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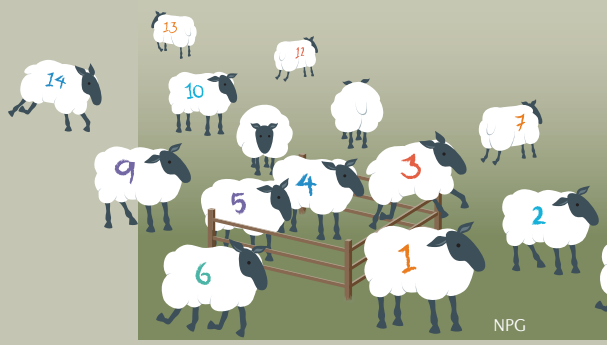
CELL CYCLE

Maintaining centrosome copy number



Centrosomes, which are composed of two centrioles and pericentriolar material, serve as the main microtubule-organizing centre in animal cells. They duplicate once per cell cycle so that each daughter cell inherits one centrosome. Hossain and Stillman now reveal the mechanism by which the origin recognition complex subunit 1 (ORC1) controls centrosome and centriole copy number and how this function may relate to Meier–Gorlin syndrome.

ORC1 is known to regulate centrosome duplication in addition to its role in DNA replication, and human ORC1 had previously been shown to inhibit both cyclin A–cyclin-dependent kinase 2 (CDK2) and cyclin E–CDK2 kinase activities, the latter of which is important for centrosome duplication. In this study, the authors identified a carboxy-terminal PACT domain in ORC1 that is responsible for its localization to the centrosome. Furthermore, by testing the capacity of different purified human ORC1 fragments to inhibit CDK2 activity, they identified the amino-terminal amino acids 1–250 as the CDK inhibitory domain (CID), which inhibits both cyclin A–CDK2 and cyclin E–CDK2. Interestingly, both the PACT and CID domains were found to be necessary and sufficient to prevent centrosome reduplication.

Recent studies reported mutations in ORC1 that are associated with Meier–Gorlin syndrome, which is a form of microcephalic primordial dwarfism. Hossain and Stillman found that one of these mutations (which changed Arg 105 to Glu) specifically abolished the ability of ORC1 to inhibit cyclin E–CDK2 and also allowed centrosome and centriole reduplication. Furthermore, the authors identified a cyclin-binding domain within the CID that specifically binds to and inhibits cyclin A–CDK2.

Thus, the ORC1 CID contains two distinct regions that mediate the inhibition of cyclin A–CDK2 and cyclin E–CDK2, and these control both DNA replication and centrosome copy number. Other mutations associated with Meier–Gorlin syndrome alter pre-replication complex assembly and reduce proliferation in human cells, and this suggested that microcephaly and dwarfism seen in patients with Meier–Gorlin syndrome are due to defects in DNA replication. Hossain and Stillman now propose that the more severe Meier–Gorlin syndrome phenotypes of people carrying ORC1 mutations are due to defects in both DNA replication and centrosome duplication.

> “Meier–Gorlin syndrome phenotypes … are due to defects in both DNA replication and centrosome duplication.”

Kim Baumann

ORIGINAL RESEARCH PAPER Hossain, M. & Stillman, B. Meier–Gorlin syndrome mutations disrupt an Orc1 CDK inhibitory domain and cause centrosome reduplication. *Genes Dev.* 1 Aug 2012 (doi:10.1101/gad.197178.112)