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Pathway of Force Production by the Kinesin-Microtubule ATPase[1]

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Kinesin is the smallest of the molecular motors, consisting of a dimer of motor domains that interact with microtubules and ATP to generate motion towards the plus ends of microtubules for fast axonal transport of membranous organelles. It operates via an alternating site ATPase pathway in which the binding of ATP to one motor domain stimulates the release of ADP from the neighboring domain as the motor walks "hand over hand" along the microtubule surface. This alternating site pathway is accomplished in part due to strain that distinguishes the leading from the lagging motor domains when both are bound to the microtubule. This strain leads to a weak nucleotide binding state in the leading motor and a strong nucleotide binding state in the lagging motor. The ATPase activity is linked to alternating weak and strong nucleotide binding states that are coupled to association and dissociation at the microtubule surface to produce a force for forward motion. Strain in the leading motor domain appears to be due to the disruption of the "neck linker" in the leading motor. Release of the trailing motor domain from the microtubule surface is the rate-limiting step and, by relaxing the tension, allows the leading domain to bind ATP and continue the cycle and forward motion. Although many of the rate constants for steps in this pathway are known, details regarding the structural and thermodynamic basis for the coupling of ATP hydrolysis to force production remain to be established. I will review our current understanding and describe some of our early attempts to resolve intermediates during movement using single molecule fluorescence methods.

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