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Annual Industrial Biotechnology and Bioprocessing Congress_ Cryogel based on polyelectrolyte complex for growth factor delivery_ Berillodmitrity_Professor _Poland

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Bone regeneration is one of the most actively researched fields of regenerative medicine and bone fractures are the most common injuries of all large organs, especially in the aging population. Critical size defects require large-scale surgical interventions and auto-grafting is accepted as the gold standard treatment due to its osteogenic, osteoconductive and osteoinductive potentials. Issues such as a shortage of allografts, rejection issues and associated pain and morbidity from autografts require the development of alternative tissue engineering approaches that combine the principles of engineering and biology to create biomaterials, which are able to mimic or regenerate functionally active tissues. In this study a variety of natural polymer-based macroporous materials (biomaterials) were developed. Cryogels composed of chitosan (CHI), hydroxyapatite (HA), heparin (Hep) and polyvinyl alcohol (PVA) were prepared cross-linked by glutaraldehyde (GA) and treated with glycine. Addition of PVA into the reaction mixture slowed down the formation of a polyelectrolyte complex (PEC) between chitosan and heparin, allowing proper mixing, and producing to homogeneous preparation. Freezing of the CHI-HA-GA and PVA-Hep-GA mixture led to the formation of a non-stoichiometric PEC between opposite charged groups of CHI and Hep, which makes further efficient immobilization of bone morphogenic protein 2 (BMP-2) possible, due to electrostatic interactions. It was shown that the obtained cryogel matrix, loaded with BMP-2, stimulates the differentiation of rat BMSCs into the osteogenic lineage. Rat BMSCs attach to cryogel loaded with BMP-2 and express osteocalcin in vitro. Obtained composite cryogel with PEC may have a high potential for bone regeneration applications. In our future work, we plan to demonstrate the clinical efficacy of prepared cryogel for bone regeneration in an animal model. The following work is devoted to exploration of similar PEC and other biocompatible scaffolds for efficient attachment, migration and differentiation of BMSCs into chondrocytes for efficient regeneration of intervertebral disc.

Due to the biocompatibility and biodegradability of chitosan (CHI), natural CHI scaffolds are promising tools for bone regeneration. Structurally, the bone is mainly composed of an extracellular collagen matrix, which consists of 90% type I collagen, incorporated with hydroxyapatite (HA) (Ca10 (PO4) 6 (OH) 2) crystals). On average, compact bone is made up of 70% calcium salts and 30% matrix. Mineralized scaffolds have been shown to support osteogenic activity and overall bone formation. The presence of HA helps in imitation of the natural extracellular bone matrix (ECM), providing a native chemical and physical structure for the formation of new bone. Therefore, it is advantageous to increase the rate of formation of HA in the healing of bone tissue In addition, HA is known to be biocompatible and osteoconductive, and is currently used in many orthopedic applications, including bone fillings and implant coatings.

Another main problem that should be taken into account when designing a scaffold suitable for bone regeneration is the ability of the scaffold to support vasculogenesis, which could be done either by immobilization of growth factors or by inclusion of substances with intrinsic ability to bind to growth factors.

The current study is focused on a one-step preparation of heparin (Hep)-containing composite cryogel. Usually, protonated amino groups of CHI immediately form polyelectrolyte complex (PEC) with sulfo and carboxyl groups of Hep, which limits the possibility of mixing and obtaining a homogeneous solution for cryogel synthesis. There is a limited number of studies related to PEC-based cryogel scaffolds, however, extensive research has been done on hydrogel-based PEC, especially with CHI . In one study, researchers were able to obtain CHI-Hepcryogel by blending PEC followed by glutaraldehyde (GA) cross-linking .Previously, the possibility of preparing a biocompatible PEC cryogel composed of CHI, gelatin, and dextran dialdehyde that possesses an internal porosity of cryogel walls was shown. In the current research, we produced CHI-PVA-Hep-GA biocompatible PEC cryogel that also possesses internal porosity of cryogel walls as a sign of PEC formation represents PEC cryogel structure, highlighting the interactions between each component. We hypothesized that introduction of Hep into CHI-PVA cryogel would allow the immobilization of bone morphogenic protein 2 (BMP-2) without additional chemical modifications of a growth factor or cryogel. Obtained cryogel, which was biocompatible with the cells, possessed biological activity and supported differentiation of rat bone marrow mesenchymal stem cells (BMSCs) into osteogenic lineage via release of BMP-2.

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