of a chromatin-based lineage barrier that restricts the apparent totipotency of these cells.

However, there is an important difference to consider between these two studies. The findings of Zijlmans et al.[2], which are well-supported at multiple experimental levels, point towards PRC2 functioning as a barrier during trophoblast induction. In the absence of instructive signals, PRC2 inhibition per se does not cause spontaneous differentiation of naive hPS cells. This dispensable role of PRC2 in naive culture conditions is an observation that seems in line with previously published studies[12,13]. Only when cultured under differentiation media were hPS cells converted more efficiently towards trophoblast cells in the presence of the EZH2 inhibitor[2]. By contrast, the study by Kumar et al.[3] shows that a loss of function of PRC2 resulted in increased trophoblast and mesodermal subpopulations in naive culture conditions[3]. By interrogating the possible technical discrepancies between these two studies, Kumar et al.[3] indeed find that the two systems used to expand the naive hPS cells (PXGL media[2] versus t2iLGo media[3]) are responsible for the different experimental outcome. These important studies underscore the existence of inductive or opposite differentiation signals in distinct culture media.

These two studies are an extraordinary starting point for further study of the implications of PRC2 in early lineage specification in human embryos. Especially relevant, and still enigmatic, is the existence of two different responsive patterns of H3K27me3 genomic distribution between naive and primed hPS cells. Intriguingly, Kumar et al.[3] report a significant reduction of the H3K27me3 mark in more than 50% of the genome in primed as compared to naive hPS cells. However, the levels of H3K27me3 at gene promoters remain largely unchanged in the two pluripotent conditions[3]. What is the function of the H3K27me3 mark coating non-promoter loci in naive hPS cells? How does this distribution change occur? In addition to the core subunits, PRC2 associates with additional accessory factors that define the two distinct holocomplexes, PRC2.1 and PRC2.2 (ref. [14]). A recent study suggests that these subcomplexes differ in their genomic occupancy in human induced pluripotent stem cells[15]. Thus, understanding the PRC2 composition in naive and primed hPS cells might provide mechanistic insights into the naive-to-primed change of this chromatin-based barrier during human embryo development.

The legal restrictions on the access and use of human embryos limit a research area that can substantially impact infertility and human developmental disorders. In this regard, the scarcity of the allowed studies will benefit largely from explorative studies such as the two highlighted here. Thus, the exploitation of stem cell-based models of pluripotent stem cells offers a unique opportunity to illuminate a dark period of knowledge about the molecular functioning of our early life. ❐

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Competing interests

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AGEING

Long life depends on open communication

The lysosome is an essential organelle that degrades extra- and intra-cellular components and acts as a signaling hub. A study in *Caenorhabditis elegans* now shows that the lysosome mediates inter-tissue communication from periphery to neurons to regulate lifespan via fatty acid breakdown and secretion.

Jason Wayne Miklas and Anne Brunet

Ageing is a complex process that results in organismal decline and death. The progressive loss of homeostasis during ageing occurs at multiple levels — cells, tissues, and organism. Understanding the mechanisms that regulate lifespan could identify ways of slowing, and perhaps reversing, the ageing process. Organelles, such as the lysosome, have been shown to maintain cellular and organismal homeostasis during ageing[1]. In this issue of *Nature Cell Biology*, Savini et al.[2] find that the lysosome is critical in regulating lipid signals from peripheral tissues to neurons to regulate whole organism longevity.

Lysosomes are dynamic organelles involved in a number of cellular and organismal functions — autophagy, nutrient and stress sensing, plasma membrane repair, and development. Lysosome dysfunction is implicated in ageing and age-related diseases such as Parkinson's disease and amyotrophic lateral sclerosis[1]. Lysosomes also have a role in modulating lifespan. Indeed, a lysosomal acid lipase, LIPL-4, is upregulated in multiple longevity mutants of the nematode *C. elegans* and LIPL-4 overexpression extends lifespan in this species[3,4]. Notably, overexpression of LIPL-4 only in the intestine is sufficient for lifespan extension in *C. elegans*[3,4]. But how a lysosomal lipid enzyme that acts in the intestine can extend whole organismal lifespan remained unclear.

