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Review

Centrosome aberrations in hematological malignancies

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Abstract

As the primary microtubule organizing center of most eukaryotic cells, centrosomes play a fundamental role in proper formation of the mitotic spindle and subsequent chromosome separation. Normally, the single centrosome of a G_1 cell duplicates precisely once prior to mitosis in a process that is intimately linked to the cell division cycle via cyclin-dependent kinase (cdk) 2 activity that couples centrosome duplication to the onset of DNA replication at the G_1/S transition. Accurate control of centrosome duplication is critical for symmetric mitotic spindle formation and thereby contributes to the maintenance of genome integrity. Numerical and structural centrosome abnormalities are hallmarks of almost all solid tumors and have been implicated in the generation of multipolar mitoses and chromosomal instability. In addition to solid neoplasias, centrosome aberrations have recently been described in several different hematological malignancies like acute myeloid leukemias, myelodysplastic syndromes, Hodgkin's as well as non-Hodgkin's lymphomas, chronic lymphocytic leukemias and multiple myelomas. In analogy to many solid tumors a correlation between centrosome abnormalities on the one hand and karyotype aberrations as well as clinical aggressiveness on the other hand seems to exist in myeloid malignancies, chronic lymphocytic leukemias and at least some types of non-Hodgkin's lymphomas. Molecular mechanisms responsible for the development of centrosome aberrations are just beginning to be unraveled. In general, two models with distinct functional consequences can be envisioned. First, centrosome aberrations can arise as a consequence of abortive mitotic events and impaired cytokinesis. Second, evidence has been provided that centrosome amplification can also precede genomic instability and arise in normal, diploid cells. Accordingly, this review will focus on recent advances in the understanding of both, causes and consequences of centrosome aberrations in hematological malignancies.

Keywords: Centrosome; Acute myeloid leukemia; Lymphoma; Leukemia; Hematological malignancy; Hodgkin's disease; Myelodysplastic syndrome; Multiple myeloma

1. Centrosomes

Centrosomes are the major microtubule organizing centers of animal cells. As such, they function in the maintenance of cytoplasmic architecture through the nucleation and organization of microtubules during interphase and play a vital role in bipolar spindle formation, which is necessary for balanced chromosome segregation in mitosis. Structurally, centrosomes consist of a pair of centrioles, barrel-shaped cylinders formed by nine parallel bundles of microtubule triplets (Krämer et al., 2002a; Bornens, 2002). Centrioles are surrounded by a protein lattice known as the pericentriolar material (PCM) which consists of several different large coiled-coil proteins including pericentrin, AKAP450, and ninein. These coiled-coil proteins of the PCM serve as

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a framework to anchor microtubule nucleation sites, other essential centrosome proteins and key regulators of centrosome function. Microtubules are nucleated by γ-tubulin ring complexes which are anchored within the PCM via pericentrin and are increasingly recruited into an expanding pericentriolar matrix during the G_2 phase of the cell cycle.

2. Centrosome duplication

In order to allow the formation of a strictly bipolar mitotic spindle, the centrosome needs to be duplicated exactly once per cell cycle (Kellogg et al., 1994). Duplication of centrosomes is initiated at the G_1/S transition and completed before mitosis. At mitosis the two centrosomes of a cell are segregated such that each of the two cells resulting from division receives only one. Duplication of the centrosome is semiconservative: the paired centrioles of a single centrosome split and a new centriole forms in association with each, creating two centrosomes (Kochanski and Borisy, 1990). Centrioles replicate during S phase concurrent with DNA replication. In analogy to DNA replication, centrosome duplication is controlled by Cdk2-cyclin A/E activity (Hinchcliffe et al., 1999; Lacey et al., 1999; Matsumoto et al., 1999; Meraldi et al., 1999). Centrosome duplication is blocked by the chemical Cdk2 inhibitors butyrolactone and roscovitine (Matsumoto et al., 1999) as well as by p21 and p27 or immunodepletion of Cdk2 or cyclin E and restored by excess purified Cdk2–cyclin E (Hinchcliffe et al., 1999; Lacey et al., 1999; Matsumoto et al., 1999). Mechanistically, an early event in centrosome duplication, the initial separation of the centriole pair, is dependent on Cdk2 activity, suggesting that a Cdk2-mediated phosphorylation event regulates centriole cohesion (Lacey et al., 1999). In addition to Cdk2 activation, centrosome duplication seems to be strictly dependent on phosphorylation of the retinoblastoma (Rb) protein and subsequent transcriptional activity of E2F (Meraldi et al., 1999).

