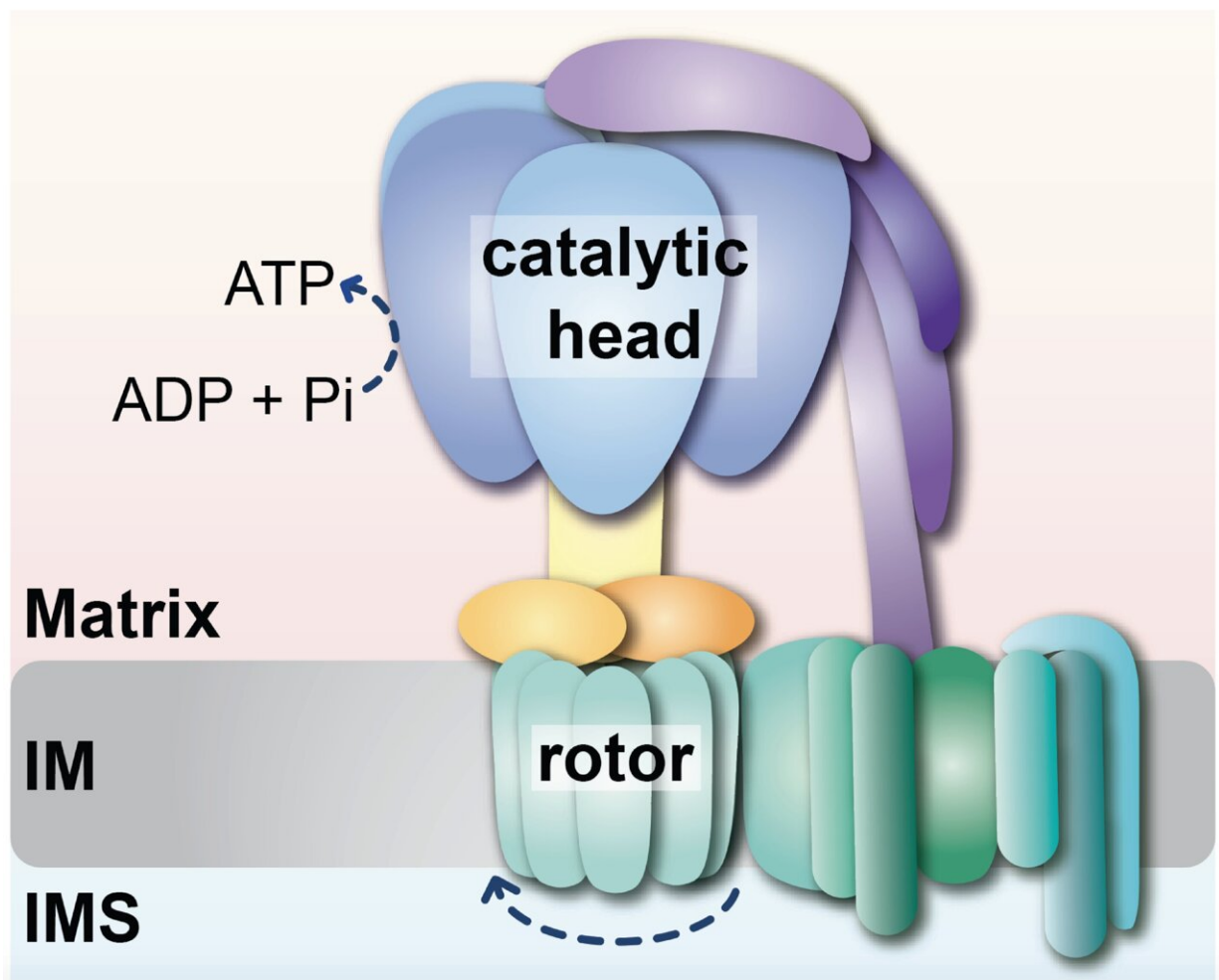


# Insights into the formation of ATP synthase: A new important function of the folding helper Hsp70

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Credit: University Hospital of Bonn

Scientists led by Prof. Thomas Becker, Director of the Institute of Biochemistry and Molecular Biology at the University Hospital Bonn (UKB), have gained new insights into the formation of ATP synthase, the turbine of the cells' power plants, the mitochondria.

