Cellular Motors for Molecular Manufacturing

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ABSTRACT

Cells are composed of macromolecular structures of various sizes that act individually or collectively to maintain their viability and perform their function within the organism. This review focuses on one structure, the microtubule, and one of the motor proteins that move along it, conventional kinesin (kinesin 1). Recent work on the cellular functions of kinesins, such as the organization of microtubules during cellular division and the movement of the organelles and vesicles, offers insights into how biological motors might prove useful for organizing structures in engineered environments. Anat Rec, 290:1203–1212, 2007. © 2007 Wiley-Liss, Inc.

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CELLS ARE A DYNAMIC ENTITY

A cell is a biological factory composed of relatively small proteins of typical dimension of approximately 10 nm that work together to fulfill complex biological functions (Alberts, 2002). The "program" is the DNA molecule, and the work is done mainly by the proteins. Proteins are responsible for reading the program, making new proteins, assembling the cell in the first place as well as maintaining it, transporting molecules, conveying information in and out of the cell, for cell division and locomotion (Lodish et al., 1995; Alberts et al., 2002; Pollard and Earnshaw, 2002).

Epithelial cells exemplify biological factories (Engelhardt, 2002). These cells make up the epithelial tissue, which separates the outside and inside compartments of the body. They are responsible for importing nutrients (in the intestines), removing waste (in the kidneys), receiving information (in the sensory cells), and for exporting proteins (in the pancreas). These functions are driven by transmembrane proteins that transport ions and small molecules, secrete proteins, and sense external forces and extracellular molecules. Inside the epithelial cell, there is the complex machinery that synthesizes proteins, that packages them into vesicles and fuses the vesicles with the plasma membrane, all guided by signals that the cells receive from the outside environment and from the other cells. The building of such a tiny factory and the transport of materials are made possible by the cytoskeleton and its associated motor proteins.

CYTOSKELETON AND MOTOR PROTEINS: ACTIVE PLAYERS IN CELL FACTORY

The cytoplasmic network of protein filaments called cytoskeleton determines the shape of cells (Alberts et al., 2002). Identified by electron microscopy in 1956 (Schliwa, 1986), the cytoskeleton filaments have been divided into three major classes that play different roles: the intermediate filaments, with a rope-like structure and a diameter of approximately 10 nm that provide mechanical strength and resistance to any stress that might affect the cell (Herrmann and Aebi, 1998); actin filaments cable-like structure with a diameter of approximately 6 nm that act under tension to preserve cell shape (Rzadzinska et al., 2004) but also push the front

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of the cell forward during cell locomotion (Bray, 1992); and microtubules pipe-like structures that serve as tracks for intracellular transport (Scholey and Vale, 1993; Lodish et al, 1995; Alberts et al., 2002) and that, in addition, form the mitotic spindle (Cooper, 2000; Howard, 2001a).

Molecular motors are essential components of the cell factory. Precisely, each factory generates a unique set of products, which are then distributed to different compartments using three sets of molecular transporters: the myosin, kinesin, and dynein motors, respectively. The reason is that the eukaryotic cells are so large and their cytosols so crowded that diffusion is too slow to efficiently transport material from one part of the cell to another (Luby-Phelps et al., 1987). Molecular motors circumvent this problem by using ATP (adenosine triphosphate) as a fuel to produce directed movement (Kull, 2000). Directed transport can only work along polar filaments—filaments whose surfaces are structurally asymmetric so that the motor, upon binding, can read the direction toward which the filament is pointing. Actin filaments and microtubules are polar structures because the constituent protein subunits are arranged in a head-to-tail fashion that preserves the asymmetry of the individual filaments. However, intermediate filaments have no polarity because the subunits have mixed orientations; thus, they do not serve as tracks for motors. Myosins motors, which move along actin filaments, produce the forces necessary for muscular contraction and the transport of secretory vesicles in yeasts (Govindan et al., 1995), while dyneins and kinesins are involved in retrogradate (Brady et al., 1990) and anterograde (Coy et al., 1999a) axonal transport of synaptic precursors vesicles in neurons. This review focuses on one structure, the microtubule, and one of the motor proteins that move along it, conventional kinesin (kinesin 1).

MICROTUBULES

Microtubules are hollow, stiff cylinders with an internal diameter of approximately 18 nm and an external one of approximately 25 nm (Nogales et al., 1999). The building block is a heterodimer α- and β-tubulin (Tilney et al., 1973; White et al., 1987). The heterodimers bind together in a head-to-tail manner to form a protofilament. Usually 13 protofilaments bind side-by-side to form the microtubule wall. The parallel association of the protofilaments preserves their polarity.

