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Centrosome Dysfunction and Senescence: Coincidence or Causality?

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Abstract

Centrosomes are the tiny organelles found in most eukaryotic systems. By virtue of their ability to anchor, organize and nucleate microtubules, they play a crucial role in establishing spindle bipolarity and in ensuring the fidelity of cell division. Defects in centrosome structure and function often result in mitotic catastrophe, cell cycle arrest, cell death, genomic instability and/or aneuploidy, leading to human disorders such as primary microcephaly, cancer and ciliopathies. Interestingly, genomic instability and aneuploidy are also hallmarks of aging and cellular senescence, but our understanding of the connection between centrosome dysfunction and senescence remains rudimentary. In this review, we focus on existing evidence suggesting that these two phenomena are indeed related, along with the emerging view that centrosome aberrations represent a form of cellular stress that is necessary and sufficient to trigger a permanent cell cycle arrest and senescence. The molecular mechanisms underlying cellular senescence as a consequence of centrosome aberrations and the involvement of p53 will be discussed.

Keywords: Centrosomes; Centrioles; PCM; Aging; Senescence; Genomic instability; Aneuploidy; Stress; p53; Phosphorylation

Abbreviations: Pericentriolar matrix (PCM), Retinoblastoma (Rb)

Review

Centrosome structure and function

Although originally discovered and described by Flemming, Van Beneden and Boveri in the late 1800s as a tiny cellular organelle, the centrosome is a remarkably complex structure with diverse functions [1-4]. It is composed of a pair centrioles surrounded by an amorphous cloud of proteins called the pericentriolar matrix (PCM) (Figure 1). Each centriole is made up of nine triplet of stabilized microtubules arranged in a cylindrical manner. The two centrioles are termed the mother and daughter centrioles, and can be distinguished by the presence of sub-distal and distal appendages at the mother centriole. While sub-distal appendages anchor cytoplasmic microtubules, distal appendages are believed to be important for the formation of cilia, cellular antennae possessing motility and/or sensory function [5,6]. Centrioles are responsible for organizing the PCM, the major site of microtubule nucleation from which cytoplasmic microtubules emanate and elongate. In addition, there are centriolar satellites, small and granular structures that cluster around the centrosome and participate in microtubule-dependent protein trafficking towards the organelle [7,8]. The centrosome coordinates all microtubule-related functions, including cell division, cell shape, polarity, motility and adhesion.

The number of centrosomes within a cell is tightly regulated during the cell cycle (Figure 1). A single centrosome duplicates once in the S phase, and the two centrosomes, once separated, migrate to opposite poles of a cell and establish the bipolar spindle in mitosis. A functional bipolar spindle ensures faithful chromosome segregation, wherein each incipient daughter cell receives one centrosome and a diploid set of chromosomes. Perturbations known to disrupt centrosome structure and function often have deleterious consequences. For instance, abnormal cell division in mitosis can result in genomic instability and aneuploidy which are characteristics of many types of cancer. In other cases, abnormal mitosis can trigger programmed cell death and impair spindle alignment of neural progenitor cells, leading to their depletion and limiting the total number of neurons that can be generated. These are believed to be the underlying mechanisms responsible for reduced brain size in patients with primary microcephaly and Seckel syndrome. Furthermore, defects in cilia formation and function can cause in a wide variety of human diseases collectively known as ciliopathies. For a general review of the role of centrosomes and cilia in human disorders, we direct the reader to several excellent review articles [9-11].

Centrosomes and senescence: are they related?

Senescence or aging is a biological process found in all living organisms and is characterized by changes that disrupt cellular metabolism and function with time, resulting in progressive deterioration, cell cycle arrest and cell death. Although observed at the level of the whole organism (in vivo) [12,13] and individual cells (cellular senescence) [14], the molecular and cellular basis of senescence are not fully understood. At a cellular level, it is well-established that senescence is associated with chromosomal instability and aneuploidy in different cell types from various species [15-19]. Several physiological stresses are thought to contribute to the aging process, including the shortening of telomeres [20-22], oxidative stress [23,24], DNA damage [25,26], over-expression of tumor suppressor genes [27] and strong oncogenic signaling [28-30]. Interestingly, increasing evidence also supports a link between centrosome dysfunction and senescence, suggesting that this organelle could directly or

