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# Evolution of a Dynamic Cytoskeleton

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# Evolution of a dynamic cytoskeleton

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## SUMMARY

Actin filaments and microtubules form the cytoskeleton of all eukaryotic cells, and they are responsible for organizing the cytoplasm and supporting motile processes. Both polymers are highly dynamic, and their polymerization dynamics are central to their organization. Though their evolutionary origins appear to be distinct, actin and tubulin have a similar mechanism for promoting polymerization dynamics in which the energy of nucleotide triphosphate hydrolysis during polymerization is used to weaken the bonds between subunits, thus promoting subsequent depolymerization. The evolutionary origins of actin and tubulin are unclear. It is likely that motile mechanisms driven by reversible polymerization, termed thermal ratchets, are older than those based on ATPase motor proteins. Such mechanisms are still important in modern eukaryotes, and may have powered early versions of the critical motile processes of phagocytosis and chromosome segregation in primitive cells. Thus evolution of dynamic cytoskeletal polymers may have been one of the earliest and most important steps leading to the evolution of eukaryotes. Plausible evolutionary pathways can be constructed leading from simple enzymes to dynamic cytoskeletal polymers.

## 1. INTRODUCTION

The cytoskeleton of modern eukaryotic cells is based on actin filaments and microtubules: polymers of the proteins actin and tubulin. These are among the most highly conserved of all eukaryotic proteins in sequence, and the mechanisms of motility and cytoplasmic organization they mediate are thought to be similarly conserved. In keeping with its modern role as a conserved hallmark of eukaryotes, cytoskeletal polymers are thought to have played central roles in the early evolution of the eukaryotic cell (reviewed by Doolittle in this volume). Development of a cytoskeleton may have freed primitive eukaryotes from their dependence on a cell wall for protection against physical and osmotic stress. Loss of the cell wall and development of the capacity for phagocytosis in turn set the stage for acquisition of endosymbiotic organelles. Equally as important, the development of mitosis set the stage for splitting the genome into multiple chromosomes and expanding its size and complexity. To understand how these critical early processes arose, we need to consider the origin of actin and tubulin, and the likely properties of their ancestors in primitive cells.

Once the early, primitive eukaryotes arose, they are thought to have radiated relatively rapidly towards more complex cell types. This included developing specialized feeding and locomotory methods and the capacity for multiple cells to function together in the ancestors of metazoans. Multicellularity then set the stage for specialization of cell function, and development of complex body plans. We need to understand how the cytoskeletal polymers contributed to this eukaryotic radiation. The conservation of actin and tubulin dependent processes among modern cell types demonstrates the adaptability of the modern cytoskeleton. This adaptability was probably important in allowing rapid evolution of eukaryotes towards greater complexity.

In this article I review the properties of modern actin and tubulin that are important in considering their evolution, focusing on dynamic behaviour. I then discuss scenarios for the evolutionary origins of actin and tubulin, and their subsequent role in eukaryotic evolution.

## 2. CONVERGENT EVOLUTION OF DYNAMICS

Actin filaments and microtubules must solve two, apparently contradictory, problems. At any instant they must be physically strong; to support the tension and compression associated with cell movement, shape maintenance and positioning of internal organelles. At the same time they must be dynamic; and able to reposition themselves rapidly in response to changes in the environment or internal cues. Examples of rapid (time scale of minutes) repositioning include the generation and resorbtion of an actin-based phagocytic cup during feeding of an amoeba, and the rapid breakdown of interphase microtubules followed by assembly of the mitotic spindle during the cell cycle.

Strength is an inherent feature of multi-stranded protein polymers. Several protein–protein interactions per monomer, repeated along the polymer lattice, and worth only a few kilocalories each, build a structure easily capable of supporting the piconewton per polymer forces associated with motility phenomena. Actual strength, and response to compression versus

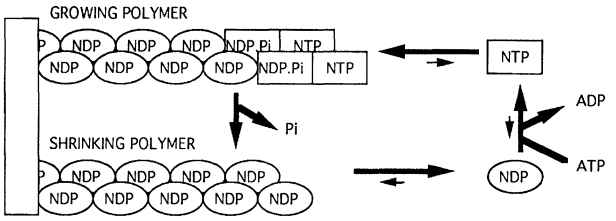


Figure 1. Nucleotide triphosphate (NTP) hydrolysis drives polymerization dynamics of actin and tubulin. The basic polymerization cycle is similar for actin (NTP = ATP) and tubulin (NTP = GTP). For both polymers NTP binds to monomer, and is hydrolyzed after polymerization. Hydrolysis and phosphate release cause a conformational change, weakening the polymer lattice and promoting depolymerization. For tubulin the difference in stability between the GTP and GDP lattices is very large, while for pure actin it is relatively small. Other proteins, perhaps from the cofilin–ADF family, may help destabilize the ADP polymer *in vivo*.

