Single Molecule Views of Nature's Nano-Machines

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At the most fundamental level, virtually all biological reactions occur between individual biomolecules such as enzyme, DNA and RNA. In the last several years, exciting developments in single-molecule imaging and manipulations have transformed the way we look at these biological problems. They provide us with previously attainable data that deepen our understanding of molecular mechanisms and help formulate new paradigms. Basic understanding will ultimately guide us in developing cure or containment for serious human diseases and lead to the construction of man-made nano-machines via 'reverse engineering' of what Nature has optimized over billions of years.

In the first part, I will review how single-molecule imaging with one nanometer precision has settled an outstanding question on how two-legged motor proteins move on molecular highways. Do they crawl like babies or walk like grownups? Previous studies monitored the movement of the body so could not distinguish between the two models. By attaching a single dye to one of the feet, researchers were able to show that myosin V's foot moves in steps of 74 nm, twice as large as the step size of the body, 37 nm, proving that myosin V walks instead of crawling. The same technique has been used to show that other motor proteins such as kinesin and myosin VI also walk. These motor proteins are ideal candidates for man-made nano-engines.

In the second part, I will review how single-molecule manipulation and spectroscopy are revealing inner workings of motor proteins moving along DNA. Helicases were initially discovered as DNA unwinding enzymes but recent studies showed that they can do many other things. For instance, they track DNA directionally, kick proteins off DNA and induce rapid migration of DNA four-way junction. Defects in human helicases are responsible for serious genetic diseases, including Werner syndrome which causes premature aging. Single-molecule measurements show that these helicases can act as a DNA pump and a molecular rectifier, again attractive candidates for building blocks for hybrid nano-machines.

In the third part, I will review new exciting direction of building nano-scale machines using these biological molecules as building blocks. Kinesin molecules can shuttle microtubules back and forth which in turns carries DNA molecules that may be used for building a DNA network. Myosin molecules can pump actin filaments directionally in response to external stimulus. Branch migration of DNA junction can be used to drive DNA-fueled DNA nano-machines.

<u>Keywords:</u>

Molecular motors: Cellular proteins that convert chemical energy derived from ATP hydrolysis into mechanical work. examples are myosin, kinesin and helicase.

Single-molecule imaging and manipulation: Experimental approach to detect the location, movement and shape changes of biological molecules via fluorescence or force.