pound $Bi_2Sr_2CaCu_2O_{8+\delta}$ (or Bi2212), appear to have a 'pseudogap' in their excitation spectrum — a depletion of electrons on the Fermi surface. The pseudogap develops long before superconductivity, indicating that some new kind of correlated motion is developing within the electron fluid. But is the pseudogap caused by superconducting correlations that begin to develop in the normal state[6–8]? Or is it an independent phenomenon, perhaps a 'spin gap' caused by correlations between the orientation of spins in adjacent copper-oxide layers[9–11]?

The first ARPES studies of underdoped Bi2212 showed that the pseudogap appears principally on the flattened faces of the Fermi surface, where its effect on the spectrum is almost identical to that of fully developed superconductivity[12–14]. These early results showed that the Fermi surface remained intact at the corners.

The latest results confirm this, and show in a lot more detail what is going on as the temperature falls. Norman *et al.*[1] see the pseudogap develop on the faces of the Fermi surface, breaking it up but leaving the shape of the remaining arcs unchanged (Fig. 1). As the temperature is lowered further, each arc is progressively eaten away, finally vanishing at the superconducting transition temperature.

This is a controversial exercise, for many aspects of the temperature dependence of ARPES spectra are poorly understood even in conventional materials. Nevertheless, the new results add credence to the view that the pseudogap is a prelude to superconductivity. In the simplest view, electrons on the Fermi surface fleetingly come together as pairs long before superconductivity is fully developed. The results do not rule out another interpretation, but they demand that the correlations that produce the pseudogap should be the very same ones that form the superconductor. Electron-tunnelling measurements[15] on Bi2212 point in the same direction, showing that the pseudogap in the normal state evolves smoothly into the superconducting gap.

These results can be quite simply understood[16] in terms of virtual d-wave pair formation: as the temperature is lowered, the pairs decay more slowly. According to the energy uncertainty principle, the lifetime Δt of a pair is inversely proportional to the uncertainty in the pair binding energy, $\Delta\epsilon = h/\Delta t$. When this uncertainty in the binding energy becomes comparable to the size of the d-wave superconductivity gap at a particular point on the Fermi surface, a pseudogap opens up. As the d-wave gap is large on the faces but vanishes on the corners, this naturally leads to the development of arcs at the corners, which shrink and eventually disappear.

More experiments will be needed to confirm or refute this interpretation. One vital question is why the pseudogap has not been seen in all cuprate superconductors: is this a matter of resolution, or a fundamental difference between materials? The electron-tunnelling experiments[15] clearly show that the pseudogap can be present, albeit reduced, in overdoped compounds, and a pseudogap has also been seen in a single-layer compound[17]. So perhaps the pseudogap is a feature of all high-temperature superconductors.

The true nature of the curious metal that gives birth to high-temperature superconductivity is still obscure. But almost everyone agrees that electron physics is undergoing a revolution, one in which experiments like that of Norman *et al.* will be the final arbiters. □

Piers Coleman is in the Department of Physics and Astronomy, Rutgers University, 136 Frelinghuysen Road, Piscataway, New Jersey 08854-8019, USA.
e-mail: coleman@physics.rutgers.edu

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Membrane sorting

Endosome marker is fat not fiction

Sandra L. Schmid and Pieter R. Cullis

Each organelle in a eukaryotic cell performs a specific set of functions that are reflected in the unique protein composition of that organelle, and such organelle-specific or 'marker' enzymes have been invaluable in monitoring the purification of organelles by subcellular fractionation. Appropriately labelled antibodies directed against organelle-specific marker proteins have also been used to identify organelles and study their structure by immunofluorescence or immuno-electron microscopy.

On page 193 of this issue Kobayashi and colleagues[1] report how, in characterizing a new monoclonal antibody that specifically identifies late endosomes, they unexpectedly found that the antigen recognized is a lipid — lysobisphosphatidic acid (LBPA). The presence of the antibody perturbs both the structure and function of the late endosomes, suggesting a critical role for LBPA. Moreover, the authors found that this same lipid antigen is recognized by autoimmune sera from patients with antiphospholipid syndrome, providing new insights into the pathological basis of this disease.