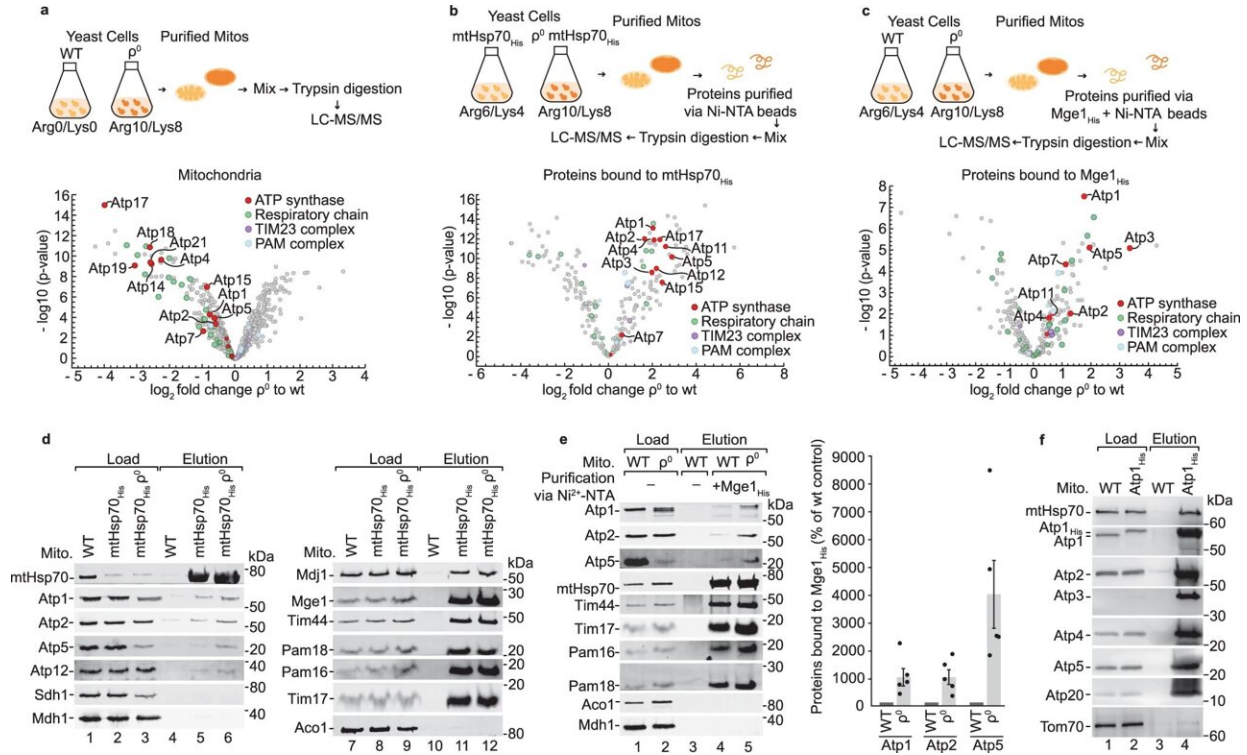
A so-called "molecular chaperone", the protein Hsp70, carries out more functions in the maturation of proteins than previously thought. As the researchers have discovered, Hsp70 not only acts as a "folding helper" of proteins in mitochondria, but also promotes the assembly of ATP synthase. The new findings provide important findings for understanding how the ATP synthase is formed and is now published in the prestigious journal *Nature Communications*.

As it is well known, humans consist of many cells. If one considers each cell in the [human body](#) as a city with different buildings, then a mitochondrion is the power plant. Mitochondria produce the cellular energy currency ATP ([adenosine triphosphate](#)), which is essential for various processes in the cell. In particular, nerve and muscle tissues require a lot of energy for their functions. As usual in [power plants](#), it needs workers in it, and in the case of mitochondria, these are proteins that are imported into the power plant from the cytosol.

The protein Hsp70 is involved in the import of many of these proteins into the interior of the mitochondria, the mitochondrial matrix, where it catalyzes the folding of the proteins so that they adopt the correct shape and do not clump together. Many proteins form together with partner proteins a functional unit called protein complexes. ATP synthase is one of such protein complexes, located in the inner membrane. ATP synthase produces the bulk of cellular energy and can therefore be considered as the turbine of cellular power plants.

"The ATP synthase protein complex consists of a spinning rotor driven by the back transport of protons into the mitochondrial matrix. This part

is connected to the enzyme's catalytic head by a stalk, the molecular stator. The rotation of the rotor is transmitted to the catalytic head, causing it to produce ATP. How the stator and the catalytic head are formed and linked together was previously only partially understood," explains Prof. Thomas Becker.



