In This Issue

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Zfp521 works its zinc fingers to the bone

The clavicle (arrow) is underdeveloped in mice lacking one copy of *Runx2* (left) but is partially restored when *Zfp521* expression is also reduced (right).

A zinc finger protein controls two stages of bone formation by opposing the master regulator of osteogenesis, Hesse et al. report.

Runx2 is a transcription factor essential for the differentiation of mesenchymal precursors into bone-forming osteoblasts. Mutations in human *Runx2* cause the skeletal disorder cleidocranial dysplasia, in which certain bones are underdeveloped. The zinc finger protein Zfp521 also controls bone formation and is a binding partner of Runx2. Hesse et al. examined how the two proteins combine to regulate osteogenesis in vivo.

Mice lacking one copy of *Runx2* have underdeveloped bones similar to cleidocranial dysplasia patients. This phenotype was largely rescued by removing one copy of *Zfp521*, whereas overex-

pressing the zinc finger protein exacerbated the bone defects. Accordingly, Hesse et al. found that Zfp521 inhibits Runx2 to limit the differentiation of mesenchymal cells into osteoblasts. Zfp521 blocked Runx2 by recruiting the histone deacetylase HDAC3 to switch off Runx2-mediated transcription. Zfp521 was unable to inhibit Runx2 activity in the absence of HDAC3.

Some evidence suggests that Runx2 itself has an inhibitory function at later stages of bone development, preventing osteoblasts from reaching their fully mature state. Indeed, overexpressing Runx2 in adult mice resulted in reduced bone density and the accumulation of immature osteoblasts. This was reversed by simultaneously overexpressing Zfp521, suggesting that the zinc finger protein antagonizes Runx2 at this stage of bone development as well.

Zfp521 therefore maintains the correct balance of Runx2 activity for osteoblast commitment and maturation. The authors now want to identify other transcription factors regulated by Zfp521.

Hesse, E., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201009107.

Telomeres get SIRT-ified
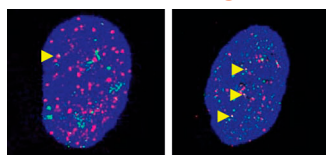
A cell lacking SIRT1 (right) shows increased DNA damage (green) at chromosome ends (red).

A protein that protects against aging-related diseases maintains telomere length and integrity, Palacios et al. reveal.

Telomeres protect chromosome ends but grow shorter with age, potentially contributing to several age-associated illnesses. Budding yeast telomeres are partly maintained by a deacetylase called Sir2, but whether the mammalian orthologue of this protein, SIRT1, has a similar function is unclear. Mice overexpressing SIRT1 have an increased healthspan—remaining healthy for longer than wild-type littermates. Palacios et al. examined telomeres from these mice, as well as from animals that lack SIRT1 entirely.

SIRT1-deficient mice had shorter telomeres, whereas SIRT1 overexpression boosted telomere length, preventing them from short-

ening as the mice grew older. This latter effect required the activity of telomerase enzyme, a major contributor to telomere production. Yet SIRT1 may also influence a second maintenance pathway called alternative lengthening of telomeres, or ALT. SIRT1 overexpression increased the amount of homologous recombination at chromosome ends, a key step in the ALT pathway. SIRT1 boosted homologous recombination along the rest of chromosomes as well, suggesting that the deacetylase promotes DNA repair. On the other hand, SIRT1-deficient cells showed increased damage at their chromosome ends.

SIRT1 therefore maintains telomere length and integrity, which may explain why SIRT1-overexpressing mice stay healthier for longer. Telomeres re-grow when differentiated cells are reprogrammed into an embryonic stem cell–like state. Palacios et al. found that SIRT1 binds to the elongated telomeres of these induced pluripotent stem cells. Senior author Maria Blasco now wants to investigate whether SIRT1 contributes to telomere extension during reprogramming.

Palacios, J.A., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201005160.

Myo1 provides a ring in the tail
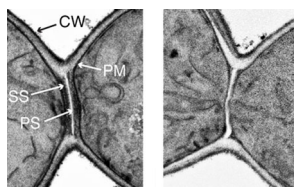
Yeast expressing the Myo1 tail (right) still form a primary septum (PS), which promotes cytokinesis in the absence of Myo1 motor activity.

Fang et al. describe two distinct pathways that target the tail of yeast myosin II to the bud neck to direct cell division.

Myosin II motors drive cytokinesis by assembling a contractile actomyosin ring at the site of cell division. The budding yeast myosin II, Myo1, is targeted to the bud neck by its C-terminal tail, and this domain alone is sufficient to separate mother and daughter cells, even though it lacks the actin-binding and motor activity of Myo1's head domain.

By constructing a series of deletion mutants, Fang et al. discovered two separate mechanisms that localize the tail of Myo1 at different points in the cell cycle. Before cytokinesis, Myo1 local-

ized to the bud neck by binding Bni5, a protein that in turn binds to septin GTPases. During cytokinesis, however, Myo1 targeting depended on the actin-binding protein IQGAP instead.

The Myo1 tail was sufficient to assemble an actomyosin ring at the bud neck, perhaps because IQGAP can compensate for the loss of Myo1's actin-binding head. But how does the Myo1 tail promote cytokinesis in the absence of any motor activity? Fang et al. found evidence to suggest that the "headless" actomyosin ring directs the deposition of vesicles around the bud neck to form the primary septum—a specialized cell wall region that pushes the cytokinetic furrow inward. Senior author Erfei Bi says that the actomyosin ring therefore coordinates membrane deposition and contractile force during cytokinesis. He now wants to investigate how Myo1 and IQGAP promote actomyosin ring assembly and how the ring is coordinated with septum formation.

Fang, X., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201005134.