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REVIEW

Advances in bone repair with nanobiomaterials: mini-review

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Abstract Nanotechnology has emerged to be one of the most powerful engineering approaches in the past half a century. Nanotechnology brought nanomaterials for biomedical use with diverse applications. In the present manuscript we summarize the recent progress in adopting nanobiomaterials for bone healing and repair approaches. We first discuss the use of nanophase surface modification in manipulating metals and ceramics for bone implantation, and then the use of polymers as nanofiber scaffolds in bone repair. Finally we briefly present the potential use of the nanoparticle delivery system as adjunct system in promoting bone regeneration following fracture.

Keywords Bone repair · Nanotechnology · Scaffolds · Nanoparticle · Gene delivery · Ceramics · Self-assembling peptides

Introduction

Nanotechnology has emerged to be one of the most powerful engineering approaches in the past half a century, since Feynman's famous talk in 1959. Nanotechnology represents the manner to manipulation atoms and molecules over the scale of nanometer, and generates the materials with at least one dimension in nanoscale. The nanomaterials posses many specific characteristics in comparison to the bulk material due to the "quantum mechanical effect" (Sato and Webster 2004; Wang 2005; Powell and Kanarek 2006; Slocik and Naik 2010). Nanomaterials also have a much larger surface to volume ratio when compared to bulk materials. Nowadays, most nanomaterials can be applied to many aspects in biomedical research. One intriguing application of nanomaterials is to mimic the natural tissues and provide the proper extracellular environment for cells to grow and survive inside of the material (Venugopal et al. 2008; Scheller et al. 2009; Khang et al. 2010); moreover, these bio-compatible biomaterials, pre-implanted with cells or not, implied prospective approaches for tissue repair and regeneration in injured or disease conditions.

Orthopaedic surgeons have recognized the needs for proper materials to repair large defects in bone fracture (Hing 2004; Laurencin et al. 2009; Pellegrini et al. 2009). Many kinds of tissue grafts including allo-grafts and auto-grafts were used in past days; however problems including the immune rejection, infection, pain and inflammation, limited availability and ethic questions exist. Moreover, the surface of these materials might not be cell-coated and tissue compatibility is very low. Biomaterials were therefore synthesized as alternative sources for

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transplantation. Their characteristics vary according to the size of pores, water content, surface interaction, physical properties and the ability to host cells inside or on the surface. Nanomaterials being developed for repair and regeneration of bones included nanoparticle-containing materials with enhanced mechanical properties, nanofibrous scaffolds that can host cells, and nano-delivery systems for delivering drugs into the injured area that promote bone healing (Khan et al. 2008; Laurencin et al. 2009).

Bone healing and repair with grafts

In small bone fraction cases, initial inflammation is followed by soft callus formation, hard callus formation, and, ultimately, bone remodelling. Such automatic recovery does not happen for large bone fractures, which suggests a need for bone repair with grafts to fill the gap. The easiest way is to fix the two ends of broken bones with different metal plates or rods, which was called "internal fixation" (Venable and Stuck 1948; Burch 1958; Deyerle and Bowers 1962; Schatzker et al. 1975). In many years of study, people have optimized stainless steel, cobalt chrome alloys, titanium, and titanium alloy materials with surface modifications and proper screws for internal fixation over other materials (Schatzker et al. 1975; Uhthoff et al. 1981; Head et al. 1995; Disegi and Eschbach 2000). However all these metal-based materials were not bioresorbable, and were susceptible for long-term fatigue or even fracture (Khan et al. 2008); sometimes they also caused immune reactions in the surrounding tissues (Torgersen et al. 1995; Voggenreiter et al. 2003).