α-Tubulin is exposed at one end, and β is exposed at the other. The end terminated by β-tubulin is called the plus end because it grows faster than the slow-growing end terminated in α-tubulin and called the minus end. The microtubule ends define the transport direction of molecular motors (Burns and Surridge, 1994). The molecular basis of the complex polymerization of microtubules was examined in vitro and in vivo (Desai and Mitchison, 1997). The αβ-tubulin subunit addition or loss from the ends of a microtubule results in its growth or shrinkage with microtubule assembly being similar to microfilament assembly. At αβ-tubulin concentrations above the critical concentration (C_c), the dimers polymerize into microtubules, whereas at concentrations below the C_c, microtubules depolymerize (Alberts et al., 2002). Both assembly and disassembly occur preferentially at the plus end of the microtubule with microtubules exhibiting the ability to treadmill, in which subunits add to one end and dissociate from the opposite end with the rate of microtubule growth slower than the rate of shortening, termed dynamic instability. Briefly, a microtubule becomes unstable and depolymerizes rapidly if the plus end becomes capped with subunits containing GDP–β-tubulin rather than GTP–β-tubulin. This situation can arise when a microtubule shrinks rapidly, exposing GDP–β-tubulin in the walls of the microtubule, or when a microtubule grows so slowly that hydrolysis of GTP bound to β-tubulin converts it to GDP before additional subunits can be added to the plus end of the microtubule.

In the past decade or so, several proteins that can bind tubulin and influence its dynamics inside cells have been identified (Cassimeris and Spittle, 2001). One is a microtubule-severing protein, katanin, which may generate nuclei at centrosomes. Another factor is Op 18, which increases the frequency of catastrophe, possibly by binding the tubulin dimers. Some proteins are known to stabilize and destabilize microtubules, for instance small molecules such as taxol and colcemid have proved to be very powerful for probing microtubule function, partly because they bind only to αβ-tubulin or microtubules and not to other proteins, and also because their concentrations in cells can be easily controlled. There are also proteins known to influence polymerization equilibrium by sequestering tubulin subunits in conformations that cannot allow assembly into the microtubule polymeric structure.

KINESIN-MEDIATED TRANSPORT

Kinesins are a superfamily of microtubule-based ATPase motors (Dagenbach and Endow, 2004). Humans have around 45 kinesins (Miki et al., 2001) that split into 14 major families (Lawrence et al., 2004) and are found in all eukaryotic organisms (Karcher et al., 2002) to mediate intracellular transport pathways.

Kinesin 1, the most studied motor protein, plays important roles in the centrifugal movement and placement of the lysosomes away from the cell center (Hollenbeck and Swanson, 1990). Recent studies have shown that kinesins 1 transport vesicles carrying around amyloid precursor protein (Kamal et al., 2000) and jun amino-terminal kinase signaling complexes (Verhey et al., 2001). Also, there is a strong evidence for the role of kinesin 1 on the mitochondrial motility (Tanaka et al., 1998). Kinesin 1 is also involved in the axonal transport (Hirokawa et al., 1991; Muresan, 2000) and in the posterior transport of mRNA in *Drosophila* (Brendza et al., 2000). There have also been suggestions that kinesin 1 or a related motor protein might play role in elaborating endoplasmic reticulum (ER) structure (Feiguin et al., 1994) and in Golgi-to-ER transport (Johnson et al., 1996; Schmitz et al., 1994).

Kinesin 2 motors drive radial movement of melanosomes along microtubules in axonemes (Rogers et al., 1997; Tuma et al., 1998) and transports rafts complexes (Cole et al., 1998), retinal photoreceptors (Marszalek et al., 2000), and even some protein complexes (Marszalek and Goldstein, 2000).

Kinesin 3 motors (Unc-104/ KIF1A) transport one set of synaptic vesicles precursors (Hall and Hedgecock, 1991; Okada et al., 1995). Another kinesin 3, motor

KIF1B, is likely involved in the transport of mitochondria (Nangaku et al., 1994). There is some evidence that KIF1C is required in some cells for Golgi-to-ER transport (Dorner et al., 1998).

Different kinesins are involved in chromosomes movement during mitosis and meiosis as well as in microtubule spindle formation (Chang et al., 2004). For example, members of the kinesin 4 family (KIF4, chromokinesin, XPLP1 from *Xenopus*, KLP38B from *Drosophila*, Kid from humans) are located at the chromosomes arms mediating their interactions with the plus end of the microtubules (Vernos et al., 1995). These motors possess plus end–directed motor activity (Sekine et al., 1994). Also, the kinesin-like protein called centromeric protein-E binds to the kinetochore throughout mitosis and to the microtubules during late stages of mitosis (Cooke et al., 1997). This binding produces chromosomes's congression and alignment on the metaphase plate (Wood et al., 1997; Schaar et al., 1997).

