at each step. This reduces the number of particles by half, but more importantly, it means that the massive, sluggish ions, not the speedy electrons, determine the minimum time-step, so a few days' calculation can cover the microsecond timescale on which ordering of the ions would occur.

Pohl and colleagues' simulations of a spherically symmetric plasma, with an initial ion density of around 10^8 cm^{-3} and a diameter of 20 μm, show that the ions first crystallize into a lattice structure as the plasma is cooled. If the cooling is rapid relative to the timescale of the plasma's expansion, the ions relax further into concentric shells, in each of which there is two-dimensional hexagonal ordering of the ions (Fig. 1).

The first step towards achieving such crystallization has already been taken, with the demonstration of a laser spectroscopic probe[5] of ions in the plasma. Here, the temperature of the ions and the expansion of the plasma are monitored through the Doppler shifts in the spectrum of laser radiation absorbed by the ions. Further studies along these lines will reveal the forces at work during the expansion, and the laser–ion interaction that allows spectroscopy is the same as that required for laser cooling. Pohl *et al.*[1] have developed a powerful tool with which to model crystallization in laser-cooled neutral plasmas. Now it's up to the experimenters to make it happen. ■

Thomas C. Killian is in the Department of Physics and Astronomy, Rice University, Houston, Texas 77251-1892, USA.
e-mail: killian@rice.edu

1. Pohl, T., Pattard, T. & Rost, J. M. *Phys. Rev. Lett.* **92,** 155003 (2004).
2. Itano, W. M. *et al. Science* **279,** 686–689 (1998).
3. Waki, I., Kassner, S., Birkl, G. & Walther, H. *Phys Rev. Lett.* **68,** 2007–2010 (1992).
4. Morfill, G. E., Thomas, H. M., Konopka, U. & Zuzic, M. *Phys. Plasmas* **6,** 1769–1780 (1999).
5. Simien, C. E. *et al. Phys. Rev. Lett.* **92,** 143001 (2004).
6. Kuzmin, S. G. & O'Neil, T. M. *Phys. Plasmas* **9,** 3743–3751 (2002).
7. Killian, T. C. *et al. J. Phys. A* **36,** 6077–6085 (2003).

Cell biology

A channel for protein waste

Randy Schekman

Cells destroy misshapen proteins; viruses use the same methods to destroy healthy cellular proteins that are involved in antiviral defences. A long-sought intermediary in the process has now been uncovered.

Cells go to great lengths to ensure that protein molecules fold properly and function in the correct cellular compartment. Mistakes are dealt with harshly: the offending proteins are destroyed. On pages 834 and 841 of this issue, Lilley and Ploegh[1] and Ye *et al.*[2] describe how they identified a molecule that helps redirect proteins out of one compartment, the endoplasmic reticulum, to the waste-disposal machinery.

At first glance, the process of weeding out unwanted proteins seems straightforward enough. An elaborate cellular machine, the proteasome, attacks misfolded proteins that have become tagged with a small polypeptide marker, called ubiquitin. This machine is driven by the cellular energy store, ATP.

For many years, this editing function was thought to target only proteins that are found in the body of the cell — the cytoplasm — and it was assumed that other degrading enzymes would deal with proteins in distinct compartments. But around a decade ago, converging lines of investigation highlighted a role for the proteasome in the degradation of proteins that misfold in the endoplasmic reticulum (ER)[3–5], a major site of protein synthesis and the first port of call for proteins that are destined for the cell surface or to be secreted. Thus, mutant glycoproteins are somehow regurgitated to the cytoplasm, where ubiquitin tagging promotes the recruitment of the proteasome to the surface of the ER. ATP then drives the ubiquitin-tagged protein into the clutches of the proteasome through the intervention of another protein, called p97 in mammals[6]. The net outcome is that damaged goods are reduced to peptides and glycans.

Certain viruses that seek to subvert the capacity of an immunologically competent cell to mount an antiviral defence have exploited this editing pathway. Proteins known as class I major histocompatibility complex (MHC) molecules are essential in alerting the immune system to the presence of viruses, but cytomegalovirus has evolved a devious means of diverting newly synthesized MHC molecules from this task. Two viral glycoproteins, US2 and US11, insert themselves into the ER membrane and interrupt the flow of class I molecules to the cell surface, redirecting them to an enzyme that is responsible for ubiquitination and thus into the jaws of the proteasome[7].

