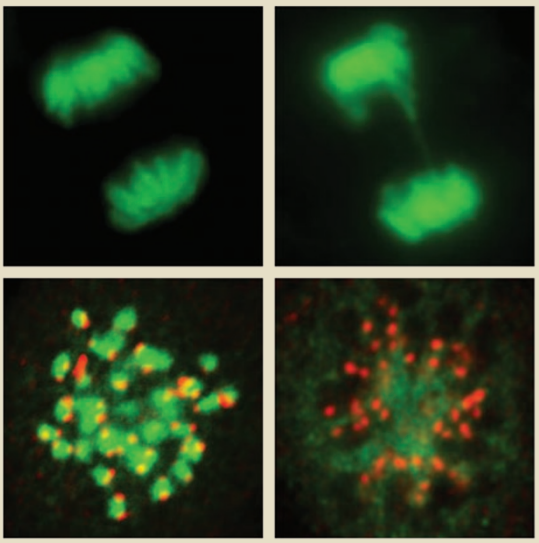
RanBP2 resolves sister centromeres

Chromosome missegregation in mitosis can result in aneuploidy, which is closely associated with tumorigenesis. During S phase and the metaphase–anaphase transition in mitosis, Topoisomerase IIα (Topo IIα) disentangles sister chromatids to enable their separation in anaphase. Van Deursen and colleagues have now discovered that RanBP2, a nucleoporin with SUMO E3 ligase activity involved in both nucleocytoplasmic transport and mitosis, is essential for Topo IIα localization to inner centromeres and proper sister centromere resolution (*Cell* **133,** 103-115, 2008).

During interphase, RanBP2 (or Nup358) functions mainly as a facilitator of macromolecular nuclear export as part of a multiprotein nuclear-pore complex that includes the Ran GTPase-activating protein 1 (RanGAP1) and the SUMO E2-conjugating enzyme Ubc9. At the onset of mitosis, however, RanBP2, RanGAP1 and Ubc9 accumulate at the kinetochore of spindle-associated chromosomes, and previous work has shown that depletion of RanBP2 in cancer cell lines causes mitotic defects, including chromosome misalignment and multipolar spindles. To assess the the physiological role of mammalian RanBP2 and its SUMO E3 ligase activity, van Deursen and colleagues generated an allelic series of mutant mice that express graded levels of RanBP2, and showed that there is an inverse correlation between RanBP2 expression levels and aneuploidy.

Whereas cells from RanBP2-deficient mice did not display obvious transport-related defects, a significant fraction of the cells with lower amounts of RanBP2 formed chromatin bridges during anaphase. Curiously, none of the mitotic defects described previously in RanBP2-depleted cancer cell lines were detected in primary mouse embryonic fibroblasts (MEFs) from RanBP2-deficient mice, an observation that highlights the divergence between model systems.

Previously, bridge formation during anaphase was linked to impaired Topo IIα-mediated decatenation of sister chromatids. Van Deursen and colleagues noticed that Topo IIα failed to accumulate at inner centromeres when RanBP2 levels were critically low. Indeed, RanBP2 associated with and SUMOylated Topo IIα both *in vitro* and *in vivo*. Significantly, RanBP2 mutants with defective SUMO E3 ligase activity showed aberrant chromosome segregation and Topo IIα centromeric localization, whereas the ectopic expression of the RanBP2 SUMO E3 ligase domain in RanBP2-deficient cells was sufficient to restore proper localization of Topo IIα and to prevent anaphase-bridge formation. Thus, Topo IIα is likely to mediate the mitotic effects of RanBP2.



Wild-type MEFs undergo accurate chromosome separation in anaphase (top left, YFP–H2B-labelled DNA in green), whereas RanBP2-deficient MEFs form chromatin bridges due to incomplete DNA decatenation (top right). Topo IIα (bottom panels, green) nomally accumulates at pericentromeric regions in prometaphase (bottom left, centromeres in red), whereas RanBP2-deficient cells show diffused Topo IIα cytosolic localization (bottom right).

Interestingly, mice with very low levels of RanBP2 were more prone to tumorigenesis. These findings establish a requirement for RanBP2 in the maintenance of genomic stability and the suppression of tumorigenesis, at least in part through the mitotic SUMOylation of Topo IIα. The tumour-suppressive activity of RanBP2 is consistent with data showing that RanBP2 expression is decreased in certain human cancers. A number of proteins that mediate nuclear transport of macromolecules through nuclear pores have been implicated in mitosis (for example, Nup107-160 and the small GTPase Ran). It will be interesting to further address the potential contribution of all these factors to human tumorigenesis.

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