News & views

Cell biology

Phosphate-storing organelle found in flies

Emily Strachan & Irene Miguel-Aliaga

Inorganic phosphate is an essential mineral for cellular metabolism and signalling. It emerges that a fruit-fly organelle can store this chemical in the form of phospholipids, releasing it in times of need. See p.798

Without inorganic phosphate (P_i), our cells would have no DNA, no ATP molecules to store energy and no phospholipids to form membranes. However, researchers do not fully understand how phosphate is metabolized or stored in animal cells, nor how it might act as a signal that allows cells to communicate[1]. On page 798, Xu *et al.*[2] have identified an organelle in the guts of fruit flies (*Drosophila melanogaster*) that can store P_i. The discovery sheds light on how flies maintain P_i levels to safeguard against starvation.

Xu and colleagues were investigating the turnover of epithelial cells that line the intestines of fruit flies. As with the human small intestine, the epithelial tissue in the midgut of adult fruit flies is made of both absorptive and secretory cells, regularly replenished by progenitors. The authors made the intriguing observation that, if they prevented P_i intake into gut cells (which they achieved in several ways, including through the use of chemical treatments and by diet), there was a large increase in the proliferation of gut-progenitor cells. They therefore looked for a gene that might encode a phosphate sensor or transporter, and thereby couple P_i deficit to proliferation.

The researchers identified one such gene, which they named P_i-sensitive XPR1 orthologue (*PXo*). This gene encodes a highly evolutionarily conserved phosphate transporter. They showed that inhibiting PXo protein production or deleting *PXo* in fly gut cells caused an increase in gut-cell production that mirrored the effect of blocking P_i intake. Importantly, several experiments indicated that this was not caused simply by nutrient deficiency making the gut cells sick and triggering a tissue-damage response.

Xu *et al.* demonstrated that PXo is not located at the cell membrane. Instead, it is present in previously uncharacterized organelles that the authors found in absorptive cells and some progenitors, but only rarely in cells located elsewhere in the fly. The authors named these organelles PXo bodies.

How can one be sure that these structures are genuine organelles? Organelles are defined as intracellular (often membrane-bounded) compartments that perform a specific function[3]. For example, an organelle called the endoplasmic reticulum (ER) is a major site of protein synthesis, and another, the Golgi complex, processes and stores these proteins. Xu *et al.* used tissue-staining techniques to show that PXo bodies are acidic, lipid-rich and located close to the ER, supporting their identity as organelles. They then used electron microscopy to show that the bodies are multilamellar – that is, composed of multilayered membranes in an onion-like structure.

To analyse the exact make-up of PXo bodies, Xu and colleagues designed a clever purification protocol to extract only PXo-containing organelles from cells. High-resolution mass spectrometry showed that they are strongly enriched with phospholipids, which make up the organelles' many membranes and can be broken down for energy. The authors showed that P_i starvation and enrichment through diet can modulate both PXo body size and the proportion of phospholipids, suggesting that PXo bodies are responsible for dynamic P_i storage (as phospholipids) and release (Fig. 1).

Using sophisticated genetics tools to visualize P_i, the authors showed that deletion of *PXo* greatly reduces levels of cellular P_i, neatly linking PXo bodies to maintenance of P_i levels. And when P_i is low, PXo bodies are engulfed by organelles called lysosomes that

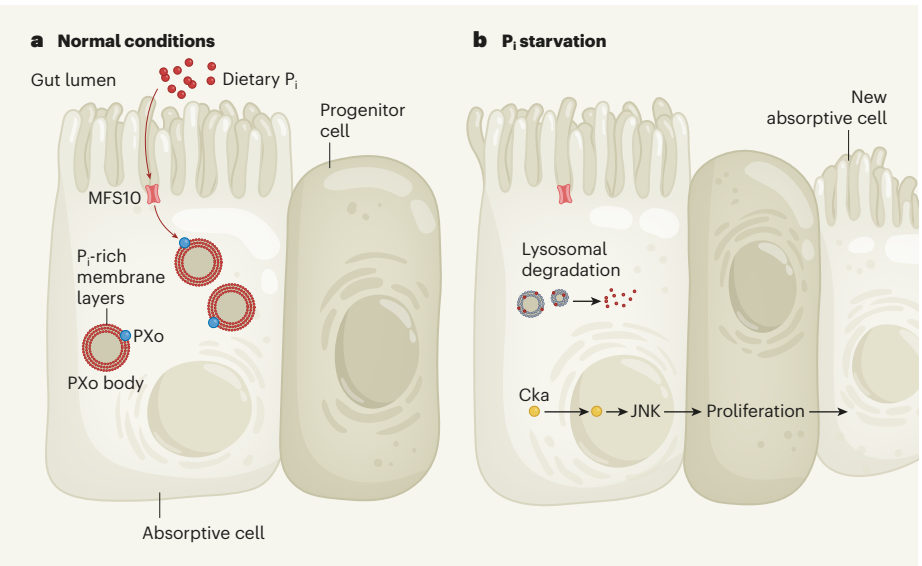

Figure 1 | An organelle for phosphate regulation in flies. **a**, Under normal conditions, inorganic phosphate (P_i) from the diet enters absorptive cells in the gut, transported by the protein MFS10. Xu *et al.*[2] report that P_i is sensed by a phosphate-transporter protein called PXo, and taken up to form the phospholipid membrane of multi-membrane-layered organelles called PXo bodies. These organelles thus act as intracellular P_i stores. **b**, When P_i is lacking in the diet, PXo bodies show reduced phospholipid content, shrinking in size and ultimately being degraded by organelles called lysosomes (not shown) to release P_i for use by the cell. This triggers activation of Cka protein, which moves to the nucleus to activate another protein called JNK. JNK activity causes nearby progenitor cells to proliferate and form new absorptive cells – perhaps to help cope with the nutrient deficiency.

contain degradative enzymes, allowing the P_i to be released and used by the cell.

