CELL METABOLISM

Autophagy transcribed

Two studies find that an intracellular quality-control mechanism called autophagy is regulated by nuclear receptor proteins that govern the expression of autophagy genes. SEE LETTERS P.108 & P.112

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During periods of starvation, cells survive by changing their status, minimizing the energy spent on biosynthesis and instead activating catabolic pathways that release energy from intracellular stores. This adaptation requires autophagy[1], a process by which intracellular substrates are transported to a subcellular compartment called the lysosome, then degraded and recycled. Although the mechanisms underlying the regulation of autophagy have long been considered to be post-transcriptional, recent studies[2] have uncovered a role for transcriptional networks in the process. Two papers[3,4] in this issue describe a previously unknown transcriptional mechanism that regulates autophagy in response to nutrient availability.

The emerging picture of how autophagy is regulated is of a biphasic mechanism of short- and long-term responses. In the cytoplasm, post-translational protein modifications and protein–protein interactions mediate the rapid induction of the pathway, but nuclear transcriptional mechanisms are necessary for a sustained response[2]. Such transcriptional regulation ensures that the proteins required for lysosome formation and autophagy are produced in appropriate quantities during long periods of nutrient shortage.

FXR is a nuclear receptor protein that is active during normal feeding conditions and regulates bile-acid, lipid and glucose metabolism[5]. Using mouse models and pharmacological approaches, Seok *et al.*[3] (page 108) and Lee *et al.*[4] (page 112) both demonstrated that FXR is a repressor of autophagy in the liver, the first direct evidence of a link between nuclear receptors and autophagy. However, the two studies report different underlying mechanisms for this repression. Seok and colleagues found that active FXR blocks autophagy by inhibiting the transcriptional activity of CREB, a protein that promotes the expression of several autophagy genes. FXR mediates such inhibition by disrupting the functional interaction between CREB and its coactivator protein CRTC2. By contrast, Lee and co-workers showed that FXR binds directly to the promoter-DNA regions that regulate the expression of several autophagy genes, leading to their repression.

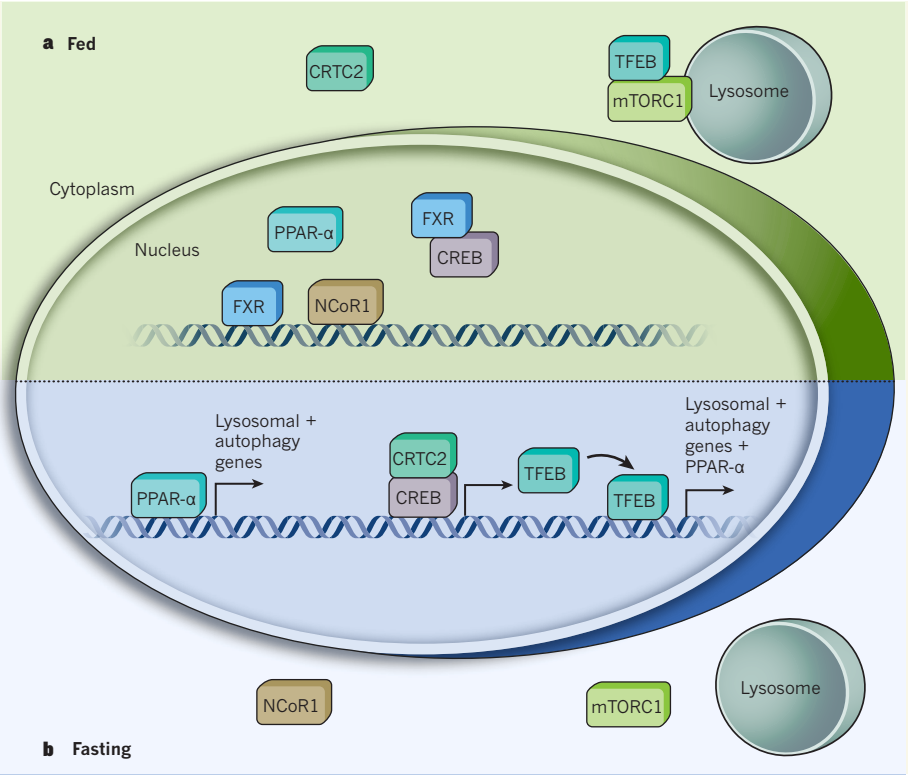

Figure 1 | Regulation of starvation-induced autophagy. Seok *et al.*[3] and Lee *et al.*[4] report that the nuclear receptor protein FXR regulates autophagy. **a**, In normal feeding conditions, FXR inhibits the formation of the CRTC2–CREB protein complex by binding CREB, and competes with another nuclear receptor protein, PPAR-α, for binding sites on gene-promoter regions. Fed conditions also mean that the autophagy-promoting transcription factor TFEB is unable to enter the nucleus because it is bound by the protein mTORC1, which is located on structures called lysosomes. Finally, the transcriptional repressor protein NCoR1 (which is activated by mTORC1) binds DNA. Together, these actions repress the transcription of autophagy genes. **b**, During fasting, FXR is inactive, leading to PPAR-α–promoter binding. This activates the transcription of lysosomal and autophagy genes. In the absence of FXR, the CRTC2–CREB complex forms, which activates transcription of the gene encoding TFEB. This protein is not held by mTORC1 in fasting conditions and can therefore promote transcription of autophagy genes, including that encoding PPAR-α. The co-repressor NCoR1, however, is no longer activated by mTORC1 and is held in the cytoplasm.

