In Brief

Morphology, Motility, and Signaling

Morphology and Signaling

Combining experimental data and computer modeling, Fink et al. (page 929) demonstrate that cellular geometry is important in the spatiotemporal control of intracellular signaling. The researchers examined the dynamics of inositol-1,4,5-trisphosphate ($InsP_3$)-mediated calcium signaling in neuroblastoma cells with complex morphology, and also simulated $InsP_3$ signaling in a computer model called Virtual Cell. The close agreement between the experimental data and the computer model suggest that Virtual Cell could be applied to a broad range of problems in cell biology.

In an initial series of experiments, the team found that the neuroblastoma cell's neurite produces a higher $InsP_3$ signal than the soma, and that the higher concentration of $InsP_3$ in the neurite is required for initiating a wave of calcium release. The computer model, which integrates experimental data on the geometric, biochemical, and electrophysiological components of the system, allowed the researchers to simulate the same phenomenon while altering a variety of parameters. These simulations suggest that because $InsP_3$ is produced from the plasma membrane, the high surface-to-volume ratio of the neurite causes the $InsP_3$ signal to reach a higher level in the neurite than in the soma. Conversely, the soma has a greater density of endoplasmic reticulum than the neurite, making the soma release more calcium than the neurite for a given amount of $InsP_3$. The team is now using Virtual Cell to simulate a variety of other intracellular and intercellular signaling events (http://www.nrcam.uchc.edu).

Signaling and Morphology

Although cell morphology appears to affect signaling, Sander et al. (page 1009) focus instead on the effect of signaling on morphology. Using a novel biochemical assay to analyze the activation state of the small GTPases Rac and Rho, the researchers provide convincing evidence that Rac can unidirectionally inhibit the activity of Rho, leading to changes in cellular morphology. The results suggest a model in which a reciprocal balance between the activities of Rac and Rho determines a cell's migration behavior.

Most previous studies on the activation of Rho-like GTPases have relied on analyses of downstream cytoskeletal changes. In the new study, Sander et al. took advantage of the properties of two downstream effectors, Pak and Rhotekin, to confer specificity in a biochemical assay for Rho-like GTPase activity. Pak binds to GTP-, but not GDP-loaded Rac and Cdc42, and Rhotekin binds specifically to GTP-loaded Rho. Activation of Rac, or signaling by constitutively active mutants of Cdc42 and Rac, down-regulates endogenous Rho activity, but activation of Rho has no effect on Rac activity. The down-regulation of Rho by Rac causes an epithelioid, nonmigratory phenotype in NIH3T3 fibroblasts, an effect that can be reversed by expressing constitutively active Rho, indicating that the reciprocal balance of the two proteins determines cell morphology and migratory behavior. The scientists found a similar down-regulation of Rho by Rac in several other cell types, and are now trying to identify factors that mediate signaling between the two proteins.

Motility and Invasion in Apicomplexan Parasites

In contrast to the mammalian cells they invade, *Plasmodium* and other Apicomplexan parasites exhibit gliding motility, and both motility and cell invasion are powered by the parasite's microfilaments. Beginning on page 937, Kappe et al. present genetic evidence that thrombospondin-related anonymous protein (TRAP) of *Plasmodium* is a key component of a capping process that underlies both behaviors. The work also demonstrates that the same process is conserved among diverse genera of *Apicomplexa*.

Previous work supported a model in which TRAP expressed on the surface of the parasite binds to a substrate or the surface of a host cell, and backward translocation of TRAP along the parasite drives gliding motility or cell invasion. Kappe et al. generated strains of *Plasmodium* sporozoites that express modified forms of TRAP. Deletions in the TRAP cytoplasmic tail cause defects in both motility and invasion, and the cytoplasmic tails of TRAP-related proteins from other genera of *Apicomplexa* can rescue both phenotypes. Amino acid substitutions suggest that the anterior to posterior translocation of TRAP and the shedding of the protein from the posterior end of the parasite are mediated by distinct domains of the cytoplasmic tail.

Since the mechanism appears to be conserved within a phylum that includes several human pathogens, Robert Ménard, corresponding author on the study, adds that "hopefully...Apicomplexan gliding motility is specified by a unique actin–myosin submembranous system against which specific drugs might be found."

Distribution of Viral RNA during Infection

Using a combination of immunostaining, in situ hybridization, and infection of cells with viral mutants, Mas et al. (page 945) studied the relationship between sites of tobacco mosaic virus (TMV) RNA accumulation and the distribution of host and viral proteins in the course of a TMV infection. Though complexes between viral RNA (vRNA) and host proteins have a central role in viral pathogenesis, the formation and movement of these complexes has remained poorly understood.

TMV vRNA localizes to different subcellular compartments throughout the infection, but consistently colocalizes with specific host and viral factors. When superimposed on in situ hybridization data, immunostaining shows that the vRNA colocalizes with the ER and microtubules, suggesting that the cytoskeleton may be involved in distributing vRNA. The viral movement protein (MP) and

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replicase also colocalize with vRNA, and a mutant virus lacking MP shows abnormal vRNA localization.

Based on these data, the authors propose a model in which cytoskeletal elements target vRNA replication complexes to the ER. "Our best guess is that the virus is making use of cellular mechanisms, and that the MP is facilitating the process by sequestering membranes to gather and hold the replication complexes together," says Roger Beachy, senior author on the study.

A-Type Lamins and Muscular Dystrophy

Beginning on page 913, Sullivan et al. describe the phenotype of mice in which A-type lamin expression has been eliminated by targeted gene disruption, findings that help illuminate the role of lamins and inner nuclear membrane (INM) proteins in nuclear membrane maintenance. The mice also develop muscular dystrophy, making them a potentially useful model for studying one form of the disease found in humans.

Earlier work showed that the expression of A-type lamins, in contrast to B-type lamins, is developmentally regulated, but the role of A-type lamins in cell differentiation remained unclear. Sullivan et al. disrupted the *Lmna* gene in mice and found that, although the mutant mice are phenotypically normal at birth, they develop muscular dystrophy postnatally. The mice also exhibit altered nuclear envelope integrity and aberrant localization of emerin in muscle cells. Emerin is an INM protein involved in human Emery-Dreifuss muscular dystrophy, one of the three major X-linked dystrophies. The findings are consistent with recent work that showed a direct interaction between emerin and lamin-A (Fairley, E.A., J. Kendrick-Jones, and J.A. Ellis. 1999. The Emery-Dreifuss muscular dystrophy phenotype arises from aberrant targeting and binding of emerin at the inner nuclear membrane. *J. Cell Sci.* 112:2571–2582), and support a model in which this interaction stabilizes the nuclear membrane against the stresses generated in muscle cells.

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