Some members of kinesins are also known for their ability to depolymerize microtubules. Microtubule depolymerization is involved in establishment and maintenance of the mitotic spindle involved in chromosome segregation during cell division (Inoue and Salmon, 1995; Rogers, 2004). Kinesin subfamily KinI (Desai et al., 1999), explicitly XKCM1 in *Xenopus* (Desai et al., 1999; Kline-Smith and Walczak, 2002), MCAK in mammals (Wordeman and Mitchison, 1995; Hunter et al., 2003), Kif2 (Aizawa et al., 1992) have been shown to depolymerize microtubule in vitro (Desai et al., 1999).

CONVENTIONAL KINESIN (KINESIN 1)

Conventional kinesin or kinesin 1 (commonly referred to simply as kinesin; Brady, 1985; Vale et al., 1985a) is a heterotetramer composed of two heavy chains (approximately 125 kDa each) each containing a motor domain (Yang et al., 1989), a long mainly coiled-coil tail, and two light chains that bind cellular cargos (Hirakawa et al., 1989).

Expressed in all cells, kinesin moves toward the plus end of the microtubule (Vale et al., 1985b). Kinesin is a processive motor (Howard et al., 1989), meaning that a single molecule is able to move continuously along the microtubule for up to several microns (Howard et al., 1989; Block et al., 1990). High-resolution optical measurements show that kinesin takes 8-nm steps, corresponding to the stepwise movement from one tubulin dimer to the next (Ray et al., 1995; Howard, 2001a). This finding is well correlated to the rate at which ATP is hydrolyzed, one ATP every 8-nm step (Coy et al., 1999b) and up to 100 ATP molecules being hydrolyzed during one processive run (Hackney, 1995). The mechanism of walking is bipedal—termed "hand-over-hand"—with the two heads of kinesin binding alternatively to the microtubule (Howard, 2001a; Schief and Howard, 2001; Yildiz et al., 2003). Evidence comes from biochemistry (Hackney, 1994) and microscopic assays; the two heads alternate without any net diffusion release of the microtubule (Kaseda et al., 2003). The heads move in a coordinated manner, the detachment of one head is contingent upon the attachment of the second head (Hancock and Howard, 1998).

Kinesin converts chemical energy directly into mechanical work without passing through a high-temperature intermediate like a car engine (Howard, 2001a). The reason that motors are not heat engines is that the diffusion of heat is so rapid over their nanometer dimensions that the necessary thermal gradients would dissipate within picoseconds, which is a higher scale compared with the transition between different chemical states within the motor (milliseconds time scale; Howard, 1996). The maximum force that kinesin can generate defines the efficiency of the motor. Because its movement with respect to the microtubule ensues from the mechanical change within the motor region, several laboratories have measured how energy transduction could underlie the definition of the force originated within the motor binding domain (Svoboda and Block, 1994; Meyhofer and Howard, 1995). It has been found that the force exerted by a single kinesin on the microtubule scaffold is of approximately 4–8 pN (Hunt et al., 1994; Higuchi et al., 1997). Therefore, the motor efficiency (defined as the actual work performed by the motor divided by the input energy; Maes and Weeren, 2003) is approximately 48 pN·nm (Howard, 2001a) taking into account the step size (8 nm) and the force (6 pN). This finding means that the energy efficiency is almost 50% (Howard, 2001a), assuming one step per ATP where the free energy derived from ATP hydrolysis is approximately 100 pN·nm with ATP, ADP, and P_i at their cellular concentrations. The 50% efficiency is not only attractive from the biological point of view (representing a considerable reserve of force for intracellular transport of vesicles and other biological compounds through a crowded cytoplasm; Howard, 1996; Gittes et al., 1996) but also make the kinesin molecule an attractive model to be emulated in artificial devices, a nanomotor operating in synthetic environment.

FROM CELLULAR FUNCTIONS TO ENGINEERING TASKS

The idea of exploiting nature's biological machineries as assembly units in synthetic environments has gained a lot of interest in the past decade. The interest was stimulated and justified by the development of in vitro motility assays in which the movement of purified motor proteins along cytoskeletal filaments is reconstituted under cell-free conditions (Scholey, 1993; Howard, 2001b). There are two types of assays for in vitro motility both performed in flow cell systems that permit exchange of solutions by perfusion. The flow cell system can be constructed with a microscope slide and a cover slip pressed down on a double-sided spacer with a thickness of approximately 100 μm (Fig. 1a). The cell is filled by capillary force; solutions are being perfused by simultaneously presenting new solution at one end and removing away fluid from the other end of the flow cell (Howard, 1993).

