mutant is phenotypically similar to the *aux1* mutant, which suggests that both genes act in the same process. Dharmasiri *et al.* now provide an explanation for this phenotypic similarity by identifying AXR4 as an endoplasmic reticulum–resident protein required for proper AUX1 sorting to the plasma membrane. AXR4 appears specific for AUX1 trafficking, because other membrane proteins such as the PINs are not mislocalized in the *axr4* mutant. Interestingly, in the root tissues examined, the only cell types affected by the *axr4* mutation were those in which AUX1 localization is polar. In the lateral root cap, where AUX1 is uniformly distributed, there are no obvious effects in the *axr4* mutant background, whereas in the epidermis and protophloem where AUX1 is polarly localized, AUX1 is retained in the endoplasmic reticulum. This suggests that AXR4 plays a specific tissue-dependent role in the polar sorting of AUX1 to a particular plasma membrane face, rather than a general chaperone-like function. The biochemical basis for AXR4 action is not yet clear. Apart from a predicted transmembrane motif and a putative α/β hydrolase fold, AXR4 does not contain any known protein domains.

These discoveries demonstrate clear tissue-specific elements in the membrane targeting of both PIN and AUX1. So far, however, there is no evidence of any coordination of these events, although there is some suggestion of common elements because both are sensitive to the protein traffic inhibitor brefeldin A (*13*, *17*). As the mechanisms for polar localization of these proteins are revealed, it will be interesting to see the extent to which they are independent.

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MATERIALS SCIENCE

Toward Devices Powered by Biomolecular Motors

Biomolecular motors can be used in nanometer-scale devices to perform mechanical work. This approach will assist the development of active nanostructures.

Henry Hess

Biomolecular motors, such as the motor protein kinesin, convert chemical energy derived from the hydrolysis of individual adenosine triphosphate (ATP) molecules into directed, stepwise motion (*1*). This process enables them to actively transport designated cargo—such as vesicles, RNA, or viruses—to predetermined locations within cells. For engineers, active transport in biology inspires visions of nanofluidic systems for biosensing, of active materials that can rearrange their components, and of molecular conveyor belts and forklifts for nanometer-scale manufacturing.

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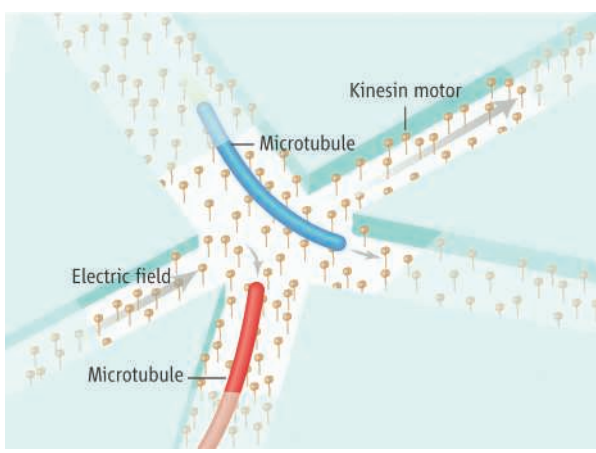
Nanofluidic devices, which extend the lab-on-a-chip paradigm to systems with picoliter volumes and submicrometer channel diameters, present an immediate opportunity for the application of biomolecular motors. On page 910 of this issue, van den Heuvel *et al.* (*2*) show that kinesin motor proteins can drive the directed transport of microtubules (filamentous assemblies of thousands of tubulin proteins) in closed channels with submicrometer dimensions. Controlled application of an external electric field steers the microtubules into either one of two arms of a Y junction (see the figure).

The setup is an adaptation of the classic gliding motility assay (*3*), in which the kinesin motor proteins adhere to a surface via their rotationally flexible tails, bind to the leading ends of approaching microtubules with their two heads, and move the microtubules by stepping forward with alternating heads until they reach the trailing end and detach. In biological systems, the motors move and the microtubules are stationary. The key advantages of the inverted geometry used in the assay are that the microtubules are continuously bound to the surface over transport distances of more than a millimeter (*4*) and that the large microtubule allows the attachment of fluorescence tags for observation and of specific linkers for cargo binding (*5*).

Open or micrometer-scale closed channels have previously been fabricated to confine microtubule movements (*6*–*8*). Van den Heuvel *et al*. have now created closed channels with submicrometer dimensions. The channels not only provide better confinement, but they also mimic the dimensions of axons, in which motor–driven transport plays a central role. They may thus enable more realistic model studies at the system level of active transport in biology. Electric fields for active steering provide direct control over the paths of individual microtubules. By coupling fluorescence detec-



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Nanofluidics with molecular motors. In van den Heuvel *et al.*'s work (*2*), an electric field is used to steer the microtubules into one of two arms of a Y junction; the microtubules move perpendicular to the field. The microtubules are transported by kinesin motor proteins.

