How do carrier proteins transport ADP and ATP in and out of mitochondria?

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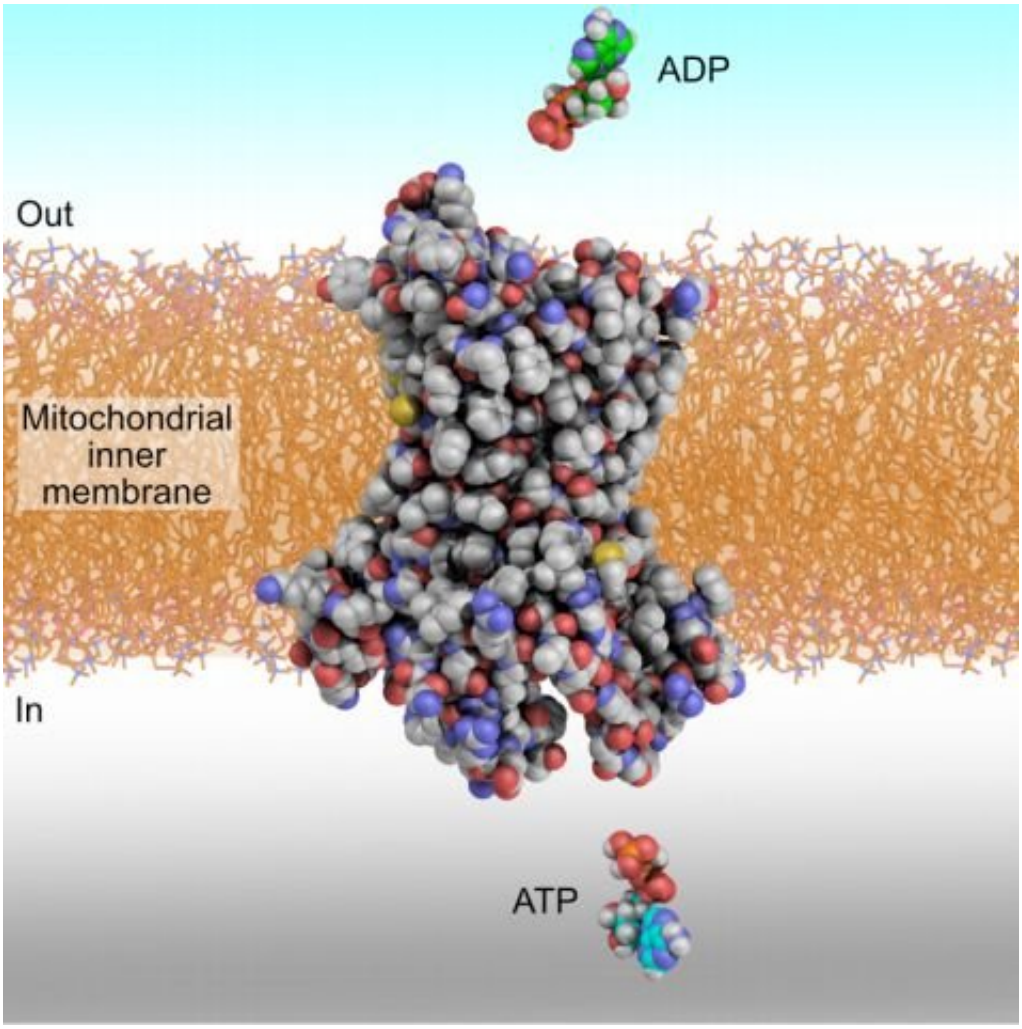

The mitochondrial ADP/ATP carrier protein in the mitochondrial inner membrane, which carries out the vital task of transporting ADP into mitochondria and ATP out. Credit: MRC Mitochondrial Biology Unit

Scientists at the MRC-MBU in Cambridge, U.K., have discovered how a key transport protein, called the mitochondrial ADP/ATP carrier, transports adenosine triphosphate (ATP), the chemical fuel of the cell. This process is vital to keep us alive, every second of our lives, for all of our lives. This work will help us understand how mutations can affect the function of these proteins, resulting in a range of neuromuscular, metabolic and developmental diseases.

Cellular structures, called mitochondria, are the powerhouses of our cells. Every day, we humans need our own body weight in ATP to fuel all of the cellular activities. Nerve impulses, muscle contraction, DNA replication and protein synthesis are just some examples of essential processes that depend upon a supply of ATP. Since we only have a small amount of ATP in our body, we need to remake it from the spent product ADP (adenosine diphosphate) and phosphate using an enzyme complex, called ATP synthase, which is located in mitochondria. In this way, every molecule of ATP is recycled roughly 1300 times a day. For ADP to reach the enzyme, and for the product ATP to refuel the cell, each molecule has to cross an impermeable lipid membrane that surrounds the mitochondria. The mitochondrial ADP/ATP carrier is involved in the transport of ADP in and ATP out of mitochondria.

The carrier cycles between two states; in one state, the central binding site is accessible for binding of ADP, called the cytoplasmic-open state, and in another, the binding site is accessible for binding newly synthesized ATP, called the matrix-open state. A key question has been how the protein is able to convert between these two states, changing its shape to transport ADP and ATP specifically, without letting other small molecules or ions leak across the membrane.

The paper, "The molecular mechanism of transport by the mitochondrial ADP/ATP carrier," published in *Cell*, describes how scientists have solved the structure of the carrier trapped in the matrix-open state. The

carrier was trapped in this state by using a compound called bongkrekic acid, a lethal toxin that binds to the protein and stops it from working. The researchers could also rely on Nanobody technology. Nanobodies are fragments of llama antibodies, which bind specifically to the matrix-open state, and the structure of carrier-nanobody complex with bound bongkrekic acid was determined by X-ray crystallography. Together with earlier structures of the cytoplasmic-open state, this discovery reveals how the carrier works at the atomic scale. The carrier is incredibly dynamic, using six moving elements to transport ADP or ATP across the membrane in a unique and carefully orchestrated way.

The ADP/ATP carrier is just one member of a large family of related transport proteins that bring different compounds in and out of mitochondria, and based on this discovery, the scientists believe that this mechanism is likely to work in a similar way for the whole family. There are many diseases associated with dysfunction of these carriers and for the first time we understand how mutations affect their molecular function.

More information: Jonathan J. Ruprecht et al. The Molecular Mechanism of Transport by the Mitochondrial ADP/ATP Carrier, *Cell* (2019). DOI: 10.1016/j.cell.2018.11.025

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