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MOLECULAR MOTORS

Feeling the tension in every step

Kinesin-1 (referred to as kinesin) can transport molecular cargoes over long distances in a precise manner. It does this without dissociating from the microtubules by coordinating its two motor domains in a hand-over-hand manner — a property that is known as processivity. Reporting in *Cell*, Ronald Vale and colleagues show that this coordination between the motor domains is mediated by intramolecular tension, which is required for kinesin motility.

Kinesin is a dimer, with two catalytic motor domains that are connected through a stalk to the cargo-binding C-terminal tail. Each motor head is joined to the stalk by a flexible 'neck linker' that interacts with the motor. The neck linker drives the characteristic hand-over-hand 'stepping' movement of the two kinesin heads, a mechanism that ensures that both heads do not dissociate from the microtubules simultaneously. So how do the neck linkers coordinate processive movement?

Most theories propose that coordination occurs through a 'gating' mechanism, in which a step in one head is blocked until a certain step is taken in the other head; such gating could be chemical (for example, ATP) or mechanical (for example, conformational changes). However, when two heads of wild-type kinesin are bound to the microtubule, the native linkers are fully extended, which indicates that tension between the two heads could provide a gating mechanism.

Vale and colleagues used mutant kinesin constructs and optical trapping microscopy to investigate how altering the length of the neck linker — and thereby the tension between the heads — affects gating and therefore kinesin movement. Reducing tension by artificially lengthening the neck linkers impaired coupling between ATP hydrolysis and stepping, and although processive movement still occurred, it was slower. However, the speed of processive movement recovered to nearly normal levels when these molecules were pulled in the correct direction, by applying external tension through an optical trap. External tension can also cause kinesin to step forward or backward in the absence of an energy source (ATP) or its mechanical element (the neck linker). It is becoming clear that ATP binding and hydrolysis bias the direction of kinesin steps, so in the absence of ATP, an externally applied tension can fulfil the direction-biasing role of ATP.

These findings show that the motor domain of kinesin senses and responds to strain, which regulates communication between the two head subunits of the molecule. The authors propose that "for kinesin to take an 8 nm step, two events have to happen: the rear head has to detach and the neck linker has to dock to pull the detached head forward".

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> "…coordination between the motor domains is mediated by intramolecular tension…"

ORIGINAL RESEARCH PAPER Yildiz, A. *et al.* Intramolecular strain coordinates kinesin stepping behavior along microtubules. *Cell* **134**, 1030–1041 (2008)
FURTHER READING Cochran, J.C. & Kull, F.J. Kinesin motors: no strain, no gain. *Cell* **134**, 918–919 (2008)