How calcium regulates mitochondrial carrier proteins

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Mitochondrial carriers are a family of proteins that play the key role of transporting a chemically diverse range of molecules across the inner mitochondrial membrane. Mitochondrial aspartate/glutamate carriers are part of this family, and play a central role in human physiology, with roles in the malate–aspartate shuttle, urea cycle, gluconeogenesis and myelin synthesis. They are unique amongst the mitochondrial carrier family in having three domains - a calcium-regulated N-terminal domain, a mitochondrial carrier domain, and a C-terminal domain. Despite their importance, little is known about the structure of these proteins, or how calcium regulates their activity.

A group led by Dr Edmund Kunji from the MRC Mitochondrial Biology Unit, Cambridge, has recently determined the structures of the N- and C-terminal domains of two types of human aspartate/glutamate carriers, in both the calcium -bound and calcium-free forms. The structures, published in *Nature Communications*, reveal a novel arrangement of calcium-binding units (EF-hands) in the N-terminal domain, only one of which is responsible for calcium binding.

Unexpectedly, the N-terminal domain is involved in dimerization of the carrier. Binding of calcium to the N-terminal domain triggers a large rigid-body rotation of part of the domain, opening up a vestibule that binds the C-terminal domain. These movements provide the first explanation for how calcium binding regulates the activity of the carrier protein. Furthermore, the structures provide key molecular insights into the effect of mutations caused by the life-threatening mitochondrial disease citrin deficiency.

More information: Thangaratnarajah, C. et al. "Calcium-induced conformational changes of the regulatory domain of human mitochondrial aspartate/glutamate carriers." *Nat. Commun*. 5:5491 DOI: 10.1038/ncomms6491 (2014).

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