under different conditions, and showed that there is a correlation between the levels of Yph1 and the rate of proliferation that occurs in response to the energy source that is used. So, levels of Yph1 are high when glucose is plentiful and proliferation is high, but low (or absent) when slow proliferation occurs due to poor energy sources.

When these findings are combined, a picture emerges in which Yph1 might help to link processes that require high levels of energy — for example, DNA replication and ribosome biogenesis — to a regulatory mechanism that senses the amount of an available energy source. Elegant though this explanation is, however, the authors point out that Yph1 could turn out to be involved in these processes independently.

Alison Mitchell

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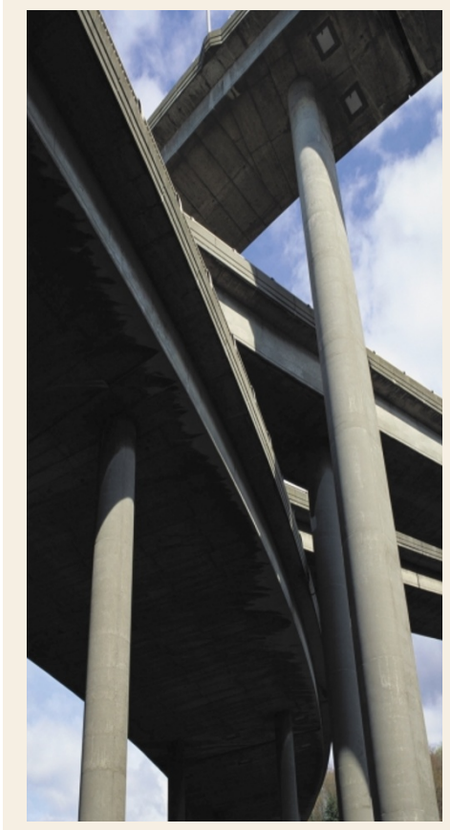

PROTEOLYSIS

A new family

It has generally been thought that the presenilin component of the γ-secretase complex catalyses the intramembrane proteolysis of transmembrane (TM) substrates such as Notch and β-amyloid precursor protein. However, recent observations have indicated that, in fact, another component of this complex might be responsible for this catalytic activity. But now, in *Science*, Martoglio and co-workers reaffirm the catalytic role of presenilin by reporting the identification of a new presenilin-like aspartic protease — human signal peptide peptidase (SPP).

Many integral membrane proteins need a signal sequence for correct membrane insertion, and signal peptidase releases the signal-sequence peptide into the membrane after insertion. So, where does SPP come in? It is thought that SPP catalyses the intramembrane proteolysis of signal peptides, and releases functional signal-peptide fragments — for example, cell-surface epitopes — from the endoplasmic reticulum (ER) membrane.

Martoglio and colleagues therefore set about identifying human SPP. They modified a known SPP inhibitor to contain a photoreactive group (to allow irreversible covalent binding of SPP on inhibitor activation by ultraviolet (UV) light) and a biotin moiety (to enable detection of tagged SPP). The authors then mixed this inhibitor (called TBL_4K) with detergent-solubilized ER membranes, and exposed the mixture to UV light. This method allowed them to isolate two differentially glycosylated forms (42 and 40 kDa) of SPP.

Using mass-spectrometric analysis of the 42-kDa form and database searches, the authors identified more than 15 proteins from many species that are homologous to human SPP. Unfortunately, these proteins have unknown functions, although the authors noted that the most highly conserved regions contain YD and LGLGD motifs in two putative TM segments. These motifs are characteristic of presenilin-like aspartic proteases.

The authors verified that the TBL_4K-targeted protein is an SPP by expressing it in *Saccharomyces cerevisiae*. They observed TBL_4K-sensitive SPP activity, and also showed that mutating the conserved aspartate residue in the LGLGD motif to alanine abolishes SPP catalytic activity without affecting TBL_4K labelling.

Analysis of the amino-acid sequence and potential glycosylation sites of human SPP allowed the authors to propose that it has a seven-TM topology with its amino terminus in the ER lumen, its carboxyl terminus (which contains an ER-retrieval signal) in the cytosol, and the YD and LGLGD aspartic-protease motifs in the middle of adjacent TM helices. The latter feature is found in presenilins, although the orientation of these TM helices is reversed in presenilins. This fits with the opposite orientation of presenilin and SPP substrates — presenilin substrates are type I TM proteins, whereas SPP substrates have a type II orientation.

The identification of SPP as a presenilin-like aspartic protease by Martoglio and co-workers supports the view that presenilins are proteases. Among the components of the γ-secretase complex, only the presenilins now resemble a known protease. This work has potentially identified a new family of polytopic membrane aspartic proteases, and future studies of SPP might help to determine the mysterious mechanism of intramembrane proteolysis.

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