Glycolipids anchor laminin

Two decades ago researchers considered the possibility that glycolipids could link laminin and other extracellular matrix proteins to the cell, but once integrins were discovered the focus switched to protein–protein interactions. Now on page 179, Li et al. show that the glycolipid galactosyl-sulfatide (gal-sulfatide) is a crucial anchor for laminin in Schwann cells and is necessary for basement membrane assembly. However, intracellular signaling requires protein receptors, such as integrins and dystroglycan.

Laminin was known to interact with sulfated glycolipids, but the significance of the interaction was not known. Li et al. found that laminin aggregated on the surface of Schwann cells in vitro only in the presence of gal-sulfatide. Treatment of the cells with an enzyme that removed the sulfate groups from the surface blocked laminin binding. Fibroblasts do not normally make a basement membrane, but when the team seeded them with gal-sulfatide, the cells bound laminin. In both cell types, basement membrane formation occurred only after laminin bound to the glycolipid. However, intracellular signaling was triggered when laminin had access to functional β1-integrins and dystroglycan, not because of the interaction with the glycolipid.

The team has started to look at other systems to see if this phenomenon is common. Already they have found hints that gal-sulfatide is used for the polymerization of lamins and basement membrane formation in embryoid bodies.

Signal for ER-associated degradation

A major pathway for misfolded proteins is the ER-associated degradation (ERAD) pathway. On page 73, Spear and Ng show that misfolding is not enough to target a protein to ERAD. Rather, particular sugar residues act as signals.

The team used a shortened CPY protein as a model unfolded protein. CPYΔ1 lacked the terminal 154 amino acids of the protein. Surprisingly, it was retained in the ER, rather than being targeted for ERAD. Although CPY contains four N-glycosylation sites, the team found that if they disrupted the last site—the one missing in CPYΔ1—the protein was retained in the ER.

To further test whether a single glycan could act as a signal for degradation, the team created two novel mutations in the ERAD substrate proteinase A⁺. When they mutated the first of two N-glycosylation sites in the protein, it was retained in the ER, like CPYΔ1; but mutating the second site had no effect.

The team has started to further narrow down the features of the glycosylation sites that act as ERAD-entry signals. They have preliminary evidence that it is a bipartite signal, with a polypeptide sequence acting in conjunction with the sugar. If they move both together they can transfer the ERAD-targeting signal, independent of the rest of the protein. Remarkably, the glycosylation sites identified by Spear and Ng do not appear to have a function in the correctly folded protein, suggesting that they evolved for the purpose of targeting the protein for degradation when it misfolds.