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Review

Effects of orthopaedic wear particles on osteoprogenitor cells

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Abstract

Wear particles from total joint arthroplasties are constantly being generated throughout the lifetime of an implant. Since mesenchymal stem cells and osteoprogenitors from the bone marrow are the precursors of osteoblasts, the reaction of these cells to orthopaedic wear particles is critical to both initial osseointegration of implants and ongoing regeneration of the periprosthetic bed. Particles less than 5 μm can undergo phagocytosis by mature osteoblasts, with potential adverse effects on cellular viability, proliferation and function. The specific effects are dependent on particle composition and dose. Metal and polymer particles in non-toxic doses stimulate pro-inflammatory factor release more than ceramic particles of a similar size. The released factors inhibit markers of bone formation and are capable of stimulating osteoclast-mediated bone resorption. Mesenchymal stem cells and osteoprogenitors are also profoundly affected by wear particles. Titanium and polymethylmethacrylate particles inhibit bone cell viability and proliferation, and downregulate markers of bone formation in a dose- and time-dependent manner. Future studies should delineate the molecular mechanisms by which particles adversely affect mesenchymal stems cells and the bone cell lineage and provide strategies to modulate these effects.

Keywords: Osteoblast; Mesenchymal stem cell; Osteoprogenitors; Wear particles; Total joint arthroplasty

Contents

1. Introduction

The generation and biological effects of wear debris are major factors determining the longevity of hip and knee arthroplasties [1]. Research in this area has largely focused on the properties of the retrieved implants and periprosthetic tissues, in vivo and in vitro models of implant loosening, and the activities of key cells such as macrophages and fibroblasts that dominate the interface tissue [1]. These latter cells release important pro-inflammatory mediators that induce osteoclast differentiation and maturation, and subsequent bone resorption. Only recently has attention been directed to the effects of wear particles

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on bone cells and their progenitors. Although bone formation and resorption are closely linked events, the progenitor cells are different. Bone-resorbing osteoclasts are derived from the monocyte/macrophage haematopoietic cell lineage, whereas osteoblasts develop from mesenchymal stem cells [2–8]. In prosthesis-associated osteolysis, numerous cell types communicate via an intricate paracrine network of cytokines, chemokines, oxygen-containing radicals and other molecules resulting in the undermining of the prosthetic bed [1,9]. Although macrophages and osteoclasts are integral elements underlying bone destruction in periprosthetic osteolysis, the effects of wear particles on cells of the osteoblastic lineage significantly impact the replacement of bone at the prosthetic interface [10–26]. Recent studies confirm that wear particles profoundly alter the differentiation, maturation and function of osteoprogenitors, thereby contributing to the osteolytic process by decreasing bone formation.

2. The bone cell lineage

Bone cells have a common stem cell with other mesenchymal-derived tissues including muscle, fat, cartilage, tendon, ligament, marrow stromal tissue and cardiac and neural tissue [2,3,8,27–30]. Exposure of the stem cells to specific growth factors, cytokines and other signalling mechanisms causes stem cells to commit to a particular lineage. There are intermediate stages of cell differentiation and maturation before the fully differentiated and functional cell becomes manifest. During the stages of development, the differentiating cells display unique surface antigenic profiles and may secrete specific proteins [2,3,8,27–30]. In the case of the osteoblastic lineage, the generally accepted progression includes osteoprogenitors, pre-osteoblasts, transitory osteoblasts, secretory osteoblasts, osteocytic osteoblasts and osteocytes, although this sequence of events is probably an underestimation of the numerous intermediary stages [2–4,8,27–30]. Furthermore, there may be more plasticity in mesenchymal stem cell lineage that is dependent on numerous factors in the local biological and mechanical environment, rather than a rigid, progressive, directed lineage as previously thought [27–30].

3. Exposure of bone cells to orthopaedic wear particles

As a starting point to explore the effects of particles on osteoprogenitors, several groups have investigated the biological response of bone cells to metallic, polymeric and ceramic particles in vitro. Vermes et al. [10] exposed MG-63 osteoblasts to particles of commercially pure titanium (cpTi), Ti–6Al–4V alloy (Ti–A), chromium orthophosphate, medical grade ultra-high-molecular weight polyethylene (UHMWPE) and polystyrene at concentrations of up to 0.2% (vol/vol). 90% of the particles were $<3\,\mu m$ in diameter. Osteoblasts phagocytosed the particles in a time-dependent fashion over 72 h. The particles had no effect on cell viability but induced a dose-dependent decrease in cell proliferation. Particle-stimulated osteoblasts released increased amounts of interleukin-6 (IL-6) and TGF-β1. All particle types significantly suppressed procollagen a1[I] gene expression but did not suppress other osteoblast-specific genes including osteonectin, osteocalcin (OC), and alkaline phosphatase (AP). This study demonstrated that osteoblasts can phagocytose particles which may have a significant, potentially adverse effect on bone cell metabolic activity in vitro.

Shida and associates [11] exposed MG-63 osteoblast-like cells to titanium particles at a concentration of 0.30% v/v. Particle exposure resulted in a 15-fold increase in IL-6 release into the culture medium after 24 h, when compared with cells without particles. IL-6 mRNA signal levels increased by 9.6-fold. Pretreatment of the cells with cytochalasin B prevented the particle-induced increase of IL-6 expression. The protein kinase C inhibitor, H7, and the serine/threonine kinase inhibitor, genistein (but not the inhibitor of protein kinase A, HA1004) abolished the particle-induced increase in IL-6 release at a concentration of 100 μM for each compound. The transcription factors, nuclear factor IL-6 and nuclear factor κB, translocated into the nucleus within 1 h of particle exposure. This study showed that osteoblast-like cells respond to titanium particles through increased expression of the proinflammatory cytokine, IL-6, in a process requiring phagocytosis and intracellular signalling pathways.

Lohmann and colleagues exposed primary human osteoblasts and MG-63 osteoblast-like cells to cpTi, Ti–A, cobalt–chrome alloy (CoCr) and UHMWPE (GUR 4150) particles approximately 1 μm in diameter for 24 h [12,13]. As visualized by transmission electron microscopy, the cells phagocytosed the particles and demonstrated extensive ruffling of the cell membranes, swelling of the mitochondria, inclusion vacuoles and a less-developed endoplasmic reticulum, compared with untreated cells. When exposed to metallic particles, MG63 cell number was dependent on the chemical composition of the particles. Ti–A and CoCr increased cell number in a dose-dependent manner whereas the effect of cpTi particles was biphasic. AP activity was inhibited more by cpTi than the other metals. Production of prostaglandin E2 was increased by all particle types, with CoCr being the most reactive material.

Sung, Piolettti and co-workers have examined the effects of cpTi particles on osteoblasts from humans and rats [14–20]. In a study using two human osteoblast-like cell lines (MG-63 and SaOS-2) they showed an additive effect of TNF-α and titanium particles on inhibition of cell proliferation and AP production [14]. However, TNF-α and titanium particles increased IL-6 production by osteoblasts. This suggested that particles might lead to a dual effect: reduced periprosthetic bone formation due to inhibition of osteoblast proliferation and AP production, and increased bone resorption by IL-6 osteoblast-mediated osteoclastogenesis.

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