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Review Article

Regulatory mechanisms that control mitotic kinesins

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ABSTRACT

During mitosis, the mitotic spindle is assembled to align chromosomes at the spindle equator in metaphase, and to separate the genetic material equally to daughter cells in anaphase. The spindle itself is a macromolecular machine composed of an array of dynamic microtubules and associated proteins that coordinate the diverse events of mitosis. Among the microtubule associated proteins are a plethora of molecular motor proteins that couple the energy of ATP hydrolysis to force production. These motors, including members of the kinesin superfamily, must function at the right time and in the right place to insure the fidelity of mitosis. Misregulation of mitotic motors in disease states, such as cancer, underlies their potential utility as targets for antitumor drug development and highlights the importance of understanding the molecular mechanisms for regulating their function. Here, we focus on recent progress about regulatory mechanisms that control the proper function of mitotic kinesins and highlight new findings that lay the path for future studies.

Contents

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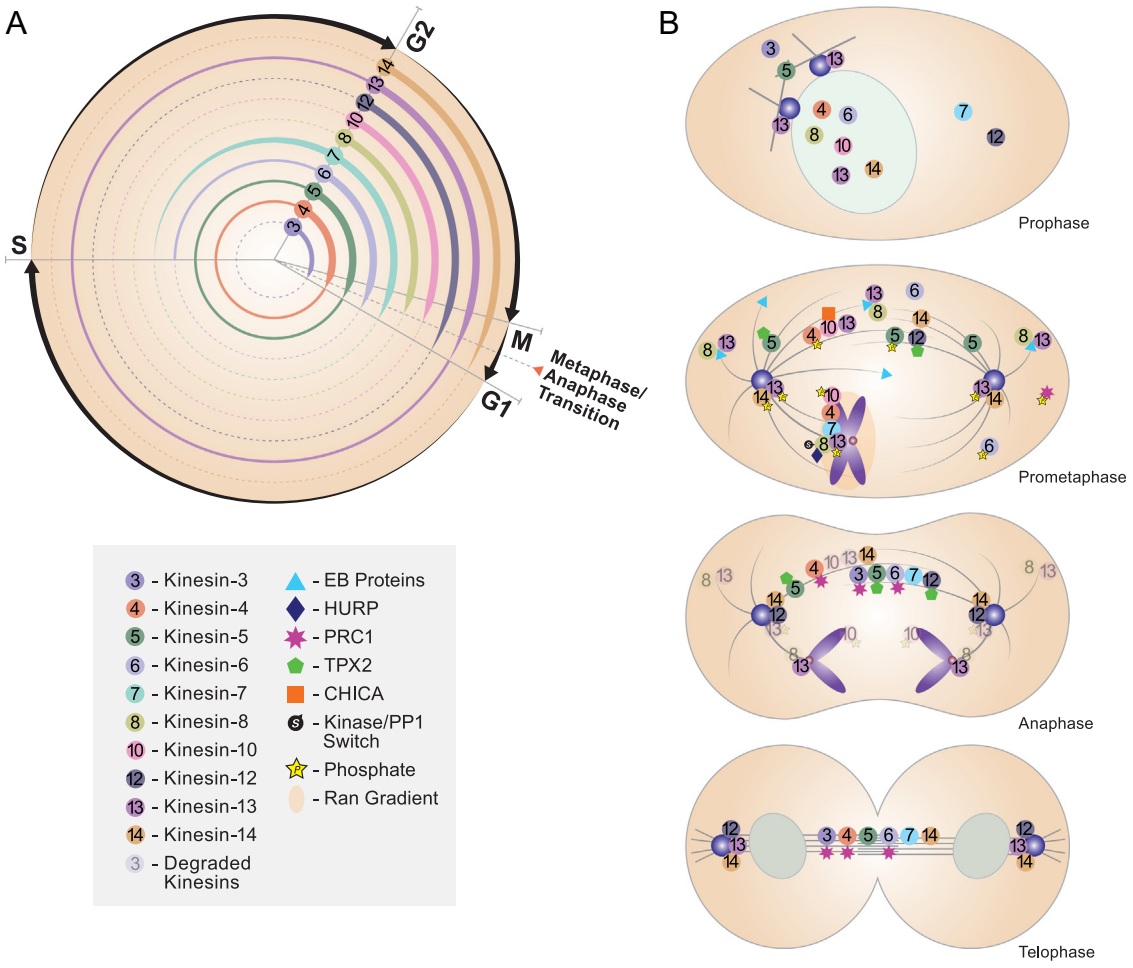

Fig. 1 – Mechanisms that control mitotic kinesin localization. (A) Mitotic kinesins are regulated during the cell cycle through synthesis and degradation. The numbered circles represent different kinesin families and are in general representative of vertebrate kinesins. (B) Distinct kinesin family members are localized to different regions of the spindle, which is often controlled by binding partners and by regulatory proteins. Note that the precise localization of individual motors may vary between systems, and this provides a general overview of motor localization as it relates to motor function. Cartoon representations are modeled after [37].

Mitotic motors are controlled temporally to function during mitosis

Many mitotic kinesins are regulated through temporal synthesis and degradation so that the protein is only present when needed during mitosis (Fig. 1A). Early studies of kinesin cell cycle expression came from simply analyzing protein expression and localization throughout the cell cycle. More recent studies include genomic approaches that have begun to uncover the transcriptional networks by which kinesin expression can be regulated. For example, binding of one or more mitosis-specific transcription factors, such as FOXM1, can promote expression of many cell cycle regulated genes at the G2/M transition [1]. This is interesting because FOXM1 is aberrantly expressed in many cancers and could contribute to the upregulation of kinesins seen in cancer cells [2]. Other important transcriptional networks controlling kinesin expression include those genes regulated by the DREAM/MMB (Myb-MuvB) complexes [3]. This is a multi-subunit complex that associates with repressive subunits, which inhibit gene expression during G1/S, and with activating subunits, which stimulate gene expression during G2/M. The promoters of the DREAM/MMB regulated genes often contain either a cell cycle homology region or a cell cycle dependent element, which can be bound by either the repressive or activating subunits of the DREAM/MMB complex. The DREAM/MMB complex is also highly integrated with the p53 control network, and p53 is mutated in a large number of cancers, highlighting the importance of the exquisite cell cycle control networks. In addition, the DREAM/MMB complex is important in controlling developmental expression of many proteins and may help tie together the understanding of the differential regulation of kinesin expression during development and in different cell types and how this relates to cell proliferation in general.

The levels of kinesin proteins are also controlled by their regulated destruction at the end of mitosis. Several kinesins contain destruction box (D-box) or KEN box sequences that are targeted by APC^{Cdc20} and by APC^{Cdh1}, which are ubiquitin ligases that tag proteins for destruction at the metaphase/anaphase transition and during early G1, respectively. The Kinesin-10, Kid, is one of the best-characterized examples of regulated destruction of a kinesin. Kid is a plus-end directed kinesin that is localized to chromosome arms and contributes to chromosome congression by mediating the polar ejection force [4]. It is destroyed at the

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