AMPKα1
SUMO Wrestling Runx2 as a Strategy to Inhibit Arteriosclerotic Calcification

Dwight A. Towler

With our increasingly aged and dysmetabolic population, the deleterious consequences of globally perturbed calcium metabolism become increasingly apparent. Net loss of bone mineral quantity and quality increases risk for osteoporotic fracture, whereas accumulating arterial calcium loads stiffen conduit arteries and impairs Windkessel physiology—the rubbery elasticity of conduit vessels that ensures smooth distal tissue perfusion throughout the cardiac cycle. Murine models were first used to identify that reciprocal change in skeletal versus vascular calcium accrual can occur in response to the dysmetabolic states of diabetes mellitus, uremia, and dyslipidemia. However, the Multiethnic Study of Atherosclerosis (MESA) firmly established the general connection between accrual of metabolic syndrome parameters—impaired fasting glucose, hypertension, obesity, low high-density lipoprotein, hypertriglyceridemia, or frank type 2 diabetes mellitus (T2D)—and arterial calcium load in humans. Recent studies implementing high-resolution peripheral quantitative computed tomography have shown that older men and women with T2D exhibit greater cortical bone porosity—a feature that compromises bone strength and increases fracture risk. Patients with calcified peripheral arterial disease also exhibit deficiencies in trabecular bone structure on high-resolution peripheral quantitative computed tomography, further solidifying the relationship. Elegant human genetic studies by Mani et al highlighted that osteoporosis–atherosclerosis relationships are genetically determined in part by LRP6 signaling—with the cell-autonomous (osteoblast and vascular smooth muscle) contributions of LRP6 to bone and vascular dysfunction subsequently confirmed and mechanistically enlightened by murine genetic models. However, the means and mechanisms whereby clinically relevant dysmetabolic states simultaneously perturb arterial and skeletal health are only beginning to be understood. Although parathyroid hormone, FGF23, and oxylipid signals have uncovered relationships between inflammation and bone–vascular interactions, the contributions of intracellular energy sensing—a fundamental component of healthy adaptation to states of altered fuel and lipid metabolism—have been largely overlooked.

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In this issue of Circulation Research, Cai et al begin to address this issue by examining the roles of AMPKalpha1 and AMPKalpha2 in atherosclerotic calcification, using the apolipoprotein E–null mouse model of diet-induced dyslipidemia. The AMP kinases are master regulators that sense cellular energetics in part through the AMP/ATP ratio and mitochondrial reactive oxygen species production and coordinate cell-autonomous responses to metabolic stresses. Using conditional knockout strategies, they demonstrate that vascular smooth muscle (VSM) AMPKalpha1 plays a uniquely important role in the arterial defense to calcific responses arising from dyslipidemia. Loss of VSM AMPKalpha1 profoundly increased aortic calcium accrual in apolipoprotein E double-knockout mice, with concomitant upregulation of the osteochondrogenic differentiation program in VSM. Both processes were driven by the osteogenic transcription factor, Runx2. Importantly, deletion of AMPKalpha2 in the myeloid series had no impact on arterial calcification, nor did the removal of AMPKalpha2 in either cell lineage. Conversely, metformin, a first-line agent in the war on T2D that activates AMPK, significantly inhibited arterial calcification and downregulated arterial Runx2 expression, mediated via metformin-dependent enhancement of Runx2 turnover. In the osteoblasts of bone, Runx2 is prodigiously regulated at the level of ubiquitin E3 ligases Smurf1 and Smurf2, with ubiquitination directing Runx2 proteasomal degradation. This was not the case in VSM. Rather, the authors demonstrate that AMPKalpha1 enhances VSM Runx2 SUMOylation on lysine residue 181—a modification with a small ubiquitin-like modifier (SUMO)—that is dependent on the SUMO E3 ligase PIA1. AMPKalpha1 was shown to activate PIA1-dependent ligase function by phosphorylating PIA1 on Ser-510. Moreover, a Ser-to-Ala mutation at this PIA1 residue completely abrogated metformin-dependent SUMOylation and destabilization of VSM Runx2, as did PIA1 knockdown. This same signaling relay was required to inhibit induction of Runx2 by oxidized LDL, thereby linking modulation of fuel-sensing mechanisms to mitigation of inflammatory signals arising in the dysmetabolic state. Thus, the authors conclude that the prosclerotic VSM Runx2 program is held in check by AMPKalpha1-regulated mechanisms that control Runx2 stability in a cell-specific fashion and that pharmacological activation of AMPKalpha1 can mitigate atherosclerotic mineralization.

Why is this article so intriguing and important? First and foremost, these data provide compelling rationale for a
AMPKα1 inhibits arterial calcification

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