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CORBIS

GENOME INSTABILITY

Forbidden CIN

> These studies add to our molecular understanding of how cells might prevent CIN, genome instability and cancer.

Aberrant mitosis results in chromosomal instability (CIN; the gain or loss of whole or large fragments of chromosomes), which is the major form of cancer genome instability. Two papers provide new insight into how the yeast Bub1 and *Drosophila melanogaster* BUB1-related (BUBR1) kinases help to ensure accurate chromosome separation and prevent CIN.

Sister chromatids are anchored to the mitotic spindle at their centromere by kinetochores and are held together by a ring-shaped cohesin complex. Cohesin is protected from early dissociation from centromeres by the protein phosphatase 2A (PP2A)–shugoshin (Sgo) complex until all sister chromatids are ready for segregation, when it is then cleaved by separase. The spindle assembly checkpoint (SAC) senses unattached kinetochores and stalls mitosis by preventing separase activation. Bub1 recruits SAC components to kinetochores and has a role in chromosome alignment at the spindle, although its phosphorylation target is unknown. Kawashima *et al.* reveal that Bub1 phosphorylates histone 2A (H2A) at Ser121, which allows the correct positioning of Sgo proteins at the centromere and prevents inappropriate chromosome partitioning.

The authors created *Schizosaccharomyces pombe* expressing H2A with a Ser to Ala mutation at position 121 (H2A-SA cells), and compared them with cells expressing kinase-dead Bub1 (Bub1-KD cells). The localization of Sgo1 (required for PP2A loading) and Sgo2 (required for SAC activation and kinetochore attachment) to centromeres is abolished in H2A-SA and Bub1-KD cells, which have defects in the SAC, kinetochore attachment and cohesin protection. Forced localization of Sgo1 and Sgo2 at centromeres restores these defects, suggesting that Bub1-mediated H2A Ser121 phosphorylation regulates Sgo localization. This method of regulation might be conserved to ensure accurate chromosome separation and prevent CIN, as blocking H2A phosphorylation at Ser121 in *Sacchoromyces cerevisiae*, and the analogous site in mammalian cells, also impairs Sgo localization.

Royou *et al.* looked at the mechanisms of CIN by studying mitosis in *D. melanogaster* larvae with damaged X chromosomes, generated by expressing an endonuclease that cuts the heterochromatic region near the centromere. This results in chromosomal fragments with (centric) and without (acentric) the centromere. Although acentric fragments lack kinetochores, they can still segregate to opposite poles. Notably, live cell imaging of neuroblasts from larvae shows that acentric and centric X chromosome fragments are connected by a 'DNA tether', which is decorated with BUBR1, its interacting partner Polo kinase, and other mitotic regulators. Acentric segregation defects, and the number of acentric fragments not tethered to their centric partners, are increased in cells with compromised BUBR1 or Polo functions, and this correlates with decreased larvae survival. Therefore, BUBR1 and Polo help to prevent CIN by ensuring the accurate segregation of acentric chromosomes.

These studies add to our molecular understanding of how cells might prevent CIN, genome instability and cancer.

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ORIGINAL RESEARCH PAPERS
Kawashima, S. A. *et al.* Phosphorylation of H2A by Bub1 prevents chromosomal instability through localizing shugoshin. *Science* **327**, 172–177 (2010) | Royou, A. *et al.* BubR1- and Polo-coated DNA tethers facilitate poleward segregation of acentric chromatids. *Cell* **140**, 235–245 (2010)