In the gliding assay, the motor proteins are fixed to the surface and they allow the microtubules, which diffuse down from solution, to attach and to move along the surface. The kinesin-driven motility can be directly monitored in cell-free assays by observing, under the light microscope, the microtubule movement (Gittes et al., 1996; Hancock and Howard, 1998; Bohm, 2000a,b; van den Heuvel, 2005). The polar microtubules always glide such that one end leads: this assay, together with assays using microtubules fluorescently marked at

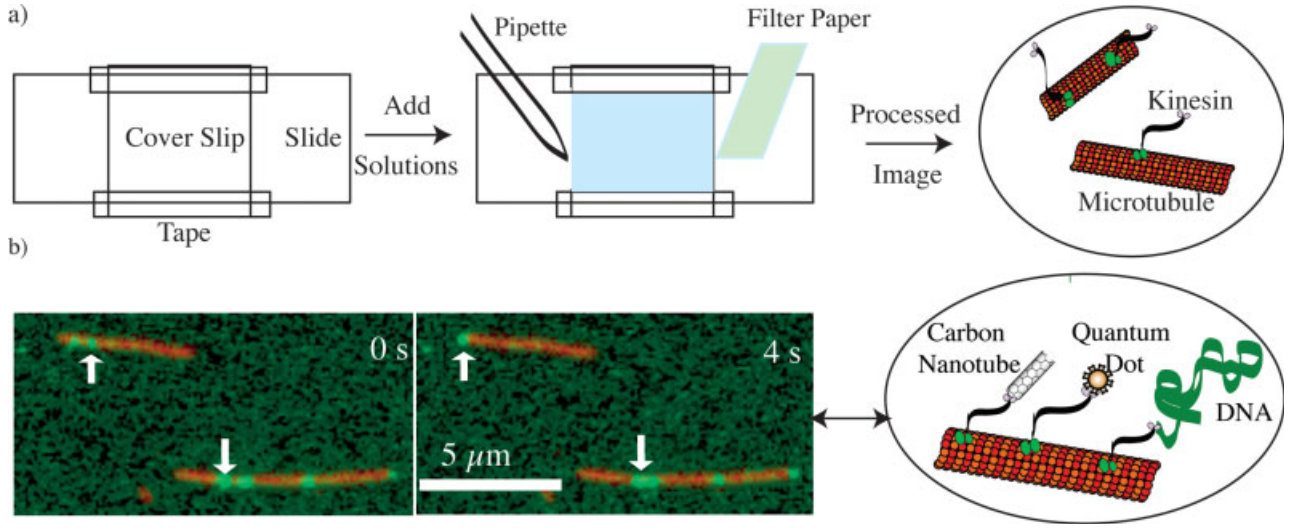

Fig. 1. **a:** Flow cell formed from a microscope and a slide separated by double-sided tape. Different solutions are perfused into the system by capillary forces. The flow cell system is used to transport kinesin on immobilized microtubules tracks. **b:** Proof of principle: green fluorescent protein (GFP) kinesin walking on the microtubules. Series of micrographs showing the movement of single kinesin molecules (labeled with GFP) on immobilized microtubule (labeled with rhodamine) on a glass substrate. Proposed mechanism of kinesin cargo transport of a carbon nanotube, a quantum dot, and a DNA molecule.

the minus ends, indicates that kinesin always moves toward the plus, or fast-growing, end of the microtubule (Fig. 1a). In the bead assay, the microtubules are fixed to the surface and beads with motors bound to them are then carried along the microtubule track (Fig. 1a). The visualization of fluorescently labeled motors traveling across the microtubule tracks is shown in Figure 1b (Pierce, 1997) using fluorescence microscopy and a CCD camera (Hackney, 1994). This opens up the road to the single molecule level, with the biochemistry of a single motor possibly being investigated.

KINESIN-BASED MICROTUBULE MOTILITY CAN BE CONTROLLED

Various techniques, relying on surface topography and surface chemistry (Suzuki et al., 1997; Turner et al., 1995; Dennis et al., 1999) as well as flow fields (Stracke et al., 2000), have been developed to guide the movement of molecular motors in synthetic environment. Varying the ATP concentration can serve as a means of choosing and influencing the speed of movement, thus ensuring temporal control. By controlling the ATP concentration one can also move microtubules in separate groups. It was found that kinesin can be turned on or off by exploiting the ultraviolet (UV) -induced release of caged ATP combined with ATP degradation by hexokinase (Hess et al., 2001). Also, some other studies have shown that, by exchanging ATP with its nonhydrolyzed form AMPPNP and vice versa, the motors could be switched on and off under direct user control (Schnapp et al., 1990). There are other identified inhibitors of motility: adociasulfate-2 (Sakowicz et al., 1998) and monastrol (Mayer et al., 1999). Adociasulfate-2 with a rodlike aggregate mimics the structure and electrostatics of microtubules in a competitive manner. Kinesins, therefore, preferentially associate with adociasulfate instead of microtubules, resulting in inhibition of the ATPase activity (Reddie et al., 2006). Monastrol locks the motor in a state in which it holds on to the microtubule, but slips freely along them; it also promotes a dramatic decrease in the observed rate of motor association with microtubule; thus, the ADP release is slowed down (Cochran et al., 2005).

