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Review

Mechanical forces during muscle development

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ABSTRACT

Muscles are the major force producing tissue in the human body. While certain muscle types specialize in producing maximum forces, others are very enduring. An extreme example is the heart, which continuously beats for the entire life. Despite being specialized, all body muscles share similar contractile mini-machines called sarcomeres that are organized into regular higher order structures called myofibrils. The major sarcomeric components and their organizational principles are conserved throughout most of the animal kingdom. In this review, we discuss recent progress in the understanding of myofibril and sarcomere development largely obtained from *in vivo* models. We focus on the role of mechanical forces during muscle and myofibril development and propose a tension driven self-organization mechanism for myofibril formation. We discuss recent technological advances that allow quantification of forces across tissues or molecules *in vitro* and *in vivo*. Although their application towards muscle development is still in its infancy, these technologies are likely to provide fundamental new insights into the mechanobiology of muscle and myofibril development in the near future.

Contents

1. Introduction

Mature body muscles can produce very high forces. The 1992 Guinness Book of World Records reports an American with a masseter (jaw) muscle bite strength of 442 kg and at the 2016 Rio Olympics, a Georgian managed to lift 258 kg in a technique called 'clean and jerk' to win a gold medal. These maximum forces can only be produced for a few seconds until the muscles fatigue. However, body muscles can also produce forces over long time periods enabling body posture, walking or lifelong heart beating. Similarly enduring muscle forces support the flight of animals. During *Drosophila* flight, the indirect flight muscles contract at 200 Hz and sustain an estimated power of about 80 W/kg muscle mass over many hours of flight (Dudley, 2000; Götz, 1987; Lehmann and Dickinson, 1997).

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Although different body muscle types differ significantly in their physiology (Schiaffino and Reggiani, 2011; Schönbauer et al., 2011; Spletter and Schnorrer, 2014), the molecular basis for force production is shared amongst all of them. The contractile unit of all muscles is the sarcomere, which shortens using a sliding mechanism: bipolar myosin thick filaments pull themselves into cross-linked actin thin filaments and thus shorten the sarcomere (Huxley and Niedergerke, 1954; Huxley and Hanson, 1954). Sarcomeres are arrayed in series into linear myofibrils, which span the entire muscle. Thus, coordinated contraction of all sarcomeres along a myofibril shortens the entire muscle and produces a mechanical force. Interestingly, not only the mechanism of muscle contraction, but also most of its molecular components are evolutionarily conserved from worms and flies to humans, hence the sarcomere is an ancient molecular machine (Ehler and Gautel, 2008; Vigoreaux, 2006).

While the identity and in many cases the function of the sarcomeric proteins during muscle contraction is known in molecular detail (Hill and Olson, 2012), the mechanisms of sarcomere assembly during muscle development are much less well understood. Here, we review recent advances in understanding muscle development, with a particular focus on the role of mechanical forces in myofibril and sarcomere formation. We propose a tension-driven model of myofibrillogenesis and discuss recent technological advances to quantify mechanical forces *in vitro* or in developing muscles *in vivo*. These technologies should provide further mechanistic insight into how muscles are built during development to allow both the maximal strength and endurance observed in the amazing muscle performances during adult life.

2. The muscle 'dimension problem'

Mature skeletal muscles are connected at both ends via tendons to the skeleton (Fig. 1). This connection allows muscle contractions to move the skeleton of the animal, leading to locomotion. Large vertebrate muscles are generally composed of several hundred muscle fibers, which are the cellular units of the muscle. In humans, muscle fibers can be several centimeters long, and even in the small fruit fly *Drosophila*, the flight muscle fibers have a length of about 1 mm (Fig. 1). Every muscle fiber is filled with many myofibrils. Each myofibril linearly spans the entire length of the muscle fiber from one tendon attachment to the other. However, the sarcomeres, the repetitive units that build the

