BMP-2 Increases Survival of Mesenchymal Stem Cells and Fracture Healing When Deployed in Photopolymerizable Hydrogels

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Purpose: Mesenchymal stem cells (MSCs) have great therapeutic potential for the repair of nonhealing bone defects due to their proliferative capacity, multilineage potential, trophic factor secretion, and lack of immunogenicity. However, a major challenge to the translation of cell-based therapies into bone regeneration constructs is ensuring their survival and function upon implantation. Composite constructs utilizing growth factors such as bone morphogenetic proteins (eg, BMP-2) and MSCs are under investigation for use in the clinic, yet the effect of BMP-2 delivery on MSC survival and function remains poorly studied. We investigated cell survival and subsequent effects on bone regeneration in MSCs codelivered with BMP-2. Our aim was to determine the efficacy and survival of MSCs when delivered with BMP-2 via a photopolymerized, modified alginate carrier in a rat critical size defect (CSD) model.

Methods: Diaphyseal CSDs (6 mm) were created in the right femora of 10- to 12-week-old male athymic rats and stabilized with a radiolucent PEEK (polyetheretherketone) plate and 6 angular stable bicortical titanium screws. Sodium alginate modified with methacrylate side chains, to enable photopolymerization, and Arg-Gly-Asp (RGD) peptide, to promote adhesion, was used as the carrier. Human MSCs genetically modified to express luciferase (3 x 106 cells/150 μL gel) were suspended in the gel, cross-linked (0.05% w/v photoinitiator 3.5 mW/cm2) for 30 min, and then incubated at 37ºC in α-MEM (minimum essential medium) up to 12 hours. Animals were randomly assigned to two treatment groups: (1) -BMP (alginate modified with the cell adhesive ligand sequence RGD) or (2) +BMP (RGD modified alginate containing 2 μg BMP-2). Persistence of transplanted cells was determined by whole body bioluminescence at 1, 2, and 4 weeks. Surveillance radiographs were obtained at 4, 8, and 12 weeks, and scored 0 (no bone formation), 1 (possible union), or 2 (union). All rats were sacrificed at 12 weeks.

Results: Bioluminescence was used to assay cell viability of transplanted cells within the defect (Figure 1A). Alginate hydrogels containing BMP-2 had significantly more cells at each time point than gels without BMP-2 (Figure 1B). All animals in the BMP group demonstrated 100% radiographic union by 8 weeks. None of the rats in the RGD group fully united at the time of sacrifice.

Conclusion: The delivery of BMP-2 in RGD-modified alginate gels increased MSC survival compared to alginate with MSCs alone, resulting in increased bone formation in a critical size defect model. The interplay between BMP and cell survival using photopolymerized hydrogel systems merits further study.

See pages 47 - 108 for financial disclosure information.

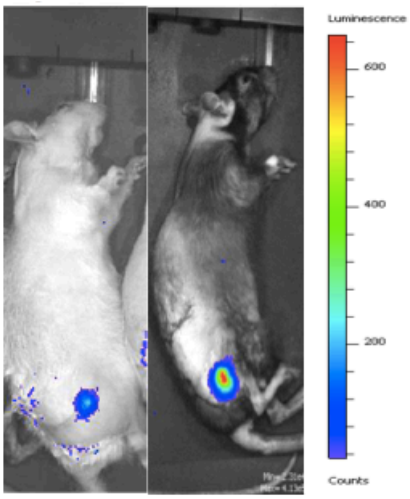

Figure 1A: Representative bioluminescence at 4 weeks.

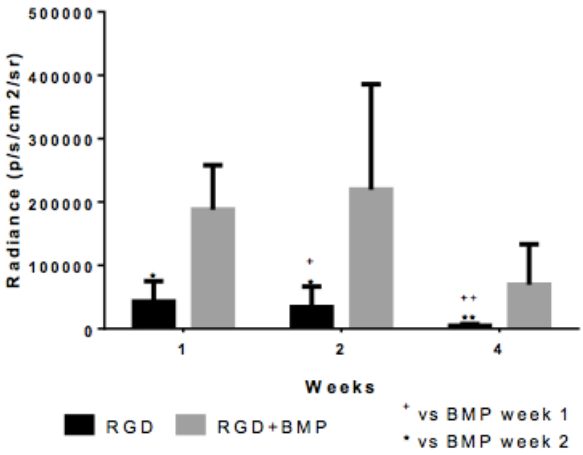

Figure 1B: Quantification of bioluminescence over time. (P<0.05 at all time points)