Spatial control was achieved by means of topographical changes of the surface. It was shown that, by using a nanoscale surface architecture with shear-deposited polymer film (PTFE-poly [tetrafluoroethylene]), the microtubules could be directed along one preferential axis (John et al., 1999). By changing the channel geometry (such as width or wall height), guidance could be achieved (Clemmens et al., 2003). By ensuring certain surface-guiding geometries (such as arrows and ratchets; Hiratsuka et al., 2001; Hess et al., 2002) one can also control the direction of movement. Coating a glass or silicon surface with resist polymers such as PMMA, SU-8, or SAL601 and using UV, electron beam, or soft lithography to remove resist from defined regions (Suzuki, 1997; Bunk, 2003; Sundberg, 2003) ensures spatial control. By choosing appropriate properties of the motor solution, the motility was restricted to either the unexposed, resist surface or to the exposed, underlying substrate.

Novel approaches for the dynamic control of gliding microtubule motility by external stimuli were also developed. For instance, fabrication of a composite surface where functional kinesin motor molecules are adsorbed onto a silicon substrate between surface-grafted polymer chains of thermoresponsive poly(*N*-isopropylacrylamide) controlled the reversible landing, gliding, and releasing of motor-driven microtubules in response to conformational changes of the polymer chains. This finding represents a versatile means to control the activity of biomolecular motors, and other surface-coupled enzyme systems, in bionanotechnological applications (Ionov et al.,

2006). Also, combining the actions of depolymerizing kinesins with the gliding kinesins can open up new avenues in nanotechnology. For instance, in one approach kinesin can pattern microtubules in predefined locations on the surfaces while MCAK can depolymerize the misplaced microtubules to form regular tracks to be used for cargo transport.

CARGO TRANSPORT MECHANISM

Cargo transport in a synthetic environment is an important task for engineering applications as it was proved that hooking cargo to the microtubules does not alter their speed or motion (Hess and Vogel, 2001). In vitro, cargos can be attached to the kinesin-gliding microtubule tracks using different strategies. The prospective cargo can be coated with an antibody to the filament (Wada et al., 2000) or it can be coated with streptavidin, which binds to filaments that have been derivate with biotin (Gittes et al., 1996).

One of the first ideas advanced in the field is the one of the molecular shuttles built up from motor proteins capable of moving cargo along engineered pathways. Practically, these nanoscale machines are functionally equivalent to trains or conveyor belts (Hess and Vogel, 2001). Features of the conveyor belt are that they are driven by force-generated motors to transport cargo unidirectionally between well-defined positions and to accommodate loading and docking while being externally switched on and off (Hess et al., 2001). Thus motors and microtubules were used to transport various synthetic loads such as microscopic beads (Stracke et al., 1999; Asbury et al., 2003), glass particles (Svoboda et al., 1993), and quantum dots (Bachand et al., 2004). A general state of the art of the kinesin cargo transport system is shown in the Figure 1b.

Molecular motors were also used to transport DNA. The flexibility of DNA (persistence length, 50 nm; Hagerman, 1998) combined with its addressability (given by its sequence) makes this polymer an interesting construction material (Seeman et al., 1997). It has been shown that biotinylated DNA molecules can be attached to the biotinylated microtubules by means of streptavidin (Fig. 2). Using surface-bound kinesin motor proteins, the DNA molecules have been transported and stretched along glass surfaces (Diez et al., 2003). This could be the first step toward patterning DNA molecule by means of motor proteins and microtubules in a fashionable and controllable manner. Figure 2 illustrates this process. Moreover, a new technique was developed to manipulate bifunctional DNA molecules: one end is thiolated to bind to a patterned gold surface and the other end is biotinylated to bind to a microtubule gliding over kinesin motors (Dinu et al., 2006). It was found that DNA molecules were stretched and overstretched into a straight wire-like conformation between the gold patterns and the motile microtubules (Fig. 3), and they can form dynamic networks. This finding serves as a proof-of-principle that biological machineries can be used in vitro to accomplish the parallel formation of structured DNA templates that will have applications in biophysics and nanoelectronics. Such a system could next be used for future enzymatic studies (DNA–enzyme interaction; Yokota et al., 1997) or as templates for the metallization (Richter et al., 2001) to serve as scaffold for nanoelectrical circuits (Bhalla et al., 2003). Parallel manipulation of many DNA molecules by motor proteins might allow the rapid and reproducible formation of complex structures on synthetic surfaces, structures dictated and performed under user control (Dinu et al., 2006). One can think about changing

