Three AMIGOs grow a brain

Amphoterin, a heparin-binding protein isolated from perinatal rat brain, has the intriguing ability to promote neurite outgrowth, but its mechanism of action remains unknown. On page 963, Kuja-Panula et al. use mRNA differential display to identify an amphoterin-induced gene called AMIGO, leading to the discovery of a small family of similar proteins that may mediate extracellular interactions in both neurite outgrowth and other types of cell movement.

After cloning the AMIGO gene, the authors identified two related genes, AMIGO-2 and AMIGO-3, by sequence homology. All three appear to encode type I transmembrane receptors, each with six leucine-rich repeats (LRRs) and one immunoglobulin-like domain. AMIGO is expressed at high levels in the nervous system, while AMIGO-2 and AMIGO-3 are distributed in a variety of tissues. Chimeric AMIGO bound to a surface can act as a substrate for neurite outgrowth, apparently through homophilic interactions with AMIGO on the neuron. The three AMIGOs are also heterophilic, interacting with each other.

AMIGO expression peaks at two points in mammalian development, corresponding to the periods when myelination and the perinatal growth of axonal connections occur. During the perinatal peak, homophilic binding by AMIGO may direct fasciculation, forging interactions between new axons and the pioneer axons that act as guides for growth. Continued expression of AMIGO into adulthood suggests that it may help during the healing of fiber tracts.

Mechanistic similarities between growth cone migration and tumor cell invasion, and the broad tissue distribution of the new protein family, suggest that AMIGOs may be general purpose directors of cell migration. The new work also identifies a potential function for the LRR domain, a structural motif that is widely distributed among animal proteins but has remained largely uncharacterized. In the new protein family, LRRs may mediate ligand binding. The authors are now looking for additional proteins that interact with the AMIGOs, and are generating mice lacking each of the newly discovered genes.

Stem cells to build muscles

Beginning on page 909, De Bari et al. describe a cell-based therapeutic strategy for Duchenne muscular dystrophy (DMD), the most common lethal genetic disorder in children. Although clinical studies are still a long way off, the results highlight the importance of secondary events in the pathogenesis of DMD and demonstrate the potential of a novel source of human adult stem cells.

DMD is caused by a lack of dystrophin at the sarcolemma of muscle fibers, resulting in irreversible degeneration of skeletal muscle once the satellite cells needed for regeneration have been depleted. Having identified a population of mesenchymal stem cells that can be cultured from the synovial membranes of adult human donors, the authors tested the muscle-regenerating capacity of the cells in two mouse models.

When transplanted into nude mice, the stem cells contribute to the formation of myofibers and give rise to functional satellite cells. Molecular markers suggest that the differentiation of the stem cells recapitulates embryonic myogenesis. Implanting the stem cells into mdx mice, a model of DMD, results in the appearance of human dystrophin at the sarcolemma and the expression of mouse mechano growth factor in skeletal muscle, a surrogate marker for the restoration of muscle contractility. Direct replacement of dystrophin expression has yielded less than spectacular results. In contrast, the success of the stem cell approach reinforces the idea that the clinical progression of DMD is at least partly due to loss of stem cells—a secondary effect of the loss of dystrophin. Thus, restoring satellite cell populations, even while a patient retains a defect in dystrophin, could be an effective treatment strategy. The authors are now characterizing the existing synovial membrane–derived human stem cells in detail, in the hopes of identifying a cell population with predictable and reproducible biological behavior for use in human patients. Additional studies will focus on analyzing muscle function in mdx mice directly over long periods, rather than relying on surrogate markers.