tension versus bending depends on the polymer architecture, but conceptually, in terms of strength, there is little difference between a microtubule and a virus coat or other polymeric structures.

Dynamics, in contrast, requires a special mechanism. A simple protein polymer will polymerize to thermodynamic equilibrium, that is until the monomer association and dissociation reactions are exactly balanced. Once at equilibrium the polymer is strongly constrained in its kinetic behaviour and the only form of subunit turnover is the thermally driven reversible association of subunits. This process can change polymer length slowly by a kind of random walk, but rapid relocation in the cytoplasm or performing work by polymerization cannot occur. Actin and tubulin have escaped these constraints by using a similar mechanism in which the polymer bonds are weakened by nucleotide hydrolysis (see figure 1). Coupling to nucleotide hydrolysis makes the polymerization cycle energy dissipating, allowing for rapid dynamics and force production.

Evolution of ATP hydrolysis by actin and GTP hydrolysis by tubulin appear to be a case of convergence on a common function. Because the sequence and three-dimensional structures of actin and tubulin are presumably quite different, they almost certainly arose from different ancestors. Actin is a distant cousin of the heat shock proteins and glycolytic enzymes: notably hexokinase which has a similar fold and binds ATP in a similar way (Flaherty *et al.* 1991). Without a three-dimensional structure it is more difficult to trace relatives of tubulin. It is related to the eubacterial FtsZ proteins (Erickson 1995), but perhaps not to the EFTu-G protein family of GTPases.

It should be noted that NTP hydrolysis during polymerization is not the only way of escaping equilibrium constraints and promoting polymerization dynamics. Intermediate filaments turn over fairly rapidly *in vivo*, and reversible phosphorylation is thought to promote such turnover, as it does for the related nuclear lamins (Eriksson *et al.* 1992). In this case a kinase–phosphatase system serves to transduce ATP hydrolysis energy into the filament system. MSP filaments in nematode sperm also have a rapid turnover and appear to do work, to drive motility as they do so (Roberts & Stewart 1995). It is not known at present how energy is transduced into this enigmatic polymer system.

## 3. ROLE OF NTP HYDROLYSIS

In the case of pure tubulin polymerization, a large fraction of the energy of GTP hydrolysis goes into destabilizing the microtubule lattice, promoting subsequent depolymerization (Caplow *et al.* 1994). Elongating microtubules are thought to be stabilized by a cap of subunits with a conformation different from the bulk microtubule, perhaps containing unhydrolyzed GTP. When this cap is lost, the microtubule rapidly depolymerizes which results in dynamic instability: a process in which individual microtubules alternate between growing and shrinking (Kirschner & Mitchison 1986). Dynamic instability of microtubule occurs *in vivo*, promoting microtubule turnover with a half-life in the range of a few minutes in interphase tissue culture cells, and much faster during mitosis. In the case of pure actin polymerization, ATP hydrolysis causes a much less spectacular change in polymer stability. Thus, relatively little of the ATP hydrolysis energy is captured to destabilize the lattice, and as a result pure actin filaments are relatively undynamic *in vitro* (Mitchison 1992). However, actin filaments in cytoplasm have a rapid turnover, presumably with the aid of actin binding proteins. For example, proteins of the actophorin–ADF–cofilin family may promote dynamics by selectively weakening the ADP-bound filament (Maciver & Weeds 1994). At an earlier stage of evolution actin presumably used the energy of ATP hydrolysis to destabilize the lattice without the help of accessory factors. The more complicated modern situation probably evolved to allow regulation of polymerization dynamics, for example, to promote selective polymerization at specific sites in the cell.

