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The Potential Roles of DNA-Repair Proteins in Centrosome Maintenance

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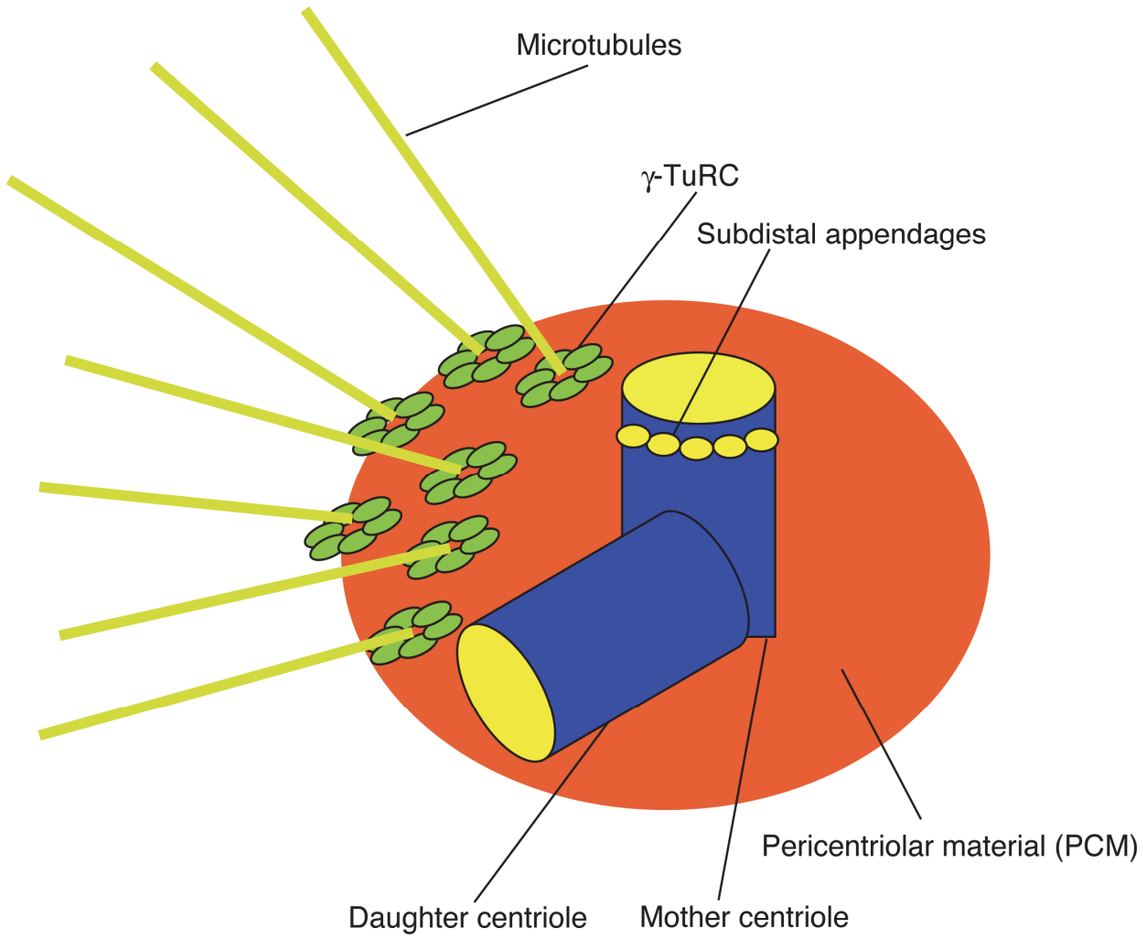
1. Introduction

