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STRUCTURAL INSIGHTS INTO THE DYNEIN MOTOR DOMAIN MECHANISM

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The dynein motor protein family, consisting of cytoplasmic and axonemal isoforms, generates movement along microtubules in the minus end direction in eukaryotic cells. Cytoplasmic dynein-1 (dynein-1) carries out most microtubule minus end directed transport and its cargoes include mitochondria, nuclei, as well as protein and mRNA complexes. It also plays important roles during mitosis, where dynein-1 participates in the breakdown of the nuclear envelope and the control of the spindle assembly checkpoint. Cytoplasmic dynein-2 (dynein-2) is involved in the intraflagellar transport in cilia and axonemal dyneins drive the beating movement of the motile cilia subpopulation. Mutations in dynein motors are associated with neurodegenerative diseases, skeletal ciliopathies and primary ciliary dyskinesia. All dyneins exist as multi protein complexes with molecular weights of around 1.4 MDa. They contain a 3500 amino-acid residue motor domain consisting of a ring of six AAA+ domains (ATPases associated with diverse cellular activities), the linker and an elongated coiled-coil helix with the microtubule binding domain (MTBD) at its tip. ATP hydrolysis causes the linker to switch between a post and pre-powerstroke conformation to produce the necessary force for movement. The linker swing is also synchronized with cycles of microtubule binding/release in the MTBD; another important prerequisite for efficient movement. Previously, it was unknown how ATP hydrolysis causes linker remodeling and how this remodeling is correlated with microtubule binding/release. We intend to present two dynein motor crystal structures: dynein-1 from *Saccharomyces cerevisiae* in the apo state and dynein-2 from *Homo sapiens* in complex with the ATP hydrolysis transition state analogue ADP.vanadate. These two structures reveal that ATP hydrolysis causes the AAA+ ring to change from an open to a closed conformation. The closure of the AAA+ ring leads to a steric clash with the linker N-terminal domain, which is subsequently forced to switch from the post- to the pre-powerstroke conformation by a rigid-body movement. AAA+ ring closure also induces a sliding movement within the coiled-coil helix that causes the MTBD to release from the microtubule. The open-to-closed transition of the AAA+ ring is therefore crucial for the coordination of linker swing and the regulation of microtubule binding.

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