TITIN

... its role in cardiomyopathy

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Whenever I found out anything remarkable, I have thought it my duty to put down my discovery on paper, so that all ingenious people might be informed thereof.  Antony van Leeuwenhoek. Letter of June 12, 1716
TITIN is the largest known protein with a megaDalton molecular weight and a contour length greater than one micron.

One molecule of titin spans half a sarcomere connecting both the M-line and the Z-disc. This giant protein plays a pivotal role in myocardial passive stiffness, structural integrity and stress-initiated signaling pathways.
Coronary arteries supply blood and oxygen to the muscles of the heart.
We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.

T.S. Eliot --- "Little Gidding" ... *Four Quartets*
Fig. 10-3. Myofibrils are surrounded by calcium-containing sarcoplasmic reticulum.
myocardial cell: 50% engine (contractile elements), 33% powerhouse (mitochondria) ... by volume
isolated myocardial cells
myocardial cells in tissue culture
Myosin molecules are bundled together to form thick filaments in skeletal muscles. A myosin molecule has two heads which can move forward and backward and binds to ATP molecule and an actin binding site. This flexible movement of head provides power stroke for muscle contraction.
The thin filaments are composed of three molecules - actin, tropomyosin and troponin. Actin is composed of actin subunits, joined together and twisted in a double helical chain. Each actin subunit has a specific binding site to which myosin head binds. Tropomyosin entwines around the actin. This cover the binding sites of actin subunits, preventing myosin heads from binding to them in an unstimulated muscle. Troponin molecules are attached to tropomyosin strands and facilitate tropomyosin movement so that myosin heads can bind to the exposed actin binding sites.
Muscle is the tissue that gives action to animals. 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.

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.

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.
*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.
(a) sequence and secondary structure

(b) native structure
(c) extension of 10 Å
(d) extension of 25 Å
Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually exhibit inappropriate ventricular hypertrophy or dilatation.
Fig. 4
Schematic section of cardiomyocyte depicting genes associated with non-syndromic familial DCM (Hershberger et al. 2013). Sarcomeric gene TTN is the major DCM gene, accounting for 25% of familial DCM cases.
TITIN: thin-filament binding

extensible thick-filament binding

Thick filament

Thin filament

M-line

sequence

sequence

kinase

COOH

T-cap

MLP

minK

N2B

N2A
FIGURE 1. Layout of titin in the half-sarcomere and atomic structures of titin domains available to date. Shown are two strands of the cardiac N2BA titin isoform I. Atomic structures were obtained from the Protein Data Bank; for original references, see the text. X-Ray indicates that the structure was resolved by x-ray crystallography, and NMR indicates that the structure was determined by nuclear magnetic resonance.
Heart failure (HF) is a complex clinical syndrome which concerns the impaired ability of the heart to pump and/or fill with blood, resulting in inadequate cardiac output to meet metabolic demands or, more commonly, adequate cardiac output but only due to compensatory neurohormonal activation.
VT
Functional properties of the titin/connectin-associated proteins, the muscle-specific RING finger proteins (MURFs), in striated muscle

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