Editorial for issue #1 2018

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Issue #3 of *Biophysical Reviews* last year contained nine articles devoted to the giant protein titin and its binding partners. These articles told only part of the story of this extraordinary large protein. This issue contains the remaining contributions to this issue.

The review by Wei Guo and Mingming Sun (2018) from the University of Wisconsin entitled “RBM20, a potential target for treatment of cardiomyopathy via titin isoform switching” is interesting because it discusses the possibility of controlling the elasticity of titin isoforms from stiff to more compliant “springs” through RBM20 transcription regulator protein.

The N-terminal region of titin extends from the Z disc structures that comprise the boundaries of the sarcomere to the edge of the A band. The stretchable part of titin lies in the I band and includes a critical amino acid motif (PEVK) on the edge of the A band. By controlling the isoform switching the *TTN* gene in this region, the internal elastic recoil of the sarcomere can be adjusted. For example, if a patient has a cardiomyopathy where the heart fails to relax because it fails to fill sufficiently before the onset of the next contraction, the left ventricular ejection fraction can be reduced to the point where the patient’s heart fails to pump a sufficient volume of blood (cardiac output) to meet the needs of the body. Under these circumstances, it might help to be able to switch the titin gene (*TTN*) from a stiff isoform to a more compliant one.

In this article, the authors discuss a novel role of the thyroid metabolic hormone (T3) in regulating the titin isoform expression, shifting it from the longer N2BA to the shorter N2B isoform. Using neonatal rat ventricular cardiomyocytes, they

show that *TTN* switching requires RBM20. The story is fascinating but it is more complex than this because the activity of RBM20 is itself regulated by the PI3K/Akt/mTor signalling pathway.

The second article comes from the laboratory of James A. Spudich and his colleagues (Trivedi et al. 2018) at Stanford. Their focus is on another titin-binding protein called myosin binding protein C (MyBP-C). This protein somehow regulates the activity of myosin crossbridge heads that project from the surface of the thick filaments. In this article, the authors discuss in detail the role of the myosin “mesa” (the so-called interacting heads motif) and its “possible” interaction with MyBP-C. Preventing this interaction can lead to the hypercontractility that characterises the familial disease hypertrophic cardiomyopathy.

MyBP-C not only binds to myosin but it also binds to titin, thereby providing the physical link that might explain how myosin crossbridges develop greater force when cardiac sarcomeres are rapidly stretched. This part of the complex story is explained in more detail by another review, “The Frank–Starling Law: a jigsaw of titin proportions”, by Vasco Sequeira and Jolanda van der Velden that appeared in issue #3 last year (Sequeira and van der Velden 2017).

Finally, we cannot resist the opportunity of drawing attention to our very recent paper (Lin et al. 2017) that provides detailed mechanistic insights into the molecular functions of MyBP-C in both skeletal and cardiac muscle.

Compliance with ethical standards

Conflict of interest Cristobal G. dos Remedios declares that he has no conflict of interest. A. Li declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by the authors.

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