# Mechanisms for mitochondrial-targeted cancer therapy detected

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Postdoctoral researcher Mara Mennuni and Professor Nils-Göran Larsson. Credit: Shreelatha Bath

In a recent study published in the scientific journal *EMBO Reports*, the Nils-Göran Larsson group has identified responses to acute and chronic impairment of mitochondrial gene expression. These findings can be

valuable for future mitochondria-targeted therapy for cancer and other mitochondrial-related disorders. We have talked to postdoctoral researcher and the study's first author Mara Mennuni about their findings.

## How could your study influence patient care and treatment?

"Cancer cells rely on mitochondria to fulfill their increased metabolic needs, biomass production and cell proliferation. Recently, mitochondrial-targeted therapies for cancer have shown some promising results in pre-clinical models. However, cancer cells are able to adapt and reprogram their metabolism to develop therapy-induced resistance. In this study we identified mechanisms responsible for resistance to a novel compound, the inhibitor of mitochodnrial transcription (IMT). These findings will be valuable for designing future mitochondrial-targeted therapies for cancer. Moreover, the pathways identified also provide more general insights into cellular responses to acute and chronic impairment of mitochondrial function, which can be of interest in the case of mitochondrial-related disorders."

## What are the most important results of your study?

"We studied the effects of both acute and chronic inhibition of mitochondrial gene expression in cancer cells, by using a novel, a small molecule inhibitor of mitochondrial transcription (IMT). We have previously shown that IMT impaired cancer cells survival and xenograft growth in mice. By using a whole genome CRISPR-Cas9 screen we identified that loss of genes belonging to the mammalian target of rapamycin (mTORC1) and Von-Hippel Lindau (VHL) pathways conferred resistance to the acute IMT treatment in cancer cells. Vice versa, further impairment of mitochondrial function, such as

mitochondrial translation or decreased mitochondrial DNA (mtDNA) levels, sensitized IMT-resistant cells to IMT treatment."

## How did you perform the study?

"This study was performed by following an unbiased and a more targeted approach. We employed a CRISPR-Cas9 whole genome screen together with the the High Throughput Genome Engineering Facility (HTGE) to identify cellular pathways conferring resistance to acute IMT treatment in cancer cells." In parallel, we have also generated IMT-resistant cell lines via dose escalated treatment of originally IMT-sensitive cells and studied the cellular responses to the chronic impairment of mtDNA expression. Eventually, we validated the identified responses by chemical or genetic modulation of mTORC1, VHL and mitochondrial gene expression machinery."

**More information:** Mara Mennuni et al, Metabolic resistance to the inhibition of mitochondrial transcription revealed by CRISPR-Cas9 screen, *EMBO reports* (2021). DOI: 10.15252/embr.202153054

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