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Precursor Muscle Cell's Phenotype under Compression in a Biomimetic Mechanical Niche

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Abstract : Muscle growth and regeneration critically depend on satellite cells (SCs) which are muscle stem cells located between the basal lamina and myofibres. Upon damage, SCs become activated, enter the cell cycle, and give rise to myoblasts that form new myofibres, while a sub-population self-renew and re-populate the muscle stem cell niche. In aged muscle as well as in certain muscle diseases such as muscular dystrophy, some of the SCs lose their regenerative ability. Although it is demonstrated that the chemical composition of SCs quiescent niche is different from the activated niche, the mechanism initially activated in the SCs remains unknown. While extensive research efforts focused on potential chemical activation, no such factor has been identified to the author's best knowledge. However, it is substantiated that niche mechanics affects SCs behaviors, such as stemness and engraftment. We hypothesize that mechanical stress in the healthy niche (homeostasis) is different from the regenerative niche and that this difference could serve as an early signal activating SCs upon fiber damage. To investigate this hypothesis, we develop a biomimetic system to reconstitute both, the mechanical and the chemical environment of the SC niche. Cells will be confined between two elastic polyacrylamide (PAA) hydrogels with controlled elastic moduli and functionalized surface chemistry. By controlling the distance between the PAA hydrogel surfaces, we vary the compression forces exerted by the substrates on the cells, while the lateral displacement of the upper hydrogel will create controlled shear forces. To establish such a system, a simplified system is presented. We engineered a sandwich-like configuration of two elastic PAA layer with stiffnesses between 1 and 10 kPa and confined a precursor myoblast cell line (C2C12) in between these layers. Our initial observations in this sandwich model indicate that C2C12 cells show different behaviors under mechanical compression if compared to a control one-layer gel without compression. Interestingly, this behavior is stiffness-dependent. While the shape of C2C12 cells in the sandwich consisting of two stiff (10 kPa) layers was much more elongated, showing almost a neuronal phenotype, the cell shape in a sandwich situation consisting of one stiff and one soft (1 kPa) layer was more spherical. Surprisingly, even in proliferation medium and at very low cell density, the sandwich situation stimulated cell differentiation with increased striation and myofibre formation. Such behavior is commonly found for confluent cells in differentiation medium. These results suggest that mechanical changes in stiffness and applied pressure might be a relevant stimulation for changes in muscle cell behavior.

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