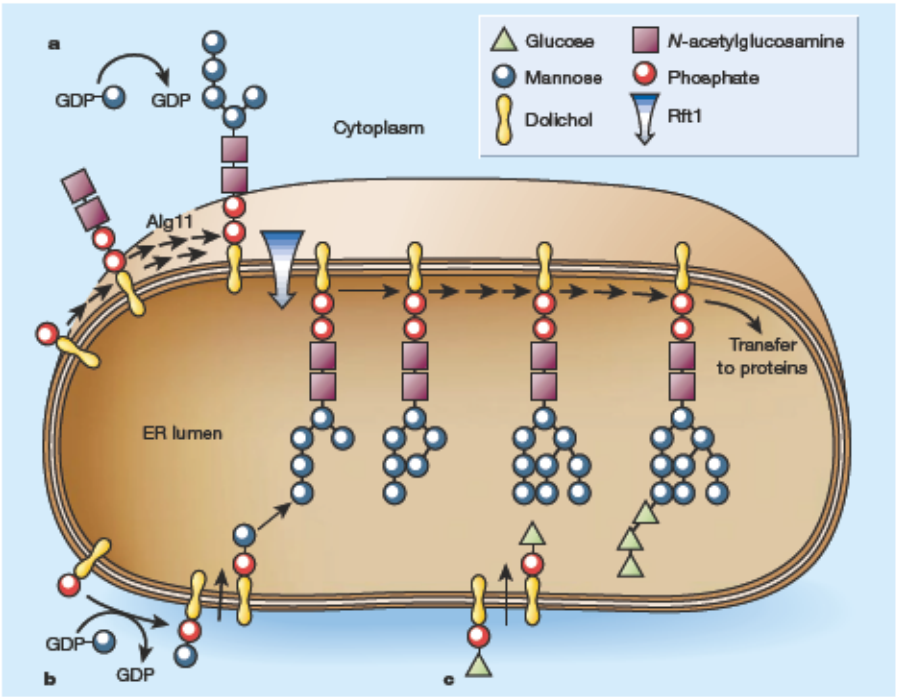

Figure 1 **Cellular events that lead to the modification of proteins with sugar groups. a, The process starts with the sequential addition of seven monosaccharides (*N*-acetylglucosamine–phosphate, *N*-acetylglucosamine and five mannose units) to a lipid derivative (dolichylmonophosphate). This lipid-linked oligosaccharide is then flipped into the endoplasmic reticulum (ER), probably by the protein Rft1, as Helenius *et al.*[1] now show. Inside the ER, this oligosaccharide is further modified with four more mannose units and three glucose units before it can be attached to target proteins. b, c, The sources of mannose and glucose are, respectively, dolichylmonophosphate-linked mannose and dolichylmonophosphate-linked glucose, which are also flipped into the ER, by unknown mechanisms.**

to the ER lumen where four more mannose units are added. Helenius *et al.*[1] overexpressed Rft1 in yeast lacking Alg11, and found that fewer glycoproteins were underglycosylated. Moreover, the cellular levels of lipid-linked $Man_3GlcNAc_2$ were reduced, but levels of lipid-linked $Man_7GlcNAc_2$ were increased. This oligosaccharide was later transferred to proteins. The implication of these and further results is that Rft1 is involved in moving polyprenol-bound sugars into the ER lumen. In these particular mutant cells, Rft1 moves $Man_3GlcNAc_2$ into the lumen. (In normal yeast, it would flip $Man_5GlcNAc_2$ inwards.) Significantly, *RFT1* has counterparts in all eukaryotic genomes sequenced to date, with the notable exception of *Plasmodium falciparum* — the malaria-causing parasite — which lacks *N*-glycosylation[6].

Despite this advance there are still many longstanding unanswered questions. For example, is there a permanent physical association between the flipping protein (or proteins) and the polyprenol group? Such an association would presumably facilitate flipping, as dolichols are extremely large lipids (with up to 105 carbon atoms in mammalian cells) that are not expected to travel through the ER membrane as quickly as do phospholipids, the main cell-membrane components. In addition, what are the energy requirements involved in flipping a hydrophilic oligosaccharide into the ER? What structural rearrangements occur in the flipping proteins? And do the flipping proteins interact with those that add sugar units to the oligosaccharide?

Finally, why can the membrane protein glucosidase I remove the outer glucose unit from the target-protein-linked oligosaccharide when the protein is still being synthesized, but not when the oligosaccharide is linked to the polyprenol? Does the flipping protein somehow protect this glucose? This is an important point, as $Glc_2Man_9GlcNAc_2$ is transferred to protein much less efficiently than the complete oligosaccharide. A defenceless lipid-linked oligosaccharide would undoubtedly lead to glycoprotein underglycosylation and misfolding.

Helenius *et al.*'s paper[1] does not answer any of these questions. But, rather like Ariadne in Greek mythology, it provides the beginning of a thread that will guide researchers out of the labyrinth of the flipping process. ■

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1. Helenius, J. *et al. Nature* 415, 447–450 (2002).
2. Parodi, A. J. *Annu. Rev. Biochem.* 69, 69–95 (2000).
3. Abeijon, C. & Hirschberg, C. *Trends Biochem. Sci.* 17, 32–36 (1992).
4. Kornfeld, R. & Kornfeld, S. *Annu. Rev. Biochem.* 54, 631–664 (1985).
5. Ng, D. T., Spear, E. D. & Walter, P. *J. Cell Biol.* 150, 77–88 (2000).
6. Davidson, E. A. & Gowda, D. C. *Biochimie* 83, 601–604 (2001).

Daedalus

Electric air drier

All modern plastic films have long-chain molecules. Stretching aligns them in the plane of the film, making the film stronger and highly impermeable to small molecules. Daedalus now wants a film with molecules oriented perpendicular to its plane. Langmuir–Blodgett films are like this, but they are normally too thin for the purposes Daedalus has in mind.

Langmuir–Blodgett films are made from a substance whose long-chain molecules float on a solvent such as water; their chains are vertical and nearly touch. When a substrate is passed through the water's surface, the film is transferred to the substrate. Many such passes build up a Langmuir–Blodgett film of numerous perpendicular layers. To make the films thicker, DREADCO chemists will lay them on a flexible substrate, perhaps paper or non-woven porous film. Many passes through a polymer solution will then be needed to build a thick Langmuir–Blodgett film. The frail product will be retained on the substrate, although it may be stripped off if it is strong enough. Its molecules will run across the film.

Unlike normal films, DREADCO's 'Langblofilm' will have little strength and will be highly permeable. With its molecular chains side-by-side across its whole width, it is in effect riddled with long, narrow, intermolecular holes lying between the chains. Small molecules will percolate through them. Daedalus recalls that in electro-osmosis a liquid is impelled along a narrow capillary by a voltage across its ends. This works best for capillaries of small radius, and for fluids of high permittivity. Water has a very high permittivity, so Langblofilm is an ideal pump for water.

One obvious use is air conditioning. Daedalus will evaporate a thin layer of aluminium on the film faces, and will lay it as a wallpaper on a porous wall. An electro-osmotic voltage applied across the faces will then suck water out of the air and into the film. At the other face it will be desorbed, and will diffuse through the porous wall to the outside. In this way the whole area of wall will dehumidify the room. Traditional air-conditioning systems, with their complex machines and pipework, will be totally outclassed. To suit popular taste, the DREADCO team may have to print floral patterns on their product, overlaying the aluminium electrode layer. This itself must be thin enough not to block the holes of the film, but weak electrostatics over a wide area will then take over from air-conditioning motors pumping on a tiny cross-section. **David Jones**