Centrosome: Insight into Carcinogenesis

Ying Chen[1]*, Yan Zhou[1], Li-Yong Huang[2], Qing-Zhong Kong[3]*

([1]*School of Life Science and Technology, Henan Institute of Science and Technology, Xinxiang 453003, China;* [2]*Department of Neurosurgery, the First Affiliated Hospital of Xinxiang Medical College, Weihui 453100, China;* [3]*Shandong Lanjin Bioengineering Co., Ltd., Jinan 250100, China*)

Abstract The centrosome functions as the major microtubule nucleating center in animal cells. The two centrosomes ensure the equal division of chromosome into the two daughter cells during cell division. Therefore, defects in centrosome either in the structure or in the function may eventually result in genetic abnormalities, thereby leading to the development of cancer. Since chromosome instability (CIN), one of the typical characteristics of cancer cells, was mainly caused by abnormal centrosome, and CIN has been closely associated with the development of drug resistance, it is not difficult to imagine how important roles that centrosome plays in carcinogenesis. We, in this article, emphasized the novel roles of centrosome in cell control, particularly the cellular activities that are closely related with carcinogenesis and the development of drug resistance, which is expected to be useful for better understanding the mechanism underlining drug resistance, and for guiding the designs of anticancer agents, and centrosome-associated drugs in particular.

Key words centrosome; cell cycle; DNA repair; cancer therapy

Cancer development is a very complicated process, involving multiple genes and/or tremendous epigenetic factors, and interactions thereof. Since the understanding of mechanism underling the development of cancer and drug resistance is limited, most of the present techniques or drugs used for the treatment of patients with cancer, particularly for those in the advanced stages, are less effective. Since chromosome instability emerged as one of the main characteristics of cancer cells, the roles of centrosome and the proteins thereof have started to attract more and more attentions in cancer research. Most recently, a growing body of evidence has further confirmed the critical roles of the centrosome in the maintenance of normal cell functions as well as in carcinogenesis.

As far as cancer is concerned, although the function of centrosome in carcinogenesis has elucidated, detailed discussion on the importance of centrosome in cancer therapy is relatively less[1,2] (Fig.1). Although there are a lot of works to be done, an emerging data has suggested that centrosome might be involved in the regulations of DNA synthesis, DNA repair, cell cycle and apoptosis[3]. Such novel roles of centrosome in cell control and in the maintenance of genetic stability in particular, have made centrosome a new focus in the post-genetic era[4]. As for cancer therapy, better understanding of the novel roles of centrosome in cell control is expected to bring some insights.

1 Novel roles of centrosome in cell cycling

The balance of proliferation and apoptosis, which ensures the homeostasis of normal cells, is maintained by a precisely regulated cell cycling mechanism, through which a malignant cell with dysregulated cell cycle might be abolished. This self-defense mechanism effectively prevents cells from being transformed. Theoretically, perturbation of any parts of the centrosome in the structure or function may result in disorders of cell cycle, then leading to cancer because, up to now, more than 150 kinds of kinases have been found as centrosome-located protein. Indeed, increasing studies have provided favoring results to this thought.

Centrosome was recently found to be required not only for progression through G_1 into S phase, metaphase

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*Corresponding author. Tel: 86-373-3040337, E-mail: yingch@yahoo.cn; Tel: 86-531-81219100, E-mail: kongcellbrain@hotmail.com

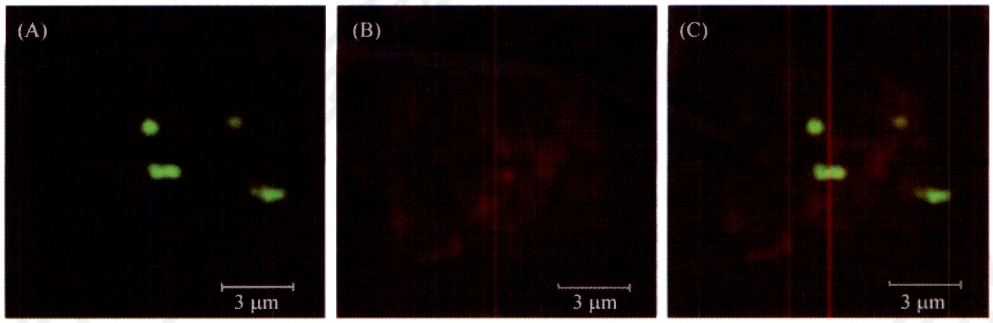

Fig.1 Centrosome amplification in mouse squamous cell carcinoma

Immunofluorescent staining of mouse skin tissue. A: γ-tubulin (green); B: nucleus (red); C: merge of the two. Numerous centrosomes were irregularly distributed in a tumor cell.

