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EDITORIAL

Biophysical studies of the cytoskeleton

Abstract This Special Issue of the European Biophysics Journal contains articles dealing with topics associated with a variety of biophysical studies of the cytoskeleton. These original peer-reviewed contributions derive from authors who were invited contributors to a meeting on "Molecular Biophysics of the Cytoskeleton" organised in August 1997 in Banff, Alberta, by Jack Tuszynski of the University of Alberta, Edmonton. Dr Tuszynski and I have been joint editors for this issue. The organisation of the papers runs from structural studies of individual proteins, their interactions and assembly properties; motor proteins, kinesin and dynein, and general properties of mechanochemical motility; physical and mechanical properties of cytoskeletal polymers, including flexibility and elasticity of microtubules, and diffusion within microtubules; modelling of actin networks, deformation and cellular locomotion.

Biophysical studies of the cytoskeleton have of course been conducted over a long period of time, addressing problems at a variety of levels of structural resolution. At the molecular level, much is already known in terms of the physical and structural properties of individual identified major subcellular components, which are generally proteins. These comprise the well-known set of tubulin, actin, intermediate filament proteins, together with a vast, and increasing array of "associated proteins", namely MAPs, the microtubule associated proteins, the actin binding proteins, and many proteins associated with, and comprising, the diverse intermediate filament family. These studies have also examined the self-interactions of the major proteins, namely the assembly properties of microtubules, polymeric fibrous F-actin, and intermediate filaments. The potentially multifarious interactions between them and their associated proteins, which can result in permanent, semi-permanent or transient cross-linking structures, and leading to complex and dynamic cytoskeletal networks have attracted sophisticated theoretical and elegant experimental approaches.

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It is clear that the increased level of information available from high resolution X-ray and NMR structures of individual proteins can stimulate the design of even more definitive experiments on individual cytoskeletal proteins and their interactions. In this issue is reported the high resolution structure of tubulin, a study which has been in progress for many years, and which now counts as another major success of the relatively recent method of electron crystallography of two-dimensional molecular arrays. It has also been aided by the availability of individual isotypes of tubulin, thus removing a degree of structural diversity which has previously limited structural studies. It is a testimony to the skill and commitment of these workers that we now have a molecular model of the tubulin alpha-beta heterodimer, in the form of a linear protofilament structure, as seen in the (Zn^{2+}-induced) two-dimensional sheets of tubulin. The sheet structure contains antiparallel protofilaments, but this should in due course provide the basis for the modelling of the natural microtubule lattices containing parallel protofilaments. The detail of the dimer structure is such that it immediately invites questions about the interactions of tubulin with drugs, often cytostatic agents which find applications in cancer chemotherapy, as well as those such as members of the colchicine group, which have an established role in the modulation of the assembly properties of microtubules extensively studied in cells and in vitro. Does the knowledge of the three-dimensional structure of tubulin signal the beginning of the end of the mysteries for the microtubule? It would be a rash judgement to believe so. The structure emphasises quite remarkably the strong polarity of the tubulin dimer, which translates into the functional structural and kinetic polarity (plus end, minus end) of the assembled microtubule. The behaviour of the microtubule is however determined by a combination of physical properties, (symmetry, lateral interactions, protofilament number, curvature etc) which

help to define the possible structural properties (flexural rigidity), and dynamic properties (dynamic instability of growth and shortening) which convey a number of the biological roles of the microtubule.

