In This Issue

Harvesting a new KASH crop

Zhou et al. reveal that plants express diverse KASH-like proteins that perform discrete functions at the outer nuclear membrane. In animals and fungi, LINC complexes—compromised of inner nuclear membrane SUN proteins and outer nuclear membrane KASH proteins—connect the nucleus to the cytoskeleton to control a variety of processes including nuclear positioning and chromatin organization. Plants express SUN proteins, but their genomes lack KASH homologues. They do, however, encode at least one family of proteins that, like animal and fungal KASH proteins, bind to SUN family members and localize to the outer nuclear membrane.

Endocytosis in its natural state

Grassart and Cheng et al. use genome editing and quantitative microscopy to examine the dynamics of actin and dynamin2 during clathrin-mediated endocytosis. Clathrin coat proteins form invaginated pits at the plasma membrane, which are subsequently released by the GTPase dynamin into the cytoplasm as coated vesicles. The dynamics of clathrin and dynamin assembly are incompletely understood, however, in part because overexpressing fluorescently tagged versions of these proteins might interfere with the endocytic process. Grassart and Cheng et al. therefore used genome-edited cell lines that express fluorescent versions of dynamin2 and clathrin light chain at wild-type levels uniformly across the cell population, allowing the researchers to quantitatively analyze their dynamics in an unbiased manner without perturbing endocytosis.

In the initial phase of endocytosis, which was highly variable in duration, clathrin accumulated in membrane punctae that transiently recruited small numbers of dynamin2 molecules. In a final, more regular phase lasting around 20 seconds, approximately 26 molecules of dynamin2—enough to form a single loop around the neck of the invaginated pit—stably associated with each clathrin puncta before it disappeared from the plasma membrane and internalized into the cell.

The researchers then examined genome-edited cells expressing fluorescently tagged actin. Whether actin is an integral component of the clathrin-mediated endocytosis machinery has been uncertain, but the researchers found that actin accumulated at almost every endocytic site, typically before the appearance of dynamin2. Treating cells with actin inhibitors such as jasplakinolide or cytochalasin D indicated that actin polymerization promotes dynamin2 recruitment and aids vesicle scission.

Senior author David Drubin now wants to analyze the many accessory factors that assist dynamin and clathrin in order to build a quantitative model of clathrin-mediated endocytosis.

Talin’s invasive side

The integrin-binding protein talin stimulates invadopodia formation and tumor cell metastasis by recruiting the sodium/hydrogen exchanger NHE1, Beaty et al. reveal. Tumor cells form actin-rich protrusions called invadopodia that degrade the extracellular matrix and facilitate cell invasion and metastasis. The adhesion receptor β1 integrin promotes invadopodial maturation, but whether integrin-associated proteins such as talin assist in this process is unknown. Beaty et al. found that talin localizes to invadopodal precursor structures and that knocking down talin prevented their maturation into matrix-degrading protrusions by inhibiting the recruitment of the sodium/hydrogen exchanger NHE-1.

NHE-1 promotes invadopodial maturation by increasing the local cytoplasmic pH, thereby activating the actin-severing protein cofillin to generate free barbed ends and stimulate actin polymerization. The researchers discovered that talin’s C terminus binds directly to the FERM domain of the ERM protein moesin, which, in turn, recruited NHE-1 into invadopodial precursors. Tumor cells lacking talin thus formed fewer invasive protrusions and showed reduced migration through their surrounding tissue when injected into mouse mammary glands. Accordingly, loss of talin impaired the tumor cells’ ability to enter the bloodstream and form metastases in the lung.

Talin localized to invadopodia independently of β1 integrin, but the adhesion receptor was nevertheless required to recruit moesin and NHE-1 into the protrusions. Lead author Brian Beaty therefore wants to investigate how talin and β1 integrin combine to regulate NHE-1 activity and cell invasion.