Emerging Connection Between Centrosome and DNA Repair Machinery

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Centrosome/Tumorigenesis/Genome instability/DNA repair.

Centrosomes function in proper cell division in animal cells. The centrosome consists of a pair of centrioles and the surrounding pericentriolar matrix (PCM). After cytokinesis, daughter cells each acquire one centrosome, which subsequently duplicates at the G1/S phase in a manner that is dependent upon CDK2/cyclin-E activity. Defects in the regulation of centrosome duplication lead to tumorigenesis through abnormal cell division and resulting inappropriate chromosome segregation. Therefore, maintenance of accurate centrosome number is important for cell fate. Excess number of centrosomes can be induced by several factors including ionizing radiation (IR). Recent studies have shown that several DNA repair proteins localize to the centrosome and are involved in the regulation of centrosome number possibly through cell cycle checkpoints or direct modification of centrosome proteins. Furthermore, it has been reported that the development of microcephaly is likely caused by defective expression of centrosome proteins, such as ASPM, which are also involved in the response to IR. The present review highlights centrosome duplication in association with genotoxic stresses and the regulatory mechanism mediated by DNA repair proteins.

INTRODUCTION

The centrosome, first described by Theodor Boveri in the early 1900’s, is an important organelle necessary for proper cell division in mammalian cells. The centrosome has a role as a microtubule organizing center (Fig. 1). Although it must duplicate once per cell cycle division, an excess number of centrosomes can be induced by both genotoxic agents, including ionizing radiation (IR), and aberrant cell cycle checkpoints.1,2) This abnormal centrosome number results in the formation of multipolar spindles and aneuploidy. Since aneuploidy is frequently observed in cancer cells,3,4) the excess number of centrosomes might facilitate tumorigenesis through aneuploid cells.5–7) Thus, regulation of centrosome duplication is indispensable for proper cell proliferation.

Recent studies have demonstrated centrosomal localization and involvement in its maintenance of several DNA damage response and repair proteins, including NBS1, BRCA1 and ATM/ATR kinases. The dysfunction of these proteins is known to cause tumorigenesis due to defective maintenance of centrosomes, in addition to impaired DNA repair.

In light of centrosome maintenance with DNA repair pro-

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Fig. 1. Structure of the centrosome. The centrosome consists of a pair of centrioles and the surrounding pericentriolar matrix (PCM). The mother centriole has a set of appendages at the distal ends, whereas the daughter centriole does not. Centrosomes function as a microtubule organizing center (MTOC) at mitosis, in which γ-tubulin provides a microtubule anchoring machinery by forming a γ-tubulin ring complex (γ-TuRC).
teins, we discuss the mechanisms of centrosome maintenance after genotoxic stresses, including IR, and how these failures contribute to tumorigenesis.

CENTROSOMES AND GENOME INSTABILITY

Bipolar spindle formation with two centrosomes is required for normal cytokinesis. Supernumerary centrosomes, defined by more than two centrosomes, might cause multiple spindle pole formation and lead to abnormal cell division or apoptosis. For example, most tripolar spindle cells can undergo cytokinesis; however, they generate aneuploid cells. Cells containing more than three polar spindles fail to undergo cytokinesis and cause cell cycle arrest, which is mediated by p53 signaling and leads to apoptosis. On the other hand, p53 mutated cells continue cell cycle progression, which might lead to tumorigenesis. Furthermore, some cells containing overduplicated centrosomes can form pseudo-bipolar spindles, in which the excess centrosomes are positioned to a bipolar axis in a process called centrosome clustering. Therefore, the presence of overduplicated centrosomes does not necessarily result in the formation of multipolar spindles. Cells with pseudo-bipolar spindles can progress through cytokinesis, but are prone to chromosome segregation errors. As a result, overduplicated centrosomes frequently generate polyploid cells through abnormal segregation. Genome-wide RNAi screening by Kwon et al revealed the suppressing mechanism of multipolar mitosis by spindle assembly checkpoint (SAC), which contains Mad2, Bub1, and CENP-E. SAC machinery contributes to the prevention of tumorigenesis arising from centrosome overduplication.

Exposure to IR induces overduplication of centrosomes, which, in turn, causes abnormal cytokinesis. In many cases, failure to proper cell division results in mitotic cell death. Therefore, IR-induced centrosome overduplication may cause mitotic cell death.

