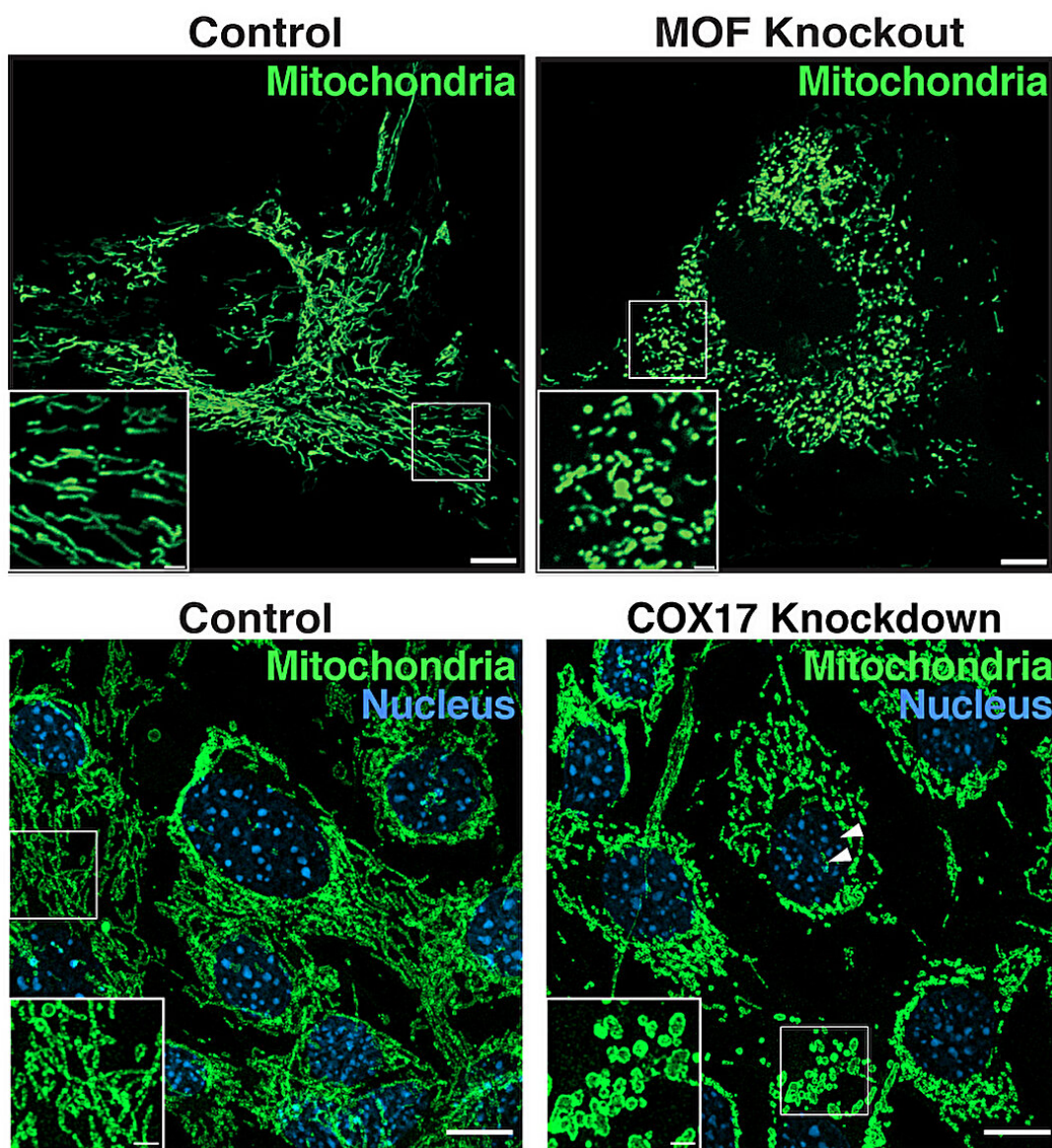


# Epigenetic regulator MOF drives mitochondrial metabolism, new study shows

October 9 2023



Healthy mitochondria existing as elongated network (left panels) become fragmented and functionally deficient upon MOF and COX17 genetic depletion (right panels). Immunofluorescence microscopic images of mouse embryonic fibroblasts. Credit: MPI of Immunobiology and Epigenetics, Akhtar

The intricate control of cellular metabolism relies on the coordinated and harmonious interplay between the nucleus and mitochondria. On the one hand, mitochondria are the hub for the production of essential metabolites, which aside from being required to meet the energy demands of the cell, also serve as the building blocks for constructing both genetic and epigenetic landscapes in the nucleus. On the other hand, the majority of mitochondrial metabolic enzymes are encoded by the nuclear genome, making the function of these two organelles highly interdependent on one another.