The second way is to employ bones from humans (including both autograft and allograft) and animals in repair. Autografts often contain osteogenic cells, bone marrow cells and the existing collagen matrix can promote the healing processes; this method was also considered as the "gold standard" (Fleming et al. 2000). However the harvest of autograft leads to donor site deficiency, and surgical pain. At the same time, allografts from other individuals or animals could bring diseases to the recipient host and immunological rejection with a long-term failure in follow up studies (CDC 2001; Wheeler and Enneking 2005). In recent decades, the use of synthetic materials for bone repair has achieved significant progress with the progresses in nanotechnology, and brought new approaches in clinical bone repair.

Nanotechnology and nanomaterials for bone repair

Feynman suggested: "there's plenty of room at the bottom". Nanotechnology has emerged to be one of the most powerful technologies in applied biomedical sciences. Nanomaterials include all types of materials with at least one dimension in less than 100 nm. The scale differences and surface modifications let nanomaterials vary in physical and chemical properties. Currently there are several major applications of nanotechnology for bone repair materials. One important property of bone repair materials is the mechanical property, and many nanomaterials have superior mechanical characteristics (Balasundaram and Webster 2006; Webster and Ahn 2007). The other way is to perform surface modification at nano-level, which provide better matrix for osteoblasts to grow and to function. For instance, osteoblasts on nanosized Ti, Ti6Al4V, and CoCrMo powder-modified metal surfaces as well as ceramics have improved adhesion and functions when compared to macrophase ones (Webster et al. 2000a; Webster and Ejiofor 2004; Webster and Smith 2005). The third way is to generate degradable polymers or use nanotechnology to modify some natural polymers such as collagen. The nano-scaffolds are much more porous and could better mimic the real extracellular matrix (ECM) in terms of number, sizes of pores and physical properties when compared to micro-scaffolds. It has been found that these nano-rough materials could also improve osteoblast functions when compared to macro-rough scaffolds (Balasundaram and Webster 2006; Marquis et al. 2009; Scheller et al. 2009; Tran and Webster 2009). Finally, nanoparticles enabling delivery of drugs and growth factors were used to promote healing and functional recovery (Fig. 1; Table 1).

Nanotechnology based metal and ceramic materials

It is easier to perform surface modifications on currently used metal plates and screws in comparison to generate a whole plate of nanomaterials for

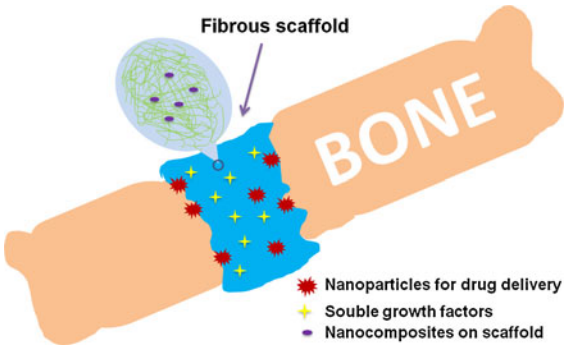

Fig. 1 Nanotechnology enables repair of bone fracture in bone fracture cases, nanomaterials were implanted into the wound area. The *figure* represents the use of nanocomposites of polymer scaffolds and ceramics as well as nanoparticles. Many drugs and growth factors can be included in the scaffold for controllable release over the time period to promote bone healing

internal fixation. The bio-compatibility of these materials was largely determined by surface properties, such as immunogenicity, hydrophilicity, the ability to host cells and processes, and adhesion of osteoblasts. These modifications were reported to elongate the integration of implanted plates and bone tissues over extended time periods (Buser et al. 1999; Ferris et al. 1999; Webster and Ejiofor 2004; Oyane et al. 2005; Liu et al. 2006; Fan et al. 2007; Yokoyama et al. 2007; Harvey et al. 2010). As mentioned above, with nanosized Ti, Ti6Al4V, and CoCrMo powder-modified (pressed onto the surface) metal surfaces, seeded osteoblasts showed improved functions including adhesion, proliferation, and deposition of calcium-containing minerals (Webster et al. 2000a; Webster and Ejiofor 2004; Webster and Smith 2005). Another way to change the surface property of metals is the anodization that can bring nano-sized pores (Yao et al. 2007; Yao et al. 2008), which could be further used for installation of other nano-structures such as carbon nanotubes as biosensors for bone regrowth (Sirivisoot et al. 2007). The fact that nanometer roughness is most suitable for biological tissues to grow one can emphasize the importance of nanotechnology in bone repair in the coming decades.