In recent years there has been immense interest in the properties of the cytoskeletal motor proteins, that is those proteins which use microtubules as the route along which they convey vesicles, often in a fully defined directional sense (plus-end or minus-end directed motion) using the energy of ATP hydrolysis in the mechanochemical process. Knowledge of the structure of such molecules is likely to stimulate provision of molecular models for the central problem of ATP driven force generation in muscle, and the principles may also relate to membrane-associated ATP-dependent ion pumps. Two prominent members of this class of cytoskeletal motors are kinesin and cytoplasmic dynein: the structure of the kinesin monomer domain is now known at atomic resolution by X-ray studies, and the evidence for the role of the kinesin dimer is becoming understood. A critical feature of the microtubule-associated motor proteins lies in the nature and details of the interactions with the microtubules themselves. By their very nature these must be transient and mobile: nonetheless, important progress is being made in studying the way in which kinesin heads interact with the microtubule lattice, which will be further stimulated by the new information on tubulin protofilament structure. By contrast, studies of cytoplasmic dynein, a much more complex multiprotein structure, are at an earlier stage, but the combination of genetic manipulation to generate specific portions of the molecule and the associated electron microscopy is unravelling fundamental structural details at the level of molecular resolution.

While there is a natural emphasis in this issue on the properties of tubulin and microtubules, the properties of actin and microfilaments are also well represented. A major question of interest, from the mathematical and modelling point of view, is the degree of mobility and flexibility which exists in cytoskeletal networks. Such networks exist as relatively permanent structures in some non-dividing cells, where their ability to adopt different macroscopic configurations is of prime biological importance. In addition cross-linked networks, although certainly present, can have only a relatively transient existence in dividing cells. As with microtubules, a fundamental feature of cytoskeletal fibrous polymers is the need for sufficient stability to carry out their structural and directional role, but possession of a high degree of adaptability to allow remodelling or disassembly to suit the changing demands of the state of the cell. In this context biophysical investigations have a special and important role: they offer the means to relate physical and mechanical properties to the more macroscopic state where the concepts of material science become valid, but they can also define the limits of a purely physical treatment to explain what are ultimately biological properties. At some level, biochemical regulatory processes must come into play, using enzymatic modifications, for example, phosphorylation and dephosphorylation by kinases and phosphatase, acetylation, peptidase and transpeptidase reactions modifying the primary sequences, glycation and addition of hydrophobic tails to control often specific targetting and hence redistribution of specific molecules. But this biochemical scenario takes place at the molecular level with individual proteins and molecular assemblies which are required to exhibit their polymer properties for normal cytoskeletal function. The scope for regulatory processes, both enzymatic and physical are boundless, and, a most encouraging prospect, methods are now appearing to deal with this characteristically high level of molecular complexity.

Recent developments have in fact opened up surprisingly extensive vistas for biophysical research, based on a synergism of technical advances. At the molecular biological level, protein engineering techniques offer the possibility of the molecular design of molecules available in amounts sufficient for well-defined physical studies. These molecules may often lack the subtle enzymatic post-translational modifications of eukaryotic expression, but their strict sequence definition makes them ideal for detailed crystallographic and nmr studies. They can also help to define more precisely the experimental observations on which modelling of structure and dynamics are based. Such simulations are generally based on assumptions of molecular homogeneity. Even more powerful, the ability experimentally to manipulate structures by protein engineering allows the precise definition of parts of often large and complex molecules, deletions of putative important sequences, or substitution of suspected definitive individual residues is now possible, and becoming routing. Coupled to these developments, the possibilities of physical techniques for physical manipulation of single molecules and force measurements by atomic force microscopy and optical tweezer methods, offer the capability of relating mechanochemical processes to specific parts of the three-dimensional structure of motor proteins. The techniques of microfabrication and nanotechnology are rightly seen as being on the point of a revolutionary development.

The articles in this Special Issue relate to many of these topics. It is hoped that they will convey at least a part of the exciting new developments in this active field of biophysical research, and point the way to new areas of experiment and theory. I should like to thank my guest Editor, Jack Tuszynski, for his foresight in arranging the stimulating multidisciplinary meeting which has acted as the origin of this publication. This followed an equally stimulating meeting in April 1996 in Houston, organised by Wah Chiu, Dimitri Nanopoulos and Bill Brinkley, papers from which appeared in the Journal of Structural Biology 118:83–168 (1997). I should also like to thank the present contributors for their enthusiastic participation in this venture.

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Managing Editor