CENTROSOE DUPLICATION CYCLE

Like DNA synthesis, centrosome duplication is synchronized with the cell cycle and initiated at S phase (Fig. 2). However, when p53-mutated cells arrest at the S phase upon treatment with hydroxyurea, centrosome duplication continues despite the block of DNA synthesis. Whereas CDK2/cyclin-E is known as an important factor for DNA synthesis, its activity also has a crucial role in the initiation of centrosome duplication. The progression of centrosome duplication after inhibition of DNA synthesis is likely due to high CDK2 activity in the S phase, since centrosomes are not duplicated in the absence of CDK2/cyclin-E activation. Cyclin-E has a centrosome localization signal (CLS), and the CLS deletion mutant of cyclin-E cannot localize at centrosomes. CDK2 forms a complex with cyclin-A, which has also been implicated in the regulation of centrosome duplication.

CDK2/cyclin-E has several target proteins in centrosome regulation. Nucleophosmin (NPM) functions as molecular chaperone in several cellular events and is frequently mutated in cancer cells. NPM localizes at centrioles to function in the pairing of two centrioles. NPM is phosphorylated by CDK2/cyclin-E and then dissociates from the centrosome; this is an initial event in centrosome duplication.

There are several centrosome regulation kinases, such as polo-like kinase 2 (PLK2), polo-like kinase 4 (PLK4), and Aurora A. These kinases are frequently overexpressed in cancer cells. PLK2 and PLK4 localize at centrosomes, and the siRNA knockdown of PLK2 or PLK4 suppresses the initiation of centrosome duplication. Aurora A also localizes at centrosomes, and overexpression of this kinase leads to centrosome overduplication.

DNA REPAIR PROTEINS AND CENTROSOMES

DNA double strand breaks are repaired by two major pathways, which are homologous recombination (HR), and non-homologous end-joining (NHEJ) repair. ATM/ATR kinases, NBS1-MRE11-RAD50 complex, BRCA1 and BRCA2 are involved in HR repair. DNA-PKcs, Ku70 and Ku80 are involved in NHEJ repair.

Recently, there have been many reports showing that DNA repair proteins localize at the centrosome. In addition, HR repair proteins are suggested to be involved in centrosome regulation. Ataxia-telangiectasia (AT), which is caused by a mutation in ATM, is an autosomal recessive disorder characterized by cerebellar ataxia, telangiectasia, immunodeficiency, and predisposition to malignancy. AT patient cells show hyper-
sensitivity to IR, defective cell cycle checkpoints, and chromosomal instability. ATM is a serine/threonine kinase, which is a member of the phosphatidylinositol 3-kinase (PI3-K)-like family. ATM auto-phosphorylates itself for its own activation at an initial step of the DNA damage response. ATM localizes at centrosomes and regulates the number of centrosomes through the cell cycle checkpoint. The knockdown of ATM by siRNA suppresses centrosome duplication, while exposure to IR induces an excess number of centrosomes.

ATR (ATM- and Rad3-related) is one of proteins responsible for Seckel syndrome, an autosomal recessive disorder characterized by intrauterine growth retardation, severe proportionate short stature, and microcephaly. The cells from patients with Seckel syndrome show hypersensitivity to UV and defective cell cycle checkpoints. ATR is involved in the DNA damage response, cell cycle regulation, and re-replication at the stalled fork. ATR localizes at centrosomes, and patient’s cells display centrosome overduplication at M phase. This is consistent with the observation that knockdown of ATR by siRNA leads to centrosome overduplication.

BRCA1, which is associated with breast cancer, is involved in DNA repair, cell cycle checkpoints, transcriptional control, and chromatin remodeling. Recent studies have demonstrated that BRCA1 has a crucial role in centrosome maintenance. BRCA1 localizes at centrosomes, and knockdown leads to centrosome overduplication. BRCA1, an E3 ubiquitin ligase, is involved in the ubiquitination of γ-tubulin, a component of the PCM, and hence, inhibition of this ubiquitination activity causes centrosome overduplication and abnormal astral formation.

BRCA2, which is also associated with breast cancer, plays a mediator role in homologous recombination by directly binding to RAD51. BRCA2 also localizes at centrosomes, and its inhibition results in centrosome overduplication and abnormal cell division.