Besides metals, people have found nanostructured ceramics promoted bone functions when compared to micro-structured ones (Webster et al. 1999; Webster et al. 2000a; Webster et al. 2000b; Li et al. 2009). These include: (1) metallic oxides such as aluminium, zirconium, and titanium; (2) calcium phosphates such as hydroxyapatite (HA), tricalcium phosphate (TCP) and calcium tetraphosphate; (3) glassceramics such as Bioglass and Ceravital (Tran and Webster 2009). These materials showed similar material properties as surface modification of metals, such as increased osteoblasts adhesion, proliferation, alkaline phosphatase activity, and calcium deposition (Webster et al. 1999; Webster et al. 2000a, b; Kay et al. 2002). More updates of ceramics such as protein based surface modifications are now being developed and explored (Webster et al. 2000b; Balasundaram and Webster 2006; Colilla et al. 2008; Tran and Webster 2009).

Nanomaterials based polymers and scaffolds

Synthetic materials also include polymers that could form scaffold like structures, and when seeded with osteoblasts, provide ideal environment for cell proliferation and growth matrix. During the process of bone healing, these materials could be degraded and even used (as in the case of self-assembling peptides), without causing any immunological response. Because they are synthetic, there is no risk of viral infection or bringing diseases to the recipient hosts. The degradation time depends on the property of the scaffold itself, the density of scaffold, and the available enzymes in

Table 1 Available nanomaterials being employed for bone repair

Type	Major application	Bio-compatibility	Stability
Metal	Internal fixation; bone replacement; physical supports	Could be improved with surface modification	Long-term efficiency
Ceramics			
Polymers	Cell seeding; soft tissue replacement; surface application; weak physical support	Depending on materials	Depending on biodegradation
Scaffolds, hydrogels		High	
Nanoparticles	Drug delivery; gene delivery; protein delivery; controlled and targeted release	Could be improved with surface modification	Could be controlled

the bone tissues (Marquis et al. 2009; Harvey et al. 2010; Khang et al. 2010; Kubinova and Sykova 2010; Vallet-Regi 2010). Therefore this is a system with controllable degradation, which could be combined with drug or growth factor release during bone healing.

Collagen was one of the first nanofiber scaffolds that was generated due to its common presence in natural tissues (Laurencin et al. 2009; Prabhakaran et al. 2009). The high biocompatibility suggested collagen to be the ideal choice for soft tissue repair or transplantation when seeded together with types of cells of interest. However, there is lack of good mechanical properties and the use for bone repair is therefore weakened. Some other candidates with better mechanical characteristics include poly-lactic acid (PLA), poly-glycolic acid (PGA), and poly-lactic-co-glycolic acid (PLGA). They have been approved by the US Food and Drug Administration (FDA) for clinical uses. When these polymers form nanofiber scaffolds, these materials were found to be able to enhance the protein adsorption functions of osteoblasts (Wei and Ma 2004; Xiao et al. 2008). Additionally, the polymer casts of nanophase carbon fibers rather than conventional fibers showed improved properties in supporting the functions of osteoblasts (Price et al. 2003, 2004). In other studies, Ceramic/Polymer nanocomposites were designed and developed to create better materials as bone implant scaffolds with improved mechanical strength. It was found that the mixed material showed better support for osteoblasts than each individual component (Marra et al. 1999; Ma et al. 2001; Blaker et al. 2003; Jung et al. 2005). More and more nanocomposites of different compositions and thus different mechanical properties as well as diverse biocompatibilities are yet to be developed.