Inter-organelle communication is aided by molecules that shuttle between these two compartments. The histone acetyltransferase MOF, an enzyme and a classical epigenetic regulator, is such a wanderer between these two worlds.

A team of researchers from the Max Planck Institute of Immunobiology and Epigenetics, in collaboration with scientists from the Universities of Freiburg and Bonn, now reveals the critical impact of MOF on the cellular physiology and function in compartments outside the nucleus.

The study, published in the journal *Nature Metabolism*, uncovers the critical role of MOF in maintaining mitochondrial integrity through a process called [protein](#) acetylation. The findings shed light on the specific machinery responsible for regulating protein acetylation of

mitochondrial proteins and deepens the understanding of how cells fine-tune their metabolic output.

## **MOF as a molecular bridge between epigenetics and metabolism**

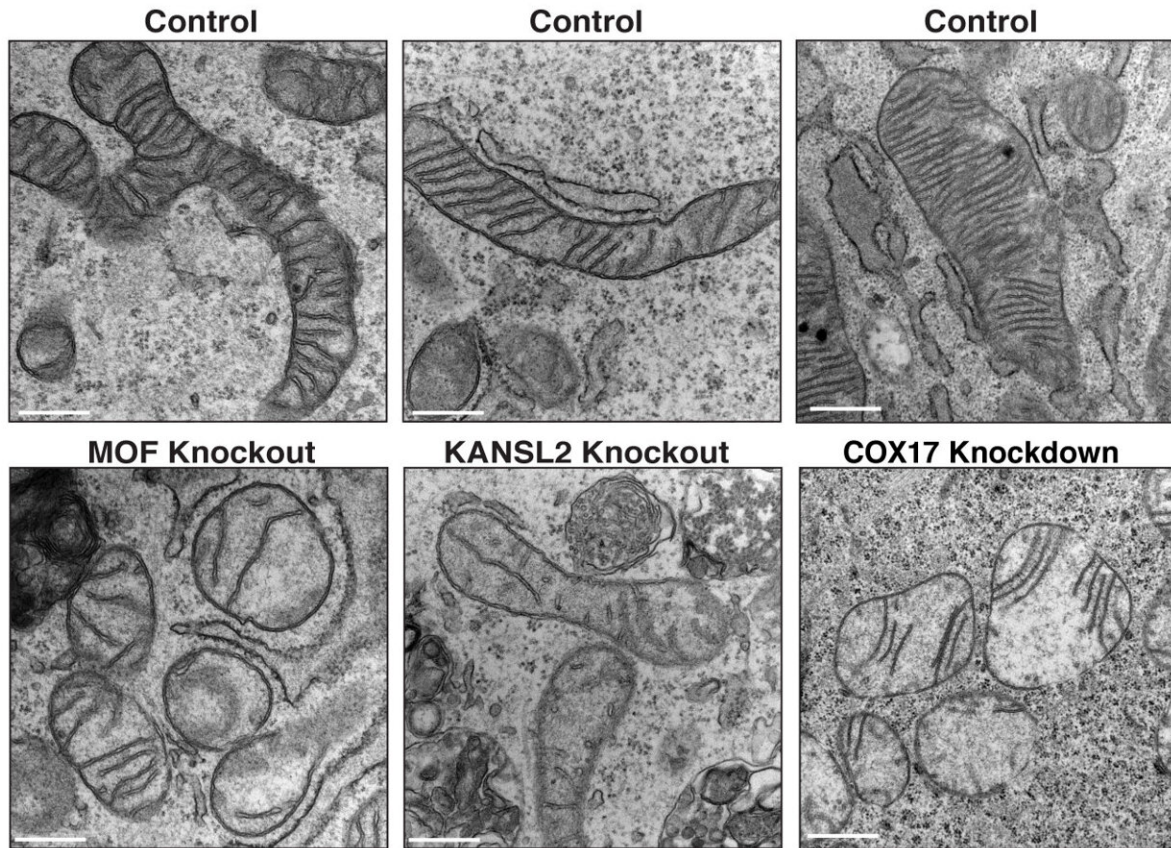
"MOF is a highly conserved protein. We find it in *Drosophila*, in mice and in humans. Together with other molecules, it forms a complex that acetylates histone proteins and thereby promotes transcriptional activation. In the nucleus, our DNA is wrapped around these histones and forms chromatin," explains Asifa Akhtar. Akhtar is Director at the MPI of Immunobiology and Epigenetics in Freiburg and member of the Cluster of Excellence CIBSS—Center for Integrative Biological Signaling Studies at the University of Freiburg.

