New Structure and Energy Cycles of Kinesin Dimers Walking on Microtubules Revealed from Molecular Simulations

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Kinesins are motor proteins that move unidirectionally along microtubules as they hydrolyze ATP. Although the general features of the kinesin walking mechanism are becoming increasingly clear, some key questions remain unanswered, such as how they convert the chemical energy of ATP into mechanical energy and walk processively. In this study, through molecular simulations and free energy calculations, we found that in aqueous solution, kinesin favors an extended form with its microtubule-binding interface (MTBI) motif unfolded, as seen in a recent x-ray structure of kinesin-8. Through the flexible fitting of two newly released cryo-electron microscopy (cryo-EM) maps, we derived atomic structures of the kinesin dimer-microtubule complexes in both two-head-bound and one-head bound states. Free energy calculations showed that kinesin bound to microtubules has a lower free energy than the extended form and that the free energy difference is in the range of the free energy released by ATP hydrolysis. The transition between the extended and compact forms, the structural differences of the leading and trailing heads, and atomic force simulations suggest a completely new mechanism by which kinesin dimers walk on microtubules. A structure cycle and energy cycle are presented to describe kinesin dimers walking on microtubules. Identifying the extended form of kinesin provides a new target for the regulation of kinesins.

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