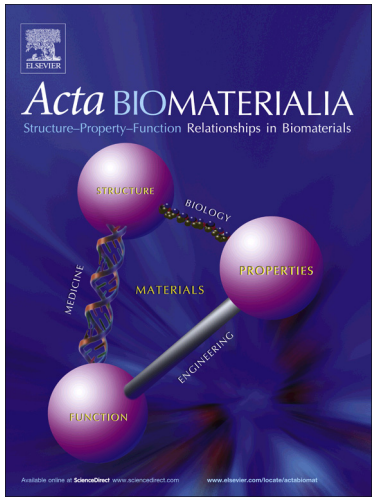

Full length article

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Injectable and tunable hyaluronic acid hydrogels releasing chemotactic and angiogenic growth factors for endodontic regeneration

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Abstract

Bioengineered soft tissues on any meaningful scale or complexity must incorporate aspects of the functional tissue, namely a vasculature, providing cells oxygen and nutrients critical for their survival. However, the ability of tissue engineering strategies to promote a fast revascularization is critically limited. Particularly in endodontic regenerative therapies, the complicated anatomy of the root canal system, and the narrow apical access limit the supply of new blood vessels and pulp tissue ingrowth.

Here we characterize the viscoelastic and microstructural properties of a class of injectable hyaluronic acid (HA) hydrogels formed *in situ*, reinforced with cellulose nanocrystals (CNCs) and enriched with platelet lysate (PL), and test its ability to promote cells recruitment and proangiogenic activity *in vitro*. The incorporation of CNCs enhanced the stability of the materials against hydrolytic and enzymatic degradation. Moreover, the release of the chemotactic and pro-angiogenic growth factors (GFs) (PDGF and VEGF) from the PL-laden hydrogels showed an improved sustained profile proportional to the amount of incorporated CNCs. The PL-laden hydrogels exhibited preferential supportive properties of encapsulated human dental pulp cells (hDPCs) in *in vitro* culture conditions.

Finally, PL-laden hydrogels stimulated chemotactic and pro-angiogenic activity by promoting hDPCs recruitment and cell sprouting in hDPCs/human umbilical vein endothelial cell co-cultures *in vitro*, and in an *ex vivo* model. These results support the use of the combined system as a scaffold for GFs delivery and cells recruitment, thereby exhibiting great clinical potential in treating injuries in vascularized tissues.

Statement of Significance

Innovative strategies for improved chemotactic and pro-angiogenic features of TE constructs are needed. In this study, we developed an injectable HA/CNC/PL hydrogel with improved structural and biologic properties, that not only provide a sustained release of chemotactic and proangiogenic GFs from PL but also enhance the cells' viability and angiogenic activity. As a result of their unique traits, the developed hydrogels are