The centrosome, an organelle that regulates microtubules, is necessary for proper cell division in mammalian cells (Doxsey, 2001; Nigg, 2002, 2007). The existence of centrosomes was first reported 100 years ago by Theodor Boveri (Boveri, 2008). A centrosome is composed of two centrioles and is surrounded by pericentriolar material (PCM), which provides a binding site for the γ-tubulin ring complex (γ-TuRC). The γ-TuRC acts as a microtubule nucleation template, and it attaches to the PCM to form microtubules (Fig. 1). The number of centrosomes is precisely regulated, and the duplication cycle is synchronized to the cell cycle. Centrosomes duplicate once in the S phase and mature in the G2 phase, and in the M phase, centrosomes are divided into daughter cells (Fig. 2). The number of centrosomes and their functions are regulated by many proteins including centrosome proteins, cell-cycle proteins, and DNA-repair proteins, and recently, the role of DNA-repair proteins in centrosome maintenance has been clarified. In this chapter, we introduce recent findings about the roles of DNA-repair proteins in centrosome maintenance.

2. Centrosomes and aneuploidy

Many cancer cells possess extra centrosomes, which is called centrosome amplification and means overduplication of centrosomes. Extra centrosomes can lead to multipolar cell divisions, subsequent aneuploidy, and cell death (Kwon et al., 2008). Although almost all multipolar cell division results in cell death via mitotic catastrophe (Ganem et al., 2009), some multipolar cells divide into daughter cells to maintain aneuploidy. Aneuploidic cells are believed to potentially cause tumorigenesis. Recent studies suggest that aneuploidic cells are produced by a clustering of extra centrosomes, which accumulate at the two poles, and microtubules from each of the extra centrosomes attach to the chromosomes prior to mitosis (Kwon et al., 2008) (Fig. 2). The tension created by the extra centrosomes leads to improper chromosome segregation (Godinho et al., 2009).

Several environmental factors and chemicals, or carcinogens, including ionizing radiation and benzopyrene, can induce extra centrosomes (Sato et al., 2000). Thus, failure of the centrosome duplication cycle could cause tumorigenesis via chromosome aneuploidy.

