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Single molecule analysis of cytoplasmic dynein motility

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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. By tracking the stepping motion of both heads at nanometer resolution, 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 and establishing the basis of high variability in dynein step size. By engineering the mechanical and catalytic properties of the dynein motor domain, we show that a rigid linkage between monomers and dimerization between N-terminal tail domains are not essential for processive movement. Instead, 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. The release of a dynein monomer from the MT can be mediated either by nucleotide binding or external load. Nucleotide dependent release is inhibited by the tension on the linker domain at high interhead separations. Tension dependent release is highly asymmetric, with faster release towards the minus-end. Reversing the asymmetry of the MT binding interface results in plus end directed motility, even though the force was generated by the dynein motor activity. On the basis of these measurements, we propose a model that describes the basis of dynein processivity, directionality and force generation.