tension. Furthermore, although cell tension-mediated inhibition appears to be critical in maintaining neutrophil polarization, it is unlikely to be the only inhibitory signal. In fact, the most recent model for cell migration proposes that two parallel activator and inhibitor branches are required (Iglesias and Devreotes, 2011). In this context, the identification of the molecular components involved in transducing membrane tension signals will provide important insight into our understanding of how cells establish polarity.

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Maintaining Muscle Mitochondria via Transsynaptic Signaling

Jennifer B. Long[1] and David Van Vactor[1,*]
[1]Department of Cell Biology and Program in Neuroscience, Harvard Medical School, Boston, MA 02115, USA
*Correspondence: davie@hms.harvard.edu
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Dominant VAPB mutations are implicated in neurodegenerative disease, including amyotrophic lateral sclerosis and spinal muscular atrophy. In the current issue, Han et al. (2012) uncover a mechanism through which the secreted VAPB MSP domain regulates actin organization and mitochondrial function in muscle cells through LAR and Robo receptor activation.

Motor neuron diseases such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) are characterized by progressive motor neuron loss and subsequent muscle atrophy, leading to paralysis and ultimately death via respiratory failure (Van Den Bosch and Timmerman, 2006). Both environmental and genetic factors have been attributed to the pathology of ALS; familial cases account for approximately 10% of all cases. Despite the limited genetic susceptibility of ALS, it is now known that a variety of mutations identified in familial ALS may also contribute to many sporadic cases (Pasinelli and Brown, 2006). Thus, understanding the mechanisms by which these mutations cause motor neuron death may lead to novel therapeutic strategies.

New work by Han et al. (2012) investigates the role of synaptobrevin/VAMP (vesicle-associated membrane protein)-associated protein B (VAPB) in muscle mitochondrial regulation. VAPB has been implicated in motor neuron survival and mutations in VAPB have been identified both in ALS and SMA patients (Van Den Bosch and Timmerman, 2006). Moreover, functional and morphological defects in skeletal muscle mitochondria have been linked to both familial and sporadic ALS (Duffy et al., 2011; Pasinelli and Brown, 2006). Here, the authors demonstrate that VAPB has a cleaved and secreted major sperm protein (MSP) domain that signals through leukocyte-antigen related (LAR) and Roundabout (Robo) family receptors on the muscle cell surface and that ultimately leads to alterations in actin organization and changes mitochondrial morphology and function.

VAPB is a member of a highly conserved protein family that localizes to the endoplasmic reticulum (ER) and is involved in a variety of functions, including maintenance of ER morphology, vesicular trafficking, and intracellular lipid transport regulation (Tsuda et al., 2008). The N-terminal MSP domain of VAPB is cleaved and secreted, serving as an extracellular ligand. MSP was originally identified as a sperm-derived secreted protein that is required for oocyte maturation in nematodes. Previous work by this group identified a role for secreted MSPs in motor neuron degeneration via the conserved axon guidance receptor Eph (Tsuda et al., 2008). A dominantly inherited proline 56 to serine (P56S) mutation within the secreted MSP domain is associated with both ALS and SMA (Tsuda et al., 2008; Van Den Bosch and Timmerman, 2006). The P56S mutation serves as a dominant-negative and antagonizes the endogenous wild-type function of VAPB by promoting VAPB ubiquitination, recruitment into cytoplasmic

inclusions, and abnormal MSP processing, ultimately leading to motor neuron degeneration and death (Tsuda et al., 2008). Now Han et al. (2012) highlight an important role for the MSP domain of VAPB in the pathophysiology of motor neuron disease through its influence on postsynaptic partners, contributing to muscle atrophy and cell death.

