In This Issue

Loopy Sec61 mutants

Sec61 forms the pore through which proteins enter the ER. On page 67, Cheng et al. show that its cytoplasmic face makes at least two contributions to translocation before the protein passage event.

The predicted structure of yeast Sec61 suggests that several conserved charged residues, which are in cytoplasmic loops that link adjacent membrane-spanning domains, may interact with the ribosome during cotranslational translocation. The authors mutated many of these candidate residues within Sec61. Several of the mutations blocked cotranslational protein translocation in vivo, but the particular effect depended on which loop was mutated.

Point mutations in loop 8 (L8) interfered with the binding affinity between the ribosomal large subunit and the pore. Without this contact, normally ER-localized proteins accumulated in the cytoplasm. Cytoplasmic protein accumulation was also seen when loop 6 (L6) was mutated, although the binding affinity of the L6 mutants for the ribosome was not affected, suggesting that the cytoplasmic face of Sec61 has yet another function in translocation.

This function might be to improve the efficiency of ribosome binding by signaling that a channel is unoccupied. Before transferring to the translocon, the ribosome first binds to the signal recognition particle (SRP) and its receptor (SR). The authors hypothesize that interactions between an unoccupied L6 and the SR might place the SR-SRP-ribosome intermediate near open channels and thus hasten its transfer. They are now looking for definitive evidence of L6–receptor interactions.

MITF links maturation and quiescence

The coordination of cell differentiation with exit from the cell division cycle may help to limit organ size and prevent tumor formation. But the mechanism that links these two processes is unknown for most cell types. On page 35, Loercher et al. show that, in melanocytes, the link is the MITF transcription factor.

MITF was already known for its differentiation-inducing activity. Now it is also shown to slow cell growth by activating transcription of a cell cycle inhibitor gene (in addition to pigment and melanocyte survival genes). This mitotic inhibitor, p16\textsuperscript{Ink4a}, arrests cells in G1 by blocking phosphorylation of Rb. Hypophosphorylated Rb binds to E2F and thus prevents it from activating cell cycle progression genes.

The cell cycle arrest is needed for differentiation, as precursor cells lacking p16\textsuperscript{Ink4a} did not show features of melanocyte differentiation in response to MITF. The authors speculate that free E2F, which accumulates when p16\textsuperscript{Ink4a} is inactive and Rb is phosphorylated, may transcribe genes that repress differentiation as well as genes that promote cell cycle progression. Alternatively, differentiation may be jumpstarted (or made possible) by long-lasting chromatin remodeling (e.g., via the recruitment of polycomb group proteins) that occurs when cells permanently exit from the cell cycle.

Later, MITF is needed to maintain the quiescent state. RNAi-induced loss of MITF inhibited expression of \textit{INK4A} (the gene that encodes p16\textsuperscript{Ink4a}) and sent differentiated melanocytes back into the cell cycle. Cultured melanocytes occasionally escaped from the cell cycle block on their own by inactivating p16\textsuperscript{Ink4a}.

Many natural melanomas are also deficient in \textit{INK4A} expression. The selective pressure to proliferate probably favors mutation of \textit{INK4A} over MITF, as the latter is needed for transcription of survival genes.