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TopBP1 in DNA Damage Response

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1. Introduction

DNA, the genetic material of cells, is constantly exposed to a range of endogenous and environmental damaging agents (Jungmichel & Stucki, 2010). DNA molecule is the target of endogenous cellular metabolites such as reactive oxygen species (ROS) (Ciccina & Elledge, 2010; Poehlmann & Roessner, 2010). ROS may cause different alterations in a genome, e.g. simple DNA mutations, DNA single and double strand breaks (SSBs and DSBs, respectively), or more complex changes, including deletions, translocations and fusions (Poehlmann & Roessner, 2010). Alterations may be generated spontaneously due to dNTP misincorporation during DNA replication, interconversion between DNA bases caused by deamination, loss of DNA bases following DNA depurination or depyrimidination and modification of DNA bases by alkylation. Hydrolytic deamination (loss of an amino group) can directly convert one base to another. For example, deamination of cytosine results in uracil and with much lower frequency converts adenine to hypoxanthine. In depurination or depyrimidination, purine or pyrimidine bases are completely removed, leaving deoxyribose sugar depurinated or depyrimidinated that may cause breakage in the DNA backbone (Ciccina & Elledge, 2010; Rastogi et al., 2010). Altogether, it has been estimated that every cell could experience up to 10^5 spontaneous DNA lesions per day (Ciccina & Elledge, 2010). Environmental DNA damage can be produced by physical or chemical sources, such as ionizing radiation (IR), ultraviolet (UV) light from sunlight and organic and inorganic chemical substances (Muniandy et al., 2010; Rastogi et al., 2010; Su et al., 2010). Exposure to ionizing radiation from, e.g. cosmic radiation and medical treatments employing X-rays or radiotherapy inflicts DNA single and double strand breaks, oxidation of DNA bases and DNA-protein crosslinks in the genomic DNA (Ciccina & Elledge, 2010; Su et al., 2010). Ionizing radiation provokes DNA damage directly by energy deposit on the DNA double helix and indirectly by reactive oxygen/nitrogen species (ROS/RNS) (Corre et al., 2010). Ultraviolet radiation (mainly UV-B) is a powerful agent that may lead to the formation of three major classes of DNA lesions, such as cyclobutane pyrimidine dimers (CPDs), pyrimidine 6-4 pyrimidone photoproducts (6-4 PPs) and their Devar isomers (Rastogi et al., 2010). Cells may become transiently exposed to external sources of DNA damage, such as cigarette smoke or various toxic chemical compounds (Jungmichel & Stucki, 2010). Many antineoplastic drugs currently used in cancer treatment express their cytotoxic effects through their ability to directly or indirectly damage DNA and thus resulting in cell death. Major types of DNA damage induced by anticancer treatment include single and double strand breaks, interstrand, intrastrand and DNA-protein crosslinks, as well as interference

with nucleotide metabolism and DNA synthesis (Pallis & Karamouzis, 2010). Alkylating agents, such as methyl methanesulphonate (MMS), tenozalamide, streptozotocin, procarbazine, dacarbazine, ethylnitrosourea, diethylnitrosamine and nitrosoureas attach alkyl groups to DNA bases, while crosslinking agents such as mitomycin (MMC), cisplatin, psoralen and nitrogen mustard induce covalent links between bases of the same DNA strand (intrastrand crosslinks) or of different DNA strands (interstrands crosslinks) (Ciccia & Elledge, 2010; Muniandy et al., 2010; Pallis & Karamouzis, 2010). Other chemical agents, such as topoisomerase inhibitors induce the formation of single or double strand breaks by trapping topoisomerase-DNA covalent complexes (Ciccia & Elledge, 2010). Camptothecin and novel noncamptothecins in clinical development target eukaryotic IB type topoisomerase (Topo I), whereas human IIA type topoisomerases (Topo II α and Topo II β) are the targets of widely used anticancer agents, such as etoposide, anthracyclines (doxorubicin, daunorubicin) and mitoxantrone (Pommier et al., 2010).

The biochemical consequences of DNA lesions are diverse and range from obstruction of fundamental cellular pathways like transcription and replication to fixation of mutations. Cellular malfunctioning, cell death, aging and cancer are the phenotypical consequences of DNA damage accumulation in the genome. To counteract DNA damage, repair mechanisms specific for many types of lesions have evolved. Mismatched DNA bases are replaced with correct bases by mismatch repair (MMR) (Ciccia & Elledge, 2010). The bases excision repair (BER) exerts its biological role by removing bases that have been damaged by alkylation, oxidation, ring saturation, as well as a short strand that contains the damaged bases. BER also plays an important role in the repair of DNA single strand breaks generated spontaneously or induced by exogenous DNA-damaging factors such as cytotoxic anticancer agents (Pallis & Karamouzis, 2010). DNA single strand breaks may be also repaired by single strand break repair (SSBR) (Ciccia & Elledge, 2010). Nucleotide excision repair (NER) is a highly conserved pathway that repairs DNA damage caused by UV radiation, mutagenic chemicals or chemotherapeutic drugs that form bulky DNA adducts (Pallis & Karamouzis, 2010). The most toxic lesions in DNA are double strand breaks where the phosphate backbones of the two complementary DNA strands are broken simultaneously (Hiom, 2010). Double strand breaks are repaired by two major repair pathways depending on the context of DNA damage, i.e. homologous recombination (HR) and nonhomologous end-joining (NHEJ) (Hiom, 2010; Pallis & Karamouzis, 2010). While NHEJ promotes potential inaccurate rejoining of double strand breaks, HR precisely restores genomic sequence of the broken DNA ends by using sister chromatids as template for repair (Ciccia & Elledge, 2010). Additionally, some specialized polymerases can temporarily take over lesion-arrested DNA polymerases during S phase, in a mutagenic mechanism called translesion synthesis (TLS). Such polymerases only work if a more reliable system, such as homologous recombination, cannot avoid stumpled DNA replication (Essers et al., 2006).

DNA repair is carried out by the plethora of enzymatic activities that chemically modify DNA to repair DNA damage, including nucleases, helicases, polymerases, topoisomerases, recombinases, ligases, glycosylases, demethylases, kinases and phosphatases. These repair tools must be precisely regulated, because each in its own right can wreak havoc on the integrity of DNA if misused or allowed to gain access to DNA at the inappropriate time or place (Ciccia & Elledge, 2010). The DNA repair mechanisms function in conjunction with an intricate machinery of damage sensors, responsible of a series of phosphorylations and chromatin modifications that signal to the rest of the cell the presence of lesions on DNA.

Together DNA repair mechanisms and DNA damage signaling system form a molecular shield against genomic instability.

