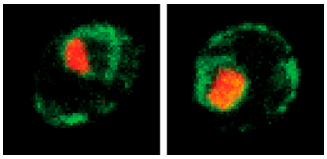
In This Issue

Text by Ben Short
bshort@rockefeller.edu

Cohesin pathway makes the necessary arrangements



The nucleolus (red) of yeast with mutations in cohesin regulatory proteins (right) is enlarged compared with wild-type cells (left).

Cohesin proteins arrange chromatin within the nucleus, and defects in this organizational role may underlie two human diseases, suggest Gard et al.

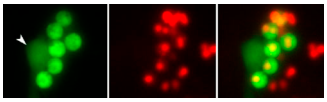
The cohesin complex and its accessory factors are best known for holding sister chromatids together before their separation in mitosis, but the cohesin pathway may have other functions, too. Cornelia de Lange syndrome (CdLS) and Roberts syndrome (RBS) patients have mutations in these proteins and suffer developmental problems such as growth and mental retardation. Yet their cells have no significant defects in chromosome segregation.

Gard et al. recreated CdLS and RBS mutations in the cohesin pathway proteins of budding yeast. Sure enough, none of the mutants had problems with chromosome cohesion, but two mutants in particular were unable to order their genomes correctly. Yeast with point mutations in either Eco1 or Scc2—two cohesin complex regulatory proteins—couldn't condense their chromosomes as much as wild-type cells. The mutants also had abnormally shaped nucleoli and showed defects in the subnuclear localization, clustering, and silencing of several genes.

Gene expression may be similarly affected during the development of CdLS and RBS patients. Senior author Jennifer Gerton now wants to explore the connection between the cohesin network, chromosome organization, and transcription in more detail. Her laboratory has already performed a screen for factors that genetically interact with Eco1 and Scc2 mutants, identifying a number of chromatin-modifying proteins.

Gard, S., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200906075.

Germ cells decide for themselves



Homogenous germ cell cultures contain immortal SSCs that replace differentiated cells as they die (red).

Rat spermatogonial stem cells (SSCs) choose their developmental fate by chance, independently of their surroundings, say Wu et al.

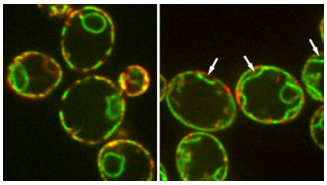
Most stem cell populations reside in a specialized "niche," where the microenvironment keeps them from differentiating. One of the best examples is the hub of *Drosophila* gonads that maintains the fly's SSCs, but researchers have failed to identify a similar niche in mammalian testes. Instead, mammalian SSCs and their differentiating progeny are found side by side and experience the same environment, making it unlikely that extrinsic factors alone determine germ cell fate decisions.

Wu et al. grew rat germ cells for extended periods under homogenous conditions, and found that the cultures contained two cell types: immortal SSCs and differentiated cells that multiplied for a limited time before undergoing apoptosis. The dead cells were replaced by newly differentiated cells descended from SSCs, yet the SSCs could also self-renew, ensuring that the proportion of the two cell populations remained constant over time. Because the culture microenvironment was identical for SSC daughters that differentiated or maintained stemness, the researchers wondered whether cell fate was simply a stochastic choice made by the daughter cells themselves. Mathematical modeling indicated that the proportion of each cell type observed in the culture was consistent with stochastic fate choice if the probability of remaining an SSC was 67%.

Although the choice that a particular daughter cell makes might depend on an intrinsic determinant such as random fluctuations in gene expression, lead author Zhuoru Wu says that this doesn't preclude the cell's environment from having any influence at all. She is searching for physiological factors that might nudge cell fate in one direction or the other.

Wu, Z., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200907047.

Sizing up the ER stress response



ER membranes (green) expand in response to ER stress (right).

Schuck et al. report that, when it comes to counteracting ER stress, size matters.

When stressful conditions impair protein folding in the ER, the cell responds by producing more ER-resident chaperone proteins and by increasing the organelle's size. ER membrane expansion involves ramping up lipid biosynthesis, but it's unclear whether the growth has a direct role in alleviating stress, or whether it simply provides more space to accommodate the additional protein-folding machinery.

Schuck et al. found that budding yeast need Ino2 and Ino4, two transcription factors that induce a range of lipid synthesis enzymes, to expand their ER in response to stress. ER enlargement also relied on key components of the signaling pathway that coordinates the cell's unfolded protein response, but yeast could bypass this requirement if Ino2 and Ino4 were constitutively activated. Cells lacking Ino2 were more sensitive to stress, whereas Ino2 activation and subsequent ER growth offered a degree of protection to yeast unable to increase their chaperone levels, indicating that membrane expansion alone can alleviate ER stress.

Most of the extended ER is in the form of membrane sheets, but converting these to tubules by overexpressing the reticulon protein Rtn1 didn't change the protective effects of membrane expansion. This suggests that size, rather than shape, is the key factor, says lead author Sebastian Schuck. One possibility is that unfolded proteins are diluted in a larger ER, making them less likely to collide and aggregate.

Schuck, S., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200907074.