News & views

Metabolism

A zinc-sensing protein that controls fly growth

Y. Rose Citron & Roberto Zoncu

A zinc-sensing ion channel, Hodor, has now been found in the intestine of fruit flies. Hodor activates the TORC1 signalling pathway, and in doing so, influences organism-wide growth and metabolism. See p.263

Cells and organisms must sense nutrients in their surroundings and adjust internal conditions in response. An abundance of nutrients (such as sugars, fats and amino acids) triggers programmes that lead to proliferation, whereas a scarcity of nutrients blocks growth and often results in a redistribution of internal resources. Metal ions such as zinc (Zn^{2+}), iron and copper are a subset of nutrients called micronutrients, and act as cofactors for proteins that have roles in growth and development[1]. But how organisms sense metal availability is unclear. On page 263, Redhai *et al.*[2] report the identification of a Zn^{2+} sensor in flies. Characterization of this protein reveals a pathway for Zn^{2+}-dependent control of food intake and growth.

A plethora of proteins rely on Zn^{2+} to carry out their functions. As a result, extensive cellular resources are devoted to ensuring that Zn^{2+} concentrations in cells are kept within an optimal range. Notably, many DNA-binding proteins require Zn^{2+}, including some that coordinate the production of proteins that themselves help to balance metal levels. Thus, a cellular feedback loop keeps Zn^{2+} levels in check. Proteins that shuttle Zn^{2+} into or out of the cell are part of this feedback mechanism, along with those that transport Zn^{2+} between intracellular compartments[3].

Much of our understanding of Zn^{2+} regulation comes from studying fruit flies, because genetic, biochemical and metabolic analyses are relatively straightforward to perform in this model organism[3]. However, few studies have moved beyond investigating how intracellular Zn^{2+} regulation helps to maintain steady physiological conditions to ask whether and how Zn^{2+} abundance can affect organism-wide programs for growth and development.

A specialized set of cells that absorbs copper and iron ions has been identified in the fruit-fly gut[4]. Redhai *et al.* showed that Zn^{2+} also amasses in the region of the gut in which these cells reside. The researchers downregulated the expression of the genes that encode 111 putative nutrient-sensing proteins in the specialized cells of this region, and identified one protein whose downregulation caused a delay in fly development. In reference to this delay, they named the protein Hodor (short for 'hold on, don't rush').

The authors showed that mutation of Hodor, a transmembrane protein, leads not only to a reduction in growth of the fruit-fly larvae, but also to a diminished body-fat content and to lower food intake throughout the flies' development. They demonstrated that Hodor is not a Zn^{2+} transporter, but instead behaves as a Zn^{2+}-regulated channel that, when activated by Zn^{2+} binding, allows chloride ions (Cl^-) to cross plasma membranes.

Zn^{2+}-regulated Cl^- transport could affect metabolism in multiple ways. For instance, Cl^- influx could alter the concentrations of intracellular solutes or the acidity of membrane-bound organelles called lysosomes that have key roles in waste disposal and regulatory signalling in the cell[5]. In line with the latter idea, the authors found high levels of Hodor on the membranes of lysosomes, and observed a loss of lysosomal acidification when they downregulated Hodor in flies.

How can a single protein, which is expressed in only a small subset of cells, have such profound effects on the physiology of a whole organism? Redhai *et al.* made several observations that could help to explain the broad effect of Hodor.

