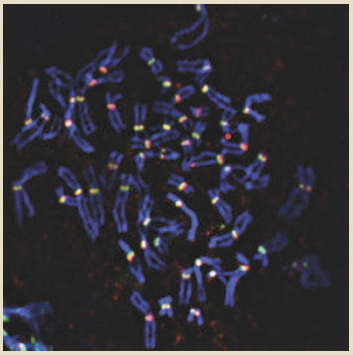
Separating sisters

Successful cell division depends on the accurate segregation of sister chromatids into daughter cells. It is equally important that chromatids do not separate before the metaphase–anaphase transition, and this is controlled by the presence of the cohesin protein complex that links the chromatids together. Bub1 (a serine/threonine protein kinase) and Sgo1 are known to be necessary for ensuring cohesin remains unharmed during prophase, and a recent study by Tang *et al.* (*Dev. Cell* **10,** 1; 2006) describes the mechanism underlying their protective action.

The removal of cohesin in mitosis occurs by a two-step process: first, it is removed from chromosome arms in prophase; second, it is removed from centromeres at the metaphase–anaphase transition. This second step occurs when centromeric cohesion is cleaved by separase, releasing sister chromatids from one another. Before this step, Sgo1 protects centromeric cohesin by counteracting the actions of mitotic kinases in prophase.

As the Sgo1 protein does not have inherent catalytic activity, the authors looked for Sgo1-binding proteins that might help block the action of these kinases. Immunoprecipitation experiments identified specific subunits of protein phosphatase 2A (PP2A) as a binding partner of Sgo1, suggesting that this phosphatase may be important for its protective effects. Inactivation of PP2A, either by chemical inhibition or RNA interference (RNAi), caused chromosomal mis-segregation in HeLa cells. Furthermore, a point mutation in the amino terminus of Sgo1 that disrupts the interaction with PP2A prevented the localization of Sgo1 to the centromere and caused chromosome segregation defects. This suggests that a PP2A–Sgo1 interaction is necessary for accurate chromosome segregation and that PP2A is required for centromeric localization of Sgo1. Similar RNAi experiments that depleted Sgo1 and Bub1 indicated that the latter is necessary for centromeric localization of PP2A whereas the former is not.



Metaphase chromosome spread of HeLa cells stained with anti-Sgo1 (red), CREST (green) and DAPI (blue).

The *Drosophila* homologue of Sgo1, MEI-S332, requires phosphorylation by Polo kinase before it is released from the centromere in anaphase. Tang and colleagues examined whether a similar mechanism was necessary for the release of Sgo1 from centromeres in PP2A-depleted cells. Although centromeric localization of Sgo1 was diminished in PP2A-depleted cells, in cells where Plk1 (a polo-like kinase) was codepleted the centromeric localization of Sgo1 was restored and chromosomes segregated correctly; this indicates that the presence of Sgo1 at the centromere requires PP2A to counterbalance the removal of Sgo1 by Plk1.

This paper establishes that binding of PP2A to Sgo1 is necessary to ensure its correct localization and for proper chromosomal segregation. It also indicates that Bub1 regulates the centromeric localization of PP2A, which, in turn, maintains Sgo1 at centromeres by counteracting Plk1-mediated removal. As no binding has been shown between Bub1 and Sgo1, it now seems that PP2A is the missing link between these two proteins that together protect centromeric cohesin.

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