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Review Article

Centrosome positioning in polarized cells: Common themes and variations

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ABSTRACT

The centrosome position is tightly regulated during the cell cycle and during differentiated cellular functions. Because centrosome organizes the microtubule network to coordinate both intracellular organization and cell signaling, centrosome positioning is crucial to determine either the axis of cell division, the direction of cell migration or the polarized immune response of lymphocytes. Since alteration of centrosome positioning seems to promote cell transformation and tumor spreading, the molecular mechanisms controlling centrosome movement in response to extracellular and intracellular cues are under intense investigation. Evolutionary conserved pathways involving polarity proteins and cytoskeletal rearrangements are emerging as common regulators of centrosome positioning in a wide variety of cellular contexts.

Contents

1. Introduction

The centrosome, which is generally localized near the geometric cell center, displays a remarkably well-conserved structure among distant organisms [8]. It consists of a pair of centrioles formed of nine-triplet microtubules. Surrounding the two centrioles, the pericentriolar material supports microtubule nucleation and microtubule minus end stabilization. In most eukaryotic cells, the

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centrosome is the main microtubule-organizing center (MTOC) and thus participates in the control of cell shape, cell division and cell motility [60]. Beyond its function as MTOC the centrosome should also be considered as a signaling platform. This is well illustrated in the *Caenorhabditis elegans* one-cell embryo. The entry of the sperm-supplied centrosome provides signaling molecules that initiate the anterior–posterior cell polarity axis [11,7]. In differentiating neurons, a centrosomal signaling involving CaMKIIβ controls dendrite retraction and pruning [73].

In 1888, Theodor Bovery, who coined the term centrosome, provided the first experimental data on the importance of this "dynamic center" in chromosome segregation and spindle maintenance. Following duplication, the so-called mother and daughter centrioles form the mother and daughter centrosomes. The position of the two centrosomes define the position of the mitotic spindle and hence the orientation and the position of the division plane [68]. The control of mitotic spindle orientation is essential for symmetric and asymmetric cell division. Spindle positioning depends on intracellular cues, in particular in single cell organisms such as budding yeast and in the *C. elegans* zygote. In multicellular organisms, extracellular signals resulting from cell adhesion to the extracellular matrix or from cell–cell interactions serve as major polarity cues. Spindle orientation relative to these environmental cues has a profound impact on tissue architecture. During epithelial morphogenesis, for instance, spindle orientation parallel to the plane of the epithelium drives symmetric cell divisions and tissue spreading [4,14,29], whereas spindle orientation along the baso-apical axis leads to asymmetric division and tissue thickening [55,72]. Defects in centrosome positioning will result in abnormal mitotic spindle orientation and defects in planar division [65]. In the case of asymmetric cell divisions, the orientation and the localization of the mitotic spindle insure that cell fate determinants are differently distributed between the daughter cells [51]. Moreover, the specific segregation of the two centrosomes in the daughter cells suggests that each centrosome detains specific functions during differentiation and that the regulation of centrosome positioning is associated with centriole specific factors. In *Drosophila* male germline stem cells and in mouse embryo neural progenitors, the mother centrosome is retained by the stem cells [101,95]. In contrast, in *Drosophila* neuroblasts, the daughter centrosome remains trapped near the neuroblast apical cortex while the differentiated Ganglion Mother Cell inherits the mother centrosome [47]. In this case, the daughter centriole, in which the protein centrobin is exclusively found, retains most of the pericentriolar material and most of the MTOC activity at the onset of mitosis [74,79].

In interphase cells, the centrosome is tightly associated with the nucleus. The interaction between the centrosome and the nucleus involves the cytoskeleton and multiple proteins of the nuclear envelope [38]. In non-polarized cells, the centrosome and the nucleus localize near the cell center with no preferential orientation of the nucleus–centrosome axis. In polarized cells, the relative position of the centrosome compared to the nucleus corresponds to the main cell polarity axis and has clear implications in cellular functions. In differentiated epithelial cells, the centrosome is localized near the apical surface above the nucleus and contributes to the formation of an apical–basal microtubule network and epithelial polarity [28]. During neuronal differentiation, the centrosome is located between the nucleus and a neurite that will become the single axon while all other neurites will differentiate into dendritic processes [16]. The Golgi apparatus localizes contiguously to the centrosome in a microtubule and dynein dependent manner [76]. Thus, the centrosome together with the Golgi apparatus promotes microtubule polymerization, membrane and protein delivery to favor axonal growth [16]. Because of its essential role in intracellular organization, the centrosome is precisely positioned in the cytoplasm and changes in centrosome positioning occur to facilitate specific cell functions, such as immune cell response or cell migration. When a T cell encounters a target antigen-presenting cell, the centrosome delocalizes to the newly formed immunological synapse (IS) [3]. The reorientation of the centrosome in front of the nucleus and its translocation to the membrane is essential to ensure the polarized delivery of secretory granules to the IS [91]. This event occurs within few minutes after T cell receptor (TCR) engagement and relies on major rearrangements of both the actin and the microtubule networks [3]. In migrating cells, the centrosome generally localizes between the nucleus and the leading edge [36,106]. The Golgi apparatus and the recycling compartment localize with the centrosome in front of the nucleus in the direction of migration. Microtubules emanating from the centrosome and the Golgi complex, extend toward the protrusion most likely to serve as delivery tracks for membrane components and signaling molecules [1,23]. Centrosome re-positioning in response to extracellular and intracellular cues is essential for centrosomal functions and delays in this process have been shown to directly impact how fast the first asymmetric division of *C. elegans* embryo, zebrafish neurulation, T cell immune response, or cell migration are achieved [94,12].

The central position of the centrosome in interphase cells may simply result from a balance of pushing or pulling forces reflecting the cell geometry [60,107]. Both microtubule dynamics and microtubule-associated motors anchored at the cell cortex can promote the centering of microtubule asters in microfabricated chambers [41,53]. The same force generators are likely to be involved in moving the centrosome to a specific location in response to extra or intracellular stimuli. However, the directed movement of the centrosome leading to its precise positioning necessitates the generation of polarized forces and therefore the localized regulation of the force generators. The intimate connection between the centrosome and microtubules has led to an intense investigation of the signaling cascades that control microtubule dynamics and cortical anchoring during centrosome positioning. More recently, the role of acto-myosin contraction has also emerged. In this review, we will examine the latest advances in the understanding of the different mechanisms that ensure correct centrosome positioning. Comparison of the mechanisms involved in various cellular functions gives evidence of redundant pathways that simultaneously control centrosome position and points to recurrent principles and cell-specific variations.

2. Centrosome positioning during cell division

The positioning of the mitotic spindle poles requires the precise localization of both centrosomes and therefore the directed movement of at least one of the centrosomes. Forces generated by the microtubule minus-end directed motor dynein are crucial for correct spindle orientation in various organisms from budding yeast to mammalian cells [56,66,90]. The commonly accepted model involves a cortical pulling mechanism, in which dynein anchored at the cell