Editorial

Targeting Vascular Calcification: Up-Date

Keywords: Calcification, blood vessels, arteries, targets, biomarkers.

Our society faces a growing burden of atherosclerosis and arteriosclerosis, diseases that result from dysregulated lipid and mineral metabolisms. Atherosclerosis and arteriosclerosis lead to increased acute cardiovascular events. A number of risk factors, including hypercholesterolemia, metabolic syndrome, diabetes mellitus and endstage renal diseases, have been found to contribute to acceleration of vascular calcification [1-5]. Vascular calcification occurs as a result of the deposition of calcium, predominantly in the form of hydroxyapatite, in both the tunica intima and the tunica media of the arterial wall [2-5]. Vascular calcification is known to occur in two distinct forms: intimal calcification, which always occurs in the context of atherosclerosis, and medial calcification, which can occur in its absence [12, 13, 19]. These two processes differ not only in morphology, but also in the pathological mechanisms involved [6, 12, 13, 19]. Inflammatory cells such as macrophages and mast cells infiltrating plaque lipid-rich regions play an important role in atherosclerotic calcification [5, 10-20]. In contrast to intimal calcification, medial calcification is known to occur in the absence of inflammatory cell infiltration and lipid deposition [5,10-20]. Apart from arteriosclerotic calcification of the media in large elastic-type arteries of nondiabetic individuals, the calcification process, known as Monckeberg's sclerosis, commonly affects the media of peripheral medium-sized arteries in aged and diabetic individuals [19].

Over the last decades, there has been growing interest in the identification of molecular and cellular mechanisms involved in vascular calcification [1-24]. Accumulating evidence suggests that the pathological processes that are instrumental for cardiovascular calcification utilize the mechanisms which are the same or similar to those of bone development, such as osteoblastic differentiation and biomineralization [1-24]. A significant body of evidence has accumulated to support a view that arterial calcification is not a passive but an active cell-regulated process similar to osteogenesis [1-24]. This view is supported by the findings of the expression of a variety of bone-associated proteins in atherosclerotic plaque, particularly at sites prone to or undergoing calcification as well as by identification of cases of the formation of bone in arterial tissue. Several cell types have been suggested to be responsible for arterial calcification. Vascular smooth muscle cells (SMCs), microvascular smooth muscle-like cells, and pericytes can differentiate in culture to form osteoblast-like cells producing a calcified matrix and the concept of multipotent mesenchymal calcifying vascular cells, which are capable of forming calcifying nodules, has been developed [2, 23]. The association of vascular calcification with SMC phenotypic transition, in which several osteogenic proteins including osteopontin, osteocalcin, the bone-determining factor Cbfa, S100 proteins were gained [1-24]. It has been reported that both vascular SMCs and macrophages express a variety of chondrocytic, osteoblastic, and osteoclast-associated proteins that may govern the calcification process in the arterial wall. The invasion of pluripotent bone marrow-derived cells into atherosclerotic plaques has been suggested as well, adding a new dimension to speculations about the origin of vascular calcifying cells [5, 10, 22].

Currently, no therapies are available to prevent vascular calcification. Despite the clinical importance of the elucidation of the mechanisms and the identification of biomarkers of vascular calcification, the mechanisms of vascular calcification and biomarkers are insufficiently studied and insufficiently understood. In 2010, the National Heart, Lung and Blood Institute (NHLBI) Working Group on Calcific Aortic Stenosis emphasized the importance of understanding the mechanisms of vascular calcification markers and the need to develop new imaging modalities for detection of subclinical calcification [15].

A special issue entitled" Targeting vascular calcification: Up-date" highlights the recent advances in our understanding of the mechanisms of vascular calcification and discuss challenges for treatment or suppression of the involved pathological processes. Vascular calcification is common in aging as well as a number of genetic and metabolic disorders. Ectopic mineralization in the arteries complicates the prognosis and increases the morbidity in diseases such as atherosclerosis, diabetes and chronic kidney disease (CKD). In this special issue, several reviews provide up-date information about the mechanism of vascular calcification associated with several human diseases [25-35], including atherosclerosis [25, 26], diabetes [27], and CKD [28]. Traditionally abdominal aortic calcification (AAC) has received less intensive study than artery calcification in atherosclerosis and diabetes, but the widespread use of abdominal imaging has however encouraged recent investigation of this problem. In this issue, Jonathan Golledge (Australia) provides the current information about AAC [29].

In a review article entitled "Modulators of networks: Molecular targets of arterial calcification identified in man and mice" Yvonne Nitschke, Frank Rutsch (Germany) show that genetic studies of rare monogenic human disorders and studies of naturally occurring or mutant mouse models have identified specific inductors and inhibitors of arterial calcification, which can be classified according to the networks they participate in [30]. These networks include ATP and pyrophosphate metabolism, Phosphate homeostasis and Vitamin D Receptor Signalling [30]. Furthermore, intracellular signalling molecules, including SMAD6 and a number of systemic circulatory inhibitors of arterial calcification, including fetuin, tumor necrosis factor receptor superfamily member 11b, matrix GLA protein, adiponectin and Family with sequence similarity 20 member A have been identified by human and mouse genetics [30]. Based on the in vivo evidence of their functional relevance, the above listed proteins will serve as excellent targets for the prevention and treatment of arterial calcification [30]. The involvement of the osteoprotegerin (OPG)/ receptor activator of nuclear factor-κB (RANK)/ Receptor activator of nuclear factor-κB ligand (RANKL) triad and tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) in cardiovascular pathology is well recognized nowadays and attracts increasing interest. In this special issue, two review articles highlight the most current information on the relationship between RANKL, OPG and TRAIL, and unambiguously demonstrate that a better understanding of RANKL-mediated signalling may help develop more sophisticated cell-based therapies to inhibit calcification of the vessel wall [31,32]. Another review article, entitled "Role of Bone-Type Tissue-Nonspecific Alkaline Phosphatase and PHOSPO1 in Vascular Calcification" shows that pathologic roles of bone-type TNAP and PHOSPHO1 make them to be attractive targets for cardiovascular anti-calcification therapy [33]. In a paper entitled "Blood Serum Atherogenicity and Coronary Artery Calcification' a collaborative research group (Russia and Germany) reports an interesting finding indicating that serum-induced intracellular cholesterol accumulation is not related to the processes of calcium deposition in arterial wall [34]. Despite of a remarkable progress in our understanding of cell elements involved in arterial calcification, there is still controversy about the contribution of mesenchymal cell progenitors and blood origin circulating cell precursors to vascular calcification. In this issue of the journal, Mattia Albiero and colleagues (Italy) discuss potential roles of different populations of circulating calcifying cells in vascular calcification [35].

Thus, in this special issue, a team of international experts discuss the most novel topics relating to the problem of vascular calcification. I would like to thank the contributors to this issue for their participation. We hope that this special issue will be helpful for the development of novel therapeutic drugs against vascular calcification and novel approaches for prevention, diagnosis and treatment of this pathological condition.

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