## 4. WORK FROM POLYMERIZATION DYNAMICS

Once NTP hydrolysis is coupled to polymerization dynamics, the cell can use cytoskeletal polymers to perform physical work. In principle both polymerization and depolymerization can be coupled to generation of force; the potential magnitude of which is governed by how far each reaction is from equilibrium. The simplest mechanism for coupling polymerization dynamics to force production is the thermal ratchet model (see figure 2). This mechanism is potentially capable of generating the forces and rates characteristic of many modern intracellular motile processes such as protrusion of the leading edge of motile cells driven by actin polymerization at the plasma membrane (Cramer *et al.* 1994), and polewards movement of chromosomes driven by microtubule depolymerization at kinetochores (Desai & Mitchison 1995).




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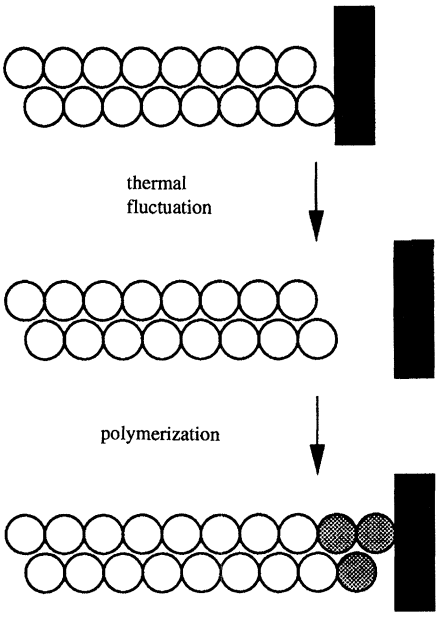


Figure 2. Motility driven by a thermal rachet. The simplest mechanism for transducing polymerization energy into force poduction is a thermal rachet. Small, thermally driven fluctuations in position of the object to be moved (solid bar) generates small gaps between it and the end of the polymer (open circles). This allows the polymer to add new subunits (hatched circles), preventing backwards movement. Polymerization effectively rectifies the brownian motion of the object. Thermally driven fluctuations in polymer length could also serve to open a transient gap between the polymer end and the object. In this kind of mechanism the rate of movement is governed by the rate of thermal fluctuations. The maximal force is related to the amount of free energy released by polymerization, and thus to how far the polymerization reaction is from equilibrium. A similar mechanism operating in reverse can couple depolymerization to movement, requiring in addition only a favourable interaction energy between the polymer and the object. For a more quantitative treatment see (Hill 1985; Peskin *et al.* 1993).

## 5. WHICH CAME FIRST, DYNAMICS OR MOTORS?

ATPase motor proteins (myosins, dyneins and kinesins) are now ubiquitously involved in the biology of the cytoskeleton. For modern motility events, such as protrusion and chromosome movement, it is difficult to sort out the relative importance of dynamics versus motor protein activity. Therefore, in discussing the evolution of such processes we need to think about which type of motility mechanism evolved first. It could be argued that ATPase-motors moving on non-dynamic polymers might have arisen early in evolution, with NTP hydrolysis by polymer and dynamics developing later. One argument in favour of such a scenario is the fact that it is much easier to evolve an equilibrium polymer than a dynamic one. However, for several reasons I favour the idea that dynamics preceded motors, and that the earliest forms of motility were driven by polymerization dynamics of the ancestors of modern actin and tubulin. First, the basic actin and tubulin folds are ancient. We can recognize diverged relatives of these proteins in modern prokaryotes (see Doolittle in this volume) which is so far not the case for ATPase motor proteins. Second, it would be difficult for evolution to retrofit hydrolysis-driven dynamics onto a polymer that formed from subunits that were not initially enzymes. Third, one can come up with plausible evolutionary scenarios by which dynamic polymers might have evolved directly from soluble proteins (see below). Fourth, thermal ratchets provide an inherently primitive force generating mechanism, with simple, and therefore easy to evolve, structural requirements. To deform a membrane, the polymer need only physically touch it; no stereospecific contacts are required outside the polymer lattice itself. Finally, it can be argued that polymerization dynamics play a more fundamental role than ATPase motors in some modern motile processes required for the viability of simple eukaryotic cells: protrusive motility, cytokinesis and mitosis. These processes probably arose early in eukaryotic evolution, and we can model their evolutionary development from initially motor-independent to modern motor-dependent mechanisms.

