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EDITORIAL

Nanotechnology for Bone and Cartilage Engineering

Bone and cartilage defects remain challenging and common problems for Orthopaedic and Plastic & Reconstructive surgeons today [1]. Autologous bone grafting remains the gold standard to restore bone defects; this is limited by donor site morbidity, tissue availability and resorption or failure of the transplanted bone [1]. Similarly, to restore the cartilaginous framework of the ear or nose, rib cartilage is carved into a suitable shape and size and placed beneath the subcutaneous tissue [1]. To overcome these problems, synthetic materials have been investigated for the replacement of bone or cartilage tissue [1]. However, these materials have been limited in their ability to regenerate new tissue or by causing infections or foreign body reactions [1]. A new approach to developing better biomaterials is the consideration of 'nano' based materials, a rapid and growing field of 'Nanotechnology'.

Scaffolds are the constructs responsible for carrying cells or growth factors that direct the cell behaviour towards the regeneration of new tissue [2]. Using nano-based materials has the ability to create better scaffolds for tissue regeneration. A nanoparticle is a particle that ranges from 1 to 100 nm in size [2]. By definition a nanomaterial is a scaffold that consists of elements that have components that are less than 100 nm. The extracellular matrix of bone and cartilage consists of a hierarchy of nano-sized parts *e.g.* collagen fibrils and hydroxyapatite crystals [2]. Therefore, it is not surprising that nanotechnology and nanobiomaterials have populated the field of bone and cartilage engineering. A scaffold mimicking the native ECM provides appropriate cues for cellular cytoskeletal arrangement and intracellular signalling for gene and protein expression for tissue regeneration [2].

Several types of nanobiomaterials exist including the manufacturing of nanofibres and nanocomposites to act as scaffolds for cartilage and bone regeneration. In electrospinning, fibres are created by applying an electric charge to a polymeric solution [3]. Nanofibres provide high surface area to volume ratio, providing an environment for good cell adhesion, proliferation and differentiation, enhancing tissue engineering. Many synthetic materials have been investigated using electrospinning for tissue regeneration including poly(lactic acid) (PLA), polyurethane (PU), poly(caprolactone) (PCL) and poly(lactic-co-glycolic acid) (PLGA) [3]. For example, PCL nanofiber meshes cultured in a perfusion bioreactor demonstrated chondrogenic differentiation of human bone marrow stem cells using morphological and RT-PCR analysis [4]. An advantage of nanofibres is the ability to incorporate chemical cues such as growth factors within nanofibres during the manufacturing process [5]. The addition of chemical cues allows the development of scaffolds that more closely resembles the native environment [5]. Bone formation *in vivo* required the support of growth factor including therefore scaffolds that have signals for osteoinduction could be designed to mimic the native signalling *in vivo* [5]. From this technology, further questions are posed including what to release and how much to release to have a significant effect *in vivo*.

Bone is a connective tissue, consisting of a collagen matrix and hydroxyapatite minerals within it [6]. Hence, nanocomposite materials are widely studied for bone tissue engineering to mimic the native bone tissue [6]. Bioceramics including calcium phosphate, calcium sulphate and β-TCP, hydroxyapatite are all used for bone-tissue engineering [6]. However, such materials are limited by their brittle nature. Synthetic polymers such as poly(lactic acid) (PLA) and poly (lactide-co-glycolide) (PLGA) are biocompatible used in combination with such ceramics to improve the bioactivity and mechanical properties [6]. For example, PLA/collagen/hydroxyapatite (HA) composite showed a similar elastic modulus to bone as well as good osteoblast adhesion, proliferation and bone formation in a segmental bone rabbit defect [7, 8]. Natural polymers have also been incorporated into nancomposites with ceramics and shown to positively influence cell adhesion and function [9]. Gelatin and HA demonstrated good MSC adhesion and an elastic modulus similar to bone [9]. Key issues when making inorganic/organic composites is the dispersion of the

nanoparticles within the scaffold with different approaches including mixing the particles in polymer solution. However, mixing the nanoparticles with other materials can create problems with agglomeration and so is under current exploration [10].

Other than in combination with scaffolds, nanoparticles offer several other uses to improve bone and tissue engineering. Nanoparticles can be used for labelling of stem cells to observe stem cell behaviour or direct cell to certain locations within the body. For example, magnetic based nanoparticles have been used to track stem cells when placed *in vivo* [11]. Furthermore, labelling of MSCs with nanoparticles can home cells to desired tissue by conjugating them with antibodies [12]. Further research aims to completely understand balancing the toxicity and effect of the nanoparticles and understanding their activity and life time *in vivo.*

Carbon nanotubes are another dimension of nanotechnology that shows promise for tissue engineering of cartilage and bone [13]. Carbon nanotubes are single or rolled multiple graphene sheets that form single or multi walled nanotubes [13]. The advantages of such scaffolds include the high surface area-to-volume ratio with excellent electronic, mechanical and thermal properties [13]. CNTS have been explored in terms of being mixed with other materials or by functionalising different surfaces [13]. For bone tissue engineering this could be useful by reinforcing biomaterials to improve the scaffolds ability to substitute hard tissues [13]. Carbon nanotubes also holds promised to act as biosensors or for delivery of molecular signals for tissue replacement [13]. Further work, will be to fully understand the effect on cell function and ability for tissue regeneration.

