Title:	Functionalised Carbon Biomaterials for Bone Tissue Engineering
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Keywords:	Bone -- Tissue Engineering
Issue Date:	Apr-2022
Publisher:	IISER Mohali
Abstract:	Functionalized carbon biomaterials for bone tissue engineering Abstract Although bone has a natural ability to heal, remodel and undergo repair following injury, the natural compensation mechanism in the case of critical size defects is however hindered. A critical size defect is defined when 50% bone loss occurs with respect to the bone circumference. These can arise due to trauma, developmental deformities and/or the pathophysiological conditions such as tumour resection, osteomyelitis, osteoporosis etc. The consequences are poor vascularisation, loss of tissue differentiation ability, and fracture progression necessitating the need for interventional strategies. According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) the number of new cases of fracture was around 178 million in 2019. The traditional gold standards of autografts and allografts are rendered inadequate due to donor site morbidity, immune rejection, disease transmission, sterilisation requirements and limited tissue availability. Bone tissue engineering approaches are being used to overcome these limitations. Bone tissue engineering applications focus on the triad of using, (i) scaffolds alone, (ii) scaffolds with cells, and (iii) scaffolds with signalling factors. Despite evidence of cells and growth factors-induced bone regeneration, ectopic bone formation, antibody development, and in some cases, carcinogenesis indicates the need for caution in using this approach for inducing bone repair. Such contraindicating responses can be attributed to the growth factor's dose-dependent biphasic response. Hence, apart from the multiple uncertainties like the release pattern of the growth factors at the site of implantation and the biphasic effect of the incorporated growth factors; the regulatory hurdles and the high cost of production serve as deterrents for the clinical development of growth-factor releasing scaffolds. In order to circumvent the use of growth factors, the scaffold to be implanted in vivo, should have the inherent biophysical and biochemical cues that render it osteoconductive, osteoinductive, angiogenic and promote osteointegration with the host tissue. In this regard, this thesis focuses on scaffolds that can provide a growth factor-free approach for osteoinduction, osteoconduction, osteointegration, and angiogenesis along with improvement in the biophysical, mechanical, and antimicrobial properties of the scaffold. This is based on a strategy to incorporate various ions in a hydroxyapatite-reduced graphene oxide polymeric biocomposites. In the first study, silver nanoparticles on hydroxyapatite nanorods were synthesised in situ, and used in a gelatin-reduced graphene oxide cryogel system. This system was evaluated for its physical and mechanical properties which were found to be improved from their existing counterparts in the literature. The biological assessment showed good antimicrobial properties, along with no cytotoxicity on normal fibroblastic cells. The osteogenic potential was also upregulated and revealed higher levels of mineralisation. The angiogenic potential however couldn't be established. In order to attain proangiogenic activity, zinc was doped into the hydroxyapatite structure in the next study. These zinc doped nanohydroxyapatite was synthesised in situ on reduced graphene oxide sheets using a hydrothermal synthesis technique. These nanocomposites were further explored for their degradation, protein adsorption, biomineralization and zinc release profiles. The antimicrobial and biocompatibility properties were verified. The osteogenic differentiation was found to be upregulated and there was an improvement in calcium mineralisation. The in vitro angiogenic profile of these composites were assessed using proliferation, attachment, migration and tubulogenesis assays. The upregulation of angiogenic markers like VEGF, FGF and PDGF further confirmed the potential role of zinc as a vascularisation promoter. The enhanced in vivo bone healing and angiogenic properties of these composites further corroborated the in vitro results. Despite its promising properties, the limited retention of the biocomposite at the site of the defect posed a challenge, necessitating the need for a delivery system. To enable this, a gelatin (ECM mimetic) nanofiber system that incorporated pristine zinc doped hydroxyapatite (HapZ) and HapZ@rGO composites was developed. The physical, antimicrobial, angiogenic and osteogenic properties were assessed and verified. The structural limitations of these scaffolds prevent its ability to fill irregular void/defect completely. To overcome this, the next study focused on the development of an antibiotic eluting injectable bone cement. Here gold nanodots and nanohydroxyapatite particles were synthesised on rGO sheets, as an osteoinductive, osteoconductive and angiogenic agent. The mechanical and physical properties of these bone cements showed a significant improvement over the existing bone cements. A sustained antimicrobial activity, apart from enhanced osteogenic and angiogenic property was observed in the synthesized cement. The ability of the cement to accelerate bone callus development was verified in an in vivo animal model. Overall, this thesis demonstrated the role of various ions incorporated with ceramics and carbon materials for improved osteogenic, angiogenic and antimicrobial properties. These nanocomposites can be used alone, coating materials, bio inks, and/or in combination with scaffolds for multigenic bone tissue engineering applications.
URI:	http://hdl.handle.net/123456789/5326
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