to anaphase of the cell cycle, but also for exiting M phase [3, 5~9]. Consequent studies have further evidenced the roles of the centrosome and the associated proteins in the cycle regulation. For example, Nek2, Polo-like kinases (Plks), aurora-A, and cyclin E were found recently to be associated with centrosome and/or microtubules[10~12]. Polo-like kinases (Plks), which regulates the activity and function of many key cell cycling regulators, such as p53, Cdc25, cyclin B, APC (anaphase-promoting complex), and mitotic motor proteins, was found to be in centrosome in interphase, but in mitotic apparatus in mitosis[13]. Recently, cyclin B1-Cdk1 (the key initiator of mitosis) was found to be initially phosphorylated on the centrosome in prophase and moved rapidly into the nucleus in late prophase, a process that is necessary for M-phase. Interestingly, other studies have shown that cyclin B1-Cdk1 activation was induced by cysteine proteases that are required not only for centrosome organization and microtubule spindle assembly but also for triggering S-phase and for promoting M-hase entrance in sea urchin eggs[14,15]. Most recently, a novel vertebrate-specific centrosome/spindle pole-associated protein (CSPP) was isolated and characterized as a key player in the regulation of G_1/S-phase progression and spindle assembly[16].

In carcinogenese, many centrosome associated proteins have been found.

2 The roles of centrosome in DNA replication and DNA repair

Proper DNA replication ensures the inheritable material being equally separated into each daughter cell. In this process, the timely and accurate response to DNA damage is very important. As the signaling and coordinating center, centrosome has been confirmed to exert its roles in controlling DNA replication and repair through the cell brain associated proteins[17].

In DNA repairing, DNA damage is first recognized by DNA damage-recognizing complex that was originally thought to contain the XP group C responsible gene product (XPC). And some centrosome proteins such as centrin 2/caltractin 1(CEN 2) are found to be major components of XPC[18]. The DNA single-strand breaks (SSBs) repair induced by oxidative DNA damage is considered to be the most common insult affecting the genome, and the centrosome-localized XRCC1 protein plays a key role in this process. In addition, DNA ligase III alpha was found to be essential for XRCC1 translocation from centrosome to mitosis chromosome, with the dynamic states of XRCC1 and DNA ligase III alpha to SSBs being prerequisite for the recruitment to the centrosome of the DNA repairing proteins, like PAR polymerase, which is indispensable for XRCC1 response to DNA damage[19]. Topoisomerase II beta binding protein 1 (TopBP1), another centrosome-localized protein in late mitosis, has been implicated in DNA replication and in DNA damage response, and coupled with centrosome localized promyelocytic leukemia protein (PML) that may lead to centrosome amplification when defects occur[20~22]. Furthermore, 8-Oxoguanine DNA glycosylase (OGG1), a major component of base excision repair (EBR), being involved in the recognition and excision of

oxidative base lesions in human cells, was found to be associated with the cytoskeleton by specifically binding the centriole and microtubules at interphase and spindle assembly at mitosis in response to oxidative DNA damage[23]. DNA polymerase beta (DNA Pol β) and NELL2, the others two components of BER pathway were also found to be associated with microtuble, implying that microtubule may regulate the EBR pathway activity during the cell cycle[24].

Centrosome also plays important roles in DNA double strand break. Rad51, for example, acting as a major protein in the recombination repairing of DNA double-strand breaks and DNA crosslinking adducts, was reported to be coupled with gamma-tubulin linking DNA recombination repair protein and the centrosome[25]. BRCA1 and BRCA2 were reported to interact with Rad51 with formation of the γ-tubulin-RAD51 nuclear complexes that participate in DNA double-stranded breaks repairs[26].

In DNA replication, the assembly of an origin recognition complex (ORC)-dependent pre-replicative complex is required for the initiation of DNA replication in S phase. Orc2 subunit is localized not only at nucleus but also at centrosome throughout the entire cell cycle. Absent of Orc2 may result in DNA replication arrest and centrosome amplification[27]. Cep 170, a forkhead-associated protein, interacting with and being phosphorylated by Polo-like kinase 1(Plk1), has been localized at the centrosome at interphase and at the mature mother centriole and spindle microtubule at mitosis[28]. Furthermore, Cyclin E/Cdk2, a central regulator of the G_1/S transition, coordinates multiple cell cycle events, including DNA replication, centrosome duplication, and activation of the E2F transcriptional program. Of cyclin E/Cdk2, a 20 amino acids peptide acting as a centrosomal localization signal (CLS) is essential for both centrosomal targeting and DNA synthesis promotion. CLS peptides localized on the centrosome may, in turn, prevent endogenous cyclin E and cyclin A from being localized to the centrosome, thereby inhibiting DNA synthesis[29].