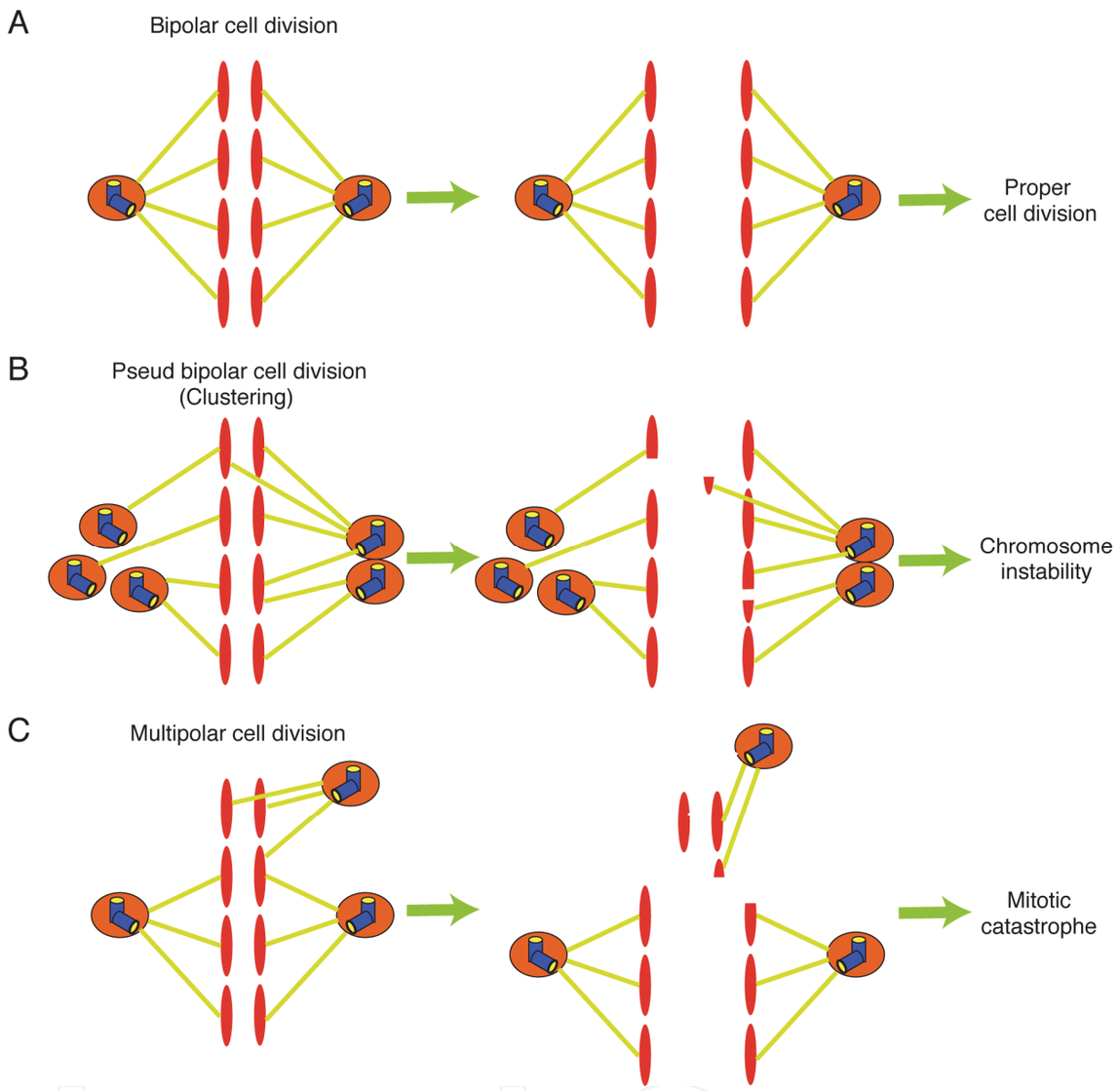


Centrosomes are located at the periphery of the nucleus and consist of a mother centriole and a daughter centriole, surrounded by the pericentriolar material (PCM). The γ-tubulin ring complex (γ-TuRC) binds to the PCM to form microtubules.

Fig. 1. Centrosome structure.

3. Centrosomes and the cell cycle

Centrosome duplication is controlled by several cell-cycle regulators (Fukasawa, 2007). The cyclin E/CDK2 complex is responsible for initiating DNA synthesis and regulates cell-cycle progression (Matsumoto et al., 1999). This complex also contributes to centrosome duplication (Fig. 3). Cyclin E contains the centrosome localization signal (CLS), and overexpression of mutated cyclin E through a CLS deletion results in failed centrosome duplication (Matsumoto and Maller, 2002). The *CDKN1A* product, p21, is a negative regulator of CDK2. As the expression of p21 is regulated by p53-dependent transcription, the absence of p53 abrogates p21-dependent repression of CDK2 and subsequently leads to centrosome duplication. The DNA synthesis inhibitor, hydroxyurea (HU), induces cell-cycle arrest at the G1/S phase. Cells possessing wild-type p53 prevent HU-induced overduplication of centrosomes by inhibiting CDK2 through p53/p21. In contrast, the absence of functional p53 abolishes the p21-dependent repression of CDK2, leading to centrosome amplification. p53



(A) Two centrosomes separate at the two poles, and normal cell division progresses. (B) Overduplicated centrosomes accumulate into the two poles and form a pseudo-bipolar spindle, leading to improper cell division and chromosome instability. (C) Overduplicated centrosomes form a multipolar spindle, leading to a failure of cytokinesis and mitotic catastrophe.

Fig. 2. Cell division during mitosis with normal and abnormal number of centrosomes.

also contributes to abrogation of the linkage between the cell cycle and the centrosome duplication cycle because the p53-dependent G2/M checkpoint is activated in an ataxia telangiectasia mutated (ATM)/ATM- and Rad3-related (ATR)-dependent manner after DNA damage such as from irradiation.

4. Centrosomes and DNA-repair proteins

DNA-repair-related proteins, including ATM, ATR, checkpoint kinase 1 (CHK1), CHK2, PARP1, Nijmegen breakage syndrome (NBS1), BRCA1, BRCA2, RAD51, RAD51 paralogs,

and TOPBP1 localize at centrosomes, and defects in these proteins cause several functional aberrations in centrosomes (Fig. 4).