In this exciting new study, Han et al. (2012) use both *Drosophila melanogaster* and *Caenorhabditis elegans* to demonstrate that VAPB mutants have abnormal mitochondrial morphology and aberrant interconnected mitochondrial tubules. Mitochondria are highly dynamic structures. Mitochondrial number and the morphology of the mitochondrial network rely on cycles of fission and fusion events. For example, as mitochondria cannot replicate de novo, fission may occur to ensure enough mitochondria are present to meet energy demands (Knott and Bossy-Wetzel, 2008). In contrast, mitochondrial fusion often serves to repair or restore damaged segments of mitochondria, as metabolites, proteins, and mitochondrial DNA can move between fused segments. The phenotype Han et al. (2012) observe in VAPB mutants suggests an imbalance of mitochondrial fission and fusion in muscle, which has been implicated in neurodegeneration (Knott and Bossy-Wetzel, 2008). In addition to morphology defects, VAPB mutants display mislocalized mitochondria, which suggests defects in mitochondrial motility. Finally, both worm and fly VAPB mutants display impaired mitochondrial function, decreased electron transport chain activity, and reactive oxygen species (ROS). These data reinforce previous work implicating muscle mitochondrial function in the pathogenesis of ALS (Pasinelli and Brown, 2006). Interestingly, this novel activity of VAPB is strictly dependent on the cleavage and secretion of the MSP domain in neurons. The VAPBP56S mutant protein is retained within the ER in neurons and therefore neither cleaved nor secreted. When Han et al. (2012) express VAPBP56S in muscle, they find no phenotype, but neuronal expression induces mitochondrial defects in muscle, revealing a nonautonomous mechanism. In motor neurons, secreted MSPs signal through EphR (Tsuda et al., 2008), but in muscle, loss of EphR does not alter mitochondrial phenotypes. Thus, Han et al. (2012) search for an alternate receptor to account for MSP transsynaptic signaling to muscle cells.

Using genome-wide microarrays and subsequent functional analysis, Han et al. (2012) identify two additional MSP receptors. Like Eph receptors, LAR and Robo family receptors are highly conserved and mediate multiple axon guidance decisions during nervous system development (Lowery and Van Vactor, 2009). The authors demonstrate that both *LAR* and *Robo* mutants have altered muscle mitochondrial morphology and function in *C. elegans*. Interestingly, both VAPB and Robo antagonize LAR signaling in muscle. Other groups have demonstrated evidence of genetic interactions, shared signaling pathways, and downstream effectors between LAR and Robo in neurons. For example, Robo and LAR have opposing functions during midline axon guidance in *Drosophila*, indicating some type of inhibitory crosstalk between these two receptors (e.g., Sun et al., 2000). The data presented by Han et al. in muscle provides additional evidence of crosstalk between LAR and Robo. Han et al. propose the intriguing hypothesis that Robo and LAR act as co-receptors, with Robo promoting LAR-MSP binding to inhibit LAR activity. This model shares features with another signaling role for Robo, which underlies a switch in responsiveness of commissural axons to Netrin following midline crossing by binding to and silencing the receptor DCC (Stein et al., 2001).

Robo and LAR regulate downstream signaling molecules that control cytoskeletal dynamics and network organization. In the current study, the authors show that the MSP-dependent activation of Robo and subsequent downregulation of LAR signaling alters the activity of the actin-related protein (Arp2/3) complex, an actin nucleator and branching factor that has been implicated in cell morphogenesis and motility in many contexts (Boldogh et al., 2001). However, in neurons, LAR and Robo engage multiple signaling molecules and cytoskeletal effectors, including Rho-family GTPase regulators and the Abelson kinase, the actin assembly factor Enabled (Ena), the actin nucleator Diaphenous (Dia), the actin-microtubule crosslinker Short Stop (Shot), and the microtubule plus-end tracking factor CLASP (Lowery and Van Vactor, 2009). Interestingly, mitochondrial transport and localization in axons is primarily microtubule-dependent (Duffy et al., 2011).

The arsenal of actin and microtubule effectors downstream of LAR and Robo raises intriguing questions regarding the complexity and specificity of the regulatory process that supports normal mitochondrial structure and function in muscle cells downstream of VAPB. Is the integration between Robo and LAR at the cell surface where the VAPB MSP binds or somewhere downstream inside of the responding cell? Is it possible that specialized mitochondrial properties are required at synaptic sites for normal physiology, thus explaining both the role of motor neurons in defining a specific spatial domain for mitochondria in muscle via VAPB-Robo/LAR signaling and the importance of this pathway in protecting neuromuscular circuits from neurodegenerative losses? Han et al. (2012) have opened an exciting doorway to the cell biology of mitochondria through which many new answers will undoubtedly arrive.

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