Editorial

Stem Cell INVESTIGATION

Role of adventitial MSC-like cells in chronic kidney disease

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Provenance: This is an invited Editorial commissioned by Editor-in-Chief Zhizhuang Joe Zhao (Pathology Graduate Program, University of Oklahoma Health Sciences Center, Oklahoma City, USA).

Comment on: Kramann R, Goettsch C, Wongboonsin J, *et al*. Adventitial MSC-like cells are progenitors of vascular smooth muscle cells and drive vascular calcification in chronic kidney disease. Cell Stem Cell 2016;19:628-42.

Received: 01 December 2016; Accepted: 08 December 2016; Published: 18 January 2017.

doi: 10.21037/sci.2016.12.03

View this article at: http://dx.doi.org/10.21037/sci.2016.12.03

Cardiovascular diseases are the principal cause of death in the industrialized countries. Vascular wall calcification occurring in the late stages of cardiovascular diseases is an independent risk factor in patients with chronic kidney disease (CKD) (1,2). This process of arterial calcification in CKD may affect different arterial layers: the intima in association with atherosclerosis, and the media mostly in association with reduced kidney function (3).

It is generally accepted that osteoblast-like cells, originating from dedifferentiated smooth muscle cells resident in the media, are responsible for the calcifications occurring in the arterial wall (4). The activation of this osteogenic program is triggered by injury and modulated by a number of inflammatory, metabolic, and genetic disorders (5). On a molecular point of view, the induction of bone morphogenetic proteins and osteochondrogenic transcription factors play a central role (6). Whereas this process is well established for calcifications of the tunica media, those occurring in the intimal layer are less characterized. The contribution of bone marrow-derived circulating calcifying cells after the activation of an osteogenic program has been proposed (7). In a recent issue of *Cell Stem Cell*, Kramann and colleagues (8), using genetic fate mapping, clearly identified a new player in the calcification process: the mesenchymal stem cell (MSC) population located in the tunica adventitia.

MSC, a population of mesenchymal cells with stem-like properties, have been detected in virtually all organs (9) as perivascular pericytes (10). In capillaries, these cells are in contact with the endothelium, and in large arteries localize in the external adventitial layer (11). Indeed, it must be noted that adventitia is rich in small vessels, i.e., vasa vasorum, that possibly represent the MSC niche. In a physiological context, MSC have been considered to mainly display a trophic function, stabilizing vessels and contributing to tissue and immune system homeostasis (12).

MSC have been also actively involved in organ repair after injury in a variety of tissues (13). Consequently, administration of cultured MSC appears a promising tool for regenerative medicine. However, the lack of a specific MSC marker has hampered the possibility to trace their fate during damage and repair and to gain insights into the physio-pathological role of resident MSC. In fact, the characterization of MSC relies on the co-expression of a variety of mesenchymal markers shared by fibroblasts and other cell types. Recently, Gli1 has been shown to represent a specific selective marker for vascular MSC (14-16). By inducible genetic fate tracing experiments, Gli1$^+$ MSC were reported to proliferate following injury and to differentiate into myofibroblasts *in vivo* (14). The effects resulting from the observed MSC activation appeared different and opposed in acute and chronic injury settings. During an acute vascular injury, due to wire injury of the femoral artery, Gli1$^+$ cell differentiated into vascular smooth muscle cells and contributed to the healing effect. In particular, Gli1$^+$ cells migrated into intima and media and replaced lost smooth muscle cells in the media. In parallel, other studies reported the activation and dedifferentiation of vascular smooth muscle cells, possibly deriving from Gli1$^+$ cell themselves, after a vessel wall injury (17). These cells have been shown to undergo phenotypic changes, with production of less contractile

proteins, proliferation and migration into the neointima and media.

On the other hand, Gli1$^+$ progenitor cells contributed to tissue fibrosis and calcifications in chronic injury settings (8,14). In fact, in a model of atherosclerosis in ApoE$^{-/-}$ mice with concomitant CKD, Gli1$^+$ cells differentiated into osteoblast-like cells and significantly contributed to the arterial calcification process (8). In analogy, in chronic injury models of liver, lung, kidney or heart, the same authors showed that Gli1$^+$ MSC promoted organ fibrosis. The relevance for human pathology, and in particular for the calcification occurring in CKD, has been confirmed by the detection of Gli1$^+$ cells in human arteries from CKD patients.

These experiments together support a prominent negative effect of adventitial MSC in organ repair and identify Gli1$^+$ cells as a possible therapeutic target. Importantly, the genetic ablation of Gli1$^+$ cells before the induction of CKD significantly reduced the mineralization of the vascular wall (8). Similarly, Gli1$^+$ cell ablation prevented the development of fibrosis in injured kidneys, liver and lungs (14,18,19). This opens a new strategy in the treatment of fibrosis and vascular calcifications that could be of benefit for patients with chronic diseases. On the light of the role of Gli as transcriptional effectors of the hedgehog pathway, pharmacological suppression of the hedgehog pathway itself resulted to reduce organ fibrosis (20).

Some questions rise from these studies. The first deals with the mechanisms of the epi-genetic changes of MSC involved in their transformation into detrimental cells. It is clear that the microenvironment occurring in chronic diseases may modulate MSC and favor their acquisition of a pro-calcifying phenotype (21,22). Indeed, the fibrotic and calcifying process occurring in CKD patients has been shown to result from a number of epigenetic changes in the tissue (23). Environment-induced changes in MSC should be considered for autologous MSC-based therapy. For example, it has been shown that tumor priming may converse MSC from an anti-tumor to a pro-tumorigenic phenotype (24). In addition, this detrimental environment may also affect heterologous MSC once administered to patients for regenerative purposes. Although many studies have shown the lack of toxic effects of MSC in clinical trials, their efficacy in chronic injury models has not been proven yet.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/sci.2016.12.03
Cite this article as: Bussolati B, Deregibus MC, Camussi G. Role of adventitial MSC-like cells in chronic kidney disease. Stem Cell Investig 2017;4:2.