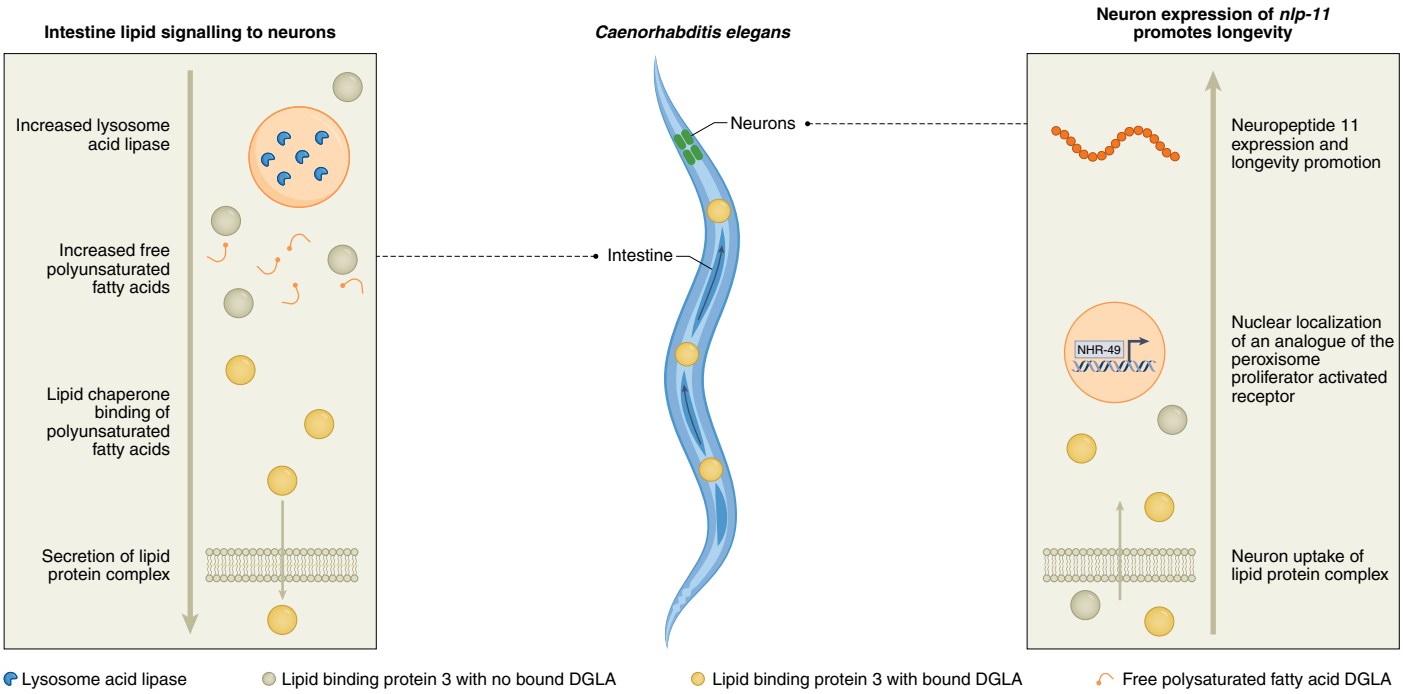

Fig. 1 | Lysosomal lipid signaling from intestine to neurons for longevity regulation. Increasing lysosome acid lipase expression can lead to the release of free polyunsaturated fatty acids such as dihomo-gamma-linolenic acid (DGLA). An increase in DGLA promotes the secretion of the lipid binding protein LBP-3, which Savini et al.[2] suggest can bind DGLA. LBP-3 is released from the intestine and taken up by neurons and may directly or indirectly promote nuclear localization of the nuclear receptor analogous to peroxisome proliferator activated receptor alpha (PPARα), NHR-49, which leads to up-regulation of neuropeptide-processing genes and expression of a neuropeptide, *nlp-11*, and in turn extends lifespan.

