ΔPossible Inhibitory Effect of Bone Marrow–Derived Mesenchymal Stem Cell Application on BMP-2–Mediated Bone Healing in a Critical Size Defect Model

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Purpose: Healing of critical size defects (CSDs) remains a critical clinical challenge in fracture care. Bone morphogenetic proteins (BMPs) are commonly utilized in the setting of defect repair; however, large doses are required with associated costs and complications. Mesenchymal stem cells (MSCs) have been studied as an alternative to BMPs for bone defect repair. Composite constructs utilizing both BMPs plus osteogenic materials are commonly utilized. The purpose of this study was to investigate the relationship of MSCs and BMP response in a reproducible rodent CSD model. Our aim was to determine the efficacy of BMPs, MSCs, and combined application of BMPs plus MSCs deployed via an inert carrier in healing a validated critical size femoral defect model.

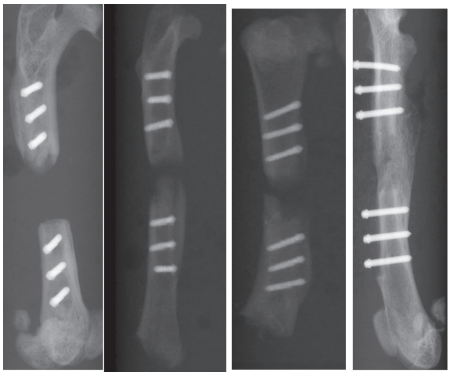
Methods: 6-mm diaphyseal CSDs were created in femora of skeletally mature male Fischer 344 rats and stabilized with a radiolucent PEEK (polyetheretherketone) plate and 6 angular stable bicortical titanium screws. MSCs were harvested from the intramedullary canal of a sacrificed Fischer 344 rat and expanded in MSC growth until confluent to 1×10^6 cells (4 passages). Rats were randomly assigned to four treatment groups: carrier alone (ICBM [insoluble collagenous bone matrix]), 2 μg BMP-2 with carrier (positive control), 1×10^6 MSCs with carrier, and 2 μg BMP-2 and 1×10^6 MSCs on carrier. Surveillance radiographs were obtained at 2-week intervals until the end of treatment and scored 0 (no bone formation), 1 (possible union), or 2 (union) by two blinded investigators. All animals were sacrificed at 8 weeks to examine bone formation using radiographs and micro-CT.

Results: All of the 2-μg group demonstrated 100% radiographic union by week 4 (D). None of the rats in the carrier (A) or the MSC group (B) fully united at the time of sacrifice. Rats in the MSC/BMP-2 group also failed to heal (C). Compared to BMP-2 or MSC alone, bone volume (BV) and bone mineral density were both decreased in the MSC/BMP-2 treatments (E). A qualitative analysis was preformed for all groups. Differences in mean values for all groups were tested using the analysis of variance (ANOVA). The analysis was significant for both BV ($P < 0.01$) and bone mineral density ($P < 0.01$) for all groups. Difference in mean values between the BMP-2 group and BMP/cells group were significant using a two-sided t-test, BV ($P = 0.014$) and for bone mineral density ($P < 0.01$).

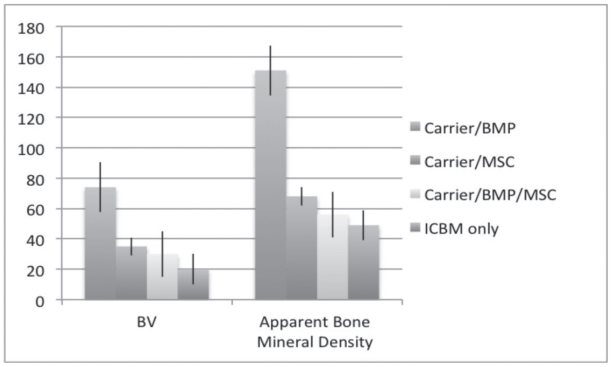
Conclusion: BMP-2 delivered with an inert carrier in our mechanically stable rodent CSD model results in consistent, high-quality bone regenerate. The unmodified MSCs do not reliably heal the critical size defect. The addition of MSCs to the BMP-2 carrier construct demonstrated significantly reduced bone formation and failed to heal. The interplay between BMP-2 and unmodified MSCs merits further study.

Δ OTA Grant

See pages 99 - 147 for financial disclosure information.



Carrier (A) MSC (B) MSC/BMP (C) BMP (D)



(E)

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