Along with studies, more proteins, such as Kruppel-like transcription factor 4 (KLF4) and Ckap2 (cytoskeleton associated protein 2), are found to be associated with cell brain localized protein when functioning in DNA damage and repair[30,31]. Therefore, although the mechanisms underlining DNA replication and DNA repair are unclear, the roles of the cell brain in this process should not be neglected.

3 The roles of centrosome in signal transduction

Although little is known about the roles of centrosome in signal transduction, a growing body of evidence has demonstrated that many signaling proteins localize at centrosome. For example, protein kinase C (PKC) and its major substrate MARCKS (myristoylated alanine-rich C-kinase substrate), exerting multiple roles, such as controlling microtubule organization, spindle function, and cytokinesis, were found to colocalize to pericentrin and gamma-tubulin within MTOCs[32~34]. Since only phosphorylated PKC was anchored at centrosome by centrosome and Golgi localized PKN-associated protein (CG-NAP)[35], it is difficult at present to outline signaling pathways that clearly describe the roles of the cell brain in all the cellular processes.

The Wnt signaling pathway and its key component β-catenin play critical roles in embryonic development as well as in various malignant tumors. The Wnt signal pathway was found to be regulated by the duplicated centrosomes[36]. The location of β-Catenin at the centrosome is critical for normal centrosome fragmentation. Any wrongs with it would dramatically increase the frequency of monoastral mitotic spindles[37].

Aberrant signaling induced by signal transducers and activators of transcription (STAT) proteins have been observed in a wide variety of cancer cell lines and primary tumors, and these aberrant signals may promote cell cycle progression and survival, stimulate angiogenesis, and impair immunological responses and tumor surveillance[38]. Stat3 was found to play important roles in this process and being involved in centrosome duplication by regulating γ-tubulin through post-transcriptional levels and increasing PCM-1 level by inhibition of Stat3. These studies also implicated that Stat3 may be a fundamental signaling molecule that indirectly directs the syntheses of various centrosomal proteins[39].

Additionally, cell brain is involved in Ca^{2+} signal

pathway via a novel Ca^{2+}-binding protein centrin partner, Sfi1p, functioning in reorienting centrioles, altering centrosome structure, and regulating centriole duplicaton[40]. Cell brain also has a relation with apoptosis signal pathway which is supported by recent findings of S-allylmercaptocysteine (SAMC) and DAP-like kinase (Dlk). S-allylmercaptocysteine (SAMC), a compound extract from garlic, may trigger JNK1 and caspase-3 signal pathways by disruption of MT assembly[41]. DAP-like kinase (Dlk), co-localizing with gamma-tubulin and pericentrin both in mitosis and in interphase, interacts with pro-apototic protein Par-4, thereby being implicated in apoptosis[42].

4 Centrosome in cancer therapy

Current techniques used for cancer therapy have mainly focused on the inhibition of some specific proteins or pathways that are relatively up-regulated in cancers. However, the signaling center being responsible for self-defense leading to the development of resistances has not caught enough attentions. As discussed above, centrosome play such important roles in cell control that any defects in the composing parts of it may cause genetic instability. As for the transformed cells, genetic instability in turn contributes greatly to the development of cancer. Therefore, it is not surprising to see that various centrsome associated protein inhibitors are being developed, including protein inhibitors of kinase C (PKC), proteasome, Aurora, NEDD1, angiogenesis factors, and centrosome-associated regulators[43~48].

