KOSMOS
PROBLEMY NAUK BIOLOGICZNYCH
Tom 50, 2001
Numer 4 (253)
Strony 337–338
Polskie Towarzystwo Przyrodników im. Kopernika

# MOLECULAR MOTORS

One of the features distinguishing living organisms from their inanimate surroundings is their ability to execute vectorial processes, such as directed movements and the assembly of macromolecules or organelle systems. The vast majority of directional movements are powered by molecular motors that convert the chemical energy of hydrolysis of the β-γ phosphate bond in nucleoside triphosphates, ATP or GTP, into mechanical energy. The most extensively studied have been cytoskeletal protein motors: myosin, kinesin and dynein, all using ATP as the energy source and cooperating with fibrous polymers in the generation of force. Actin filaments are the partners to myosin, and microtubules to kinesin and dynein. These polymers stimulate the ATPase activity of their motor proteins and serve the function of tracks along which the motors move.

Myosin, initially known as the major structural protein of muscle, was the first protein recognized as a molecular motor. In 1939, V. A. Engelhardt and M. N. Lyubimova reported on its ATPase activity. Three years later, Albert Szent Győrgyi and his students became aware of the importance of actin-myosin interaction for muscle contraction, but contraction was still thought of as a large-scale folding of long protein chains. Only ten years later J. Hanson and H. E. Huxley documented that in sarcomers (structural units of the striated muscle fiber) myosin and actin are organized in two sets of partially interdigitating filaments, and in 1954 H. E. Huxley and J. Hanson and, independently, A. F. Huxley and R. Niedergerke proposed that shortening of the muscle fiber takes place by relative sliding movement of these two sets of filaments. A. F. Huxley suggested that contributions to force are provided by "independent force generators" uniformely spaced along each zone where myosin and actin filaments overlap. These force generators were later identified by H. E. Huxley as the active parts of the myosin molecule (myosin heads) projecting out of the shaft of the myosin filament. By the end of 1960s the researchers in the field were beginning to think in terms of a molecular motor that couples ATP hydrolysis to changes in conformation. This assumption has been confirmed by kinetic studies showing that the hydrolysis of ATP by myosin and by actomyosin are multistep processes, and that the liberation of the energy of the terminal phosphate bond in ATP (hydrolysis itself) and its conversion into work are separated in time. A milestone towards identification of a conformation change coupled to conversion of chemical to mechanical energy was the solution, during the past decade, of crystal structures of the myosin head "frozen" in different intermediate stages of ATP hydrolysis. It appears that the enzymatic transitions elicit small changes in protein structure surrounding the nucleotide site, and these changes are amplified into larger interdomain motions, that may be responsible for producing force, by a rotation of a small structural element. This idea has become a paradigm for studies on other motor proteins. An alternative view is that the intermediate of the chemical cycle storing the energy of ATP/GTP hydrolysis has no unique conformation but represents an equilibrium between several conformations, and the energy conversion occurs when it is trapped — by the strong binding to the polymer protein — in the conformation most suitable for the generation of force. These views and the supporting experimental evidence with regard to the myosin function in muscle contraction are presented in the article by BARBARA PLISZKA in this issue of KOSMOS. The articles by ZENON GRABAREK and by RENATA DĄBROWSKA and ROBERT MAKUCH present the current views on the mechanisms of the regulation of contraction of the striated and smooth muscles, respectively. ANNA MOCZARSKA describes the effects of mutations in the genes encoding cardiac myosin isoforms that may be linked to the development of familial hypertrophic cardiomyopathy.

The two-headed muscle type myosin (myosin II) is referred to as conventional myosin because it was the only type of myosin known for long. Only in the 1960s various laboratories begun to search for nonmuscle myosin and

actin. In 1966 S. Hatano and F. Oosawa obtained the first convincing evidence for a nonmuscle actin, and in 1973 T. D. Pollard and E. D. Korn reported on the discovery, in *Acanthamoeba*, of an unconventional, single-headed myosin. Today, in addition to the conventional myosin isoforms that are able to form bipolar filaments and are present in both muscle and nonmuscle cells, 17 classes of structurally and functionally distinct unconventional myosins are distinguished in the myosin phylogenetic tree. MARIA J. RĘDOWICZ describes the specific structural features and possible roles of these diverse myosins in many forms of eukaryotic motility such as cell crawling, cytokinesis, phagocytosis, maintenance and changes of cell shape, and organelle/particle trafficking.

Among the microtubule-based motors, the earliest discovered (by I. R. Gibbons and A. J. Rowe, 1965) was dynein from cilia. The coordinated action of ciliary and flagellar dyneins, which constitute the inner and outer arms of the microtubular axoneme in eukaryotic cilia and flagella, generates sliding forces between the outer doublet microtubules. This sliding is converted by other structures of the axoneme into bending waves resulting in the beating of cilia and undulation of flagella. In contrast, cytoplasmic dynein is involved in a variety of intracellular motile processes including the trafficking of membraneous vesicles and other intracellular particles, the assembly and orientation of mitotic spindles, the perinuclear positioning of the Golgi apparatus and lysosomes, and the transport of microtubules. All dyneins move toward the minus ends of microtubules — the ends proximal to the basal body, whereas most of the kinesin motors studied so far transport cargo toward the plus ends of microtubules — those distal to the basal body of the cell. Since the discovery of the first conventional (two-headed) kinesin by R. D. Vale and his colleagues in 1985, more than 50 kinesin-related proteins have been identified. To date, crystal structures of seven kinesins have been reported. Although they all are in the same stage of ATP hydrolysis (with bound ADP), models explaining the processive movement of kinesin along the microtubule have already been proposed. Current views on this subject are presented by ANDRZEJ KASPRZAK in this issue of KOSMOS.

The recent solving of the solution structure (by multi-dimensional NMR, ang. nuclear magnetic resonance) of the LC8 protein, the component of the outer arm of the axonemal dynein and of brain cytoplasmic dynein, and solution of the X-ray crystal structure of the LC8 dimer are steps toward understanding the structural basis for the dynein functions.

Actin and tubulin themselves belong to a class of molecular motors that convert Gibbs free energy of hydrolysis of their bound nucleotide (ATP in actin and GTP in tubulin) into length changes of their polymers. Microtubules generate a pushing force when they assemble, and a pulling force when they disassemble. These forces are thought to contribute to partitioning of chromosomes during mitosis and to positioning of centrosomes and other organelles that are involved in the establishment of cell polarity and differentiation. Cellular motions driven by polymerization/depolymerization of actin and the molecular mechanism of their generation are described in the article by HANNA STRZELECKA-GOŁASZEWSKA.

Another class of molecular motors is constituted by rotary motors, such as $F_1$ATPase and bacterial flagellar motors. The latter ones are the only known protein motors for which the source of energy is not ATP/GTP hydrolysis but the electromotive gradient of protons or sodium ions across the cell membrane. The structure and function of these motors are described by KRZYSZTOF SKOWRONEK.

Many other proteins, some of them known for long, have recently been considered as molecular motors. Their common features shared with the other motors are sliding along polymers and a conformational-change mechanism in (or in the vicinity of) the active site of their nucleotidase activity (a conformational switch). One class, nucleic acid motors, includes DNA and RNA polymerases and helicases. To yet another class (of ring motors) belong chaperonins, double-ring assemblies that mediate ATP-dependent folding of the polypeptide chains of a large variety of proteins. The motor activity has recently been ascribed to the G proteins that act as switches ensuring directionality and fidelity to many synthetic and signal-transduction processes. It would be good to have the activities of also these proteins collectively presented, from the point of view of their motor function, in one of the future issues of KOSMOS.

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