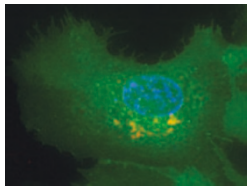
A new tool for the trade



Membrane trafficking in the cell is a highly regulated process. One pathway in which these trafficking events are found is protein secretion, whereby proteins synthesized and translocated into the endoplasmic reticulum (ER) are trafficked to the plasma membrane via the Golgi apparatus. This process is fast and complex, making it difficult to study by genetic and biochemical means. Traditionally, small molecules like brefeldin A and exo1 have been used to examine transport between the ER and Golgi, but they disrupt Golgi morphology and localization, making them unsuitable for examining traffic between the Golgi and target membranes. Now, Shair, Kirchhausen and colleagues have identified a compound called secramine that can quickly and reversibly inhibit transport out of the Golgi while leaving ER-to-Golgi transport and Golgi appearance and positioning unaffected. They found that secramine prevents activation of the Rho GTPase Cdc42, which participates in membrane traffic and Golgi and actin dynamics. Prenylated Cdc42 is shuttled between the cytosol and target membranes by the Rho guanine nucleotide dissociation inhibitor 1 (RhoGDI1). At the membrane, an activating signal triggers GDP-GTP exchange on Cdc42 by a guanine nucleotide exchange factor. The activated Cdc42-GTP communicates with effector molecules to produce a cellular output, such as a change in trafficking events or cytoskeletal dynamics. The data suggest that secramine reduces prenylated Cdc42 binding to membranes by stabilizing the interaction between Cdc42 and RhoGDI1, making less Cdc42 available for activation and downstream signaling events. This compound is sure to prove useful in examining the role of Cdc42 in protein secretion and other trafficking events, and it may reveal critical roles for RhoGTPases in other processes. (*Nat. Chem. Biol.* advance online publication 20 November 2005, doi:10.1038/nchembio751) *MM*

One step at a time

During transcription, RNA polymerase (RNAP) adds one ribonucleotide at a time in a cycle that consists of binding of the appropriate NTP, pyrophosphorolysis, incorporation of the nucleoside monophosphate into the growing RNA chain and release of pyrophosphate. RNAP can also pause, backtrack along DNA or both, making the interpretation of bulk kinetic studies quite complicated. Single-molecule measurements, in principle, can help to untangle such complex behavior. Using an ultrastable optical trap capable of measuring angstrom-level changes in the position of a single molecule, Block and colleagues show that RNAP moves along DNA one base pair per nucleotide added. These findings rule out two previously proposed models in which movement of RNAP was discontinuous: in the inchworm model, the front end of RNAP is always ahead of the rear, whereas in the scrunching model, RNAP pulls in a loop of DNA, transcribes that loop, then grabs another loop. While the new data are consistent with a model in which RNAP takes single base-pair steps, what drives this molecular motor? The studies are consistent with a Brownian (or thermal) ratchet model, in which random diffusion of RNAP along the DNA results in net forward movement because diffusion of the enzyme in the opposite direction is unfavorable. The development of this new apparatus promises new insights into other molecular machines, particularly those involved in replication, transcription and translation. (*Nature* advance online publication 13 November 2005, doi:10.1038/nature04268) *BK*

Research highlights written by Boyana Konforti and Michelle Montoya.

Male meiosis

Most sexually reproducing organisms have a DNA content of 2*n*. For mating to occur, the DNA content of the germ cells must be reduced to 1*n*, so that the fertilized egg will be 2*n*. This reduction in chromosome number is accomplished by a process known as meiosis. A germ cell undergoes a single round of DNA replication followed by two successive rounds of chromosome segregation. Before segregation can occur homologs must pair with each other. This pairing typically results in recombination and the formation of physical connections (chiasmata) between homologs. When homologs segregate to opposite poles so that they end up in different cells, these connections are lost. Homolog pairing is almost universally required for proper meiotic chromosome segregation, but in some species, such as *Drosophila* males, recombination and chiasmata are not. Male flies do have physical connections between homologs, but the nature of these physical connections has been unclear. Now, McKee and colleagues identify two meiotic proteins, MNM and SNM, a homolog of a protein essential for cohesion of sister chromatids during mitosis, that are required for proper segregation in male flies. These proteins are required to hold together both sex chromosomes and autosomal homologs, because mutations in either gene result in the random assortment of homologs. SNM and MNM colocalize to regions of the chromosome implicated in homolog pairing and disappear once meiosis I is complete. These findings suggest a direct role for SNM and MNM in establishing or maintaining homolog connection, but how they do so, and how their function is regulated, must still be determined. (*Cell* **123**, 555–568, 2005) *BK*

Genetic links

Disruptions to the gene *DISC1* (disrupted in schizophrenia-1) have been implicated in schizophrenia and severe mood disorders, but it is not understood how the molecular functions of the DISC1 protein relate to mental illness. Sawa and colleagues now show that DISC1 is a component of the microtubule-associated dynein motor complex. This complex is important for microtubular dynamics and regulates neuronal migration and axon formation during neural development. They find that DISC1 contributes to microtubular organization by anchoring the dynein protein complex at the centrosome. This suggests that mutations in *DISC1* may underlie impaired neuronal growth and development in schizophrenia. In a related paper, Millar and colleagues have identified a chromosomal translocation involving the phosphodiesterase 4B gene (*PDE4B*) in several psychotic illness patients. PDE directly inactivates cAMP, which is a key second messenger in learning, memory and mood; gene mutations or deletions of PDE family members have been linked to learning and memory defects as well as mood alteration. The authors find that PDE4B binds directly to DISC1. The proteins colocalize in the mitochondria, and overlapping expression patterns are observed in neurons and proliferating non-neuronal cells. They show that the DISC1-PDE4B interaction is dynamic and can be directly controlled by cAMP levels. The data suggest a role for DISC1 in PDE4B regulation, where DISC1 forms a complex with inactive, unphosphorylated PDE4B that is disrupted by PKA-mediated PDE4B phosphorylation and activation in response to elevated cAMP levels. These findings indicate a possible molecular link between schizophrenia and mood disorders, and they may provide a starting point in the development of future drug therapies. (*Nat. Cell Biol.* advance online publication 20 November 2005, doi:10.1038/ncb1328 and *Science* **310**, 1187–1191, 2005) *MM*