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CELL CYCLE

Passengers travel together

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The chromosomal passenger complex (CPC) regulates several mitotic events, including chromosome segregation and cytokinesis. The CPC consists of Aurora-B kinase and three regulatory subunits: INCENP, survivin and borealin. The targeting of Aurora-B by these subunits to the right substrate at the right place and time (to centromeres in metaphase and, later, to the central spindle and midbody) is crucial for the functioning of the CPC. Structural studies of the regulatory subunit complex shed new light on how interactions between these subunits relocalize the CPC during mitosis.

> "…the three regulatory subunits form a three-helix bundle, each contributing one helix."

Elena Conti and colleagues defined the minimal domains of INCENP, survivin and borealin that could form a functional ternary complex, revealing a 1:1:1 complex between full-length survivin, borealin$_{10–109}$ and INCENP$_{1–58}$. The crystal structure of the complex showed that the three regulatory subunits form a three-helix bundle, each contributing one helix.

Using site-directed mutagenesis combined with RNA-interference complementation studies, Conti and co-workers tested the requirements for CPC localization. Borealin mutants that could bind to INCENP but not to survivin, or that could bind to survivin but not to INCENP, failed to localize to either centromeres or the central spindle and midbody in cells in which endogenous wild-type borealin was knocked down. This implies, among other things, that survivin is not sufficient for centromere targeting of the CPC, as had previously been suggested. In addition, an engineered INCENP–Aurora-B subcomplex, which exists in the absence of survivin and borealin, is not functional — it does not localize to centromeres or to the central spindle and midbody and is unable to restore CPC function in CPC-depleted cells.

The structure further revealed a negatively charged cluster of conserved amino acids on INCENP and a positively charged cluster on borealin. By mutating either cluster to the opposite charge in the context of the full-length protein, the CPC was able to form and localize to centromeres but not to the central spindle or midbody. Cells progressed through early mitosis but were defective in cytokinesis. So, localization of the CPC to the central spindle and midbody is essential for cytokinesis. Taking the structural and functional studies together, the authors conclude that "…the intertwined structural interactions of the core components lead to functional interdependence." The three regulatory subunits therefore seem to function as a single unit.

Another interesting aspect of the structure is that survivin is monomeric within the complex, whereas the unbound form exists as a homodimer. The crystal structure reveals that the interaction of borealin$_{10–109}$ and survivin mimics that of the survivin homodimeric interaction. Similar findings have been reported by Andrea Cochran and colleagues; they showed that survivin binds borealin as a monomer, and that borealin structurally mimics and displaces a survivin monomer in the survivin dimerization interface. In a short commentary, Bill Earnshaw and colleagues speculate that survivin functions in mitosis as a monomer in complex with borealin and INCENP, whereas homodimeric survivin might function to regulate apoptosis — a hypothesis that will be interesting to test.

Arianne Heinrichs

ORIGINAL RESEARCH PAPERS Jeyaprakash, A. A. *et al.* Structure of a survivin–borealin–INCENP core complex reveals how chromosomal passengers travel together. *Cell* **131**, 271–285 (2007) | Bourhis, E. *et al.* The mitotic regulator survivin binds as a monomer to its functional interactor borealin. *J. Biol. Chem.* 19 Sep 2007 (doi:10.1074/jbc.M706233200)
FURTHER READING Ruchaud, S. *et al.* The chromosomal passenger complex: one for all and all for one. *Cell* **131**, 230–231 (2007) | Ruchaud, S. *et al.* Chromosomal passengers: conducting cell division. *Nature Rev. Mol. Cell Biol.* **8**, 798–812 (2007)