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Calcification in atherosclerotic lesions

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Calcification in atherosclerotic lesions has long been recognized and there is evolving evidence that it is an active participant in plaque rupture [1,2]. This bimonthly update summarizes selected recent publications that have explored roles of cartilage oligomeric matrix protein (COMP) [3■], sortilin [4■], and discoidin domain receptor-1 (DDR-1) [5■] on calcification in the spectrum of atherosclerotic lesion development.

In one study, Fu *et al.* [3■] demonstrated that global deficiency of COMP in apolipoprotein E^{-/-} mice led to larger atherosclerotic lesion size, which was accompanied by enhanced calcification in lesions. COMP is a component of vascular extracellular matrix [6], and is present in vascular smooth muscle cells and leukocytes [3■]. Forward and reverse bone marrow transplantation was then performed to determine whether myeloid cells are the principal source of COMP-mediated calcification in atherosclerotic lesions. COMP deficiency in bone marrow-derived cells augmented vascular calcification in a hypercholesterolemic background. Calcification was further increased when both bone marrow-derived cells and resident-recipient cells had COMP deficiency. Thus, COMP from both leukocytes and resident cells have effects on calcification of atherosclerosis in hypercholesterolemic mice.

Aikawa's group [4■,5■] reports that sortilin [4■] and DDR-1 [5■] regulate calcification derived from extracellular vesicles in vascular smooth muscle cells, a mechanism that contributes to atherosclerotic calcification. Using a state-of-the-art technique, three-dimensional collagen hydrogels, which simulate discrete structural features of atherosclerotic fibrous caps, the authors demonstrated that aggregation of calcifying extracellular vesicles contributed to calcification of vascular smooth muscle cells in atherosclerotic lesions [7■]. In one study, the authors determined the effects of sortilin on vascular calcification in hypercholesterolemic mice [4■]. Sortilin is a multiligand receptor that regulates lipoprotein metabolism and contributes to atherosclerosis [8]. Sortilin was highly expressed in smooth muscle cells, but not macrophages of atherosclerotic lesions

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Conflicts of interest

There are no conflicts of interest.

from humans or mice. Global deficiency of sortilin did not affect bone structure in mice, but reduced calcification of both atherosclerotic lesions and aortic wall of LDL receptor^{-/-} mice fed either a diet enriching in both fat and cholesterol or a Western diet containing high saturated fat with limited cholesterol enrichment. As expected, sortilin deficiency in bone marrow-derived cells had no effects on vascular calcification. In both in-vitro and ex-vivo analyses, sortilin promoted smooth muscle cell calcification through its recruitment into extracellular vesicles [4■]. It is clear that sortilin is not the only contributor to vascular calcification in vascular smooth muscle cells. DDR-1, a collagen receptor, contributed to atherosclerotic calcification in hypercholesterolemic mice fed an atherogenic diet [9]. Aikawa's group [5■] used in-vitro cell culture system to demonstrate that DDR-1 in vascular smooth muscle cells, through a transforming growth factor- β signalling-mediated mechanism, induced release of calcifying extracellular vesicles.

Findings from these recent studies provide insights that calcification of atherosclerotic lesions is promoted by multiple mediators in leukocytes or smooth muscle cells. Currently, associations between calcification and plaque rupture have not been unravelled [10]. Of clinical relevance, it will be important to determine whether calcification regulated by these contributors is a risk factor for plaque rupture or the consequence of plaque rupture.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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- 3■. Fu Y, Gao C, Liang Y, et al. Shift of macrophage phenotype due to cartilage oligomeric matrix protein deficiency drives atherosclerotic calcification. *Circ Res* 2016; 19:261–276. The article reports effects of cartilage oligomeric matrix protein on atherosclerotic calcification using bone marrow transplantation strategy in mice and cell culture system.
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[PubMed: 26950419]

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[PubMed: 26800565]

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[PubMed: 26752654]

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FURTHER RECOMMENDED READING

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[PubMed: 27102966]

- . Bailey G Meadows. Morrison AR. Imaging atherosclerotic plaque calcification: translating biology. *Curr Atheroscler Rep* 2016; 18:51. The review article introduces recent advances of the biologic process of atherosclerotic calcification and molecular imaging systems to assess it.

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