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LETTER

Are calcifying microvesicles another analogous substructure of calcifying nanoparticles?

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Dear editor

We correspond in response to the article entitled, "Contrast-enhanced MR imaging of atherosclerosis using citrate-coated superparamagnetic iron oxide nanoparticles: calcifying microvesicles as imaging target for plaque characterization" by Wagner et al.[1] In this article, the authors have used a new term "calcifying microvesicles" for the first time in the literature. We think our commentary will highlight these calcifying microvesicles with the similar analogous structures already existing in nature. We hope our discussion will clear up many of those questions.

Scientific advances in imaging technology offer many enticing prospects, including detection of early events that accelerate the progression of inflammatory lesions and atherosclerotic plaques,[2,3] which have been the subject of endless debate. These imaging modalities could be used to monitor how atherosclerosis changes over time, perhaps indicating the ability of medical therapy to modify the plaque structure.[4] Most recently, Wagner et al[1] devised an innovative, clinically relevant method that would further help to study the exact location, composition and inflammatory activity of progressive atherosclerotic lesions, a process that can occur slowly and 'silently' over time.

One of the most interesting results of this study is the identification of "calcifying microvesicles" – a term used for the first time in the literature. Such particles were significantly related to atherosclerosis and calcification.[5,6] Once believed to be a passive degenerative disease, cardiovascular calcification is now increasingly recognized as an active inflammatory process.[7,8] A number of microscopic features were reported in the plaque, most notably calcifying nanoparticles (CNPs),[9] matrix vesicles,[10] and microcalcification,[11] however attempts to characterize these atherogenic mechanisms to particular etiology have failed, requiring further investigations. Subsequent work on calcifying microvesicles can provide an understanding to study plaque biology–physiological as well pathophysiological events in atherosclerotic plaques as they mature and start to become "complex" typically have associated calcification, the hallmark of advancing atherosclerosis, seen in the aorta, coronary, and other muscular arteries.[12]

In the literature, the terms microvesicles and microparticles have been used interchangeably. A forum hosted by the International Society of Thrombosis and Haemostasis, however, provided a consensus definition of plasma microvesicles as vesicles of less than 1 μm in diameter which bear at least half of the surface protein and/or receptors of their cells of origin.[13,14] Remarkably, typical sizes of calcifying nanopar-

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ticles are comparable to membrane-bound vesicles released by a variety of cells, globular proteins and matrix vesicles that are present at sites of physiological and pathological mineral deposition, such as normal bone and soft tissues in mammals and birds.[15] For example, when examined under a high resolution electron microscope, calcifying microvesicles morphologically appear akin to calcifying nanoparticles, which were originally obtained from calcified arteries.[16]

The observations of Wagner et al raise several important questions. First, this study provides only a preliminary account of the presence of calcifying microvesicles. Second, without knowing the lipid composition of the endosomal membrane, one cannot conclude that calcifying microvesicles originate from a specific membrane domain. Is this the case or are they functionally distinct features of endosomes that produce different intraluminal vesicles?[17] Also, if both types of particles, either calcifying microvesicles or calcifying nanoparticles, are present in the same plaque, they must somehow be biologically distinct from each other, or be calcifying microvesicles, another analogous substructure of calcifying nanoparticles? However, development of specific biomolecular markers against all biologically existing particles, including recently added bions,[18] holds the promise of putting an end to all ambiguities pertaining to their identities.

