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CHROMOSOMES

Single is sometimes best

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URLs

CENP-A
http://ca.expasy.org/uniprot/P49450

CID
http://flybase.bio.indiana.edu/.bin/fbidq.html?FBgn0040477

KLP59C
http://flybase.bio.indiana.edu/.bin/fbidq.html?FBgn0034824

The centromere-specific histone variant CENP-A, which is known as CID in *Drosophila melanogaster*, and the centromere-associated kinetochore are crucial for the attachment of the microtubule spindle, congression to the metaphase plate and the subsequent chromosome separation in anaphase. A single centromere–kinetochore association per chromosome ensures accurate chromosome segregation during mitosis and meiosis. Gary Karpen and colleagues now show that the overexpression of CID leads to its mislocalization and the formation of functional ectopic kinetochores, which might provide a possible mechanism for genome instability during cancer progression.

The overexpression of CID caused a widespread mislocalization of CID in cultured cells, and led to growth defects, abnormal development and lethality in flies. Cytological analysis of fixed cells revealed several mitotic defects, including stretched, fragmented and lagging chromosomes during anaphase. In addition, time-lapse studies confirmed these results in live cells and also showed delays in mitosis and chromosome loss. The authors further established that these mitotic defects were distinct from those caused by the loss of endogenous centromere function or caused by the failure to separate sister chromatids. So, Karpen and colleagues concluded that the phenotypes that were observed are a direct result of the mislocalization of CID.

Kinetochore formation is poorly understood, but is thought to depend on the presence of CID. Indeed, the Karpen team obtained several lines of evidence, which indicated that ectopic kinetochores are formed in response to mislocalized CID. First, several proteins that are associated with centromeric chromatin and inner- and outer-kinetochore proteins colocalized with the mislocalized CID. Second, the kinetochore-associated kinesin KLP59C, the dynein motor protein and the microtubule plus-end binding protein MAST colocalized at multiple, ectopic chromosome regions. Lastly, the authors observed microtubule attachments at ectopic sites that also contained CID and an outer-kinetochore protein.

Together, these findings indicate that CID mislocalization leads to the formation of ectopic kinetochores that are probably functional. The presence of multiple centromere–kinetochore associations per chromosome could therefore be responsible for the observed chromosome separation defects and the consequent cellular and organismal phenotypes. It will be interesting to investigate the prevalence of mislocalized CENP-A in human cancers to test this hypothesis.

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ORIGINAL RESEARCH PAPER Heun, P., Erhardt, S. *et al.* Mislocalization of the *Drosophila* centromere-specific histone CID promotes formation of functional ectopic kinetochores. *Dev. Cell* **10**, 303–315 (2006)