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Novel role of PKC epsilon in mitotic spindle stability

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Mitosis is a highly regulated process characterized by dramatic and coordinated morphological changes to ensure the fidelity of chromosome segregation. Missegregation of mitotic chromosomes leads to a condition that underlies chromosomal instability(1), which is a hallmark of cancer. In order to assure symmetry and bipolarity of the cell division process, mitotic spindle microtubules properly segregate mitotic chromosomes (2). Among the several isoforms of serine/threonine kinases, PKCε is one of the best understood for its role as a transforming oncogene, and it has been found overexpressed in different types of tumors. In 2008, Saurin and colleagues demonstrated the involvement of PKCε in the regulation of the late stage of mitosis (3). Through its association with 14-3-3 at the midbody, PKCε is essential for the successful completion of cytokinesis, and the inhibition of functional PKCε-14-3-3 complex leads to abscission failure and multinucleated phenotype in cells. In this study, we found that PKCε is involved in mitotic spindle stability. Using fluorescence microscopy, we found that the active form of PKCε (phosphorylated at Ser-729), colocalizes to the centrosome in cells in metaphase, where the mitotic spindle nucleation occurs. Furthermore, experiments of co-immunoprecipitation revealed that, when cells are synchronized in metaphase, PKCε is associated to γ-tubulin, a member of the tubulin superfamily localized to the microtubule organizing centers and is essential for microtubule nucleation from centrosomes. Consequently modulation of PKCε expression affects spindle stability: PKCε downregulation by specific shRNA results in mitotic spindle disorganization with a reduction of the amount of centrosomal and mitotic γ-Tubulin and αβ-tubulin fluorescence. Mitotic spindle formation assays using Nocodazole, known to interfere with the polymerization of microtubules, revealed that cells lacking PKCε were unable to regrow microtubules after depolymerization. These results reveal a novel role of PKCε in mitotic spindle stability, which likely determinant for genome stability.

References:

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Keywords

Mitotic spindle; PKCε; microtubules.

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