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Multiscale mechanical constitutive equation of the passive properties of murine skeletal muscle: application to the influence of the Klf10 gene on the extra cellular matrix

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1. Introduction

Striated skeletal muscle is a complex tissue with a hierarchical structure composed of many components at different scales influencing its overall mechanical response. Its stress response is characterized by a highly anisotropic behavior and a large contribution of its components at each scale (Pouletaut et al. 2023). One of the most efficient ways to describe its global behavior through the scales is to represent the tissue by a finite element (FE) model using multiscale constitutive laws. The macroscopic behavior is then predicted by upscaling the local constituents' interactions through the different scales.

Most studies focused on macroscopic or microscopic scale as the recent studies have highlighted the effect of Klf10 (*Krüppel-like factor 10*) gene on the passive and active mechanical properties of muscles (Kammoun et al. 2021). However, its upstream implication on the global mechanics of the muscle remains unknown. We recently showed significant passive mechanical influence of Klf10 expression at the microscopic scale (fiber) while no variation was observed at the macroscopic (muscle) and submicron (myofiber) scales, suggesting an important role of Klf10 gene on the extracellular matrix (ECM) (Tatarenko et al. 2024). However, mechanical tests on muscle ECM are still limited, and numerical modeling is essential to identify these mechanisms.

Thus, the purpose is to use numerical simulations to assess the influence of the ECM on the macroscopic passive mechanical response of healthy (wild-type, WT) and Klf10 knock-out (KO) muscles. To achieve this aim, a multiscale behavior constitutive law of the murine striated skeletal muscle was developed. The mechanical properties of the ECM, fast and slow fibers, volume fractions and pennation angles were included. This anisotropic hyperelastic law was identified on *ex vivo* multiscale tensile tests for a primarily slow-twitch fiber muscle (soleus) and a primarily fast-twitch fiber muscle (extensor digitorum longus, EDL) and for two genotypes (WT, Klf10 KO). Then, its implementation in a FE model of simplified muscle geometry was performed.

2. Methods

2.1 Multiscale constitutive equation

Adapted from (Liu et al. 2022), the transition between microscopic and macroscopic scales is achieved by weighting the strain energy function W of the muscle fiber and ECM phases via the fibers volume fraction ϕ^f (Fig 1A):

$$W = \phi^f [W_{iso}^f(I_1) + W_{ani}^f(I_4^f, I_5^f) + W_{vol}^f(J)] + (1 - \phi^f) [W_{iso}^m(I_1) + W_{ani}^m(I_4^m, I_5^m, I_6^m, I_7^m) + W_{vol}^m(J)]$$

where I_1, J, I_4, I_5 are the 1st, 3rd, 4th, 5th invariants of the right Cauchy-Green tensor \mathbf{C} . The W relative to the fibers ($k = f$) and the ECM ($k = m$) are composed of:

- an isotropic hyperelastic Neo-Hookean part:

$$W_{iso}^k = \frac{c_1^k}{2} \left(J^{-\frac{2}{3}} I_1 - 3 \right)$$

- an anisotropic part, with 1 orientation (fibers):

$$W_{ani}^f = \frac{c_2^f}{k^f} \left[e^{k^f (I_4^f - 1)^2} - 1 \right] + c_3^f (I_5^f - 2I_4^f + 1)$$

with $I_4^f = \mathbf{M}^f \cdot (\mathbf{C} \cdot \mathbf{M}^f)$ and $I_5^f = \mathbf{M}^f \cdot (\mathbf{C}^2 \cdot \mathbf{M}^f)$

- and 2 orientations (ECM collagen fibers):

$$W_{ani}^m = \frac{c_2^m}{k^m} \sum_{i=(4,6)} \left[e^{k^m (I_i^m - 1)^2} - 1 \right] + c_3^m (I_5^m + I_7^m - 2I_4^m - 2I_6^m + 2)$$

with $I_4^m = \mathbf{M}_1^m \cdot (\mathbf{C} \cdot \mathbf{M}_1^m)$, $I_5^m = \mathbf{M}_1^m \cdot (\mathbf{C}^2 \cdot \mathbf{M}_1^m)$,

$I_6^m = \mathbf{M}_2^m \cdot (\mathbf{C} \cdot \mathbf{M}_2^m)$ and $I_7^m = \mathbf{M}_2^m \cdot (\mathbf{C}^2 \cdot \mathbf{M}_2^m)$

