Bone Morphogenetic Protein 2 Induces an Inflammatory Profile in MSCs on Microstructured Titanium

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Statement of Purpose: Modifications to biomaterial surface properties have been created to induce mesenchymal stem cell (MSC) differentiation and bone formation. Microtextured metallic surfaces promote osteoblast differentiation and high surface energy further increases osteoblast differentiation, and peri-implant bone formation.

Recombinant human bone morphogenic protein 2 (BMP2) is approved to induce bone formation in a number of applications and is used clinically in combination with biomaterials to improve peri-implant bone formation and osseointegration. However, the amount of BMP2 that is required is large and inflammatory complications (swelling, seroma) and bone-related complications (ectopic bone/bone resorption) have been reported after BMP2 treatment. The aim of this study is to determine whether human MSCs modulate inflammatory molecules in response to surface microstructure and if BMP2 can affect the inflammatory microenvironment created by MSCs.

Methods: Human bone marrow derived MSCs were cultured on tissue culture polystyrene (TCPS), or titanium substrates: smooth (PT) [Ra<0.4μm], sandblasted/acid etched (SLA) [Ra=3.2μm], or hydrophilic-SLA (modSLA). In the first experiment, MSCs were cultured on TCPS or Ti substrates and treated daily with 0, 100, or 200 ng/ml BMP2. After 7 days of culture, osteogenic differentiation (alkaline phosphatase specific activity, osteocalcin,), local factor production (osteoprotegerin, vascular endothelial growth factor (VEGF)), and interleukin production (IL6, IL8, IL10) were measured.

In the second experiment, SLA and modSLA substrates were dip coated in 300 ng or 600 ng BMP2 and surfaces dried for 24 hours. MSCs were cultured on uncoated or coated surfaces for 48 hours. Levels of mRNA were measured for interleukins (IL6, IL8, IL10) and markers of osteoblastogenesis (OCN, OPG, RUNX2).

Results:

MSCs cultured on Ti surfaces had lower cell number, IL6, and IL8 and higher alkaline phosphatase specific activity, and levels of osteocalcin, osteoprotegerin, VEGF, and IL10 in their conditioned media than cells on TCPS. Addition of 100 ng/ml BMP2 increased differentiation (alkaline phosphatase specific activity, osteocalcin), but increased bone resorption factors (IL6, IL8) and decreased IL10 and osteoprotegerin (Figure 1). Higher doses of BMP2 (200 ng/ml) abolished the increase in differentiation and growth factor production and induced a larger increase in IL6 and IL8 production.

MSCs cultured on BMP2 dip coated SLA surfaces had higher IL1B, IL6, and IL8 production and lower IL10, an effect reduced by culture on modSLA surfaces. However, there was no effect on osteogenic differentiation at the lower dose. Cells cultured on the higher dose BMP2 substrates had lower mRNA levels of all factors measured in comparison to control.

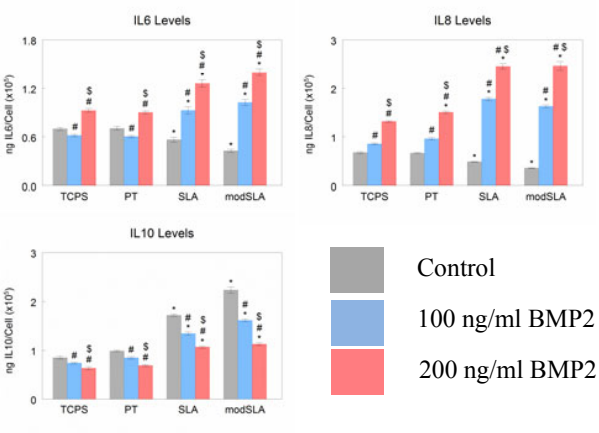

Figure 1. Production of interleukins secreted by MSCs cultured on TCPS, PT, SLA, or modSLA treated daily with 0 ,100ng/ml BMP2, or 200 ng/ml BMP2. *p<0.05, vs. TCPS; #p<0.05, vs. control ; $p<0.05, vs. 100 ng/ml BMP2.

Conclusions: Addition of BMP2 induced differentiation. However, BMP2 also induces a pro-inflammatory response, an effect dependent on dose. Culture of MSCs on BMP2 dip-coated titanium surfaces yielded similar effects at low doses, but all regulation was prevented by culture on higher dose BMP2 surfaces. BMP2 in combination with microtextured orthopaedic and dental implants may increase inflammation and possibly delay bone formation. Dose, location, and delivery strategies are important considerations in BMP2 as a therapeutic and require optimization to minimize complications.

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