Lysosomes are the digestive organelles of the cell — they have highly acidic contents, rich in hydrolytic enzymes. Macromolecules such as nutrients, growth factors and foreign antigens are captured by receptors on the cell surface, for uptake and delivery to lysosomes via the endocytic pathway[2]. Other intracellular receptors, particularly the mannose-6-phosphate receptor (MPR), capture and divert hydrolytic enzymes from biosynthetic pathways to the lysosomes. For efficiency, both the endocytic and biosynthetic receptors must be retrieved before they encounter the hostile environment of the lysosome.

Endosomes are common intermediates along both the biosynthetic and endocytic pathways to the lysosome (Fig. 1, overleaf). They are a structurally diverse population of vacuoles and tubules, and they serve as sorting stations for the retrieval of recycling receptors. ▶

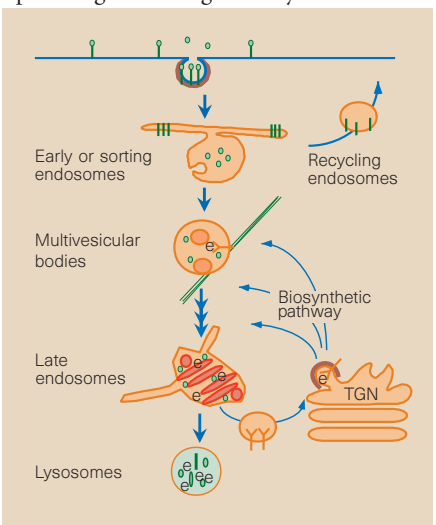

Figure 1 **Endosomes — sorting stations along the endocytic pathway. Cell-surface receptors capture extracellular nutrients and other macromolecules (green spots), whereas receptors in the trans-Golgi network (TGN) capture inactive precursors of hydrolytic enzymes (e), for eventual delivery to lysosomes via the endosomal intermediates. Before the contents of the endosomes are delivered to lysosomes — where the hydrolases are activated and degradation occurs — the receptors must be recycled. Endosomes carry out this sorting and recycling function as they mature and accumulate intraluminal membrane. Kobayashi *et al.*[1] have found that a unique lipid and autoantigen, lysobisphosphatidic acid, is specifically localized to the intraluminal membrane of late endosomes and lysosomes. Its function there remains unknown.**

Most cell-surface receptors are recycled from 'early' or 'sorting' endosomes (that is, those first encountered by endocytic tracers) where the pH is mildly acidic, favouring dissociation of the cargo from receptors. The released luminal contents are collected in large vacuolar portions of sorting endosomes, and the receptors are laterally segregated into long tubular extensions. The vacuoles then dissociate and move along microtubules towards the centre of the cell, where they start to mature. Maturation involves the removal of residual, recycling surface receptors, delivery of lysosomal hydrolases, and involution of the surrounding membrane to form multivesicular bodies[3].

At the end of this process, the so-called 'late' endosomes contain large amounts of intraluminal membrane, and they are enriched in lysosomal hydrolases and lysosomal membrane proteins. Having delivered their cargo of lysosomal hydrolases, MPRs are removed and recycled to the trans-Golgi network before the late endosomes fuse with the lysosomes. The mechanisms underlying maturation of the late endosomes and the sorting and retrieval of recycling receptors are poorly understood. Perplexingly, the recycling MPRs are concentrated on the intraluminal membrane, whereas lysosomal membrane proteins are found on the limiting membrane of the late endosome[4].

Cell biologists are only beginning to understand why cellular membranes contain so many types of phospholipid, and what particular species of lipid do in signal transduction, vesicle formation and fusion, and membrane protein-sorting[5–7]. The finding that LBPA is a 'marker' lipid of late endosomes (and lysosomes[8]) raises the question, what late-endosome-specific function might this unique lipid fulfil? Its structure may provide some clues. The small, negatively charged headgroup and polyunsaturated acyl-chain composition[9] would be expected to result in physical properties similar to those of cardiolipin, which is a marker lipid in the highly convoluted inner mitochondrial membrane. Cardiolipin tends to adopt the non-bilayer lipid structures that might facilitate the mixing of lipid bilayers required for membrane fusion.

There are several possibilities for the function of LBPA. It may play a structural role in the maturation of late endosomes — its tendency not to form a bilayer could help in developing the complex intraluminal membrane system. Alternatively, its unique structure means that LBPA is resistant to phospholipases, so it may stabilize the late-endosome/lysosomal membranes against degradation. In this case, however, we might expect to find LBPA on external, rather than internal, membranes.

