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L2. How the lysosome tells the nucleus what to do

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In the early 50s, Christian De Duve identified a new cellular structure, the lysosome, defined as the cell's "suicide bag". Sixty years later, it is clear that the lysosome greatly exceeded the expectations of its discoverer. The lysosome mediates intracellular clearance by degrading and recycling a variety of substances that reach this organelle through endocytosis, phagocytosis and autophagy. Over 50 different types of lysosomal storage diseases have been identified, each due to the deficiency or malfunction of a specific lysosomal protein. In addition, an important role of the lysosome has been unveiled in several common human diseases, such as cancer, obesity, neurodegenerative diseases, and infection. We have identified a lysosomal gene network and a master gene, TFEB, that regulates lysosomal biogenesis and autophagy. TFEB and his gene network enable the lysosome to adapt to environmental cues, such as nutrient availability. The activity of TFEB is regulated by the mTORC1 kinase complex through a lysosomal signaling pathway. In addition, we found that TFEB and mTORC1 are involved in a feedback loop that is mediated by the RagD GTPase. This feedback mechanism plays an important role in the response to starvation and physical exercise and is deregulated in cancer. Overall these data reveal that the lysosome acts as a signaling hub that signals to the nucleus through the shuttling of the TFEB transcription factor to control cell homeostasis and the switch between anabolism and catabolism.