Title:	Injectable Self-Healing Hydrogels for Cartilage Tissue Engineering
Authors:	Thomas, Jijo
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Abstract:	Articular cartilage has limited regenerative potential owing to its avascular nature and restricted access to progenitor cells. Various surgical reparative methods employed till date have been found to be inadequate in terms of efficacy and efficiency. Tissue engineering approaches involving cells and scaffolds appear to be promising for inducing cartilage repair. The fate of the cells following its implantation is dependent on the scaffolds. The scaffolds need to be engineered to support long-time viability and chondrogenicity of the cells. Among the various scaffold architectures evaluated, hydrogels have demonstrated great potential by providing 3D support and matrix mimetic characteristics. But the implantation of these scaffolds requires multiple surgical procedures leading to further complications and patient noncompliance. To overcome this, injectable hydrogels can be used, which enables minimally invasive delivery and better integration with tissue defects. Even though researchers were able to develop the hydrogels based on Schiff base cross-linking, many of them lag behind in terms of mechanical integrity, chondrogenic efficiency, and ability to support long time viability of the cells. The main hurdle faced in cell-laden injectable hydrogel development is the reduction in cell viability by the shear stress generated during the injection. In an injectable hydrogel system, the perfect balance of these critical parameters is essential for cartilage tissue engineering (CTE) application. Previous attempts to improve the biophysical properties of the hydrogels compromised the essential features of the scaffold. In my thesis, I have tried to develop injectable hydrogels with optimized values of the above- mentioned parameters for cartilage regeneration application. The injectable hydrogels were designed using ECM-mimetic polysaccharides, which were modified for making in-situ gelling hydrogel. Initially, an injectable hydrogel (CMCh-D) was developed using modified chitosan and carboxymethyl cellulose. Chitosan of different molecular weight grades was explored to develop hydrogels with tunable properties. The hydrogel was then evaluated for its ability to support the growth and proliferation of human mesenchymal stem cells. To impart biomimetic properties for better chondrogenic outcome and mechanical stability, an injectable hydrogel was prepared using a combination of carboxymethyl cellulose, chitosan and chondroitin sulfate. The ability of the as-synthesized hydrogel to support cell proliferation and chondrogenesis was assessed using primary human articular chondrocytes. As mechanical strength is imperative for imparting the chondrocytes with optimal chondrogenic potential, CMCh-D hydrogel was modified to introduce a double network system to increase the hydrogel stiffness. To enable this, CMCh-Dhydrogel was reinforced with supramolecular self-assembled peptide nanofibers. The effect of mechanical reinforcement on chondrogenesis was evaluated by in vitro methods. Using another approach, a bioinspired, thermo-responsive, in situ forming double network hydrogel was developed. The hydrogel, prepared using a combination of natural cartilage ECM components and a synthetic polymer with lower critical solution temperature (LCST) behavior, exhibited improved stiffness upon gelation. The hydrogel was evaluated for mechanical and chondrogenic properties using relevant studies. To summarize, I have been able to consistently improve the biophysical properties of injectable hydrogels using various approaches. Given the ease of injectability, excellent post-implantation viability, improved chondrogenic outcome, and optimal biodegradability, I propose this approach can be explored for the regeneration of other tissues. In addition, considering the rapid gelation kinetics of the material, it can be further explored for 3D bio-printing of tissues.
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