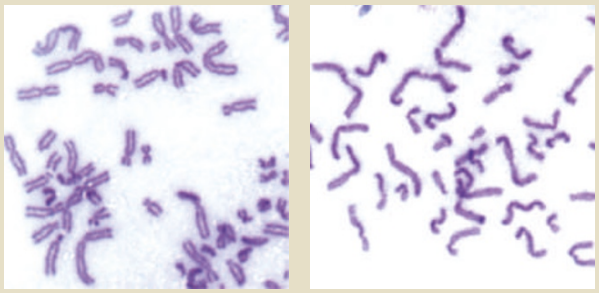
Wapl takes cohesin off chromosome arms



Chromosomes from wild-type mitotic cells are only attached by their centromeric region (left), whereas in Wapl-depleted cells, where cohesin is still bound to chromosomes arms, sister chromatids are unresolved (right). Picture kindly provided J.-M. Peters.

Sister-chromatid cohesion is initiated during DNA replication and is essential for correct biorientation of the chromosomes on the mitotic spindle. Cohesion is mediated by the conserved multiprotein complex, cohesin, which is thought to adopt a ring shape around the DNA. Now, two studies from the laboratories of Jan-Michael Peters (*Cell* **127,** 1–13; 2006) and Tatsuya Hirano (*Curr. Biol.* **16,** 1–12; 2006) suggest that the heterochromatin protein Wapl controls cohesin dissociation from the vertebrate chromatin.

In budding yeast, the activity of the protease separase leads to cohesin degradation at anaphase and to the separation of sister chromatids. In vertebrates, however, cohesin is removed from chromosome arms without degradation at the beginning of mitosis. This leads to the resolution of sister chromatids into the well known X-shape, in which the chromatids are only attached by their centromeres where cohesin persists until it is degraded by separase at anaphase. How exactly cohesin dissociates from chromosome arms in early mitosis without being degraded is currently unclear.

To find regulators of cohesin function, Peters and colleagues immunoprecipitated the cohesin complex from mammalian cell extracts and used mass spectrometry to identify a protein of unknown molecular function, the orthologue of *Drosophila* Wapl (Wings apart like 1). Wapl mutant flies exhibit chromosome segregation defects, an observation that led Hirano and colleagues to independently examine its role in vertebrates. Both studies show that, in mammalian cells, Wapl is a chromatin-associated protein, which interacts with cohesin subunits and leaves the mitotic chromosomes at the same time as cohesin.

Both groups report that in cells lacking Wapl, cohesin remains associated with the chromatids during mitosis, indicating that Wapl is neither required for formation of the complex nor for its loading on the chromosomes. As a result of persistent cohesin on the chromosomes, sister-chromatid resolution is impaired and progression through the early stages of mitosis is delayed (see figure). Overexpression of Wapl has the opposite effect and leads to premature separation of sister chromatids. In addition, Peters and colleagues showed that cells lacking Wapl accumulate more of the cohesin subunit Smc1 on interphase chromatin than wild-type cells, and fluorescent recovery after photobleaching (FRAP) data indicates that Smc1 remains on the chromatin for longer in the absence of Wapl. This suggests that Wapl also regulates the dynamic chromosome association of cohesin in interphase — a characteristic that may be required for the known role of cohesin in DNA repair during G2.

In mice, Wapl overexpression leads to tumorigenesis, and in *Drosophila,* Wapl is required for heterochromatin formation. Interestingly, its more distant relative in budding yeast, Rad61, has been shown to be involved in DNA cohesion. The biochemical mechanism of how Wapl mediates the removal of cohesin from chromatid arms in mammalian cells awaits further study.

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