In This Issue

**Sticky cells in a prickly system**

The olfactomedin (OLF) protein domain appears in a strange assortment of places: its namesake, olfactomedin, is found in the mucus covering the bullfrog olfactory neuroepithelium, while mutations in the OLF domain of human myocilin/TIGR protein are associated with a form of familial glaucoma, and the OLF-containing protein noelin appears to be involved in neural crest formation in vertebrates. But what does this conserved domain do? On page 597, Hillier and Vacquier identify another OLF-containing protein, show that it mediates a novel form of intercellular adhesion, and describe a simple but powerful model system for future work in this area.

The authors set out to understand how cells in the coelom of a sea urchin clot in response to an injury. In contrast to vertebrate or arthropod blood clotting, sea urchin clotting involves rapid aggregation of phagocytic immune cells. A factor that promotes clotting was isolated from the coelomic fluid, partially sequenced, and cloned. The plasma protein, called amassin, forms disulfide bonds to aggregate into large complexes. About half of the amassin sequence is an OLF domain, and structural predictions show a strong resemblance to OLF domains from other species.

Since amassin, calcium, and plasma-free cells from the coelom are the only components required for sea urchin clotting, the system is a simple model for studying OLF-mediated intercellular adhesion. The authors speculate that clot-like cell adhesion may be a general function of OLF domains. In familial glaucoma, for example, mutant myocilin/TIGR is thought to mediate a cellular clustering process that decreases aqueous outflow from the eye, increasing intraocular pressure.

Amassin appears to require a cell surface receptor for clot formation, but the receptor and the mechanism that triggers clotting remain unknown. Hillier and Vacquier are now trying to determine the crystal structure of the amassin OLF domain and understand its regulation.

**TRAP builds a better translocon**

For over a decade, mechanistic studies of protein translocation into the mammalian ER have relied on proteoliposomes with translocons reconstituted from purified components, a system that efficiently translocates simple model proteins like prolactin, but often fails to match in vivo translocation efficiency for other substrates. On page 529, Fons et al. explain why by showing that the TRAP complex, previously considered dispensable for translocation, is actually a substrate-specific functional component of the mammalian translocon. The work suggests that accessory complexes like TRAP could help to drive both normal and pathological cell physiology.

In the standard reconstituted system, prion protein (PrP) either fails to translocate or becomes stuck as a transmembrane protein, problems that are also observed in some neurodegenerative prion diseases. The authors exploited this defect to purify a factor that stimulates complete translocation of PrP, and identified the factor as TRAP. TRAP also stimulates the translocation of several other proteins. The TRAP dependence of a protein is determined primarily by its signal sequence: the less efficient a signal sequence is at initiating substrate translocation, the more it requires TRAP.

Thus, the core machinery of translocation may be assisted by accessory factors for different classes of substrates. As signal sequences are highly divergent among substrates, factors like TRAP might be regulated to control specific physiological events within the cell. The apparent defects in PrP translocation in certain prion diseases raises the intriguing possibility that changes in the expression or activity of TRAP could also contribute to pathogenesis.

The authors are now extending their analysis of translocons with and without TRAP. They hope to determine whether TRAP acts directly by binding to the translocating substrate, or indirectly by altering the structure of the translocon.