Another approach to manipulate and enhance tissue regeneration is to create nano sized topographies on the surfaces. It has been shown that nano-scale surface modifications can influence cell behaviour, improving regenerative outcomes [14]. Topographies include imparting grooves, ridges, wells, islands or pits on materials surfaces to modify cell morphologies and protein adsorption to influence cell proliferation and differentiation [14]. A seminal paper by Dalby *et al* demonstrated that the order of pits effected the osteogenic differentiation of hMSCs [15]. Future work in this area of research will explore the shape and size of the topographic feature that can reliably influence specific proteins and cell responses expanding the impact of surface topography.

Although nanomaterials offer a considerable step forward to enhancing musculoskeletal regeneration, there is still progress to be made to advance nanotechnology in the field of bone and cartilage regeneration. Although implementing nanotopographies into scaffold manufacture has enhanced cell survival and osteogenic and chondrogenic differentiation of MSCs, further understanding into the surface interphase is required before nanoscaled scaffolds can be tailored to complex skeletal defects at different anatomical sites [2]. Further understanding into the effect of surface roughness, chemistry and nanoscale featues on cell behaviours is required [2]. For nanotechnology to have the greatest impact on musculoskeletal regeneration fields of material science, biology, engineering and surgery will need to combine to create meaningful strategies for the restoration of bone and cartilage defects [2].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Griffin M, Kalaskar DM, Butler PE, Seifalian AM. The use of adipose stem cells in cranial facial surgery. Stem Cell Rev 2014; 10(5): 671-85. [http://dx.doi.org/10.1007/s12015-014-9522-3] [PMID: 24913279]

[2] Walmsley GG, McArdle A, Tevlin R, *et al.* Nanotechnology in bone tissue engineering. Nanomedicine (Lond) 2015; 11(5): 1253-63. [PMID: 25791811]

[3] Vasita R, Katti DS. Nanofibers and their applications in tissue engineering. Int J Nanomedicine 2006; 1(1): 15-30. [http://dx.doi.org/10.2147/nano.2006.1.1.15] [PMID: 17722259]

[4] Alves da Silva ML, Martins A, Costa-Pinto AR, *et al.* Cartilage tissue engineering using electrospun PCL nanofiber meshes and MSCs. Biomacromolecules 2010; 11(12): 3228-36. [http://dx.doi.org/10.1021/bm100476r] [PMID: 21105638]

[5] Ji W, Sun Y, Yang F, *et al.* Bioactive electrospun scaffolds delivering growth factors and genes for tissue engineering applications. Pharm Res 2011; 28(6): 1259-72. [http://dx.doi.org/10.1007/s11095-010-0320-6] [PMID: 21088985]

[6] Sahoo NG, Pan YZ, Li L, He CB. Nanocomposites for bone tissue regeneration. Nanomedicine (Lond) 2013; 8(4): 639-53. [http://dx.doi.org/10.2217/nnm.13.44] [PMID: 23560413]

[7] Liao SS, Cui FZ. *In vitro* and *in vivo* degradation of mineralized collagen-based composite scaffold: nanohydroxyapatite/collagen/poly(L-lactide). Tissue Eng 2004; 10(1-2): 73-80. [http://dx.doi.org/10.1089/107632704322791718] [PMID: 15009932]

[8] Liao SS, Cui FZ, Zhang W, Feng QL. Hierarchically biomimetic bone scaffold materials: nano-HA/collagen/PLA composite. J Biomed Mater Res B Appl Biomater 2004; 69(2): 158-65. [http://dx.doi.org/10.1002/jbm.b.20035] [PMID: 15116405]

[9] Barbani N, Guerra GD, Cristallini C, *et al.* Hydroxyapatite/gelatin/gellan sponges as nanocomposite scaffolds for bone reconstruction. J Mater Sci Mater Med 2012; 23(1): 51-61. [http://dx.doi.org/10.1007/s10856-011-4505-2] [PMID: 22116662]

[10] Saiz E, Zimmermann EA, Lee JS, Wegst UG, Tomsia AP. Perspectives on the role of nanotechnology in bone tissue engineering. Dent Mater 2013; 29(1): 103-15. [http://dx.doi.org/10.1016/j.dental.2012.08.001] [PMID: 22901861]

[11] Wahajuddin AS, Arora S. Superparamagnetic iron oxide nanoparticles: magnetic nanoplatforms as drug carriers. Int J Nanomedicine 2012; 7: 3445-71. [http://dx.doi.org/10.2147/IJN.S30320] [PMID: 22848170]

[12] Yang SY. Dual immobilization and magnetic manipulation of magnetic nanoparticles. J Magn Magn Mater 2008; 320: 2688-91. [http://dx.doi.org/10.1016/j.jmmm.2008.05.048]

[13] Newman P, Minett A, Ellis-Behnke R, Zreiqat H. Carbon nanotubes: their potential and pitfalls for bone tissue regeneration and engineering. Nanomedicine (Lond) 2013; 9(8): 1139-58. [PMID: 23770067]

[14] Stevens MM, George JH. Exploring and engineering the cell surface interface. Science 2005; 310(5751): 1135-8. [http://dx.doi.org/10.1126/science.1106587] [PMID: 16293749]

[15] Dalby MJ, Gadegaard N, Tare R, *et al.* The control of human mesenchymal cell differentiation using nanoscale symmetry and disorder. Nat Mater 2007; 6(12): 997-1003. [http://dx.doi.org/10.1038/nmat2013] [PMID: 17891143]

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