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clearing the clamour

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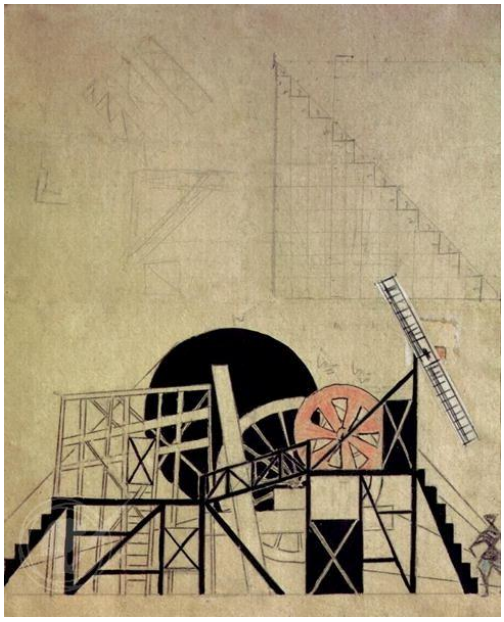
There is an invisible and silent law that causes clutter to emerge and grow unless action is taken to deal with it. Who has not stood in the middle of a littered room and thought "Right, this needs clearing.". And for some reason, clearing clutter has this wonderful ability of also rinsing your mind. The same goes for cells. It begins at the molecular level and is called cell homeostasis, which is at the heart of any organism's health. Intracellular bodies (organelles) known as lysosomes have a major role in animal cell homeostasis, as they degrade components that are toxic to the cell, or foreign, or simply – like foodstuffs gone well beyond their sell-by dates – too old to be of any more use. When infected by bacteria, for instance, our body organises a swift initial response by calling up specialised cells known as macrophages whose role is to engulf and destroy invading pathogens. Macrophages perform this by way of their numerous lysosomes – but more importantly thanks to a protein known as TFEB that, upon infection, is activated to stimulate lysosome biosynthesis.



Stage set design for 'The Magnanimous Cuckold' by Meyerhold

Lyubov Popova (1889-1924)

The immune response involves several of the most intricate metabolic pathways known to biologists. When a pathogen finds its way into our body, it begins by sparking off what can be described as a rather basic immune response: a first line of defence known as the innate immune response. This involves cells specifically equipped to get rid of material that is foreign to the body. Among these specialised cells are those known as macrophages. Macrophages are full of organelles, or lysosomes, themselves filled with enzymes whose prime function is to break down what comes in.

Lysosomes were discovered, quite by chance, in the very early 1950s by the Belgian cytologist and biochemist Christian de Duve. Famously, the scientist is known to have unveiled their existence not by examining cells under a microscope but by sheer inference as he and his group strove to understand the distribution of an enzyme, hexose phosphatase, in various cell fractions they were examining. One thing leading to another, it became clear that their enzyme was protected by "membrane sacs". These sacs marked the very beginnings of the "lysosome" concept, that is to say a membrane-bound organelle that contains acid hydrolases whose main role is to digest intracellular macromolecules.

Accordingly, for years, lysosomes were seen as a place where cells dump their waste to have it recycled. But, as time went by, things turned out to be far more nuanced than that. Lysosomes are delimited by a membrane. They vary in size and morphology as well as in enzyme content, meaning that they are destined to deal with different substrates – a little like the different bins we use for

recycling paper, aluminium or organic waste for example. What is digested is exported and recycled, which is why lysosomes were long regarded as mere cellular bins. We now know, however, that besides regulating cell homeostasis, lysosomes also play major roles in processes such as signal transduction, autophagy regulation, ageing, plasma membrane repair, animal development and… the immune response.

Not so long ago, a surprising find was made. Itaconic acid, or itaconate, is widely used in the manufacture of polymers to make plastics and paint. One day, however, someone noticed that it had antibacterial properties. Itaconate is produced by the Krebs cycle – the cycle that provides cells with energy. As researchers sought to understand the acid's biological activity, they discovered that large amounts were produced in macrophages. Could itaconate play a role in macrophage immune response? The answer is yes. It does this by modifying, via alkylation, a transcription factor known as TFEB whose role is to regulate the biosynthesis of lysosomes. In macrophages, notably.

Transcription factor EB (TFEB) is a member of the microphthalmia family of basic helix-loop-helix – leucine-zipper transcription factors, or simply MiT family, all of whom share an identical domain required for DNA-binding. The MiT family is particular in that its various members are able to bind to one another, forming either homodimers or heterodimers. In "dormant" macrophages, phosphorylated TFEB is sequestered in the cell cytoplasm by regulatory proteins. Upon bacterial infection, the production of itaconate in macrophages is rapidly increased, and the acid goes on to alkylate cytoplasmic TFEB. Alkylation interferes with the cytoplasmic phosphorylation of TFEB causing the regulatory proteins to lose their grip. TFEB is then free to migrate to the nucleus – a move elegantly explained by the possible unmasking of TFEB's nuclear localization signal (NLS), previously hidden by the regulatory proteins. In the nucleus, TFEB binds specifically to what are known as CLEAR (Coordinated Lysosomal Expression And Regulation) elements found on the promoter of lysosomal genes – thus prompting their activation and expression, and subsequent lysosomal biosynthesis.

To cut a long story short, TFEB orchestrates the transcription of a large array of genes whose products clear cells of undesirable material – a job so crucial to cell homeostasis and an organism's general health that evolution has made sure to conserve it. Several well-known diseases are caused by an over-accumulation of substrates in cells such as in Parkinson's, Huntington's or Alzheimer's disease, or even in lysosomes themselves – a disease known as lysosomal storage disorder (LSD). The overexpression of TFEB in murine models of these diseases has actually shown benefits, suggesting that TFEB could represent a common therapeutic strategy. But things are not so straightforward. Depending on its post-transcriptional modification and the level of cell stress, TFEB seems to be involved in several pathways other than cell homeostasis, such as ageing, DNA damage repair, or glucose and lipid metabolism. Far too many roles for TFEB to be taken lightly.

Cross-references to UniProt

Transcription factor EB, *Homo sapiens* (Human) **:** P19484

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