References

1. Wagner S, Schnorr J, Ludwig A, et al. Contrast-enhanced MR imaging of atherosclerosis using citrate-coated superparamagnetic iron oxide nanoparticles: calcifying microvesicles as imaging target for plaque characterization. *Int J Nanomedicine*. 2013;8:767–779.
2. Aikawa E, Nahrendorf M, Figueiredo JL, et al. Osteogenesis associates with inflammation in early-stage atherosclerosis evaluated by molecular imaging in vivo. *Circulation*. 2007;116:2841–2850.
3. Schenker MP, Dorbala S, Hong EC, et al. Interrelation of coronary calcification, myocardial ischemia, and outcomes in patients with intermediate likelihood of coronary artery disease: a combined positron emission tomography/computed tomography study. *Circulation*. 2008;117:1693–1700.
4. Agarwala A, Billheimer J, Rader DJ. Mighty minipig in fight against cardiovascular disease. *Sci Transl Med*. 2013;5:166.
5. Miller VM, Rodgers G, Charlesworth JA, et al. Evidence of nanobacterial-like structures in calcified human arteries and cardiac valves. *Am J Physiol Heart Circ Physiol*. 2004;287:H1115–H1124.
6. Schlieper G, Kruger T, Heiss A, Jahnen-Dechent W. A red herring in vascular calcification: 'nanobacteria' are protein-mineral complexes involved in biomineralization. *Nephrol Dial Transplant*. 2011;26:3436–3439.
7. Rajamannan NM, Evans FJ, Aikawa E, et al. Calcific aortic valve disease: not simply a degenerative process: A review and agenda for research from the National Heart and Lung and Blood Institute Aortic Stenosis Working Group. Executive summary: Calcific aortic valve disease-2011 update. *Circulation*. 2011;124:1783–1791.
8. Aikawa M, Manabe I, Chester A, Aikawa E. Cardiovascular inflammation. *Int J Inflam*. Epub March 19, 2012.
9. Bratos-Perez MA, Sanchez PL, Garcia de CS, et al. Association between self-replicating calcifying nanoparticles and aortic stenosis: a possible link to valve calcification. *Eur Heart J*. 2008;29:371–376.
10. Jahnen-Dechent W, Heiss A , Schafer C, Ketteler M. Fetuin-A regulation of calcified matrix metabolism. *Circ Res*. 2011;108:1494–1509.
11. Abedin M, Tintut Y, Demer LL. Vascular calcification: mechanisms and clinical ramifications. *Arterioscler Thromb Vasc Biol*. 2004;24:1161–1170.
12. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature*. 2011;473:317–325.
13. Jy W, Horstman LL, Jimenez JJ, et al. Measuring circulating cell-derived microparticles. *J Thromb Haemost*. 2004;2:1842–1851.
14. Lynch SF, Ludlam CA. Plasma microparticles and vascular disorders. *Br J Haematol*. 2007;137:36–48.
15. Hunter LW, Shiekh FA, Pisimisis GT, et al. Key role of alkaline phosphatase in the development of human-derived nanoparticles in vitro. *Acta Biomater*. 2011;7:1339–1345.
16. Shiekh FA, Charlesworth JE, Kim SH, et al. Proteomic evaluation of biological nanoparticles isolated from human kidney stones and calcified arteries. *Acta Biomater*. 2010;6:4065–4072.
17. Marsh M, van Meer G. Cell biology. No ESCRTs for exosomes. *Science*. 2008;319:1191–1192.
18. Wu CY, Young D, Martel J, Young JD. Bions: A family of Biomimetic mineralo-organic complexes derived from biological fluids. *PLOSone*; 2013;8(9);1–19.

Authors' reply

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Dear editor

Atughonu et al wrote a letter in response to our article entitled "Contrast-enhanced MR imaging of atherosclerosis using citrate-coated superparamagnetic iron oxide nanoparticles: calcifying microvesicles as imaging target for plaque characterization"[1] and addressed an important issue, namely that of using consistent terminology for what has been referred to in the literature as microvesicles, nanoparticles, and matrix vesicles in studies investigating the development and progression of atherosclerotic vessel wall changes.

The letter by Atughonu et al could be interpreted as criticism that, by referring to these structures as "calcifying microvesicles", we may have introduced yet another term into the context of cross-sectional imaging of inflammatory arterial wall lesions using targeted probes, and possibly without being aware of it.

In this field, as far as light-microscopic and electron-microscopic investigations are concerned, the situation is such that the scientific community has not yet agreed upon appropriate and well-defined terms, based on biochemical composition, for what are variably designated as microvesicles, microparticles, or matrix vesicles. The variation in terminology appears to reflect the fact that the structure and function of these entities is not yet fully understood.

