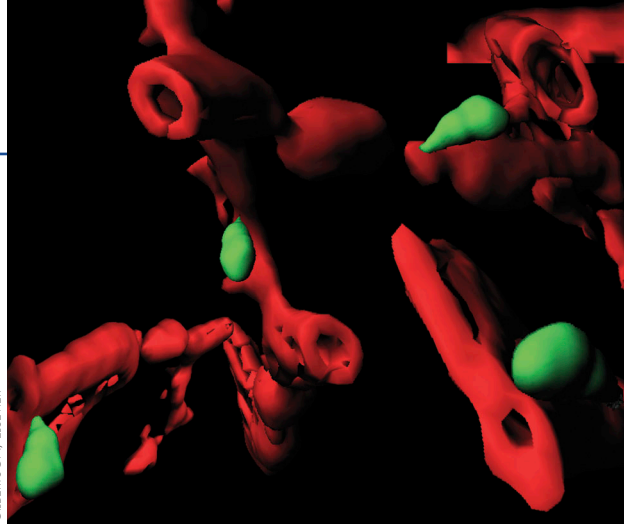
Research Roundup

Coddling cancer



GILBERTSON/ELSEVIER

Cancer stem cells (green) snuggle up to blood vessels (red).

The brain pampers not just its normal stem cells, but also the cancer stem cells responsible for most tumor growth, report Christopher Calabrese, Richard Gilbertson (St. Jude Children's Research Hospital, Memphis, TN), and colleagues. The study is the first to demonstrate that tumors contain a stem cell niche and may help researchers devise ways to evict the cells from their cushy digs.

Neighboring cells cradle stem cells within a structure termed a niche. Besides providing protection, niche cells release factors that maintain stem cells' ability to divide. But researchers weren't certain whether cancer stem cells (CSCs) also reside within niches in tumors.

Using multiphoton laser scanning microscopy, Gilbertson and colleagues observed that CSCs adhere to capillaries within brain tumors, suggesting that the vessels fashioned a niche. To determine whether this interaction was vital for cancer growth, the researchers nurtured balls of CSCs in partitioned wells that allowed the cells to exchange molecules with—but not touch—other cell types. CSC spheres cultivated with endothelial cells grew faster than did CSCs reared with control cells.

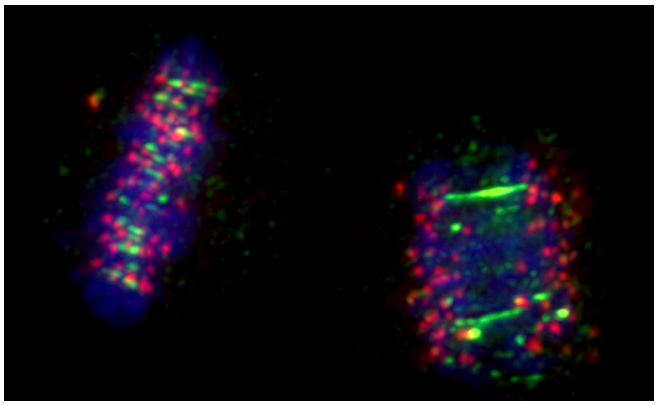
Gilbertson and colleagues also gauged whether niche cells control CSCs's ability to seed new tumors by injecting cell mixtures into the brains of immune-deficient mice. The combination of CSCs and endothelial cells spawned enough tumors to kill the rodents within four weeks, versus seven weeks for CSCs alone. The scientists then implanted CSCs into the brains of mice and treated the animals with two types of antiangiogenesis drugs. The medications reduced the density of capillaries in the implants and slashed the rate of tumor growth by removing CSCs. "The immediate microenvironment is likely to be generating or maintaining CSCs," says Gilbertson. What researchers don't understand, he adds, is why the niche for CSCs promotes rampant cell division, whereas the niche for normal stem cells encourages more leisurely growth. JCB

Reference: Calabrese, C., et al. 2007. *Cancer Cell.* 11:69–82.

Chromosomes can't let go

Like lovers reluctant to part, sister chromatids prolong their physical attachment during mitosis, according to Christoph Baumann, Erich Nigg (Max Planck Institute of Biochemistry, Martinsried, Germany), and colleagues. The researchers observed previously unreported chromatin threads that tether separating chromatids until late in anaphase. By monitoring tension in the forming threads during metaphase, a protein called PICH might help to ensure that microtubules are correctly attached to the kinetochores.

Nigg and colleagues chanced on the filaments while hunting for proteins under the control of Polo-like kinase 1. This kinase strips off the cohesins that bind chromosome arms together and performs a variety of other tasks during mitosis. The protein they discovered, PICH, is a predicted helicase that congregates on the kinetochores and centromeres. To the team's surprise, it also adorns enigmatic threads that connect sister chromatids during metaphase and anaphase. The researchers suspect that these filaments are composed of catenated strands of centromeric chromatin. "The last connection between sister chromatids might be breaking much later than previously thought," says Nigg.



NIGG

A chromatin thread (green) stretches between anaphase chromatids (right).

PICH is part of the spindle assembly checkpoint (SAC), which halts mitosis if the chromosomes aren't properly hitched to the mitotic spindle. When researchers depleted PICH with siRNA, for example, a SAC protein called Mad2 was lost from kinetochores, and two drugs that normally spur the SAC to block mitosis failed to work, indicating that the SAC was disabled.