MtHsp70 binds to subunits of the ATP synthase. **a** Wild-type (WT) and  $\rho^0$  mitochondria were analyzed by SILAC labeling and mass spectrometry. Depicted are the mean  $\log_2$  value of the fold changes of protein intensities in  $\rho^0$  versus WT mitochondria of four replicates, plotted against their statistical significance ( $-\log_{10}$  of  $p$  values). **b** mtHsp70<sub>His</sub> and mtHsp70<sub>His</sub>  $\rho^0$  mitochondria from SILAC-labeled cells were subjected to affinity purification via Ni-NTA agarose in the absence of ATP followed by mass spectrometry. Depicted are the mean  $\log_2$  values of fold changes of mtHsp70<sub>His</sub>-bound proteins in  $\rho^0$  versus WT background mitochondria of four replicates, plotted against their statistical significance ( $-\log_{10}$  of  $p$  values). The signals for Lys2 and Ccp1 had unusually high values, indicating an unspecific interaction, and were removed from the

plot. **c** Differentially SILAC-labeled WT and  $\rho^0$  mitochondrial lysates were subjected to affinity purification via Mge1<sub>His</sub>-coated Ni-NTA agarose in the absence of ATP followed by mass spectrometry. Depicted are the mean  $\log_2$  values of fold changes of Mge1<sub>His</sub>-bound proteins in  $\rho^0$  versus WT mitochondria of four replicates, plotted against their statistical significance ( $-\log_{10}$  of p-values). **d** MtHsp70<sub>His</sub> and mtHsp70<sub>His</sub>  $\rho^0$  mitochondria were subjected to affinity purification via Ni-NTA agarose in the absence of ATP followed by SDS-PAGE and immunodetection. Load: (1% right panel, 2.5% left panel), elution 100%. **e** Left panel, WT and  $\rho^0$  mitochondria were subjected to affinity purification via Mge1<sub>His</sub> in the absence of ATP followed by SDS-PAGE and immunodetection. Load, 1% (Atp1, Atp2, Atp5, mtHsp70, Mdh1) and 2.5% (other proteins), elution 100%. Right panel, Quantification of the co-purified Atp1, Atp2 and Atp5 with Mge1<sub>His</sub>. Depicted are mean values  $\pm$  SEM of 5 independent experiments. The fractions of Atp1, Atp2 or Atp5 co-eluted with Mge1<sub>His</sub> in WT mitochondria were set to 100% (control). Subsequently, the amount of Atp1, Atp2 or Atp5 co-eluted with Mge1<sub>His</sub> in  $\rho^0$  was determined and the co-purification efficiency was correlated to WT. Source data are provided as a Source Data file. **f** WT and Atp1<sub>His</sub> mitochondria were subjected to affinity purification via Ni-NTA agarose followed by immunoblotting. Load: 1%, elution: 100%. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-022-35720-5

The research group led by Prof. Thomas Becker at the UKB has now been able to gain new insights into this assembly process. The scientists have identified a central function of the protein Hsp70 in the formation of ATP synthase: Hsp70 is not only a folding helper, but also contributes to the assembly of this protein complex, according to the researchers.

Dr. Jiyao Song, a post-doctoral researcher in Prof. Becker's group, discovered that Hsp70 is involved with partner proteins in the assembly of the catalytic head. Together with Dr. Dominic Winter's team, she was able to show that subunits of the ATP synthase accumulate at the Hsp70 when the assembly of the ATP synthase is disturbed. Dr. Song further

discovered that Hsp70 monitors the linkage of the catalytic head to the stator.

Thus, mitochondrial Hsp70 fulfills a dual function in the formation of ATP synthase: the assembly of the catalytic head and the controlled linkage of the head to the stator.

This research project within Collaborative Research Center 1218 provides new insights into the functional spectrum of Hsp70 and the formation of a central [protein](#) machinery for energy production in cells. "Defects in the formation of ATP synthase or mitochondrial Hsp70 lead to diseases, especially of the nervous system. Therefore, the new results can provide important contributions to the understanding of these defects," said Prof. Dr. Thomas Becker.

**More information:** Jiyao Song et al, The mitochondrial Hsp70 controls the assembly of the F1FO-ATP synthase, *Nature Communications* (2023). [DOI: 10.1038/s41467-022-35720-5](https://doi.org/10.1038/s41467-022-35720-5)

Provided by University Hospital of Bonn

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