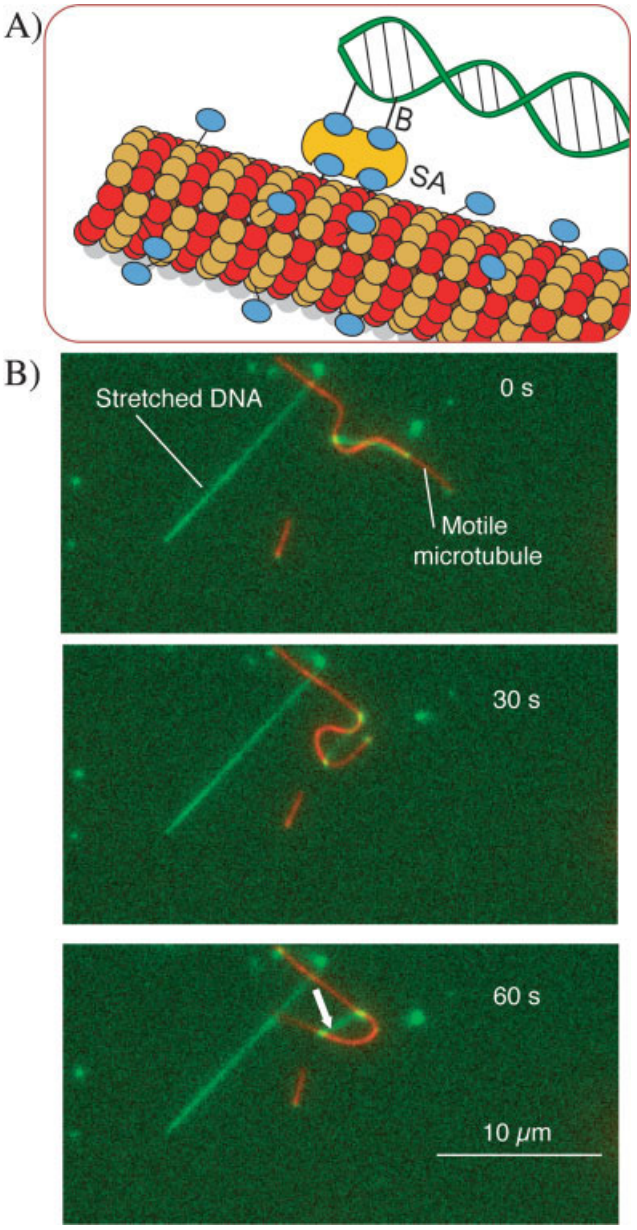

Fig. 2. Manipulation of the DNA by motor proteins and microtubules. Movement of a gliding microtubule on a kinesin-coated glass surface. **A:** Illustration of the way the DNA molecule is bound to a microtubule. The microtubule is biotinylated and rhodamine labeled. Using streptavidin as a ligand, end-biotinylated DNA is connected to the biotinylated microtubule. **B:** The biotinylated microtubule picks up and manipulates the DNA. Sequence of fluorescent images showing motile microtubules (rhodamine labeled, red) patterning and manipulating DNA molecules (YOYO labeled, green). The arrow points to a stretched DNA that crosslinks the microtubule to itself and causes it to snake around.