3. Centrosomes as cell cycle regulators

In addition to the well characterized functions of centrosomes in the organization of interphase microtubule arrays and the mitotic spindle, it has long been speculated that centrosomes might be involved in several cell cycle regulatory events like G_1/S transition, monitoring of DNA damage, entry into mitosis, and cytokinesis (Krämer et al., 2004a). This assumption is mainly based on a growing list of cell cycle regulatory proteins that localize to the centrosome such as p53, Brca1, Chk1, Chk2, TopBP1, Aurora-A, Plk1, cyclin B1, cyclin E, cyclin A, and Cdk1. Most recently, it has been described that centrosomally localized cyclin E is essential for Cdk2-independent S phase entry (Matsumoto and Maller, 2004). In addition, it has been shown that ablation of centrosomes in late G_2 phase leads to a cell cycle arrest at the G_1/S boundary of the next cell cycle suggesting that centrosomes are necessary for entry into S phase (Khodjakov and Rieder, 2001; Hinchcliffe et al., 2001).

Recently, it became evident that the initial activation of cyclin B1–Cdk1 in early prophase of the cell cycle – a process necessary for entry into mitosis – takes place at the centrosomes and from there spreads to induce both cytoplasmic and nuclear mitotic events like spindle formation, nuclear envelope break down and chromosome condensation (Jackman et al., 2003). In addition, both positive and negative regulatory pathways controlling cyclin B1–Cdk1 activation seem to converge at the centrosome; whereas Aurora-A is required for initial activation of the centrosomal pool of cyclin B–Cdk1, Chk1 – a protein previously known to serve as a nuclear checkpoint kinase – unexpectedly seems to restrain centrosome-associated Cdk1, thereby preventing premature entry into mitosis and counterbalancing the effect of Aurora-A (Hirota et al., 2003; Krämer et al., 2004b).

Exposure to DNA damage during mitosis seems to result in centrosome inactivation or fragmentation in both *Drosophila* embryos and somatic mammalian cells (Sibon et al., 2000; Hut et al., 2003). At least in *Drosophila* this process relies on the presence of centrosomal Chk2 – the second principal nuclear checkpoint kinase (Takada et al., 2003); whereas increasing evidence suggests that Chk2 localizes to centrosomes of mammalian cells as well (Krämer et al., 2004; Tsvetkov et al., 2003). Data on the role that Chk2 might play at mammalian centrosomes are somewhat conflicting. Of note however, most recently, it has been reported that DNA damage in chicken DT40 lymphoma cells leads to centrosome amplification during a prolonged G_2 phase arrest, a process in which both ATM and ATR – the upstream regulatory kinases of Chk1 and Chk2 – are involved (Dodson et al., 2004).

4. Centrosome amplification

In order to ensure strictly bipolar mitotic spindle formation, the centrosome needs to be duplicated exactly once per cell cycle. As described above, centrosome duplication in somatic cells is controlled by the phosphorylation status of the Rb protein, release of the transcription factor E2F from Rb binding, and subsequent activation of Cdk2 in late G_1 phase in a manner highly reminiscent of DNA replication. Consequently, the commonly observed abrogation of the Rb pathway in human malignancies will not only facilitate progression towards DNA replication, but may also lead to several rounds of centrosome duplication within the same cell cycle. Certain tumor derived cell lines can