Cell biology

Regulated self-cannibalism

Daniel J. Klionsky

Cells consume parts of themselves to survive starvation and during development. But how do they control this process of self-eating so that it begins at the right time and does not end up killing the cell?

When you are fasting or are otherwise deprived of food, your body starts to break down stored nutrients to keep essential processes and organs (such as your brain) supplied with fuel. Similarly, when a cell is deprived of nutrients it will degrade some of its own constituents to stay alive. It does this by the process of autophagy — literally, 'self-eating'. Writing in *Developmental Cell*, Scott and colleagues[1] and Rusten and co-workers[2] provide new insights into how autophagy is regulated in the cell, both as a response to starvation and during development.

Autophagy is marked by the formation of autophagosomes — large vesicles, bounded by a double membrane, that sequester cytosol and organelles such as mitochondria. Fusion of an autophagosome with a lysosome releases the inner vesicle into the lysosome, where enzymes break the vesicle down. Degradation and recycling of the vesicle's constituents enable the cell to continue to carry out essential processes.

Because autophagy has the capacity to degrade entire organelles, it could be harmful if it occurred randomly. Autophagy must therefore be tightly regulated. The question is: how is this regulation accomplished? How does a cell or organism sense its environment and trigger an appropriate signal to induce or suppress autophagy? The process occurs in organisms ranging from yeast to worms to humans[3], and Scott *et al.*[1] and Rusten *et al.*[2] chose the fruitfly *Drosophila melanogaster* as their subject.

Drosophila larvae have a storage organ called the fat body, which has analogous functions to those of the liver and adipose (fat) tissue in vertebrates: it is a source of large amounts of potential energy. If an animal has just eaten, of course, there is no need to tap into these energy stores. In response to food, the hormone insulin is produced; this binds a receptor on the surface of cells in the fat body and throughout the organism, and triggers a signalling cascade (Fig. 1). An important part of this cascade is an enzyme termed class I phosphatidylinositol-3-OH kinase (PI(3)K). This adds a phosphate group to a particular position on the lipid phosphatidylinositol, which is part of the cell membrane. Various proteins in turn bind the phosphorylated lipid and become activated, thus transmitting the external signal (in this case, insulin) into the cell. A central player in this pathway is the enzyme Tor, which is involved in many regulatory events connected with energy metabolism, and which suppresses autophagy[4].