▪ a term for compressibility:

$$W_{\text{vol}}^k = \frac{K^k}{2} (J - 1)^2$$

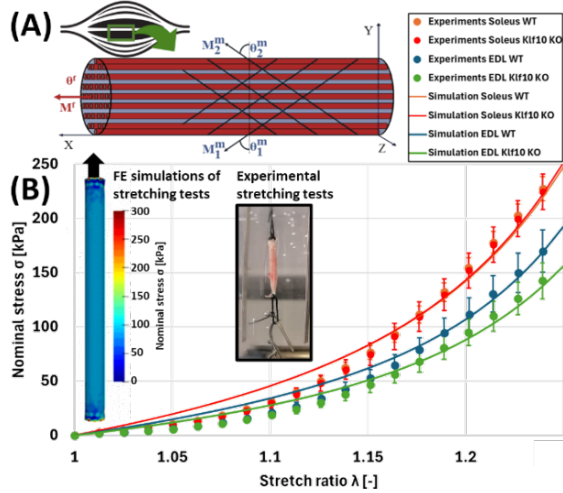


Figure 1. (A) Constitutive model with fibers (red), ECM (blue) and the anisotropic directions (black lines). (B) Tensile tests and FE simulation curves in function of genotype.

2.2 Identification

The mechanical parameters are identified from N experimental tensile tests performed on isolated slow ($N_{\text{WT}}=17$, $N_{\text{KO}}=16$) and fast ($N_{\text{WT}}=16$, $N_{\text{KO}}=15$) fibers, as well as on soleus ($N_{\text{WT}}=9$, $N_{\text{KO}}=6$) and EDL ($N_{\text{WT}}=9$, $N_{\text{KO}}=8$) muscles (Tatarenko et al. 2024). The parameters of volume fractions ($\phi^f = 0.9$), compressibility (bulk moduli $K^{f,m} = 500$ MPa), and anisotropy ($\theta^f = +95^\circ$, $\theta_{1,2}^m = \pm 55^\circ$) are initialized from values of literature (Kjaer 2004, Purslow 2010). Then, the identification is carried out in 2 successive steps: (1) fibers parameters are identified for the 2 muscle types (slow, fast) and the 2 genotypes (WT, Klf10 KO); (2) ECM parameters are identified on complete muscle with the previously identified fibers parameters fixed.

2.3 Numerical implementation

The experimental tensile tests on WT and Klf10 KO soleus and EDL are then numerically simulated using FE (*CodeAster 14.4.0*) on a simplified cylindrical ($L = 10$ mm, $\phi = 1$ mm) meshed geometry (1,470 tetrahedrons, 300 to 500nm) and the constitutive laws.

3. Results and discussion

After identification (Table 1), numerical and experimental results are compared (Fig 1B) to adjust the physiological ECM parameters. The result showed that the ratio between muscle fibers and ECM as well as the two orientations of the anisotropic part of ECM

play the most important role, reproducing at best the passive WT and Klf10 KO behaviors.

Table 1. Identified parameters for the constitutive law

	Soleus		EDL	
	WT	KO	WT	KO
c_1^f (kPa)	30.03	55	54.5	33.44
c_2^f (kPa)	15	23.97	18.22	8.801
c_3^f (kPa)	3.527	1	2	1
k^f (-)	0.3	0.405	0.4	0.431
c_1^m (kPa)	324.4	121.1	13.32	113.2
c_2^m (kPa)	387.5	296.3	134.1	223.4
c_3^m (kPa)	1	2	1	1
k^m (-)	15	17	22	16

This result goes along with Rowe's study (2010) demonstrating the important effect of the ECM on the passive mechanical properties of muscle. This identification confirms the importance of investigating the ECM for a better understanding of the impact of the Klf10 gene on the mechanical behavior of collagenous tissue, as we previously observed experimentally for ECM collagen network in tendons (Doucet et al. 2011).

4. Conclusions

This study represents a first step in the experimental/numerical coupling to understand the impact of mechanical properties on the macroscopic behavior of the muscle, making up for the lack of experimental data on certain subcomponents, such as the ECM, which have a major effect in passive response. The role of the ECM has been experimentally related to the Klf10 gene expression. We defined to what extent we can link the levels of behavior to predict the passive mechanical behavior of healthy or Klf10-deficient muscle.

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Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

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