termini contain domains that have enzymatic activity (Fig. 1). LTRPC7, for example, has an unusual protein kinase domain, which can catalyse the transfer of phosphate from adenosine triphosphate (ATP) to several substrates⁵, including LTRPC7 itself.

Although the natural activators of LTRPC7 remain unknown, Runnels *et al.*⁵ conclude that its kinase activity is strictly required for its channel function. They found that the addition of ATP to the inside of cells increased the flow of ions through the channel, suggesting that ATP (and, by inference, the kinase domain) is needed to open the channel.

This conclusion is challenged in one of the new papers¹. The discrepancy centres on the relationship between Mg^{2+} ions and ATP. Nadler *et al.*¹ find that the channel's activity is suppressed by Mg^{2+} ions, whether free or bound to ATP. They suggest that the addition of ATP by itself would lower the concentration of free Mg^{2+} ions. So, the channel activity observed by Runnels *et al.* in the presence of ATP might be explained by a fall in the concentration of free Mg^{2+} , without needing to invoke a role for LTRPC7's kinase activity. Other results, obtained with a hydrolysis-resistant analogue of ATP², provide further evidence against phosphorylation-dependent gating of LTRPC7. But this is a debate that is likely to rumble on.

As the authors show in the second paper², the long TRP channel LTRPC2 also has an enzymatic domain at its carboxy tail. This domain enables the protein to remove the terminal ribose-5-phosphate moiety of ADP-ribose. ADP-ribose also activates the channel, suggesting that, in this case, the enzymatic activity might actually be involved in opening or closing the channel. Once activated, the channel can remain open for a prolonged period even after ADP-ribose has been removed — a molecular memory worth pursuing further.

The LTRPC7 channel needs to be regulated properly for cells to survive: when Nadler *et al.*¹ either overexpressed or knocked out LTRPC7 in different cell types, the cells died. Under normal conditions, LTRPC7 is a strong outward rectifier¹, meaning that the inward current (carried by Ca^{2+} or Mg^{2+} ions) is smaller than the outward current (carried by monovalent cations, such as K^+). It seems plausible that, when LTRPC7 is overexpressed or knocked out, the levels of Ca^{2+} , Mg^{2+} or possibly other polyvalent cations might become unbalanced. Moreover, both LTRPC2 and LTRPC7 might be affected by ischaemic conditions, which result from oxygen depletion. Intracellular ATP-bound Mg^{2+} blocks both inward and outward currents through LTRPC7 (ref. 1), and Na^+ selectively blocks inward currents through LTRPC2 (ref. 2). In response to ischaemia, levels of Na^+ inside cells would rise and levels of Mg^{2+} — ATP would fall. So ischaemia might block

inward currents through LTRPC2, and activate inward and outward currents through LTRPC7.

These papers^{1,2} might also have a bearing on one of the major puzzles in ion-channel biology: the identity of 'store-operated' Ca^{2+} channels. When a cell's Ca^{2+} stores are emptied in response to some signal, Ca^{2+} enters the cell, because Ca^{2+} channels in the plasma membrane open. The Ca^{2+} -release-activated Ca^{2+} (CRAC) current found in the immune system is one of the best-characterized store-operated currents, yet the molecular identity and mechanism of activation of the CRAC channel have been elusive. However, TRP4 and CaT1, which are both members of the TRP family, are leading contenders^{6–8}.

LTRPC2 and LTRPC7 are also expressed in immune cells^{1,2}, and Nadler *et al.* and Perraud *et al.* describe currents that resemble those through these channels in some types of immune cell. These results imply that the conditions used to investigate CRAC and other store-operated channels in immune cells might have unintended effects on cellular physiology, by perturbing cellular ions and metabolites during whole-cell recording. My group recently characterized single channels in human T cells activated under conditions that deplete Ca^{2+} stores passively (using strong Ca^{2+} buffers). These channels resemble CaT1 channels in some aspects and LTRPC7 channels in others⁹. The molecular identity of CRAC channels is yet to be pinned down, but further characterization of single channels and the development of molecules that block specific channels would help in the investigation.