Protrusion of the cell margin, and the related process of phagocytosis, definitely require actin polymerization in modern cells (Cramer *et al.* 1994). Many authors have argued that these processes also require myosin activity, but this is far from clear. Myosin-I molecules localize to membranes undergoing protrusive activity, but mutants in myosins have not so far affected protrusion (Fath & Burgess 1994). Recent research using the myosin inhibitor butane dione monoxime supports the arguement against a myosin requirement in protrusive motility (L. Cramer, unpublished results). It is possible that myosin-I's function in translocating adhesion and sensory molecules out to the tip of the cell, without being required for physical protrusion. The argument is that myosins were added later to an exisiting polymerization-based motile mechanism (see figure 3*a*). Cytokinesis by the contractile ring mechanism requires myosin-II in modern cells. However, dicytostelium cells lacking myosin-II can use a more primitive process, 'traction-mediated cytofission', to achieve separation of daughter cell fragments (Wessels *et al.* 1988). Again, myosin was probably added later in evolution to an actin-based mechanism under the selective pressure for more efficient daughter cell separation (figure 3*b*). Mitosis is more difficult to dissect into motor-based and dynamics based mechanisms, but the mechanistic simplicity of depolymerization-driven chromosome movement supports the arguement for a primitive role.

## 6. EVOLUTION OF A DYNAMIC POLYMER

It is relatively easy to evolve a protein that will polymerize by self assembly, requiring only self-complementary surfaces with the correct geometry. In principle evolution could start with almost any protein fold, and create such surfaces. Evolving a protein that will not only polymerize, but will also rapidly depolymerize again under the same solution conditions seems much harder, but I will argue by example that it is not as difficult as one might suppose. In fact I




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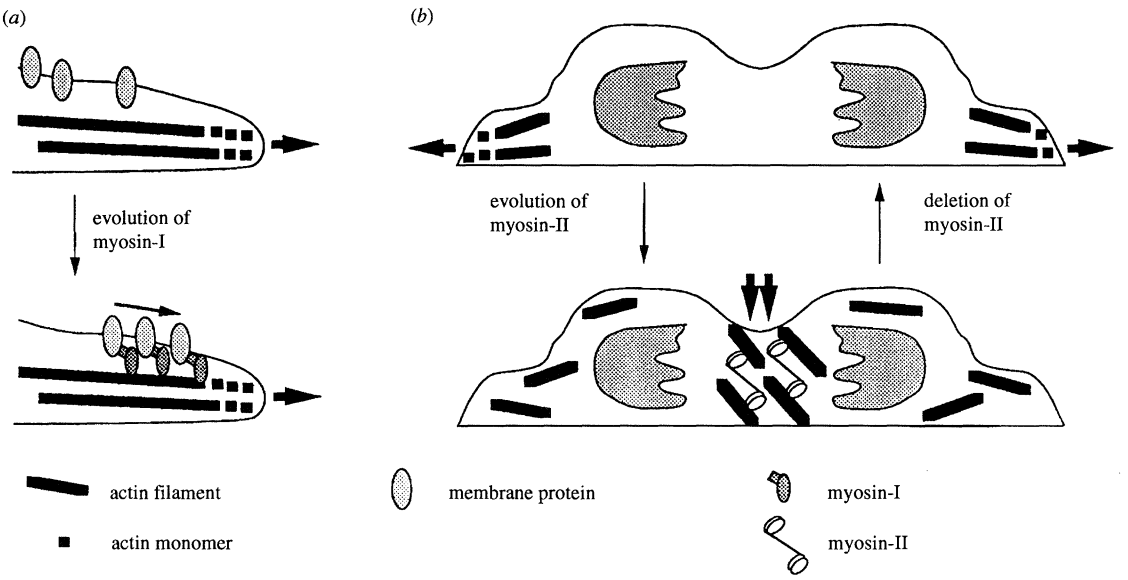


Figure 3. Addition of motors to polymerization-based motile systems. (*a*) Primitive protrusive motility may have been driven by actin polymerization in the absence of myosin activity, using a thermal ratchet mechanism. Membrane proteins, such as adhesion and sensory receptors, could only get to the leading edge by diffusion. Evolution of myosin-I (single headed myosin) allows the membrane proteins to be moved actively to the leading edge, with advantages for directed motility. (*b*) Cell division after mitosis in primitive cells may have occurred by 'traction mediated cytofission' in which the actin polymerization based motility system at leading edges serves to split daughter cells. Evolution of myosin-II (double headed, bipolar filament myosin) allows development of the more accurate and reliable system of modern cytokinesis using a contractile ring. The primitive system was re-recreated by mutation of the myosin-II gene (Wessels *et al.* 1988).

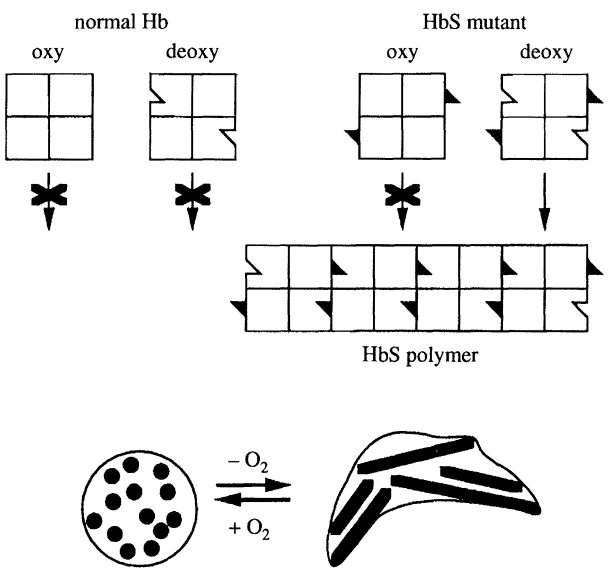


Figure 4. Sickle cell hemoglobin provides a model for the evolution of a dynamic polymer. The sickle-cell molecule (HbS) is generated from normal hemoglobin by a single point mutation, indicated by the solid triangles. Normal Hb and HbS can adopt two conformations, regulated by oxygen binding. In the deoxy- (but not the oxy-) form of HbS, the mutant amino acid generates an interface that leads to polymerization. The resulting polymers deform the shape of the red blood cell, and deformation is regulated by oxygen binding (lower panel).

suspect almost any protein that can exist in more than one conformation regulated by ligand binding could in principle mutate to form some kind of dynamic polymer.

Sickle-cell haemoglobin is produced by a single point mutant in human beta globin (Glu6 to Val). This mutation confers resistance to malaria in heterozygotes, but at the price of causing serious anaemia in homozygotes (reviewed in Stryer 1981). The oxy form of sickle cell hemoglobin is relatively normal, but the deoxy form tends to polymerize into long helical polymers (see figure 4). These polymers produce protrusions of the red cell membrane, causing the sickle shape and blocking of capillaries. Binding of oxygen changes the conformation of the protein and promotes depolymerization, reversing the sickle shape. In effect the sickle red cell has evolved a form of dynamic cytoskeleton, though not one that provides any advantage. A similar type of mutation in the ancestor of actin may have lead to evolution of a useful dynamic cytoskeleton.

## 7. EVOLUTION OF ACTIN AND TUBULIN

What were the primordial roles of actin and tubulin that led to the evolution of NTP hydrolysis-driven dynamics? As with many of the characteristic proteins of eukaryotes, the success of the modern molecules has competed out any traces of ancestral forms, leaving us free to speculate. I suspect that actin evolved to allow reversible protrusion of the cell margin and thus phagocytic feeding. It is easy to imagine an early enzyme that bound ATP as one of its substrates, changing conformation as it did so (see figure 5*a*). The identity of this ancestral enzyme is unclear. Modern hexokinase and modern HSC70 proteins share a common ancestor with actin, but it is not clear whether these or the cytoskeleton evolved first. The gene for this primordial enzyme then duplicated and one copy




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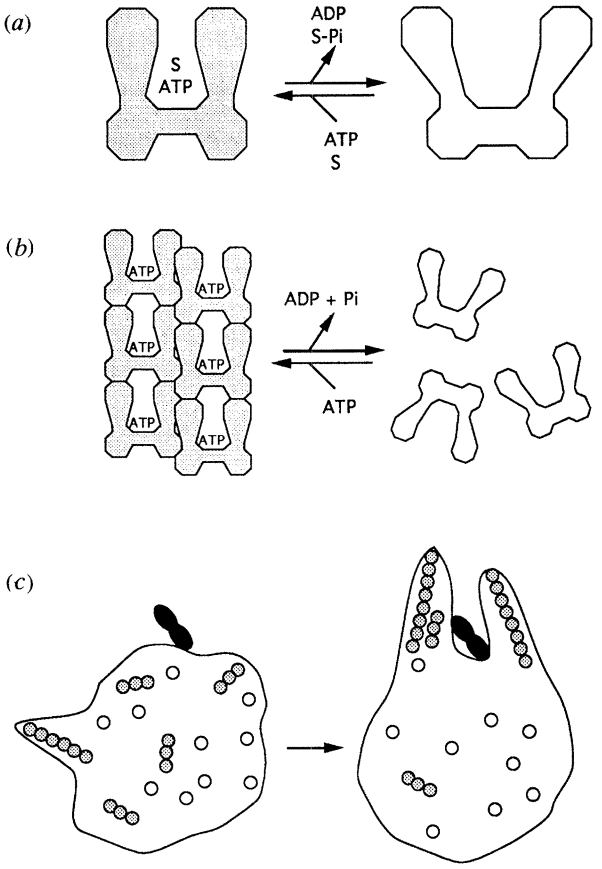


Figure 5. Evolution of actin. (*a*) Shows a primitive enzyme that phosphorylates a substrate. The enzyme exists in two conformations, regulated by ligand binding, much like modern hexokinase. (*b*) The enzyme in (*a*) mutates so that the ATP-bound conformation polymerizes while the apo-enzyme (or ADP-bound form) does not. Binding and phosphorylation of substrate has been lost. (*c*) Polymerization of the enyme in (*b*) leads to reversible deformation of the cell surface of a primitive eukaryote, using the simple thermal rachet mechanism. Polymerization can generate a primitive phagocytic cup, shown engulfing a prokaryote.

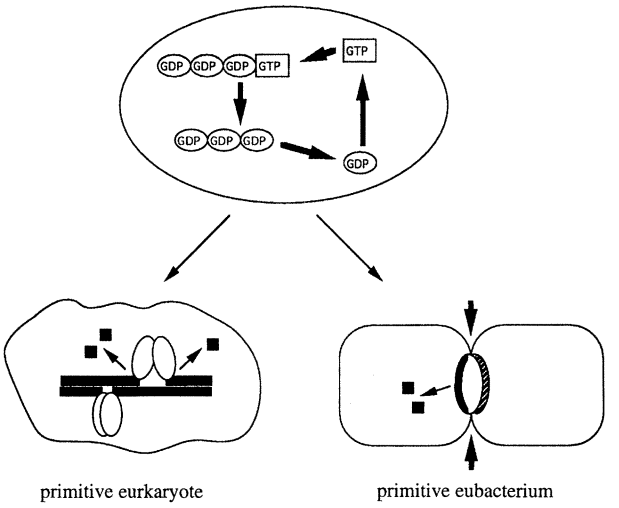


Figure 6. Evolution of tubulin and FtsZ. The basic hydrolysis-driven polymerization cycle of an ancestral tubulin-like model evolves in a primitve prokaryote (top). This gives rise to a dynamic polymer capable of depolymerizing when it is no longer needed. In the ancestor of modern eukaryotes (lower left), this dynamic polymer is adopted to drive chromosome segregation on a primitive spindle. Active depolymerization allows the spindle to disassemble after cell division is finished. Separation of sister chromosomes may have been powered by this depolymerization in a reverse thermal rachet mechanism. This spindle-forming polymer evolved into modern tubulin. In the ancestors of modern eubacteria (lower right) the ancestral polymer was utilized to drive efficient septation. The septation structure depolymerizes before the next cell cycle, and again depolymerization may have powered contraction. The septation-promoting polymer evolved into modern ftsZ.

mutated so that the ATP-bound conformation gained a tendency to polymerize (figure 5*b*). This produced a situation like the sickle red cell, except that cycles of polymerization and depolymerization were spontaneous and driven by ATP hydrolysis rather than regulated by an external variable. If there was enough of this reversibly polymerizing enzyme, it would produce transient deformation of the cell membrane. By combining protrusion with adhesion, phagocytosis becomes possible (figure 5*c*). Phagocytosis allowed the primitive eukaryote to feed efficiently, and also led to the acquisition of endosymbiotic organelles. It is not a large conceptual step from this hypothetical, reversibly polymerizing proto-actin ATPase to the modern actin cytoskeleton: actin binding proteins that fine tune the basic dynamic behaviour could evolve one by one, giving rise to the modern network of proteins and spatial control of polymerization.

For tubulin a probable primordial role was in cell division, more specifically in physically segregating the products of DNA replication. Segregation mechanisms become important once the genome is broken into multiple chromosomes (Nasmyth in this volume). Comparisons between mitotic mechanisms in modern higher eukaryotes and 'primitive' algae shows that the physical relation between microtubules and chromosomes has changed during the evolution of eukaryotes, but that a basic role for microtubules in separating sister chromatids is conserved (Heath 1980). Segregation in modern prokaryotes is less well understood, but eubacteria are now known to physically separate sister chromosomes rapidly at a specific point in the cell cycle (Hiraga 1993). Eubacteria contain a tubulin-like protein, FtsZ that can polymerize into microtubule-like structures, hydrolyzing GTP as it does so (Erickson 1995). The structure of the FtsZ polymers *in vivo*, and whether GTP hydrolysis destabilizes them is not yet known. Surprisingly FtsZ appears to function in septation (cell division), and not in chromosome segregation. The polymer is thought to assemble into a ring-like structure that contracts during septation. Another protein, FtsA, is also required for septation. This protein has an actin related sequence and may be a candidate for the ancestor of modern actin (Doolittle in this volume). The septation role of FtsZ in *Escherichia coli* seems very different from the chromosome segregation role of tubulin in animals, making it diffcult to discern the most likely primordial role of their common ancestor. The problem is further confused by the situation in modern plants and fungi, where microtubules (made of tubulin) appear to function in




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both segregation and sister cell separation. Analysis of primitive eukaryotes and archebacteria might shed light on the evolution of these diverse roles. There are intriguing reports of microtubule-like structures in various eu- and archebacteria in the literature, but definitive information is lacking (reviewed by Bermudes *et al.* 1994). Genome sequencing may help address these issues in the future.

Can we devise an evolutionary scenario reconciling the different roles of modern tubulin and FtsZ? Perhaps the underlying theme is rapid depolymerization. A common feature of structures required for cell division is that the cell needs to assemble them transiently during division and disassemble them rapidly afterwards. If proto-tubulin evolved such a transient polymerization capability through GTP hydrolysis and dynamics, different primitive cells might have used this property for different ends (see figure 6). In the ancestors of modern eukaryotes, the dynamic proto-tubulin polymers were used to construct transient spindles for segregation, while in eubacterial ancestors they were used to build a transient, contractile septation structure. In each case, disassembly of the structure during cell cycle progression may have been coupled to useful motility; respectively segregation and contraction.

## 8. EVOLUTION OF COMPLEXITY

Once the dynamic actin and microtubule cytoskeletons had evolved to fill their primordial role they probably played an important role in eukaryotic radiation and the evolution of complexity. The modern cytoskeleton, with its diverse array of motors and polymerization-regulators is incredibly adaptable in function. Any change in developmental processes in modern metazoans – selection for a cell type with a new morphology, a more rapidly moving cell, etc. – will be supported by a cytoskeleton that is effectively preadapted to function in the new cell. Polymerization dynamics also allows for a specific, highly adaptable mechanism by which specialized cell morphologies can be generated, namely stabilization of organized spatial arrays from a dynamic population of polymers (discussed for microtubules by Kirschner in this volume, similar mechanisms likely hold for actin).

The primitive cytoskeleton, lacking motors and regulators, would have been less adaptable to new functions. This put a tremendous premium on evolving new proteins that could modify basic cytoskeletal processes and generate new forms of motility and organization. Such molecules could initially improve existing processes while setting the stage for development of new processes, or vice versa. For example the first microtubule motor-proteins might have arisen as a result of the pressure to increase the fidelity of chromosome segregation during mitosis, but their development also set the stage for evolution of cilia and active vesicle transport. Alternatively the interphase roles might have been selected for first, and the mitotic role evolved later. Presumably it was the combination of both types of selective pressure that led to rapid evolution and diversification of the ATPase motor proteins, as well as the numerous proteins that modulate polymerization dynamics. Increasing complexity of the cytoskeleton was probably a major factor in allowing radiation of the early eukaryotes in both metazoan and protist directions. Studying the diversification of molecules, such as motor proteins and actin binding proteins, will probably throw light on this stage of evolution. Actin and tubulin themselves changed much less during eukaryotic radiation, partly because they needed to contact other newly evolving proteins, but also because their dynamic behaviour made them highly adaptable to new functions from the outset.

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