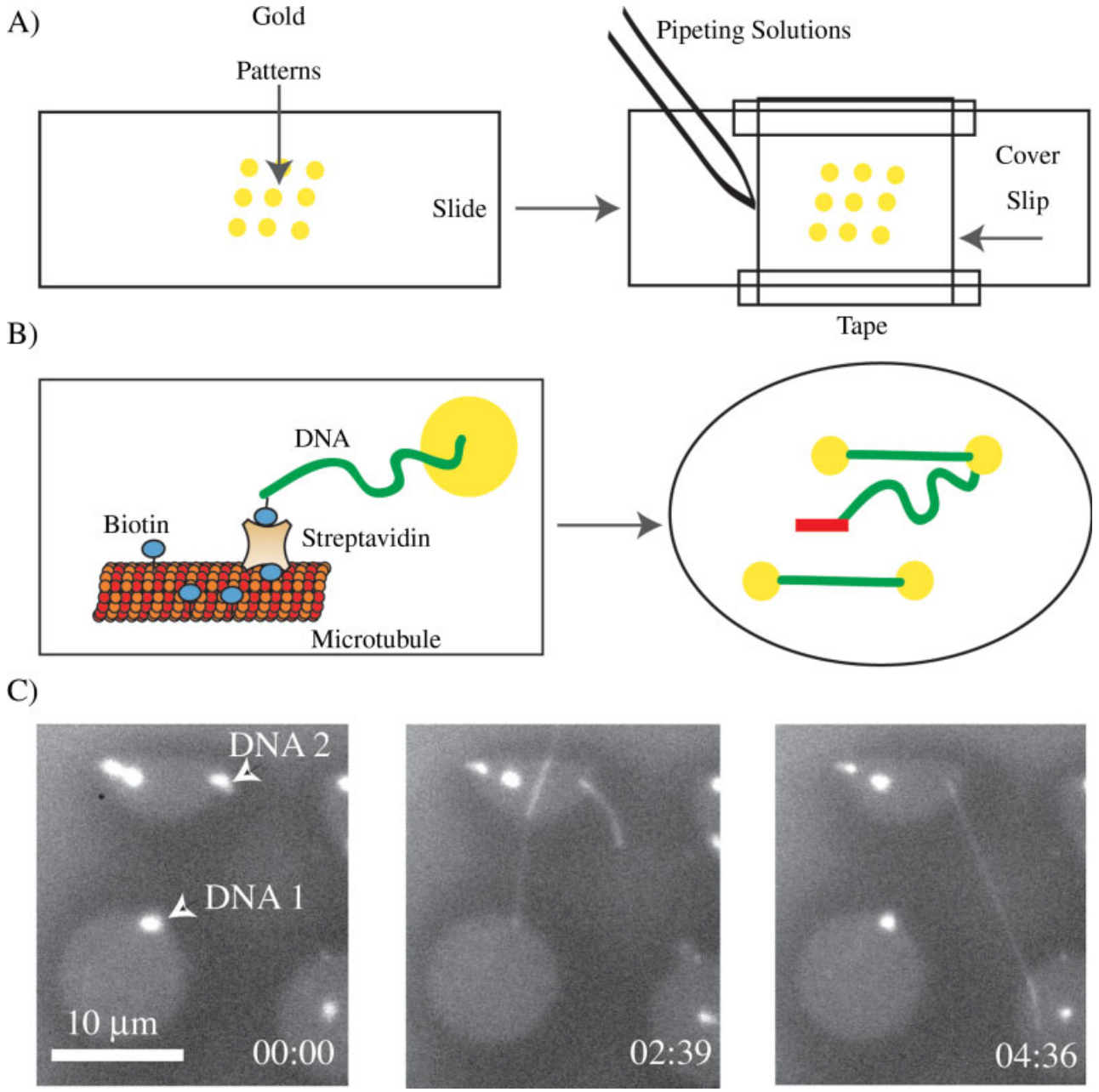

Fig. 3. Patterning DNA in a synthetic environment. **A:** A flow cell system formed from one slide and a cover slip that contains patterns of gold and a cover slip separated by a double-sided tape. **B:** Proposed mechanisms for in vitro manipulation of DNA molecules on engineered surfaces using kinesin motor proteins and microtubules. Bifunctional DNA (one end thiolated and the other end biotinylated) is attached with one end to the gold patterns (by means of covalent interaction between a gold surface and the thiolized end of the DNA molecule) and with the other end to a gliding biotinylated streptavidin-coated microtubule (by means of the biotin–streptavidin interaction). Microtubule moves along the surface and stretches the DNA coil into a wire-like conformation. In this example, the motors determine whether the connection is made to the left or to the right. **C:** YOYO-1–labeled DNA molecules are manipulated by gliding microtubules (not shown) in such a way that linear geometries are formed. The arrows point to two DNA molecules that were stretched by the microtubules.

the kinesin densities and/or number of microtubules bound to the surface and study the influence on the transport mechanism as well as any leading structure formation.

The challenges for the future studies are to design efficient tracks and to define suitable surfaces so that molecular motors could function. A big step forward will be to mimic the ability of the cell to move objects in an engineered three-dimensional space. This accomplishment could lead to the setup of combined nanometer scale assemblers and sorting or sensing systems that can explore the tridimensional space in a stepwise manner.