To gain insight into the mechanisms by which intestinal lysosomes could influence other tissues, Savini et al.[2] performed transcriptomics in worms expressing the lysosomal lipase LIPL-4 in the intestine, which revealed an enrichment for neuropeptide signaling pathway genes. Neuropeptides are small peptides secreted by neural cells (neurons and in some cases glia). They have long-range impact on distal tissues. Neuropeptides regulate a number of physiological processes, including lifespan[5]. Combining overexpression of LIPL-4 in the intestine with a loss-of-function mutant for neuropeptide processing, the authors found that neuropeptide processing was needed for intestinal lysosomal lipolysis to impact longevity. A targeted RNAi screen pointed to the neuropeptide NLP-11 as being required for lifespan extension by intestinal LIPL-4. Interestingly, expression of *nlp-11* in neurons was higher when lysosome acid lipase expression in the intestine was increased, and overexpression of NLP-11 in neurons was sufficient to extend lifespan. Together, these results suggested that communication between intestine and neurons impacts longevity.

How does a lysosomal acid lipase in the intestine regulate neuropeptide expression in neurons? One of the main functions of lysosomal acid lipases is to release fatty acids by breaking down triacylglycerides (TAGs) and cholesteryl esters (CEs). Savini et al.[2] used lipidomics to identify an increase in free polyunsaturated fatty acids (PUFAs) due to increased lysosomal acid lipase expression. The authors hypothesized that these free PUFAs may act outside intestinal cells to signal to other cells, including neurons. Because fatty acids have low aqueous solubility, they need to be bound to fatty acid binding proteins (FABPs) to diffuse through the plasma membrane. The researchers found that one family member, lipid binding protein 3 (LBP-3), associated with a specific PUFA resulting from increased lysosome lipase activity, dihomo-gamma-linolenic acid (DGLA). Both the fatty acid, DGLA, and the fatty acid binding 'chaperone', LBP-3, were necessary for the upregulation of neuropeptide *nlp-11* in neurons to extend lifespan.

Finally, Savini et al.[2] focused on the cascade of events by which the polyunsaturated fatty acid–chaperone complex was secreted from the intestine, taken up by neurons, and affected neuropeptide expression. Leveraging the powerful *C. elegans* toolkit, the authors showed that supplementation of DGLA increased the amount of secreted LBP-3 protein and increased the expression of neuropeptide-processing enzyme genes. LBP-3 expressed from the intestine could indeed be found in neurons, suggesting that DGLA is shuttled to neurons while bound to LBP-3. Finally, the authors found that the up-regulation of *nlp-11* in neurons was at least in part due to the nuclear translocation of a nuclear receptor analogous to the peroxisome proliferator activated receptor alpha (PPARα), NHR-49 (Fig. 1). Together, these results suggested that the lysosome acts as a signaling hub for the coordination between lipid metabolism and lifespan regulation, and highlighted fatty acids as inter-organ communication molecules that extend lifespan.

This study raises several tantalizing questions and future directions. An immediate future direction is how does the neuropeptide NLP-11 act to extend lifespan and what are its target tissues? Neuropeptides have a wide variety of biological functions both within the mammalian brain and between the brain and distal organs. In mice, neuropeptides expressed in the nervous system, such as calcitonin-related polypeptide alpha[6], regulate lifespan. In *C. elegans*, neuropeptides play a key role in lifespan extension[5]. Important questions are whether

and how neuropeptide expression can be leveraged in humans to delay ageing and age-related diseases. This study uncovers a way of regulating neuropeptides with longevity-promoting effects, which involves the activation of a specific pathway in the intestine. Given the intricacies of neuropeptide expression in the brain and the presence of a blood–brain barrier in mammals, such a mechanism, if conserved, could be easier to target pharmacologically for countering ageing decline.

