In This Issue

Homing therapy

Stem cells become much more efficient at muscle repair if they first get a boost of cytokines and migratory adhesion molecules, report Galvez et al. (page 231). The improved repair stems from better homing abilities.

Skeletal muscle can be repaired by a class of stem cells known as mesangioblasts, which reside within blood vessels. Injection of mesoangioblasts into the femoral artery of mice improves muscle function in a mouse model of muscular dystrophy. Only a small fraction of the injected cells enters the tissue after injection, however. With their new findings, the authors report how to increase this fraction.

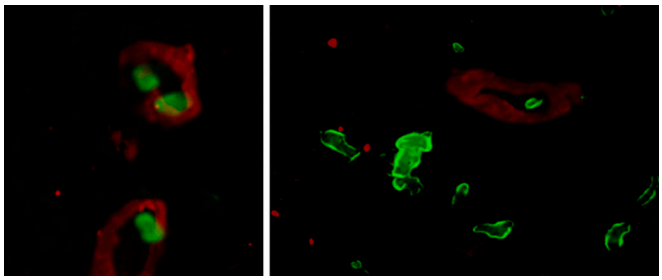
The authors found that mesoangioblasts efficiently crossed endothelium-coated filters in vitro when the other side held either mature myotubes or muscle-associated cytokines, such as SDF-1. Immature myoblasts, which secrete less of these cytokines, did not induce strong migration.

In addition to cytokines, adhesion molecules also improved migration. Transfection of mesoangioblasts with L-selectin or α4 integrin increased the cells' migration efficiency across the endothelium-coated filters. L-selectin and α4 integrin are not normally expressed by mesangioblasts, but are known to help leukocytes migrate through vessels walls into nearby tissues.

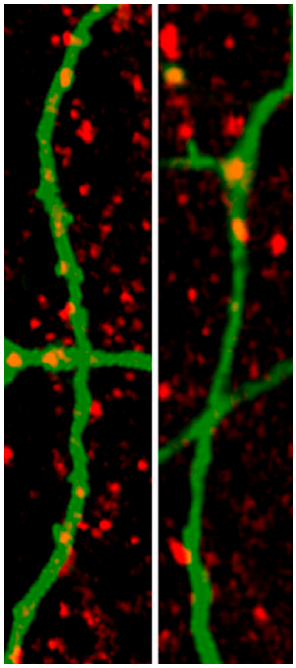
In vivo experiments demonstrated that both strategies improved the stem cells' homing ability in a mouse model of muscular dystrophy. When cytokine-pretreated cells were injected in the femoral artery, ~20% of the cells migrated to the thigh muscle, compared with 10% of untreated control cells. A similar improvement was detected for α4 integrin–expressing stem cells.

Both modifications together made an even better improvement. Approximately 50% of the mesoangioblasts that were pretreated with SDF-1 and that expressed α4 integrin entered the muscle.

After receiving the juiced-up stem cells, the mice had improved muscle function. Galvez et al. are now testing the same strategy in a dog model of muscular dystrophy. Moreover, they hypothesize that, with the right cytokines, a similar experimental approach could be used to improve the homing ability of other stem cell types. JCB



Mesoangioblasts (green) are better able to cross blood vessels (red) when they are first pretreated with cytokines (right).



The BDNF-induced increase (left) in synapses (red) on a neuron (green) is lost if β-catenin and cadherin are locked together (right).

Scattering synaptic vesicles

Synaptic vesicles get dispersed to new sites, according to Bamji et al. on page 289, via neurotrophin-induced disruption of adhesion complexes. The dispersal increases synaptic density, number, and size.

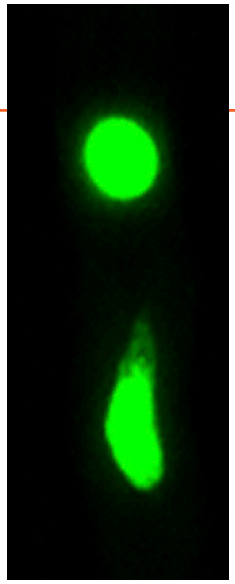
Dispersal is triggered by the neurotrophin called brain-derived neurotrophic factor (BDNF), which is produced and secreted by active nerve terminals. BDNF turns on TrkB tyrosine kinase receptor to enhance synaptic communication and increase synaptic size and density.

As synapses communicate via the secretion of neurotrophin-containing presynaptic vesicles, the authors studied BDNF's effect on vesicle behavior. They found that treatment of hippocampal neurons with BDNF dispersed synaptic vesicles into the region surrounding the original synapse. The dispersal of synaptic vesicles might help to form new synapses as the clusters of mobile vesicles populate new territories, although this theory remains to be tested.

The authors next addressed how the vesicles were released by BDNF. A likely target for this neurotrophin is the cell adhesion complex formed by cadherin and catenin proteins, which the authors had shown helps to localize synaptic vesicles to the presynaptic terminals. Indeed, BDNF caused a transient increase in β-catenin phosphorylation and a decrease in the amount of β-catenin bound to cadherins, resulting in adhesion complex disruption.

Expression of a nonphosphorylatable mutant of β-catenin eliminated both disruption of the catenin–cadherin complex and synaptic vesicle dispersion. The β-catenin mutant also blocked the formation of new synapses after BDNF treatment.

