R. & Yaffe, M.B. (2010). A mitotic phosphorylation feedback network connects Cdk1, Plk1, 53BP1, and Chk2 to inactivate the G(2)/M DNA damage checkpoint. *PLoS Biol*, Vol. 8, No.1, (January 2010), pp.e1000287, ISSN 2012-6263

Vaseva, A.V.; Marchenko, N.D. & Moll, U.M. (2009). The transcription-independent mitochondrial p53 program is a major contributor to nutlin-induced apoptosis in tumor cells. *Cell Cycle*, Vol.8, No.11, (June 2009), pp.1711-1719, ISSN 1941- 1846

Vaze, M.B.; Pellicioli, A.; Lee, S.E.; Ira, G.; Liberi, G.; Arbel-Eden, A.; Foiani, M. & Haber JE. (2002) Recovery from checkpoint-mediated arrest after repair of a double-strand break requires Srs2 helicase. *Mol Cell*, Vol. 10, No.2, (August 2002), pp. 373–385, ISSN 1219-1482

Vaziri, H.; Dessain, S.K.; Ng Eaton, E.; Imai, S.;, Frye, R.A.; Pandita, T.K.; Guarente, L. & Weinberg, R.A. (2001). hSIR2(SIRT1) functions as an NAD-dependent p53 deacetylase. *Cell*, Vol.107, No.2, (October 2001), pp. 149-159, ISSN 1167-2523

Waldman, T.; Lengauer, C.; Kinzler, K.W. & Vogelstein, B. (1996). Uncoupling of S phase and mitosis induced by anticancer agents in cells lacking p21. *Nature*, Vol.381, No.6584, (June 1996), pp.713-716, ISSN 864-9519

Waldman, T.; Zhang, Y.; Dillehay, L.; Yu, J.; Kinzler, K.; Vogelstein, B. & Williams, J. (1997). *Cell cycle*, arrest versus cell death in cancer therapy. *Nat Med,* Vol.3, No.9, (September 1997), pp. 1034-1036, ISSN 928-8734

Wang, M.; Wu, W.; Wu, W.; Rosidi,B.; Zhang,L.; Wang, H. & Iliakis, G. (2006). PARP-1 and Ku compete for repair of DNA double strand breaks by distinct NHEJ pathways. *Nucleic Acids Res,* 2006;Vol.34, No.21, (November 2006), pp.6170- 6182, ISSN 1708-8286

Ward, I.M. & Chen, J. (2001). Histone H2AX is phosphorylated in an ATR-dependent manner in response to replicational stress. *J Biol Chem*, Vol.276, No.51, (October 2001), pp.47759-47762, ISSN 1167-3449

Warbrick, E.; Lane, D.P.; Glover, D.M. & Cox, L.S. (1995). A small peptide inhibitor of DNA replication defines the site of interaction between the cyclin-dependent kinase inhibitor p21WAF1 and proliferating cell nuclear antigen. *Curr Biol*, Vol.5, No.3, (March 1995), pp.275-282, ISSN 778-0738

Wefel, J.S.; Kayl, A.E. & Meyers, C.A. (2004). Neuropsychological dysfunction associated with cancer and cancer therapies: a conceptual review of an emerging target. *Br J Cancer*, Vol. 90, No.9 (May, 2004), pp.1691-1696, ISSN 1515-0608

Weissman, L.; de Souza-Pinto, N.C.; Stevnsner, T. & Bohr, V.A. (2007). DNA repair, mitochondria, and neurodegeneration. *Neuroscience*, Vol. 145, No.4 (November, 2006), pp.1318–1329, ISSN 1709-2652

Wilker, E.W.; van Vugt, M.A.; Artim, S.A.; Huang, P.H.; Petersen, C.P.; Reinhardt, H.C.; Feng, Y.; Sharp, P.A.; Sonenberg, N.; White, F.M. & Yaffe, M.B. (2007). 14-3-3sigma controls mitotic translation to facilitate cytokinesis. *Nature*, Vol.446, No.7133 (March 2007), pp.329-332, ISSN 1736-1185

Wilson, D. M. 3rd. & McNeill, D. R. (2007). Base excision repair and the central nervous system. *Neuroscience,* Vol.145, No.4 (August 2006), pp.1187–1200, ISSN 1693-4943

Xiong, Y.; Hannon, G.J.; Zhang, H.; Casso, D.; Kobayashi, R. & Beach, D. (1993). p21 is a universal inhibitor of cyclin kinases. *Nature*, Vol.366, No.6456, (December 1993), pp.701-704, ISSN 825-9214

Xu Y, Sun Y, Jiang X, Ayrapetov MK, Moskwa P, Yang S, Weinstock DM, Price BD. (2010). The p400 ATPase regulates nucleosome stability and chromatin ubiquitination during DNA repair. *J Cell Biol,* Vol.191, No.1, (September 2010), pp.31-43, ISSN 2087-6283

Yamaguchi, H.; Woods, N.T.; Piluso, L.G.; Lee, H.H.; Chen, J.; Bhalla, K.N.; Monteiro, A.; Liu, X.; Hung, M.C. & Wang, H.G. (2009). p53 acetylation is crucial for Its

transcription-independentproapoptotic functions. *J Biol Chem*, Vol.284, No.17, (March 2009), pp. 11171-11183, ISSN 1926-5193

