Cells only exit metaphase if all their chromosomes are both attached and under tension from microtubules of the bipolar spindle, which pull on sister kinetochores that face in opposite directions. Now, Benjamin Pinsky, Sue Higgins, and colleagues (Fred Hutchinson Cancer Research Center, Seattle, WA) report that tension creation requires Mtw1p and associated proteins, and is sensed by the conserved Ipl1p/Aurora B protein kinase.

In the current model for Ipl1p action, many chromosomes initially have both kinetochores attached to a single pole. Ipl1p detaches tensionless chromosomes (left, arrow) and then strengthens elongating spindles (right). Ipl1p in green, spindles in red.

**Managing tension**

The resulting lack of tension turns on Ipl1p, which detaches kinetochores so that they are free to have another go at attaching to opposite poles. This detaching activity can be mimicked by adding low doses of microtubule-depolymerizing drugs to cells lacking Ipl1p.

But what feeds in to Ipl1p? Most kine-tocho problems cause attachment-related defects and delays, but cells that don’t generate tension should rely specifically on Ipl1p to delay the cell cycle. The Seattle group found that Mtw1p and several associated proteins fit the bill.

In cells lacking Mtw1p, chromosomes floated free, presumably after Ipl1p detected the apparent lack of tension and set them loose. Sure enough, removing Ipl1p from the mutant cells allowed these chromosomes to maintain their attachments. Just how Mtw1p creates tension is unknown. It could convert initial side-on microtubule attachments at the kinetochores into force-producing end-on attachments, or stimulate microtubule dynamics that pull on kinetochores. It will be easier to differentiate between these and other models after determining the compositional and structural differences between attached and unattached kinetochores.

Once attachment is complete, the connection between sister chromatids is dissolved by separase, leading to anaphase movement and an immediate loss in tension. It would be disastrous if Ipl1p now took over, sensed the lack of tension, and caused a mass dumping of chromosomes before they are pulled to opposite ends of the cell. Ipl1p does indeed leave, in a complex with the inner centromere protein (INCENP) Sli15p. It remains unclear what triggers the departure from kinetochores. But Gislene Pereira and Elmar Schiebel (University of Manchester, Manchester, UK) now shed some light on what eventually targets Ipl1p–Sli15p to spindles. They find that separate activates some Cdc14p phosphatase so that it can dephosphorylate Sli15p, thus directing the complex to the spindle where it can recruit proteins that stabilize the elongating spindle.


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**Civil war in the immune system**

Autoimmunity seems like a model for the immune system gone awry, but things could be a lot worse, say Gizi Wildbaum, Menahem Nahir, and Nathan Karin (Technion, Haifa, Israel). They find that the immune system responds to autoimmunity, and thus keeps itself in check, by making antibodies to its own pro-inflammatory mediators.

Clues to this self-regulatory behavior emerged from earlier immunization studies. The group succeeded in combating autoimmune diseases by injecting adjuvant plus DNA vaccines encoding pro-inflammatory mediators. Antibodies against the vaccine-encoded mediators apparently dampened both inflammation and disease. But this antibody response looked less like a de novo response and more like the amplification of an existing response. Sure enough, when the Israeli group looked in models of autoimmunity, they found antibody responses against common pro-inflammatory mediators such as TNF-α. The anti–TNF-α response could be prevented by inducing neonatal tolerance to TNF-α; this resulted in a much more serious disease after subsequent induction of autoimmunity mimicking rheumatoid arthritis.

The natural antibody response was directed at pro-inflammatory rather than regulatory mediators, and was seen only during auto-immune rather than local inflammatory reactions. This specificity remains a mystery. “The next question is to find the difference between an immune response and an autoimmune response,” says Karin. “Nobody has really found a difference.” One possibility is that the immune system somehow reacts to any self protein that rises far above its normal level. Or there may be earlier controls on the production or regulation of the cells that make the antimediator antibodies. “We’re entering an empty field here,” says Karin. “It’s not an easy question to answer.”