LBPA may also be involved in protein sorting by the late endosomes. Indeed, other species of lipid with long-chain fatty acids, such as sphingomyelins, can form microdomains in the plane of the membrane that is implicated in protein sorting in polarized cells[6]. The exclusive localization of LBPA, within the internal membranes of late endosomes, suggests that these membranes represent a specialized functional domain. Furthermore, Kobayashi *et al.*[1] have shown that uptake of anti-LBPA antibodies into late endosomes perturbs the normal recycling of the MPR back to the trans-Golgi network. And the closely related lipid semi-LBPA has been shown[10] to be enriched in tubular vesicular elements of the trans-Golgi network, where protein sorting is known to occur.

Late endosomes/lysosomes are degradative organelles, so LBPA may be involved in lipid catabolism. For example, fatty acyltransferases[11] for LBPA exist in lysosomal fractions from rat liver, so LBPA could be involved in the sequestration and eventual transport of fatty-acid catabolites generated by lysosomal phospholipases. The effect of anti-LBPA antibodies on late endosomes — accumulation of membranes — is suggestive of other lysosomal storage diseases resulting from the aberrant accumulation of digestive products. Whether perturbation of any of these functions of LBPA accounts for the symptoms associated with antiphospholipid syndrome remains to be seen.

The work of Kobayashi *et al.* adds to the growing appreciation of the part played by lipids in membrane transport and sorting. Because the structure of lipids can be rapidly altered by the modification or removal of headgroups, or by acyl-exchange reactions, their associated functional properties can be tightly regulated. And given that cells contain over 200 unique species of lipid, it is not unlikely that others will turn out to be 'marker' lipids, involved in the structure and function of specific organelles. □

Sandra L. Schmid is in the Department of Cell Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA.
e-mail: slschmid@scripps.edu
Pieter R. Cullis is in the Department of Biochemistry, University of British Columbia, 2146 Health Sciences Mall, Vancouver, British Columbia, Canada V6T 1Z3.
e-mail pieterc@unixg.ubc.ca

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Daedalus

Breathable water

When animals came out of the sea, they had to learn to breathe air. In fact, says Daedalus, they never did. They took their own water with them. Even today, we still breathe water: we absorb the oxygen which dissolves in the moist lining of our lungs.

So why can't we still breathe water? Sadly, bulk water contains too little oxygen for our modern needs — only about 0.7% by volume, compared to 21% in air. But Daedalus has a way out. Imagine, he says, a dense foam of tiny air-bubbles in water. If all the bubbles had the same diameter, and were packed closely together, they could not easily rise to the surface. The result would be a curiously viscous stable foam, analogous to those 'rigid' close-packed emulsions of oil in water, whose droplets can hardly move past one another.

To make this foam breathable, Daedalus will dissolve suitable salts in it, bringing it into osmotic balance with lung tissue, and will add the natural polysaccharides that give saliva and sputum their viscosity, and a detergent like the one that helps the lungs to expand. He will aerate the solution through a battery of uniform nozzles, compress it briefly to collapse bubbles smaller than the standard size, and drain it to pack the remainder tight. It will then contain 74% of air by volume, giving it a density of 0.26 g ml^{-1}.

Daedalus's 'Liquid Air' will be a novel environment. You will sink into it, but will still feel somewhat buoyed up. It will be easier to move through than water, more opaque and sound-deadening than the densest fog, and rather an effort to breathe. Extra oxygen may be needed to make it feel comfortable and safe. But then the novelty of the experience, the sense of entering a silent, private fluid world, should make the Liquid Air immersion bath a popular relaxation.

Other more serious uses should also develop. With its high water content, Liquid Air will be utterly fireproof. Pumped in volume from fire-tenders, it will blanket rescuers as they enter burning buildings; injected into threatened aircraft, it will extinguish fires and blind and disorientate hijackers. Even better, bullets and explosion-fragments would be rapidly halted by Liquid Air. Pumped into and around suspicious vehicles and packages, it would damp an explosion wonderfully. The blast would expend its energy in 'inverting' the air–water emulsion to a dense spray of liquid droplets.

David Jones