The Mechanism of Cytoplasmic Dynein Motility

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Abstract

Cytoplasmic dynein is a homodimeric AAA+ motor that transports a multitude of cargos towards the microtubule (MT) minus end. The mechanism of dynein motility remains unclear, due to its large size (2.6 MDa) and the complexity of its structure. We developed single molecule imaging approaches to dissect the mechanism of dynein motility. We observed that dynein heads move independently along the MT, in contrast to hand over hand movement of kinesins and myosin. Stepping behavior of the heads varies as a function of interhead separation. By engineering the mechanical and catalytic properties of the dynein motor domain, we show that dynein processivity minimally requires the linker domain of one active monomer to be attached to an inert MT tether retaining only the MT-binding domain. Nucleotide-dependent release is inhibited by the tension on the linker domain at high interhead separations. The directionality is determined by the asymmetric binding and release properties of the MT binding interface. Reversing the asymmetry of the MT binding interface resulted in plus-end directed motility. On the basis of these measurements, we propose a quantitative model that describes the basis of dynein processivity, directionality and force generation.