The Genetics and Molecular Biology of the Titin/Connectin-Like Proteins of Invertebrates

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Introduction

The basic sarcomeric organization from both vertebrate and invertebrate muscles is very similar but shows a wide range of structural and physiological adaptations from the length of the individual filaments to the speed of contraction/relaxation. The mechanism of striated muscle contraction is universal and has been known, for quite some time now, to be the result of the sliding of actin and myosin filaments past each other (1). During the sliding process, the thick filament, made from the assembly of myosin heavy and light chain molecules "walks" on the thin filament composed of polymerized actin and regulatory proteins. The sliding process does not change the total length or sarcomeric position of these two filaments but rather their position relative to each other. How the complex myofibrillar structure is put together during myofibrillogenesis and maintained through cycles of contraction-relaxation is still largely a mystery, as is the molecular basis for physiological properties such as resting tension, elasticity and stretch activation.

To explain some of the properties of muscle structure and function, early models suggested the existence of a third filament system with elastic properties. In particular, electron microscopy studies of insect flight muscles revealed the presence of fine connections between the Z bands and the thick filaments (2-7). The search for component(s) of the third filament system lead to the identification and characterization of several very large proteins (size ranging from about 600 kDa to 3,000 kDa) found in both vertebrate and invertebrate muscles. These include "titin" or "connectin" (8, 9) in vertebrate muscles, "twitchin" in nematode (Caenorhabditis) and molluscan (Aplysia) muscles (10-12) and the insect protein, "projectin", also called "mini-titin" (13-22).

Based on antibody cross-reactivity and physical properties, it was suggested that twitchin, projectin and titin are related (18-24). The first member of this group from which amino acid sequence was determined was twitchin, encoded by the mutationally defined gene unc-22 (11). Surprisingly, twitchin was discovered to consist almost entirely of multiple copies of immunoglobulin (Ig) and fibronectin type III (Fn) domains (11, 25). This made twitchin the first intracellular protein to join the Ig superfamily. Shortly thereafter, the sequences of both titin (26-28) and projectin (29-31) were shown to be very similar to twitchin, being composed of Ig and Fn domains, as well. In fact, in addition to these three proteins, there are 11 other proteins which fall into this intracellular, mostly muscle branch of the Ig superfamily. Nearly all of these proteins are discussed in this volume. They include the four proteins represented schematically in Fig. 1. These are