First, increasing the Zn^{2+} content of flies' diets led to increased feeding; this effect was abrogated by depleting Hodor. Second, growth-promoting insulin-like peptides (ILPs) built up in the brain of Hodor-depleted larvae. When ILPs are activated, they are secreted from the brain; the authors' observation therefore suggests that Hodor is required for the activation of insulin signalling after feeding. Third, Hodor acts upstream of a protein complex that is integral to growth regulation: target

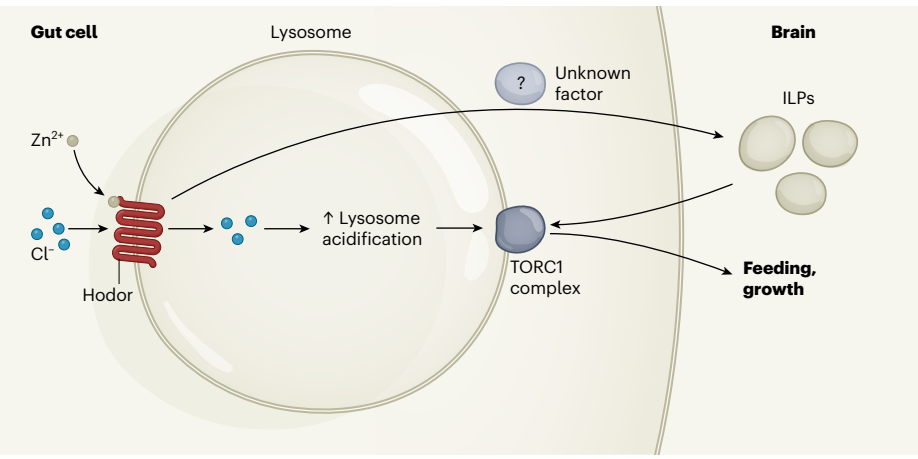

Figure 1 | Complex control of fly feeding and growth by zinc ions. Redhai *et al.*[2] have identified a membrane-spanning protein, Hodor, that senses zinc ions (Zn^{2+}) in the guts of fruit flies. Following binding by Zn^{2+}, Hodor enables passage of chloride ions (Cl^-) into organelles called lysosomes in the cell. Activation of Hodor leads, through unknown mechanisms (perhaps involving a signalling factor), to the release of insulin-like peptides (ILPs) in the brain. ILPs activate the protein complex known as target of rapamycin complex 1 (TORC1), which is enriched on lysosomes. Furthermore, activation of Hodor causes a Cl^- influx into the lysosome; this has an acidifying effect that also stimulates TORC1. Activation of TORC1 triggers signalling pathways that might have organism-wide effects, including promotion of feeding and growth.

of rapamycin complex 1 (TORC1). Mutations that would usually cause hyperactivation of TORC1 signalling instead restored normal growth and food intake in Hodor mutant flies. Taking this evidence together, Redhai and colleagues propose a model whereby Zn^{2+}-dependent Hodor activity in the mid-gut drives TORC1-dependent metabolic programs that enable larval feeding and growth.

That Hodor acts through TORC1 signalling is not surprising, although it is difficult to draw conclusions about the exact nature of the link between the two. In a similar way to insulin in mammals, ILPs are potent activators of TORC1 in flies[6]. In turn, TORC1 is a prime driver of metabolic processes and growth in all animals. At the cellular level, TORC1 activation occurs on the lysosomal membrane and requires lysosomal acidification[7]. Thus, loss of Hodor might impair TORC1-driven growth through loss of insulin signalling, loss of lysosomal acidity, or both (Fig. 1).

The link between Hodor and TORC1 is not the only avenue for further research opened up by the current study. Another question concerns the relationship between feeding behaviour and TORC1 signalling, which is currently only partially characterized. ILPs are secreted from the brain in response to feeding and stimulate TORC1, placing TORC1 signalling downstream of feeding[5]. However, Redhai and co-workers' observation that increasing TORC1 activity restores growth and feeding behaviour in Hodor mutants, in which ILP secretion seems to be impaired, suggests that the picture is more complex. TORC1 might act both upstream of feeding (in the brain) and downstream of it (in the gut and other tissues).

How exactly does activation of Hodor by Zn^{2+} stimulate feeding and ILP release? It seems reasonable to suppose that a factor secreted from the gut in response to Hodor activation might affect the neuronal circuits that control feeding in the brain[8]. But identification of such a factor will require more work.