Arthritis (left) gets worse if the immune system is prevented from making antibodies to its own TNF-α (right).
Catenin keeps vesicles close

Synapse creation and maintenance takes more than the transport of proteins to the correct site, according to Shernaz Bamji, Louis Reichardt (University of California, San Francisco, CA), and colleagues. They find that synaptic vesicles are kept localized, ready for action on the presynaptic side, thanks to a PDZ-binding domain on β-catenin. The β-catenin is localized by cadherin adhesion proteins, thus linking axon–dendrite adhesion to the localization of presynaptic vesicles.

Loss of β-catenin is not exactly disastrous. Mice with β-catenin deleted from hippocampal neurons after synapse formation showed normal levels of docked neurotransmitter vesicles, and broadly similar short-term responses to stimulation. But, in the mutants, nondocked vesicles were not as well localized at the site of action, so prolonged stimulation led to a faster drop-off in transmission. Similar results were seen in vitro after expression of a β-catenin lacking its PDZ-binding domain.

With β-catenin functioning as a scaffold, “it’s not clear to me how much adhesion you need as opposed to signaling,” says Reichardt. “Cadherins do nucleate this diversity of signaling pathways. Whether you need contact [between axon and dendrite] because that nucleates something or contact because that puts you into position [for signaling] is not known.”


Worms delay in deep sleep

Worms deprived of all oxygen can pause, take a deep breath, and enter a suspended animation from which they can emerge unscathed several days later. Now, Mark Roth (Fred Hutchinson Cancer Research Center, Seattle, WA) and colleagues show that these worms use the spindle checkpoint to prevent passage through mitosis during anoxia. This arrest is essential for the worms’ survival.

The Seattle group knew that the anoxic response was not just an exaggerated version of the hypoxic (low oxygen) response, because hypoxia-inducible factor 1 (HIF-1) was not needed for survival in anoxia. They conducted an RNAi screen, and found that two genes are uniquely required for survival in anoxia: san-1 (suspended animation 1, which is similar to the spindle checkpoint gene mad3) and mdr-2 (similar to mad2). Worm embryos lacking either protein die after their cells fail to arrest in metaphase during anoxia.

Anoxic worm cells arrest at several points in the cell cycle, presumably using a variety of proteins to mediate these arrests. And the cell cycle is not an anoxic worm’s only concern. “There are some pretty profound things it has to think about to do with bioenergetics,” says Roth. Entropy must be fought, and in particular ion gradients need to be maintained. “If you don’t do that,” says Roth, “you’re dead.”

The details of how that is achieved remain a mystery, but Roth has ideas about the general goal. For an anoxic worm, he says, “you may not have the furnace, but you better not blow out the pilot light. We think glycolysis is the pilot light.”

Anoxic survival capabilities extend up to larger animals—pigs can have all their


S is for sticky

A kinase better known for triggering DNA replication also helps create the sticky heterochromatin at centromeres of fission yeast, according to Julie Bailis, Susan Forsburg (Salk Institute, La Jolla, CA), and colleagues.

The dual action makes sense, as chromosomes must be stuck together as soon as they are replicated. The responsible kinase activity, Hsk1 (CDC7)–Dfp1, is restricted to S phase, when DNA replication takes place.

Dfp1 turned up in a two-hybrid screen with Swi6, the fission yeast equivalent of heterochromatin protein 1 (HP1). Cells with a mutant Dfp1 that no longer binds Swi6 can replicate their DNA but suffer segregation errors when their defective centromeres fall apart. Swi6 localization is normal in these cells but, based on in vitro results, Swi6 phosphorylation may be reduced. This is the first indication that Swi6 localization is not sufficient to define heterochromatin function.

An interesting parallel is known in budding yeast, where establishment of silent heterochromatin at the mating type locus requires passage through S phase, though not DNA replication. Budding yeast lacks an HP1 homologue, but perhaps other proteins serve an equivalent heterochromatic function.