In Focus

The different ties that bind

Two homologues of the cohesin protein Scc3 have specialized roles in chromatid cohesion.

B efore they separate into daughter cells during mitosis, sister chromatids are held together by cohesin complexes. But these complexes aren't the same along the entire length of the chromatids, according to Canudas and Smith: The version of cohesin that links sister telomeres is different from the form that fastens centromeres together (1).

Cohesin consists of four subunits, three of which (Smc1, Smc3, and Scc1) form a ring associated with the fourth subunit, Scc3. In vertebrate cells, Scc3 comes in two, slightly different versions, called SA1 and SA2. It's not clear why vertebrate cells express both of these variants—one possibility is that they have different functions. In 2007, Silvia Canudas, Susan Smith, and their colleagues at the New York University School of Medicine found that, unlike SA2, SA1 interacts with a telomere protein called TIN2. Cells unable to separate their telomeres during mitosis are rescued by knocking down SA1, suggesting that SA1 might be specifically involved in telomere cohesion (2).

Canudas and Smith therefore took a closer look at the chromosomes of cells lacking SA1, using fluorescent probes to

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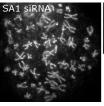
different regions of sister chromatids to determine how closely they were held together. Cohesion between sister telomeres was prematurely lost in the absence of SA1, and chromatid arms drifted further apart, too. Sister chromatids remained attached at their centromeres, however. The situation was reversed in cells missing SA2—sister centromeres were prema-

turely separated while chromatid arms and telomeres retained their association.

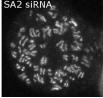
Telomere and centromere cohesion are thus regulated by different versions of the cohesin complex, containing either SA1 or SA2, respectively. Why should

FOCAL POINT











separated

Silvia Canudas (left) and Susan Smith (right) reveal that different regions of sister chromatids are held together by cohesin complexes containing different versions of the cohesin subunit Scc3. Cells lacking Scc3^{SA1} can't keep sister telomeres and chromatid arms attached (center panels), whereas cells deficient in Scc3^{SA2} lose cohesion at sister centromeres (right panels).

these chromosomal regions be held together in different ways? Smith speculates that some of the unique features of telomere replication might require cohesion to be regulated differently at chromatid ends.

Knocking down SA1's telomeric binding partner TIN2 also caused chromatid arms to separate, indicating that telomere cohesion is particularly important for sister chromatid attachment. Smith is excited by this unexpected finding: "There must be something special happening at telomeres for it to have such a dramatic influence on cohesion." Telomeric cohesin complexes contain-

ing SA1 and TIN2 might help stabilize cohesins on chromatid arms, preventing them from slipping off the chromosome ends.

Sister telomere cohesion is important for other reasons, too. Canudas and Smith found that cells lacking either SA1 or TIN2 were unable to repair double-stranded DNA breaks and were also prone to completely losing their telom-

eres. Both phenotypes could be caused by a failure to keep sister chromatids close enough for them to undergo homologous recombination, preventing the cells from repairing damaged DNA or lengthening telomeres via a replication pathway called ALT (3). Some tumor cells rely exclusively on the ALT pathway to maintain or lengthen their telomeres. Smith plans to investigate the effect of removing SA1 and TIN2 from these cells, predicting that the loss of telomere cohesion should have particularly dramatic consequences. The researchers are also interested to see whether aging cells with shorter telomeres suffer decreased levels of chromatid cohesion.

The major question in the cohesin field, however, is to understand how the complex holds chromatids together. The most widely supported mechanism is the one-ring model, in which a single ring of Smc1, Smc2, and Scc1 surrounds both sister chromatids (4). But recently an alternative, "handcuff" model was proposed in which separate rings around each chromatid are linked by a single molecule of Scc3 (5). Smith thinks that their data support the latter model, with SA1 doing the job at telomeres and SA2 filling in at centromeres. "Our results fit nicely with the handcuff mechanism," says Smith. "If you believe in that model, you'd predict that depleting SA1 or SA2 would cause a loss of cohesion just as we've seen."

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