2. DNA damage checkpoints

To maintain genomic integrity and faithful transmission of fully replicated and undamaged DNA during cell division, eukaryotic organisms evolved a complex DNA surveillance program (Reinhardt & Yaffe, 2009). Apart from DNA repair mechanisms mentioned above, DNA damage response represents a complex network of multiple signaling pathways involving cell cycle checkpoints, transcriptional regulation, chromatin remodeling and apoptosis (Dai & Grant, 2010; Danielsen et al., 2009). In response to DNA damage, eukaryotic cells activate a complex protein kinase-based signaling network to arrest progression through the cell cycle. Activation of signaling cascade recruits repair machinery to the site of DNA damage, provides time for repair or if the genotoxic insult exceeds repair capacity, additional signaling pathways leading to cell death, presumably *via* apoptosis, are activated (Reinhardt et al., 2010; Reinhardt & Yaffe, 2009). When DNA damage occurs, distinct, albeit overlapping and cooperating checkpoint pathways are activated, which block S phase entry (the G1/S phase checkpoint), delay S phase progression (the S phase checkpoints) or prevent mitotic entry (the G2/M phase checkpoint). The primary G1/S cell cycle checkpoint controls the commitment of eukaryotic cells to transition through G1 phase and enter DNA synthesis phase. In G1 phase, cells have to make a decision between continuing proliferation or exiting the cell cycle to become quiescent differentiated, senescent or apoptotic (Dijkstra et al., 2009). The S phase checkpoints are activated when DNA damage occurs during DNA synthesis, or when DNA replication intermediates accumulate. Depending on the type and magnitude of damage, cells activate one of three distinct S phase checkpoint pathways: an intra-S phase checkpoint induced by double strand breaks, a replication checkpoint by the stalled replication fork and the S/M checkpoint blocking premature mitosis. The S/M checkpoint differs from the well-defined G2/M checkpoint. The S/M checkpoint is ATM-independent, it is measurable only several hours after DNA damage and is initiated in cells that were in S phase at the time of insult (Hurley & Bunz, 2009; Rodriguez-Bravo et al., 2007). When cells encounter DNA damage in G2, the G2/M checkpoint stops the cell cycle to prevent the cell from entering mitosis. Defects in cell cycle arrest at the respective checkpoint are associated with genome instability and oncogenesis (Houtgraaf et al., 2006).

3. Checkpoint signaling cascade

Proteins of checkpoint signaling pathways are classified as sensors, transducers and effectors (Fig. 1). Following DNA damage, sensor multiprotein complexes, e.g. MRN (MRE11-Rad50-NBS1) or 9-1-1 (Rad9-Rad1-Hus1) recognize damage and recruit proximal transducers, i.e. ATM (ataxia telangiectasia mutated) and ATR (ATM and Rad3-related) kinases to lesions where they are initially activated. ATM and ATR transduce signals to distal transducer, i.e. checkpoint kinases Chk1 and Chk2 (Dai & Grant, 2010; Niida & Nakanishi, 2006). Chk1 and Chk2 kinases, distal transducers, transfer the signal of DNA damage to effectors, such as Cdks (cyclin-dependent kinases), Cdc25 (cell division cycle 25) and p53 (Dai & Grant, 2010; Houtgraaf et al., 2006; Nakanishi, 2009; Nakanishi et al., 2009). The key difference between ATM and ATR is the signal that activates them. ATM is

activated exclusively by DSBs, which can arise from endogenous (ROS, eroded telomeres, intermediates of immune and meiotic recombination) or exogenous (IR, genotoxic drugs) sources (Lopez-Contreras & Fernandez-Capetillo, 2010). In contrast, ATR responds to many types of DNA damage and replication stress including breaks, crosslinks and base adducts. ATR senses abnormally long stretches of single strand DNA that arise from the functional uncoupling of helicase and polymerase activities at replication forks or from the processing of DNA lesions such as the resection of DSBs (Mordes & Cortez, 2008). ATR but not ATM is essential for viability. The early embryonic death in ATR knockout mice shows that ATR is essential for cell growth and differentiation at an early stage of development (Smits et al., 2010). In addition, disruption of ATR in mouse or human cells results in cell cycle arrest or death, even without exogenous DNA damage (Cortez et al., 2001; Smits et al., 2010). Although complete inactivation of ATR is lethal, a hypomorphic mutation was found in humans suffering from the rare autosomal recessive disorder, Seckel syndrome, characterized by growth retardation and microcephaly. In homozygosity, that mutation affects ATR splicing which results in the reduction of ATR protein levels to almost undetectable, yet the remaining protein is sufficient for viability (Kerzendorfer & O'Driscoll, 2009; O'Driscoll et al., 2004; Smits et al., 2010).

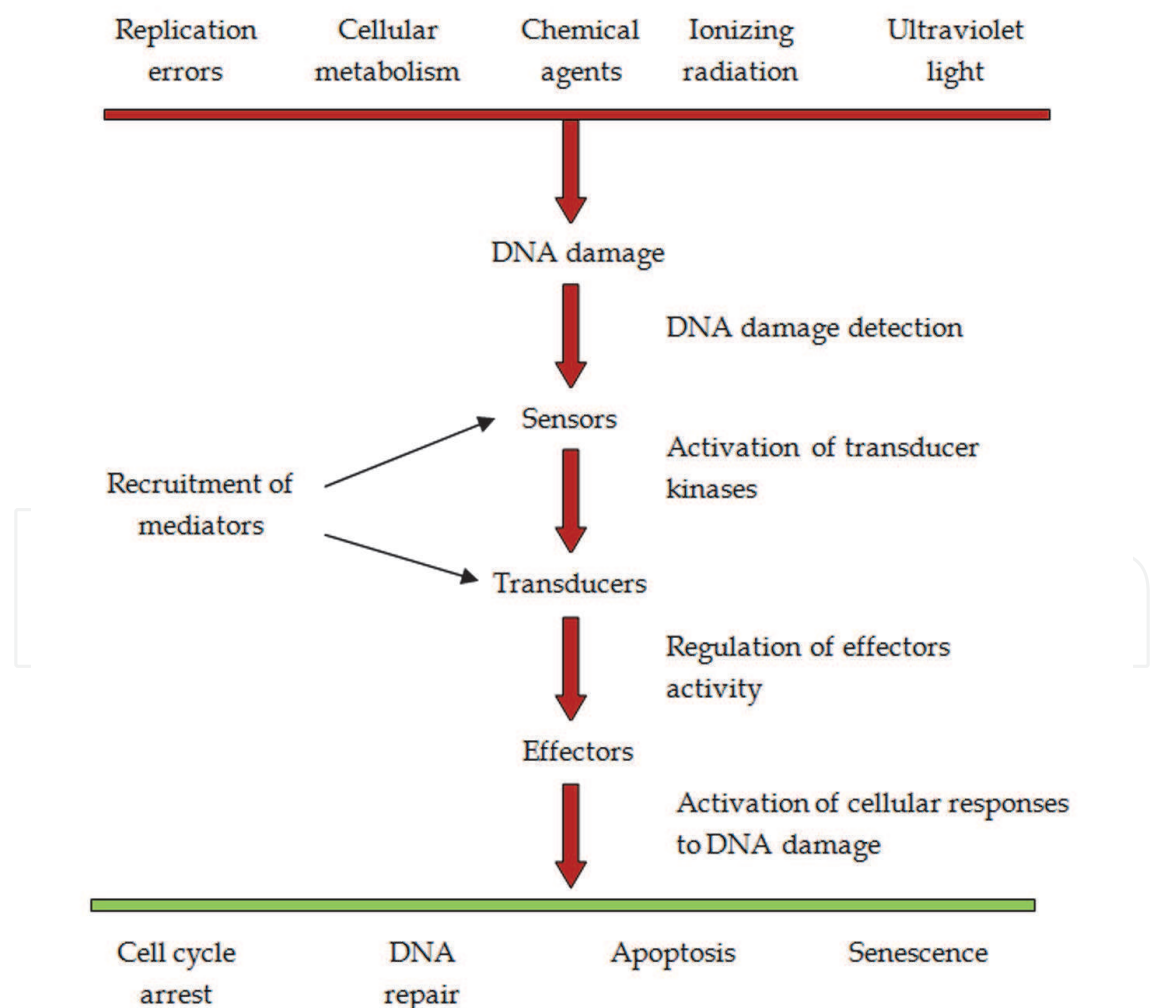


Fig. 1. Signal transduction of DNA damage response (DDR)

In addition to damage sensors and signal transducers, many other proteins called mediators are involved in DNA damage response. Mediators are mostly cell cycle specific proteins associated with damage sensors and signal transducers at particular phases of the cell cycle and, as a consequence, help provide signal transduction specificity. ATM and ATR phosphorylate most of these mediators. Well-known examples of mediators are 53BP1 (p53 binding protein 1), MDC1 (mediator of DNA damage checkpoint 1), BRCA1 (breast cancer 1), SMC1 (structural maintenance of chromosomes 1), FANCD2 (Fanconi anemia, complementation group D2), Claspin, Timeless, Tipin and histone H2AX (Dai & Grant, 2010; Houtgraaf et al., 2006; Yang et al., 2010). This group of regulators involves also TopBP1 protein (topoisomerase II β binding protein 1) (Cimprich & Cortez, 2008). Certain molecules may have multiple functions in this signal transduction pathway. For example ATM and ATR can simultaneously act as a sensor and a transducer. Consequently, signal transduction in DNA damage response is not one-dimensional but a complex network of interacting molecules (Poehlmann & Roessner, 2010).

