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Mechanism of MDCK II cell polarization during the cell division: A computational study

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ABSTRACT

Some epithelial cells form a monolayer and individual cell in the monolayer is polarized with respect to the membrane protein location and the intracellular structure. It is observed that mitosis and cytokinesis occur in parallel to the monolayer plane so that the monolayer structure is maintained. The centrosome locations of non-mitotic cells, however, are not necessarily positioned to lead the parallel cell division. Therefore, there must be mechanisms by which centrosomes get relocated, for example in MDCK II cells, from the apical domain to lateral domain to have a proper mitosis and moved back to the apical domain after the cytokinesis. The mechanisms, however, remain poorly understood, especially the mechanical part. A computational model is constructed for centriolic microtubule asters which are driven by localized molecular motors on the cortical layer. This model shows that the interaction between the cortical bound molecular motors and microtubules can lead the two-way relocation of the centrosome. The model also shows that the microtubule dynamic instability plays an important role in initiating the relocation, the tight junction is a key element in positioning the centrosome, and the swelling nucleus can accelerate the movement of centrosome to the lateral side.

1. Introduction

The orientation of the mitotic spindle determines the direction in which a mother cell divides into two daughter cells [1]. The beginning of mitotic spindle formation can be simply understood as following steps (a) centriolic microtubule aster dissolves microtubules, (b) the mother centrosome produces a daughter centrosome, (c) one centrosome starts growing microtubule aster and moves in a direction toward the cortical layer, (d) the other centrosome starts growing microtubule aster and moves in another direction. The direction that the second centriolic microtubule aster follows is most likely to be toward the opposite direction to which the first centrosome headed because of the volume exclusiveness between two microtubule asters or the repulsive relation between two daughter microtubule asters [2]. Two centrosomes don't need to start the microtubule growth sequentially; simultaneous microtubule growth (steps c and d) will also be subject to the volume exclusiveness or the repulsion between two microtubule asters. The final positions of two daughter centrosomes are likely to be on opposite sides of the nucleus to form the mitotic spindle around the nucleus. Having two centrosomes in opposite sides can be a sufficient condition to collect the right combination of chromosomes and to halve the intracellular material so that the mother cell produces functioning two daughter cells. However, the successful reposition of centrosomes for the spindle formation may not be sufficient condition for cells in organism development at some stages or for some types of cells for their functionality and survival. The directions of mitosis and cytokinesis, that is, the direction mitotic spindle

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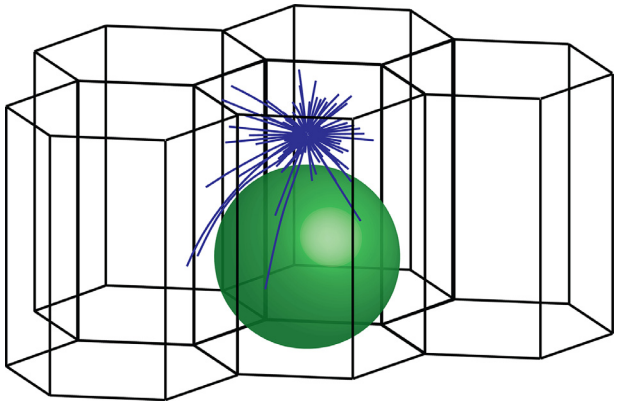

Fig. 1. Schematic diagram of epithelial cells in a monolayer. A single cell is idealized as a columnar cell with identical six sides. Thus, the top view of the monolayer shows the hexagonal lattice. In this diagram, five cells are shown for a better view. Inside the cell, there are microtubule aster and nucleus.

relative to the surroundings, matter in some developmental stages and some cell types. Proper cell division orientation is crucial to morphogenesis of embryos [3,4], and for cell types such as epithelial cells, the cell division direction should not be random for their functionality and to keep the monolayer structure [5–7]. Therefore, the cell division direction choice in embryonic cells and epithelial cells demands more explanation than those simple descriptions such as step c and d above.

There are well-established connections between dynein molecules or cadherin and mitotic spindle polarization. It is well known that molecules on the cortical layer such as dynein molecule and cadherin play key roles in regulating centrosome and mitotic spindle. It was shown that the mutations in genes which are related to the cytoplasmic dynein molecule led to the disruption in spindle orientation or centrosome attachment to the nucleus [8,9]. Blocking the function of cadherin also disrupted the spindle orientation during a mammalian epithelial cell division [10]. The suggested role of dynein molecules in literature (e.g. [8,11]) is that cortical layer bound dynein molecules can contribute to centrosome relocation and spindle orientation by pulling centrosome via microtubules when dynein motors and the cortical layers are well anchored by cadherin. The mechanical interaction between dynein molecule and microtubule also has been studied through computational models in the context of mitotic pole separation [12] and of the centrosome reorientation of T-killer cell engaged with target cells [13]. While there are on/off level connections between dynein molecules or cadherin and mitotic spindle polarization, those connections are not enough to explain the orientation specificity in embryonic or epithelial cells and mechanical details are poorly investigated compared to genomic or biochemical counterparts [14].

To shed a light on the mechanical details of centrosome relocation and to provide explanation toward the epithelial cell mitotic spindle orientation specificity, a computational model for epithelial (MDCK II) cell intracellular mechanics is constructed. The dynein molecule localization on the lateral cortex with the E-cadherin is hypothesized as suggested in [15]. This hypothesis implies that if a microtubule is in contact with the side cortex it will be pulled by dynein molecules on the side cortex [13,16]. Under this hypothesis, a model is designed to study centrosome relocation when the cell undergoes the mitotic processes such as microtubule cytoskeleton reformation, cell growth, and nuclear swelling. Using the model, the dynein pulling is tested as the mechanism of centrosome relocation. There is no other assumption on the nature of the dynein molecule pulling on microtubules than that the pulling direction is from minus end to plus end. Yet, this pulling mechanism must first, guide two daughter centrosomes from the apical domain to two opposite sides of the lateral domain around the nucleus, and second, should move them back to near apical domain after the cytokinesis. Furthermore, the spindle orientation spindle orientation should be parallel to the epithelial plane. The model in this article demonstrates that the dynein molecule microtubule pulling mechanism can achieve the tasks, the round trip of the centrosome, in two different directions with the help of cell shapes change which occur during the mitosis. The cortical layer bound dynein pulling mechanism is modeled following the model that was used to model the centrosome oscillation in killer T cell [13].

2. Methods (model description)

Based on experimental observation [5], an idealized and simplified model of an epithelial cell in monolayer is built. A single epithelial cell is idealized as a hexagonal column, and the monolayer as an assembly of hexagonal columnar cells which constitute hexagonal lattice (top view) as in the diagram in Fig. 1, which is a naturally efficient way of packing two-dimensional space. Inside of the hexa-columnar cell, there are microtubule asters and the nucleus. Cell boundary surfaces are non-deformable walls in each simulation, and the microtubules are elastic rods clamped on centrosomes. Microtubule asters are free to move around inside the cell. The nucleus is an impenetrable immobile ellipsoidal object (including sphere) which may perform prescribed deformation as swelling and become an elongated and bigger ellipsoid. On the cell cortical layer (surface of the hexagonal column), it is assumed that dynein molecules are bound on the lateral cortex, and when microtubules are close enough to the cortical layer, the heads of dynein molecules bind to the microtubules and try to walk,