Bamji et al. speculate that the mechanism they uncovered may be a general model for how other ligands and tyrosine kinase receptors influence synaptic plasticity in various neuronal cell types, such as the ephrins and Eph receptors that influence synaptogenesis and axon guidance. Given the prevalence of both tyrosine kinase receptors and catenin–cadherin complexes, they think that tyrosine kinases might regulate other cell behaviors as well through β-catenin phosphorylation. JCB



Pollen PCD, as seen by DNA fragmentation (green), is induced by actin filament destabilization.

Text by Rabiya S. Tuma
rabiya@nasw.org

Actin senses self-incompatibility

Actin depolymerization is a death trigger for poppy pollen, according to Thomas et al. (page 221), that prevents self-fertilization.

Some plants prefer not to be fertilized by pollen grains that are genetically similar to themselves. These plants express self-incompatibility (S) proteins. A match between the pistil's S-proteins and the pollen's *S*-allele triggers a rapid calcium influx, actin filament destruction, and pollen cell death.

Several years ago, the researchers noticed that the amount of actin depolymerization far exceeded that required to inhibit pollen tube growth. The persistent actin destabilization also resembled that associated with animal cells about to undergo programmed cell death (PCD).

The authors now find that blocking actin depolymerization prevents pollen cell death in self-incompatible plants. Inducing actin depolymerization, on the other hand, activated pollen cell death. The dying cells showed the same pattern of DNA fragmentation and caspase-like activity as did pollen killed by self-incompatibility.

Changes in actin dynamics have been linked to PCD in animal and yeast cells, and a variety of noxious external stimuli triggers actin rearrangement in plants. Actin may thus serve as a sensor for extreme environmental stress to initiate PCD or other changes in cell behavior. As even a short exposure to depolymerizing drugs killed pollen cells, a brief change in actin dynamics seems to be all that is needed to kick off signaling cascades. JCB

Funky FAK proliferation

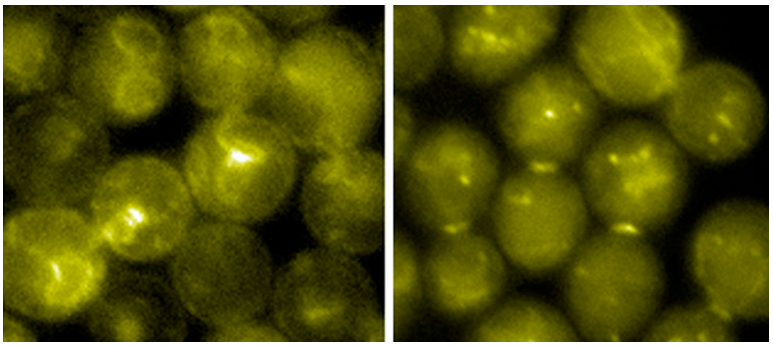
Focal adhesion kinase (FAK) transduces adhesion forces into pro-proliferation signals in a variety of cell types. Now, Pirone et al. (page 277) show that FAK also inhibits proliferation when cells lack adequate attachments. The two-sided modulation of proliferation by FAK suggests that adhesion is not a simple on–off switch. Rather, the cell monitors and modulates adhesion in a more graded fashion.

Current dogma suggests that more adhesion leads to more FAK activation and thus proliferation, and that loss of FAK activity would prevent proliferation. But Pirone et al. found that cells lacking FAK or expressing a dominant-negative form of the protein (FRNK) proliferated constitutively, whether they were cultured in high or low adhesive conditions.

Further analysis showed that FAK-null cells or those expressing FRNK had higher levels of RhoA expression than control cells. The increased RhoA led to more cytoskeletal tension and the formation of additional focal adhesions. Wild-type FAK thus seems able not only to sense adhesive forces, but also to limit their generation somehow.

A kinase-dead mutant restored normal proliferation responses to adhesion in FAK-null cells. Thus, unlike its proliferation-inducing function, FAK's ability to inhibit cell division does not require its kinase activity. JCB

Linking secretion and cell cycle



Chitin synthase (yellow) prematurely localizes to the bud neck at metaphase if the mitotic kinase is inactivated (bottom).

The end of mitosis triggers the export of the Chs2p chitin synthase from the ER to the bud neck, report Zhang et al. on page 207. The Chs2p chitin synthase lays down the primary septum, which divides mother and daughter yeast cells. Previous work showed that Chs2p arrives at the neck in late telophase, but what controls the timing was unknown.

Zhang et al. found that the timing of Chs2p localization to the neck correlated with the destruction of the mitotic kinase, Clb2p. Mutations in the mitotic exit network, which normally destroys Clb2p, prevented chitin synthase localization, though the myosin that constricts the neck localized normally. Direct inactivation of Clb2p restored chitin synthase localization, suggesting that the loss of mitotic kinase activity activated the synthase's movement.

The chitin synthase was restricted to the ER during metaphase when Clb2p activity was at its peak, but premature destruction of Clb2p triggered synthase movement to the neck. This relocalization required the secretory pathway. The transport of other secretory pathway cargos was not affected by Clb2p activity. The destruction of the mitotic kinase thus specifically ensures that the septum forms at the end of mitosis when cell separation is necessary. Zhang et al. are now looking for the mechanism that links mitosis and secretion. JCB