emission and propagation of dislocations, depending on how the load is applied. Analytical[3,4], computational[5,6] and experimental[7,8] studies have been carried out in an attempt to pin down the relationships between applied thermo-mechanical loading and the way in which a material will react. A combination of factors are usually involved: temperature[8]; motion or dynamics of existing defects[6,7]; the specific elements and alloys that make up the crystal[5]; the orientation of the crystal lattice with respect to the load; the rate at which the load is applied; existing microstructural barriers such as crystal-grain boundaries; and properties of the material that determine its resistance to ductile and brittle deformation.

This last factor was well summarized by Rice[3], who compared the energetic 'cost' of creating new surfaces within the crystal (the surface energy) with the energy barrier that must be overcome to allow atomic planes to slip over one another (the unstable stacking fault energy). Rice used fracture mechanics to perform a straightforward analysis, and found that a critical ratio of these energies separates ductile from brittle behaviour for a particular crystal-lattice type and orientation.

Given the above list of factors, it is clearly difficult to predict whether a material will fail in a ductile or a brittle fashion. Materials scientists try to determine the competing mechanisms involved and to identify properties in the material that influence nucleation and propagation. Prevailing theories of failure mechanics use quantities that are related to the load-bearing ability of a material, such as yield and fracture stresses, whereas newer methods rely on evaluating the energetic barriers described above. Complex systems will require a combination of these criteria to adequately describe any irreversible deformation process. Although it has yet to be used for this, the model devised by Li *et al.*[1] has the potential to predict whether brittle or ductile behaviour will occur.

It is in the area of predictive modelling that the work of Li *et al.* will be immensely useful. The authors present a methodology for using their stability parameter in finite-element calculations — a simulation technique that models materials as a continuum, but uses the same interatomic potentials as in atomistic simulations. This enables systems with larger-than-atomic dimensions to be simulated, and can take into account microstructural features such as grain boundaries and different phases of the material. There is also the exciting possibility of refining the approach to operate effectively at finite temperatures and high loading rates. Li *et al.* have achieved a significant step towards understanding the defective world of materials in which we live. ■

Jonathan A. Zimmerman is at Sandia National Laboratories, PO Box 969, Livermore, California 94551-0969, USA.
e-mail: jzimmer@sandia.gov

1. Li, J., Van Vliet, K. J., Zhu, T., Yip, S. & Suresh, S. *Nature* **418,** 307–310 (2002).
2. Askeland, D. R. *The Science and Engineering of Materials* (PWS-Kent, Boston, Massachusetts, 1994).
3. Rice, J. R. *J. Mech. Phys. Solids* **40,** 239–271 (1992).
4. Beltz, G. E., Lipkin, D. M. & Fischer, L. L. *Phys. Rev. Lett.* **82,** 4468–4471 (1999).
5. Farkas, D. *MRS Bull.* **25,** 35–38 (2000).
6. Abraham, F. F. *J. Mech. Phys. Solids* **49,** 2095–2111 (2001).
7. Wall, O. *Eng. Fract. Mech.* **69,** 835–849 (2002).
8. Šmida, T. & Bošanský, *J. Mater. Sci. Eng. A* **323,** 21–26 (2002).

Cell biology

The extraordinary phagosome

Joel A. Swanson

The finding that a cellular compartment called the endoplasmic reticulum can merge with the cell's outer membrane is surprising. It would not have been predicted from our knowledge of cell organization.

Within our cells are many membrane-bounded compartments, each of which communicates with only a subset of other such 'organelles' — generally when small vesicles bud off from one and merge with another. The efficiency with which cells use their organelles to carry out complex tasks has led to the belief that movement through the system of organelles occurs in strictly defined directions. So, the endoplasmic reticulum (ER) — in which proteins destined for export from the cell are synthesized and modified — communicates primarily with the Golgi apparatus. This in turn interacts with a limited set of other organelles and, eventually, with the plasma membrane, defining an avenue of vesicular traffic for protein export. In the reverse direction, extracellular molecules internalized by endocytosis first enter endosomes and later reach lysosomes, where they are degraded (Fig. 1).

Although lateral communication between the organelles for export and import is well documented, their vectorial organization has been supported by the positions of ER and lysosomes at the ends of the two avenues. But faith in these traditional routes, already shaken by studies of phagosome biogenesis[1], is tested again by a report from Gagnon and colleagues[2] in *Cell*, which shows that proteins characteristic of the ER are present in phagosomes. This has implications for our understanding of cellular organization and of how microbes manipulate that organization.

