News & views

Developmental biology

Lipid dismantling of lens organelles for clear vision

Patricia Boya

In the eye, the transparent lens focuses light on the retina. This transparency is achieved during lens development by a newly identified mechanism — whole organelles are destroyed by the degradation of their lipid membranes. **See p.634**

The eye consists of three main tissue types; the cornea, lens and retina. The lens is a biconvex, transparent structure that functions like a camera lens, allowing the passage of light and focusing it on the retina. Cataracts are the result of changes in lens transparency that impede the passage of light, and they account for almost 50% of the total cases of blindness in adults aged 50 years and over[1]. Identifying the mechanisms underlying lens transparency might thus improve our understanding of cataract biology. On page 634, Morishita *et al.*[2] provide crucial, long-sought information about how lens transparency is achieved during normal development.

Thanks to its high refractive index, the lens can easily bend light to focus it on the retina — a consequence of the tight packing of structural proteins in the lens called crystallins. Crystallins comprise up to 60% of the total mass of the mature lens, a much higher protein-concentration level than that of any other tissue[3]. The lens contains a type of epithelial cell that has evolved to undergo a unique process of differentiation that enables the cells to become transparent and to minimize light scattering. To achieve transparency, intracellular organelles are degraded during development to produce what is termed the organelle-free zone of the lens[4]. Retention of organelles compromises lens transparency, and results in the formation of cataracts[5].

An intracellular degradation pathway called autophagy — the only previously known pathway for eliminating whole organelles — was initially thought to contribute to the formation of the organelle-free zone. However, researchers subsequently found that organelle degradation still occurs during lens differentiation in autophagy-deficient mice[6,7]. Now, the same research group describes a previously unknown, two-step mechanism by which organelles are cleared in lens cells (Fig. 1). The group finds that this mechanism is evolutionarily conserved in both zebrafish and mice. The first step consists of the formation of small pores that permeabilize the lipid membranes of organelles. This serves as a trigger for the second step: recruitment of an enzyme that degrades the organelles' lipid membranes.

Morishita and colleagues took a microscopy-based approach to monitor the degradation of fluorescently tagged organelles in the zebrafish lens. They identified genes expressed at high levels in the lens, and used a gene-editing method to block the expression of these genes and then assessed the effect. This revealed that the gene *hrasls* is required for organelle degradation during lens differentiation. The gene encodes a phospholipase enzyme, which is a member of the HRASLS (also known as PLAAT) family of proteins. These enzymes catalyse the breakdown of phospholipids — the main structural component of cellular membranes. Crucially, Morishita *et al.* report that, in zebrafish deficient in *hrasls*, and in mice deficient in the equivalent gene, *Hrasls3*, organelles are retained during lens differentiation. This results in defects in lens transparency, alterations in the light-refractive functions of the lens, and cataracts.

The authors show that the targeting of HRASLS in zebrafish to organelles depends on a particular region of the protein — the carboxy-terminal transmembrane domain. HRASLS is located in the cytosol in the early stages of cellular differentiation, and then relocates to organelles, including mitochondria, the nucleus, lysosomes and the endoplasmic reticulum, immediately before their degradation. This work is the first to demonstrate the dismantling of entire organelles by direct lipid degradation.

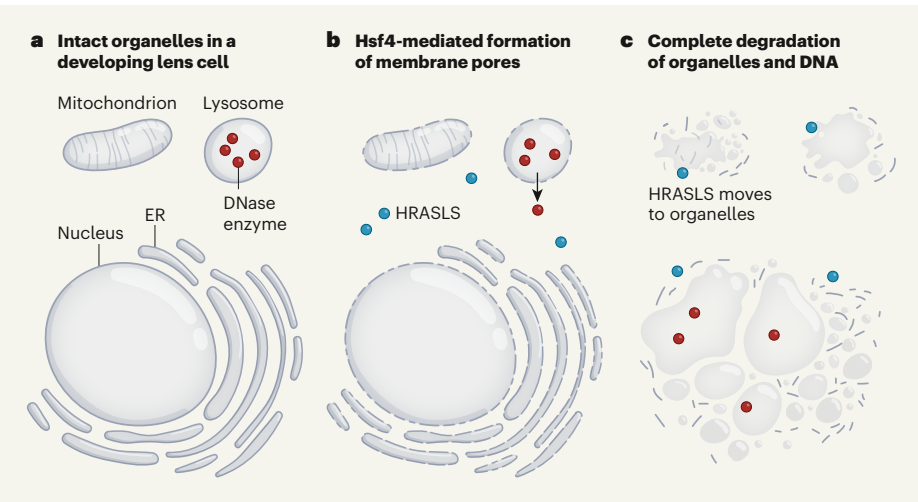

Figure 1 | A mechanism for organelle degradation in the developing lens. a, The lens of the eye must be transparent for light to enter. Lens cells achieve transparency during development by the degradation of whole organelles, including the nucleus, the endoplasmic reticulum (ER), lysosomes and mitochondria. Morishita *et al.*[2] report experiments in mice and zebrafish that reveal the mechanism responsible for organelle degradation. **b**, The authors find that expression of the transcription factor Hsf4 (not shown) leads to the formation of small pores that permeabilize the membranes of organelles in developing lens cells. When lysosomes are permeabilized in this way, they begin to release some of their enzymes, such as DNA-degrading DNases, into the cytosol. **c**, This membrane damage provides a cue for a cytosolic phospholipase enzyme belonging to the HRASLS family to move to organelles and degrade phospholipids, the main structural component of cellular membranes. This results in the complete organelle degradation necessary for lens transparency.

