Using energetics to understand the basis of diverse muscle function

C.J. Barclay, School of Allied Health Sciences, Griffith University, Gold Coast, QLD 4222, Australia.

Skeletal muscles exhibit a wide performance range The characteristics of a particular muscle suit its functional requirements, for example rapid contraction for muscles that control eye position, high power output for frog jumping muscles and slow, low power contractions for muscles used for postural tasks. Muscle contraction is produced by a molecular motor, the myosin cross-bridge, that during interactions with an actin filament converts chemical energy, produced from hydrolysis of ATP, into the mechanical energy required to produce muscle shortening. Despite the great functional diversity among muscles, the fundamental properties of cross-bridges appear to be the same in all skeletal muscles. That is, the amount of force than can be generated by an individual cross-bridge and the maximum amount of work that can potentially be performed in a single myosin-actin attachment cycle are the same in different muscles. The mechanism that allows one basic motor design to have a broad performance range is revealed through study of muscle energetics.

The first comprehensive study of the basis of different muscle contractile properties was the work by Woledge (1968) using tortoise muscle. He showed that the slow tortoise muscle produced heat at a very low rate during sustained contraction, consistent with slow cross-bridge turnover. Woledge used Huxley's model of force generation by cross-bridges (Huxley, 1957) to provide a mechanistic explanation for the different properties of the slow tortoise muscle and the fast frog sartorius muscle. That model integrates information from muscle mechanical performance with energetic data to determine the rates at which cross-bridges attach to and detach from the actin filament. A similar approach was subsequently adopted by the author to determine the basis of differences between fast and slow mammalian muscles (Barclay *et al.*, 1993). These analyses reveal that the wide range of muscle properties can be produced using the same basic myosin motor and by independently varying the rates at which cross-bridges attach and detach.

The same approach casts light on the basis of differences in efficiency among muscles. The overall efficiency of a muscle is the fraction of the energy derived from metabolic substrates that is converted into mechanical work. Muscle efficiency ranges from 15% for rapid-contracting, high power muscles of the mouse (Barclay & Weber, 2004) to 35% for slow, low-power tortoise muscle (Woledge, 1968). Overall efficiency is the product of the efficiency with which cross-bridges convert free energy from ATP hydrolysis into work and the efficiency with which mitochondria transfer free energy from metabolic substrates into ATP (Wilkie, 1960). Differences in efficiency among muscles are largely due to differences in cross-bridge efficiency, which range from 20 to 45%, whereas mitochondrial efficiency varies relatively little among muscles (between 70 and 80% in all muscles studied) (Barclay, 2015). Differences in cross-bridge efficiency among muscles are primarily due to differences in the rate at which attached cross-bridges detach from the actin filament. This observation reinforces the idea that diverse muscle function arises from differences in the kinetics of the interaction between actin and myosin.

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