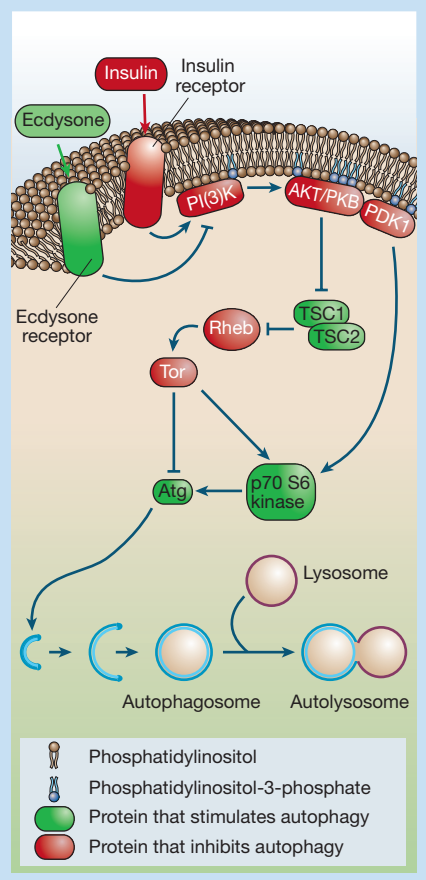


Figure 1 **Cellular self-eating: the basics. Insulin produced in response to food inhibits autophagy. This signal is passed into the cell by way of the insulin receptor, which activates the enzyme phosphatidylinositol-3-OH kinase (PI(3)K). This in turn modifies the lipid phosphatidylinositol in the cell membrane, leading to the activation of other enzymes, including AKT/PKB and PDK1. AKT/PKB inhibits TSC1–TSC2, which can therefore no longer inhibit Rheb; Rheb then activates Tor, which suppresses autophagy by inhibiting Atg proteins. Rusten *et al.*[2] suggest that ecdysone, a hormone in fruitfly larvae, overrides the nutrient-inhibited response and activates autophagy by inhibiting PI(3)K, although the exact mechanism is unknown. Scott *et al.*[1] show that p70 S6 kinase is needed for full activation of autophagy, and may prevent excessive autophagy when Tor is inactive. Autophagy involves the formation of double-membraned vesicles that sequester cytoplasm and organelles. Fusion of these autophagosomes with lysosomes containing acid hydrolase enzymes allows the degradation and recycling of macromolecular constituents that are needed for cell survival under starvation conditions and for remodelling of the organism during development.**

So this pathway provides a mechanism by which cells can block self-eating if the organism has just fed. On the flip side, the pathway also provides a means of inducing autophagy when the organism is starved: a lack of food (particularly of the sugar glucose) leads to a lack of insulin, leaving the pathway inactive and enabling the cell to tap into its storage reserves. But how does the cell regulate the degree of autophagy so that it does not get out of hand?

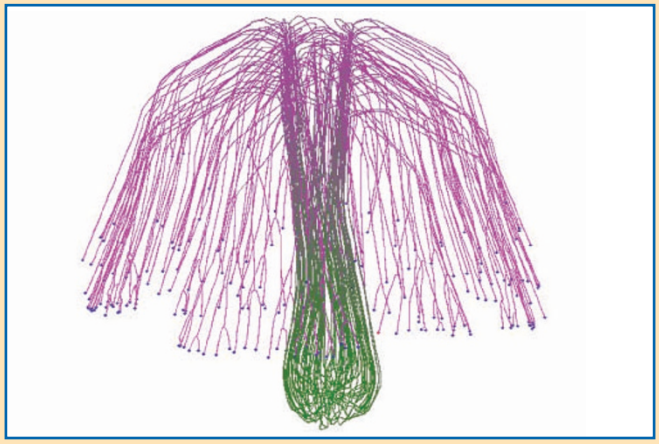
An interesting explanation for this additional level of control comes from Scott and colleagues[1]. The activity of the enzyme p70 S6 kinase has been shown increase when Tor is turned on — that is, when nutrients are abundant[5,6]. This led to the proposal that p70 S6 kinase is itself a negative regulator of autophagy[7]. However, Scott *et al.* now show that this enzyme must be active for autophagy to be maximally induced.

How can this finding be reconciled with the fact that Tor activates p70 S6 kinase? The result seems to suggest that p70 S6 kinase needs to be active under conditions (starvation) in which its activator is turned off. Perhaps, after Tor is switched off, any active p70 S6 kinase remains active for some time, allowing maximal autophagy. But other mechanisms might then gradually deactivate the p70 S6 kinase, thereby preventing excessive autophagy, which could be harmful. These authors also show that autophagy is essential in supplying nutrients to promote survival in the absence of Tor function. Thus, a starvation signal results in the down-regulation of insulin/PI(3)K signalling, followed by a consequent inhibition of cell growth, and a concomitant upregulation of autophagy to supply essential nutrients.

In simple organisms such as yeasts, autophagy is primarily a response to starvation. But in more advanced organisms such as *Drosophila*, autophagy is also involved in various developmental pathways[8]. This adds another level of complexity to its regulation, because there are more occasions when an organism may need to activate autophagy — during growth, for example, or, in an insect, when the pupa forms. A starvation response must be able to cope with the unexpected (a sudden loss of food), but for the purposes of development, cellular responses, including autophagy, must be programmed. In other words, there must be a mechanism to initiate autophagy at precise times. This is achieved

Theoretical biology

Mushrooms in cyberspace



Mushrooms arise largely from the inflation of pre-existing cells, which in part accounts for the startling speed with which they can appear. But what developmental processes are responsible for shaping those cells first into the primordial mushroom structure and then into the full-grown 'fruiting body' itself? Audrius Meškauskas and colleagues, writing in *Mycological Research* (**108,** 341–353; 2004), provide a new angle on this question. They have grown cyber fungi like the mushroom shown here. As well as creating primordial fruiting bodies whose cell arrangements mimic the real things, the authors' computer models provide predictions that can be tested.