On their way out of the ER, redirected MHC class I molecules are assumed to pass through the same portal that is used for the regurgitation of misfolded cellular proteins. But no such connection has been firmly established, nor is the identity of this portal known. One candidate for such a channel is Sec61, a protein that creates the pore through

100 YEARS AGO

It is eighteen months or more since Mr. Marconi succeeded in establishing wireless communication across the Atlantic. On that occasion a few congratulatory messages were exchanged, a great deal was written on the subject in the Press, and the more timorous of cable shareholders were reported to be much troubled. A little later the attempt was made to demonstrate that this achievement was not merely a firework display, but was capable of direct commercial application; the Marconi Co. entered into a contract to supply the *Times* with news from America by wireless telegraphy, and for a day or so there appeared items of news in that paper under the heading "By Marconigraph." But after a few messages something went wrong, and the public were given to understand that a piece of auxiliary machinery had broken down. It is to be presumed that this piece of machinery has at length been repaired, for Mr. Marconi has once again come very much to the front with long-distance transmission work. The announcement, which we published last week, that he had been successful in maintaining a supply of news to the *Campania* on her voyage across the Atlantic with a regularity sufficient to allow of the publication of a daily paper on board that vessel affords evidence that he is still steadily pushing forward the practical development of wireless telegraphy. We have repeatedly urged in these columns that the real work of wireless telegraphy lay in communication with ships, and it is therefore a greater pleasure to record this latest development than it would be to announce the reopening of Transatlantic communication.
From *Nature* 23 June 1904.

50 YEARS AGO

In the House of Commons on June 15, Mr. Geoffrey de Freitas asked the Under-Secretary for Air whether the physical sub-committee of the Meteorological Research Committee had yet considered the problem of weather modification; and what conclusions it reached… Mr. George Ward, in a written reply, stated that the committee had recently considered this subject and come to the conclusion that there is no reliable evidence that rainfall has ever been artificially increased on an economically useful scale, and that there is no scientific basis for believing that any method yet proposed would be successful in achieving such a result.
From *Nature* 26 June 1954.

which secretory and membrane proteins become inserted into the ER during their biosynthesis. Numerous experiments have hinted that Sec61 molecules transiently interact with MHC class I molecules as they are diverted to the proteasome[8], and that mutations in Sec61 retard the degradation of misfolded secretory proteins[9,10]. Unfortunately, these experiments did not reveal a direct molecular contact between Sec61 and proteins being redirected out of the ER. Other genetic studies have identified other membrane proteins that participate in the degradation of misfolded secretory proteins[11,12]. But, until now, no evidence linked these molecules directly to the transport of proteins out of the ER.

The two reports in this issue[1,2] highlight the role of a mammalian equivalent of the yeast Der1 protein — which is found in the ER membrane and is required for the degradation of certain misfolded glycoproteins[11] — in removing proteins from the ER. Lilley and Ploegh[1] used the cytomegalovirus US11 protein to probe the environment of MHC class I proteins as they are diverted from the ER. By using tagged forms of wild-type and non-functional US11, the authors could track molecules in the ER membrane. They found that several previously unknown proteins could be precipitated in a complex with wild-type, but not mutant, US11.

One subunit of this complex was one of several mammalian relatives of yeast Der1. Like its yeast counterpart, this mammalian protein, Derlin-1, is found in the ER membrane, with the protein's chain snaking back and forth across the membrane a possible four times. It binds to wild-type US11 and MHC, but the complex decomposes quickly unless the proteasome is chemically inhibited.

A crucial experiment, documenting the physiological importance of Derlin-1, came with the demonstration that a hybrid protein containing Derlin-1 and green fluorescent protein blocks the US11-dependent degradation of MHC molecules. Surprisingly, though, this hybrid does not interfere with the action of US2, the other cytomegalovirus protein that diverts MHC molecules from the ER. So, US11 and US2 have distinct mechanisms of action. An obvious possibility is that US2 acts through one of the other mammalian Derlin proteins. In uninfected cells, each Derlin might proofread a restricted cohort of molecules.

Meanwhile, Ye *et al.*[2] pursued a different path to discover the ER proteins involved in MHC degradation. Given an essential role for the ATP-driven molecule p97, the authors probed the ER membrane for a p97 receptor. Their efforts were rewarded with a complex of two proteins, one of which was Derlin-1 and one of which they named VIMP (which might be one of the other unknown proteins that Lilley and Ploegh found).

Derlin-1, VIMP and p97 co-localize to the ER, and might constitute the complex to which US11 and MHC class I molecules are recruited to initiate the export event. Using a cell-free reaction that reproduces MHC export[13], Ye *et al.* trapped an intermediate consisting of VIMP, Derlin-1, US11, ubiquitinated MHC class I protein and p97. The stable formation of this complex required functional US11.

Broadening their findings, Ye *et al.* also found that when cells were treated with dithiothreitol, a reducing agent that causes misfolded proteins to be directed out of the ER, more newly synthesized proteins that were bound up with VIMP accumulated. And blocking Derlin-1 expression in nematode worms promoted a form of cellular stress referred to as the unfolded-protein response, consistent with a general problem in the disposal of misfolded proteins.