Phospholipid-rich multilamellar organelles similar to PXo bodies, known as lamellar bodies (LBs), have been described in several mammalian cell types[4]. LBs secrete specialized mixtures of lipids and proteins that maintain protective barriers in the skin, lung and stomach[4]. However, Xu and colleagues showed that *PXo* deletion in flies does not affect the integrity of the gut barrier. Moreover, mass spectrometry of PXo bodies showed that the fly equivalents of the proteins required to make LBs are not present, and revealed that the phospholipids present in PXo bodies are different from those in LBs. The authors therefore conclude that PXo bodies are distinct from LBs.

In a final set of experiments, the authors revisited their initial observation, to determine what mediates gut proliferation in the absence of P_i. They looked for PXo-interacting proteins and identified STRIPAK, a protein complex involved in communication between organelles[5]. Deletion of *PXo* in absorptive cells caused large increases in levels of the STRIPAK-complex component Cka, which accumulates in the cells' nuclei. Cka then recruits the stress-induced protein kinase enzyme JNK, which is known[6] to induce proliferation of nearby progenitor cells.

It seems counter-intuitive that the gut activates cell proliferation in times of nutrient starvation, but the authors suggest that this might be a compensatory mechanism to produce more absorptive cells, thus maximizing absorption of scarce dietary P_i. Response to starvation of different micronutrients is understudied, and these scarce nutrients might require specialized mechanisms to ensure enough is acquired from the diet. Other micronutrients, such as zinc, are stored in vesicles in flies[7], nematode worms (*Caenorhabditis elegans*)[8] and rodents[9]. In flies, these zinc-storage granules are found in the Malpighian tubules, the insect equivalent of the kidney[7]. However, zinc deficiency might not trigger gut-cell proliferation[10], and it remains to be seen whether the authors' suggestion in the context of P_i is borne out.

An alternative hypothesis is that P_i scarcity increases proliferation to give rise to different absorptive cells that have reduced phospholipid content, which could affect their membrane properties. By modulating the membrane composition of its absorptive cells, the gut might be able to handle nutrients differently, perhaps allowing the fly to cope better with the nutritional challenge.

Xu and colleagues' work is an excellent example of how the complex physiology of fruit flies, and the ease with which genetic mutations can be induced, can be applied to analysis of fundamental cell-biological processes, revealing links between diet, organelle physiology and tissue homeostasis. The findings also add to an increasing body of work pointing to roles for micronutrients in physiology. Another case in point is the intestinal protein Hodor, which drives zinc-induced changes in appetite and food preference in fly larvae[11]. It would be interesting to know whether P_i starvation also leads to a change in feeding behaviour. Conversely, possible links between zinc availability, Hodor and intestinal epithelial renewal, such as those described for PXo, deserve further investigation.

The gut, alongside the kidneys and bone, is thought to be one of the key organs in regulation of P_i levels in the body, but mammalian P_i sensing is not fully understood[12]. It will be crucial to see whether multilamellar organelles similar to PXo bodies can be found in mammalian cells, especially in the gut. The ability of PXo organelles to dynamically change their phospholipid content is of particular interest, given that membrane composition is known to change with age[13] and disease[14].

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Metrology

Photon lights a path towards a nuclear clock

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A long-sought photon that is emitted by the nucleus of a thorium isotope has now been observed. The feat is a key step in efforts to build a nuclear clock, a device that is precise enough to probe the Universe's best-kept secrets. **See p.706**

The most precise timekeepers today are atomic clocks, which measure time using the frequency associated with transitions that electrons make between the different energy levels of an atom. But atomic nuclei make similar transitions, and these jumps could potentially offer an even better way of keeping time. In particular, the nucleus of the isotope thorium-229 undergoes a transition with an energy and a frequency that make it uniquely suitable for very precise timekeeping. But observing this transition and identifying its energy precisely are difficult tasks. On page 706, Kraemer *et al.*[1] have detected the photon that is emitted in this transition, an advance that is crucial for the development of nuclear clocks.

Originally discovered in a mineral found off the Norwegian coast in 1828, thorium is named after Thor, the Norse god of thunder. It would take another century and a half for scientists to determine that one specific thorium isotope displays an anomaly that sets it apart from the rest[2] – and perhaps makes the element worthy of its other-worldly name. The thorium nucleus in question has 229 nucleons (protons and neutrons), and can transition to an excited state that is only around 8 electron-volts more energetic than its lowest energy (ground) state. This difference is so tiny by nuclear-physics standards that the two states could barely be distinguished when they were first reported[2]. And it is the transition between these states that could make extraordinary nuclear timekeeping possible.

The working principle behind the nuclear clock closely resembles that of its atomic siblings[3]. The idea is that a light wave can induce a nucleus to jump between energy levels; the light's frequency simply must precisely match that corresponding to the energy difference between the levels. This