Fungi use a single cell type — the filamentous hypha — to generate mushrooms and other multicellular organs such as the cords and rhizomorphs that function as exploratory devices for colonies once they run out of food. This reliance on hyphae distinguishes fungi from plants and animals, both of which produce a variety of cell types that are specialized for different functions. For this reason, a model of mushroom development need only specify the positions of cells. Unfortunately, simple anatomy has not led to a clear explanation of the processes that make cells lying parallel to one another in the stem of a mushroom, blossom into the bell-shape of the cap.

What Meškauskas *et al.* show is that baby cyber mushrooms develop simply by applying rules of mutual attraction and repulsion to every one of thousands of gravity-sensing hyphae. As long as all of the filaments behave in precisely the same way at the same time, there is no requirement for the exercise of global, or organ-level, control in fabricating the whole structure. This means that the intricate shapes of different mushrooms might be specified in a clockwork fashion, solely by genes activating successive waves of cellular attraction and repulsion. This is good news for mycologists, because the kinds of hormone-pumping meristems that are found at the tips of shoots and roots, and that regulate plant development, have not been found in fungi.

With the evidence of the computer animations, experiments on single cells take on new significance. Manipulation of genes that steer fungi in rotting wood, for example, may be likely to change the arrangement of cells in a mushroom and result in some extraordinary fruiting body forms. If more progress can be made in understanding what makes a hypha bend towards or away from its neighbours, mycologists will be closer to solving the mystery of mushroom development.

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through the use of specific hormones. In *Drosophila*, the main hormone that controls pupation is ecdysone.

Rusten *et al.*[2] focus on the developmental regulation of autophagy in the *Drosophila* fat body, where cells undergo developmentally programmed autophagy during the larval stage. In contrast to the inhibitory role of PI(3)K signalling, the hormone ecdysone appears to promote autophagy. But how are these two regulatory factors coordinated during development? The authors find that the occurrence of autophagy increases from early through to late larval stages. This progression correlates with a gradual increase in the level of ecdysone and a corresponding decrease in the level of PI(3)K-modified lipids. Conversely, inactivation of ecdysone signalling has the opposite effect. Thus, ecdysone appears to negatively regulate PI(3)K signalling, allowing autophagy to occur (Fig. 1).

The two stories come together in the finding of Rusten *et al.* that developmentally programmed autophagy is subject to regulation by Tor: inhibiting this protein results in an increase in autophagy. The implication is that under normal conditions Tor is not completely inhibited during developmental autophagy in the fat body — some Tor molecules must be active, providing a pool that can be inhibited to increase the occurrence or amount of autophagy. The fat body therefore allows developmentally and nutritionally triggered autophagy to be coordinated. An understanding of the nuances of this coordination — and whether it occurs in other organisms, including ourselves — must await further studies. ■

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Planet formation

The core problem

William B. Hubbard

Controversy over shock-wave experiments on the compression of hydrogen has broad implications — for understanding the cores of Jupiter and Saturn, and even the formation of extrasolar planets.

In July of this year, NASA announced that it will fund further study of a proposed mission to Jupiter, as part of its New Frontiers programme[1]. A prime objective of this orbiter mission, called Juno, would be to measure Jupiter's gravitational and magnetic fields at very close range, to discern whether the planet has a dense core. Meanwhile, in the *Astrophysical Journal* Saumon and Guillot[2] write that the existence of a massive core in Jupiter may depend on the validity of an experiment here on Earth.

Over the past decade, it has become possible in the laboratory to squeeze hydrogen to pressures more than a million times greater than atmospheric pressure, while simultaneously heating it to temperatures exceeding 10,000 kelvin. Compression experiments on the hydrogen isotope deuterium — driven by NOVA, a huge laser-implosion device at the US Lawrence Livermore National