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Emergence of Patterned Stem Cell Differentiation within Multicellular Structures.

Ruiz SA, Chen CS

Stem Cells 2008 Aug 14 [abstract on PubMed] [citations on Google Scholar] [related articles] [full text]

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Jeffrey Gimble with Barbara Gawronska-Kozak Louisiana State University System, United States of America Rheumatology & Clinical Immunology New Finding	**This study provides an outstanding biomechanical analysis of the differential regulation of bone marrow mesenchymal stem cell (MSC) adipogenesis and osteogenesis.** This work is a direct extension of previous work from the authors' laboratory documenting a role for ROCK and spatial constraints imposed by extracellular matrices on MSC differentiation. This outstanding manuscript takes us beyond the initial findings. The authors elegantly demonstrate that morphology in 2- or 3-dimensions imposes constraints on the undifferentiated stem cell fate, driving it to a particular lineage pathway. They have patterned shapes (circles, squares, ellipses) onto culture surfaces with adhesion molecules, thereby promoting a particular configuration of MSCs growth patterns. Cells in areas associated with a high degree of biomechanical stress, i.e. the outer edge of the geometric shape, undergo osteogenesis while those in areas associated with reduced biomechanical stress, i.e., the inner surface of the geometric shape, selectively undergo adipogenesis. At the simplest level, the work has direct relevance to issues relating to osteoporosis, where adipogenesis is promoted at the expense of osteogenesis and occur in association with an altered biomechanical microenvironment, that is, the loss of trabecular networks. The geometry of the bone matrix itself may play a critical role in regulating and directing the differentiation pathway of newly formed MSCs. Many biologists fail to take into account the role of biophysics in determining cell fate. This manuscript addresses this issue in a concise and simple manner using state of the art biomechanical methodologies with appropriate statistical and mathematical tools. The study has no significant weaknesses with respect to its methodology, quality of data, or conclusions. It is likely that the authors' hypotheses and findings will have greater implications beyond the bone marrow microenvironment. Biomechanical constraints generated by geometrical shapes of extracellular matrix proteins may influence stem cell fate in the context of other diseases and tissue types. For example, geometric considerations in tissue sites such as the crypts of Lieberkuhns, where epithelial stem cells are located in the intestinal mucosa, or in the ovary,

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where asymmetric division regulates the fate of germinal stem cells, may play a role in directing cell proliferation and differentiation through similar mechanisms. Thus, the findings have direct relevance not only to stem cell biologists interested in bone marrow MSCs but also those studying stem cells in other locations. Future experiments should include further analyses evaluating the mechanism by which biomechanical constraints and forces influence MSC differentiation at the biochemical and molecular biological levels. Furthermore, the effect of geometry on stem cell types other than MSCs should be undertaken, first in vitro and then in vivo.

Competing interests: No potential interests relevant to this article were reported.
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