Chemo-resistance is the major clinical problem failing cancer chemotherapy. Although the mechanisms underlying chemo-resistance are largely unknown, amplification or over-expression of the P-glycoprotein family of membrane transporters (e.g. MDR1, MRP, LRP), changes in cellular proteins involved in detoxification or activation of the chemotherapeutic drugs, and the alterations in molecules involved in DNA repair and activation of oncogenes such as *Her-2/neu, bcl-2, bcl-XL, c-myc, ras, c-jun, c-fos, MDM2*, p210 *BCR-abl*, or mutant *p53* are believed to be major players[49]. Among those factors, mounting evidences have confirmed that chromosome instability (CIN) may be the fundamental cause in chemo-resistance. Although several factors may contribute to CIN, centrosome abnormalities may be a critical one. Abnormal centrosome itself may lead to formation of poly- or monopolarity spindle resulting in chromatin mis-segregation, which further result in or accelerate inactivation of tumor suppressor genes and/or activation of tumor genes, thereby leading to the development of chemoresistance. Indeed, majority of drugs used today exerts their anticancer roles by interfering with DNA metabolism. The side effect of dose-dependent toxicity brought by mutagenic or cytotoxic agents may act on chromosomal fragile sites, which, plus the defects of DNA repair system in cancer cells, makes chromosome being prone to break at fragile sites, then causing break-fusion-break, thus promoting extensive CIN[50]. The resulted CIN may refer to an enhanced rate of accumulation of gross chromosomal aberrations and generation of tumor cells equipped with further malignant characteristics, consequently conferring tumor cells to selective advantages against host defense mechanisms and chemotherapeutic agents[51,52]. These findings suggested that centrosome may have close relation with chemoresistance. Support of this idea comes from the recent finding that *p53* status determines tumor response to antiangiogenic therapy and heat shock proteins (HSPs) varies with tumor progressions[53,54]. Taken together, chemoresistence is a very complicated process involving various genes and signal pathways. Choosing one of the centrosome proteins as a target for cancer therapy may be effective at some degree or at the beginning. Inevitably, consequent resistance may occur for most of the cells, for most cancer cells possess abnormal chromosomal structures being different from each other.

In our previous report, centrosome abnormalities may be one of the most earliest events in cancer development than that of *p53* mutation and telomerase up-regulation, which have been long regarded as the major factors contributing to the devlopment of carcinogenesis, so selective target of the centrosome as a whole through combination of chemotherapeutic drugs is expected to be reasonable and promising[53]. Unfortunately, up to now there is no report to confirm that any drugs can directly target to centrosome. However, Kong hypothesized that when tetrazolium salts are present with viable tumor cells, the centrosome crystals are formed. Crystal-

lization of the centrosome blocks not only DNA replication but also DNA repair through restraining the separation and movement of the duplicable organelles and cytoskletons. Despite there is no evidences to attest to whether it is true or not, there is no doult that interruption of the abnormal centrosomal functions may not only limit the formation of spindle and the segregation of chromosomes but also interfere with signal transductions from and/or to the centrosomes in cancer cells as centrosome plays such important roles in cell control. In other words, all key enzymes located in the centrosome will not function normally, and the cellular structures that are rich in the enzymes will be functionally and structurally frozen or restrained[55]. Clearly, restriction of centrosomal functions exerts its cancer killing effect, which is expected to avoid the critical problem such as the development of resistance to cancer therapy.

5 Summary

Centrosome works as an integrated complex structurally and functionally in regulating cell activities. Disrupting any components of centrosome either in structure or in function may provoke malignant transformation. Although the roles of the centrosome in carcinogenesis have been elucidated, the roles of the centrosome in cancer therapy, particularly in chemoresistance, are largely uncovered. As discussed in this paper, centrosome determines a cell's response to chemotherapeutic agents and is the fundamental cause of chromosome instability leading to chemoresistance, so it is reasonable that the centrosome-associated drugs should be developed to stop cancer cells proliferation and exert their efficacy combined with conventional therapeutic agents.

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中心体：洞悉肿瘤的发生

陈 颖[1]* 周 岩[1] 黄立勇[2] 孔庆忠[3]*

([1]河南科技学院生命科技学院, 新乡 453003; [2]新乡医学院第一附属医院神经外科, 卫辉 453100;
[3]山东蓝金生物工程有限公司, 济南 250100)

摘要 动物细胞中主要作为微管组织中心的中心体在细胞分裂时确保了染色体平均分配到两个子细胞的过程, 从而保证了基因组的稳定性。中心体的结构或功能异常都将不可避免的引起基因组不稳定, 从而导致肿瘤的发生。鉴于主要由中心体异常引起的染色体不稳定是肿瘤细胞的一个典型特征, 而染色体不稳定又与肿瘤细胞的耐药性有着密切联系, 因而不难想象以中心体为靶点的肿瘤治疗的合理性。因此, 本文将着重阐述中心体在细胞调控, 特别是与肿瘤发生密切相关的细胞活动及药物耐受中的重要作用, 以期为更好阐明药物耐受机制, 并为与中心体相关的抗肿瘤药物研发提供新思路。

关键词 中心体; 细胞周期; DNA 复制; 肿瘤治疗

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* 通讯作者。Tel: 0373-3040337, E-mail: yingch@yahoo.cn; Tel: 0531-81219100, E-mail: kongcellbrain@hotmail.com