Journal of Molecular and Cellular Cardiology 46 (2009) 490–498

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Review article

Titin-based mechanical signalling in normal and failing myocardium

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ARTICLE INFO

Article history:
Received 3 December 2008
Received in revised form 7 January 2009
Accepted 8 January 2009
Available online 20 January 2009

Keywords:
Mechanosensing
Elasticity
Stiffness
Connectin
Z-disc
I-band
M-band
Protein kinase-G
Protein kinase-A
AKT

ABSTRACT

Nodal points of mechanotransduction are found along the cardiac sarcomere, notably in the Z-disc/I-band and M-band regions. A major integrating component of these mechanosensitive complexes is the giant protein titin, which is anchored at the Z-disc, spans the I-band as an elastic spring and enters the A-band bound to myosin, then reaching all the way to the M-band. Passive-force generation and transmission of stress via the titin filaments may be central to the mechanosensory function of the myofibrillar signalosome complexes. This review discusses recent findings shedding light on mechanisms by which titin elasticity is regulated dynamically. Adjustment of titin stiffness occurs during heart development and disease through a shift in the expression ratio of the two main titin isoforms in cardiac sarcomeres, N2BA (compliant) and N2B (stiffer). Titin-isoform switching in favor of the stiffer N2B-titin can be triggered by thyroid hormone (T3) activating the phosphatidylinositol-3-kinase (PI3K)/AKT pathway. Conversely, low T3 promotes the compliant N2BA-titin. In addition, titin stiffness can be tuned acutely by protein kinase (PK)A-or PKG-mediated phosphorylation of a cardiac-specific I-band titin segment, the N2-B domain. Beta-adrenergic agonists, nitric oxide, or natriuretic peptides thus trigger a softening of the titin springs, thereby modulating diastolic function. Failing human hearts can have elevated passive stiffness in part because of a titin-phosphorylation deficit, which may contribute to mechanical dysfunction. Altered titin phosphorylation could also affect protein–protein interactions in the mechanosensory complexes associated with the sarcomere. In this context, the review highlights novel links between titin and stress-signalling pathways in the cardiomyocyte.

Contents

1. Diversity of titin filament function

The contractile unit structure of striated muscle cells, the sarcomere, is specialized in force generation through cyclic interaction between actin filaments and myosin motors. However, essential mechanical, structural, and signalling functions are associated with

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0022-2828/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.yjmcc.2009.01.004

the regions of the sarcomere that do not directly participate in actin-myosin interaction, the Z-disc, I-band, and M-band. Like a backbone of the sarcomere, giant filamentous titin molecules run from the Z-disc through the I-band and A-band all the way to the M-band, thus linking the different sarcomeric regions to one another. Titin exists in two main isoforms in mammalian heart, which are co-expressed at the level of the sarcomere (Fig. 1): a shorter, stiffer N2B isoform (3.0 MDa) and longer, more compliant N2BA isoforms (3.2–3.7 MDa). Differential expression of these isoforms is related to alternate gene splicing; in humans and other mammals there is only one titin gene [1]. The size differences between the titin isoforms arise mainly from extensive differential splicing in the I-band region, which harbors the elastic segment (Fig. 1).

Titin (first described as connectin) was already suggested some 30 years ago to have spring-like behavior and endow the sarcomeres with long-range elasticity [2,3]. The protein is well established as a main determinant of myocardial passive tension (PT), stiffness, and viscoelasticity [1,4,5], together with the extracellular matrix-based collagen fibers [6]. Titin also helps to keep the A-band in the middle of the sarcomere during the contractile cycle [7]. Furthermore, the elastic properties of titin may support elastic recoil in early diastole [8] and early systolic shortening [9]. Intriguing but still controversial is the suggestion that titin participates in determining the length-dependent activation of the cardiac sarcomere, the molecular basis for the Frank–Starling law, possibly via affecting the lateral myofilament lattice spacing [10–15].

Apart from these mechanical roles, titin was proposed to coordinate the assembly of myofibrils during muscle development and hypertrophy and to serve as a blueprint for thick filament (A-band) formation [1,16–18]. By now it is clear that titin binds to more than 20 structural, contractile, regulatory and other signalling molecules. The interactions of titin, the presence of phosphorylation sites in the Z-disc, I-band, and M-band segments [4,19,20], and an increased understanding of the role of the titin-kinase domain [4,20] adjacent to the M-band (Fig. 1) have strongly implicated titin in myocardial signal-transduction pathways.

An aspect emphasized in this short review is the connectivity provided by titin in the extensive signalling network of the cardiomyocyte. Moreover, we highlight recent findings demonstrating that the mechanical properties of I-band titin are regulated dynamically via several independent mechanisms. Current understanding of titin as an adjustable molecular spring and integrator of myofibril-based signalling events supports a concept whereby this giant polypeptide assumes a central role in the mechanosensory function of the myocyte.

