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Cell Cycle Dependent Regulation of Microtubule Dynamics by Microtubules Associated Proteins (MAPs) and its Misregulation causes Aneuploidy

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ABSTRACT

Microtubules are intrinsic dynamic polymers but programmed regulation of microtubule dynamics through different phases of cell cycle is modulated by numerous proteins known as microtubules associated proteins (MAPs) and mitotic kinases. Proper attachment of microtubules with kinetochore and adequate tension generation leads to chromosomal congression at metaphase plate, that is followed by movement of sister chromatids towards opposite poles of cells. Impairment, in this process activates spindle assembly checkpoint proteins that hamper cell cycle progression and thus maintains genetic stability. Thus, regulation of microtubule dynamics is important in normal cell cycle progression and to prevent aneuploidy.

Although microtubules are intrinsic dynamic polymers but programmed regulation of microtubule dynamics through different phases of cell cycle is modulated by numerous proteins known as microtubules associated proteins (MAPs) and mitotic kinases[1-3]. Various MAPs present inside the cell maintain balance between polymeric and soluble pool of tubulin and are also responsible for reorientation of microtubule cytoskeleton. Microtubules perform indispensable role in mitosis. During mitosis microtubules attain high dynamic state, 20-100 folds increase in microtubule dynamics is observed during mitosis. The nucleation rate of microtubules from centrosomes during mitosis shows 7-fold enhancement, compared to the interphase microtubules[4, 5]. There is drastic reduction in half-life of polymerized tubulin from 10 minute in interphase cell to merely 10–30 s in mitotic cell[5, 6].

The functional significance of enhanced dynamics after breakdown of nuclear envelope (prophase and prometaphase) is strategic kinetochore capture by highly dynamic microtubules. Highly dynamic microtubules display extended search for kinetochore and get hold of it by increasing in length followed by instantaneous shortening to bring it to metaphase plate[7].

This stochastic search-and-capture process displayed by microtubules emanating from one spindle pole capture kinetochore and a similar process allows other kinetochore of the same chromosomes to be captured by microtubules from other spindle pole, resulting in amphitelic kinetochore-microtubule attachments (51).This process involves proper tension generation and chromosomal congression at so called metaphase plate[8], followed by movement of sister chromotids towards opposite poles of cell. The poleward movement of chromatids is thought to be driven by shortening of kinetochore-attached microtubules. Some motor proteins also contribute in poleward movement of chromatids as well as in chromosomal congression process [9]. The segregation of chromosomes is followed by de-condensation in last phase of mitosis (telophase), thus two identical nuclei are formed. Finally cytokinesis takes place where in

cytoplasm is divided by the contractile action of actin-myosin ring structures originating at the central position of cell[10].

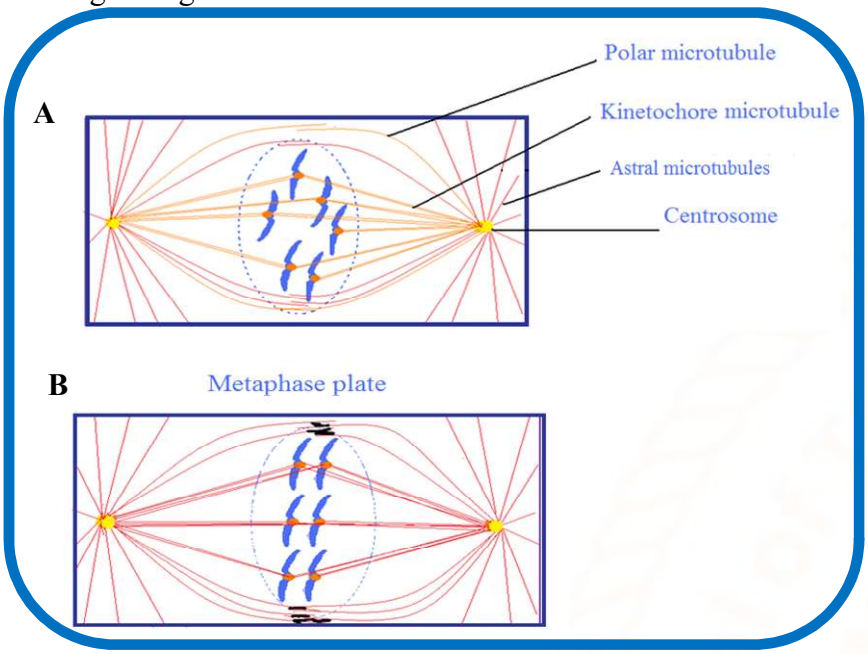

Figure 1: Microtubule dynamics and kinetochore capture: After the breakdown of nuclear envelope, microtubules emanating from centrosome called as kinetochore microtubules get hold of kinetochores of chromosomes and align chromosomes at medial position of cell called as metaphasic plate. Microtubule dynamics plays a vital role in kinetochore capture process. Panel A represents a cell in prometaphase and panel B represents cell in metaphase after chromosomes are aligned at metaphase plate.