Finally, Hodor belongs to the family of Cys-loop channels, which have been a target of efforts to develop insecticides[9]. Redhai *et al.* provide evidence that Hodor is expressed only in insects, and show that mosquitoes engineered to lack the *hodor* gene die at larval stages. Given the protein's gut-specific expression, the authors suggest that ingestible substances could be laced with drugs that block Hodor activity, and these substances could be placed at known larval breeding sites. Thus, Redhai and colleagues' study could have broader implications than might have been anticipated in the hunt for a micronutrient sensor.

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Materials science

Nanowires light the way to silicon photonics

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Silicon used for electronics has a cubic crystal lattice, which makes the material unsuitable for photonics applications. A method for producing germanium and silicon–germanium alloys that have hexagonal lattices offers a solution. **See p.205**

Silicon is a prodigious material for electronics. Its useful electronic properties, high abundance, low cost and excellent processability helped to stimulate a revolution in silicon technology: the development of mass-produced silicon chips, which allow computing capabilities to be integrated into almost any device. But, alas, silicon is an inefficient absorber and emitter of light, preventing it from being used in many photonics applications. Writing on page 205, Fadaly *et al.*[1] report the development of silicon–germanium alloys that have excellent optoelectronic properties, and could thus aid the development of photonics technologies that are compatible with currently available silicon electronic devices.

Silicon's lack of useful optoelectronic capabilities is due to its electronic properties – it is said to be an indirect-bandgap semiconductor. As an example of the problem, solar cells based on silicon must be at least 100 times thicker than those based on gallium arsenide (a direct-bandgap semiconductor, which absorbs and emits light efficiently) to collect the same amount of light, but they still convert the light into electricity much less efficiently[2]. And silicon-based lasers remain an unrealized dream, even after decades of intense research efforts. Instead, lasers are typically made using 'compound' semiconductors, which incorporate costly elements such as indium or gallium. The components used to absorb or emit light in currently available silicon photonics schemes are also mostly made from compound semiconductors, and are usually bonded to the silicon or used off-chip[3].

Several generations of scientists have tried to convert silicon and silicon-containing alloys

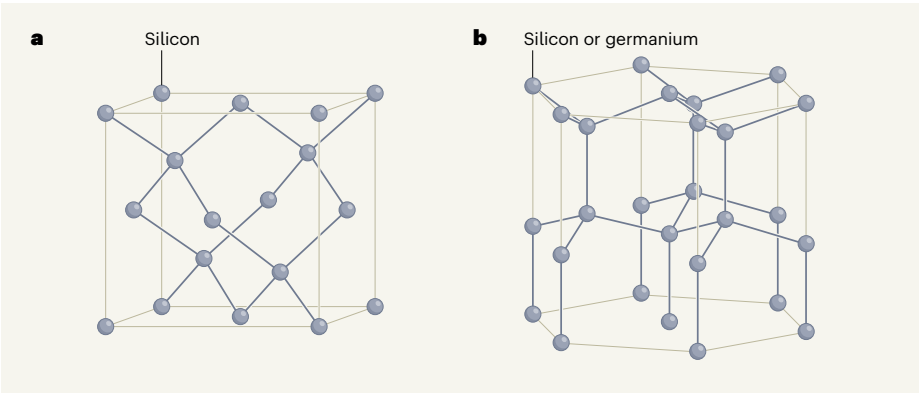

Figure 1 | Cubic and hexagonal crystal lattices. a, The silicon used for electronics has a cubic crystal lattice, which causes the material to be a poor absorber and emitter of light – limiting its use in optoelectronics. **b**, Fadaly *et al.*[1] report a way of producing germanium and silicon–germanium alloys that have a hexagonal lattice. The resulting materials are good light absorbers and emitters, and would be compatible with existing silicon electronics technology, potentially opening the way to the development of new optoelectronic devices.