PICH might help answer the long-standing question of how the SAC senses tension between sister kinetochores. If the kinetochores are correctly attached to microtubules, the tether will stretch as the sister chromatids are pulled in opposite directions. PICH could detect this change and signal the SAC to shut down, allowing mitosis to proceed. Topoisomerase enzymes would then decatenate the threads and permit the chromatids to finally part. To bolster the hypothesis, researchers now need to demonstrate that PICH responds to tension, says Nigg. JCB

Reference: Baumann, C., et al. 2007. *Cell.* 128:101–114.

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RECQ1's double duty

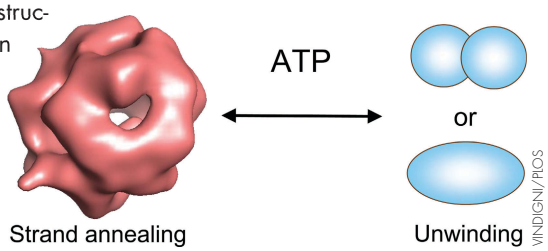
The RECQ1 helicase can unwind DNA or stitch it back together. Which job the protein performs depends on how much help it gets, say Laura Muzzolini, Alessandro Vindigni (International Centre for Genetic Engineering and Biotechnology, Trieste, Italy), and colleagues. Unwinding is the job of single molecules or dimers, whereas oligomers of five or six enzymes take on annealing.

RECQ1 peels open DNA to permit replication and transcription. Why it also reseals strands isn't certain, but it may be assisting with repair. A further mystery is how the same molecule pulls off these two opposing tasks.

The team found that RECQ1 comes in two versions: a small form that's a monomer or a dimer; and a hefty size composed of pentamers or hexamers. Mixing in single-stranded DNA pushed the balance toward the larger version, but ATP favored the smaller one. Scanning electron microscopy of the larger oligomer showed a three-ringed structure that falls apart upon addition of ATP. Together, these findings suggest that the larger oligomer is responsible for annealing and the small version for unwinding.

The researchers bolstered that inference with competition experiments. If enzymes band together to open up DNA, adding nonfunctional mutant RECQ1 under single-turnover conditions should slow unwinding. The mutant had no effect, indicating that RECQ1 works to unwind DNA either alone or in tightly bound pairs. JCB

Reference: Muzzolini, L., et al. 2007. *PLoS Biol.* doi:10.1371/journal.pbio.0050020.

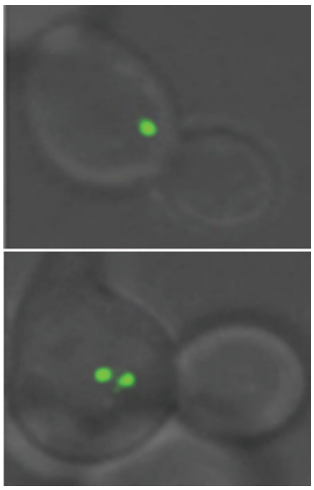


ATP binding flips RECQ1 from strand-annealing oligomer to strand-unwinding monomers or dimers.

Keeping sisters close

One mechanism for holding sister chromatids together during mitosis isn't enough, report Kenji Shimada and Susan Gasser (Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland). They identify a second mechanism that involves the origin recognition complex, which serves earlier in the cell cycle to instigate DNA replication.

The cohesin complex connects sister chromatids until the metaphase-to-anaphase transition. But Shimada and Gasser depleted one of the ORC components from yeast cells and found evidence that it helps out. When production of one ORC component was switched off after replication was complete, the cells stalled in the G2 or M phase. The spindle checkpoint was activated, indicating that chromatid cohesion had gone awry. When the researchers tracked sister chromatid adhesion in cells lacking ORC, they found that the strands were prematurely separating at all three positions they checked. Reinstating the ORC component spurred the chromatids to reunite.



Chromatids (green) fall apart when ORC vanishes (bottom).

Shimada and Gasser also determined that inserting extra copies of an ARS, an ORC-binding locus, into one yeast chromosome could restore normal sister attachment, even in cells lacking functional cohesin. The researchers conclude that, although ORC can't substitute for cohesin, the two complexes operate independently to strap sister chromatids together. Why cells need two methods to secure sister chromatids is a mystery, says Gasser. But, she adds, ORC's sister act may be a side effect of another of its suspected functions: linking heterochromatin domains. JCB

Reference: Shimada, K., and S. Gasser. 2007. *Cell.* 128:85–99.

Why are cells so tense?

Cells might be able to rapidly adjust their stiffness by contracting myosin motors, according to a new cytoskeleton model from Daisuke Mizuno, Christoph Schmidt (Georg-August-Universität, Göttingen, Germany), and colleagues.

Cells adjust their rigidity when they interact with the extracellular matrix, for example, and when an external force acts on them. To mimic cytoskeleton dynamics, the researchers sandwiched a gel of cross-linked actin fibers and myosin motors between a coverslip and a microscope slide. Using a laser to jiggle tiny beads embedded in the gel, they could gauge the gel's stiffness and measure the motions generated by the motors. Myosin's action increased tension in the actin fibers and raised the gel's stiffness by up to 100 times. Per actin filament, it only required a fraction of a piconewton to cause this dramatic effect, less force than a single myosin molecule produces, Schmidt notes.

The model captures several other aspects of cell dynamics. Random competition between motor clusters can trigger local contractions within the gel, for instance, and the slow rise of tension followed by sudden release matches behavior in real cells.

The results imply that to become more rigid, "the cell simply contracts its muscles," says Schmidt. A cell may change its stiffness through this flexing alone, without altering actin polymerization or other properties. The researchers are now using embedded beads to measure forces within living cells. JCB

Reference: Mizuno, D., et al. 2007. *Science.* 315:370–373.