In This Issue

Nerveless muscles shape up

The receiving end of a synapse holds the blueprint for its own construction, as shown by Kummer et al. on page 1077. The findings suggest that the axon may take morphology instructions from its postsynaptic partner.

The ends of axons branch into complex patterns that are precisely mirrored at the receiving end of a synapse at the mammalian neuromuscular junction (NMJ). On the muscle side, this complex postsynaptic pattern can be seen as a pretzel-shaped array of acetylcholine receptors (AChRs). Based on decades’ worth of in vitro studies, the formation of this pretzel pattern from an oval-shaped precursor was thought to depend on the branching pattern of the apposing axon. But Kummer et al. find that when muscle cells are given the right matrix, no nerve is needed.

Matrix molecules that supported pretzel formation were fibronectin and laminin—those to which the muscle cells adhered tightly. As in vivo, their formation depends on MuSK (a kinase receptor for nerve-generated agrin) and rapsyn, which binds and clusters AChRs. The pretzel-like patterns developed through a sequence of AChR addition and remodeling steps resembling those seen in vivo. AChR receptors were seen in endocytic vesicles, suggesting that the pretzel might be formed from the original oval shape via localized endocytosis of spots of receptor-rich membrane. Whether zones of tight adherence are needed in vivo for pretzel formation is not yet clear, but laminin is abundant at NMJs.

The nerve is not without its contribution, however. In its absence, some features of the muscle side of the synapse were altered, including the distribution of matrix molecules. Future studies might test whether the muscle likewise influences axonal branching.

Branching is normal for nerves, but how muscle cells design and then form such a complex pattern is harder to imagine. Since the process can now be studied in vitro, answers may be forthcoming.

Kinases speak from the Golgi

The Golgi apparatus holds more than the key to protein secretion. On page 1009, Preisinger et al. show that the Golgi harbors signaling platforms from which kinases orchestrate cell migration.

The authors find that the Golgi is home to two kinases, YSK1 and MST4. By binding to the Golgi matrix protein GM130, the kinases are autophosphorylated and thus activated. Mutants that prevented Golgi localization of activated YSK1 disrupted the normal perinuclear Golgi pattern. Some YSK1 substrates may therefore maintain Golgi structure.

Other substrates are needed for migration, even when the Golgi structure remains intact. The authors identified 14–3-3ζ as one YSK1 substrate whose phosphorylation was required for wound-induced cell migration. Overexpression of MST4, in contrast, blocked migration without altering Golgi structure. Migration could therefore be regulated by competition between the kinases for GM130 binding, although the upstream signals that regulate their Golgi association are unknown.

14–3-3 proteins regulate membrane protein assembly and could thus influence which proteins are secreted to the plasma membrane, including integrins, which are known to interact with 14–3-3 proteins. Other kinase substrates might alter Golgi polarity to direct secretion to specific plasma membrane domains. Golgi polarity was indeed lost in YSK1 mutants. Both effects would be instrumental in migration.

On the flip side, changes at the Golgi could affect kinase signaling. The authors hypothesize that intensified protein secretion, for example, might remove GM130 to other interacting proteins (such as p115 or Rabs) and thus block kinase signaling. More kinase substrates need to be found to determine what effects this might have.
The binding partner of a neuronal growth factor (NGF) receptor puts the brakes on cell division, according to results on page 985 by Chittka et al. NGF is a neuronal survival and differentiation factor expressed in the developing nervous system. NGF binds to two different classes of receptors: the TrkA tyrosine kinase receptor and p75NTR. While studying how p75NTR functions in NGF signaling, Chittka and colleagues had previously shown that this receptor interacts with SC1, a zinc finger protein that moves to the nucleus in response to NGF.

The group now shows that SC1 is a transcriptional repressor that halts proliferation in cultured cells. NGF activates the repressor, which complexes in the nucleus with histone deacetylases. At least part of the reason for the cell cycle block is that SC1 turns off cyclin E transcription, thus preventing entry into S phase. SC1’s repressive activity is enhanced by both TrkA and p75NTR, although physical interaction with SC1 has only been shown for p75NTR.

Other genes are probably also repressed by SC1, and the authors hope that upcoming microarray experiments will identify many of them. Chittka suspects that genes that are unnecessary in neural lineages will be among those turned off by SC1. In this way, SC1 could coordinate the onset of differentiation with the last mitotic cycle of precursor cells.

Ubiquitin cycles for Golgi fusion

Chains of ubiquitin (Ub) can mark a protein for degradation by the proteasome. Single Ub tags are commonly used as sorting signals for protein trafficking. Now, on page 973, Wang et al. show that Ub also regulates membrane fusion by cycling onto and off of Golgi membranes before and after mitosis.

The Golgi is dismantled during mitosis into membrane fragments; these are reassembled when division is complete. This fusion event requires the p97 AAA-ATPase and its cofactors, p47 and VCIP135. p97 has various other functions, many of which involve Ub, including extracting Ub-tagged ER proteins from the membrane for transport to the proteasome. Ub is also needed during p97-mediated Golgi reassembly, but the authors find that this requirement has nothing to do with protein degradation.

The proteasome was dispensable for Golgi membrane fusion in vitro, as were chains of Ub, suggesting that unknown substrates are decorated with single Ub units. These individual units had to be removed, however, for p97-mediated fusion to occur, and VCIP135 catalyzes this deubiquitination.

Ub tags were added during fragmentation. They may form a structure that recruits p97 to its substrates (possibly a SNARE or SNARE inhibitor). But the Ub may also inhibit p97 activity (and thus premature reassembly) until mitosis is complete and VCIP135 removes the Ub tag. This suggests that VCIP135 is cell cycle regulated, which has yet to be shown. Next, the authors hope to identify the relevant Ub-tagged Golgi substrates.

No more division

Sugar for Golgi fusion

VCIP135 must remove Ub tags for Golgi to reassemble after mitosis.

Two arms of TGFβ signaling

Cancer-associated overproliferation is thwarted in many cell types by transforming growth factor β (TGFβ), which turns on p21(WAF1/CIP1) cell cycle inhibitors via Smad transcription factors. On page 979, Sakaguchi et al. show that TGFβ’s arsenal in its antiproliferation crusade is larger than just the Smads—a calcium-binding protein called S100C/A11 also responds to the call of duty.

The group previously showed that high extracellular Ca²⁺ results in phosphorylation of cytoplasmic S100C/A11, driving it into the nucleus. Once there, it releases the transcription factor Sp1 from its binding partner, nucleolin, so that Sp1 can activate p21(WAF1/CIP1) transcription to halt division in skin cells.

The new results demonstrate that this S100C/A11 pathway requires PKC-mediated phosphorylation of S100C/A11 and, like the Smad pathway, is triggered by TGFβ. Both branches are needed to stop skin cell growth in response to TGFβ.

Sp1 turns on many genes, not just those for cell cycle inhibitors. Specificity may be conferred by Sp1’s known binding to Smads. This suggests that the two branches of the TGFβ pathway may come together at their end point, making this pathway resemble not so much a branch as a brace of parentheses.