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tion of microtubules with this control mechanism, van den Heuvel *et al*. have integrated optics, electronics, and molecular transport, thus introducing an element of real-time programmability.

This work is related to efforts by several teams of bioengineers to envision molecular motor–based technology and build proof-of-principle devices that radically depart from current engineering concepts (*9*). For example, minute volumes of biological samples can now be rapidly analyzed in credit-card–sized microfluidic devices connected to desktop-scale peripheral instruments. Downscaling of the lateral device dimensions by a factor of 100 would result in dust-particle–sized devices reminiscent of unicellular organisms. These devices would not necessarily be useful as as microscopic extensions of macroscopic peripheral devices, but would rather lend themselves to the application of the "smart dust" concept: smart dust biosensors would be immersed in the liquid sample of interest, independently perform an analysis, and be read out collectively to generate a statistically significant signal. Biomolecular motors that coat the inner surfaces of such devices and use dissolved ATP fuel as an energy source would drive the internal transport and remove the need for peripheral pumps and batteries (*10*).

In addition to fulfilling transport functions, biomolecular motors can exert localized forces on nanostructures. They can thus cause conformational changes, such as the stretching of coiled DNA molecules into a linear configuration (*11*) or the rupture of intermolecular bonds. Molecular motors could thus push supramolecular assembly and disassembly processes away from chemical equilibrium and generate dynamic, nonequilibrium structures (*12*). The force exerted by motor proteins could also be exploited in nanorobotics, where the sequential examination or manipulation of molecules by scanning probe microscopes and optical tweezers could be complemented by a parallel approach relying on arrays of microscopic, motor-driven actuators.

A key challenge in the field of molecular motors is to replicate the direct and efficient conversion of chemical energy into mechanical work by macroscopic arrays of biomolecular motors in muscles. This would pave the way toward a "molecular engine," creating an alternative to the prevailing heat engines (whose efficiency in converting chemical energy to mechanical work is limited according to Carnot) or to the two-step process of converting chemical energy into electricity via fuel cells and then into mechanical work via electrical motors. Building on insights from muscle physiology, we can pursue the engineering of either hybrid or fully synthetic molecular motor arrays of increasing size and explore a new avenue toward the design of artificial muscles (*13*).

Biomolecular motor–based hybrid devices face limitations with respect to environmental conditions (such as temperature) and lifetime (now typically on the order of hours to a few days) (*14*). Long-term storage of these devices in an inactivated state, which is reached by freezing or lyophilization technologies already used for protein pharmaceuticals, can be used to separate device fabrication and use by at least several months. However, limited lifetime and small power density are the principal disadvantages of biomolecular motors and motivate a transition to fully synthetic molecular motors in the long term.

Molecular motors, either of biological or synthetic origin, are central in the transition from passive to active nanostructures, because they enable coupling to a reservoir of chemical energy. In previous centuries, the use of human and animal power enabled the development of a wide range of technologies—including roads, carriages, and pumps—which were augmented after the invention of the steam engine and the internal combustion engine. Similarly, biomolecular motor nanotechnology, where van den Heuvel *et al*. have devised improved roads and the first traffic control system, and the on-going development of synthetic molecular motors (*15*) contribute to the same vision of fast, efficient, and controlled nanometer-scale transport systems.

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NEUROSCIENCE

Regulating Energy Balance: The Substrate Strikes Back

Jeffrey S. Flier

Hormones and dietary nutrients control appetite and metabolism by acting on the brain, where the signals they elicit promote hunger or satiety. Neurons in the hypothalamus integrate these signals to regulate energy balance.

Appetite, energy expenditure, and metabolism are critically regulated by hypothalamic neural circuits, and a "wiring diagram" through which neurons and neurochemicals exert these effects is rapidly emerging. To achieve energy homeostasis, neuronal pathways in the central nervous system receive and integrate signals from the periphery that convey information about the status of energy fluxes and stores. These signals are of several types. Hormones, such as the fat-derived hormone leptin, act directly on a subset of neurons; a deficiency of leptin is interpreted by the brain as starvation. Leptin deficiency overrides other signals to produce ongoing hunger despite massive obesity, as in rare human cases and in rodent models. Other regulatory signals include gut-derived peptide hormones released with meals that promote feeding (ghrelin) or satiety (cholecystokinin and peptide YY) through actions on the same neuronal targets.

Although these endocrine effectors have received the most attention recently, metabolic fuels and substrates, the evolutionarily ancient regulators of cellular and organismic homeostasis, also affect the neurocircuitry to regulate energy balance. For example, a low glucose level sensed by this circuitry provokes hunger (*1*). More recently, free fatty acids have been shown to act on targets in the central nervous system to regulate metabolism (*2*). On page 927 in this issue, Cota *et al*. (*3*) establish a novel, and potentially important role for

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