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Review

Deficiencies of physiologic calcification inhibitors and low-grade inflammation in arterial calcification: lessons for cartilage calcification

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Abstract

Apart from clinical parallels, similarities in the pathogenesis of arterial and articular cartilage calcification have come to light in recent years. These include the roles of aging, of chronic low-grade inflammation and of genetic and acquired dysregulation of inorganic pyrophosphate (PP_i) metabolism. This review focuses on recent developments in understanding the pathogenesis of artery calcification pertinent to interpretation of the mechanistic basis for articular cartilage calcification in aging and osteoarthritis.

Keywords: MGP; PC-1; ENPP1; Pyrophosphate; Osteoprotegerin; Osteoarthritis; Atherosclerosis; Cartilage; Calcification

1. Introduction

Calcification of articular cartilage contributes to significant morbidity because of its association with joint inflammation and worsening of the progression of osteoarthritis [1]. Articular cartilage calcification occurs in association with aging, degenerative joint disease, some genetic disorders and various metabolic disturbances [2]. Similarly, arterial calcification occurs with advanced age, atherosclerosis, metabolic disorders, including end stage renal disease and diabetes mellitus and some genetic disorders. Arterial calcification contributes to hypertension and an increased risk of cardiovascular events [3]. Hydroxyapatite crystals in arterial atherosclerotic plaques have the potential to promote low-grade inflammation that favors plaque instability and may contribute to thrombotic vascular occlusion such as myocardial infarction [4]. Apart from clinical parallels, similarities in the pathogenesis of arterial and articular cartilage calcification have come to light in recent years and are subject of this review.

2. Distinct patterns of arterial calcification

Arterial calcification can be present at the level of the intima, the arterial media or the internal elastic lamina (Fig. 1). In the context of atherosclerotic plaque formation, vascular calcification occurs in the intima and is associated with lipid-laden foam cells and macrophages. Inflammatory mediators, as discussed later in the text, predominantly drive this process. The second type of arterial calcification occurs in the media of the artery and is associated with advanced age, diabetes and renal failure. This form can be widely spread through the arterial tree. Medial calcification is often referred to as Mönckeberg sclerosis and generally does not colocalize with atherosclerotic plaques. Hyperphosphatemia has been identified as a pathogenic factor causing medial calcification, as discussed later. A variant form of artery media calcification, concentrated at the internal elastic lamina (Fig. 1) has most recently been found to be associated with pyrophosphate (PP_i) deficiency [5,6].

3. Parallels in the pathogenesis of arterial and cartilage calcification

Vascular smooth muscle cells (VSMCs), like chondrocytes, are capable to form mineralising, membrane-limited

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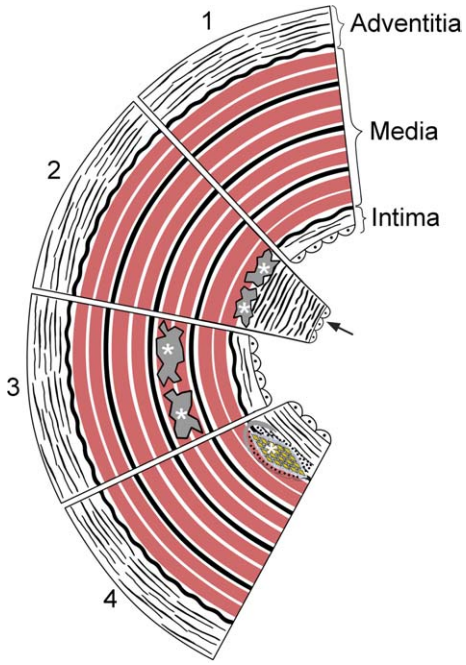

Fig. 1. Different patterns of arterial calcification. (1) Normal arterial wall, (2) 'idiopathic' infantile arterial calcification: calcification of the internal elastic lamina (*), myointimal proliferation (→). (3) Mönckeberg media sclerosis: calcification of the media (*) without significant myointimal proliferation. (4) Atherosclerosis: calcification of atheromatous plaques (*).

cell fragments (matrix vesicles) that provide a sheltered environment for the initiation of calcification [7]. Moreover, Boström et al. [8] cultured human aortic vascular smooth muscle cells from the media and demonstrated formation of nodules that showed spontaneous calcification. Calcifying vascular cells, derived largely from pluripotential cells in the artery wall, follow the critical time sequence of expression of bone-related proteins as in normal mineralising bone [9].

