FEATURES

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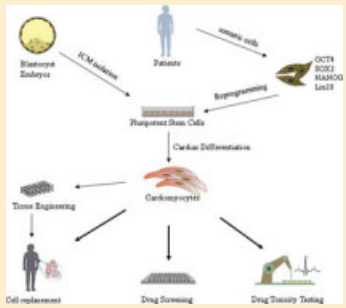
Human pluripotent stem cells (hPSC) are self-renewing cells with the potential to differentiate into a variety of human cells. They hold great promise for regenerative medicine and serve as useful in vitro models for studying human biology. For the past few years, there is vast interest in applying these cells to advance cardiovascular medicine. Human cardiomyocytes can be readily generated from hPSC and they have been characterized extensively with regards to molecular and functional properties. They have been transplanted into animal models of cardiovascular diseases and also shown to be potentially useful reagents for drug discovery. Yet, despite great progress in this field, significant technical hurdles remain before these cells could be used clinically or for pharmaceutical research and development. Further research using novel approaches will be required to overcome these bottlenecks.



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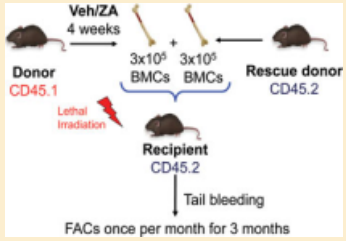
Hematopoietic stem cells (HSC) are maintained in a tightly regulated bone microenvironment constituted by a rich milieu of cells. Bone cells such as osteoblasts are associated with niche maintenance as regulators of the endosteal microenvironment. Bone remodeling also plays a role in HSC mobilization although it is poorly defined. The effects of zoledronic acid (ZA), a potent bisphosphonate that inhibits bone resorption, were investigated on bone marrow cell populations focusing on HSCs, and the endosteal and vascular niches in bone. ZA treatment significantly increased bone volume and HSCs in both young and adult mice (4 week and 4 month old, respectively). ZA increased vessel numbers with no overall change in vascular volume in bones of young and had no effect on vasculature in adult mice. Since both young and adult mice had increased HSCs and bone mass with differing vasculature responses, this suggests that ZA indirectly supports HSCs via the osteoblastic niche and not the vascular niche. Additionally, gene expression in Lin- cells demonstrated increased expression of self-renewal related genes Bmi1 and Ink4a suggesting a role of ZA in the modulation of cell commitment and differentiation toward a long-term self renewing cell. Genes that support the osteoblastic niche, BMP2 and BMP6 were also augmented in ZA treated mice. In conclusion, ZA-induced HSC expansion occurs independent of the vascular niche via indirect modulation of the osteoblastic niche.



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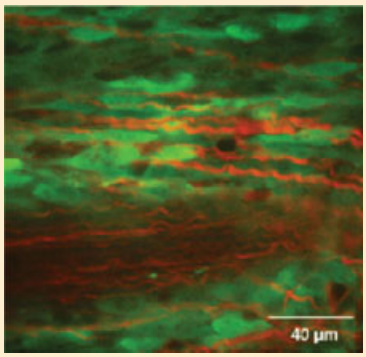

Second harmonic generation (SHG) multiphoton imaging can visualize fibrillar collagen in tissues. SHG has previously shown that fibrillar collagen is altered in various types of cancer. In the present study, in vivo high resolution SHG multi-photon tomography in living mice was used to study the relationship between cancer cells and intratumor collagen fibrils. Using green fluorescent protein (GFP) to visualize cancer cells and SHG to image collagen, we demonstrated that collagen fibrils provide a scaffold for cancer cells to align themselves and acquire optimal shape. These results suggest a new paradigm for a stromal element of tumors: their role in maintaining anchorage and shape of cancer cells that may enable them to proliferate.

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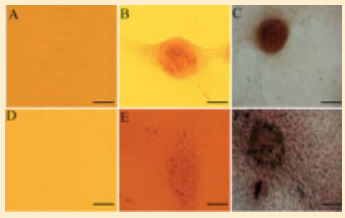

Mesenchymal stem cells (MSCs) are an important cell population in the bone marrow microenvironment. MSCs have the capacity to differentiate in vitro into several mesenchymal tissues including bone, cartilage, fat, tendon, muscle, and marrow stroma. This study was designed to isolate, expand, and characterize the differentiation ability of sheep bone marrow-derived MSCs and to demonstrate the possibility to permanently express a reporter gene. Bone marrow was collected from the iliac crest and mononuclear cells were separated by density gradient centrifugation. Sheep MSCs cell lines were stable characterized as CD44+ and CD34− and then transfected with a green fluorescent protein (GFP) reporter gene. The GFP expression was maintained in about half (46.6%) of cloned blastocysts produced by nuclear transfer of GFP+ sheep MSCs, suggesting the possibility to establish multipotent embryonic cells' lines carrying the fluorescent tag for comparative studies on the differentiation capacity of adult stem cells (MSCs) versus embryonic stem cells. We found that sheep MSCs under appropriate culture conditions could be induced to differentiate into adipocytes, chondrocytes, and osteoblast lineages. Our results confirm the plasticity of sheep MSCs and establish the foundation for the development of a pre-clinical sheep model to test the efficiency and safety of cell replacement therapy.