THREE-DIMENSIONAL SKELETAL MUSCLE MODELS AND ELECTRICAL STIMULATION IN MYOTONIC DYSTROPHY TYPE 1: APLICATIONS FOR MUSCLE-ON-A-CHIP DEVICE

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Introduction

Myotonic dystrophy type 1 (DM1) is a hereditary, progressive, degenerative disease and is the most prevalent myopathy in adults. Clinically, symptoms include myotonia, chronic fatigue, and muscular weakness [1-2]. Electrical stimulation (ES) emerges as a technique to replace electrical potentials and preserve muscular tissue functions. However, the effect of this strategy on muscle fiber adaptations remains unknown [3]. On the other hand, contemporary advancements in human-based three-dimensional (3D) cell culture techniques have facilitated preclinical research by enhancing the reproduction of neuromuscular diseases [4]. Nowadays, there is no consensus about the range of electrical parameters that should be used when applying them to 3D muscle constructs, this variability presents a difficulty in comparing results between the studies [5].

Methodology

This study presents a combined computational and experimental approach. Initially, electrochemical impedance spectroscopy was employed to characterize the electrical properties (conductivity and permittivity) of 3D tissue constructs. Secondly, a multi-physical computational model integrating solid mechanics and electrostatics was formulated using COMSOL to quantify the electric field (EF) intensity within specific domains, and the consequent biomaterial displacement resulting from 3D muscle contraction induced by an EF. Finally, human DM1 and AB1079 cells (control) were cultured in Matrigel to validate the computational model. The 3D cultures were subjected to ES, calcium fluorescence, and immunostaining assays for functional and structural characterization of the tissues. The videos and images obtained were processed in Python and statistically analyzed with the Mann-Whitney U test.

Results

This is the first attempt to estimate the dielectric properties of both the cell medium and the biomaterial (Figure 1 A-B). The cell culture medium is a conductor material due to its low electric resistance. Conversely, the biomaterial, Matrigel, reveal its high resistance to current flow and moderate polarization. Regarding to the computational simulation, an EF was obtained in the biomaterial of a magnitude of 1506mV/mm and a displacement of 11.83 µm. The structural characterization of the 3D cultures, differences were detected such as the length and nuclear fusion phenotypes of the myofibers (See Figure 1 E-F). Furthermore, the 3D tissues developed from DM1, and control group presented opening of calcium channels in response to ES (See Figure 1G)

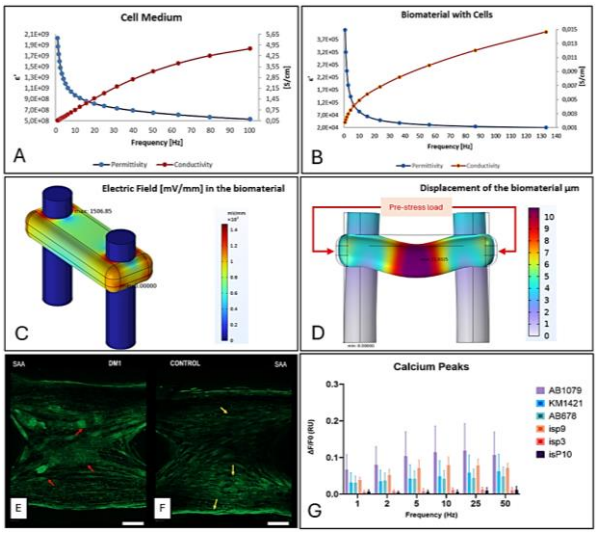

Figure 1. (A-B) Dielectric properties; (C-D) Computational model; (E-G) Experimental validation. SAA (Sarcomeric alpha Actinin)

Discussion

This research calculates the dielectric properties of cell medium and biomaterial, allowing for accurate EF estimation within cell cultures, when ES is applied. The computational model facilitates the integration of electric and mechanical stimulations, elucidating their relationship in muscle contraction. The findings highlight the potential of the DM1 model as a platform for understanding EF effects on skeletal muscle. Overall, the study emphasizes the integration of technology and engineering into health research, showcasing the time-efficient benefits of combined experimental and computational approaches for generating 3D skeletal muscle models.

References

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