Among different types of nanofiber scaffolds, one family was found to be interesting and prospective in regenerative medicine. That is the self-assembling peptides (SAP). The concept of self-assembling peptides, which is very common in biological activities such as protein aggregation, suggested that biomaterials could be designed to support cell functions in a controllable manner (Semino 2008). In past decades, many different types of SAP were designed and reported, which would start gelation in polarized solvents, such as physiological solutions. These include EAK16, RAD16-I, RAD16-II, DN1, KLN12, etc. For instance, RAD16-I would form nanofiber scaffold in ionic solutions, which has been shown to be able to support growth and proliferation of many types of cells, and when transplanted in vivo, to repair injured tissue with functional recovery (Bokhari et al. 2005; Genove et al. 2005; Garreta et al. 2007; Dubois et al. 2008; Dégano et al. 2009; Tang and Zhao 2010). RAD16-I was found to be able to promote bone regeneration and to lead to new bridge formation, as well as to inhibit demineralization (Misawa et al. 2006; Garreta et al. 2007; Kirkham et al. 2007). It was also suggested that by modification of anionic groups of the side-chains, the SAP could have better properties in attracting calcium and inducing salt precipitation (Kirkham et al. 2007), which is critical for new bone formation. The best news is that people could design any type of SAP they wanted as long as the basic physical laws are respected, which provides almost endless possibilities in new materials development and discoveries.

Last but not least, carbon nanotubes could form scaffolds for bone repair. Both single-wall and multi-wall carbon nanotubes were found to be able to interact with the biological tissues and to be useful for bone repair (Tutak et al. 2009; Zhang et al. 2009; Bhattacharya et al. 2011; Joshi et al. 2010; Mendes et al. 2010; Niu et al. 2010; Sahithi et al. 2010; Tutak et al. 2010). This has been well presented in the published literature and will not be further discussed here (see above references).

Nanoparticle delivery system for bone healing

Besides the contribution as bone implant, nanotechnology provides excellent drug and molecule delivery systems with high targeting efficiency. Currently available nanoparticles for drug delivery mainly include polymeric nanoparticle, PEG-ylation modified particles, micelle, liposome, dendrimer, and nanosized inorganic materials (Kim and Fisher 2007). These systems vary in terms of their efficiency in different biological systems, toxicity, the sizes of genetic sequences being carried, penetration depth in tissue, and targeting efficiency (Goldberg et al. 2007; Zhang and Uludag 2009). For bone healing, both genes and proteins could be delivered to promote proliferation of osteoblasts, the formation of new blood vessels, and the secretion of calcium salts. For instance, the system of VEGF-DNA loaded PLGA nanoparticles was tested in vitro and was shown to penetrate the cytoplasm and to attain the nucleus (Yi et al. 2006). Also, cationic

liposomes with BMP-2 cDNA could enhance bone regeneration in a rabbit model of cranial bone defects (Ono et al. 2004). Similar studies with BMP-2 gene delivery showed effects on cultured cells and rat models (Matsuo et al. 2003; Park et al. 2003). Given the fact that many signalling molecules for bone healing and regeneration have been identified in the past years, it is believed that with nanoparticle delivery and controlled release bone repair could be largely facilitated in the future.

Summary

In summary, in the recent years nanotechnology had greatly promoted the development of new methods and approaches for bone repair. One major aspect is the emergence of diverse nanomaterials with abundant properties for different types of applications, and experts can still further engineer these materials for individual medicinal use. This is prospective novelty. The other side of nanotechnology is nanodelivery, which is more efficient and precise than conventional approaches. Currently there is lack of sufficient preclinical and clinical studies with nanomaterials for bone repair: while there is evidence that human stem cells could be seeded onto nanomaterials for growth and amplification (Soumetz et al. 2008; Sundelacruz and Kaplan 2009; Dupont et al. 2010). The authors believe that the application of nanotechnology in modern bone repair will finally bring further benefits for patients in the future.

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