Recent studies in animal models have elucidated that calcification in the artery (and cartilage) must be actively inhibited by physiologic function of resident cells. Deficient expression of certain inhibitors of calcification may be sufficient to trigger the calcification process. Alternatively, arterial calcification can be the result of a systemic excess of procalcifying mediators, e.g., inorganic phosphate (P_i). The end result includes expression of a variety of stereotypic bone matrix proteins, which orchestrate a process resembling osteogenesis within the vessel wall [10,11].

As with arterial calcification, articular cartilage matrix calcification [1] could reflect deficiencies of physiologic calcification inhibitors (Table 1) or up-regulation of mediators that actively drive stereotypical patterns of tissue injury culminating in calcification within degenerating cartilage (Fig. 2). A special circumstance promoting chondrocalcinosis is the relatively unique capacity of chondrocytes to produce copious amounts of extracellular PP_i, stimulating CPPD crystal deposition [12–14]. As with arterial calcification, regulated changes in chondrocyte differentiation and viability appear to mediate chondrocalcinosis, including the development of chondrocyte hypertrophy associated with expression of stereotypic bone matrix proteins, and the presence of heightened hypertrophy and apoptosis of chondrocytes in proximity to articular cartilage calcifications [15].

4. Inhibition of artery and cartilage calcification

Characterization of targeted or naturally occurring mutations of a variety of genes in mice has identified nine different inhibitors of vascular calcification in vivo (Table 1). Two of these inhibitors are of specific importance in respect to our review, namely Matrix-Gla protein (MGP) and nucleotide pyrophosphatase/phosphodiesterase family member NPP1, since inborn deficiency of these proteins is associated with both calcification of arteries and articular cartilage in mice and humans.

4.1. Matrix-Gla protein (MGP)

MGP-deficient mice die 1–3 months after birth because a calcifying cartilage matrix develops in the entire vascular

Table 1
Genes for which mutations have been associated with vascular calcification in mouse model systems

Gene symbol, human protein name, [OMIM Entry#]	Mouse model	Major phenotypic features	References
MGP, Matrix-Gla protein, [154870]	$mgp^{-/-}$	Arterial and cartilage calcification, tracheobronchial stenosis. Human correlate: Keutel syndrome	[16–22]
ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase1, [173335]	ttw/ttw (twy)	Articular cartilage calcification, hyperostosis, spine and peripheral joint fusion, arterial calcification. Human correlate: 'idiopathic' infantile arterial calcification	[5,6,23,25]
OPG, Osteoprotegerin, [602643]	$opg^{-/-}$	Osteoporosis, vascular calcification	[31–36]
Smad6/Madh6, SMA- and MAD-related protein 6 [602931]	madh6-mutant	Endocardial cushion defects, aortic ossification	[37–39]
FBN-1, fibrillin-1 [134797]	mgΔ/mgΔ, mgR/mgR	Aortic aneurysm, long bone overgrowth, medial arterial calcification. Human correlate: Marfan syndrome	[41,42]
Car-2, carbonic anhydrase-2 [259730]	$car\text{-}2^{-/-}$	Osteopetrosis, renal tubular acidosis, medial calcification of small arteries. Human correlate: carbonic anhydrase II deficiency	[44–46]
KL, Klotho [604824]	$klotho^{-/-}$	Vascular calcification, rapid aging	[47,48]
AHSG, α2HS-glycoprotein/fetuin, [138680]	$ahsg^{-/-}$	Mild vascular calcification	[49–51]
OPN, Osteopontin, [166490]	$opn^{-/-}$	Enhanced valve implant calcification	[52–54]

Genetic defects have highlighted the role of various protein, enzymes and signalling molecules in the onset of vascular, but also cartilage calcifications in animal models, with human correlates.