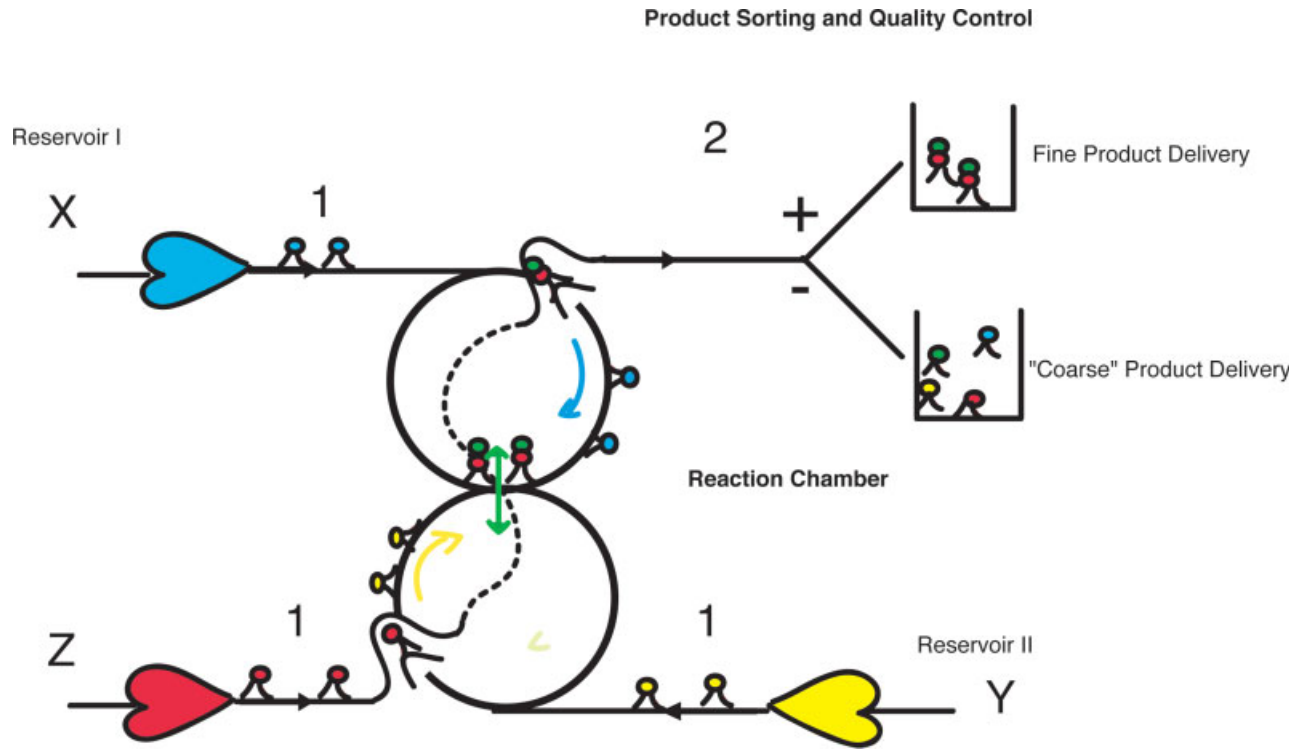

Fig. 4. An engineered factory applicable for nanotechnological applications. Model for how combinatorial interactions could allow the formation of molecular assemblies in a three-dimensional manner. X, Y, Z are reservoirs for different kinesin-associated assemblies. Kinesin carries assemblies loaded with different molecular species (red, yellow, blue) along microtubule tracks. A molecular reaction takes place in the reaction chamber where the blue and yellow assemblies collide. The red assemblies pick up the products and sort them according to some quality-control specification.

OUTLOOK

We envision nanomachines that can be moved along predefined tracks on surfaces. For instance, one could design a specific task to a microtubule, task to be performed over and over again as microtubule after microtubule rolls slowly over kinesin-coated surfaces. With the workers staying in one place (the kinesin molecules), adding parts to the evolving vehicle (the microtubule track) as it moves past on the conveyor belt (a particular surface, e.g., defined patterns of kinesins) an assembly line could be achieved. Within the framework, feasibility and robustness as well as a rapid delivery/transport to a particular "station" will be ensured. One particular example might be microtubules transporting different oligonucleotides toward a molecular "chip reservoir" for analysis, where the sequence of the oligonucleotide dictates which reaction it will be involved in.

A polymer-based assembly of large three-dimensional aggregates could be formed moving the motors along predefined microtubule-coated surfaces. The motors could traverse different reservoirs and pick up different cargos. Based on consecutive site recognition assembly, the cargos would form large polymeric structures. The "coarse" product could be eliminated through a product sorting and quality control stage, as in Figure 4. A description of such an assembly would transfer the biological principles of a cell, like a factory to the engineering environment extending and designing new tasks for the molecular entities, tasks that could be performed over and over again under user control. In this case, the ability to build up such systems is limited by our own skills to design and simulate the capabilities of the biological world.

CONCLUSION

Understanding and mimicking the cellular and molecular mechanisms of biological motors in vitro would permit a revolution in molecular manufacturing. There is still a need for multidisciplinary approaches that will lead to biomolecular motor integration into engineered environments while preserving their functions and properties. The payoff would come with the possibility of snapping together these fundamental blocks of nature in an easy, inexpensive and fascinating way to pursue molecular aggregates that would serve as scaffolding structures for objects of nanometer dimensions.

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