Figure 2 Model for the two-site cleavage of the sterol regulatory element binding protein (SREBP). **a**, Cleavage 1 cuts the luminal loop between the regulatory and transcriptional domains. This cleavage is somehow facilitated by the SREBP cleavage activating protein (SCAP), and it occurs in the lumen of the endoplasmic reticulum. **b**, Cleavage 2 occurs in a trans-membrane domain, liberating the membrane-bound transcription factor (TF). This cleavage is similar to the γ -secretase cleavage of APP.

Strooper *et al.*¹ discuss the exciting possibility that PS1 activates γ -secretase cleavage of APP, similar to the SREBP-cleavage activating protein (SCAP)⁸. SCAP facilitates cleavage of the sterol regulatory element binding protein (SREBP) to liberate its transcription-factor domain, which migrates to the nucleus and regulates the expression of genes involved in cholesterol biosynthesis and uptake. Cleavage of SREBP occurs in two steps (Fig. 2). Cleavage 1 cuts the luminal loop between the regulatory and transcriptional domains, and this cleavage is facilitated by SCAP. Cleavage 2 then liberates the membrane-bound transcription factor. Like the γ -secretase cut of APP, cleavage 2 occurs within the membrane.

At present, γ -secretase and the SREBP protease are the only known proteolytic activities that cleave in an environment which, according to textbook knowledge, should preclude proteolysis. There are other remarkable similarities between the two systems. Both SREBP and the presenilins are located in the endoplasmic reticulum², and the γ -secretase cleavage after amino acid 42 could occur, in part, within the endoplasmic reticulum and Golgi^{9–11}. Furthermore, the SCAP proteins are predicted to form six to eight transmembrane domains — a structure similar to that of the presenilins.

Based on these analogies, PS1 might be expected to regulate γ -secretase, and De Strooper *et al.*¹ now prove it. This physiologi-

cally normal activity is presumably disturbed by presenilin mutations, leading to increased cleavage of APP carboxy-terminal fragments after amino acid 42 of amyloid- β peptide. There is, however, one big difference between SCAP-activated SREBP proteolysis and presenilin-activated APP cleavage by γ -secretase: SCAP is currently known to activate only cleavage 1 within the lumen of the endoplasmic reticulum⁸, whereas γ -secretase cleavage of APP occurs within the transmembrane domain.

An alternative molecular explanation for the reduced production of amyloid- β peptide in *PS1*^{-/-} mice is that PS1 regulates the transport of membrane proteins from the endoplasmic reticulum to other cellular compartments. This explanation could support the observed phenotype of mutations in the *C. elegans* presenilin homologue, which could be due to altered sorting of membrane proteins within the endoplasmic reticulum. This could lead to reduced transport of proteins such as APP and the Notch receptor through the Golgi and onto the cell surface. In this case, mutant presenilins might retain APP within the endoplasmic reticulum and early Golgi, leading to increased production of amyloid- β (1–42) peptide^{9–11}. The lack of *PS1* expression would affect targeting not only of APP, but also of other membrane proteins in the endoplasmic reticulum.

Regardless of which molecular mechanism is responsible for the sharp reduction in generation of amyloid- β peptide in *PS1*^{-/-} mice, PS1 could serve as an unexpected therapeutic target for Alzheimer's disease. Inhibition of presenilin synthesis late during ageing, when the disease normally begins, would avoid elimination of the essential function of presenilin proteins during development^{5,6}. Expression of *PS1* could be repressed at the transcriptional level or by interfering with the post-translational processing of presenilin and presenilin complex formation (Fig. 1)⁴. And if levels of PS1 could be decreased enough in the brain, production of amyloid- β would be decreased and, therefore, accumulation of senile plaques could be retarded. □

Christian Haass is at the Central Institute for Mental Health, Department of Molecular Biology, J5, D-68159 Mannheim, Germany.

e-mail: Haass@as200.zi-mannheim.de

Dennis J. Selkoe is in the Center for Neurologic Diseases, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.

e-mail: selkoe@cnd.bwh.harvard.edu

1. De Strooper, B. *et al.* *Nature* **391**, 387–390 (1998).
2. Haass, C. *Neuron* **18**, 687–690 (1997).
3. Selkoe, D. J. *J. Biol. Chem.* **271**, 18295–18298 (1996).
4. Capell, A. *et al.* *J. Biol. Chem.* (in the press).
5. Wong, P. C. *et al.* *Nature* **387**, 288–292 (1997).
6. Shen, J. *et al.* *Cell* **89**, 629–639 (1997).
7. De Strooper, B. *et al.* *EMBO J.* **14**, 4932–4938 (1995).
8. Brown, M. S. & Goldstein, J. L. *Cell* **89**, 331–340 (1997).
9. Hartmann, T. *et al.* *Nature Med.* **3**, 1016–1020 (1997).
10. Cook, D. G. *et al.* *Nature Med.* **3**, 1021–1023 (1997).
11. Wild-Bode, C. *et al.* *J. Biol. Chem.* **272**, 16085–16088 (1997).

Daedalus

Crystalline clouds

Sunshine and cloud are traditional opposites. Yet droplets make up only about 10 p.p.m. of a cloud's volume — why does sunlight not go straight through? Sadly, a photon traversing a random array of droplets is almost certain to hit one sooner or later, and be scattered. So, says Daedalus, make the array non-random.

He recalls Faraday's use of iron filings to map a magnetic field. Each iron particle has a magnetic dipole induced in it in the local field direction. Axially arranged dipoles attract one another, and align themselves into chains along the lines of force. Equatorially arranged dipoles repel one another, so each chain spaces itself as far as possible from its neighbours.

The same principle must apply to electrostatic fields. A dielectric particle (such as a water droplet) must have an electric dipole induced in it by a local electric field. The dipoles will align themselves into parallel chains following that field. So, says Daedalus, put a cloud in an electric field whose lines of force point at the Sun, and its droplets will form parallel chains pointing the same way. Sunlight will pour down unimpeded between the chains, and the cloud will become almost perfectly transparent in that direction.

At first Daedalus envisaged some mighty system of captive balloons supporting charged wires, their positions constantly adjusted to keep the field pointing at the Sun. But he soon realized that a radio beam would do just as well — provided it was polarized to point its electric vector at the Sun. Even if its field reversed at many megahertz, the dipoles it induced in the droplets would still follow it perfectly.

DREADCO's weather-brightener will launch an intense radio signal into the cloud deck. It will be constantly adjusted to keep the signal polarized in the Sun's direction. A watcher anywhere beneath the cloud will see a hole in it, through which the Sun will beam down on him. The rest of the sky will still appear cloudy; yet, oddly, the landscape will be uniformly bright. The DREADCO weather-brightener will transform tourism. British seaside resorts and holiday towns will queue up to install this answer to their Mediterranean and tropical rivals. Even those rivals may install it, though for a converse reason. By aligning its signal at 90° to the solar direction, the thinnest cloud might be made opaque enough to screen out the scorching midday Sun.

David Jones