J Musculoskelet Neuronal Interact 2007; 7(4):346

37th International Sun Valley Workshop
August 5 - August 8, 2007
Aging and Osteoporosis Session

Hylonome

Vascular calcification

Y. Tintut, M. Huang, J. Lu, W. Tseng, A. Garfinkel, L.L. Demer

Departments of Medicine, Physiology, and Biomedical Engineering, UCLA, Los Angeles, CA, USA

Keywords: Artery, Stem Cells, Matrix GLA Protein, Bone Morphogenetic Protein

In humans and experimental models, vascular calcification causes hypertension, left ventricular hypertrophy, and congestive heart failure. The distribution of vascular calcification maps closely with atherosclerosis. Surprisingly, vascular calcification also correlates age-independently with osteoporosis. We previously identified and isolated, from the artery wall, multilineage cells that produce a mineralized matrix in a regulated process nearly identical to osteoblastic differentiation and mineralization, governed by most of the same transcription factors and signaling pathways. These cells, which are derived from single cells by dilutional cloning, have a lineage potential similar to that of mesenchymal stem cells, including chondrogenic, osteogenic, leiomyogenic, and stromogenic lineages. This capacity offers potential use in tissue bioengineering. But cells alone are not sufficient to produce tissue; architectural organization is essential to function. Thus, we were intrigued to observe that 5-10 days after uniform monolayer plating, these cells spontaneously organize into localized aggregates in macroscopically-visible patterns, such as evenly-spaced spots or stripes. We hypothesized that the patterns were arising from the uniform monolayer through a general phenomenon known as reaction-diffusion.

To test this hypothesis, we developed a mathematical model in which parameter values were determined experimentally. Results provided evidence that the pattern formation resulted from a reaction-diffusion process driven by interaction between two morphogens, bone morphogenetic protein-2 (BMP-2) and its inhibitor, matrix GLA protein (MGP). The model prospectively and accurately predicted experimental outcomes of treatment with exogenous MGP as well as of treatment with warfarin, which is known to inhibit MGP function. The former converted the pattern from stripes to spots, and the latter from widely-spaced stripes to a dense labyrinthine pattern (stripe-doubling).

These findings suggest that artery-derived, mesenchymal stem cells and reaction-diffusion principles may contribute significantly to the development and distribution of vascular calcification in atherosclerosis and that these cells may be useful in bioengineering because of their unique ability to self-organize into architectural patterns in a manner open to control by specific biochemical treatments.

The authors have no conflict of interest.

Corresponding author: Linda L. Demer, M.D., Ph.D., David Greffen School of Medicine, University of California Los Angeles, Division of Cardiology, 10833 Le Conte Avenue, 47-123 Center for Health Sciences, Los Angeles, CA 90095-1679, USA
E-mail: ldemer@mednet.ucla.edu

Accepted 10 August 2007