EORS 2023
31st Annual Meeting of the
European Orthopaedic Research Society

27-29 SEPTEMBER | PORTO, PORTUGAL

3D Biomimetic Constructs Steer Stem Cell Commitment by Synergistic Modulation of Biophysical Cues and Growth Factor Signaling

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Abstract text (max 300 words plus References and Acknowledgements)

Tendon diseases are prevalent health concerns for which current therapies present limited success, in part due to the intrinsically low regenerative ability of tendons. Therefore, tissue engineering presents a potential to improve this outcome. Here, we hypothesize that a concurrent control over both biophysical and biochemical stimuli will boost the tenogenic commitment of stem cells, thus promoting regeneration. To achieve this, we combine molecularly imprinted nanoparticles (MINPs), which act as artificial amplifiers for endogenous growth factor (GF) activity,[1] with bioinspired anisotropic hydrogels[2] to manufacture 3D tenogenic constructs.
MINPs were solid phase-imprinted using a TGF-β3 epitope as template and their affinity for the target was assessed by SPR and dot blot. Magnetically-responsive microfibers were produced by cryosectioning electrospun meshes containing iron oxide nanoparticles. The constructs were prepared by encapsulating adipose tissue-derived stem cells (ASCs), microfibers, and MINPs within gelatin hydrogels, while aligning the microfibers with an external magnetostatic field during gelation. This allows an effective modulation of hydrogel fibrillar topography, mimicking the native tissue's anisotropic architecture . Cell responses were analyzed by multiplex immunoassay, quantitative polymerase chain reaction, and immunocytochemistry.
MINPs showed an affinity for the template comparable to monoclonal antibodies. Encapsulated ASCs acquired an elongated shape and predominant orientation along the alignment direction. Cellular studies revealed that combining MINPs with aligned microfibers increased TGF-β signaling via non-canonical Akt/ERK pathways and upregulated tendon-associated gene expression, contrasting with randomly oriented gels. Immunostaining of tendon-related proteins presented analogous outcomes, corroborating our hypothesis.
Our results thus demonstrate that microstructural cues and biological signals synergistically direct stem cell fate commitment, suggesting that this strategy holds potential for improving tendon healing and might be adaptable for other biological tissues. The proposed concept highlights the GF-sequestering ability of MINPs which allows a cost-effective alternative to recombinant GF supplementation, potentially decreasing the translational costs of tissue engineering strategies.

Acknowledgements: The authors acknowledge the funding from the European Union's Horizon 2020 under grant No. 772817; from FCT/MCTES for scholarships PD/BD/143039/2018 & COVID/BD/153025/2022 (S.P.B.T.), and PD/BD/129403/2017 (S.M.B.), co-financed by POCH and NORTE 2020, under the Portugal 2020 partnership agreement through the European Social Fund, for contract 2020.03410.CEECIND (R.M.A.D.) and project 2022.05526.PTDC; and from Xunta de Galicia for grant ED481B2019/025 (A.P.).

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Abstract Category/Topic (select from the table): Tissue Engineering and Regenerative Medicine

Free keywords (up to 4): growth factors; microstructure; molecular imprinting; stem cells

Selected type of communication (Oral or Poster): Oral