Global effects from errors at single kinetochores

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***Short Abstract* — Correct chromosome segregation during mitosis relies on the mitotic apparatus, a complex macromolecular machine that specifically assembles during this cell cycle stage. We previously established a quantitative model to describe metaphase chromosome dynamics via kinetochore-microtubule (KT-MT) interactions mediated by viscoelastic linkages. Here, we used this quantitative framework in combination with experimental approaches to characterize the metaphase and anaphase KT/chromosome dynamics in cells with merotelic KT mis-attachments. We found that mis-attachment can affect the dynamics of KTs other than the mis-attached one. Moreover, we investigated the role of Kif2a in correction of KT mis-attachments in PtK1 cells.**

***Keywords* — Kinetochore, microtubule, merotelic, Kif2a**

I. Background

We previously developed a quantitative framework integrating forces that control the attachment to MTs, positioning, and dynamics of amphitelically (correctly) attached KT pairs during metaphase [1]. The model describes and predicts many aspects of spindle dynamics. Here, we utilized this model to address important biological questions. First, we investigated the chromosome dynamics (both in metaphase and anaphase) associated with erroneous KT-MT attachment, specifically merotelic attachment (a single KT bound to both spindle poles instead of just one). Merotelic KT mis-attachment is a major cause of aneuploidy in mammalian cells [2] and a major cause of chromosomal instability in cancer cells [3]. These mis-attachments arise frequently in healthy mitotic cells [4], but most of them are corrected before anaphase onset. This correction process depends upon microtubule dynamics fine-tuned by many mechanical and molecular signaling mechanisms, some of which have been extensively dissected and others that are not well understood. MT poleward flux is one such mechanism because, although there is evidence for a role of MT poleward flux in correction of KT mis-attachments [5], the exact mechanism is not clear.

II. Results

We combined mathematical modeling and quantitative live-cell microscopy to study the effect of KT mis-attachment on chromosome dynamics and the contribution of MT poleward flux to correction of KT mis-attachments.

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A. *Merotelic KT attachment and metaphase dynamics*

Our mathematical model reproduced the observed shift of merotelic KTs closer to the cell equator and their lack of oscillation [6] and predicted the sister of a merotelic KT displays reduced oscillation. Quantification of KT oscillation in live cells confirmed that the sister of a merotelic KT displayed shorter oscillation period and amplitude compared to KTs of normally attached chromosomes.

B. *MT poleward flux and correction of mis-attachments*

Model simulations predicted that reduced MT poleward flux resulted in larger numbers of MTs bound to KTs, suggesting reduced correction of KT mis-attachments. Experimental reduction of MT poleward flux resulted in a larger fraction of KT-bound MTs and increased rates of cells progressing through mitosis with merotelically attached KTs, confirming the model predictions.

C. *Merotelic KT attachment and anaphase dynamics*

We finally found that reduction of MT poleward flux did not affect overall rate of chromosome movement in anaphase. But strikingly, in anaphase cells with merotelic KTs that lagged behind at the spindle equator, not only the merotelic KT did not move poleward, but the poleward movement of all other, normally attached KTs was slower compared to anaphase cells without merotelic KTs.

III. Future directions

Computer simulations will be used to dissect the mechanism responsible for the merotelic KT-dependent effect on anaphase chromosome dynamics and formulate predictions that we can test experimentally.

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