Atherosclerosis 226 (2013) 9–15

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Aortic calcification: Novel insights from familial hypercholesterolemia and potential role for the low-density lipoprotein receptor

Daniel Fantus [a,1], Zuhier Awan [b,1], Nabil G. Seidah [b], Jacques Genest [a,*]

[a] Division of Cardiology, Department of Medicine, McGill University, Montreal, Quebec, Canada
[b] Institut de Recherches Cliniques (Affiliated to the University of Montreal), Montréal, Québec, Canada

ARTICLE INFO

Article history:
Received 22 June 2012
Received in revised form
19 August 2012
Accepted 20 August 2012
Available online 18 September 2012

Keywords:
Familial hypercholesterolemia
Arterial calcification
Low density lipoprotein receptor
Animal models
Osteoblasts
Atherosclerosis

ABSTRACT

Once thought to be a passive process of calcium accrual in arterial vascular beds, vascular calcification is considered to be a tightly regulated process mediated by osteoblast-like cells under the dys-regulated interplay of shear stress, metabolites, cytokines and transcription factors. Unfortunately, without effective medical interventions to prevent or regress vascular calcification, this process directly contributes to cardiovascular morbidity and mortality. We have previously shown that patients with familial hypercholesterolemia (FH) have severe, premature aortic calcification and calcific aortic stenosis. We showed an age-related gene-dosage effect of deletion of the low-density lipoprotein receptor (LDL-R) gene on aortic calcification in human subjects with FH. The LDL-R deficient mouse and transgenic mice overexpressing the LDL-R degrading protein PCSK9 also exhibit aortic calcification, not fully explained by increased LDL cholesterol levels. Taken together, these data suggests a novel role for the LDL-R in the inhibition of vascular calcification. Understanding the molecular role of the LDL-R and its signaling partners in vascular calcification will be instrumental in identifying novel therapies for a common age-related process associated with a large burden of disease.

Contents

It is estimated that one third of individuals over age 60 years have a progressive increase in calcium deposits in major arteries [1]. As a consequence of calcium buildup in the vasculature, aortic and arterial elasticity is reduced and cardiovascular hemodynamics becomes compromised. The clinical impact of vascular calcification is widespread and contributes to arterial hypertension, aortic valve stenosis, limb ischemia, myocardial infarction and congestive heart failure [2]. Calcific aortic stenosis is the leading cause of aortic valve replacement in Europe and North America and the third leading cause of cardiovascular disease [3–6]. In the western world, 3% of adults over 75 years of age are affected by calcific aortic stenosis [7]. Histologically, vascular calcification can occur in distinct layers of the blood vessel. Intimal calcification is associated with

* Corresponding author. Faculty of Medicine, McGill University, Division of Cardiology, McGill University Health Center, Royal Victoria Hospital, 687 Pine Avenue West, Montréal, QC H3A 1A1, Canada. Tel.: +1 514 934 1934x34642; fax: +1 514 843 2813.
E-mail address: Jacques.genest@muhc.mcgill.ca (J. Genest).
[1] Both authors contributed equally.

0021-9150/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.atherosclerosis.2012.08.026

Abbreviations

ANK	ankyrin family
AoCS	aortic calcium scores
BMP	bone morphogenetic proteins
Cbfa1	core binding factor alpha1
CCAAT	enhancer-binding proteins
DKK1	Dikkopf protein
ESRD	end-stage renal disease
FH	familial hypercholesterolemia
GSK3B	glycogen synthase kinase 3 B
Hox8	homeobox protein 8, now known as Msx2
HSP	heat shock protein
Ldlr$^{-/-}$	low-density lipoprotein receptor gene knockout
LDL-R	low-density lipoprotein receptor protein
LRP	low-density lipoprotein receptor-related protein
MGP	matrix gla protein
Msx2	MSH homeobox 2, formerly Hox-8
NPP I	ectonucleotide pyrophosphatase/phosphodiesterase I
OPG	osteoprotegerin
Osterix	zinc finger-containing transcription factor
PCSK9	proprotein convertase subtilisin/kexin type 9
PEBP2	polyoma enhancer binding protein 2
Pi	inorganic phosphate
PPARγ	peroxisome proliferator-activated receptor gamma
PPi	inorganic pyrophosphate
RANKL	receptor activator of nuclear factor kappa-B ligand
Runx2	runt-related transcription factor 2
Sox9	SRY (sex determining region Y) box 9
TGF	transforming growth factor
TNF-α	tumor necrosis factor-alpha
VSMC	vascular smooth muscle cells
Wnt	a hybrid of Wg (wingless) and Int1 (integration1) genes in Drosophila