The first to investigate these entities using light microscopy or electron microscopy included Bobryshev et al.[2–4] When they first started to unravel some secrets of these extracellular, mostly round structures, which they found in the atherosclerotic vessel wall, this group identified them as calcifying matrix vesicles. In their most recent publications, Bobryshev et al[4] modified the term to calcifying matrix microvesicles. On the other hand, to complete the confusion, Bobryshev et al seem to use the terms microparticles and microvesicles interchangeably within one publication.[2] They give the reader no clue if there is a difference between these terms or if they describe different structural or functional entities.[2]

Overall, Bobryshev et al identified a link between atherosclerotic lesion destabilization with a tendency to plaque rupture and the presence of these calcifying matrix microvesicles.[3]

Hsu et al have also done research on these vesicles, identifying them as calcifiable vesicles.[5,6] They extracted these vesicles from human- and experimentally-induced atherosclerotic lesions as early as the mild intimal thickening stage.[5,6]

Additionally, in a recent review, Kalra and Shanahan also used both "microvesicles" and "matrix vesicles", for such structures, which are a basis for microcalcification during atherosclerosis progression, without explaining whether these are two different terms or how they are related.[7]

In our publication, we deliberately avoided the terms microparticles or matrix because we only wanted to describe the light-microscopic appearance, which is very similar to the shape and location of the structures described by Bobryshev et al using electron microscopy.[4]

The term matrix particle was first used by Anderson to describe micron-sized vesicles (but referring to them as particles) located in the extracellular matrix as the basis of bone mineralization.[8] This is a physiological process and we did not wish to use the same terminology for an entity associated with the pathological process of arterial wall calcification, despite the fact that the same processes and enzymes may be involved.

For these reasons, we are convinced that currently it is better to use the term calcifying microvesicles when only describing appearance, rather than using a term that makes assumptions about function, which may ultimately turn out to be wrong. Such a term can be introduced as soon as the scientific community is able to give a clear definition regarding both the structure and function of these entities.

What we found is that matrix components, such as glycosaminoglycans, are major constituents of these vesicles. This has so far only been demonstrated for vesicles in the context of apatite formation during bone and teeth growth, and not for pathological calcification. Our discovery provides some insight into the mechanism of calcification during atherosclerosis progression, which has so far only been linked to phospholipids, but not to glycosaminoglycans. If the hypothesis of glycosaminoglycan-mediated calcification can be corroborated further, it will become clear that the calcified vesicles found in rupture-prone atherosclerotic lesions are

very similar to the vesicles found in physiological apatite formation, in terms of both structure and function. In this case, the term matrix vesicles would be appropriate from both a structural and functional point of view.

It is the task of the scientific community as a whole to further elucidate the origin, function, and structure, including the glycome, of these vesicles, which are linked to both physiological and pathological processes. Only with this knowledge can we decide on an appropriate name for these entities.

Disclosure

The authors report no conflicts of interest in this communication.

References

1. Wagner S, Schnorr J, Ludwig A, et al. Contrast-enhanced MR imaging of atherosclerosis using citrate-coated superparamagnetic iron oxide nanoparticles: calcifying microvesicles as imaging target for plaque characterization. *Int J Nanomedicine*. 2013;8:767–779.
2. Bobryshev YV, Killingsworth MC, Orekhov AN. Increased shedding of microvesicles from intimal smooth muscle cells in athero-prone areas of the human aorta: implications for understanding of the predisease stage. *Pathobiology*. 2012;80:24–31.
3. Bobryshev YV, Killingsworth MC, Lord RS, Grabs AJ. Matrix vesicles in the fibrous cap of atherosclerotic plaque: possible contribution to plaque rupture. *J Cell Mol Med*. 2008;12:2073–2082.
4. Bobryshev YV, Killingsworth MC, Huynh TG, Lord RS, Grabs AJ, Valenzuela SM. Are calcifying matrix vesicles in atherosclerotic lesions of cellular origin? *Basic Res Cardiol*. 2007;102:133–143.
5. Hsu HH, Tawfik O, Sun F. Mechanism of dystrophic calcification in rabbit aortas: temporal and spatial distributions of calcifying vesicles and calcification-related structural proteins. *Cardiovasc Pathol*. 2004;13:3–10.
6. Hsu HH, Camacho NP, Sun F, Tawfik O, Aono H. Isolation of calcifiable vesicles from aortas of rabbits fed with high cholesterol diets. *Atherosclerosis*. 2000;153:337–348.
7. Kalra SS, Shanahan CM. Vascular calcification and hypertension: cause and effect. *Ann Med*. 2012;44 Suppl 1:S85–S92.
8. Anderson HC. Electron microscopic studies of induced cartilage development and calcification. *J Cell Biol*. 1967;35:81–101.