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Controlling the Mechanical Stiffness of Hyaluronate-Alginate Hybrid Hydrogel for Cartilage Regeneration

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Extended Abstract

Hydrogels have been widely utilized as a synthetic extracellular matrix (ECM) in many tissue engineering applications, including cartilage regeneration [1]. Hyaluronate, a major ECM component, has been frequently used for hydrogel preparation. However, hyaluronate generally forms hydrogel by chemical cross-linking, and unreacted cross-linking molecules may cause severe side effects in the body unless they are completely removed after the reaction. A hybrid structure of hyaluronate and alginate was demonstrated to be useful to physically form hydrogel in the presence of calcium ions without excipient chemical cross-linking agents [2]. In the absence of calcium ions, a simple mixture of hyaluronate and alginate remained as a solution, but a hybrid solution forms hydrogel in the presence of calcium ions.

Controlling the mechanical properties of hydrogel scaffold is one of the important factors affecting cellular adhesion, migration, proliferation and differentiation. In this study, hyaluronate-alginate hybrid hydrogels with controllable mechanical stiffness were prepared by varying the molecular weight of hyaluronate while keeping the same concentration of calcium ions (60 mM). By increasing the molecular weight of hyaluronate (700 – 2,500 kDa), the storage shear modulus (G') of hybrid hydrogel increased. All hybrid hydrogels did not indicate significant cytotoxicity. To test the toxicity of hyaluronate-alginate hybrid, ATDC5 cells were treated with the hybrid solutions at various polymer concentrations ([polymer] = 0.5 – 2 mg/ml) and cell viability was determined using Ez-Cytox. Viability of cells encapsulated within hybrid hydrogel was also evaluated by live and dead assay. Chondrogenic differentiation of ATDC5 cells cultured within hyaluronate-alginate hybrid hydrogel was substantially influenced by the mechanical stiffness of the gel. Hybrid hydrogel encapsulating ATDC5 cells with higher mechanical stiffness showed more enhanced levels of chondrogenic gene expression (e.g., SOX-9, collagen type 2). This hybrid hydrogel was also useful for the delivery of primary chondrocytes into a mouse for cartilage regeneration. A lacuna, a typical structure of native cartilage, was clearly observed when hybrid hydrogel with high mechanical stiffness was used. Our approach may be useful for the design of scaffolding materials in many tissue engineering approaches, including cartilage regeneration.

References

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