Phagosomes are membrane-bounded organelles formed when one cell engulfs another, or some inanimate particle, by enclosing it in surface membrane. Early studies indicated that new phagosomes were made of plasma membrane[3], and that the subsequent merger of phagosomes with lysosomes created a phagolysosome — a toxic environment for ingested microbes. By current thinking, phagolysosomes form by progressive interactions of phagosomes with endosomes and lysosomes[4]. Delivery to phagolysosomes is considered the end of the road and a fate for ingested microbes to avoid, if possible.

So pathogens that live within host cells enter by mechanisms that often resemble phagocytosis, but then take different routes. An early challenge to the conventional view of organelle interactions came from studies of *Trypanosoma cruzi*, which enters host cells by stimulating the fusion of lysosomes directly with the plasma membrane[1]. Other pathogens, such as *Legionella pneumophila* and *Brucella abortus*, are ingested by phagocytosis, inhibit the fusion of phagosomes with lysosomes, and then inhabit an ER-like compartment[5].

And perhaps such seemingly extraordinary routes are not as uncommon as one might think. Gagnon *et al.*[2] have now found the ER acting out of order, fusing with the plasma membrane and apparently providing membrane for phagocytosis. Using a proteomics approach the authors first showed that phagosomes containing latex beads — purified from extracts of professional phagocytic cells known as macrophages — displayed several ER marker proteins. Electron microscopy then showed ER membranes in continuity with the plasma membrane near cell-bound particles. Moreover, early phagosomes contained patches of both ER and lysosomal membranes. Gagnon *et al.* also found that newly formed phagosomes were enriched with ER proteins, and, as phagosomes aged inside macrophages, the levels of ER markers diminished and the number of lysosomal markers increased. Strangely, the levels of ER markers in phagosomes increased again later, indicating that phagosomes continued to fuse with ER membranes long after phagocytosis.

Although further evidence will be needed before we can say that the ER is essential to phagocytosis, it is reasonable to conclude that the ER supplies membrane to some phagosomes. Phagocytosis has been shown to involve fusion of intracellular organelles with the plasma membrane[6]; endosomes have been considered the most likely organelles, but lysosomes and the ER can

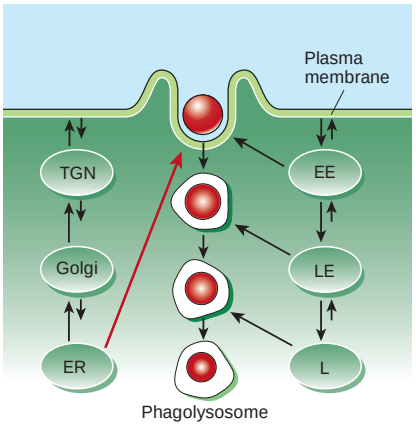

Figure 1 **Intracellular organelles that interact with phagosomes — membrane-bounded compartments for the uptake of certain extracellular substances. Organelles involved in protein synthesis and secretion, including the endoplasmic reticulum (ER), Golgi apparatus and *trans*-Golgi network (TGN), have not been thought to interact significantly with phagosomes. Rather, phagosome formation at the plasma membrane leads to progressive interactions with endocytic compartments — early endosomes (EE), late endosomes (LE) and lysosomes (L) — ultimately forming a phagolysosome. But the paper by Gagnon *et al.*[2] shows that ER markers are present in phagosomes at the earliest stages of their formation (red arrow).**

provide membrane as well. It is not clear why the delivery of ER to phagosomes was not discovered in earlier electron-microscopic studies, especially given that Gagnon *et al.* found ER markers in several different classes of phagosome, including those that take up the microbes *Leishmania donovani* and *Salmonella typhimurium*. But perhaps ER recruitment is not needed for all types of phagocytosis in macrophages.

Whatever the reason, these results[2] clearly suggest new lines of organelle communication, simplifying some previously complex models. For example, there are implications for how proteins are processed by 'antigen-presenting' cells and displayed on the cell surface for detection by the immune system. Molecules from intracellular pathogens are generally loaded onto so-called class I major histocompatibility complex proteins in the ER. Sometimes proteins from outside cells can also be loaded via this ER pathway, and some circuitous routes have been proposed for how those proteins reach the ER[7]. The results of Gagnon *et al.* suggest a more direct route. Moreover, if the ER also interacts with the plasma membrane in the absence of phagocytosis — a process that may be more difficult to detect — it could provide a short cut for some bacterial toxins to travel from the cell surface to the ER. Until now, these toxins had been thought to reach the ER by travelling 'backwards' through the Golgi apparatus[8].

