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Understanding vascular calcification from an evolutionary standpoint

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Understanding the evolutionary mechanisms that support the development of vascular calcification is a valid point, and one that may ultimately reveal novel etiologies of this complex vascular remodeling process.¹ Nonetheless, the overall supposition that vascular calcification occurs as a consequence of atherosclerosis (owing to the relatively late appearance of atherosclerosis in the history of man) may be an overly simplistic interpretation of the (mal)adaptive consequences of calcifying blood vessels. As vascular calcification can occur in the absence of atherosclerotic coronary artery disease,² suggesting that the evolution of calcified vessels is linked exclusively to atherosclerosis ignores some of the broader potential reasons that vascular calcification exists. In fact, it is far more likely that vascular calcification co-evolved as a defense mechanism concomitant with the increased prevalence of other systemic diseases now associated with increased longevity. Although vascular calcification has a negative connotation, further consideration indicates that there are adaptive advantages to this form of vascular remodeling.³ Vascular calcification creates a physical barrier, albeit a heterogeneous one, between the vessel lumen, blood vessel wall, and the extravascular space. This barrier can be impermeable and restrict communication between biological compartments. Calcification of the vessel wall interrupts translocation of circulating immune/inflammatory cells, stem cells, and progenitor cells; bidirectional flow of local and circulating bioactive signaling molecules; and, migration of vascular cells.^{3,4} Thus, as posited by Demer, one can envision that vascular calcification may be advantageous when the vessel wall is exposed to noxious stimuli that have deleterious effects on vascular structure and function, such as inflammation.³ This is plausible as evidence demonstrating that focal inflammation precedes vascular calcification in the same spot in human vessels supports this notion.⁵ While vascular calcification may transiently preserve the structural integrity of the vessel following injury, it is also clear that it increases vessel stiffness and decreases strength, which contribute to suboptimal performance.⁶ Perhaps the real question to consider when examining vascular calcification through the lens of Evolutionary or Darwinian Medicine is why there has not been a co-evolution of an ectopic calcification regression mechanism? Humans possess local and

circulating anti-calcific proteins that prevent or inhibit ectopic calcification (without affecting skeletal bone) but none that regress established vascular calcification to promote vascular healing and restore vascular structure and function.^{3,4} Only when we are able to answer this and the other questions posed by Demer³ will we understand more about the pathobiology and teleological significance of vascular calcification.

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