System identification reveals activation- and length-dependent viscoelastic properties of titin in muscles from three mouse genotypes.

Kiisa Nishikawa[1], Jenna I. Monroy[2], Siwoo Jeong[3], and Richard J. Casler, Jr.[4]
[1]Department of Biological Sciences, Northern Arizona University, Flagstaff; AZ, USA, [2]Keck Science Department, Claremont Colleges, Claremont, CA, USA; [3]Kyungil University, Seoul, South Korea; and [4]Media Lab, Massachusetts Institute of Technology and MuscleMetrix, Inc. Email: kiisa.nishikawa@nau.edu

Summary

Recent studies suggest that titin is a tunable viscoelastic element in muscles whose stiffness and damping depend on strain and activation. To test this hypothesis, we conducted passive and active ramp stretch experiments along the length tension curve in muscles from three genotypes of mice with varying exon splicing in PEVK titin. We used system identification to find viscoelastic models that best fit the ramp stretch data. In passive WT muscles, viscoelastic parameters varied over 2-4 orders of magnitude, suggesting an entropic spring. In active WT muscles, parameters varied over a small range with changes in equilibrium length that suggest engagement of a clutch. Viscoelastic properties of muscles from mutant and transgenic mice were consistent with PEVK exon expression, demonstrating that the PEVK region of titin is responsible for muscle tunable viscoelastic properties. The results have important new implications for understanding dynamic muscle function.

Introduction

The sliding-filament swinging cross-bridge model of muscle mechanics established fundamental laws of muscle contraction. but over the years has failed to explain many observations related to the length- and activation-history dependence of skeletal muscles [1]. A more contemporary view considers muscles not only as motors, but also as tunable viscoelastic materials whose stiffness and damping depend on length and activation [2]. Here, we test the "muscles-as-tunable-materials hypothesis" using passive and active ramp stretch experiments over the physiological range of the length-tension curve in muscles from wildtype, *mdm* mutant and *Ttn*$^{\Delta 112\text{-}158}$ transgenic mice with deletions and altered exon splicing in PEVK titin.

Methods

We conducted a series of ramp stretch experiments (amplitude = 5% L_0, speed = 1 L_0/s) in passive and active soleus muscles along the length-tension curve from 0.8 to 1.2 L_0. The experiments were conducted in muscles from three mouse genotypes (WT, *mdm*, and *Ttn*$^{\Delta 112\text{-}158}$; n = 7 - 9 muscles per genotype). We used system identification to find the viscoelastic model that best fit the ramp stretch data [3].

Results and Discussion

In WT and *mdm* soleus muscles, we found that the viscoelastic structure was comprised of two Kelvin-Voigt (KV) elements in series. The first element (Figure 1) corresponds to N-terminal PEVK I and II, and the second (Figure 2) corresponds to C-terminal PEVK III [4]. In muscles from *Ttn*$^{\Delta 112\text{-}158}$ mice, only a single KV element corresponding to PEVK III is present. This element becomes more compliant when activated (Figure 2), resulting in negative force enhancement.

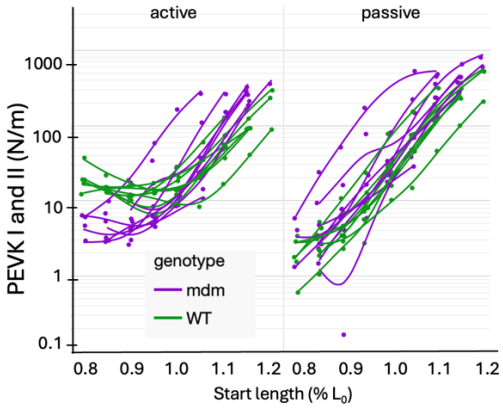

Figure 1: Stiffness of PEVK I and II in WT and *mdm* soleus.

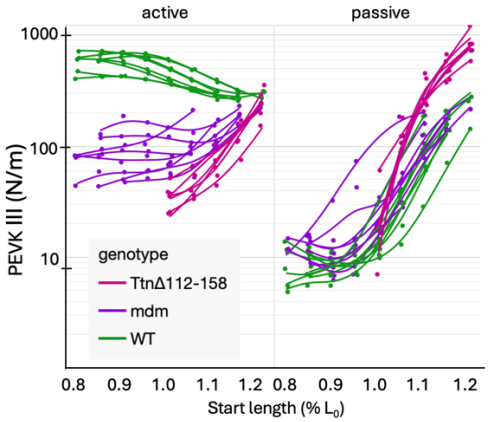

Figure 2: Stiffness of PEVK III in WT, *mdm* and Ttn$^{\Delta 112\text{-}158}$ soleus.

Conclusions

The data and models demonstrate that PEVK titin transmits passive and active forces from A-band to Z-disk during ramp stretch. The activation- and length-dependent stiffness and damping suggest significant energy storage and recovery.

Acknowledgments

Funded by NSF DBI-2319710.

References

[1] Nishikawa K. et al. (2018). *Int. Comp. Biol.,* **58**: 194-206.
[2] Nishikawa K. (2020). *Physiology,* **35**:209-217.
[3] Ljung, L. (1999. *System Identification*, 2nd Ed; Pearson.
[4] Nagy, A. et al. (2005). *Biophys. J.,* **89**: 329-336.