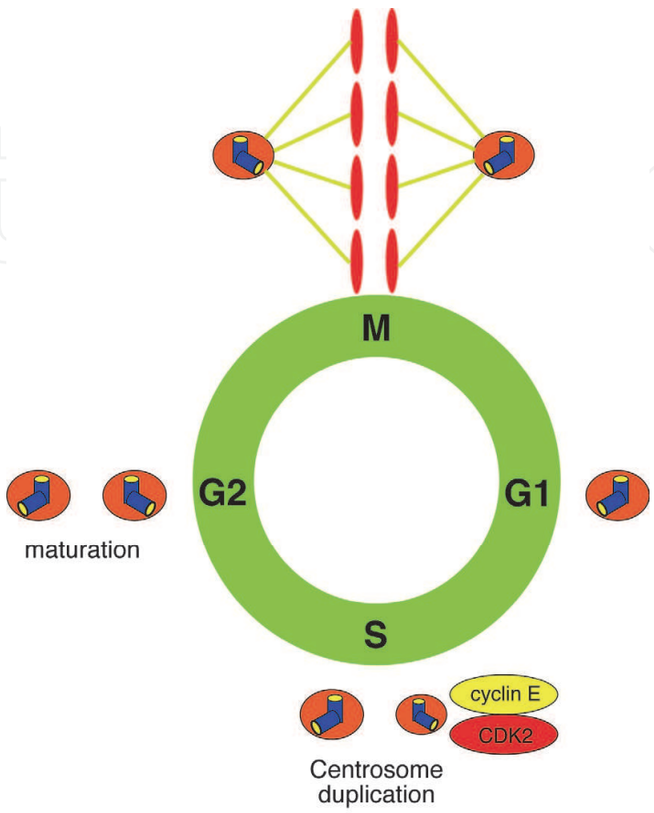
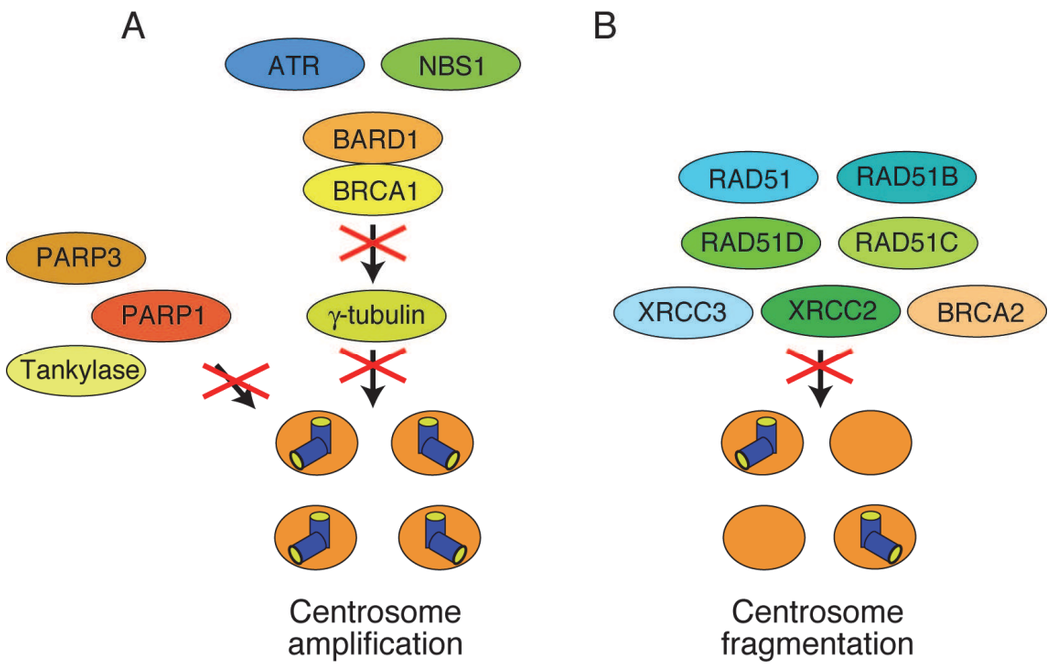


Fig. 3. Centrosome duplication and the cell cycle.