Yamasaki, L.; Jacks, T.; Bronson, R.; Goillot, E.; Harlow, E. & Dyson, N.J. (1996). Tumor induction and tissue atrophy in mice lacking E2F-1. *Cell*, Vol.85, No.4, (May 1996), pp.537–548, ISSN 865-3789

Yang, W.; Dicker, D.T.; Chen, J. & El-Deiry, W.S. (2008). CARPs enhance p53 turnover by degrading 14-3-3sigma and stabilizing MDM2. *Cell Cycle*, Vol.7, No.5, (January 2008), pp. 670-682, ISSN 1838-2127

Yang, Y. & Herrup, K. (2001). Loss of neuronal cell cycle control in ataxia-telangiectasia: a unified disease mechanism, *J Neurosci*, Vol.21, No.8, (April 2001), pp. 2661–2668 , ISSN 1130-6619

Yang, Y.; Geldmacher, D.S. & Herrup, K. (2001) DNA replication precedes neuronal cell death in Alzheimer's disease. *J Neurosci*, Vol.21, No.7, (April 2001), pp. 2661–2668 , ISSN1130-6619

Yano, K.; Morotomi-Yano, K.; Wang, S.Y.; Uematsu, N.; Lee, K.J.; Asaithamby, A.; Weterings, E. & Chen, D.J. (2008). Ku recruits XLF to DNA double-strand breaks. *EMBO Rep*, Vol.9, No.1, (January 2008), pp.91-96, ISSN 1806-4046

Yi, J. & Luo, J. (2010). SIRT1 and p53, effect on cancer, senescence and beyond. *Biochim Biophys Acta*, Vol.1804, No.8, (May 2008), pp. 1684-1689, ISSN 2047-1503

Yoo, H.Y.; Kumagai, A.; Shevchenko, A.; Shevchenko, A. & Dunphy, W.G. (2004). Adaptation of a DNA replication checkpoint response depends upon inactivation of Claspin by the Polo-like kinase. *Cell*, Vol.117, No.5, (May 2004), pp. 575-588, ISSN 1516-3406

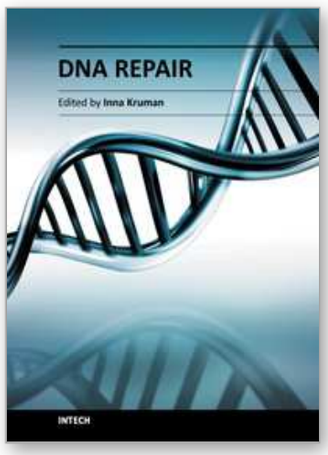
Zhang, Y.; Qu, D.; Morris, E.J.; O'Hare, M.J.; Callaghan, S.M.; Slack, R.S.; Geller, H.M. & Park, D.S. (2006). The Chk1/Cdc25A pathway as activators of the cell cycle in neuronal death induced by camptothecin. *J Neurosci*, Vol.26, No.34, (August 2006), pp. 8819–8828, ISSN 1692-8871

Zhang, Y.; Hefferin, M.L.; Chen, L.; Shim, E.Y.; Tseng, H.M.; Kwon, Y.; Sung, P.; Lee, S.E. & Tomkinson, A.E. (2007). Role of Dnl4-Lif1 in nonhomologous end-joining repair complex assembly and suppression of homologous recombination. *Nat Struct Mol Biol*, Vol.14, No.7, (June 2007), pp.639-46, ISSN 1758-9524

Zhou, B.B. & Elledge, S.J. (2000). The DNA damage response: putting checkpoints in perspective. *Nature,* Vol.408, No.6811, (November 2000), pp. 433–439, ISSN 1110-0718

Zimmermann, K.C.; Bonzon, C. & Green, D.R. (2001). The machinery of programmed cell death. *Pharmacol Ther*, Vol.92, No.1, (October 2001), pp.57-70, ISSN 1175-0036

Ziv, Y.; Bielopolski, D.; Galanty, Y.; Lukas, C.; Taya, Y.; Schultz, D.C.; Lukas, J.; Bekker-Jensen, S.; Bartek, J. & Shiloh, Y. (2006). Chromatin relaxation in response to DNA double-strand breaks is modulated by a novel ATM- and KAP-1 dependent pathway. *Nat Cell Biol*, Vol. 8, No.8, (July 2006), pp. 870–876, ISSN 1686-2143



DNA Repair

Edited by Dr. Inna Kruman

ISBN 978-953-307-697-3
Hard cover, 636 pages
Publisher InTech
Published online 07, November, 2011
Published in print edition November, 2011

The book consists of 31 chapters, divided into six parts. Each chapter is written by one or several experts in the corresponding area. The scope of the book varies from the DNA damage response and DNA repair mechanisms to evolutionary aspects of DNA repair, providing a snapshot of current understanding of the DNA repair processes. A collection of articles presented by active and laboratory-based investigators provides a clear understanding of the recent advances in the field of DNA repair.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Inna I. Kruman (2011). Cell Cycle and DNA Damage Response in Postmitotic Neurons, DNA Repair, Dr. Inna Kruman (Ed.), ISBN: 978-953-307-697-3, InTech, Available from: http://www.intechopen.com/books/dna-repair/cell-cycle-and-dna-damage-response-in-postmitotic-neurons

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen