Immunology Summit 2015: The role played by the host inflammatory cells in adult stem cells mediated tissue repair Johnny Huard- University of Texas Health Science Center

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Abstract

Murine muscle-derived stem cells (MDSCs) have been shown capable of regenerating bone in a critical size calvarial defect model when transduced with BMP 2 or 4; however, the contribution of the donor cells and their interactions with the host cells during the bone healing process have not been fully elucidated. To address this question, C57/BL/6J mice were divided into MDSC/BMP4/GFP, MDSC/GFP, and scaffold groups. After transplanting MDSCs into the critical-size calvarial defects created in normal mice, we found that mice transplanted with BMP4GFP-transduced MDSCs healed the bone defect in 4 wk, while the control groups (MDSC-GFP and scaffold) demonstrated no bone healing. The newly formed trabecular bone displayed similar biomechanical properties as the native bone, and the donor cells directly participated in endochondral bone formation via their differentiation into chondrocytes, osteoblasts, and osteocytes via the BMP4-pSMAD5 and COX-2- PGE2 signaling pathways. In contrast to the scaffold group, the MDSC groups attracted more inflammatory cells initially and incurred faster inflammation resolution, enhanced angiogenesis, and suppressed initial immune responses in the host mice. MDSCs were shown to attract macrophages via the secretion of monocyte chemotactic protein 1 and promote endothelial cell proliferation by secreting multiple growth factors. Numerous studies have shown that cycloxygenase-2 (Cox-2) deficient mice have a delayed and reduced bone fracture healing capacity. Previously, we showed that COX-2 is expressed dynamically during muscle-derived stem cell (MDSC) mediated bone regeneration; however, the identity of the COX-2 expressing cells and the role they play in the bone healing process has not been clearly elucidated. This study investigated the role of COX-2 expression by donor and host cells in MDSC-mediated bone repair utilizing a critical size calvarial defect model in mice. We found that bone morphogenetic protein 4 (BMP4) and green fluorescent protein (GFP)(BMP4/GFP) transduced MDSCs formed significantly less bone in the defect area of Cox-2 knock-out (Cox-2KO) mice than wild-type (WT) mice. Moreover, MDSCs isolated from the Cox-2KO mice and transduced with BMP4/GFP also form significantly less bone than MDSCs isolated from the WT mice when transplanted into calvarial defects created in CD-1 nude mice. Histologically, there was less collagen 1 matrix deposition and fewer GFP positive osteoblasts and osteocytes present in the new bone area in the Cox-2KO MDSC/BMP4/GFP transplantation group than the WT MDSC/ BMP4/GFP group. At day 14, there was a reduction in BMP4-pSMAD1/5/8 signaling in the Cox-2KO MDSC/BMP4/GFP group. Furthermore, there were fewer GFP+Ki67+ cells found in the Cox-2KO MDSC/BMP4/GFP group than in the WT MDSC/BMP4/GFP group medium identified total 55 and 42 compounds respectively. Whereas GCMS analysis from best bacterial antagonist Pseudomonas isolate no. 14 (JNDKSGn-30-L) inoculated onto N-agar identified total 60 compounds.