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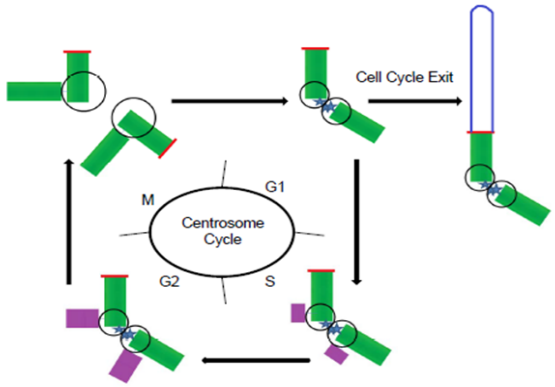

Figure 1: Centrosome structure and biogenesis. A cell in the G1 phase possesses one centrosome consisting of the mother (green rectangle with a red line) and daughter (green rectangle) centrioles surrounded by the PCM (black circle). This single centrosome duplicates in the S phase, leading to the synthesis of two new centrioles, or procentrioles (purple rectangle) adjoining the existing mother and daughter centrioles. Procentrioles elongate and mature into daughter centrioles, while the existing daughter centriole matures into a new mother centriole during S and G2 phases. The PCM becomes enlarged at the onset of mitosis, signifying competence of the two centrosomes in anchoring and organizing microtubules for cell division. After mitosis, each daughter cell can enter the G1 phase and progress through another round of cell division, or it can exit the cell cycle, in which case a cilium (blue) is formed from the mother centriole.

indirectly play a role in aging. Aged porcine oocytes exhibit a loss of γ-tubulin and NuMA, critical components of the PCM at the meiotic spindle, giving rise to abnormal and disorganized spindles [31]. Similarly, microtubules are gradually lost from the spindle of aged mouse oocytes, a feature highly suggestive of compromised centrosome structure and function [32,33]. A loss of centrosome and microtubule integrity has also been described in aged human oocyte, both *in vitro* and *in vivo* [34], and in aged Drosophila cells [35]. Furthermore, human primary fibroblasts are known to stop dividing permanently after a finite number of cell divisions as a result of telomere shortening and oxidative stress and enter a state of replicative senescence [14]. As these cells age, the frequency of abnormal mitotic figures increase, and this is accompanied by an increase in supernumerary centrosomes [16]. Primary mouse embryonic fibroblasts also undergo replicative senescence with age due to oxidative stress [23,24]; however, unlike the situation in human fibroblasts, centrosomes do not increase in number but instead fragment into smaller pieces with increasing passage [36]. Most importantly, the authors showed that disruption of core PCM components in early-passage mouse embryonic fibroblasts can also induce centrosome fragmentation and trigger premature entry to senescence [36], suggesting that centrosome dysfunction alone is sufficient to provoke the induction of a cellular senescence program. Taken together, these studies raise the intriguing possibility that centrosome aberrations, similar to oxidative stress and telomere shortening, is a type of cellular stress that can predispose cells to permanent cell cycle exit, and future studies using high-resolution and electron microscopy will be necessary to define the precise nature of these structural aberrations and the extent to which they contribute to senescence.