"The activity of MOF attaches acetyl groups to the histones relaxing the compaction of chromatin in the nucleus and makes genes readable."

In previous studies, Asifa Akhtar's lab was able to detect MOF and several of its protein partners in mitochondria. However, the precise impact of MOF's [enzymatic activity](#) on mitochondrial function and cellular metabolism remained unknown.

"The observation that MOF was localized outside the nucleus spurred our further interest to explore what this acetyltransferase does to mitochondrial proteins and to study protein acetylation as a broader phenomenon in mitochondria," says Sukanya Guhathakurta, first author of the study.





Mitochondria are beautifully packed with cristae which house the energy producing electron transport chain (top panels) and are lost from cells depleted of the MOF-KANSL complex or COX17 (bottom panels). Credit: MPI of Immunobiology and Epigenetics, Akhtar

## **Protein acetylation beyond histone proteins**

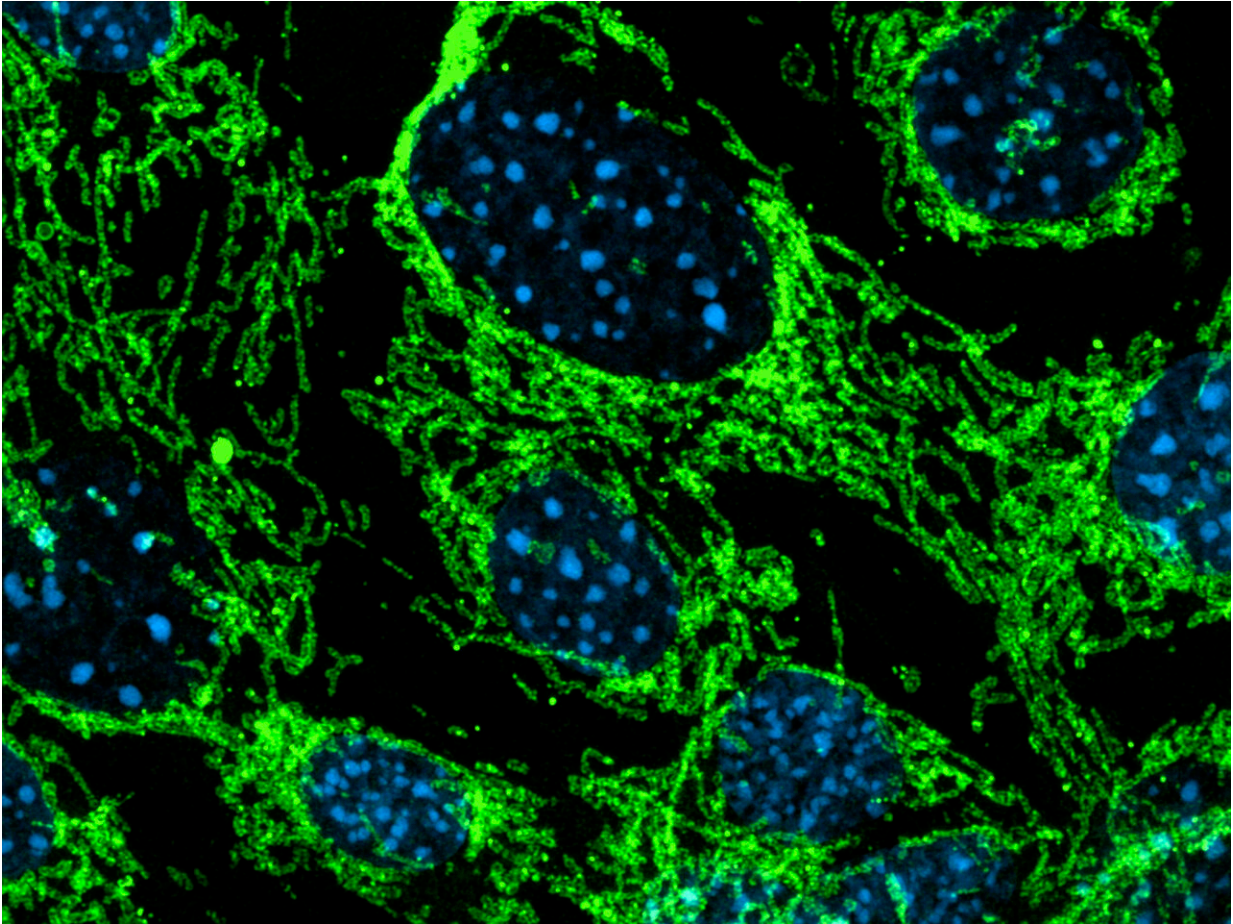
Now, a collaboration between Asifa Akhtar's team and the groups of Thomas Becker (Uni Bonn), and Nikolaus Pfanner (Uni Freiburg and CIBSS) found a pivotal role for MOF in regulating mitochondrial physiology and function.