4. Structure of TopBP1 and its similarity to BRCA1

Topoisomerase II β binding protein 1 (TopBP1) has been identified as a protein interacting with topoisomerase II β in a yeast two-hybrid screen (Morishima et al., 2007; Yamane et al., 1997). Interaction with topoisomerase II β is mediated by carboxyl-terminal region (aa 862-1522) of TopBP1 *in vitro* (Honda et al., 2002; Yamane et al., 1997). TopBP1 shares sequence and structural homologies with *Saccharomyces cerevisiae* Dpb11, *Schizosaccharomyces pombe* Cut5/Rad4, *Drosophila melanogaster* Mus101 and *Xenopus levis* Xmus101 (Araki et al., 1995; Garcia et al., 2005; Morishima et al., 2007; Ogiwara et al., 2006; Parrilla-Castellar & Karnitz, 2003; Taricani & Wand, 2006; van Hatten et al., 2002).

TopBP1 protein seems to be essential for maintenance of chromosomal integrity and cell proliferation. This protein appeared to be involved in DNA damage response, DNA replication checkpoint, chromosome replication and regulation of transcription (Bang et al., 2011; Garcia et al., 2005; Jeon et al., 2011). TopBP1 knockout mouse exhibits early embryonic lethality at the peri-implantation stage and TopBP1 deficiency induces cellular senescence in primary cells (Bang et al., 2011; Jeon et al., 2011).

TopBP1 gene comprising 28 exons is located on chromosome 3q22.1 and encodes a 1522 amino acid protein (180 kDa) (Karppinen et al., 2006; Xu & Leffak, 2010; Yan & Michael, 2009a,b). The structure of protein is characterized by the presence of interspersed throughout the whole molecule eight copies of the BRCT domain (C-terminal domain of BRCA1), originally identified as a tandemly repeated sequence motif in carboxyl-terminal region of BRCA1 (Fig. 2) (Glover, 2006; Lelung et al., 2010; Wright et al., 2006; Yamane et al., 1997; Yamane & Tsuruo, 1999). BRCT domains, about 90 amino acids in length, are hydrophobic and are involved in an interaction with other proteins and phosphorylated peptides, as well as in an interaction with single- and double-stranded DNA (Glover, 2006; Rodriguez et al., 2003; Wright et al., 2006). A sequence analysis has shown that BRCT repeats are present in a large family of proteins that are implicated in the cellular response to DNA damage. Next to BRCA1 and TopBP1, members of this family include several proteins that are directly linked to DNA repair and cell cycle checkpoints, such as XRCC1 (X-ray cross complementing protein 1), DNA ligase III and IV, MDC1, BARD1 (BRCA1 associated RING domain protein 1), Rad9, MCPH1 (microcephalin 1) (Glover, 2006; Glover et al., 2004; Hou et al., 2010; Yamane et al., 2002; Yamane & Tsuruo, 1999; Yang et al., 2008).

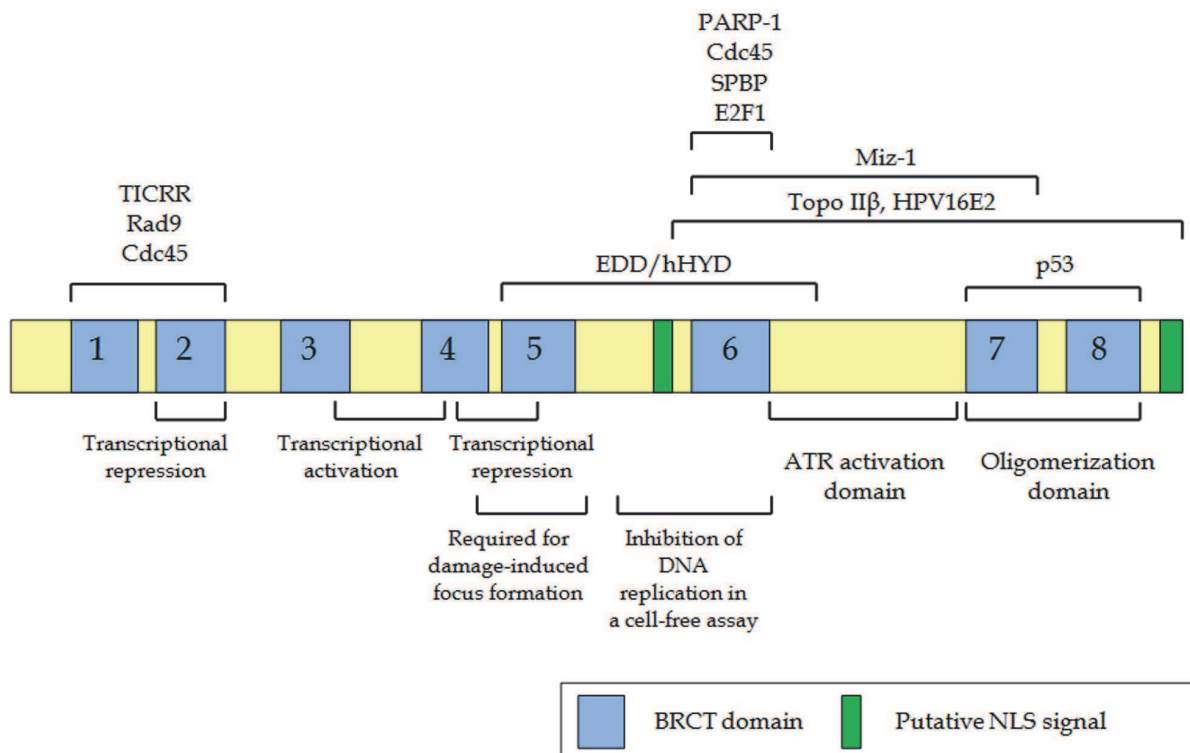


Fig. 2. TopBP1 functional domains and sites of interacting proteins

The carboxyl-terminal region of TopBP1 containing two BRCT domains shows considerable similarity to the corresponding part of BRCA1 (Going et al., 2007; Karppinen et al., 2006; Makiniemi et al., 2001; Morris et al., 2009; Yamane et al., 1997, 2003). Apart from structural similarity TopBP1 shares many other common features with BRCA1. The expression of both proteins is the highest in S phase cells. TopBP1 and BRCA1 are phosphorylated by ATM in response to DNA damage and DNA replication stress and they both colocalize with PCNA (proliferating cell nuclear antigen) at stalled replication forks (Makiniemi et al., 2001; Yamane et al., 2003). The localization patterns of TopBP1 and BRCA1 have similarities also during late mitosis, as well as in meiotic prophase I (Karppinen et al., 2006; Reini et al., 2004). Furthermore, the two proteins have been shown to possess overlapping functions in G2/M checkpoint regulation (Karppinen et al., 2006). Yamane et al. (2003) demonstrated that a BRCA1-mutant or a TopBP1-reduced background results in only partial abrogation at G2/M checkpoint, whereas the combined TopBP1-reduced and BRCA-mutant background result in the nearly complete abrogation. In response to ionizing radiation TopBP1 and BRCA1 colocalize with Rad50, ATM, Rad9, BLM (Bloom syndrome protein), PCNA, NBS1 (Nijmegen breakage syndrome 1) and γ H2AX in IR-induced nuclear foci (Germann et al., 2010; Xu et al., 2003).