Centrosome aberrations, senescence and p53

Several recent studies have begun to address whether centrosome dysfunction can indeed trigger cellular senescence and whether the underlying molecular pathways overlap with those induced by other physiological stresses. Depletion of a number of centriolar (C-Nap1, δ-tubulin, ε-tubulin), PCM (pericentrin, γ-tubulin, GCP-2, GCP-3, GCP-5, AKAP450) and centriolar satellite (PCM-1) proteins leads to a loss of centrosome integrity and cell cycle arrest in the G1 phase [37]. The G1 arrest phenotype can be induced in post-mitotic cells, indicating that it is not a consequence of mitotic defects. Prior to the G1 arrest, p38, a protein implicated in cellular stress response and senescence, becomes activated and phosphorylates p53 at Ser33 (and not at Ser15; see below), causing p53 to accumulate at centrosomes before its translocation to the nucleus. Another study also highlighted a role of pericentrin and PCM-1 in cell cycle regulation [38]. Inhibition of pericentrin or PCM-1, which recruits pericentrin to the PCM, induces a permanent cell cycle exit with a concomitant increase in cellular β-galactosidase expression, a hallmark of cellular senescence. Similar to the previous study, this arrest is also dependent on p38 and p53, and probably occurs as a result of up-regulation of p53 and p21 protein levels and down-regulation of phosphorylated retinoblastoma (Rb). Likewise, depletion of other PCM components, including Cep192 (which recruits NEDD1 to the PCM) and NEDD1 (which recruits γ-tubulin to the PCM), causes centrosome fragmentation and premature entry to senescence [36]. Furthermore, inhibition of Aurora A or its downstream target TACC3, both of which are localized to the PCM during mitosis, leads to premature senescence in p53-proficient tumor cells, characterized by an increase in p53, p21 and hypo-phosphorylated Rb [39,40]. The elevation in p53 levels could be explained in part by the fact that Aurora A normally phosphorylates p53 at Ser315 to sensitize it for degradation and, in the absence of Aurora A, p53 becomes stabilized [41]. In primary human fibroblasts, cells that have undergone either replicative senescence or premature senescence induced by oxidative stress also accumulate p53 at the centrosome, accompanied by phosphorylation at Ser15 [42]. Ser15 phosphorylation on p53 is essential for its localization to the centrosome, and has been shown to be a default pathway carried out by ataxia telangiectasia mutated, or ATM, at the centrosome in early mitosis to insure correct cell division [43-45]. When the mitotic spindle is correctly in place, Ser15 phosphorylation is rapidly removed and p53 becomes sequestered at the centrosome in an inactive form. On the other hand, when the spindle is impaired, p53 remains phosphorylated at Ser15, and this phosphoprotein is eventually translocated to the nucleus to induce cell cycle arrest and cellular senescence. Therefore, it seems plausible that in response to centrosome damage and possibly other stresses, one key event that takes place early in the senescence process is the phosphorylation and accumulation of p53 at the centrosome. It has been known for a long time that p53 localizes to centrosomes, but surprisingly little is known about its function at this organelle [42,43,46-48]. It would be interesting in the future to delineate the functional significance of centrosomal p53 and its differential phosphorylation by various kinases, as elucidating these molecular events would undoubtedly provide a better understanding of how p53 integrates signals from different types of stresses, including centrosome dysfunction, to promote cellular senescence.

Conclusions and Perspectives

The role of centrosomes in aging is an important area of research that has been largely overlooked. Despite little and fragmentary evidence, existing data strongly favor the view that centrosome dysfunction is connected to cellular senescence. We propose that in addition to existing known cellular stresses,

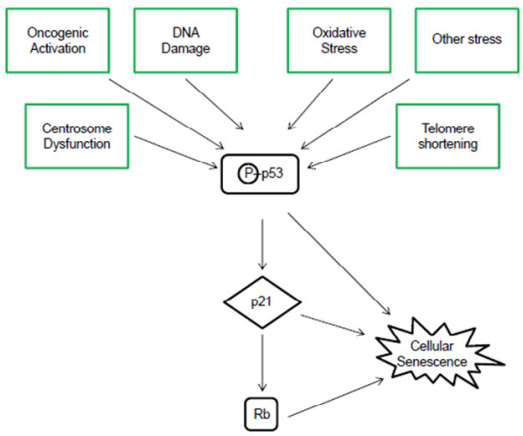

Figure 2: Molecular pathways of cellular senescence. Several types of stresses can predispose cells to undergo senescence. These stresses stimulate cellular signaling pathways resulting in the activation and accumulation of phosphorylated p53 (P-p53) at the centrosome. Phosphorylation of centrosomal p53 subsequently triggers the activation of p21 and Rb (hypo-phosphorylated Rb), and together these three proteins modulate the onset of senescence.

including telomere shortening, oxidative stress, DNA damage, over-expression of tumor suppressors and oncogenic activation, centrosome dysfunction is another form of stress that can predispose cells to cell cycle exit and senescence (Figure 2). In addition, we speculate that these diverse pathways converge on p53. Depending on the source(s) of stress, p53 is promptly accumulated at the centrosome and becomes phosphorylated on different residues by different kinases. Phosphorylation of centrosomal p53 is subsequently needed to fine-tune downstream events, such as the activation of p21 and Rb, ultimately leading to permanent cell cycle arrest and cellular senescence. While much is known about the role of nuclear p53 as a transcriptional regulator, its biological function at the centrosome warrants further investigation. For instance, what are the molecular mechanisms by which p53 is shuttled into and out of the centrosome, and how does the spatial and temporal regulation of p53 phosphorylation modulate its localization and function? Above all, what is the precise role of centrosomally localized p53 in senescence? We believe that answers to these questions should catalyze an exciting wave of research studies into the interconnections between cellular senescence, cell death, and uncontrolled cell growth, critical biological process that are inextricably linked to proper centrosome function.

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