one further mannose ring from $\text{Man}_9\text{GlcNAc}_2$ to make $\text{Man}_8\text{GlcNAc}_2$. This was unexpected because no mannosidase activity was detected when Htm1p was first characterized (although it homologous to mannosidase enzymes).

$\text{Man}_8\text{GlcNAc}_2$ is then recognized by a protein called Yos9p. This protein specifically binds to the exposed mannose residue left after Htm1p’s trimming. Yos9p was already thought to “proofread” glycans that signal protein misfolding and target them for degradation, but until now the specific signal sought by Yos9p wasn’t clear. The work therefore provides important insights into how this arbiter of protein quality control operates in the ER.

Clerc, S., et al. 2009. J. Cell Biol. doi:10.1083/jcb.200809198.

CERT loss puts the brakes on growth

Wang et al. provide new insights into how ceramide transfer protein (CERT) affects cell growth and survival.

Many cancer therapeutic agents cause ceramide-dependent apoptosis, but the cell biology of this lipid is poorly understood. Recently, it was shown that CERT is required to transport ceramide from the endoplasmic reticulum (ER), where it is synthesized, to the Golgi, where it undergoes processing to create complex sphingolipids including sphingomyelin—a major component of plasma membranes. To learn more about CERT and ceramide in vivo, Wang et al. made CERT-deficient mice.

CERT-deficient embryos, they found, die around embryonic day 11.5. To explore whether increased ceramide levels and subsequent apoptosis could be to blame, the authors examined the embryos’ cells. The ER of CERT-deficient cells was swollen, as ceramide was trapped in the organelle. This impaired ER function and also activated cellular stress pathways. Some of the trapped ceramide overflowed into mitochondria, causing these organelles to bloat too. How ceramide is transmitted from the ER to mitochondria remains unclear, but as with the ER, the ceramide accumulation impaired mitochondrial function.

Surprisingly, the stress and organelle malfunctions were not enough to kill the cells, as the cells up-regulated several adaptive responses. The cells did exhibit impaired growth rates however, as they adapted to these stressful conditions. In the growing embryos, this resulted in retarded organogenesis—the animals died when their hearts failed to develop properly. The implication for cancer therapy, on the other hand, is that targeting the CERT pathway might slow or stop a tumor’s growth, but may not kill it.

Wang, X., et al. 2009. J. Cell Biol. doi:10.1083/jcb.200807176.