Notably, Lee *et al.* showed that the binding of FXR to promoter DNA occurs at regions called DR1 sites, which can also be bound by the nuclear receptor protein PPAR-α. Like FXR, PPAR-α is involved in lipid metabolism, but unlike FXR, it is activated by fasting and promotes the production of energy from the degradation of liver fatty acid[5]. The authors found that PPAR-α induces the expression of autophagy genes, whereas FXR represses it. Thus, the two factors antagonistically regulate the autophagic response to nutrient availability by competing for the same binding sites on DNA.

The apparent discrepancy between the mechanisms proposed in the two papers probably reflects the complexity of the machinery involved in the regulation of autophagy in response to nutrient levels. FXR may repress transcription through

many mechanisms to fine-tune autophagy. Moreover, only a fraction of the DNA sites bound by FXR are bound by CREB, supporting the possibility that, under normal feeding conditions, FXR can inhibit autophagy through CREB-independent mechanisms. It is also possible that the two mechanisms reported are differentially activated in response to different nutritional cues.

The number of autophagy genes whose expression seems to be controlled either directly or indirectly by FXR/CREB and PPAR-α is remarkable, and includes genes involved in several steps of autophagy. For example, Seok *et al.* showed that CREB induces autophagy through the direct transcriptional activation of the TFEB protein, a master regulator of lysosome biogenesis and of autophagy[6]. TFEB also promotes the expression and activity of PPAR-α, thereby activating lipid-degradation pathways in the liver[7]. Thus, these findings suggest that CREB and TFEB, as well as the nuclear receptor proteins FXR and PPAR-α, all belong to the same transcriptional network, which is regulated by nutrients and controls autophagy (Fig. 1). This transcriptional program operates in the nucleus, but has intimate connections with the cytoplasmic pathways that regulate the rapid induction of autophagy. The nutrient-sensing kinase enzyme mTORC1, a regulator of starvation-induced autophagy, mediates these interactions by holding TFEB in the cytoplasm in fed conditions, but permitting nuclear entry during fasting[8], and regulating nuclear entry of NCoR1, a transcriptional repressor of PPAR-α, in the opposite manner[9].

A role for autophagy in lipid degradation has already been described — in a process called lipophagy, lipid droplets are internalized in autophagic vesicles and then delivered to lysosomes for degradation[10]. The various lipid-degradation mechanisms that operate in different cellular compartments, such as the nucleus, lysosomes, autophagic vesicles and mitochondria, require an integrated regulatory network that is just beginning to emerge. The current studies clearly show that FXR and PPAR-α regulate lipophagy at the transcriptional level.

A link between autophagy and nuclear receptors expands our knowledge of the autophagy repertoire, because nuclear receptors are involved in a multitude of pathways. More studies are needed to fully understand how different physiological and pathological conditions regulate the process. Furthermore, it remains to be determined whether or not the transcriptional mechanisms that mediate the response to starvation are also used to respond to other energy-demanding conditions, such as physical exercise and low temperature, or to diseases such as cancer. Finally, pharmacological modulation of these pathways might point to possible therapeutic strategies for combating a broad range of diseases. ■

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EARTH SCIENCE

Controls on isotopic gradients in rain

Concentrations of heavy isotopes of hydrogen and oxygen decrease in rain as storms cross land. A model examines the transport of water vapour that causes this effect, and provides insight into past and present climates.

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Water vapour is lifted from the sea by evaporation, transported by storms and then released across land as precipitation. As rain falls from clouds, it preferentially removes water containing heavy isotopes, so that both clouds and rain become progressively depleted in deuterium and oxygen-18 as they move across continents. The extent of this 'rainout' dominates all the observed trends of continental isotope gradients, but the gradients can vary by up to 50-fold. These variations reflect complex factors that have long eluded simple quantification. Writing in *Earth and Planetary Science Letters*, Winnick *et al.*[1] address this problem with their report of an improved one-dimensional model that follows rain isotopes along a storm track.

The water-cycle processes that cause isotope 'sorting' in rain are well understood, and the resulting isotope gradients in continental precipitation have been extensively documented[2]. At the mid-latitudes, where air temperatures are unstable, atmospheric mixing is particularly pronounced. This lowers isotope gradients as a result of the diffusion-like smoothing of turbulent mixing, a process called eddy diffusion[3]. And in tropical lowlands such as

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Figure 1 | Rain over the Denali National Park, Alaska. Winnick *et al.*[1] have modelled water-vapour transport along the track of a storm.