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The Hemosteoblast: Friend or Foe?

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Ectopic calcification arises in soft tissues in a variety of diseases. When it occurs in cardiovascular tissues, such as the aorta, cardiac valve leaflets, and coronary and renal arteries, it produces debilitating and sometimes fatal conditions, including coronary insufficiency, heart failure, calcific aortic stenosis, systolic hypertension, and left ventricular hypertrophy. Although calcific vasculopathy was long considered a passive process of aging, studies from the last two decades have revealed an active mechanism in which transcription factors drive osteochondrogenic differentiation of vascular cells.

In the right context, a number of extraskeletal cells display osteochondrogenic potential, including microvascular pericytes,[1] adventitial myofibroblasts,[2] a subset of resident medial smooth muscle cells,[3] multipotent vascular stem cells,[4] previously known as calcifying vascular cells,[5] interstitial cells, and mesoangioblasts.[6] Since these cells are all of purely mesenchymal origin, mineralization has been considered, until recently, solely a mesenchymal attribute.

Now, in this issue of *Circulation Research*, Fadini and colleagues[7] report mineralization potential in cells of hematopoietic origin -- circulating myeloid cells that produce calcium mineral when cultured in Matrigel™, a solubilized basement membrane matrix derived from mouse sarcoma cells. These circulating cells also express monocyte/macrophage lineage markers (CD45, CD14, and CD68) as well as the osteoblastic markers, alkaline phosphatase (BAP, also known as tissue-nonspecific alkaline phosphatase), osteocalcin, and the osteochondrogenic transcription factors, Runx2 and osterix. These findings indicate that some adult cells of hematopoietic origin -- perhaps “hemosteoblasts” or “mono-osteoblasts” -- have the capacity to take over the distinctly mesenchymal function of extracellular mineralization.

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Interestingly, these cells have a life span of over 8 months, and they increase in number in diabetes and cardiovascular disease as well as in high glucose and hypoxic conditions. It would be interesting to know whether the biologically active growth factors found in Matrigel's reconstituted basement membrane include cathelicidin; whether these cells, like other myeloid cells, secrete inflammatory cytokines, many of which induce osteochondrogenic differentiation of resident vascular cells;[8, 9] and whether the stoichiometry of their mineral deposits matches that of hydroxyapatite or amorphous calcium phosphate.

Until recently, the idea of cross-over, in either function or phenotype, between the two fundamental classes of cells -- adult mesenchymal vs. hematopoietic cells -- has been almost proscribed. The distinction was challenged a decade ago when Schmeisser et al. showed endothelial cell behavior of monocytes grown in Matrigel.[10] It was breached when Brunelli and colleagues described mesoangioblasts as multipotent progenitors, with angiopoietic progenitor markers, that give rise to multiple differentiated mesodermal phenotypes,[6] and when Metharom et al. showed certain SMC from diseased arteries have a myeloid origin.[11] The barrier was further infringed when Zhang and Shively induced osteogenic activity in monocytes, using a cathelicidin-derived peptide, LL-37. This produced what they called "monoosteophils," which express osteoblastic markers and produce mineralized nodules in vitro and in vivo, even while simultaneously expressing osteoclastic markers.[12] The new report by Fadini and colleagues[7] now crosses the border by showing these dual-origin cells without the requirement for treatment with the cathelicidin peptide.

Exciting new questions emerge. What is the purpose of these cells in the physiological condition? Are they friend or foe? Why are they unusually long-lived? Does mineralization by circulating myeloid-derived cells may explain, in part, the unexpected and severe calcification found in cardiac tissue after injection of transplanted mononuclear bone marrow cells in infarcted rodent hearts?[13] Given the large numbers of immigrant monocyte/macrophage cells in atherosclerotic lesions, it is conceivable that circulating myeloid blood cells also contribute to calcific atherosclerosis, aortic valvular stenosis, and even bioprosthetic calcification. They may even contribute to the pathological calcification associated with inflammation in kidney and liver, or to that associated with skeletal muscle injury in fibrodysplasia ossificans progressiva.

Most importantly, the finding of mineralization potential in cells of hematopoietic origin challenges us to reconsider the older, conventional hierarchy of differentiation, especially "terminal" differentiation. Perhaps, it is time to entertain a new, more fluid, view of cell maturation, where lineages intertwine and even cross the border between hematopoietic and mesenchymal origins.

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