TopBP1 protein possesses transcriptional-activation domain and two surrounding repressor domains and can play a role in regulating transcription directly (Fig. 2). A transcriptional-activation domain is located between amino acids 460 - 591 and partly contains BRCT4 domain. This region essential for transactivation is rich in hydrophobic amino acids interspersed with acidic residues, typical of identified transcriptional domains. On amino-terminal side of the transcriptional activation domain, Wright et al., (2006) identified a repressor domain involving BRCT2 that is able to repress the TopBP1 transcriptional

activation domain. Additionally, another repressor domain exists on the C terminus of the activation domain, which requires amino acids 586 – 675. TopBP1 protein exerts its function in the nucleus and the carboxyl-terminal region of TopBP1 contains two putative nuclear localization signals (Going et al., 2007; Liu et al., 2003; Sokka et al., 2010). Liu et al. (2003) showed that deletion of the BRCT7-8 and NLS region of TopBP1 induces cytoplasmic localization of the protein. Aberrant expression and intracellular localization of TopBP1 is observed immunohistochemically in breast cancer (Going et al., 2007).

5. TopBP1 as multifunctional protein

TopBP1 protein has been proposed as a transcriptional repressor of E2F1 and transcriptional co-activator with HPV16 E2 (Liu et al., 2004; Wright et al., 2006; Yoshida & Inoue, 2004). The E2F transcription factors E2F1 to E2F6 bind to E2F sites in promoters and regulate the expression of a large array of genes that encode proteins important for DNA replication and cell cycle progression. In response to growth signals, activated G1 cyclin-dependent kinase phosphorylate retinoblastoma protein (Rb) and release E2F from Rb binding. This event is critical in controlling G1/S transition. Among the E2F family members, E2F1, E2F2 and E2F3 are transcriptional activators and are induced in response to growth stimulation, with peak accumulation at G1/S. Together, they are essential for cellular proliferation since a combined mutation of E2F1, E2F2 and E2F3 completely blocks cellular proliferation. In contrary, E2F4 and E2F5 act mainly as transcriptional repressors (Chen et al., 2009; Liu et al., 2003; Poznic, 2009). TopBP1 protein interacts with E2F1 through the sixth BRCT motif of TopBP1 and N terminus of E2F1 (Fig. 2) (Lelung et al., 2010; Liu et al., 2003). This interaction is induced by ATM-mediated phosphorylation of E2F1 at Ser31 during DNA damage. By this interaction, the transcriptional activity of E2F1 is repressed and E2F1 is recruited to DNA damage induced nuclear foci (Liu et al., 2003). Moreover, the interaction between TopBP1 protein and E2F1, as well as the repression of E2F1 activity, are specific for E2F1 but are not seen in E2F2, E2F3 and E2F4, suggesting that TopBP1 is E2F1 exclusive regulator (Liu et al., 2004). Liu et al. (2004) showed that E2F1 is also regulated by a novel Rb-independent mechanism, in which TopBP1 protein recruits Brg1/BRM (Brahma-related gene 1/Brahma protein), a central subunit of the SWI/SNF (SWItch/sucrose nonfermentable) chromatin modeling complex, to specifically inhibit E2F1 transcriptional activity. This regulation appeared to be critical for E2F1-dependent apoptosis control during S phase and DNA damage. On the other hand, TopBP1 is induced by E2F1 and interacts with E2F1 during G1/S transition. Thus, E2F1 and TopBP1 form a feedback regulation to prevent apoptosis during DNA replication (Liu et al., 2003).

Human papillomaviruses (HPVs) are causative agents in a number of human diseases the most common of which is cervical cancer. More than 95% of cervical carcinomas harbor HPV sequences and HPV16 is most frequently detected. The HPV16 E2 protein is a 43 kDa phosphoprotein that binds as a homodimer to 12 bp palindromic DNA sequences in the transcriptional control region of the viral genome. After binding, E2 can either upregulate or repress transcription from the adjacent promoter depending on cell type and protein levels and this regulation controls the expression of viral oncoproteins E6 and E7. The carboxyl-terminal portion of TopBP1 interacts with E2 and TopBP1 protein can enhance the ability of E2 to activate transcription and replication (Fig. 2) (Boner et al., 2002).

TopBP1 protein also interacts with SPBP (stromelysin-1 platelet-derived growth factor (PDGF) responsive element binding protein) and enhances the transcriptional activity of Ets1 on the *Myc* and *MMP-3* promoters *in vitro* and *in vivo* (Sjottem et al., 2007). This

interaction is mediated by ePHD (extended plant homeodomain) domain of SPBP and the BRCT6 domain of TopBP1 (Sjottem et al., 2007). SPBP a 220 kDa ubiquitously expressed nuclear protein is shown to intensify or repress the transcriptional activity. Originally SPBP was identified as a protein involved in transcriptional activation of matrix metalloproteinase-3 (MMP3), stromelysin-1 promoter *via* the specific sequence element SPRE (stromelysin-1 PDGF responsive element) (Rekdal et al., 2000; Sonz et al., 1995). Later SPBP was found to act as a transcriptional coactivator since it enhanced the transcriptional activity of the positive cofactor and RING finger protein SNURF/RNF4 (small nuclear RING finger protein/RING finger protein 4) and of certain transcription factors, such as Sp1 (specificity protein 1), Ets (E-twenty-six specific), Pax6 (paired box gene 6) and Jun (Lyngso et al., 2000; Rekdal et al., 2000; Sjottem et al., 2007). On the other hand, SPBP appears to act as phosphoserine-specific repressor of estrogen receptor α (ER α) (Gburick et al., 2005; Sjottem et al., 2007).

In unstressed cells TopBP1 protein associates with Miz-1 (Myc interacting zinc finger protein 1). BRCT6 and BRCT7 of TopBP1 are required and largely sufficient to mediate the interaction with Miz-1 (Fig. 2) (Herold et al., 2002, 2008; Wenzel et al., 2003). This zinc finger protein that contains an amino-terminal POZ (poxvirus and zinc finger) was initially described as a protein that interacts with C terminus of Myc oncoprotein (Courapied et al., 2010; Herold et al., 2008). Miz-1 protein activates transcription of genes encoding the cell cycle inhibitors p15^{INK46} and p21^{Cip1}, leading to cell cycle arrest. Miz-1 can also repress transcription when it forms complexes with Myc and other transcription factors (Herold et al., 2002, 2008; Wenzel et al., 2003). In response to UV irradiation Miz-1 is released from an inhibitory complex formed with TopBP1 and binds to the start site of p21^{Cip1} promoter. Thus the dissociation of TopBP1 from Miz-1 may facilitate the induction of p21^{Cip1} (Herold et al., 2002, 2008; Wenzel et al., 2003). On the other hand, Miz-1 is required for the binding of TopBP1 to chromatin and to protect TopBP1 from proteasomal degradation. TopBP1 protein that is not bound to chromatin is ubiquitinated by HECTH9 (HUWE1) ligase. Expression of Myc leads to dissociation of TopBP1 from chromatin and reduces the amount of total TopBP1 (Herold et al., 2008). Furthermore, TopBP1 has been shown to be ubiquitinated by ubiquitin ligase EDD/hHYD (E3 identified by differential display/ human hyperplastic discs), another HECT (homologous to E6-AP C-terminus) domain E3 enzymes. The HECT E3 ubiquitin-protein ligases have been found from yeast to humans. They are characterized by the HECT domain. EDD/hHYD interacts with the minimal region of the amino acids 661 – 1080 including BRCT5 and BRCT6 of TopBP1 protein. TopBP1 was found to be usually ubiquitinated and degraded by the proteasome in intact cells. X-irradiation seems to abolish TopBP1 degradation and induce the stable complex formation of TopBP1 with other molecules in DNA double strand breaks (Honda et al., 2002; Scheffrer & Staub, 2007). Binding of the transcription factor Miz-1 and TopBP1 protein is also regulated by TopBP1 ADP-ribosylation (Table 1). ADP-ribosylation is one of the post-translational protein modifications. Polymers of ADP-ribose are formed from donor NAD⁺ molecules and covalently attached to glutamic acid, aspartic acid or lysine residues of a target protein. The process is catalyzed by the poly(ADP-ribose) polymerase (PARP) family of proteins. The best known of these proteins is PARP1 which is implicated in transcription, chromatin remodeling, apoptosis and DNA repair (Sokka et al., 2010; Woodhouse & Dainov, 2008). TopBP1 and PARP-1 interact both *in vitro* and *in vivo*. The interaction depends on sixth BRCT domain of TopBP1 and on the fact that this domain is ADP-ribosylated by PARP-1. The post-translational ADP-ribosylation of TopBP1 by PARP1 may support the release of

