Translocon: don’t pass me by

Translocon proteins are intimately involved with the proteins they import into the ER—including transmembrane portions of the incoming proteins, based on results from Peter McCormick, Arthur Johnson (Texas A&M University, College Station, TX), and colleagues.

Import of membrane proteins into the ER requires a joint effort between the ribosome and the translocon to ensure that each domain of the translocating protein is targeted correctly to either the lumenal or cytoplasmic face of the ER. Transmembrane domains present an additional problem—the hydrophobic portion must move laterally past the translocon into the lipid bilayer. Current models suggest that membrane-spanning domains have very limited contacts with translocon proteins and are instead rapidly surrounded by phospholipids. But the new results show that the translocon is more than a passer-by in this process.

Johnson’s group shows that imported transmembrane domains make prolonged contacts with translocon subunits. Photo-crosslinking experiments reveal that one side of a transmembrane helix contacts the translocon protein Sec61α, even up until translation is nearly complete. Exact binding sites on translocon proteins varied with the transmembrane sequence, but all sequences tested, including subsequent transmembrane domains, showed prolonged contacts with Sec61α.

As in past experiments, the sequences also showed rapid cross-linking with phospholipids. But this does not exclude translocon protein involvement. Rather, says Johnson, “this implies that phospholipids fill in holes in the translocon to avoid a vacuum as it expands to allow the transmembrane domain to move from the pore into the bilayer.”

What induces protein release from the translocon is not clear. The affinity of individual transmembrane domain–translocon interactions may dictate the timing of the release. Incoming transmembrane segments may also push out previous domains. If so, orchestrated binding and release may allow the ribosome and translocon to integrate every pair of transmembrane domains correctly in opposite orientations.

Centrosomes lead stem cell orientation

Stem cells in the fly male germ line can both maintain their numbers and produce differentiating progeny by correctly orienting cell division, according to Yukiko Yamashita, D. Leanne Jones, and Margaret Fuller (Stanford University, Stanford, CA).

Asymmetric cell division is associated with control over spindle orientation in several models, such as the fly neuroblast and the worm P1 cell. In both of these cases, the spindle is reoriented during mitosis. But in fly germline stem cells (GSCs), which divide asymmetrically to produce one stem cell and one cell that initiates differentiation, Fuller’s group now shows that the GSCs are oriented throughout the cell cycle, not just during mitosis.

GSCs align themselves with the surface of their niche, known as the hub—a cluster of somatic cells in the testes that instruct neighboring GSCs to retain stem cell identity. Yamashita et al. show that GSCs build their spindle perpendicular to the hub by keeping one centrosome in close contact with the hub—even during interphase. After the cell divides, one daughter remains connected to the hub, and thus maintains stem cell identity, whereas the other daughter is displaced away and differentiates. Disruption of centrosome function interferes with this polarity. As a result, both daughter cells contact the hub, leading to an excess of GSCs.

The boundary between the hub and the GSC contained high levels of cadherins and a fly homologue of APC, which is thought to help orient spindles in epithelial cells. APC mutant GSCs have mispositioned centrosomes, misoriented spindles, and an excess of GSCs. Thus, the APC–cadherin complex may anchor one GSC centrosome near the hub, leaving the other free to roam.


Grow wings for a limited time only

The shape of a fly wing is patterned by gradients of the morphogens decapentaplegic (Dpp) and Wingless (Wg), which establish the anterior–posterior and dorsal–ventral axes, respectively. Laura Johnston and Angela Sanders show now that Wg is also a timing signal that determines when wing growth should cease. The findings contradict previous views of the cell proliferation function of Wg.

Wg was thought to promote cell proliferation because loss of Wg signaling leads to a small wing structure. But Johnston now shows that small wings arise because Wg is required for cell survival in the early stages of wing development, when cells are rapidly proliferating. In these surviving cells, however, Wg actually slows cell growth and division. When the authors removed Wg but prevented cell death, the cells proliferated faster than usual. Conversely, overexpression of Wg slowed proliferation.

Wg’s negative effects on cell proliferation were seen mostly in late stages of development, suggesting that perhaps cells must first achieve some level of differentiation before Wg can arrest growth. Thus, Wg may signal that the organ has had sufficient time to differentiate and is now ready to halt growth.


Keratin for supple cells

Cancer cells are made more elastic by lipid-induced changes in keratin organization, according to Michael Beil, Joachim Spatz (University of Heidelberg, Heidelberg, Germany), Thomas Seufferlein (University of Ulm, Ulm, Germany), and colleagues. The increased flexibility may make cell movement easier and thus promote cancer progression.

Keratin forms the major intermediate filament network in several epithelial cell types, including carcinomas. The German collaborators now find that in cancer cell lines these networks are sensitive to sphingosylphosphorylcholine (SPC), a blood plasma lipid that is elevated in certain metastases. SPC is thus the first physiological compound shown to alter keratin organization. SPC treatment of pancreatic and gastric cancer cells reduced cytoplasmic keratin filaments, which relocated to form a ring of newly phosphorylated filaments surrounding the nucleus.

The group found that the keratin filaments were the main determinant of cellular elasticity. The SPC-induced rearrangement made the cells more flexible and also allowed migration—a dangerous combination for tumor cells. “The first step in metastasis is to get into the bloodstream,” says Seufferlein. “This could be facilitated by compounds like SPC. Then the cells can change shape and squeeze through [tight] areas.” Primary cells still need to be examined to determine whether keratin in noncancerous cells responds similarly to SPC.