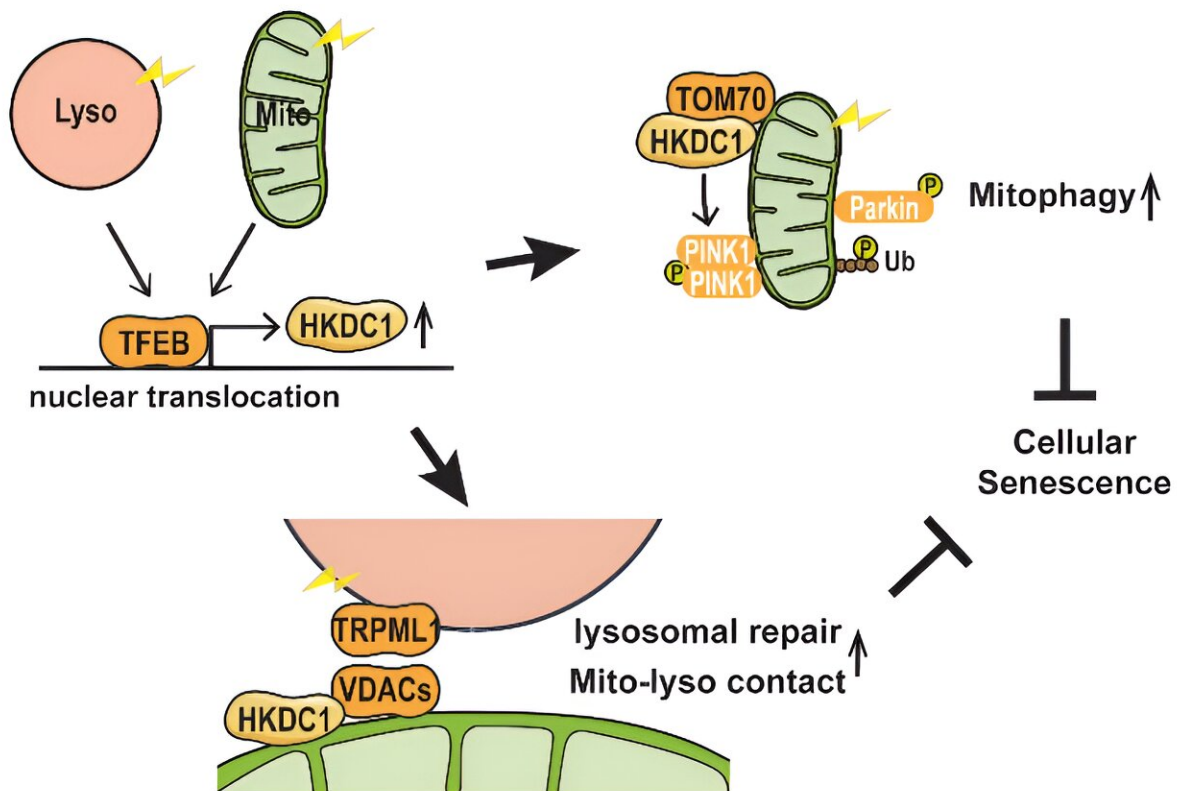


# HKDC1 protein found crucial to maintaining two mitochondria subcellular structures, mitochondria and lysosomes

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Overview: Both mitochondrial and lysosomal stress stimulate TFEB nuclear translocation, followed by increased HKDC1 expression. HKDC1 stabilizes PINK1 through interaction with TOM70, thereby facilitating PINK1/Parkin-dependent mitophagy. Additionally, HKDC1 and the VDAC proteins with which it interacts are important for repair of damaged lysosomes and maintaining mitochondria–lysosome contact. HKDC1 prevents DNA damage–induced

cellular senescence by maintaining mitochondrial and lysosomal homeostasis. Credit: 2024 Cui et al., HKDC1, a target of TFEB, is essential to maintain both mitochondrial and lysosomal homeostasis, preventing cellular senescence, *PNAS*.

Just as healthy organs are vital to our well-being, healthy organelles are vital to the proper functioning of the cell. These subcellular structures carry out specific jobs within the cell; for example, mitochondria power the cell, and lysosomes keep the cell tidy.

Although damage to these two organelles has been linked to aging, cellular senescence, and many diseases, the regulation and maintenance of these organelles have remained poorly understood. Now, researchers at Osaka University have identified a protein, HKDC1, that plays a key role in maintaining these two organelles, thereby acting to prevent cellular aging.

There was evidence that a protein called TFEB is involved in maintaining the function of both organelles, but no targets of this protein were known. By comparing all the genes of the cell that are active under particular conditions and by using a method called [chromatin immunoprecipitation](#), which can identify the DNA targets of proteins, the team was the first to show that the gene encoding HKDC1 is a direct target of TFEB, and that HKDC1 becomes upregulated under conditions of mitochondrial or lysosomal stress.

One way that mitochondria are protected from damage is through the process of "mitophagy", the controlled removal of damaged mitochondria. There are various mitophagy pathways, and the most well-characterized of these depends on proteins called PINK1 and Parkin.

"We observed that HKDC1 co-localizes with a protein called TOM20,

which is located in the outer membrane of the mitochondria," explains lead author Mengying Cui, "and through our experiments, we found that HKDC1, and its interaction with TOM20, are critical for PINK1/Parkin-dependent mitophagy."

So, put simply, HKDC1 is brought in by TFEB to help take out the mitochondrial trash. But what about lysosomes? Well, TFEB and KHDC1 are key players here, too. Reducing HKDC1 in the cell was shown to interfere with lysosomal repair, indicating that HKDC1 and TFEB help lysosomes to recover from damage.

"HKDC1 is localized to the mitochondria, right? Well, this turns out to also be critical for the process of lysosomal repair," explains senior author Shuhei Nakamura. "You see, lysosomes and mitochondria contact each other via proteins called VDACs. Specifically, HKDC1 is responsible for interacting with the VDACs; this [protein](#) is essential for mitochondria-[lysosome](#) contact, and thus, lysosomal repair."

These two diverse functions of HKDC1, with key roles in both the lysosome and the [mitochondria](#), help to prevent cellular senescence by simultaneously maintaining the stability of these two organelles. As dysfunction of these organelles is linked to aging and age-related diseases, this discovery opens new avenues for therapeutic approaches to these diseases.

The article, "HKDC1, a target of TFEB, is essential to maintain both mitochondrial and lysosomal homeostasis, preventing [cellular senescence](#)", was published in *PNAS*.

**More information:** Mengying Cui et al, HKDC1, a target of TFEB, is essential to maintain both mitochondrial and lysosomal homeostasis, preventing cellular senescence, *Proceedings of the National Academy of Sciences* (2024). [DOI: 10.1073/pnas.2306454120](https://doi.org/10.1073/pnas.2306454120).

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