"In our studies in mice, we identified a unique set of mitochondrial proteins that undergo a change in acetylation status upon loss of MOF and its associated complex members, leading to a cascade of mitochondrial defects, including fragmentation and reduced cristae density, and impaired [oxidative phosphorylation](#)," says Guhathakurta.

Mitochondrial function is essential for cellular energy production and many physiological processes. Dysregulation of mitochondrial physiology and function has been implicated in several diseases such as cancer, heart failure and neurodegenerative disorders.

Very little is known about how acetylation of mitochondrial proteins alters their biochemical properties and functional consequences. The Freiburg team shows that COX17 is an important target of MOF-mediated acetylation. COX17 helps put together a crucial part of the energy-production process in mitochondria, called complex IV. This complex is vital for producing energy through oxidative phosphorylation in cells.

"We show that acetylation of COX17 stimulates its function, highlighting the importance of protein acetylation in regulating oxidative phosphorylation, whereas loss of its acetylation impairs it, demonstrating an unprecedented gain of function via acetylation of a mitochondrial protein. This represents a significant leap forward in our understanding of how epigenetic regulators such as MOF affect cellular metabolism," says Asifa Akhtar.



Teaser Image: Healthy cells with elongated mitochondria network. Credit: MPI of Immunobiology & Epigenetics, Freiburg

### **Patients with mutations in MOF exhibit mitochondrial defects**

The implications of this discovery are far-reaching, suggesting that the balance of protein acetylation in mitochondria may be a critical factor in protecting cells from metabolic catastrophe.

This novel insight challenges conventional thinking about the role of epigenetic factors and their impact on cellular function. However, the research not only deepens our understanding of mitochondrial biology. It

also sheds light on molecular pathways driving pathologies in a developmental disorder, which may help pave the way for potential therapeutic interventions in the future.

The team extended their findings in mice to [human patients](#) harboring mutations in the coding sequence of the MOF gene. The patients suffer from global developmental delay, [intellectual disability](#), epilepsy, and other developmental anomalies.

"We were very excited to see that we were able to partially reverse the respiratory defects in patient-derived fibroblasts with the [acetylation](#)-mimetic COX17 or the mitochondrial pool of MOF," says Sukanya Guhathakurta about the cell culture experiments they did with the patients' material.

The Freiburg researchers are convinced that these findings could attract the interest of medical researchers. Mitochondrial dysfunction is known to contribute to a class of diseases, and this study reveals a potentially important link between [mitochondrial dysfunction](#) and developmental disorders.

**More information:** COX17 acetylation via MOF–KANSL complex promotes mitochondrial integrity and function, *Nature Metabolism* (2023). [DOI: 10.1038/s42255-023-00904-w](https://doi.org/10.1038/s42255-023-00904-w)

Provided by Max Planck Institute of Immunobiology and Epigenetics

Citation: Epigenetic regulator MOF drives mitochondrial metabolism, new study shows (2023, October 9) retrieved 29 April 2024 from <https://phys.org/news/2023-10-epigenetic-mof-mitochondrial-metabolism.html>



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