Miz-1 from the complex with TopBP1 (Wollmann et al., 2007; Yamane et al., 1997; Yamane & Tsuruo, 1999).

Site(s)	Modification	Enzyme	Reference
Y in BRCT1-4 region	phosphorylation	c-Abl	Zeng et al., 2005
S214	phosphorylation	ATM/ATR	Matsuoka et al., 2007
S492	phosphorylation	ATM	Sokka et al., 2010
S405	phosphorylation	ATM/ATR	Matsuoka et al., 2007
S409	phosphorylation	ATM/ATR	Matsuoka et al., 2007
S554	phosphorylation	ATM	Sokka et al., 2010
K581	acetylation	N/D	Choudhary et al., 2010
S766	phosphorylation	ATM	Sokka et al., 2010
S805	phosphorylation	N/D	Beausoleil et al., 2006; Wang et al., 2008
T848	phosphorylation	N/D	Dephoure et al., 2008
S860	phosphorylation	N/D	Dephoure et al., 2008
S861	phosphorylation	N/D	Dephoure et al., 2008
S864	phosphorylation	N/D	Dephoure et al., 2008
S888	phosphorylation	N/D	Beausoleil et al., 2006; Dephoure et al., 2008; Wang et al., 2008
900-991 (BRCT6)	ADP-ribosylation	PARP-1	Wollmann et al., 2007; Yamane et al., 1997; Yamane & Tsuruo, 1999
T975	phosphorylation	ATM/ATR	Matsuoka et al., 2007
S1002	phosphorylation	N/D	Dephoure et al., 2008; Wang et al., 2008
S1051	phosphorylation	ATM/ATR	Matsuoka et al., 2007
T1062	phosphorylation	ATM	Sokka et al., 2010
T1086	phosphorylation	ATM/ATR	Matsuoka et al., 2007
S1138	phosphorylation	ATM	Yoo et al., 2007
S1159	phosphorylation	Akt	Liu et al., 2006

Table 1. Post-translation modifications of the human TopBP1 protein (N/D – not determined)

Apart from the mentioned above ADP-ribosylation, TopBP1 undergoes other post-translational modifications, such as acetylation and phosphorylation (Table 1). Lysine acetylation is a reversible post-translational modification, which neutralizes the positive charge of this amino acid changing protein function. Lysine acetylation preferentially targets large macromolecular complexes involved in diverse cellular processes, such as chromatin remodeling, cell cycle, splicing, nuclear transport and actin nucleation. Acetylation of TopBP1 protein occurs at position 581 but the exact role of this modification remains to be resolved (Choudhary et al., 2010).

TopBP1 is a phosphoprotein and is phosphorylated in response to DNA damage (Makiniemi et al., 2001; Yamane et al., 2003). After DNA damage, TopBP1 protein localizes at IR-induced nuclear foci and is phosphorylated by ATM kinase (Yamane et al.,

2003). Human TopBP1 is phosphorylated at several S/TQ sites, which are consensus sequences of PIKK (phosphatidylinositol 3-kinase-related kinase) targets (Hashimoto et al., 2006; Matsuoka et al., 2007). However, the phosphorylation of TopBP1 protein occurs mostly on serine and to a lesser extent on threonine (Makiniemi et al., 2001). TopBP1 protein is also phosphorylated by Akt *in vitro* and *in vivo* on Ser1159. Phosphorylation by Akt kinase induces oligomerization of TopBP1 through its seventh and eighth BRCT domains. The Akt-dependent oligomerization is crucial for TopBP1 to interact with E2F1 and repress its activity. TopBP1 phosphorylation by Akt is also required for interaction between TopBP1 and Miz-1 or HPV16 E2 and repression of Miz-1 transcriptional activity, suggesting a general role for TopBP1 oligomerization in the control of transcription factors (Liu et al., 2006a).

The other TopBP1 interacting proteins are PML (promyelocytic leukemia protein), TICRR (TopBP1-interacting, checkpoint and replication regulator) and p53. PML is a multifunctional protein that plays essential roles in cell growth regulation, apoptosis, transcriptional regulation and genome stability. PML tumor suppressor gene is consistently disrupted by t(15;17) in patients with acute promyelocytic leukemia. PML colocalizes and associates *in vivo* with TopBP1 in response to ionizing radiation and both proteins colocalize with Rad50, BRCA1, ATM, Rad9 and BLM. PML plays a role in regulation of TopBP1 functions by association and stabilization of the protein in response to IR-induced DNA damage (Xu et al., 2003). TICRR is required to prevent mitotic entry after treatment with ionizing radiation. TICRR deficiency is embryonic-lethal in the absence of exogenous DNA damage because it is essential for normal cell cycle progression. Specifically, the loss of TICRR impairs DNA replication and disrupts the S/M checkpoint, leading to premature mitotic entry and mitotic catastrophe. TICRR associates with TopBP1 *in vivo* and this interaction requires the two N-terminal BRCT domains. Sansam et al. (2010) showed that interaction between TICRR and TopBP1 is essential for replication preinitiation complex. TopBP1 is also involved in regulation of p53 activity. The regulation is mediated by an interaction between the seventh and eighth BRCT domains of TopBP1 and the DNA binding domain of p53, leading to inhibition of p53 promoter binding activity. Thus, TopBP1 may inhibit expression of several canonic p53 target genes including GADD45 (growth arrest and DNA damage protein 45), p21^{Cip1}, PUMA (p53 upregulated modulator of apoptosis), NOXA, BAX (Bcl-2 associated X protein), IGFBP3 (insulin-like growth factor binding protein 3). The repression of p53 proapoptotic genes such as NOXA, PUMA and BAX suggests that TopBP1 can inhibit p53-mediated apoptosis during DNA damage. Deregulation of this control may have pathological consequences (Liu et al., 2009).