Nijmegen breakage syndrome (NBS), which is caused by a mutation in NBS1, is characterized by hypersensitivity to ionizing radiation, growth retardation, immunodeficiency, predisposition to malignancy, and microcephaly. NBS1 is involved in DNA repair, cell cycle checkpoint, and DNA re-replication. It forms a complex with MRE11 and RAD50 and functions as a sensor protein in DNA damage, similar to ATM. MRE11-RAD50-NBS1 complex activation upon exposure to ionizing radiation depends on cell cycle, mainly acting in S phase. The N-terminus of ATM directly binds to the C-terminus of NBS1. NBS1 localizes at centrosomes through the cell cycle and regulates BRCA1-mediated ubiquitination of γ-tubulin through its interaction with ATR. Knockdown of NBS1 by siRNA leads to centrosome overduplication, similar to that observed by down-regulation of BRCA1 and ATR.

Poly (ADP-ribose) polymerase (PARP)-1 localizes at the nucleus and at centrosomes. After exposure to IR, PARP-1 is recruited to damage sites and regulates several DNA repair proteins by polyADP-ribosylations. Cells from PARP1-deficient mice show centrosome overduplication. However, there are so far no reports of any human syndrome associated with PARP mutations.

Centrosomes also contain other HR repair proteins including SMC1 (Fig. 3). Expression of dominant-negative RAD51 results in centrosome overduplication. Furthermore, conditional deletion of RAD51 leads to centrosome overduplication in an ATM-dependent manner at the prolonged G2 phase. Similarly, inactivation of RAD51B, RAD51C, RAD51D, XRCC2, and XRCC3 induce centrosome overduplication and genome instability.

Although non-homologous end joining (NHEJ) proteins, such as DNA-PKcs, localize at centrosomes, their function in the centrosome is not clear.
Fig. 4. Ionizing radiation (IR)-induced centrosome overduplication. (a) After exposure to IR, cells arrest at the G2 phase, while centrosome duplication continues. This uncoupling of the centrosome cycle and cell cycle causes overduplication of the centrosome, leading to failure of cytokinesis and cell death. (b) Untreated NIH3T3 cells show normal cell division (upper), while centrosome overduplication is induced by irradiation with 5 Gy (bottom) result in cytokinesis failure. Centrosomes are indicated by staining with an antibody against γ-tubulin (red). DNA and microtubule are stained by DAPI (Blue) and α-tubulin antibody (red), respectively.
IONIZING RADIATION AND CENTROSOMES

Exposure to IR induces overduplication of centrosomes in a temporal-and dose-dependent manner (Fig. 4). This excess number of centrosomes peaked as 3-days after exposure to 10 Gy. The overduplication of centrosomes could be due to the uncoupling of centrosome duplication regulation from the cell cycle. Therefore, tumor suppressor protein p53 and the ATM/ATR-mediated G2/M checkpoint are likely involved in the overduplication of centrosomes. When cells are irradiated, ATM/ATR activation induces the upregulation of p21 by accumulation of p53, which in turn leads to suppression of CDK1/cyclin-B activity and G2 arrest. Thus p21 upregulation is accompanied by a reduction of CDK2/cyclin-E activity, although this is not strictly coupled with G2 arrest. On the other hand, p53-deficient cells show tremendous overduplication of centrosomes, since G2 arrest occurs through the CHK1/CHK2 signaling pathway in the absence of p53, even though CDK2/cyclin-E activity is still intact.

Recent reports have shown that centrosomes are maintained by microcephaly-associated proteins, such as ASPM and MCPH1. Microcephaly has been reported in in utero-exposed atomic bomb survivors from Hiroshima and Nagasaki. Since ASPM gene expression is downregulated by exposure to IR, radiation-induced microcephaly might be explained by a failure of centrosome maintenance after IR exposure.

PERSPECTIVES

Although the centrosome was first identified one hundred years ago, its roles are not fully understood. A recent analysis of protein complexes using mass spectrometry indicates that many centrosome proteins are involved in centrosome maintenance. In particular, as described above, several repair proteins have a causal relationship with centrosome aberrations. Although DNA repair factors are well understood, their functions in the maintenance of centrosomes remain to be elucidated. NBS1 and BRCA1 are involved in centrosome maintenance.

Recent reports showed that ATM/ATR kinases phosphorylate the centrosome protein CEP63 and regulate spindle checkpoint after DNA damage. In the near future, we expect to have a better understanding of DNA repair factor’s roles in centrosome maintenance and contribution to genome stability.

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