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Mechanochemistry of Molecular Motors

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Molecular motors lie at the heart of biological processes from DNA replication to vesicle transport. We seek to understand the physical mechanisms by which these nanoscale machines convert chemical energy into mechanical work. I will overview our ongoing use of single molecule tracking and manipulation techniques to observe and perturb substeps in the mechanochemical cycles of individual motors, before concentrating on our recent efforts to dissect the structural basis of a "reverse gear" in myosin VI. The basic actomyosin motor has been embellished, altered, and re-used many times through the evolution of diverse members of the myosin superfamily. Class VI myosins are highly specialized (-) end directed motors involved in a growing list of functions in animal cells, including endocytosis, cell migration, and maintenance of stereociliar membrane tension. How does myosin VI achieve reverse directionality, despite sharing extensive sequence and structural conservation with (+) end directed myosins? We generated a series of truncated myosin VI constructs and characterized the size and direction of the power stroke for each construct using dual-labeled gliding filament assays and optical trapping. Motors truncated near the end of the converter domain generate (+) end directed motion, whereas longer constructs move toward the (-) end, confirming the importance of a class-specific insert that redirects the lever arm. Our quantitative results suggest a surprising model in which the lever arm rotates $\sim 180^\circ$ during the power stroke. We are currently studying the behavior of engineered myosin VI constructs with artificial lever arms, in order to further challenge and refine our power stroke model.