Comparison Of Survival And Osteogenic Ability Of Human Mesenchymal Stem Cells In Orthotopic And Ectopic Sites In Mice

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Disclosures:

Introduction: Tissue constructs containing mesenchymal stem cells (MSCs) are appealing strategies for repairing large segmental bone defects but they do not allow consistent bone healing and early and massive MSCs death was identified as a cause of failure. However, little is known about cell survival in the clinical micro-environment encountered during bone healing process, whereas ectopic evaluation is well documented.

In vivo, luciferase-labelled human MSCs survival, within osteoconductive scaffold, was compared in orthotopic and ectopic locations, and bone formation ability of LF-hMSCs-Acropora constructs was evaluated. Interest and limits of each model were highlighted.

Methods: Osteoconductive scaffold with or without LF-hMSCs were implanted either in a critical-segmental-femoral-bone defect stabilized by plate or subcutaneously in 44 mice. Cells survival was evaluated by serial bioluminescence imaging (BLI) and osteogenic capabilities by histology and microCT. Twenty mice were sacrificed 15 days after surgery for "short term" evaluation. The other mice were kept for 10 weeks after surgery for "long term" evaluation.

Results: BLI provided evidence of fast and continuous cell death: 85% decrease of the BLI signal over the first 15 days in both location; less than 2% of the initial cell number were present in all constructs analyzed 30 days post-implantation and less than 1% of the initial cell number was present in all constructs analyzed 55 days post-implantation (Fig 1). By 2 weeks post implantation, the amount of newly formed bone was self-limited and was similar between ectopic and orthotopic group, with or without cell. By 10 weeks post implantation, bone formation was significantly enhanced in the presence of LF-hMSC. The amount of newly formed bone in the cell-containing constructs groups was significantly higher than that observed in the scaffold alone groups (Fig 2).

Most importantly, the amount of newly formed bone in cell-containing constructs implanted in orthotopic locations was significantly higher than that observed in the ectopic, cell-containing construct group.

Discussion: Corroborating previous ectopic studies, our results indicated that hMSCs promote bone formation despite early and massive cell death when loaded on ceramic scaffold. Interestingly, bone formation was higher in orthotopic than ectopic site despite a same survival pattern and a massive and early cell death, suggesting a trophic effect of hMSCs. Ectopic implantation of cell-containing constructs is suitable to evaluate cell survival, but assessment of bone formation ability requires orthotopic implantation.

Significance: Despite similar, early and massive death, hMSCs promote bone formation which was higher in orthotopic than ectopic site suggesting a trophic effect of hMSCs. Ectopic implantation is suitable to evaluate cell survival, but assessment of bone formation requires orthotopic implantation.

Acknowledgments: