

# Cytoskeleton

## Editorial overview

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#### Addresses

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**Current Opinion in Cell Biology** 1997, **9**:1–3

Electronic identifier: 0955-0674-009-00001

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One of the most exciting recent developments in the field of cytoskeletal research has been the elucidation of the molecular basis of a wide variety of dynamic cellular processes that are driven by the different networks of cytoskeletal fibers. A picture is now emerging in which the cytoskeleton both plays a dynamic/structural role in cells, affecting their shape and motility, and is intimately involved in the transduction and integration of transmembrane signals. In this issue of *Current Opinion in Cell Biology*, we have tried to cover a few selected areas that progressed rapidly in the past year or so and raise a broad interest.

How do motors read microtubule polarity? Amos and Hirose (pp 4–11) describe the three-dimensional reconstruction of microtubule–motor complexes. These high-resolution images reveal the mode of attachment of the motor domains to microtubules, as well as the structures of monomeric and dimeric motor proteins of both plus-end- and minus-end-directed types. It appears that dimeric motors move by rotating one head after the other from one site to the next on the microtubule surface lattice. So, some motors may rotate clockwise and move in one direction while others may rotate counterclockwise and move in the opposite direction.

Microtubule assembly is discussed by Wade and Hyman (pp 12–17). They describe studies that demonstrate that dynamic instability involves a conformational change of the tubulin subunit that is coupled to GTP hydrolysis. This process appears to be associated with the closure of the tubulin sheet at the tip of the growing microtubule. How microtubule polarity relates to orientation of tubulin heterodimers in the microtubule wall has been a longstanding question. After some confusion matters are clearing up, and finally it seems that the  $\beta$ -tubulin subunit is at the plus end (see Amos and Hirose, pp 4–11).

The numbers of motors are literally mushrooming and it will be urgent to sort out their functions. As reported by Goodson, Valetti and Kreis (pp 18–28), microtubules and their associated motors are involved in the positioning

of organelles and the polarized transport of vesicles. Dynein, for example, seems to play an important role in the organization of the Golgi apparatus. Important questions in this field include how specific motors interact with specific membrane compartments and how microtubule- and microfilament-based translocation is regulated and coordinated. For myosins, too, it will be intriguing to find their partner organelles.

It is also becoming clear now that microtubule motors can do more than just move different cargos along microtubules. They can also organize microtubules into arrays, as discussed by Baas (pp 29–36) for neuronal microtubules and by Waters and Salmon (pp 37–43) for the organization of the bipolar spindle during mitosis. Until recently, it was thought that the orientation of microtubules in the cell was determined mostly by the localization of nucleating centers like the centrosomes. However, the recent finding that motors can also organize microtubules suggest that there are at least two mechanisms to whereby microtubules in cells can be organized. This may be relevant not only to interphase cells but also to the different pathways of mitotic spindle assembly.

Were all myosins created equal? Apparently not. Brown (pp 44–48) reports on the entire repertoire of myosins in *Saccharomyces cerevisiae* and on their distinct functional properties. Upon completion of the *Saccharomyces* genome project it became clear that this organism has a total of just five myosins, which belong to just three classes of myosin (classes I, II and V). The minimyosins of class I are apparently involved in endocytosis; class II myosins take part in cell separation during mitosis; and class V myosins are involved in the transport of various cargos and fate determinants.

The interaction of intermediate filaments with the membrane and with other cytoskeletal networks is covered by Chou, Skalli and Goldman (pp 49–53). The longterm debate on the elusive cellular roles of the various types of intermediate filament is now entering a new phase, with increasing information available on the effects of mutations in, or deletions of, genes encoding intermediate filaments and their associated proteins. These associated proteins apparently link intermediate filaments to specific cytoplasmic sites such as desmosomes and hemidesmosomes, or to other cytoskeletal systems.

Actin dynamics *in vivo* are the subject of two reviews in this issue. Welch *et al.* (pp 54–61) focus on one of the most dynamic regions of living cells, namely the leading edge, and address the question of the mechanism underlying the

actin polymerization driven membrane protrusion. They discuss the involvement of nucleation versus filament uncapping in actin polymerization at the tip of the leading edge, and the role of the depolymerization of filaments at the base of the leading edge. The rather rapid retrograde flow of actin observed in this region (compared with the rate of treadmilling of purified actin) suggests that actin dynamics in the leading edge are controlled by additional molecules which promote polymerization at the barbed end of the filaments and depolymerization at the pointed end. Welch *et al.* conclude by presenting some promising model systems for the study of leading-edge dynamics, such as yeast and various pathogenic microorganisms.

The incredible capacity of a variety of pathogens to exploit the actin cytoskeleton for their own advantage is addressed by Higley and Way (pp 62–69). They show how different proteins that are normally involved in the local nucleation of microfilament assembly can be recruited by viruses and bacteria and function in the propulsion of the infectious agent throughout the cytoplasm and from one cell to the next. This field is attracting a very wide interest and has major implications for diverse topics, such as the basic mechanisms of actin-driven motility, the spread of bacterial infections and the complex interrelationships between the cellular host and pathogenic parasite.

The broad field of signal transduction research is currently going through an important phase in which the various cascades and networks of signaling events are being considered in a structural and cellular context. The cytoskeleton appears to be a central actor on this stage; it appears that signaling enzymes, substrates and adapter proteins can interact with, be activated by and modify different cytoskeletal filaments. One such system is the multigene family of actin-associated proteins known as the E(zrin) R(adixin) M(oesin) family. In their review, Tsukita, Yonemura and Tsukita (pp 70–75) describe the role of these proteins in the formation of the cell cortex, thus affecting membrane–microfilament interaction, cell morphogenesis and adhesion. Apparently, ERM proteins may be targets of the small G protein Rho and may regulate actin assembly and interaction with the membrane.

Signaling from adhesion complexes is addressed by Yamada and Geiger (pp 76–85). How do cells ‘sense’ the external surface to which they are attached, how are these ‘adhesion signals’ transduced, and how do they regulate cell activity? The emerging principle is that newly formed integrin- or cadherin-mediated adhesions recruit a variety of enzymes and consequently activate specific signaling pathways. In these submembrane multimolecular complexes, the specific interaction sites (for example, Src homology 2 and 3 domains) have been identified and the traditional distinction between ‘structural’ and ‘signaling’ proteins is blurred. The cytoskeleton at adhesion sites

appears to function as a signal transducer, coordinator and integrator and thus affect cell organization, growth and survival.

An especially intriguing cross-talk between small G proteins and the microfilament system is highlighted by Tapon and Hall (pp 86–92). They describe some recent studies which point to possible mechanisms that underlie the effects of Rho, Rac and Cdc42 on the cytoskeleton. GTP-bound Rho apparently activates Rho kinase, which phosphorylates (and inactivates) myosin light chain phosphatase, and, hence, induces contraction. Rac and Cdc42, on the other hand, control the synthesis of phosphatidylinositol 4,5-bisphosphate, which in turn can affect focal contact formation and actin reorganization.

The thought that cell adhesion and shape should feed back into cell growth and division in some way has been around for years. Until recently, however, the mechanism whereby cell adhesion affects cell growth remained obscure. Assoian and Zhu (pp 93–98) describe some new insights into this topic. The critical period during the cell cycle for growth factor action and extracellular matrix signaling appears to be G<sub>1</sub> phase, and the key players are G<sub>1</sub>-phase cyclins, their dependent kinases, and the retinoblastoma and related proteins. Recent evidence indicates that microfilament integrity is required for the expression of cyclin D and progression through the ‘restriction point’. This raises some exciting questions about the nature of the specific signals triggered by anchorage and the involvement of tension and mechanical forces in phosphorylation cascades.

Another level of complexity is presented by Ben-Ze’ev (pp 99–108) who addresses the involvement of cell adhesion in tumorigenesis. Recent studies have added new dimensions to the old notion that high tumorigenicity or metastatic potential is associated with a less adhesive and more motile phenotype. These include lessons from *Drosophila*, *Xenopus* and mammalian cells that indicate that junctional plaque proteins such as  $\beta$ -catenin can complex with a transcription factor (lymphoid enhancer factor-1) or a tumor suppressor (adenomatous polyposis coli), then translocate to the nucleus and thus affect (directly or indirectly) gene expression.

What are the mechanisms, cytoskeletal involvement and functional significance of RNA compartmentalization in cells? Bassell and Singer (pp 109–115) discuss the formation of RNA granules and their transport along microtubules (at least when long-distance travel occurs). On the other hand, microfilaments, and in particular intersections between actin filaments, appear to provide the major anchoring sites for RNA and the translational machinery. The specificity of RNA–cytoskeleton

interactions is now taking an interesting turn, with the identification of localization sequences in addition to specific proteins that mediate such interactions. Does the compartmentalization of RNA play an important role in the targeting of the protein it encodes, and can its translation be locally regulated? These are among the questions yet to be explored.

All in all, the new insights into the biology of the cytoskeleton cover a very broad spectrum of topics, ranging from the high-resolution structures of individual proteins and their binding domains to a more comprehensive understanding of the concerted involvement of the various filament networks in the coordination of cell structure, dynamics and, eventually, fate.