Cytotoxicity of Calcium Phosphate Crystals and Human-Derived Nanoparticles: An Overlooked Link

To the Editor:

In a recent communication, Ewence et al reported that calcium phosphate crystals induced cell death in human aortic vascular smooth muscle cells. Explicitly, crystals of approximately ≤1 μm in diameter caused rapid rises in intracellular calcium concentration, their potency depending on their size and composition.1 Crystals were natural (isolated from human carotid arteries) and synthetic (basic calcium phosphate and nanocrystalline apatite). In contrast to the continuous and slow changes caused by the uptake of molecules, incorporation of calcium phosphate particles (nanoparticles or microparticles) results in an instant jump in calcium phosphate levels. Clearly, cell death induced by increased intracellular calcium phosphate loads is not limited to vascular smooth muscle cells. Despite considerable evidence for a cytotoxicity of small calcium phosphate particles and the extraordinary relevance of the finding in biomedicine, the resonance to the data provided in the study is rather moderate. Apparently, the link between the data and the in vivo system is missing. Indeed, Ewence et al point out that vascular smooth muscle cells in vivo will not be exposed to pure, uncoated crystals. In addition, the calcium phosphate crystals used in the study were either artificially processed or synthetic. In other words, none of them is prevalent in humans. However, this is not the complete picture. Attention should be drawn to a potentially important link: the calcium phosphate nanoparticles prevailing in humans. On the level of earlier knowledge, these particles were treated as nanobacteria. Regarding their chemical composition and size distribution, they fit perfectly into the particle class explored by Ewence et al. Whereas there is ample evidence for their presence in humans (currently there are more than 50 clinical articles reporting on their identification), both their intrinsic nature and their pathogenic potential are controversial. The spectrum of their possible involvement in disease reaches from promoters of aortic valve calcification to innocent bystanders.2 Recently, it was reported that nanoparticles derived from human calcified aortic aneurysms injected into rabbit exacerbated arterial response to injury.3 According to a model study the particles are products of a homeostatic cycle designed by nature to deal with excess calcium and apatite.4 Presumably, the implications presented by Ewence et al have been overlooked by researchers involved in the investigation of the role of natural calcium phosphate particles in disease. Considering the need for fundamental information regarding the cytotoxic potential of the calcium phosphate particles found in humans, on the one hand, and the fundamental insight provided by Ewence et al, on the other hand, reciprocal cross-contamination promises progress in both directions, modeling and clinical research.

Sources of Funding

None.

Disclosures

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Circ Res. 2010;106:e10
doi: 10.1161/CIRCRESAHA.110.221374

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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