2. How the cardiac titin springs can be tuned

Like most other muscle proteins, titin is subject to relatively rapid turnover (estimated half-life in the myocyte, three days [21]) and to posttranslational modification. These attributes give rise to distinct ways by which titin elasticity can be adjusted. Two major mechanisms

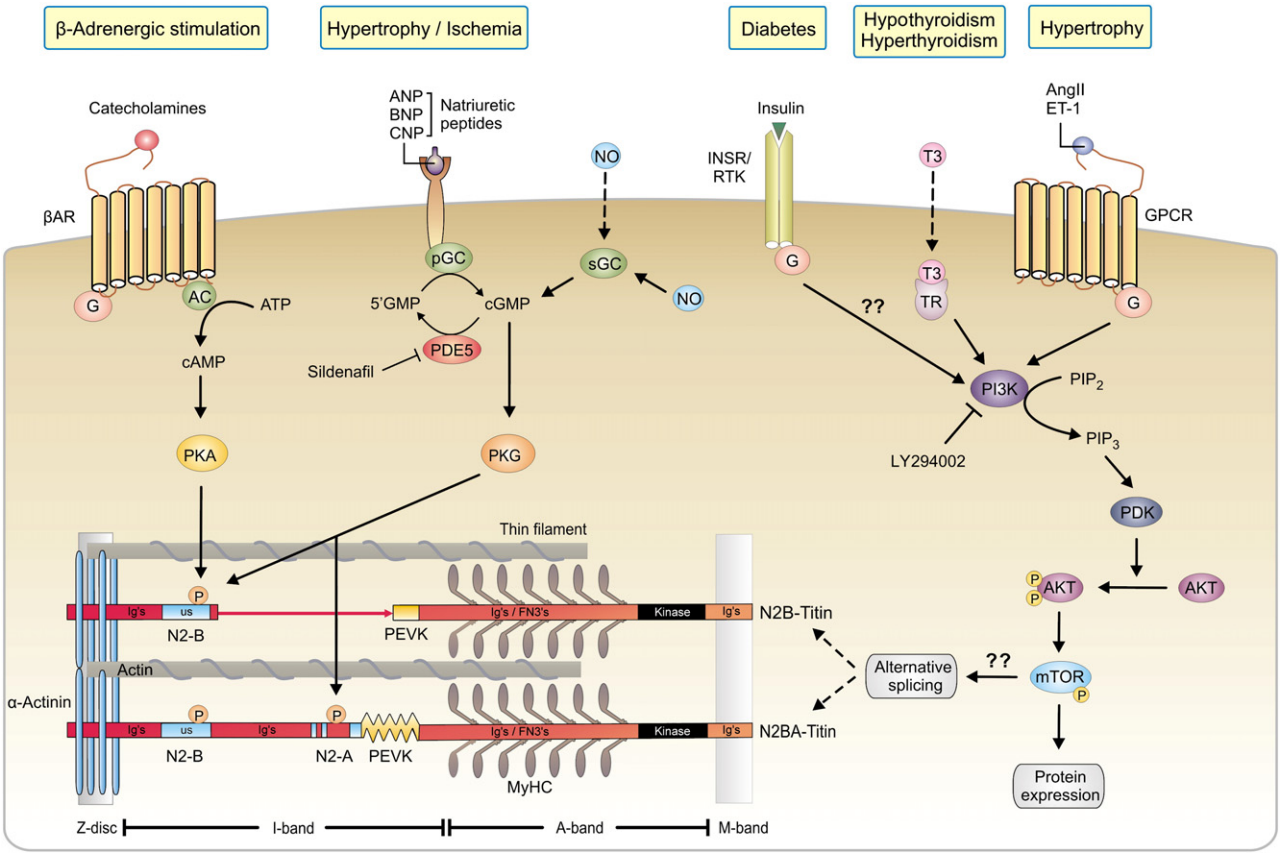

Fig. 1. Cardiomyocyte signalling pathways involved in regulating cardiac titin stiffness. Titin stiffness can be modulated either by reversible phosphorylation (P) of the N2-B_{us}, or by altering the N2BA:N2B titin isoform-expression ratio. For details, see text. AC, adenylyl cyclase; ANP, atrial natriuretic peptide; AngII, angiotensin-II; ATP, adenosine triphosphate; βAR, β-adrenergic receptor; BNP, brain natriuretic peptide; CNP, c-type natriuretic peptide; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ET-1, endothelin-1; G, small G-protein; GPCR, G-protein-coupled receptor; INSR/RTK, insulin receptor/receptor tyrosine kinase; LY294002, PI3K-inhibitor; MyHC, myosin heavy chain; mTOR, mammalian target of rapamycin; NO, nitric oxide; PDK, phosphoinositide-dependent kinase; PDE5, phosphodiesterase-5; pGC, particulate guanylyl cyclase; PI3K, phosphatidyl inositol-3-OH-kinase; PIP2, phosphatidyl inositol-4,5-bisphosphate; PIP3, phosphatidyl inositol-1,4,5-trisphosphate; sGC, soluble guanylyl cyclase; T3, triiodo-L-thyronine; TR, thyroid-hormone receptor. Titin segments: Ig's, immunoglobulin-like domains; N2-B, cardiac-specific I-band region (exon 49); us, unique sequence; N2-A, I-band region (exons 102–109); PEVK, unique sequence (>70% P, E, V, and K residues); FN3's, fibronectin-type-3-like domains; kinase, titin-kinase domain.