atherosclerosis whereas medial calcification (Monckeberg's sclerosis) is associated with age, diabetes and end-stage renal disease (ESRD). In ESRD, calcium and phosphate disorders are typically present [8]. Both intimal and medial calcification are markers of increased cardiovascular morbidity and mortality. Calcification of coronary arteries is an independent biomarker of atherosclerosis and myocardial infarction [9]. Diffuse medial calcification can lead to decreased arterial compliance and increase cardiac afterload contributing to the development of left ventricular hypertrophy and decreased cardiac perfusion [8]. Arterial calcification in ESRD is considered a predictor of cardiovascular mortality [10]. In dialysis patients, calciphylaxis represents a third form of vascular calcification; a systemic vascular calcification associated with calcific skin necrosis and global mortality [11].

The potential role of the low-density lipoprotein receptor (LDL-R) in the pathogenesis of intimal calcification was highlighted in a careful study of subjects with homozygous familial hypercholesterolemia due to mutations at the LDL-R gene locus [12,13]. Atherosclerotic intimal calcification appears to result from an interaction between inflammatory factors produced within an atherosclerotic plaque and a subpopulation of vascular cells that undergo osteogenic differentiation. Many of the conventional risk factors for coronary artery disease, namely hypercholesterolemia, hypertension, diabetes and tobacco use, have been linked to intimal calcification. It is thought that these pro-inflammatory agents induce oxidative stress in the milieu of the vascular endothelium that leads to atherosclerosis and calcification. On the basis of recent observations, this view is challenged.

1. Origin of cells involved in vascular calcification

The key regulatory mechanisms involved in vascular calcification have been described and many excellent reviews have already been written on this topic [5,14,15]. Fig. 1 illustrates the proposed signaling pathways involved in vascular calcification. In the current model, vascular calcification is a process of active bone formation

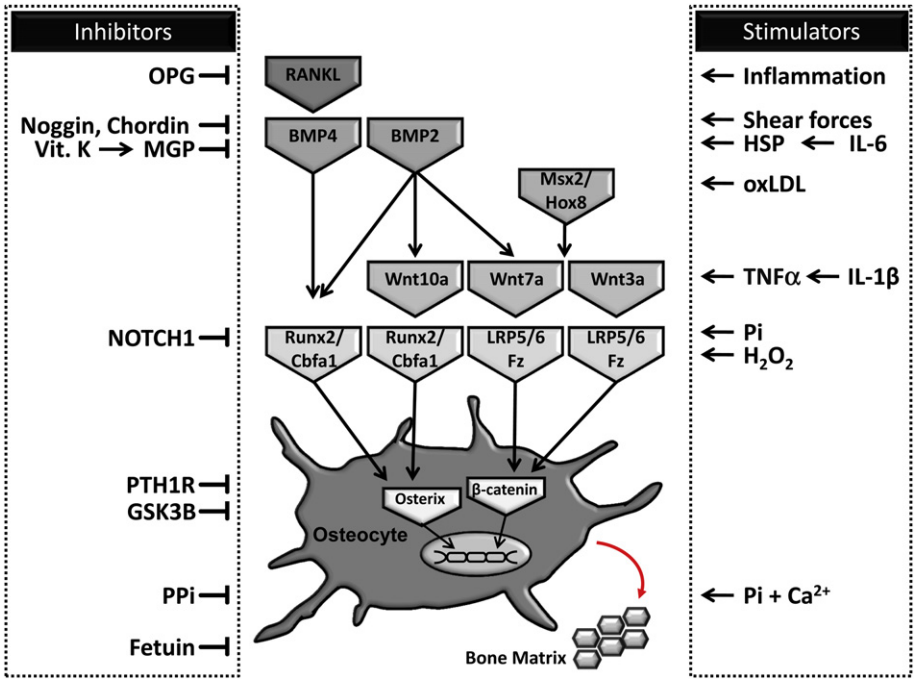

Fig. 1. A schematic representation of the signaling pathways in vascular calcification in relation to known stimulatory and inhibitory factors.