Nanotechnology: Translational Applications in Orthopaedic Surgery

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Introduction

The infinite molecular interactions that take place in the human body occur on the scale of nanometers (nm), or one billionth of a meter.[1,2] Particles of less than 100nm have drastically different behavior versus larger particles with regard to melting point, conductivity, and reactivity.[3] Materials with nanoscopic grain size have altered chemical properties that may produce unique and advantageous surface characteristics.[4] Nanotechnology has developed into a multibillion dollar industry that has applications in dozens of fields, including science, electronics, cosmetics, and medicine. Basic science and translational research has revealed many important potential applications for nanotechnology in orthopaedic surgery. In this brief overview, we will discuss current concepts and future directions of nanotechnology in total joint arthroplasty, trauma surgery, orthopaedic oncology, musculoskeletal infection, and the treatment of peripheral nerve injuries.

Nanotechnology and Bone

Bone synthesis takes place at the nanoscopic level through interactions between macromolecules that promote osteoblast function. When orthopaedic implants are introduced into the natural cell environment, interactions between the implant and extracellular proteins are critical for osteointegration. Extracellular adhesion proteins, such as fibronectin and vitronectin, mediate osteoblast activation and adhesion to biomaterials, resulting in osteointegration.[5,6] Unlike conventional implants, nanoscale surface topography mimics the topography of the natural cell environment allowing them to interact more effectively than conventional materials with extracellular adhesion proteins.[3] Adsorption of these molecules is significantly increased on nanosurfaces as compared to conventional surfaces.[4] Furthermore, nanostructured materials have been shown to inhibit the activity of cells that impede ingrowth and ongrowth, including smooth muscle cells, fibroblasts, and chondrocytes, resulting in improved osteointegration of implants.[7]

Orthopaedic Device Applications

The application of nanotextured materials may reduce the risk of implant failure through improved osteointegration.[4,8] As previously discussed, nanotextured surfaces enhance osteoblast function and decrease fibroblast function. This preferential cell activity results in increased bone formation on nanotextured hydroxyapatite coated surfaces when compared to similar materials with conventional roughness.[3,9,10] When nano-sized hydroxyapatite is added to morselized cancellous bone graft, *in vitro* acetabular cup integration and stability following impaction grafting is significantly enhanced.[11] Improved mechanical properties are also seen in bone cement reinforced with nanoclay filler material.[8] Some additional materials that display nanophase characteristics include nanoceramics, alumina, titania, carbon, selenium, nanometals Ti6AlV, cobalt chrome alloys, and nanocrystalline diamond.[4,7,9,10,12-18]

Nano-composite scaffold implants composed of Type I collagen and nanostructured hydroxyapatite are being used clinically in the treatment of osteochondral defects of the knee. This type of implant may provide an 'off the shelf' cell-free solution to chondral defect treatment that is easier and less morbid than autograft or stem cell procedures [10,19,20].

In vitro studies have shown promise for nanotechnologic applications in orthopaedic oncology. Selenium has been found to be a powerful potentiator of chemotherapeutic agents.[21] When manufactured on the nanometer scale and coated on titanium orthopaedic implants, nanophase selenium appears to inhibit malignant osteoblastic growth at the implant-tissue interface.[22] Similarly, nanophase hydroxyapatite causes *in vitro* inhibition and apoptosis of osteosarcoma cells.[23]

Advancements in nanotechnology have also shown potential for use in the prevention of infection. Nanophase silver dressings have proved to be more effective at preventing wound infections and stimulating wound healing than traditional silver-based dressings.[24,25] Nanophase silver incorporated onto the surface of titanium orthopaedic implants has demonstrated strong, immediate bactericidal and anti-adhesive effects lasting for up to 30 days.[26]

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Nanophase materials have also had encouraging results when utilized for the treatment of peripheral nerve injury. Nanophase silver-impregnated Type I collagen scaffolds increase the amount of adsorbed proteins critical to nerve healing and lead to significant decreases in the time to nerve regeneration. In one study, the use of these scaffolds for the treatment of sciatic nerve defects in rabbits showed thicker myelin sheaths, improved nerve conduction, and higher rates of laminin adsorption when compared to control Type I collagen scaffolds.[27]

Safety and Areas of Future Research

Critical unanswered questions remain regarding the safety of nanomaterials. The toxicity profiles of many nanomaterials are currently not known. Nanoparticles may be released over time through the degradation of implanted nanomaterial or may potentially enter the body through the dermal pores of individuals involved in their manufacture.[28] The metabolism of nanoparticles has been shown to involve various organ systems, including blood, liver, and kidneys, and may result in inflammation and oxidative stress.[29,30] Nanoparticle wear debris has uncertain local tissue effects,[9] and has been correlated with brain and lung toxicity in the in some studies.[9,31] In contrast, nanosize wear debris has been associated with increased cell viability in bone and lung when compared to conventional wear particles in other studies.[9] Due to the uncertainty regarding the safety of nanomaterials, studies evaluating the toxicity of nanophase materials must be conducted prior to the clinical application of these materials on a large scale.[32,33]

Conclusion

The extensive basic research on nano-scale materials may yield beneficial orthopaedic surgical applications; however, relatively few clinical studies have been performed to confirm utility and safety of these agents. Though still in its infancy, nanotechnology has promising applications in arthroplasty, trauma, sports medicine, orthopaedic oncology, orthoplastic surgery, and many other facets of musculoskeletal medicine. The vast opportunities for advancement of nanotechnology and its applications within orthopaedic surgery present an exciting frontier in orthopaedic research.

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