Research Roundup

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 tochore 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 kinetochore 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 separate, 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 separase 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.

Reference: Pereira, G., and E. Schiebel. 2003. Science. 10.1126/science.1091936. Pinsky, B.A., et al. 2003. Dev. Cell. 5:735–745.

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 autoimmune 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.”

Reference: Wildbaum, G., et al. 2003. Immunity. 19:679–688.

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