TopBP1 also plays a role in DNA replication and S phase progression. Expression of TopBP1 mRNA and protein is induced concomitantly with S phase entry (Makiniemi et al., 2001). Neutralizing TopBP1 with a polyclonal antiserum raised against the sixth BRCT domain inhibits replicative DNA synthesis in HeLa cell nuclei *in vitro*. This may indicate that the sixth BRCT domain is critical for replication activity, possibly *via* interaction with crucial replication factors (Makiniemi et al., 2001; Schmidt et al., 2008). The physical interaction between TopBP1 and polymerase ϵ also implies an involvement of TopBP1 in replication (Makiniemi et al., 2001). The loading of Cdc45 (cell division cycle 45) onto chromatin is critical for loading various replication proteins, including DNA polymerase α , DNA polymerase ϵ , RPA (replication protein A) and PCNA. Human TopBP1 recruits Cdc45 to origins of DNA replication and is required for the formation of the initiation complex of replication in human cells. The first, second and sixth BRCT domains of TopBP1 interact

with Cdc45 and this interaction inhibits transcriptional activity of TopBP1 (Schmidt et al., 2008; Sokka et al., 2010). Both proteins interact exclusively at the G1/S boundary of cell cycle. Only weak interaction could be found at the G2/M boundary (Schmidt et al., 2008).

6. TopBP1 and activation of ATR pathway

The major regulators of DNA damage response are the phosphoinositide 3-kinase (PI3K)-related proteins kinases (PIKKs), including ataxia telangiectasia mutated (ATM) and ATM and Rad3-related (ATR) (Cimprich & Cortez, 2008; Lopez-Contreras & Fernandez-Capetillo, 2010; Takeishi et al., 2010). Other members of this family comprise mTOR (mammalian target of rapamycin), which coordinates protein synthesis and cell growth, DNA-PKcs (DNA-dependent protein kinase catalytic subunit), which promotes DNA double strand break repair by nonhomologous end-joining and SMG1, which regulates nonsense-mediated mRNA decay (Cimprich & Cortez, 2008; Mordes et al., 2008). PIKKs are large proteins (2549 – 4128 amino acids) with common domain architecture. All of them contain a large region of repeated HEAT (Huntington, elongation factor 3, PR65/A, TOR) domains in the N terminus, highly conserved C-terminal kinase domain flanked by FAT (FRAP, ATM, TRAP /FKBP-rapamycin associated protein, ATM, *trp* RNA binding attenuation protein) and FATC (FAT C terminus) and PIKK regulatory domain (PRD) between the kinase and FATC domains (Cimprich & Cortez, 2008; Lopez-Contreras & Fernandez-Capetillo, 2010; Mordes et al., 2008). PRD, poorly conserved between family members but highly conserved within orthologous present in different organisms, is not essential for basal kinase activity but plays a regulatory role in at least ATM, ATR and mTOR (Cimprich & Cortez, 2008). PRD of ATM and mTOR is targeted for post-translational modifications that regulate their activity (Cimprich & Cortez, 2008; Mordes et al., 2008). The N-terminal regions of the kinases mediate interaction with the protein cofactors (Cimprich & Cortez, 2008). ATM and ATR are proteins of about 300 kDa, with a conserved C-terminal catalytic domain that preferably phosphorylates serine or threonine residues followed by a glutamine, i.e. SQ or TQ motif (Choi et al., 2009; Smits et al., 2010).

The initial step in ATR activation is recognition of DNA structures that are induced by the damaging agents (Smits et al., 2010). As mentioned, ATR responds to a wide variety of DNA damage that results in the generation of single-stranded DNA (ssDNA) (Takeishi et al., 2010). In eukaryotes, DNA damage-induced ssDNA is first detected by ssDNA binding protein complex RPA (Fig. 3) (Smits et al., 2010). RPA is a heterotrimeric protein complex composed of three subunits with a size of 70, 30 and 14 kDa, which are known as RPA70, RPA32 and RPA14 or alternatively RPA1, RPA2 and RPA3, respectively (Binz et al., 2004; Broderick et al., 2010; Fanning et al., 2006). RPA is identified to be a crucial component in DNA replication, DNA recombination and DNA repair (Ball et al., 2007; Broderick et al., 2010; Cimprich & Cortez, 2008). After binding to ssDNA either during DNA replication or in response to DNA damage, RPA is phosphorylated and this is thought to be an important event in DNA damage response (Binz et al., 2004; Broderick et al., 2010). Recent observations have shown the involvement of ATR in the RPA2 phosphorylation in response to stalled replication fork in S phase generated by genotoxic agents such as UV (Broderick et al., 2010; Olson et al., 2006).

RPA-coated ssDNA is necessary for ATR activation, but it is not sufficient, as at least several additional factors are also required. This kinase forms a stable complex with ATRIP (ATR-interacting protein) which regulates the localization of ATR to sites of replication stress and

DNA damage. Apart from ATRIP, activation of ATR requires the activator protein TopBP1 which plays dual role in the initiation of DNA replication and DNA damage response (Mordes & Cortez, 2008). ATRIP was identified as a 85 kDa an ATR binding partner that interacts directly with RPA to dock the ATR-ATRIP complex onto ssDNA (Ball et al., 2007; Choi et al., 2010; Kim et al., 2005; Warmerdam & Kanaar, 2010; Yan & Michael, 2009a,b). Independently, the Rad17-RFC complex is loaded onto these sites of damage in RPA-dependent manner (Burrows & Elledge, 2008; Lee & Dunphy, 2010). The Rad17-RFC complex consists of the Rad17 subunit and four additional subunits of replication factor C named from RFC2 to RFC5. During normal replication the RFC complex, containing RFC1 instead of Rad17, plays a role in the loading of PCNA onto DNA. PCNA is a processivity factor for DNA polymerases. Both the Rad17 and RFC complexes require RPA for their loading onto DNA (Majka et al., 2006; Medhurst et al., 2008; Warmerdam & Kanaar, 2010). However, Rad17-RFC requires 5' dsDNA-ssDNA junctions, rather than the 3' ended junctions preferred by PCNA. These types of structures are specifically created by the resection of DSBs, stalled replication forks and UV-induced ssDNA gaps. The Rad17-RFC protein complex facilitates the loading of the Rad9-Rad1-Hus1 (9-1-1) sliding clamp onto the DNA (Choi et al., 2010; Lopez-Contreras & Fernandez-Capetillo, 2010; Van et al., 2010; Warmerdam & Kanaar, 2010; Yan & Michael, 2009a). The necessity of the 9-1-1 complex in the ATR branch was explained by showing that Rad9 recruits the ATR-activator TopBP1 protein near sites of DNA damage, which was consistent with earlier reports showing interaction between Rad9 and TopBP1 protein (Greer et al., 2003; Makiniemi et al., 2001; Smits et al., 2010). The amino-terminal region of TopBP1 protein comprising BRCT1 and BRCT2 binds the C terminus of Rad9. More precisely, the interaction between Rad9 and TopBP1 depends on Ser373 phosphorylation in the C-terminal tail of Rad9 (Delacroix et al., 2007; Kumagai et al., 2006; Lee et al., 2007; Rappas et al., 2011; Smits et al., 2010; Takeishi et al., 2010). Then, TopBP1 protein binds ATR through its ATR activation domain (AAD), located between the sixth and seventh BRCT repeats, in an ATRIP-dependent manner and this interaction is required for ATR stimulation (Kumagai et al., 2006; Mordes et al., 2008; Smits et al., 2010; Takeishi et al., 2010). ATRIP contains a conserved TopBP1 interacting region, required for the association of TopBP1 and ATR and the subsequent TopBP1-mediated triggering of ATR activity (Mordes et al., 2008; Smits et al., 2010).

