Too long for translocation?

Peptides that are made too quickly can’t get into the ER, say Asvin Lakkaraju, Katharina Strub (University of Geneva, Switzerland), and colleagues. It seems that the peptides become too long for the translocation machinery to deal with.

The signal sequence at the amino terminal of a growing peptide chain is required for translocating the peptide into the ER. The signal sequence binds a signal recognition particle (SRP), which in turn binds to an SRP receptor on the endoplasmic reticulum and guides the nascent chain to a translocon—a channel that feeds the new peptides into the ER. Mammalian SRP has been known to delay elongation in vitro, but the significance of the delay, and its occurrence in vivo, was unknown.

To explore SRP’s role in vivo, the authors prepared a mutated version of human SRP14 that specifically lacked the delaying function. SRP14’s ability to bind to nascent peptides and to the SRP receptor remained intact. In cells that carried the mutant SRP, elongation sped up, but the final concentration of secreted protein dropped and growth suffered. Closer inspection revealed that translocation in these cells had slowed down and nascent peptide chains were being degraded.

The effects of mutant SRP could be mitigated with antibiotics that slowed elongation. They could also be mitigated by increasing the number of SRP receptor molecules. Together, the data suggest that overly long peptides, produced as a result of faster elongation, can still bind to the SRP receptor but do so unproductively—perhaps by inhibiting the receptor’s ability to engage with the translocon.

Translation elongation, it appears, has the ability to go at a much faster pace than the normal cellular translocation machinery can cope with, and thus requires SRP to put the brakes on. Why elongation has evolved to be so super speedy, however, is not yet clear.

Lakkaraju, A.K.K., et al. 2008. Cell. 133:440–451.

Tumor cells share oncogenic receptors

Mutant receptors made in one tumor cell can be passed to tumor cells lacking them, say Khalid Al-Nedawi, Janusz Rak (McGill University, Montreal), and colleagues, increasing oncogenicity of the entire tumor.

In a certain type of human brain cancer called glioma, the gene encoding epidermal growth factor receptor is often mutated, creating a version of the receptor that is truncated and overactive. The presence of this mutant version, called EGFRvIII, can signify a more aggressive disease state, even if many cells in the tumor don’t express the receptor gene. Expressing and nonexpressing cells both display the mutant protein, however, and both contribute to malignancy. “It was hard to understand how receptor expression in one small set of cells could upgrade the entire tumor” to the more aggressive form, Rak says.

The authors found that glioma cells expressing EGFRvIII transferred this errant receptor to nonexpressing cells via microvesicles—small plasma membrane buds. The microvesicles were produced in abundance by the mutant expressing cells and were widely taken up by receptor-negative cells. Within 24 hours, these recipient cells had increased receptor-triggered downstream signaling and, compared with cells without receptors, could form twice as many colonies in agar—a standard sign of increased malignancy.

“We propose there is a much greater level of communication between cancer cells than is usually appreciated,” Rak says. Microvesicles aren’t just shared among cells; previous work has shown that they’re also shed into the bloodstream. The finding that glioma cells are sending out microvesicles could therefore potentially lead to a less invasive means of brain tumor characterization.

Al-Nedawi, K., et al. 2008. Nat. Cell Biol. doi:10.1038/ncb1725.