IN BRIEF

MEIOSIS

Direct coupling between meiotic DNA replication and recombination initiation.

Borde, V., Goldman, A. S. & Lichten, M. *Science* **290**, 806–809 (2000)

During meiosis, information is swapped between parental chromosomes by homologous recombination. Initiation of this process requires a double-stranded DNA break (DSB) which, according to this paper, is introduced in a replication-dependent manner. The authors show that by delaying replication of a chromosomal segment, the formation of a DSB can be delayed in that segment.

CHROMOSOME BIOLOGY

Cleavage of cohesin by the CD clan protease separin triggers anaphase in yeast.

Uhlmann, F. *et al. Cell* **103**, 375–386 (2000)

Disjunction of homologous chromosomes in meiosis I depends on proteolytic cleavage of the meiotic cohesin Rec8 by separin.

Buonomo, S. B. C. *et al. Cell* **103**, 387–398 (2000)

Two distinct pathways remove mammalian cohesin from chromosome arms in prophase and from centromeres in anaphase.

Waizenegger, I. C. *et al. Cell* **103**, 399–410 (2000)

This trio of papers — two from Kim Nasmyth's lab and one from Jan-Michael Peters and colleagues — tackle the question of how sister-chromatid cohesion is regulated. The first shows that separin, a conserved protein responsible for cleaving the Scc1 subunit of cohesin, is a cysteine protease related to caspases. Moreover, *in vitro* it alone is enough to cleave Scc1, an event that triggers sister chromatid separation. The second paper shows that cleavage of Rec8 — the meiotic equivalent of Scc1 — by separin at two different sites is necessary for the resolution of chiasmata during meiosis. Finally, Waizenegger *et al*. propose that, in vertebrates, cohesin is removed from chromosome arms by a different, cleavage-independent mechanism to the one that removes centromeric cohesin and involves cleavage of Scc1.

CYTOSKELETON

Dynein, dynactin, and kinesin II's interaction with microtubules is regulated during bidirectional organelle transport.

Reese, E. L. & Haimo, L. T. J. *Cell Biol.* **151**, 155–165 (2000)

Dynein and kinesin motors transport organelles to opposite ends of microtubules, but it is a mystery what controls the net direction of the vesicles. This paper shows that dynein, dynactin and kinesin II are continuously associated with pigmented organelles in *Xenopus* melanophores, indicating that association of the motors with the organelle is not regulated. The direction is, in fact, determined by controlling the binding of motors to microtubules, and this probably occurs through phosphorylation.

DNA REPAIR

A taxing question

How does mutation of a protein involved in the response to DNA damage lead to defects in the nervous system? Reporting in *Genes and Development*, Peter McKinnon and co-workers describe a mechanism that might, they say, normally act during development to eliminate neural cells with genomic damage.

Several human syndromes with defective responses to DNA damage also lead to neurological lesions, and the best studied of these is the rare disorder ataxia-telangiectasia. Mutation of the protein responsible, the ATM kinase (reviewed by Kastan and Lim on page 179 of this issue), results in progressive neurodegeneration. But how?

To find out, McKinnon and colleagues drew on their knowledge of DNA ligase IV (Lig4) — a molecular glue that binds double-stranded DNA breaks (DSBs), particularly during the process of *V(D)J* recombination. Mice with no functional Lig4 show widespread apoptosis in the developing nervous system, as well as embryonic lethality and defects in *V(D)J* recombination and lymphocyte development. The lack of Lig4 probably allows DSBs to accumulate and, given that ATM acts as a sensor for DSBs, the authors wondered whether these lesions might activate ATM (designated Atm in the mouse).

To answer this question they turned it on its head — if Atm is activated in response to a lack of Lig4, then might a lack of Atm rescue the Lig4-null phenotype? McKinnon and colleagues generated $Atm^{-/-}Lig4^{-/-}$ double-knockout mice, and found that, in contrast to $Lig4^{-/-}$ single knockouts, these mice showed no apoptosis in the embryonic nervous system. Moreover, most of the processes required for correct neural development (as measured with markers for neuronal differentiation) were normal in the $Atm^{-/-}Lig4^{-/-}$ mice. They were smaller than their wild-type littermates, however, and they also died roughly two days after birth.

The authors then tested whether the observed defects in the immune systems of $Lig4^{-/-}$ mice were rescued in the double knockouts. And they weren't — these animals showed T-cell defects and an almost complete lack of $CD4^+CD8^+$ thymocytes. McKinnon and co-workers believe that this result reflects the tissue-specific functionality of Atm, showing that the observed neuronal rescue is highly selective.

Plenty of questions remain. One is how these findings tie in with other studies showing that a lack of p53 also rescues the embryonic lethality in $Lig4^{-/-}$ mice, albeit to a differing degree (for example, $p53^{-/-}/Lig4^{-/-}$ mice survive until six weeks of age). Another is whether other types of DNA lesion can trigger apoptosis in developing neurons, a possibility that seems very likely.

Finally, McKinnon and co-workers point out that it's remarkable how development can proceed so completely in the $Atm^{-/-}Lig4^{-/-}$ mice — after all, their neurons must contain many unrepaired DSBs. Perhaps, then, it's no surprise that the mice die so soon after birth. And thinking about these results in the context of the human disease ataxia-telangiectasia, a lack of ATM probably allows cells with endogenously produced DSBs to become part of the nervous system. Subsequent malfunctioning owing to this genomic damage would then lead to the observed neurodegeneration.

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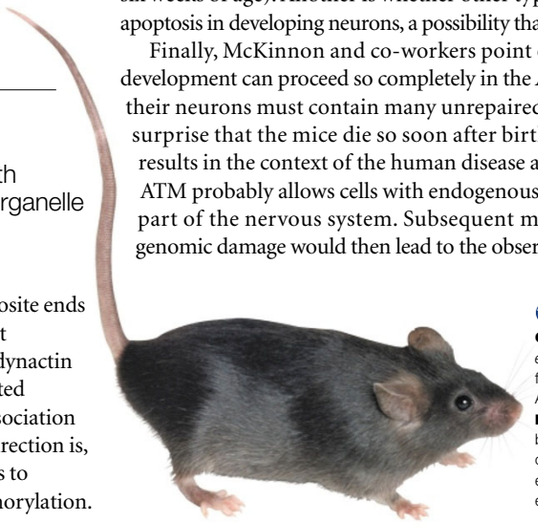

References and links

ORIGINAL RESEARCH PAPER Lee, Y. *et al*. Defective neurogenesis resulting from DNA ligase IV deficiency requires Atm. *Genes Dev.* **14**, 2576–2580 (2000)

FURTHER READING Lieber, M. R. The biochemistry and biological significance of nonhomologous DNA end joining: an essential repair process in multicellular eukaryotes. *Genes Cells* **4**, 77–85 (1999)