As a final note, TRP channels are important in disease as well as health. For example, the levels of specific LTRPC-family members change during the progression of tumours such as melanoma and prostate cancer^{10,11}. Before we can understand the role of these channels in disease, we will need to have a clearer understanding of how they function as molecular devices. Here, too, the development of selective channel blockers — both as experimental tools and as potential treatments — should be a high priority. ■

Michael D. Cahalan is in the Department of Physiology and Biophysics, University of California, Irvine, California 92697-4561, USA.
e-mail: mcahalana@uci.edu

- Nadler, M. J. S. *et al.* *Nature* **411**, 590–595 (2001).
- Perraud, A.-L. *et al.* *Nature* **411**, 595–599 (2001).
- Harteneck, C., Plant T. D. & Schultz, G. *Trends Neurosci.* **23**, 159–166 (2000).
- Clapham, D. E., Runnels, L. W. & Strübing, C. *Nature Rev. Neurosci.* **2**, 387–396 (2001).
- Runnels, L. W., Yue, X. & Clapham, D. E. *Science* **291**, 1043–1047 (2001).
- Philipp, S. *et al.* *J. Biol. Chem.* **275**, 23965–23972 (2000).
- Freichel, M. *et al.* *Nature Cell Biol.* **3**, 121–127 (2001).
- Yue, L., Peng, J.-B., Hediger, M. A. & Clapham, D. E. *Nature* **410**, 705–709 (2001).
- Fomina, A., Fanger, C. M., Kozak, J. A. & Cahalan, M. D. *J. Cell Biol.* **150**, 1435–1444 (2000).
- Duncan, L. M. *et al.* *J. Clin. Oncol.* **19**, 568–576 (2001).
- Wissenbach, U. *et al.* *J. Biol. Chem.* (in the press).

Daedalus

Four feet, one mouth

In days gone by, by-products were a valuable asset. The LeBlanc process for manufacturing sodium carbonate survived for decades on its by-products. These days they merely complicate marketing; demand for main products and by-products can fluctuate unpredictably. But one industry, farming, is stuck with by-products. Every liver brings one heart, unavoidably. And now that foot-and-mouth disease has made even farmers question their livelihood, Daedalus hopes to exploit modern biochemistry.

He points out that stem-cell research allows any number of cells of any sort to be made. Cells very close to their origin can develop into anything — new brain cells, for example. And by sticking with non-human tissue, all sorts of ethical dilemmas can be avoided. Daedalus recalls how rapidly a damaged liver can regenerate. Suppose, he says, a liver culture were fed with stem cells influenced by signalling chemicals and environment to develop as liver cells. You could haul an endless liver slowly from the dish, overcoming the problem of having a by-product.

So DREADCO biochemists are exploring Daedalus' theory that stem cells can be made in bulk by developing new cells in a very 'young' medium. In due course it should be possible to haul a cow leg, say, or a multi-jointed leg, from a dish whose cells are primed to develop in a leggy manner. Much of the by-product problem would be overcome, although there would still be a fixed amount of skin (for shoes) and bone (for soup and gelatine film). Ultimately all animal husbandry, a cruel and inefficient process, will be replaced by painless tissue culture.

Plants will be exploited too. Daedalus reckons that rhubarb grows because its stalk gains glucose diffusing down from its leaf. If so, an endless rhubarb stalk could be made by pulling a natural one while feeding it glucose. Again, the by-product problem (poisonous leaves) would be neatly overcome. The DREADCO team is now exploring the animal and vegetable kingdoms in search of suitable species. Rhubarb is possible; so is potato (a large tubular tuber could be pulled from the photosynthesizing fronds), and so are snake and eel, although most animals are badly designed for the job. Ultimately biomass, now seen as an answer to our energy needs, could take its place at the dinner-table as well. But probably synthesized liver, leg joints and rhubarb pie would be more welcome than pure masses of animal or vegetable cells. David Jones