ATR-mediated activation of Chk1 in response to genotoxic stress requires another protein that binds independently of ATR or Rad17/9-1-1 named Claspin (Kumagai et al., 2004; Liu et al., 2006b; Scora & McGowan, 2009; Smits et al., 2010). Claspin is proposed to function as adaptor molecule bringing ATR and Chk1 together (Kumagai & Dunphy, 2000; Smits et al., 2010). The Claspin-Chk1 interaction depends on ATR-mediated phosphorylation of Claspin and is required for Chk1 phosphorylation by ATR. Subsequent studies identified repeated phosphopeptide motifs in Claspin, which are required for association with phosphate binding sites in the N-terminal kinase domain of Chk1, resulting in full activation of Chk1 (Smits et al., 2010). In response to DNA damage or replication stress activated ATR and its effectors such as Chk1 ultimately slow origin firing and induce cell cycle arrest, as well as stabilize and restart stalled replication forks (Cimprich & Cortez, 2008).

The mechanism by which TopBP1 binding activates ATR is poorly defined. The primary binding site for the activation domain of TopBP1 on the ATR complex is within ATRIP and mutations in this region of ATRIP block activation (Cimprich & Cortez, 2008; Mordes et al., 2008). In addition, activation involves amino acids that are located between the ATR kinase domain and the FATC domain, of PIKK regulatory domain - PRD of ATR. Mutations in this

region have no effect on the basal activity of ATR, although they prevent ATR activation by TopBP1 protein and cause checkpoint defects and mimic a complete deletion of ATR in human somatic cells (Cimprich & Cortez, 2008; Mordes et al., 2008). Thus, efficient activation of ATR by TopBP1 protein may be required to achieve sufficient signal amplification for the proper execution of cellular response to DNA damage (Sokka et al., 2010).

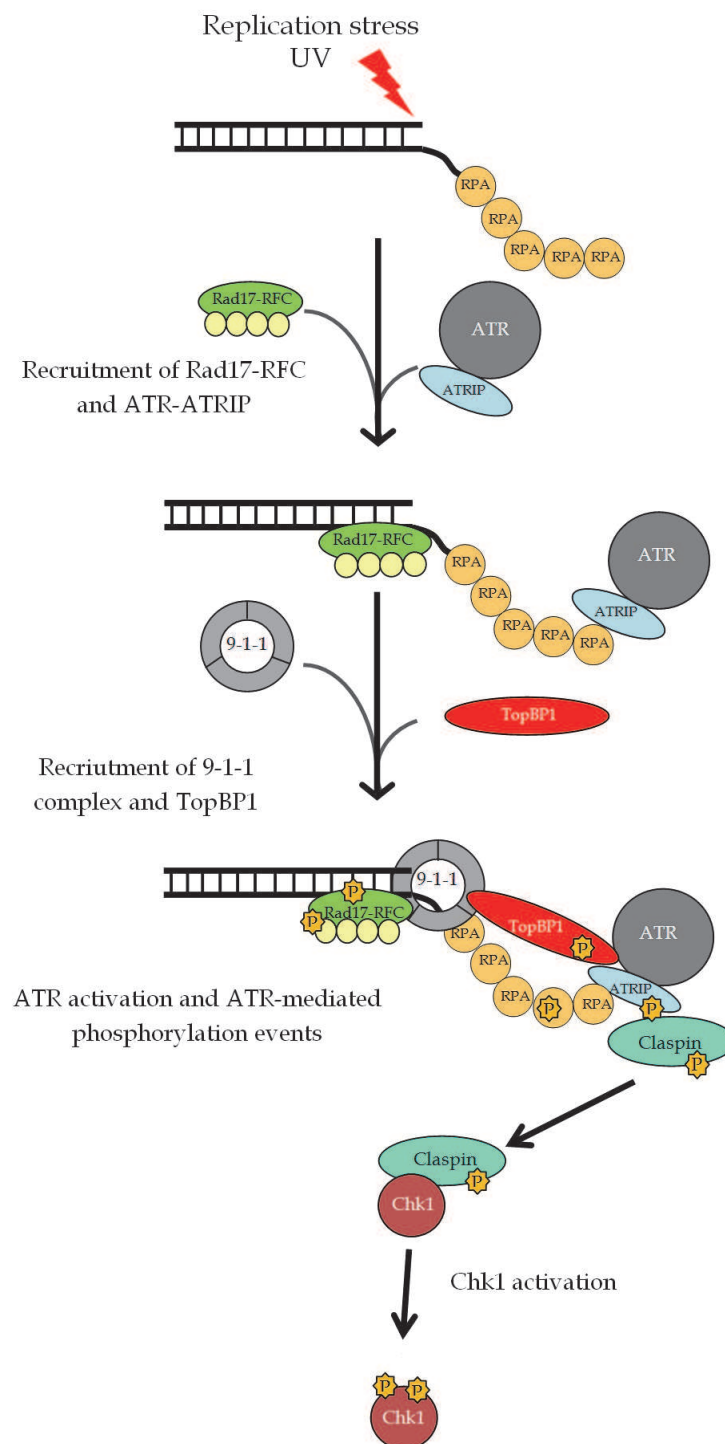


Fig. 3. Role of TopBP1 in activation of ATR pathway in response to replication stress and UV-induced DNA damage

7. Role of TopBP1 in DSB repair

TopBP1 protein also plays a direct and essential role in the pathway that connects ATM to ATR, specifically in response to the occurrence of DSBs in a genome (Yoo et al., 2007). DNA double strand breaks are among the most deleterious DNA lesions that threaten genomic integrity. DSBs are generated not only by exogenous DNA-damaging agents, but also by normal cellular processes, such as V(D)J recombination, meiosis and DNA replication. Furthermore, increased amounts of DSBs are induced by oncogenic stresses during the early stage at tumorigenesis (O'Driscoll & Jeggo, 2005; Shiotani & Zou, 2009; Williams et al., 2007). Two major forms of DSB repair are found within eukaryotic cells: nonhomologous end-joining (NHEJ) and homologous recombination (HR). NHEJ requires several complementary bases for repair and is the predominant form of DSB repair in G₀/G₁ cells. During NHEJ DNA ends are minimally processed to reveal short stretches of complementarity on either side of the break. NHEJ pathway is inherently mutagenic. In contrast, HR pathway predominates during S and G₂ phases and repairs DNA with high fidelity by employing homologous chromosomal or sister chromatid DNA as a template to synthesize new error-free DNA (Williams et al., 2007). The main PIKK that responds to DSBs is ATM, the protein that is defective in the hereditary disorder ataxia telangiectasia (O'Driscoll & Jeggo, 2005). DSBs are recognized by the MRE11-RAD50-NBS1 complex, which promotes the activation of ATM and the preparation of DNA ends for homologous recombination (Fig. 4) (Ciccina & Elledge, 2010; O'Driscoll & Jeggo, 2005; Williams et al., 2007). RAD50 contains ATPase domains that interact with MRE11 (meiotic recombination 11) and associates with the DNA ends. MRE11 has endonuclease and exonuclease activities important for the initial step of DNA end resection that is essential for homologous recombination (Ciccina & Elledge, 2010; Williams et al., 2007). The third subunit of the MRN complex, NBS1, interacts with MRE11 and contains additional protein-protein interaction domains important for MRN function in DNA damage response. NBS1 associates with ATM *via* its C-terminal region, which promotes the recruitment of ATM to DSBs, where ATM is activated by the MRN complex (Ciccina & Elledge, 2010; Jazayeri et al., 2008; Kanaar & Wyman, 2008; Rupnik et al., 2010). Mutations in the human *NBS1* gene result in Nijmegen breakage syndrome (NBS), a rare disorder with abnormal responses to ionizing radiation that resemble those in patients with ataxia telangiectasia (Horton et al., 2011). DNA end resection is regulated by ATM through CtIP (C-terminal binding protein/CtBP interacting protein), which interacts with BRCA1 and MRN (Ciccina & Elledge, 2010). In addition, Exo1 (exonuclease 1), which is involved in the processive stage of DSB resection together with BLM following the initial resection carried out by CtIP, is also stimulated by ATM phosphorylation (Bolderson et al., 2010; Ciccina & Elledge, 2010; Shiotani et al., 2009; Smits et al., 2010). DSB resection and formation of 3' ssDNA ends leads to RPA accumulation. RPA-ssDNA complexes play a critical role in activation of ATR pathway, as described in detail above.

