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Molecular mechanism of motion and force generation by cytoplasmic dynein[1]

ARNE GENNERICH, Albert Einstein College of Medicine

Cytoplasmic dynein is an intricate microtubule (MT) motor with four AAA (ATPase associated with various cellular activities) ATPases per head domain. Dynein homodimers take hundreds of consecutive steps, during which the leading and trailing heads experience intramolecular tension in opposite directions. We hypothesize that this asymmetry may differentially regulate the MT-binding and ATPase functions in each head, thereby facilitating processive movement. Here, we elucidate the function of tension in regulating dynein-MT interactions, and dissect the roles of its multiple AAA subunits in effecting and modulating this behavior. Using optical tweezers to measure unbinding forces of single S. cerevisiae dynein heads in the absence of nucleotide, we show that intrinsic dynein-MT binding is significantly weaker under forward (MT-minus-end directed) tension than under rearward tension. Thus, forward tension likely promotes rear head detachment in the dimeric motor. The nucleotide states of specific AAA sites modify this intrinsic behavior. Mutational analysis shows that ATP binding to AAA1 substantially weakens MT binding. Moreover, ADP binding to AAA3 'locks' dynein in a previously undescribed, weak MT-binding state with a relatively symmetric response to tension. Interestingly, tension also affects nucleotide affinity: ADP affinity is lower under rearward than under forward load, suggesting that the front head preferentially releases ADP (likely from AAA3), perhaps driving a transition from an ADP state with relatively weak MT attachment to a strongly MT-attached, nucleotide-free state. Our analysis suggests that intramolecular tension is key to dynein motility, and highlights the importance of including multiple AAA ATPases in models for dynein mechanochemistry.

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