In This Issue

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New function for an old master

The master regulator of muscle differentiation, MyoD, functions early in myogenesis to help stem cells proliferate in response to muscle injury, say Zhang et al.

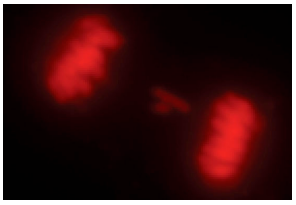
MyoD is a transcription factor that activates muscle-specific genes as myoblast precursors differentiate and fuse to form mature muscle fibers. But MyoD is also expressed at an earlier stage of myogenesis when quiescent stem cells rapidly expand in number to generate the myoblasts needed to repair tissue damage. The transcription factor's function in this proliferative phase is unknown.

Zhang et al. found that MyoD bound to the promoter of *CDC6*, a gene that initiates DNA replication, suggesting that MyoD might activate Cdc6 expression in muscle stem cells to promote their reentry into the cell cycle and rapid proliferation. Indeed, Cdc6 was expressed shortly after MyoD in stimulated muscle progenitors, and knocking down MyoD reduced Cdc6 production and slowed cells' entry into S phase. MyoD works in conjunction with transcription factors from the E2F family. E2F3a activated the *CDC6* promoter with MyoD, but was replaced by the repressive family member E2F4 as myoblasts began to differentiate.

Senior author Nikki Harter now wants to investigate how the transcription factors cooperate to control Cdc6 expression—initial results suggest that MyoD recruits E2F3a to the promoter region. The researchers also propose that a related protein, Myf5, might control Cdc6 transcription in MyoD's absence, acting as a backup mechanism to ensure that muscle stem cells expand to repair tissue damage.

Zhang, K., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200904144.

Segregating out UbcH10's role in tumorigenesis



A single chromosome lags behind the others in a dividing cell overexpressing UbcH10.

A ubiquitin-conjugating enzyme that regulates the cell cycle promotes chromosome missegregation and tumor formation, say van Ree et al.

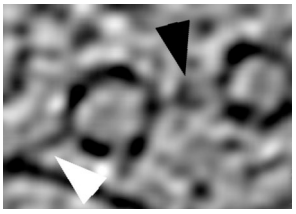
The mitotic E2 enzyme UbcH10 partners with the anaphase-promoting complex/cyclosome (APC/C) to ubiquitinate cell cycle regulators, targeting them for proteasomal destruction, and ensuring progression through mitosis. UbcH10 is overexpressed in a variety of human cancers, but whether it causes tumors or is simply up-regulated due to the increased number of proliferating cancer cells is unknown.

van Ree et al. generated mice expressing high levels of UbcH10 and found that they formed tumors in a broad range of tissues. Many of these tumors displayed aneuploidy—abnormal numbers of chromosomes resulting from errors in cell division. Live microscopy showed that cells expressing high amounts of UbcH10 had problems segregating sister chromatids correctly, possibly because the cells contained extra numbers of centrosomes that might complicate formation of a normal mitotic spindle. UbcH10 overexpression also reduced levels of the mitotic regulator cyclinB—a substrate of the APC/C—though it remains to be seen if this contributes directly to centrosome amplification and aneuploidy.

The same research group recently demonstrated that chromosome segregation defects drive tumorigenesis by promoting the loss of tumor suppressor genes like p53. Senior author Jan van Deursen now wants to investigate whether UbcH10 synergizes with other factors to promote chromosome instability in human cancers.

van Ree, J.H., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200906147.

Synaptic vesicles are well connected



Short protein filaments link synaptic vesicles to each other (black arrow) and to the plasma membrane (white arrow).

Fernández-Busnadiego et al. use cryo-electron tomography to investigate the structure of the presynapse, revealing important functions for short protein tethers in organizing synaptic vesicles at the nerve terminal.

The technique allowed the researchers to capture accurate, three-dimensional views of the presynaptic cytoplasm, and quantify the effects of different pharmacological treatments. Actin is thought to be involved in organizing synaptic vesicle release, but Fernández-Busnadiego et al. saw relatively few actin filaments in the nerve terminals. Instead, many short filaments of unknown composition linked vesicles to each other and to the active zone of the presynaptic plasma membrane, where vesicles are exocytosed.

Vesicles were clustered together through links that the researchers termed "connectors." These connections were rearranged when the synapses were strongly stimulated or treated with the phosphatase inhibitor okadaic acid. The researchers think the connectors regulate vesicle mobility and release in resting and active synapses.

In conventional electron microscopy studies, vesicles were proposed to stably contact the plasma membrane, but the team only saw direct contact when the vesicles were being exocytosed. Instead, vesicles near the active zone were docked by links that the authors named "tethers." The tethers existed in long and short versions, the latter of which were absent in samples treated with tetanus toxin, indicating that they consist of SNARE proteins involved in membrane fusion. Vesicles with longer tethers were retained after mild synaptic stimulation, suggesting that they are at an early stage of docking and haven't yet formed a readily releasable pool of SNARE-tethered vesicles.

Author Vladan Lučić now plans to examine more specific drug treatments and the effects of genetic mutants on synaptic vesicle organization.

Fernández-Busnadiego, R., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200908082.