Motor proteins may be vehicles for drug delivery

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Specialized motor proteins that transport cargo within cells could be turned into nanoscale machines for drug delivery, according to bioengineers. Chemical alteration of the proteins' function could also help inhibit the growth of cancerous tumors.

Each cell in the body contains motor proteins that ferry cargo such as chromosomes, mitochondria or bundles of proteins, either from the center of the cell to its outskirts or from the periphery toward the nucleus. Most motor proteins contain two motor domains, or heads, that are attached to a shared cargo-binding domain, or tail.

"Think of it as a freight train at the molecular level," said William Hancock, associate professor of bioengineering, Penn State. "And it runs on cylindrical tracks -- or microtubules -- made of many protein subunits meshed together into a long polymer that is one ten thousandth the diameter of hair."

Hancock and his colleagues are studying a particular motor protein known as kinesin-2. They are trying to understand the molecular mechanics of how these nanometer-scale proteins move within the cell.

"Kinesin motor proteins move by changing their shape," explains Hancock. "The two motor domains alternately bind to the microtubule, generate force and then detach, and the resulting displacement drags the cargo forward."

To power this hand-over-hand motion, the proteins convert the chemical energy of ATP molecules -- a common energy source in cells -- into mechanical work. But there is a problem if the proteins fall off their tracks.

"When a motor binds to the microtubule, it 'walks' about 100 steps -- each step being eight nanometers -- before detaching," said Hancock, whose findings appeared in a recent issue of *Current Biology*. "And the proteins are so small that if both motor domains let go, the proteins and their cargo would diffuse away within a few milliseconds. This profound effect of diffusion is one of the places where the nanoscale world fundamentally differs from the macro-scale world we normally live in."

The key to successfully hauling the cargo from one point to another lies in perfect coordination between the two motor domains. At any given time, one of the motor domains always needs to be bound to the track.

"Each motor domain is by itself an enzyme that continually alters the mechanics and the biochemistry of the other," explained Hancock, whose work is funded by the National Institutes of Health. "And we are trying to understand the mechanical coordination between the two domains. You can think of it like walking on two feet, but there's no brain to control when a step is taken, only a mechanical connection between the two feet."

The researchers have found that the tether that links the motor domains to the rest of the molecule is longer in kinesin-2 motors than in other kinesin proteins, which prevents efficient mechanical coordination between the two motor domains.

"If you think of this linker domain as a taut bungee cord, any force at one end will be communicated very efficiently to the other end. So the two motors can communicate very efficiently and the timing of their

steps is tightly coordinated," Hancock said. "But if the cord is very loose, the forces from one motor domain are poorly communicated to the other and the precise timing of their steps is disrupted. This is a big effect and it reduces the performance of kinesin-2."

To confirm their findings, the researchers artificially lengthened the tethers on kinesin-1 motor proteins. These motors ferry chemicals over much greater distances -- such as in neurons that can be a meter long -- and the coordination between their two motor domains is very efficient.

The researchers found that when the tethers on kinesin-1 motors were lengthened, the communication between the two heads was diminished.

Hancock believes that the insight into the relationship between the length of the tether and the communication between the motor domains could offer new targets for drugs that inhibit kinesins.

"There are a lot of kinesins involved in cell division, and cancer is uncontrolled cell division," said Hancock. "Our hope is that this knowledge will help in the design of new drugs that block the motors during cell division and thereby slow the growth of tumors."

The researchers also believe that the kinesin transport system could in the future be engineered onto microchips.

"Our idea is that you can hook up cargo -- drugs, antibodies, sequences of DNA or RNA -- and the motors would carry them through microchannels on a lab-on-a-chip type of device," added Hancock. "We have already had success with incorporating these proteins into microengineered channels and achieving transport in these systems."

Source: Pennsylvania State University (news : web)