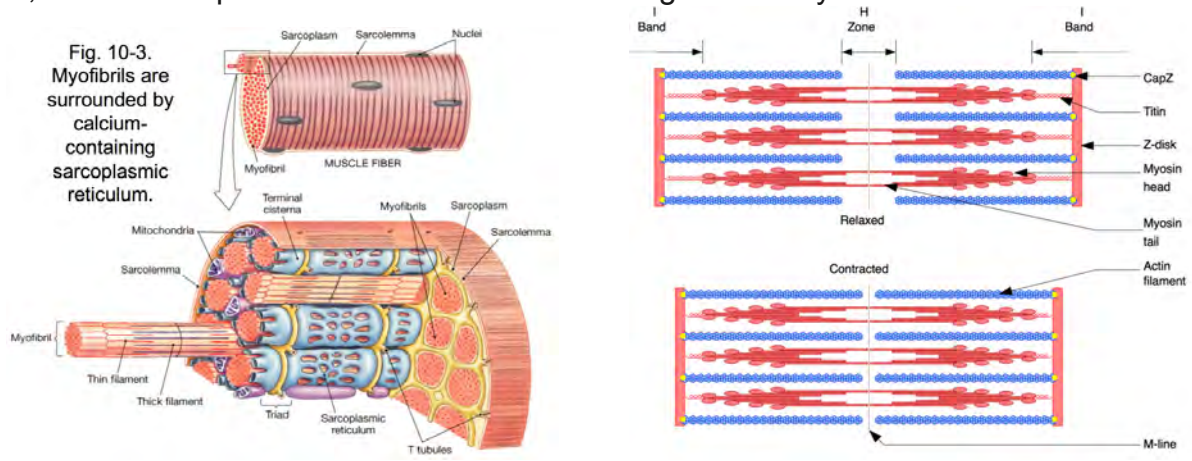
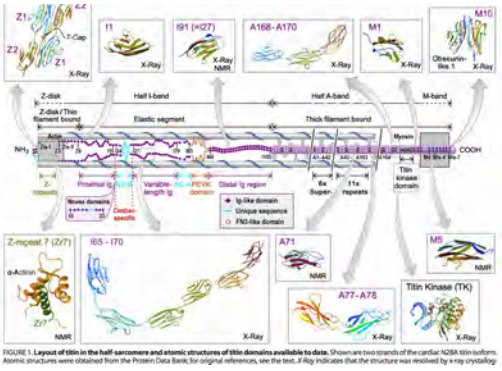
titin

Muscle is the tissue that gives action to animals. Cardiac muscle gives the heart motion to pump hemolymph or blood, while flight muscles or skeletal muscles allow animal movement through space. Contraction, the power stroke of muscle, is the activity most often discussed**:** actin and myosin, tropomyosin and troponin and their coordinated interaction in the sarcomere. That's where the action is, it seems. There's another phase of cardiac and skeletal muscle activity, however, that is as important to muscle function as night is to day.



Repetitive muscle activity requires not only repetitive *contraction*, but also repetitive *relaxation* - it's a two-stroke cycle. Only recently have we begun to understand the metabolic intricacies and structural dynamics of the *stretch phase* of muscle. In the heart, the relaxation or filling phase is termed *diastole*. In cardiac muscle, increased stretch results in generation of increased force delivered in the ensuing power stroke of contraction (Frank-Starling law of the heart). Interference with the dynamics of diastolic relaxation can have an effect similar to weakening of systolic contraction**:** increased filling pressures of the left atrium result in elevated pulmonary venous pressure. There is an important *structural element* in the cardiac sarcomere whose modification can alter the elasticity of cardiac tissue and thus affect diastolic relaxation.

Titin is the largest known protein. Human cardiac titin has over 38,000 amino acids in its primary structure. [By comparison, serum albumin has 585 amino acids and apoB (the large protein of VLDL and LDL cholesterol-transport particles) has 4500 amino acids. ApoA1, the primary apolipoprotein of HDL, has 245 amino acids.] **Titin** serves to organize contractile elements of the myocardial sarcomere and determines how easily the cell will stretch in response to a given pressure/tension load. Alterations in **titin** structure may contribute to a common cause of heart failure, called *diastolic dysfunction,* in which patients have normally-contracting hearts but because of stiffness of the relaxation phase are still short of breath.



