KNOWLEDGE-GENERATION PLATFORM FOR UNRAVELLING BONE MECHANOTRANSDUCTION MECHANISMS

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Background

Bone fractures represent a growing socio-economic burden worldwide [1]. Although orthopedic treatments based on biophysical stimuli, such as mechanical loading or externally applied pulsed electromagnetic field (PEMF) stimulation, are known to promote bone healing and regeneration [2], the triggered mechanotransduction mechanisms remain partially unknown, leading to empirical therapies, without any standardized guidelines.

Recent Advances

In this context, a pioneering knowledge-generation platform for unravelling the cell-scale signalling pathways and the tissue-scale effects induced in bone tissue by specific biophysical stimuli has been developed. In detail, the platform is based on an automated parallelized perfusion bioreactor, combined with a commercial PEMF stimulator (IGEA Clinical Biophysics) [3], designed for culturing and investigating *in vitro* three-dimensional (3D) biomimetic bone tissue models under tunable and combinable biophysical stimuli (e.g., shear stress, intermittent pressure, and PEMF stimulation). For the bone tissue models, 3D-printed polylactic acid (PLA) scaffolds [4] mimicking the trabecular bone microarchitecture were seeded with human mesenchymal stem cells (4 x 10^6/scaffold) and housed in the bioreactors to be cultured under direct perfusion (flow rate = 0.3 ml/min) for 21 days, with or without PEMF stimulation (intensity = 1.5 mT, frequency = 75 Hz) for 4 h/day (n = 3, Fig. 1). In parallel, the control group was statically cultured (n = 3). The qPCR analysis showed that direct perfusion combined with PEMF stimulation strongly upregulated the expression of collagen type-I (~6.5-fold change) and type-II (~4.3-fold change) with respect to static conditions, revealing a synergic pro-osteogenic effect of fluid-induced shear stress and PEMF stimulation. Interestingly, transcriptomic analysis pointed out the activation of immune response pathways and increased expressions of angiogenesis and osteogenesis upstream regulators triggered by biophysical stimuli combined [5].

Future directions

The proposed knowledge-generation platform, which will be further implemented for providing intermittent pressure and smart adaptive control, represents a powerful tool for investigating *in vitro* the biological response of 3D bone tissue models to defined biophysical stimuli. Combined with high throughput transcriptomics and high performance machine learning tools, it will enable reaching a thorough understanding of the correlations between the applied biophysical stimuli and the bone mechanotransduction mechanisms at the cell- and tissue-scale, with the final aim to define the rationale basis for improved biophysical stimulation treatments, in view of precision orthopedic medicine.

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Figure 1: Set-up of the knowledge-generation platform within the incubator.

References

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