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Is RBM20 a Promising Target for HFpEF Therapy?

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Mini Review

Heart Failure (HF) is a major public health issue with an estimated prevalence of over 37.7 million individuals worldwide [1], and remains the leading cause of morbidity, mortality, and hospitalization among adults and elderly [2,3]. In the USA, the total medical costs for patients with HF are expected to rise from US$20.9 billion in 2012 to $53.1 billion by 2030 [1]. About half of the patients with heart failure display preserved ejection fraction in contrast to the other half that present contractile dysfunction and a dilated heart (HF with reduced ejection fraction, HFrEF) [4,5]. Prototypical manifestations of heart failure with preserved ejection fraction (HFpEF), previously known as diastolic dysfunction, include increase in passive stiffness, insufficient recoil, and decrease in full relaxation [6]. Anaggregation of severalcontributors such as hypertension, metabolic syndrome, obesity and diabetes mellitus have been associated with the development of HFpEF [6]. Despite significant therapeutic improvements in the treatment of virtually all cardiac disorders, HF is an exception, in that its prevalence is rising, and its morbidity and mortality remain unacceptably high [7,8]. Currently, no effective therapies are available for HFpEF, at least with regard to major clinical events. Therefore, novel insights into pathophysiology and molecular mechanisms of HFpEF progression are required to develop novel therapeutic approaches.

Titin, as a major human disease gene, is emerging as a promising target for novel agents development for HFpEF therapy. Titin is a giant multi-functional sarcomeric filament withits N-terminus embedded in the Z-disk of the sarcomere. The rest of the molecule is divided between an elastic I-band region, a thick filament-binding A-band region, and the M-band region where the C-terminus is embedded [9]. The extensible I-band region of titin functions as a molecular spring that develops passive force during diastole when sarcomeres are stretched [10] and endows the sarcomeres with long-range elasticity [11,12]. Titin has been well established as a main determinant of myocardial passive tension (PT), stiffness, and viscoelasticity [6,13,14], together with the extracellular matrix-based collagen fibers [15]. The elastic properties of titin may support elastic recoil in early diastole [16] and early systolic shortening [17], which contributes to left ventricular filling. Therefore, manipulation of titin elasticity could be a strategy to adjust passive stiffness, and thus HFpEF therapy.

Titin, like most other proteins, undergoes protein turnover with half-life of three days in cardiac muscle [18], and posttranslational modifications. So far, two major mechanisms have been indicatedto adjust titin stiffness. They are titin isoform switching and phosphorylation by protein kinases such as PKA, PKG and PKC [6,9,14,19]. In this mini review article, we will give our opinion on the therapeutic potential of adjusting titin isoform switching in HFpEF.

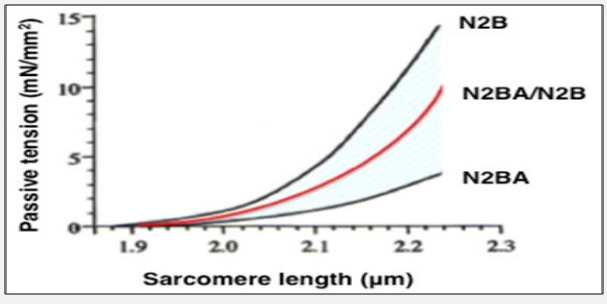

Figure 1: Relations between titin-based passive tension and sarcomere length. N2B expressing sarcomeres develop much higher passive tensions than N2BA expressing muscle. By co-expressing isoforms at varying ratios, an intermediate passive tension level can be observed

Titin produces two major isoform classes: N2BA and N2B resulting from alternative splicing. Different sizes of titin have distinct elastic properties. The smaller one, called N2B, is the stiffer isoform, and the larger one, called N2BA, is a more

compliant isoform. At varying ratios of N2BA to N2B isoforms, the sarcomeres develop an intermediate level of passive tension (Figure 1) [20,21] In normal human left ventricle (LV), the expression ratio of N2BA to N2B isoforms is about 30:70 [22]. However, in human patients, the altered titin isoform ratios have been detected. By comparing to non-failing donor heart, the larger and compliant N2BA levels was increased in ischemic cardiomyopathy [23], non-ischemic dilated cardiomyopathy (DCM) [24], and patients with HFrEF [25]. Overall, increased compliant N2BA isoforms can be commonly found in eccentric remodeled hearts with systolic dysfunction such as DCM, HFrEF and chronic ischemic cardiomyopathy, while reduced N2BA isoforms frequently can be observed in concentric remodeled hearts (compensated hypertrophy) with diastolic dysfunction developed from hypertensive heart disease. Therefore, manipulation of titin isoform ratios could be a potential therapeutic strategy for HFpEF therapy.

Recent studies indicated that RNA binding motif 20 (RBM20) is the major regulator of titin isoform switching in cardiac muscle [26,27]. Rbm20 knockout rats develop HFrEF with increased N2BA to N2B ratio [20]. Human hearts with a loss function of RBM20 in patients with HFrEF have an increased ratio of N2BA to N2B [28-31]. A couple very recent reports with mouse models of RBM20 manipulation showed the feasibility of such an approach. Reducing RBM20 levels in N2B knockout-induced diastolic dysfunction could improve diastolic stiffness [32] and inhibition of RBM20 in cardiac muscle can reduce ventricular wall stiffness induced in transverse aortic constriction (TAC) mouse model, and thus, improve diastolic function [33]. These studies suggest that adjusting RBM20 expression level could be an approach to adjust titin elasticity for HFpEF therapy. However, therapeutic modalities targeting RBM20 are currently largely theoretical due to still less-defined mechanism(s) of how RBM20 regulates titin isoform switching [34-40]. Therefore, future work should aim to address the detailed mechanisms of RBM20-mediated titin isoform switching. We believe that in the near future, RBM20 could be a real target to develop a novel therapeutic agent for HFpEF therapy [41].

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