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Fine-tuning of substrate architecture and surface chemistry promotes muscle tissue development

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ABSTRACT

Tissue engineering has been increasingly brought to the scientific spotlight in response to the tremendous demand for regeneration, restoration or substitution of skeletal or cardiac muscle after traumatic injury, tumour ablation or myocardial infarction. In vitro generation of a highly organized and contractile muscle tissue, however, crucially depends on an appropriate design of the cell culture substrate. The present work evaluated the impact of substrate properties, in particular morphology, chemical surface composition and mechanical properties, on muscle cell fate. To this end, aligned and randomly oriented micron (3.3 ± 0.8 μm) or nano (237 ± 98 nm) scaled fibrous poly(ε-caprolactone) non-wovens were processed by electrospinning. A nanometer-thick oxygen functional hydrocarbon coating was deposited by a radio frequency plasma process. C2C12 muscle cells were grown on pure and as-functionalized substrates and analysed for viability, proliferation, spatial orientation, differentiation and contractility. Cell orientation has been shown to depend strongly on substrate architecture, being most pronounced on micron-scaled parallel-oriented fibres. Oxygen functional hydrocarbons, representing stable, non-immunogenic surface groups, were identified as strong triggers for myotube differentiation. Accordingly, the highest myotube density (28 ± 15% of total substrate area), sarcomeric striation and contractility were found on plasma-coated substrates. The current study highlights the manifold material characteristics to be addressed during the substrate design process and provides insight into processes to improve bio-interfaces.

1. Introduction

Functional impairment or loss of striated muscle, as encountered in numerous clinical situations such as muscular dystrophy, spinal muscular atrophy, paralysis of facial muscle, traumatic injury, tumour ablation or myocardial infarction, entail significant physical distress. Recent therapeutic approaches such as cell therapy, involving either direct cell injection or the implantation of an engineered muscle tissue, have gained great interest and are considered extremely promising for the regeneration of skeletal or cardiac muscle. However, despite tremendous efforts in broad research areas, the translation from experimental settings to the clinic is still restricted by major obstacles. In particular, the optimal cell source and delivery mode have not yet been identified. Successful cell administration is hampered by major hurdles such as low survival rate and limited structural integrity of injected cells within the host tissue. In this regard, implantation of an in vitro developed neo-tissue may prove advantageous over injected cells by fostering cell survival and facilitating cellular preconditioning and control over spatial tissue organization [1–3].

Accordingly, multidisciplinary research efforts have been focusing on in vitro development of muscle tissue, relying on crucial features such as cellular alignment, myotube formation and density, as well as contractile function [4–8]. Keeping clinical applications in mind, it is furthermore important to consider possible scaling up procedures as well as transplantation and surgical handling of the culture substrate early in the design process. In this respect, developing an appropriate substrate and tailoring the micro-environment to match the destination tissue is of paramount importance. However, despite general agreement that mimicking the architectural and compositional characteristics of the extracellular matrix (ECM) has an important role in triggering tissue development and organization [9], there is still no consensus regarding material composition and structure to attain muscle tissue. Among the various strategies used to produce biomaterials

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