So these studies[1,2] highlight a role for the Derlin-1 protein, and possibly for other members of the gene family, in the selective extradition of undesirable proteins from the ER. It is probably not the only such channel, however; yeast with mutations in Der1 can still dispose of many mutant membrane proteins, for instance[14,15] (R. Hampton, personal communication). Cells clearly hold many more secrets about how they deal with malfunctioning parts. ■

Randy Schekman is in the Department of Molecular and Cell Biology, Howard Hughes Medical Institute, University of California, Berkeley, California 94720, USA.
e-mail: schekman@berkeley.edu

1. Lilley, B. N. & Ploegh, H. L. *Nature* **429,** 834–840 (2004).
2. Ye, Y., Shibata, Y., Yun, C., Ron, D. & Rapoport, T. A. *Nature* **429,** 841–847 (2004).
3. Sommer, T. & Jentsch, S. *Nature* **365,** 176–179 (1993).
4. Hiller, M. M., Finger, A., Schweiger, M. & Wolf, D. H. *Science* **273,** 1725–1728 (1996).
5. McCracken, A. A. & Brodsky, J. *J. Cell Biol.* **132,** 291–298 (1996).
6. Ye, Y., Meyer, H. H. & Rapoport, T. A. *Nature* **414,** 652–656 (2001).
7. Weirtz, E. J. *et al. Cell* **84,** 769–779 (1996).
8. Wiertz, E. J. *et al. Nature* **384,** 432–438 (1996).
9. Pilon, M., Schekman, R. & Römisch, K. *EMBO J.* **16,** 4540–4548 (1997).
10. Plemper, R. K., Bohmler, S., Bordallo, J., Sommer, T. & Wolf, D. H. *Nature* **388,** 891–895 (1997).
11. Knop, M., Finger, A., Braun, T., Hellmuth, K. & Wolf, D. H. *EMBO J.* **15,** 753–763 (1996).
12. Hampton, R., Gardner, R. G. & Rine, J. *Mol. Biol. Cell* **7,** 2029–2044 (1996).
13. Shamu, C. E., Story, C. M., Rapoport, T. A. & Ploegh, H. L. *J. Cell Biol.* **147,** 45–58 (1999).
14. Hill, K. & Cooper, A. A. *EMBO J.* **19,** 550–561 (2000).
15. Vashist, S. & Ng, D. T. *J. Cell Biol.* **165,** 41–52 (2004).

Cometary science

Fly-through at Wild 2

Michael F. A'Hearn

The Stardust mission has made the closest approach ever to a comet. Its 'fly-through' of the gas and dust surrounding Wild 2 presents a unique opportunity to investigate the evolution of such bodies.

On 2 January this year, the Stardust spacecraft flew through the coma of the comet Wild 2. The primary purpose of this NASA mission is to collect particles from the coma — the dust and gas escaping from the comet's solid nucleus — and return them to Earth. The sample return is scheduled for January 2006, but in the meantime the dramatic results from the fly-through itself are now reported in *Science*[1–4].

Two other comets have been visited by spacecraft — Halley in 1986 and Borrelly in 2001. But all the measurements made at Wild 2 seem very different from those taken at the other two comets. Apart from the data on dust flux, it seems that these differences cannot be explained by the fact that the distance of closest approach of Stardust to Wild 2 was much smaller — only 236 km — than in the previous cometary fly-bys. But there is a major difference between Wild 2 and the other two comets: Halley and Borrelly have been in their present orbits, with only small changes, for about 100 orbital periods, which is as far back as reliable orbital calculations can be made; Wild 2 has not.

In 1974, Wild 2 passed very close to Jupiter and was kicked by the planet's gravity into an orbit much closer to the Sun. Its orbital period dropped from 40 years to about 6 years. Today, Wild 2's perihelion (its point of closest approach to the Sun) is roughly equivalent to the size of Earth's orbit (that is, one astronomical unit, or about 150 million kilometres). At such a distance, heat from the Sun is likely to cause changes in the comet's surface and composition. Although calculations of the comet's past orbit are not accurate enough to tell us whether it ever previously had such a small perihelion distance, most astronomers assume that Wild 2 has had only a few perihelion passages close enough to cause significant evolution of the comet — unlike Halley and Borrelly. Wild 2 should be much less evolved than either of these comets.

So what are the differences seen in these early results from Stardust? In the first of the new papers, Brownlee *et al.*[1] report that the 5-km nucleus of Wild 2 is much more nearly spherical than are the nuclei of either of the other comets (Fig. 1). This would tend to support the idea that 'outgassing', which peaks at perihelion and is very sensitive to the