

Comment on "A Centrosome-Independent Role for γ -TuRC Proteins in the Spindle Assembly Checkpoint"

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Müller *et al.* (Reports, 27 October 2006, p. 654) proposed a role for microtubule nucleation in mitotic checkpoint signaling. However, their observations of spindle defects and mitotic delay after depletion of γ -tubulin ring complex (γ -TuRC) components are fully consistent with activation of the established pathway of checkpoint signaling in response to incomplete or unstable interactions between kinetochores of mitotic chromosomes and spindle microtubules.

The mitotic checkpoint (also known as the spindle assembly checkpoint) is an essential cell cycle control mechanism activated during every cell cycle, just after mitotic entry. Its action ensures accurate chromosome segregation before cell division. Each unattached kinetochore, the protein complex assembled at the centromere of each chromosome, generates an inhibitory "wait" signal that precludes mitotic advance. Production of the "wait" signal is silenced at individual kinetochores by stable attachment to spindle microtubules (1–3). Müller *et al.* (4) proposed that in addition to this kinetochore-derived signaling, the mitotic checkpoint can be activated by errors in microtubule nucleation.

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The initial evidence for this proposal included sustained checkpoint activation after reduction in γ -tubulin or other constituents of γ -tubulin ring complex (γ -TuRC), which is required for centrosomal and noncentrosomal microtubule nucleation. As expected (5, 6), reduction in γ -TuRC components produced pleiotropic effects on spindle assembly, including monopolar spindles or bipolar spindles lacking centrosomes.

In contrast to the claims of Müller *et al.*, however, this outcome offers no support for microtubule nucleation–derived mitotic checkpoint signaling. Because even a single unattached (7) or unstably attached (8) kinetochore can generate an inhibitor sufficient to delay advance to anaphase, such a conclusion would require demonstration that kinetochore-derived checkpoint signaling was silenced (for example, by the release from kinetochores of the mitotic checkpoint components Mad1 and Mad2 or by measuring the number and stability of kinetochore micro-

tubules as well as tension developed between sister kinetochores). An especially relevant example is the chronic checkpoint activation after dampening microtubule assembly dynamics in the presence of a low dose of taxol. Despite bipolar spindle assembly, in which both sister kinetochores of most duplicated chromosome pairs are attached to microtubules from opposite spindle poles, improperly attached kinetochores produce chronic mitotic checkpoint activation (9, 10).

Rather than offering support for a contribution of γ -TuRC proteins to mitotic checkpoint activation, the evidence of Müller *et al.* (4) is fully consistent with the established pathway of kinetochore-derived checkpoint signaling: Disruption of normal spindle microtubule nucleation after depletion of γ -TuRC generates deficits in kinetochore-microtubule attachment, which in turn provoke sustained mitotic delay.

References

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