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Graphene and Composite based Biomaterials in Cartilage Tissue Engineering Application

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Abstract

Absence of vascularization and poor cellularity has leads to the limited healing capacity of cartilage. Major traditional treatments for cartilage defects have limitations such as mismatching with repaired region and less integration with donor site. Tissue engineering has now attracted the attention of researchers for the treatment of critical joint defect and injury, reconstruction of cartilage tissue. A key component of engineering a biomaterial is the use of appropriate biocompatible and biomimetic scaffolds. There is no standard biomaterial available in the field of cartilage tissue regeneration and repair of the cartilage injury. Presently carbon based materials such as graphene oxide is being used as fillers in biomaterials for their excellent mechanical stability and their biocompatibility. In this present review we will summarize the development of Graphene oxide infused hybrid biomaterials in the field of cartilage tissue engineering.

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Introduction

Cartilage defects in orthopedic sites are constantly caused by trauma, sport injury, aging or degenerative diseases. Cartilage being a vascular, aneural and alymphatic and has single cell type, it has hindered regeneration capability [1]. The traditional procedures for cartilage repair include auto graft, allograft and surgical technique such as marrow stimulation [2]. The limited regeneration potential of articular cartilage damage is one of the most competing tasks in musculoskeletal therapeutics and the tissue engineered biomaterials has emerged with solution to elucidate this problem. The biomaterials used for cartilage repair should possess high biocompatibility and bioresorbability, cellular viability, expansion and differentiation. The biomaterial should be capable of providing ideal mechanical properties and it should be capable of transporting nutrients and cell waste [3]. In recent years, the researchers have been working on developing competent biomaterials to create a preferable environment to provide necessary biological signals to control cellular response towards cartilage repair and cell support [4]. Since the most important functions of orthopedic cartilage is bear weight, the engineered biomaterial for cartilage repair should be able to match the mechanical property of the native cartilage, Integrate with both subchondral bone and adjacent cartilage for stable load distribution. It should be resistance to load under large deformations and motions [5]. To solve this kind of problem, many researchers integrated natural polymer with synthetic materials and carbon based nano materials to develop a hybrid scaffold for tissue engineering. The hybrid material should not only enrich the cell proliferation and differentiation but also could elevate the mechanical strength of cartilage. The major function of tissue-engineered construct for cartilage is to augment the prolonged maintenance of physiologic loads within the joints. Bio-materials suitable for cartilage repair should be created with qualities such as high elasticity and high lubrication with cartilage-specific tissue qualities. Graphene based nano-materials are explored for use as a biomaterial for drug delivery and tissue engineering applications due to their exceptional physicochemical and mechanical properties. Graphene has considerable attention of researchers because of its mechanical and electronic features. GO is acknowledged for its high-mechanical stability, large surface area, electrical property and its ease for chemical modifications [6]. The oxygen functionalities and aqueous dispensability of Graphene oxide has extended its usage in tissue engineering [7]. Since cartilage being the maximum load bearing area, the scaffold or biomaterial used for the cartilage regeneration should be mechanically stable. Hence addition of graphene oxide in the biomaterial will increase its mechanical stability, which will be suitable for engineering cartilage specific biomaterials in future.

Natural/Synthetic Biomaterials in Cartilage Tissue Engineering

Natural and synthetic materials are being used as biomaterials in tissue engineering. Polymers and polysaccharides such as Collagen, chondroitin sulfate, hyaluronic acid, chitosan, alginate, fibrin, agarose and cellulose are some natural materials which have been used in cartilage tissue engineering, despite their bioavailability and biocompatibility, natural biomaterials has weak mechanical properties and their physical properties can vary on different source [8]. Synthetic materials such as Poly (Lactic-Co-Glycolic Acid) (PLGA), Polymer of Lactic Acid (PLA), Polycaprolactone (PCL), etc., have efficient mechanical properties such as defined porosity and elasticity, but also has the disadvantages that these materials can cause cytotoxicity [9]. The researchers then focused on composite materials to overcome the disadvantages of the single materials. Since the use of composite materials have an advantage of modifying by the material property by biochemical and physical methods.

Cell Based Biomaterial in Cartilage Tissue Engineering

The composite materials used both natural and synthetic material together to engineer a construct, which were further enhanced with addition of lineage specific cells to the scaffold/biomaterials. Studies showed that the chondrocytes grown with collagen and agarose gels retained their phenotype in 3D cultures [10]. Thus Chondrocytes being the single cell source of cartilage, it is the primary cell used for the designing of cellular biomaterial in cartilage repair. Secondly, Mesenchymal stem cell plays an important role in cellular scaffolds, since it has the greater potential in differentiation into lineage specific cells. Some of the Cellular biomaterials used in the cartilage tissue engineering are fibrin- PLGA Chondrocytes, Collagen-PL Chondrocytes, Alginate /PVA Chondrocytes, Collagen –PEG Human Mesenchymal stem cells and hyaluronan /PEG chondrocytes [10,11].

Graphene Oxide Based Hybrid Biomaterial in Cartilage Tissue Engineering

Graphene based nano-materials are currently explored for its higher potential towards tissue engineering. GO acts as a prominent nano-filler for biomaterials, with improved mechanical properties and preferable degradation rate. Wang et al., in their work, they incorporated the composite with GO, which acted as a self-healing nano-composite with higher mechanical strength. They used GO as a cross-linker and found that due to its multiple reactive site only a small amount of GO was needed to achieve an improvement in the overall mechanical property of the composite. The report by Nayak et al. [11] shows that graphene based material is a favorable biocompatible biomaterial that enhanced the proliferation of Human Mesenchymal Stem Cells (hMSCs) and extend their differentiation into osteoblast cells. In this context, GO has been selected as a supplementary material for hybrid scaffolds for cartilage tissue engineering. Liao et al. [12] fabricated the CSMA/PECA/GO hybrid scaffold with defined pore size, swelling behavior, compression module and conductivity that mimicked the three-dimensional environment of the cartilage. *In vitro* cytotoxicity test reveals that the scaffold was biocompatible with cartilage cell. Furthermore, *In vivo* Regeneration capacity of the hybrid scaffold was examined in full –thickness cartilage defect. The hybrid scaffold holds good mechanical property and favorable degradation rate which matches with healing rate of damaged cartilage tissue [12].

In a recent study, the RGO/chitosan film was used as biomaterial. The study also proved that addition of RGO to the chitosan nanoparticle has increased the mechanical stability up to 31.6%, compared with chitosan was 22.5%. The cytotoxicity of the prepared film was studied on human articular chondrocytes; the result indicates the consistent proliferation and higher viability of chondrocytes *in-vitro*. In a study carried out by Yu Luo et al. [13], they fabricated the electro-spun mat of PLGA doped with GO. The incorporation of GO has enriched the hydrophilic performance and protein adsorption ability of the fabricated mat. It has also enhanced the proliferation of hMSCs and also induces the differentiation of the stem cells into osteogenic cells, where the proliferation and differentiation rate for PLGA mat without GO was comparatively low [13]. These recent researches in cartilage repair suggest that semi-synthetic hybrid biomaterials hold the maximum therapeutic potential towards cartilage tissue engineering. Though many cellular based scaffolds had shown some favorable regeneration capacity, cell based techniques involves the procedures that are costly and laborious, which will not be economically feasible for developing a clinical therapeutic product. In contrast, the synthesis, fabrication and formulation of graphene based hybrid materials are easy and economical. Thus more advanced studies should be focused on fabricating a carbon based hybrid material to develop the more appropriate tissue engineered cartilage constructs in near future.

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