alternator cells renders them more resistant to antibiotics, particularly those targeting processes that occur only in growing cells, such as cell wall synthesis. Consistent with this notion, the authors demonstrate that alternator cells are more resistant to the cell wall synthesis inhibitors meropenem and cycloserine. However, alternator cells are more sensitive to the transcriptional inhibitor rifampicin, suggesting that there may be additional physiological differences between alternators and accelerators that are not yet clear.

The generation of heterogeneity that results from unipolar growth may constitute a type of bet-hedging strategy against antibiotics or other environmental stresses (Veening et al., 2008). More work is clearly needed to elucidate how unipolar growth occurs, how it is regulated both temporally and spatially, and what all of its functional consequences are. The work of Aldridge et al. (2012) with mycobacteria indicates that such studies could have major consequences for understanding tuberculosis and bacterial pathogenesis.

REFERENCES


Neutrophils under Tension

Philippe V. Afonso1 and Carole A. Parent1,*
1Laboratory of Cellular and Molecular Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA
*Correspondence: parentc@mail.nih.gov
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An article by Houk et al. (2012) in Cell provides insight into the mechanisms confining membrane protrusions to the front of migrating neutrophils. The authors rule out a role for diffusion of inhibitory signals and show that membrane tension is necessary and sufficient to restrict signals that lead to protrusions.

Neutrophils readily polarize in response to chemoattractants and migrate through coordinated protrusions at their leading edge and retractions at their back. Efficient and persistent neutrophil migration requires the maintenance of cell polarization. When cells migrate up a chemoattractant gradient, polarization maintenance can be envisioned as the continuous response to an anisotropic environment. However, when neutrophils migrate in a isoform, isotropic environment, maintained polarization suggests that a semiautonomous excitable network is activated (Iglesias and Devreotes, 2011). Positive and negative feedback loops have been implicated in maintaining...
persistent polarized responses. Indeed, previous work has identified positive feedback loops regulating protrusions at the leading edge, involving actin, PI3K, and small GTP binding proteins such as Rac and Ras (Brandman and Meyer, 2008; King and Insall, 2009). Furthermore, extracellular signals have been shown to act as positive feedback loops: ATP secretion at the leading edge stabilizes neutrophil polarization and migration (Chen et al., 2006). Such positive feedback loops require a balancing inhibitory factor. Otherwise, cells would extend protrusions throughout their periphery or pseudopods would spread and overtake the entire cell, precluding effective migration. Whereas positive feedback loops have been extensively studied, little is known about inhibitory signals. New work from Houk et al. (2012) now suggests that in neutrophils, membrane tension is a key factor that inhibits protrusion in other parts of the cell.

Three major inhibitory signals have been proposed (Devreotes and Janetopoulos, 2003). First, the pseudopod could act as a sink for limiting factors. For example, proteins essential for actin polymerization and protrusion formation would be sequestered at the front of cells and excluded from the back. Second, the inhibitory signal could be a fast-diffusing soluble molecule produced within the leading edge. This molecule would form a uniform inhibitory signal throughout the cell that is only overcame at the leading edge. Finally, the inhibitory signal could be a mechanical force, transmitted from the pseudopod at the front to the back of the cell surface.

Houk et al. (2012) present data aimed at defining the nature of the negative regulatory signal involved in confining the leading edge when neutrophils are exposed to a uniform stimulation of chemoattractant (Houk et al., 2012). In order to test the different models, the authors use an elegant technique to create a constrained diffusion channel between the leading edge and the back of migrating neutrophils. In response to a brief heat shock, neutrophils become elongated; the leading edge stretches, whereas the back remains inactive. As a consequence, the actin-rich pseudopod and the back of neutrophils communicate only via a thin tether, which limits diffusion and can sever (spontaneously or by laser). If the pseudopod is the site of production of a soluble inhibitor, the presence of a constriction site between the leading edge and the back should dramatically reduce passive diffusion and allow new protrusions to form at the cell body. Yet, the authors show that protrusions are still restricted to the leading edge in stretched neutrophils, thereby disproving the idea that local production of a soluble inhibitor negatively regulates pseudopod extension. If the leading edge sequesters proteins essential for actin assembly and cell protrusion, the cell body should remain immobile upon tether severing, until newly synthesized molecules accumulate. Remarkably, the authors demonstrate that the cell body generates a new cell front within seconds after severing, implying that the sequestering model does not explain how polarized signals are maintained and suggesting that rapidly propagating signals are involved.

Houk et al. (2012) then hypothesize that leading edge protrusions generate a rapidly propagating tension in the plasma membrane that inhibits the formation of protrusions in the rest of the cell (Figure 1) and use various physical means to test their hypothesis. Using optical traps, the authors show that chemoattractant addition leads to a 2-fold increase in cell tension. Most importantly, they go on to demonstrate that mechanically increasing tension, by stretching neutrophils using micropipette aspiration, inhibits both the formation of protrusions and Rac activation and that decreasing tension leads to very broad pseudopods and stronger Rac signals. Finally, the authors provide evidence that tension arising from the plasma membrane rather than the cytoskeleton is the major factor inhibiting protrusions. The importance of cell tension in regulating cell polarization has been reported in other cell types.

In the social amoebae Dictyostelium discoideum, myosin Il contraction, as well as consecutive increases in cytoskeletal cell tension, spatially regulate Ras and reduce lateral pseudopod formation (Lee et al., 2010; Wessels et al., 1988). In addition, the local application of mechanical forces to the back of Xenopus mesendoderm cells induces polarized protrusions and persistent migration—possibly similar to the tugging forces that cadherins impose on neighboring cells during collective cell migration (Weber et al., 2012).

In summary, Houk et al. (2012) demonstrate that membrane tension is necessary and sufficient for inhibiting the spread of membrane protrusions in neutrophils exposed to a uniform chemoattractant stimulation (Houk et al., 2012). It will be interesting to determine the role of tension-mediated inhibition in neutrophils exposed to chemical gradients. In Dictyostelium, this could depend on the level of differentiation or the strength of the chemoattractant gradient (Swaney et al., 2010). In early development or in shallow gradients, Dictyostelium cells orient by forming a new leading edge in the direction of the gradient, overcoming inhibitory signals from the cell body and suggesting that tension-mediated inhibition can be overridden by chemoattractant gradients. In contrast, in late development or in steep gradients, these cells maintain the same pseudopod and realign slowly by turning. Dictyostelium could therefore be a good system in which to study the interplay between chemoattractant signaling and membrane tension. It will be interesting to determine the role of tension-mediated inhibition in neutrophils exposed to chemical gradients.
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.

REFERENCES


Maintaining Muscle Mitochondria via Transsynaptic Signaling

Jennifer B. Long1 and David Van Vactor1,∗

1Department 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...