The new findings also suggest that the exotic routes of some intracellular pathogens are not so odd after all. Many pathogens define their compartmental home even before they separate from the plasma membrane, rather than remodelling a conventional phagosome after entry[9]. For example, *Legionella pneumophila* is thought to recruit ER to phagosomes, apparently by hijacking a normal cellular pathway for organelle degradation called autophagy[5]. But if further studies show that a variety of phagosomes contain ER proteins from the start, then the mechanism that creates the *Legionella* compartment can be viewed as a variation on normal phagocytosis. That said, there probably isn't a 'normal' route for a phagosome. Gagnon *et al.* find that the ER merges with phagosomes in macrophages but not in neutrophils — another kind of professional phagocyte. Apparently, even phagosomes containing inert latex beads follow different patterns of maturation after phagocytosis.

Finally, the extraordinary variation among phagosomes may also hint at greater diversity among other organelles. With the increased sensitivity of proteomic methods, we may learn that organelle marker proteins are not as specific as previously thought, and that the boundaries that distinguish organelles are not as sharp. Vectorial movements through organelles might be controlled at the level of individual molecules or patches of membrane, rather than by constrained interactions between discrete organelles. Phagosomes might then acquire unusual combinations of markers through the way in which the particles they contain affect marker dynamics. The resulting variety in marker proteins could provide a way for cells to sense the contents of their phagosomes. ■

Joel A. Swanson is in the Department of Microbiology and Immunology, University of Michigan Medical School, Ann Arbor, Michigan 48109-0620, USA.
e-mail: jswan@umich.edu

1. Andrews, N. W. *Trends Cell Biol.* 5, 133–137 (1995).
2. Gagnon, E. *et al. Cell* 110, 119–131 (2002).
3. Muller, W. A., Steinman, R. M. & Cohn, Z. A. *J. Cell Biol.* 86, 292–303 (1980).
4. Desjardins, M., Huber, L. A., Parton, R. G. & Griffiths, G. *J. Cell Biol.* 124, 677–688 (1994).
5. Dorn, B. R., Dunn, W. A. & Progulske-Fox, A. *Cell. Microbiol.* 4, 1–10 (2002).
6. Bajno, L. *et al. J. Cell Biol.* 149, 697–705 (2000).
7. Watts, C. & Amigorena, S. *Semin. Immunol.* 13, 373–379 (2001).
8. Sandvig, K. & van Deurs, B. *EMBO J.* 19, 5943–5950 (2000).
9. Amer, A. O. & Swanson, M. S. *Curr. Opin. Microbiol.* 5, 56–61 (2002).

Longevity

Don't hold your breath

Siu Sylvia Lee and Gary Ruvkun

In some organisms a reduced-calorie diet increases lifespan. Conventional thinking about the mechanism involved now comes under question from the results of experiments with yeast.

More than sixty years ago a report appeared demonstrating that rats fed a diet containing 30–50% fewer calories live for four years instead of the normal three[1]. 'Calorie restriction' (CR) has since been shown to extend the lifespan of species ranging from unicellular yeast, to worms and flies, and certain mammals[2]. As they describe on page 344 of this issue[3], Lin *et al.* have discovered that CR increases lifespan in yeast by turning up the rate of respiration by a factor of three. This finding challenges the traditional view that CR extends lifespan by decreasing metabolism and the associated production of damaging free-radical forms of oxygen. These free radicals are a by-product of the electron-transport chain by which mitochondria — subcellular organelles — generate energy during respiration.

It is not yet known if CR in humans increases lifespan, but experiments under way in primates suggest that it does[4]. Prompted by the continuing stream of press reports about the rodent experiments, a variety of optimists, hucksters and fanatics have started to promote CR and to practise it with the aim of living longer themselves — or at least transferring wealth from the rest of us. Considering how unpleasant it is to follow a low-calorie diet, if the molecular pathway downstream of CR can be identified, perhaps 'CR mimetics' can be developed which will produce the anti-ageing benefits but spare us the hunger.

The precise mechanism by which CR delays ageing has not been established, but it has been assumed that some global metabolic switch is involved, together with reduced free-radical production. Calorie restriction also reduces blood glucose and insulin levels, suggesting that neuroendocrine signalling and reduced glycation of macromolecules may also be involved. Finally, CR may act as a minor stress, which 'trains' the animal to deal with free-radical and other damage to macromolecules to delay ageing[5].

In yeast, lifespan is defined by the number of divisions a mother cell can undergo to