During the progression of cell cycle, attachment of the microtubules to the chromosomes at kinetochores and their metaphasic alignment is of utmost importance because the mitotic cell has to ensure that chromosomes are rightly aligned in metaphase before the anaphase is started to ensure proper segregation of chromosomes to the newly formed daughter cells [11]. However, the failure in this process can lead to aberrant chromosome segregation with unaligned chromosomes which could be a cause for chromosomal instability and aneuploidy[12, 13]. To prevent aneuploidy, a stringent signal transduction pathway operates called as "the spindle assembly checkpoint". It is a cell cycle surveillance mechanism which postpones the onset of anaphase till all kinetochores are firmly adhered to spindle microtubules and proper tension is achieved[12]. The spindle checkpoint signaling mechanism comprises of several highly conserved proteins like Mad1, Mad2, Mad3/BubR1, Bub1, Bub3 and Mps1 [13]. During nuclear envelope breakdown kinetochore attachment process starts and spindle checkpoint proteins are activated and recruited to unattached kinetochores and kinetochores devoid of proper tension, resulting in the inhibition of anaphase-promoting-complex/cyclosome (APC/C). An activated spindle checkpoint prevents the beginning of anaphase through inhibition of protein proteolysis and hence prevention of chromatid separation[11, 13]. However, compromised spindle checkpoint mechanism may result in faulty separation of sister chromatids even in the presence of misaligned chromosomes that could be a cause for chromosomal instability (CIN) and hence result in gain or loss of chromosomes called as aneuploidy, a striking feature in human cancer[14]. Significantly, many tumors are known with weakened spindle checkpoint function, thus lack of sustenance of signal for repair of errors[15, 16]. Hence, an impaired spindle checkpoint may directly lead to chromosomal instability and tumorigenesis in human cancer[15].

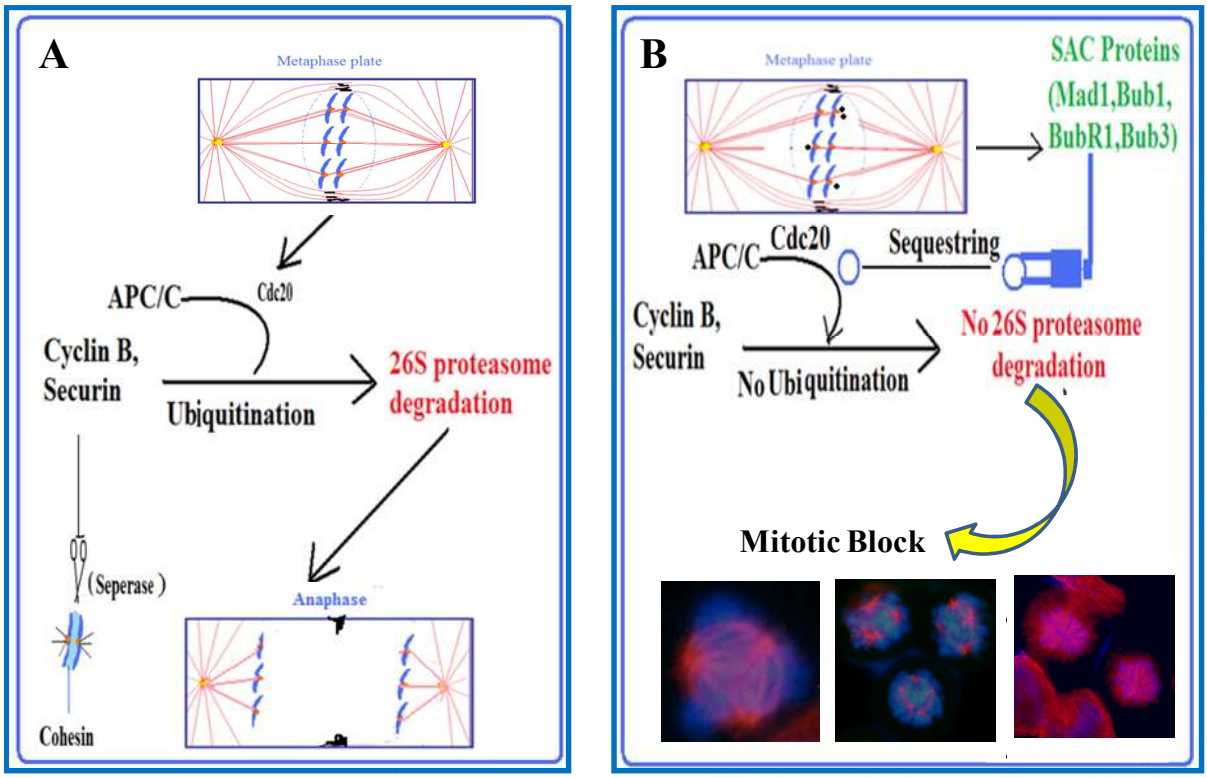

Figure 2: Mitotic progression: (A) On each kinetochore, when microtubules are adhered and proper tension is generated, the checkpoint proteins are satisfied and released. Then anaphase promoting complex (APC/C) promotes ubquitination of cyclin B and its degradation by 26S proteasome thus providing the biochemical signal for cells to proceed towards anaphase. (B) On the other hand, unattached kinetochore and imbalanced kinetochore tension leads to recruitment of SAC proteins (Mad2, BubR1) to Kinetochore. SAC proteins sequester Cdc20 a cofactor of APC/C, thus inhibiting proteosomal degradation of Cyclin B and Securin. Cyclin B is a protein which regulates early phase of mitosis and securin is inhibitor of separase. Thus, prevention of proteosomal degradation of Cyclin B and Securin leads to mitotic block.

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