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Biodegradable Cross-Linked Composite Hydrogels Enriched with Small Molecule for Osteochondral Regeneration

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Abstract : Healing of osteochondral defects requires repair of the damaged articular cartilage, the underlying subchondral bone and the interface between these tissues (the functional calcified layer). For this purpose, developing a single monophasic scaffold that can regenerate two specific lineages (cartilage and bone) becomes a challenge. The aim of this work was to develop variants of biodegradable cross-linked composite hydrogel based on natural polypeptides (gelatin), polysaccharides components (chondroitin-4-sulphate and hyaluronic acid), in a ratio of 2:0.08:0.02 (w/w/w) and mixed with Si-hydroxyapatite (Si-Hap), in two ratios of 1:1 and 2:1 (w/w). Si-Hap was synthesized and characterized as a better alternative to conventional Hap. Subsequently, both composite hydrogel variants were cross-linked with (N, N-(3-dimethylaminopropyl)-N-ethyl carbodiimide (EDC) and enriched with a small bioactive molecule (icariin). The small molecule icariin (Ica) (C33H40O15) is the main active constituent (flavonoid) of Herba epimedium used in traditional Chinese medicine to cure bone- and cartilage-related disorders. Ica enhances osteogenic and chondrogenic differentiation of bone marrow mesenchymal stem cells (BMSCs), facilitates matrix calcification and increases the specific extracellular matrix (ECM) components synthesis by chondrocytes. Afterward, the composite hydrogels were characterized for their physicochemical properties in terms of the enzymatic biodegradation in the presence of type I collagenase and trypsin, the swelling capacity and the degree of crosslinking (TNBS assay). The cumulative release of Ica and real-time concentration were quantified at predetermined periods of time, according to the standard curve of standard Ica, after hydrogels incubation in saline buffer at physiological parameters. The obtained cross-linked composite hydrogels enriched with small-molecule Ica were also characterized for morphology by scanning electron microscopy (SEM). Their cytocompatibility was evaluated according to EN ISO 10993-5:2009 standard for medical device testing. Thus, analyses regarding cell viability (Live/Dead assay), cell proliferation (Neutral Red assay) and cell adhesion to composite hydrogels (SEM) were performed using NCTC clone L929 cell line. The final results showed that both cross-linked composite hydrogel variants enriched with Ica presented optimal physicochemical, structural and biological properties to be used as a natural scaffold able to repair osteochondral defects. The data did not reveal any toxicity of composite hydrogels in NCTC stabilized cell lines within the tested range of concentrations. Moreover, cells were capable of spreading and proliferating on both composite hydrogel surfaces. In conclusion, the designed biodegradable cross-linked composites enriched with Si and Ica are recommended for further testing as natural temporary scaffolds, which can allow cell migration and synthesis of new extracellular matrix within osteochondral defects.

Keywords : composites, gelatin, osteochondral defect, small molecule
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