Until now, autophagy was the only process known to degrade whole organelles. However, in autophagy, degradation occurs by the delivery of organelles to lysosomes, which use enzymes called hydrolases to digest the organelle's various components, such as protein, DNA and lipids. The authors postulate that a phospholipase-dependent pathway could be more efficient than autophagy in circumstances such as lens development. This is because lens development requires the elimination of many types of organelle, including lysosomes, as opposed to the selective elimination of specific organelles, as occurs in autophagy. Indeed, this is the first report to describe the fate of lysosomes during lens development.

Lens differentiation is a spatio-temporally controlled process, in which organelles in the centre of the lens are degraded first, with degradation then continuing outwards to the lens periphery. Among the many transcription-factor proteins involved in this process, Hsf4 has a prominent role, and mutations in the gene encoding Hsf4 are associated with congenital cataracts[8]. Morishita and co-workers show that the development of small pores in the membranes of mitochondria and lysosomes in zebrafish occurs in an Hsf4-dependent manner, and that this acts as a signal for HRASLS-family phospholipases to relocate to these organelles. The authors report that pore formation in the lysosomal membrane triggers the partial release of its contents, including some DNA-degrading enzymes, into the cytosol. This occurs before phospholipase translocation to the lysosome results in the release of the entire contents of the organelle. Importantly, the authors demonstrate that lysosomal damage by pore-forming agents is sufficient to trigger phospholipase translocation to lysosomes.

This result underscores the key role of lysosomal-membrane permeabilization in physiological and developmental contexts, such as during cell division[9] or in the shrinkage of the mammary gland after lactation[10]. The authors further show that Hsf4-mediated permeabilization of the mitochondrial membrane is also required for HRASLS translocation to mitochondria in zebrafish, and that mitochondrial degradation is suppressed in Hsf4-deficient zebrafish.

Together, these observations suggest that the Hsf4-dependent partial permeabilization of organelle membranes is the signal required to trigger HRASLS translocation to target organelles in the lens. However, the permeabilization process seems to be cell-type dependent, because overexpression of Hsf4 and HRASLS3 in human HeLa cervical cancer cells does not induce HRASLS3 translocation to organelles (with the exception of organelles called peroxisomes) in those cells. Therefore, the precise mechanism by which Hsf4 specifically promotes the formation of pores in organelle membranes of lens cells remains to be determined. Hsf4 regulates lysosomal activity and lysosomal pH in lens cells[11]. It is therefore tempting to speculate that organelle degradation in the lens is mediated by an Hsf4-dependent connection between lysosomal pH and lysosomal pore formation, because pH alterations affect the membrane stability of lysosomes[12].

Further studies will be needed to explain the authors' observation that overexpression of HRASLS3 in HeLa cells results in the degradation of only one type of organelle — the peroxisome. Such selectivity might be mediated by protein–protein interactions, providing an extra control step, or perhaps it is due to differences between organelles, such as the composition or stability of their membranes. Yet another puzzle is why HRASLS proteins degrade the intracellular membranes of organelles in lens cells, but do not target the membrane lipids of the cell's outer boundary — the plasma membrane.

Given the high levels of expression of HRASLS3 in adipose tissue (which aids fat storage)[13], it will be interesting to learn whether HRASLS3 participates in organelle degradation during differentiation of the adipocyte cells in this tissue. Future studies could investigate whether these phospholipases can be engineered to degrade other membrane-bound structures of interest, such as those of harmful intracellular bacteria. It will also be worth investigating whether related forms of HRASLS proteins, of which there are five in humans and three in mice, also participate in organelle dismantling.

Morishita and colleagues' findings provide a wonderful example of how developmental processes are harnessed to solve complex problems. In this case, cell transparency for vision arises as a result of regulated organelle removal. Whether this process is involved in other developmental events, and whether abnormalities in it contribute to disease, remains to be determined.

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Engineering

Large-scale origami locks into place under pressure

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Inflatable, metre-scale origami structures have been designed to transform from flat structures into expanded forms and then to lock into their new shape. This technology opens the way to the use of large origami structures for engineering. **See p.545**

It might seem surprising that origami, the ancient Japanese art of paper folding, is an integral part of engineering. However, origami structures can be folded up compactly and deployed at the nano- and macroscales seemingly without effort. They are therefore well suited for a wide range of applications, including robotics[1], arrays of solar panels[2] and engineered structures known as metamaterials[3]. On page 545 Melancon *et al.*[4] report triangular origami facets that snap into 3D shapes when filled with a pressurized fluid. The authors' work provides a new method for designing large origami enclosures that can be deployed and locked into shape through inflation.

In engineering, a deployable structure is one that can change shape in a way that greatly alters its size — large-scale examples include scissor lifts and bouncy castles. Conventional deployable structures are transformed into a larger shape through the extension of linkages