Centrosomes are duplicated once in S phase and mature in G2 phase. In M phase, centrosomes divide into daughter cells. Cyclin E/CDK2 activity is important for centrosome duplication.

4.1 ATM and ATR

ATM and ATR, central protein kinases in the DNA damage response (Bensimon et al., 2010), phosphorylate CEP63, a centrosomal protein, leading to proper control of spindle assembly after DNA damage (Smith et al., 2009). Rad51-deficient chicken DT40 cell lines show centrosome amplification, but a Rad51/Atm-double knockout DT40 cell line revealed a decrease in centrosome amplification compared to Rad51-single knockout cell lines (Dodson et al., 2004). Furthermore, treating Rad51-deficient cells with wortmannin or caffeine, inhibitors of ATM and ATR, results in a decrease in centrosome amplification. These results suggest that ATM could contribute to centrosome amplification in Rad51-deficient cells by regulating the G2/M checkpoint or an unknown function in the centrosome duplication pathway. ATR is mutated in some individuals with Seckel Syndrome (ATR Seckel), which is an autosomal recessive disorder that includes intrauterine growth retardation and microcephaly. Seckel syndrome patient cells have aberrant centrosome and checkpoint regulation (Alderton et al., 2004). *Pericentrin* is a mutated gene in PCNT Seckel syndrome



(A) Ataxia telangiectasia mutated (ATM) and Rad3-related (ATR), Nijmegen breakage syndrome (NBS)1, and BRCA1-BARD1 complex-dependent γ-tubulin monoubiquitination is important for centrosome duplication. Defects in these proteins result in centrosome amplification. A defect in PARP-1, PARP-3, or tankylase also leads to centrosome amplification. (B) In contrast, a defect in RAD51, RAD51 paralogs, or BRCA2 results in centrosome fragmentation.

Fig. 4. DNA-repair proteins and centrosome maintenance.

(Griffith et al., 2008; Rauch et al., 2008) that is involved in the ATR-dependent DNA damage signaling pathway. Exposure to UV light or HU induces the activation of ATR, and activated ATR phosphorylates CHK1. Phosphorylated CHK1 accumulates at the centrosome and its localization causes inhibition of Cdc25 activity, which prevents activation of cyclin B/CDK1. Hence, the ATR-dependent G2/M checkpoint may contribute to centrosome amplification.

4.2 CHK1, CHK2

CHK1 is an essential gene for mammalian cells and functions in the cell-cycle checkpoint (Shimada et al., 2008). Loss of functional Chk1 in human or chicken cell lines causes a G2/M checkpoint deficiency and increased sensitivity to DNA damage treatment (Bourke et al., 2007). CHK1 localizes at the centrosome. Chk1-deficient chicken cell lines abolish irradiation-induced centrosome amplification. CHK1 interacts with MCPH1 and pericentrin in the centrosome, and MCPH1 knockdown decreases the accumulation of Chk1 and pericentrin in centrosomes (Tibelius et al., 2009). These results suggest that CHK1 accumulation in the centrosome is dependent on MCPH1. Thus, Chk1 participates in the regulation of centrosome number through checkpoint control or phosphorylation of unknown substrates by Chk1.

Chk2 is another important cell-cycle checkpoint kinase that is activated in response to DNA damage (Tsvetkov et al., 2003; Golan et al., 2010). Chk2 and Plk1, which are mitotic kinases,

co-localize at the centrosome. This interaction may be important for the DNA mitotic damage-dependent checkpoint, although the details remain unknown.

