MOLECULAR MODEL OF SKELETAL MUSCLE CONTRACTION

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Summary It was generally regarded that changing the filament load would lead to the proportional change of the force on individual working motors during skeletal muscle shortening. However, recent experiment has convincingly demonstrated that individual myosin motors maintain a force of about 6 pN during a working stroke at a wide range of shortening velocities. To understand how such force "homeostasis" can be so precisely regulated in an apparently chaotic system [1], here we develop a mechanics model stringent down to the molecular level, which reveals that the unique force-stretch relation of myosin motor and the stochastic behavior of actin-myosin binding cooperatively cause the average number of working motors to increase in linear proportion to the filament load, so that the force on each working motor is regulated at 6 pN [1], in agreement with experiment.

BACKGROUND

How energy from ATP hydrolysis is efficiently transduced into mechanical work during skeletal muscle contraction remains as a fascinating subject of biophysics research for many decades and quite a few questions are still open. For example, it was generally regarded that, as motors slide with respect to the actin filaments, the force change on each of the working motors would be proportional to the load change in actin filament. However, recent experiment has convincingly demonstrated that it is the number of myosin motors attached to the actin filaments, rather than the force on individual motors, which changes in proportion to the filament load during skeletal muscle contraction [2]. The same experiment [2] has also illustrated that individual myosin motors maintain a force of about 6 pN while pulling an actin filament through a 6 nm power stroke during muscle contraction in a wide range of velocities [2]. An intriguing question then arises, which is that how such precise regulation of motor force can take place in an apparently chaotic system. The answer to this question would provide important insights into many active biological contractile processes, such as cellular mitosis, neuronal growth, etc.

MODEL DESCRIPTION AND SIMULATION SCHEME

In our molecular model of skeletal muscle contraction [1], an ensemble of myosin motors drive an elastic actin thin filament toward the M-band on the left at velocity V, while the filament is subjected to an external load P to the right, as schematically shown in Fig. 1. The actin filament is considered as an elastic rod while the myosin filament is considered rigid. The bonds between myosin motors and the thin filament are numbered from right to left. A motor is at "working" state whenever it is attached to the thin filament. Otherwise, it is "idle" state [1]. During the "idle" state, the motor behaves as a linear spring. Upon Pi release, the motor switches to the "working" state, behaving as a bilinear spring, carrying pre-stored elastic energy drawn from ATP hydrolysis. At the "working" state, the motor can either detach from the thin filament as a catch bond, or it can release the ADP and then detach upon capturing an ATP [1].

We adapt a stochastic-elastic simulation scheme employed in our previous study of the effect of pretension within stress fiber on cell adhesion [3] to incorporate the stochastic processes of myosin motor binding/unbinding and the continuum elasticity of actin filament contraction, which takes

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advantage of the fact that the elastic response of actin filament occurs at a much smaller time scale than the stochastic events of motor binding/unbinding. It is a two-level hierarchical scheme each associated with a different characteristic time scale. At the upper time scale of 30ms, a Monte Carlo scheme is employed to simulate the binding/unbinding of myosin motors, while, at the lower time scale less than 1ms, the system is considered elastic and finite element method is employed [1]. The forces and displacements of the filament-motor complex based on the elastic equations are solved at each step of Monte Carlo simulation [1]. The results from the elastic calculations are then used to determine the reaction rates of motor binding/unbinding and to update the system configuration [1].

SIMULTION RESULTS AND CONCLUSIONS

Our simulation results indicate that the unique mechanical properties of myosin motor and the stochastic behavior of actin-myosin binding cooperatively regulate the motor force into homeostasis during muscle contraction [1]. The classical Hill's law [4] between muscle shortening/lengthening velocity and the filament load is also recovered in our model [1]. The coordinated action of multiple motors revealed in this work [1] provides insights into a class of self-regulated force homeostasis in a chaotic system and is of importance not only in muscle contraction but also in cell mitosis, cellular motility, etc.

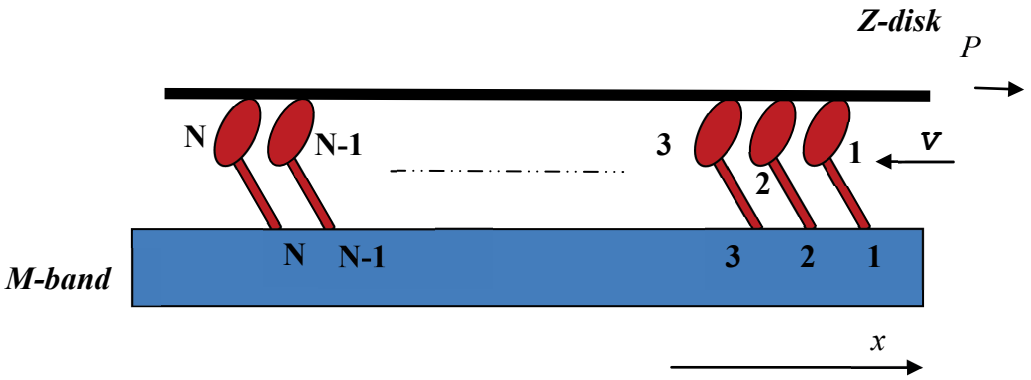

Fig. 1 Molecular model of skeletal muscle contraction (Adapted from [1]).

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