features or those of mesenchymal origin by influencing brachyury levels. The ΔNp63-brachyury nexus hence may be relevant for a spectrum of human cancers that express high levels of these transcription factors and offer new targets and strategies for therapy.

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Kip3 Clusters Kinetochores

Comment on: Wargacki M, et al. Cell Cycle 2010; 9:2581-8.

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During mitosis chromosome segregation relies on the action of microtubules within the mitotic spindle. Each chromosome is attached to spindle microtubules via its sister kinetochores, the proteinacious complexes found at opposite sides of its centromere.[1] The subset of microtubules that becomes attached to the kinetochores is referred to as kinetochore microtubules (kMTs). While each kinetochore attaches to ~25 microtubules in higher eukaryotes,[2] the budding yeast kinetochore binds only a single microtubule.[3] Chromosome movement is coupled to kMT polymerization/depolymerization dynamics. During metaphase, as sister kinetochores establish bipolar attachments with dynamic kMTs, chromosomes are congressed and aligned at the center of the spindle.[1] In budding yeast, congression clusters the sister kinetochores in two regions on either half of the spindle.[4] The mechanism(s) regulating the dynamics of individual kMTs to attain metaphase chromosome congression remains largely unclear.

Cells utilize motor proteins to facilitate and coordinate mitotic events. Kinesin-8 is a conserved subclass of Kinesin microtubule motors that regulates microtubule dynamics in diverse organisms. When Kinesin-8 is knocked-down in higher eukaryotic cells chromosomes are unable to achieve metaphase congression resulting in failure to enter anaphase and mitotic arrest.[5, 6] The budding yeast Kinesin-8, Kip3, functions both as a conventional plus-end directed motor and a plus-end specific microtubule depolymerase.[7, 8] Yeast cells lacking Kip3 do not arrest in mitosis, suggesting that Kip3 is not essential for establishing bipolar sister kinetochore attachments and/or alignment prior to anaphase onset. However, recent work by Wargacki and colleagues[9] provides evidence that Kip3 function is important to achieve proper kinetochore clustering during metaphase.

Imaging fluorescently-tagged kinetochores in live yeast cells, Wargacki et al.[9] observed variability in kinetochore positioning along the spindle axis in the absence of Kip3. One possibility is that Kip3 uses its length-dependent microtubule depolymerization activity[8] to ensure that the kMTs of sister kinetochores are of equal length. This would in turn cluster sister kinetochores equidistant from either spindle pole. Paradoxically the authors report a decrease in kMT length in the absence of Kip3, and it remains unresolved how the loss of this depolymerase results in shorter kMTs.

Movement and congression of chromosomes requires coordination between the dynamic states of sister kMTs. Interestingly, Wargacki and colleagues[9] find that the shorter kMTs are accompanied by increased inter-kinetochore distance, which may reflect perturbed tension at kinetochore-microtubule attachments. Kip3 may therefore play a role in coordinating sister kinetochore directional movement by correlating kMT dynamics with the amount of tension and/or compressive forces experienced at either kinetochore. Presumably such coordination in higher eukaryotes must be extended to all ~25 microtubules at each kinetochore rather than the single kMT found in budding yeast. Perhaps the complexity in synchronizing large numbers of kMTs is one reason why higher eukaryotes display more adverse metaphase defects than do budding yeast following perturbation of Kinesin-8. However, the molecular mechanism(s) through which Kip3 controls the dynamics of individual kMTs remains to be determined.

In previous work, Tytell and Sorger[10] observed an increase in lagging chromatids during anaphase and that a subset of chromatids experienced prolonged interruptions during anaphase poleward movement in cells lacking Kip3. Based on these and other findings Tytell and Sorger[10] concluded that Kip3 facilitates the synchronous anaphase movement of chromatids toward the spindle poles, a process intimately connected to kMT depolymerization. In light of the current study, Wargacki and colleagues[9] propose that defects in kinetochore clustering and the resulting disparate starting positions upon anaphase onset may be the major cause of the lagging anaphase chromatids. While the failure to congress could explain in large part the accumulation of lagging chromatids, it does not directly account for discontinuous poleward movement unless unclustered chromatids also experience subsequent problems with anaphase movements. As it stands, it would appear that Kip3 distinctly functions in metaphase to cluster chromatids and in anaphase to facilitate poleward chromatid movement. Determining the overlap between Kip3 function during metaphase and anaphase may be particularly tractable in budding yeast because the loss of Kip3 does not prevent progression into anaphase.

Overall, these findings highlight the conserved role of Kinesin-8 in chromosome congression across different systems and raise interesting questions about the mechanisms underlying the role of Kip3 in regulating kinetochore clustering.

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