4.3 BRCA1 and BRCA2

About 10% of women diagnosed with breast cancer have inherited mutations in *BRCA1* or *BRCA2* (Irminger-Finger and Jefford, 2006). Both *BRCA1* and *BRCA2*, products of the familial breast cancer susceptibility gene, are involved in several cellular functions, such as DNA repair, transcriptional regulation, cell-cycle checkpoints, and centrosome maintenance. BRCA1 forms a heterodimer complex with BRCA1-associated RING domain (BARD1), which functions as an E3 ubiquitin ligase. Both BRCA1 and BARD1 contain a RING domain, which mediates DNA–protein and protein–protein interactions, a nuclear export signal sequence at their N-terminus, and tandem BRCT (BRCA1 carboxy-terminal) domains. The BRCA1–BARD1 complex monoubiquitylates γ-tubulin at Lysine 48 and Lysine 344, and overexpression of mutated γ-tubulin at the K48 ubiquitination site results in centrosome amplification and aberration of microtubule nucleation (Starita et al., 2005; Simons et al., 2006). Overexpression of mutated γ-tubulin (K344R) results in an aberration of microtubule nucleation only, suggesting that BRCA1 controls centrosome function by monoubiquitination of γ-tubulin. The BRCA1–BARD1 complex also ubiquitylates the nucleolar phosphoprotein nucleophosmin (NPM also known as B23), which functions in nucleolar organization, cell-cycle regulation, and centrosome duplication. The BRCA1–BARD1 complex polyubiquitinates NPM, leading to its degradation. Aurora A, which localizes at the centrosome and is an important factor for mitotic progression, phosphorylates BRCA1, which contributes to regulation of centrosome duplication. Furthermore, the BRCA1–BARD1 complex regulates microtubule organization through a Ran-dependent import pathway.

A BRCA2 mutation is involved in approximately 50% of hereditary breast cancers (Yoshida and Miki, 2004). BRCA2 has no sequential or structural similarity with either BRCA1 or BARD1 and localizes at the centrosome. Interaction of BRCA2 with plectin, a cytoskeletal cross-linker protein, is necessary for centrosome anchoring to the nucleus (Niwa et al., 2009). BRCA2 also forms a complex at the centrosome with NPM and ROCK2, an effector of Rho small GTPase. A definite BRCA2 deletion can abrogate the association of BRCA2 with NPM, and cells expressing this deletion mutant show centrosome amplification (Wang et al., 2011), suggesting that the BRCA2–NPM complex maintains centrosome duplication and controls cell division.

4.4 NBS1

NBS, which is caused by an *NBS1* gene mutation, is characterized by growth retardation, a birdlike face, immunodeficiency, predisposition to malignancy, and microcephaly (Matsuura et al., 1998). NBS patient cells have a defect in the cell-cycle checkpoint and hyper-radiosensitivity. NBS1 is a multifunctional protein that participates in homologous recombination repair, DNA replication, the cell-cycle checkpoint, and apoptosis (Tauchi et al., 2002). NBS1 forms a complex with MRE11 and RAD50 (MRN complex), and this complex is required for recruitment of ATM to DNA damage sites and for efficient phosphorylation of ATM substrates (Iijima et al., 2008). NBS1 contains a forkhead-associated (FHA) domain and a BRCT domain at the N-terminus, the binding motif for MRE11, ATM, and RNF20, which is a E3 ubiquitin ligase for H2B, at the C-terminus (Nakamura et al., 2011). The NBS1 FHA domain is required for ATR interaction (Shimada et al., 2009). NBS1

knockdown by siRNA in human or mouse cells causes centrosome amplification and decreases BRCA1-dependent monoubiquitination of γ-tubulin. Furthermore, the NBS1 N-terminus, which interacts with ATR, is indispensable for the monoubiquitination of γ-tubulin. NBS1 potentially plays a role in genome integrity via centrosome and nucleus volume control (Shimada and Komatsu, 2009; Shimada et al., 2010).

