Smooth muscle cells in pathogenesis of vascular medial cartilaginous metaplasia

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This editorial refers to ‘Arterial injury promotes medial chondrogenesis in Sm22 knockout mice’ by J. Shen et al., pp. 28–37, this issue.

Vascular medial calcification (VMC), also known as Mönckeberg’s medial sclerosis, is commonly associated with ageing and occurs in patients with type II diabetes mellitus (T2D) and end-stage renal disease (ESRD). In these cases, calcium phosphate salts deposit in arterial media associated with elastin/collagen-rich extracellular matrix, typically in a linear fashion along the elastic lamina of arterial mediae. As the lesion advances, the mediae are filled with circumferential rings of calcium phosphate crystals, resulting in decreased vessel wall compliance that leads to increased arterial pulse wave velocity and pressure, impaired coronary artery perfusion, and cardiovascular dysfunction.1 In T2D and ESRD patients, arterial medial calcification is highly prevalent and believed to be a major risk factor for cardiovascular mortality, stroke, and lower-limb amputation.2–4

VMC has long been considered a degenerative process leading to passive deposition of calcium phosphate salts associated with tissue necrosis. However, the presence of bone- and cartilage-related proteins, osteoblast- and chondrocyte-like cells, and outright bone- and cartilage-like tissue in calcified lesions has underscored its cell-mediated, actively regulated nature that resembles, at least in part, embryonic bone formation and remodelling.2–5 These findings have also driven researchers to explore the cell types that contribute to the development of bony and cartilaginous elements in the vasculature as well as the mechanisms regulating VMC.

A shared feature of VMC among various sources of disease is its loss of smooth muscle cell (SMC) marker proteins and its gain of osteochondrogenic regulatory molecules and marker proteins in calcified areas of vascular media.2,5,7,8 SMCs are the predominant cell type found in arterial wall and are essential for the structural and functional integrity of the vessel. Unlike most cell types that undergo terminal differentiation, SMCs retain substantial phenotypic plasticity in response to injurious stimuli from the local micro-environment. Indeed, phenotypic change of vascular SMCs in response to local environmental cues is not only seen in cultured SMCs, but also triggered under various disease circumstances in vivo, such as observed in atherosclerotic vessels of human and ApoE null mice9 and in carotid media where transforming growth factor-β1 was delivered to the endothelium of the carotids.10 Finally, a recent study using genetic fate mapping of matrix Gla protein mutant mice (MGP–/–) provided definitive evidence indicating that vascular SMCs were able to transdifferentiate toward an osteochondrogenic state and become the predominant cell source for osteochondrogenic precursors and chondrocytes seen in VMC of this model.11 Despite growing acceptance of osteochondrogenic differentiation of SMCs in calcifying vasculature, it remains unclear whether down-regulation of SMC lineage genes may in itself drive osteochondrogenic phenotype change to induce matrix calcification.

In this issue of Cardiovascular Research, Shen et al.12 struck into this interesting theme via targeting of a well-defined SMC lineage protein, SM22α, to determine whether deficient SMC cytoskeletal gene expression mediates arterial medial chondrogenesis. While SM22α mutant (SM22–/–) mice showed uncompromised vascular development, morphology, and function in blood vessels,13 denudation of carotid endothelium of SM22–/– mice induced prominent chondrogenesis in arterial media,13 a likely process of vascular SMC transdifferentiation toward osteochondrogenesis in response to the injured environmental cues.7–11 Of note, SM22α deficiency in SMCs resulted in a disruption of actin cytoskeleton and increased actin dynamics in cells, leading to a compromised actin stress fibre formation and increased G/F actin ratio.12 These interesting findings provide strong evidence supporting the notion that disruption of cytoskeletal proteins, i.e., SM22α, can compromise normal SMC development upon arterial injury and thereby promote reprogramming of their lineage fate from promyogenesis to osteochondrogenesis. This notion is also aligned with the role of SM22α deficiency in atherosclerotic lesion augmentation of ApoE–/– vessels14 and enhanced inflammatory response upon carotid denudation of SM22–/– mice.15 One weakness of this report is the lack of visual and quantitative data from VMC in the injured carotids of SM22–/– mice. Presumably, a prolonged lesion development post-surgery would clarify whether osteochondrogenic differentiation of SMCs in denuded vessels will eventually lead to a maturation of chondrocytic cells followed by matrix calcification, a typical pathological feature often seen in blood vessels of T2D patients. It is also undetermined in this paper...
whether cells of osteochondrogenic properties in injured SM22–/– media were indeed derived from vascular SMCs.

Another exciting finding reported in this paper is that the transcriptional shift of promyogenesis toward prochondrogenesis in SM22–/– carotids post-injury is likely mediated through increased reactive oxygen species (ROS) and redox-sensitive NF-κB signalling. This is of special relevance for the pathobiology of vascular calcification in patients with atherosclerosis, T2D, and ESRD with respect to the long-lasting oxidative stress signals elaborated in response to inflammatory cytokines in this population. According to the studies by Shen et al., disrupting SM22α expression in vascular SMCs hampered cytoskeletal filament formation and resulted in transcriptional reprogramming toward prochondrogenesis, whereas blocking ROS–NF-κB signalling resulted in suppressed osteochondrogenic differentiation of SMCs in response to the cytoskeletal protein disruption. Consistent with these findings, prominent inflammation, SOD2 expression, and active NF-κB signalling were seen in injured carotid media of SM22–/– mice. It is also significant to note that ROS–NF-κB signalling was unlikely responsible for the loss of promyogenic properties of SM22–/– cells.

In summary, the report by Shen et al. poses a novel and important role of the cytoskeletal gene, SM22α, in prochondrogenesis of arterial media in response to injury, a process likely mediated through ROS- and redox-sensitive NF-κB signalling. Whether prochondrogenesis of SM22–/– media leads to chondrocytic proliferation and maturation and eventually to the development of vascular calcification remains to be determined. It would also be interesting to investigate whether SM22 deficiency contributes similarly to the shift of promyogenic to prochondrogenic differentiation of arterial media in T2D and ESRD settings, diseases featured with increased oxidative stress and active NF-κB signalling.

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