TopBP1 protein appeared to be involved in ATR-dependent DSB repair. In human cells, DSB induces formation of distinct TopBP1 foci that colocalize with BRCA1, PCNA, NBS1, 53BP1 and γ H2AX (Germann et al., 2011). *In vitro* studies showed that in nuclear foci, TopBP1 protein physically associates with NBS1. Several of TopBP1 foci increased and colocalized with NBS1 after ionizing radiation, whereas these nuclear foci were not observed in Nijmegen breakage syndrome cells. The association between TopBP1 and NBS1 involves the first pair of BRCT repeats in TopBP1. In addition the two tandem BRCT repeats of NBS1 are required for this binding. Functional studies with mutated forms of TopBP1 and NBS1

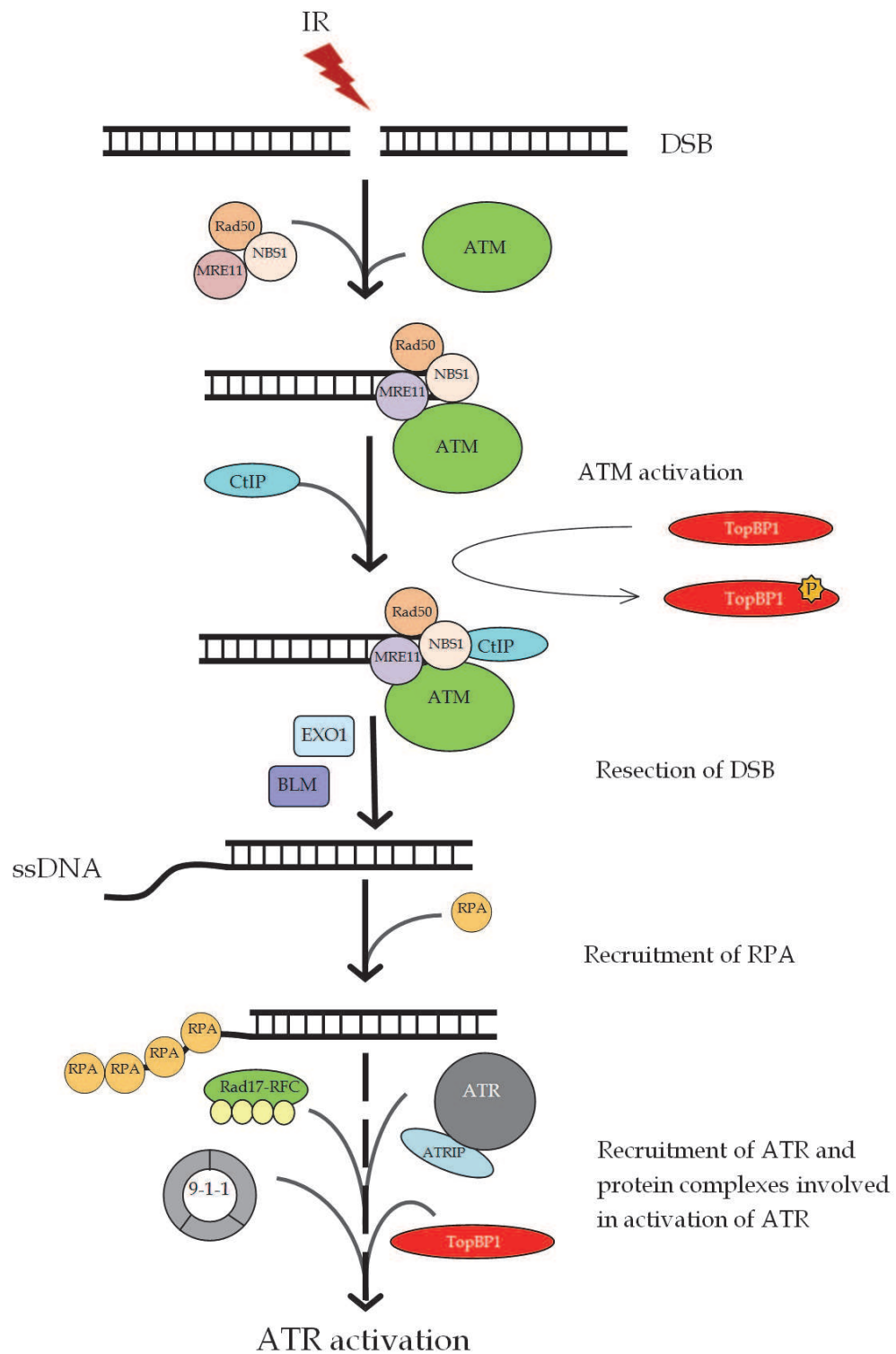


Fig. 4. Role of TopBP1 in ATR activation in response to DNA double strand breaks

suggest that the BRCT-dependent association of these proteins is critical for normal checkpoint response to DSB (Morishima et al., 2007; Yoo et al., 2009). The MRN complex is a crucial mediator in the process whereby ATM promotes the TopBP1-dependent activation of ATR-ATRIP in response to DSBs (Morishima et al., 2007; Yoo et al., 2009). In *Xenopus* egg extracts, ATM associates with TopBP1 protein and phosphorylates it on Ser1131. This

phosphorylation enhances the capacity for TopBP1 protein to activate ATR-ATRIP (Yoo et al., 2009). Yoo et al. (2009) showed that ATM can no longer interact with TopBP1 protein in NBS1-depleted egg extracts. Thus, the MRN complex helps to bridge ATM and TopBP1 together. ATM contributes to the activation of ATR through two collaborating mechanisms. First, ATM helps to create appropriate DNA structures that trigger activation of ATR. Second, ATM strongly stimulates the function of TopBP1 protein *via* its phosphorylation that directly carries out the ATR activation (Yoo et al., 2007).

8. Conclusion

DNA is continuously exposed to a range of damaging agents, including reactive cellular metabolites, environmental chemicals, ionizing radiation and UV light. To prevent loss or incorrect transmission of genetic information and development of abnormalities and tumorigenesis all cells have evolved DNA damage response pathways to maintain their genome integrity. The DNA damage response involves the sensing of DNA damage signal to a network of cellular pathways, including cell cycle checkpoint, DNA repair and apoptosis. TopBP1 protein was first identified as an interacting partner for topoisomerase II β . This protein shares structural and functional similarities with BRCA1 and plays a critical role in the DNA damage response and checkpoint control. TopBP1 is essential for ATR activation in response to replication stress and UV-induced damage and also plays a direct role in the pathway that connects ATM to ATR in response to DSBs. The biological functions of TopBP1 protein, as well as its close relation with BRCA1 suggest a crucial role of TopBP1 in the maintenance of genome integrity and cell cycle regulation.

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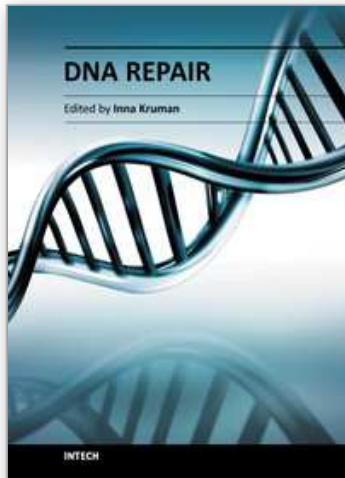
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