Before this study, hormones (including steroid hormones) and peptides were commonly appreciated long-range signaling molecules with specific action on target cells. For example, leptin is a hormone secreted from peripheral fat that acts on the hypothalamus to regulate feeding[7]. Circulating factors from old mice other than hormones, such as cytokines, have also been shown to reduce cognitive function and neurogenesis in young animals[8]. Fatty acids bound to proteins can now be added to this list. While lipid–protein complexes are known to circulate in mammals, they are often associated with broad (and often adverse) action. This study reveals that specific lipids may have long-range regulatory functions. However, some complexity still surrounds the role of fatty acids in lifespan extension. For example, different types of lipids — polyunsaturated fatty acids (such as DGLA)[2,3] and monounsaturated fatty acids[9] — can extend lifespan in *C. elegans*. It will be important to systematically identify all fatty acids that impact lifespan, their binding partners, and their cell of action. It will also be interesting to determine if the fatty acid moieties that are critical for longevity have specific functions in inter-organ communication to affect whole organism homeostasis.

Finally, this study highlights the importance of the lysosome not only as a cellular signaling hub[1], but also as an inter-organ communication hub. Neuronal signals were found to promote intestinal activation of lysosomes, improved protein homeostasis, and lifespan extension[10]. It is interesting that this study identifies a 'reverse' signal, from intestine to neurons, which also involves lysosomes. Hence, lysosomes could act as a central age- and metabolism-sensing organelle that could orchestrate inter-organ communication to coordinate whole organism homeostasis. It will be important to explore whether breakdown of lipids by lysosomes also leads to benefits for whole organism homeostasis in mammals, and how this could be used to counter ageing and age-related diseases. ❐

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Competing interests
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NUCLEAR TRANSPORT

Forced entry into the nucleus

The nuclear pore complex (NPC) regulates transport of macromolecules into and out of the nucleus. A study now shows that mechanical force applied on the nucleus affects the transport rates across the NPC diffusion barrier, modulating the nuclear localization of certain cargos.

Stefan Petrovic and André Hoelz

A fundamental property of cells is the ability to detect and respond to environmental cues. Signalling pathways initiated by these cues oftentimes result in the alteration of gene expression patterns. In eukaryotic cells, the nucleus provides an opportunity for controlling gene expression through selective import or export of transcriptional regulators. The conduits for nucleocytoplasmic trafficking of molecules are pores that arise from the circumscribed fusion of the two lipid bilayer membranes of the nuclear envelope. These nuclear pores are gated by nuclear pore complexes (NPCs), ~110 MDa assemblies composed of ~1,000 proteins with a central transport channel that mediates both passive and active bidirectional transport of folded macromolecular cargo between the nuclear and cytoplasmic compartments[1]. The NPC positions natively unfolded protein regions that contain repeating phenylalanine-glycine (FG) motifs into its central transport channel to establish a diffusion barrier. Through self-associating interactions, FG repeats establish a mesh-like phase-separated compartment that limits the diffusion rates of transiting molecules in a size-dependent manner (Fig. 1a). Whereas small cargos, typically around 40 kDa or less, can passively overcome the diffusion barrier, larger cargos must associate with mobile transport factors — importins and exportins, collectively termed karyopherins — whose binding affinity for FG repeats and ultrafast exchange kinetics allow for efficient ferrying across the diffusion barrier. The directionality of active transport is established by the small GTPase Ran, which exists in two distinct nucleotide-bound states. Inside the nucleus, Ran is maintained in its GTP-bound state, which both disassembles importin•cargo complexes and participates in the formation of exportin•Ran(GTP)•cargo complexes. In the cytoplasm, the GTPase activity of Ran is stimulated to break exportin•Ran(GTP)•cargo complexes apart and, conversely, prevent the disassembly