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Bioadaptability: An Innovative Concept for Biomaterials

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Biocompatibility is the basic requirement of biomaterials for tissue repair. However, the present concept of biocompatibility has a certain limitation in explaining the phenomena involved in biomaterial-based tissue repair. New materials, in particular those for tissue engineering and regeneration, have been developed with common characteristics, i.e. they participate deeply into important chemical and biological processes in the human body and the interaction between the biomaterials and tissues is far more complex. Understanding the interplay between these biomaterials and tissues is vital for their development and functionalization. Herein, we suggest the concept of bioadaptability of biomaterials. This concept describes the three most important aspects that can determine the performance of biomaterials in tissue repair: 1) the adaptability of the micro-environment created by biomaterials to the native micro-environment in situ; 2) the adaptability of the mechanical properties of biomaterials to the native tissue; 3) the adaptability of the degradation properties of biomaterials to the new tissue formation. The concept of bioadaptability emphasizes both the material's characteristics and biological aspects within a certain micro-environment and molecular mechanism. It may provide new inspiration to uncover the interaction mechanism of biomaterials and tissues, to foster the new ideas of functionalization of biomaterials and to investigate the fundamental issues during the tissue repair process by biomaterials. Furthermore, designing biomaterials with such bioadaptability would open a new door for repairing and regenerating organs or tissues. In this review, we summarized the works in recent years on the bioadaptability of biomaterials for tissue repair applications.

1. Introduction

Over the past decade, major advances have occurred in understanding the interaction between cell and biomaterials[1–4]. There is increasing evidence that biomaterials provide more than a temporary scaffold because they serve as assistants to orchestrate both cell adhesion and tissue morphogenesis[5–7]. Biocompatibility is a widely accepted concept for evaluating the feasibility of biomaterials in clinical applications for tissue repair[8]. However, with the development of immunology and biology science, biocompatibility exposes certain limitations in describing and defining some important characteristics that excellent biomaterials should possess. For instance, most investigations into the biocompatibility of biomaterials were conducted using only one type of cells. Hydroxyapatite particles have good biocompatibility because they can promote the proliferation and osteogenic-related protein/gene expression of osteoblasts[9,10]. However, due to the complicated environment in the human body, multiple types of cells reside on tissue or organ. In bone, for example, there are osteoblasts, osteoclasts, stem cells and some immunologic cells[11–15]. Therefore, evaluating the feasibility of hydroxyapatite for bone tissue repair by only measuring the biology properties using osteoblasts is not scientific. Another paradigm is that inert materials, such as steels, carbon materials, silicones, and poly(methyl methacrylate), were once thought to be biocompatible materials. However, most of them suffer from a certain limitation due to their non-degradation properties. For example, the stress shielding of metallic biomaterials could lead to the loosening of implant after 10–20 years service[16]. Moreover, most of these materials have weak interactions with cells and tissues[17–19]. Additionally, the surface and structural properties are normally ignored whether determining one biomaterial is biocompatible or not. It is well known that poly(lactic-co-glycolic acid) (PLGA) is a synthetic polymer for drug release and tissue repair applications[20–22]. PLGA has excellent processability and can be fabricated with various morphologies[23]. Although PLGA is an FDA approved biocompatible material, PLGA flat and micropatterned films possess different properties in harnessing cell arrangement and specific protein/gene expression[24–26]. Therefore, a more systemic benchmark to evaluate the feasibility of biomaterials for tissue repair applications should be explored.

Hereby, we suggest the concept of bioadaptability of biomaterials as that (1) the micro-environment created by biomaterials should

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be harmonized with the micro-environment of the tissue to be repaired; (2) biomaterials should have matched mechanical properties with misfunctional tissues, and support the mechanical stability of the defected tissue during tissue repair; (3) biomaterials should possess adaptable biodegradability which matches the new tissue formation. Therefore, biomaterials with excellent bioadaptability should have one or several important characteristics, such as adaptable component simulating cell response and tissue reconstruction, matched mechanical properties with misfunctional tissues, suitable surfaces with beneficial tissue reaction and biomimic multi-level structures. Compared to biocompatibility, bioadaptability requires the biomaterials to not only be safe for defected tissues, but also to be biofriendly and to biomimic (complementing component, microstructures and mechanical properties with defected tissue). The concept of bioadaptability may provide new inspiration to uncover the interaction mechanism of biomaterials and tissues, to foster the new ideas of functionalization of biomaterials and to investigate the fundamental issues during the tissue repair process by biomaterials. Furthermore, designing biomaterials with such bioadaptability would open a new door for repairing and regenerating organs or tissues.

In this review, we provide an overview on the design of bioadaptive materials for tissue regeneration. First, we review the component of biomaterials on bone repair. Elements such as calcium, strontium, zinc, and silica involved in biomaterials can significantly stimulate and promote bone repair and regeneration. Additionally, composite scaffolds show excellent properties compared with scaffolds composed of a single component. Second, the mechanical properties of biomaterials are also of great importance. Cells in various tissues can sense the elasticity of the matrix and transduce the mechanical signals into various physiological responds. Therefore, biomaterials with matched mechanical properties with the defective tissue can facilitate tissue reconstruction. Third, we review the influence of surface properties (such as surface chemical modification, surface physical/chemical coating and micro/nano patterning) of biomaterials for enhancing or inducing tissue regeneration. Finally, we review biomaterials that were designed using multi-level construction.