4.5 PARP family

PARP1 catalyzes the formation of long branched polyADP-ribosylation covalently attached to target proteins using NAD^+ as a substrate. Many proteins are poly(ADP-ribosyl)ated by PARP1, and this modification may be involved in transcriptional regulation and DNA repair (Miwa and Masutani, 2007). PARP1$^{-/-}$ mouse cell lines show centrosome amplification (Kanai et al., 2003). Other PARP family proteins, such as PARP3 and tankylase (also known as PARP5a), localize at the centrosome (Smith and de Lange, 1999; Augustin et al., 2003). These reports suggest that PARP family proteins are involved in the control of centrosome duplication.

4.6 RAD51 paralogs

RAD51 and five paralogs, RAD51B (RAD51L1), RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3, play important roles in homologous recombination (HR) repair (Date et al., 2006; Renglin Lindh et al., 2007; Cappelli et al., 2011). These proteins have a consensus domain including Walker A and B ATPase domains and are necessary for chromosome stability and the control of chromosome segregation. In mammalian cells, XRCC2 forms a complex with RAD51B and RAD51C, and XRCC3 forms a complex with RAD51C. The XRCC2 complex is involved in the RAD51 loading step to ssDNA in HR repair. The XRCC3 complex is involved in Holliday junction resolution. Loss of RAD51, RAD51B, RAD51C, RAD51D, XRCC2, or XRCC3 leads to centrosome amplification and chromosome instability. RAD51C, XRCC2, or XRCC3-deficient cell lines show centrosome amplification in the M phase, but only XRCC2-deficient cell lines show centrosome amplification at interphase (Renglin Lindh et al., 2007), suggesting that RAD51C and XRCC3, but not XRCC2, may be involved in the same centrosome duplication pathway.

4.7 Nonhomologous end-joining repair proteins

Nonhomologous end-joining (NHEJ) repair proteins such as DNA-PKcs also localize at centrosomes (Zhang et al., 2007). Our previous reports showed that DNA-PKcs-deficient cell lines (SCID) have a slightly increased centrosome number compared to wild-type cell lines. Moreover, another NHEJ factor, Ku70, found in a Ku70-deficient cell line also has a slight increase in centrosome number compared to complementary cell lines (Shimada et al., 2010), indicating that NHEJ factors may be involved in centrosome functions different from HR factors.

4.8 Other DNA-repair-related proteins

TopBP1, a sensor protein involved in the DNA damage response, localizes at the centrosome during mitosis but not at interphase (Bang et al., 2011). TopBP1 interacts with the centrosome through its C-terminus and eliminates TopBP1 localization, resulting in a delay in mitotic progression. SMC1, a condensin protein important during chromosome condensation, also localizes at the centrosome but its role in centrosome maintenance is unclear.

5. Conclusion

DNA-repair proteins are necessary for genome integrity. Their main functions are to control DNA repair and control the cell-cycle checkpoint. Recent studies have not clarified the role of DNA damage repair proteins in centrosome maintenance, although interactions between DNA-repair proteins and centrosomal proteins may have an important role in centrosome maintenance and microtubule regulation such as ATM/ATR-dependent CEP63 phosphorylation. How these interactions contribute to centrosome maintenance and microtubule regulation is unclear, so investigating the relationship between DNA-repair proteins and centrosomal proteins is important. Furthermore, the linkage between centrosome amplification and tumorigenesis is key to developing clinical targets. Inhibitors of the DNA-repair protein PARP-1 and the centrosomal protein Aurora A could be a focus for anticancer drugs. Investigations into the molecular signaling pathway of DNA-repair proteins during centrosome maintenance may contribute to advanced options for clinical therapeutics.

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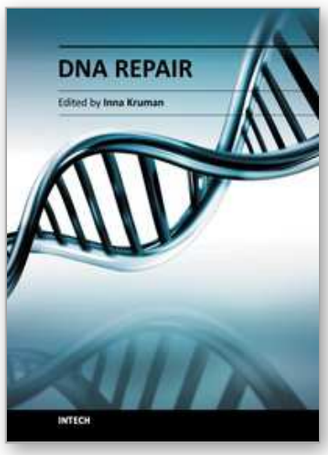

DNA Repair

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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.

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