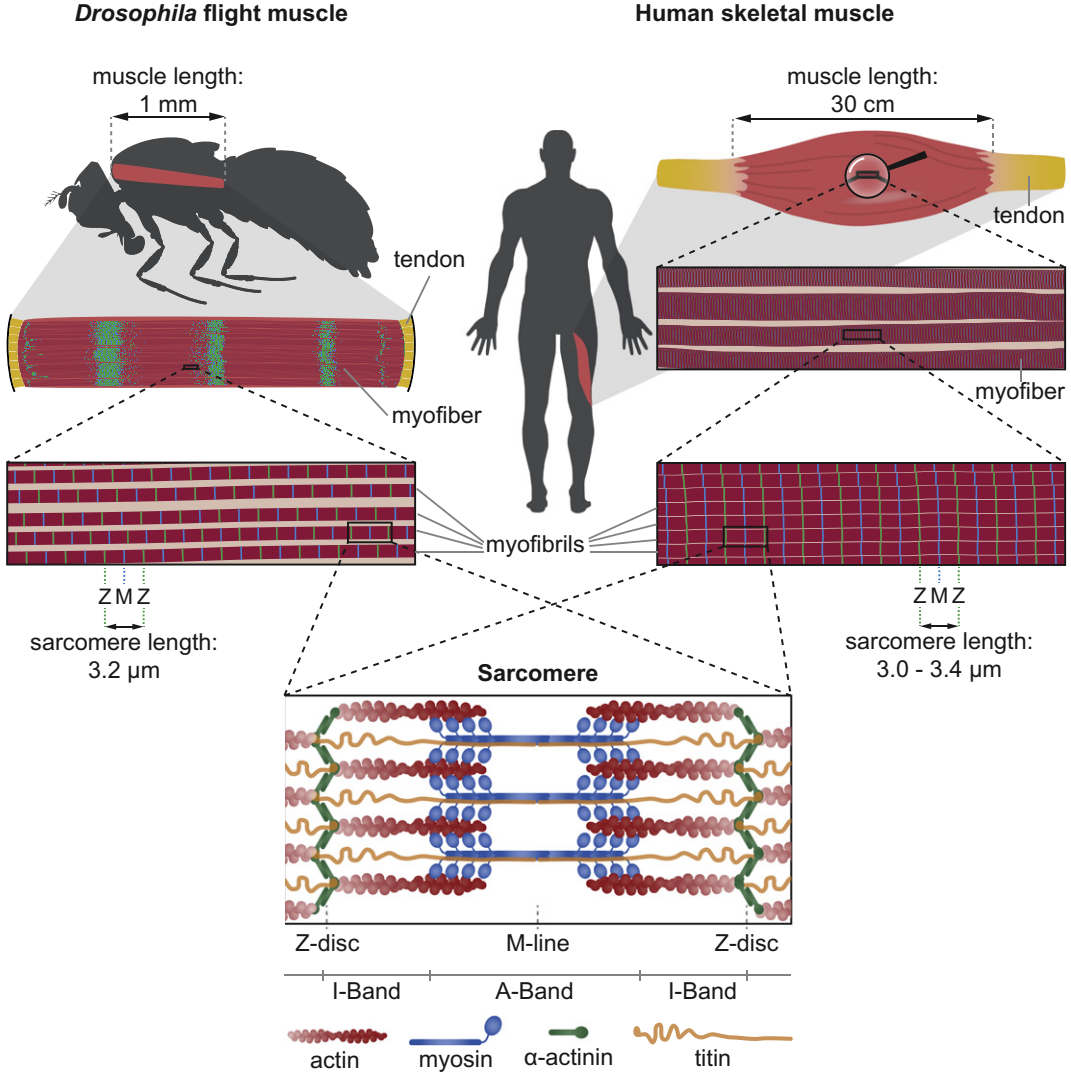

Fig. 1. 'The muscle dimension problem': structure and dimensions of muscles in fly *versus* human. Top: Schematic representation of *Drosophila* and human muscles in a series of magnifications. Each muscle fiber contains hundreds of myofibrils that span the entire length of the myofiber. Sarcomeres are several orders of magnitude shorter but must be assembled perfectly into a myofibril to connect both muscle-tendon attachments at the fiber ends. In fly and human, sarcomeres are similar in length (3.2 µm in flight muscles and 3.0 to 3.4 µm in relaxed human muscles) and many sarcomeric proteins are well conserved. **Bottom:** Schematic of the sarcomere. Polar actin filaments (also called thin filaments) are anchored at the Z-disc (Z, green) by α-actinin. Thick filaments comprised of myosin bundles are centred at the M-line (M, blue) and interact with actin with their myosin heads. Titin, a connecting filament, is anchored at the Z-disc and spans through the I-band all the way to the M-line.