2. Construction of Biomaterials by Bioadaptable Component

In the human body, metal ions participate in many important chemical and biological processes, and most of them interact with nucleic acids, enzymes and proteins[27]. Metal ions in the body not only positively affect some physiological functions (such as promoting tissue repair) but are also involved in various metabolic disorders and diseases[28–30]. Due to their unstable and potential toxic effects if they are directly ingested, biomaterials with a function of delivery of metal ions would have an extensive application in tissue regeneration and disease therapy[31].

Calcium, which is primarily contained in hydroxyapatite, is an important element in a bone. Calcium phosphate has been widely used as a biomaterial for bone repair due to the similarities with natural bone[32–34]. Yang et al.[35,36] evaluated the shape effect of hydroxyapatite microparticles on cell behaviors. The spherical hydroxyapatite was much better than rod hydroxyapatite.

The process of bone formation is tightly regulated by multiple agents. Bone minerals and elements facilitate bone formation and resorption by affecting bone cells. Some elements have similar chemical properties with calcium, such as strontium, which has significantly pharmacological effects on bone regeneration[37–39]. Strontium has been reported to regulate bone balance in osteoporotic patients and is a potential treatment for osteoporosis[40]. Therefore, strontium-involved inorganic biomaterials would be an ideal candidate for bone repair. Huang et al.[41] synthesized strontium-involved calcium phosphate microspheres using yeast as a template. Compared with pure calcium phosphate microspheres, the strontium contained microspheres that significantly promoted the proliferation of stem cells.

In addition to strontium, a rare earth element, ytterbium, has similar properties (such as atomic size and elastic modulus) to calcium. Yu et al.[42] reported that ytterbium can not only improve the ductility of metallic glasses but also enhance their bioadaptability. Ytterbium can enhances the ductility of metallic glass by increasing the density of shear bands near the fracture end and enlarging the plastic zones on the surface of the fracture. Compared with the ytterbium free metallic glass, ytterbium contained materials remarkably promote the adhesion and proliferation of osteoblasts and fibroblasts[42].

Zinc is an essential element for human growth. Zinc deficiency can induce the retardation of bone growth, which suggests that zinc plays an important physiological role in the mineralization and growth of bone[43]. Zinc can activate aminoacyl-tRNA synthetase in osteoblasts and stimulate the secretion of bone-related proteins[44]. Due to the effective functions of zinc on bone regeneration, zinc-containing biomaterials have been widely developed. Xiong et al.[45] synthesized submicrometer willemite phase zinc silicate using a microwave-assisted hydrothermal method and investigated the zinc ion release behaviors. The synthesized materials with poor crystallinity had weak toxicity and thus have a great potential in the application of bone repair[45].

Silicon plays an important role in bone metabolism[46,47]. Therefore, silicon has become a common element in inorganic biomaterials, such as bioactive glasses, calcium silicate, and silicon-substituted calcium phosphate[48–50]. Lei et al.[51,52] developed various mesoporous bioactive glass, which can be used as materials for bone repair and vehicles for drug release. Bioactive glass, which was developed by Hench and his colleagues in the late 1960s, was used to confirm that silicon could directly bond with bone and muscle[53]. Calcium silicate bioceramics have excellent osseointegration, but their high dissolution has limited their applications in bone repair[54]. Xiong et al.[55] modified the surface structure and chemical composition of calcium silicate with Zn_2SiO_4 particles. The results indicated that the modified materials showed retarded dissolution, better mineralization and higher bioadaptability compared with calcium silicate[55]. Shi et al.[56] developed a novel hydroxyapatite–mesoporous silica composite. Hydroxyapatite was assembled into mesoporous silica in situ. The composite materials have been used to load osteogenic differentiated factors (such as bisphosphates) to induce the osteogenic commitment of stem cells[57]. Additionally, the composite materials showed excellent bioadaptability, which can significantly promote cell proliferation compared with pure mesoporous silica[57].

Though they are generally used as mere inorganic material ingredients, metal ions are also widely used in composites containing polymers. A hydroxyapatite/collagen nanocomposite was synthesized by Kikuchi et al.[58] which could be resorbed by osteoclast-like cells and induce bone regeneration through osteoblasts. Lee et al.[59] fabricated chitosan–silica xerogel hybrid membranes using a sol-gel method and proved that they had superior affinity to osteoblastic cells, which contributed to guided bone regeneration. According to the research of Xie et al.[60], a complicated bone cement that contained sintered zinc-calcium-silicate phosphate and hybrid polyalkenoates as its components was synthesized. Due to its optimized formulation and good biocompatibility, the bone cement was considered a promising material for bone defect filling and repair[60]. In all, elements such as calcium, strontium, zinc, and silica involved in biomaterials can significantly stimulate and promote bone repair and regeneration, and enhanced the bioadaptability of the biomaterials. Additionally, composite scaffolds show excellent