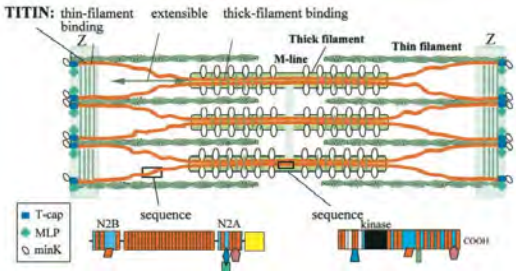


Figure 1. Layout of titin in cardiac sarcomere. Titin's N- and C-terminal regions are embedded in the Z-disc and M-line, respectively. Titin-binding ligands located in Z-disc, I-band, and M-line are also shown. Shown I-band sequence is that of N2BA cardiac titin. Vertical gray lines in Z-disc region denote α-actinin and those in A-band region MyBP-C. Figure not to scale.

Titin in human skeletal muscle serves a similar role as in cardiac muscle. In insects, including *Apis mellifera*, the honeybee, an analogous protein, ***projectin***, organizes the structural elements and elasticity of cardiac and flight muscle sarcomeres. Flight muscle metabolism is among the most active of any tissue, and the rapidity of wing motion required for flight places great demand on the efficiency of both contraction and relaxation cycling of the sarcomere. In fact, honeybee flight muscles trigger contractions at frequencies much higher than rates of incoming neural impulses, by a mechanism called *stretch-activation*, and are therefore called asynchronous.

As you may know, typical muscle contraction is triggered by a sudden rise in Ca++ in the vicinity of the actin-myosin filaments, while relaxation requires quick removal of Ca++. This requirement poses a challenge at the extreme contraction / relaxation rates required for honeybee flight.

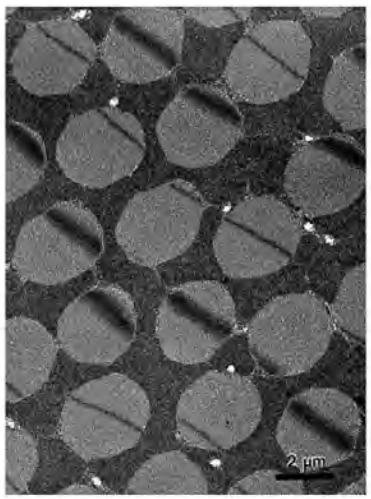


Fig. 1. Electron micrograph showing flight muscle myofibrils in cross section surrounded by abundant mitochondria. The latter appear darker because of their high cristae surface density. Small white areas are tracheae in cross section. Scale bar, 2 µm.

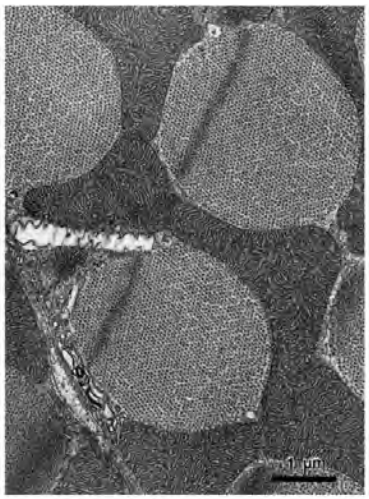


Fig. 2. Higher-magnification electron micrograph showing myofilaments within myofibrils and abundant cristae within mitochondria. Part of a tracheal tube is seen in close contact with mitochondria. Scale bar, 1 µm.

"*Rather than adapt to different contractile regimes by varying the nature of the molecular motor itself, insect flight muscles vary the regulatory processes that turn muscle contraction on and off. The most radical such change is that between synchronous and asynchronous muscle activation. Synchronous muscles have a 1:1 relationship between neural stimuli and contractions, with contraction initiated by intracellular calcium release and terminated by calcium uptake by the SR. This is the typical regulatory mechanism for striated muscle. Asynchronous muscles are divergent; they show an approximately 1:10 ratio of neural stimuli to con- tractions. Neural stimulation in asynchronous muscles releases intracellular calcium that removes thin filament inhibition, but the cross bridges themselves are activated by stretch and deactivated by sarcomere shortening. Asynchronous flight muscles are stretched by thoracic deformation caused by contraction of antagonistic muscles, and this mechanical feedback keeps asynchronous muscles contracting over many cycles. The large power-producing asynchronous muscles are controlled by a set of small synchronous muscles that produce little power (some in fact absorb power) but are capable of rapid and finely graded responses to neural stimuli. This dichotomy of muscle size and function has led to the colorful characterization of "big dumb power-producing muscles" versus "small smart steering muscles*"." (Marden, J.H., Annu Rev. Physiol. 2000)

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Additional references here: imagessays.com -> titin