Materials Science and Engineering B 176 (2011) 1133–1141

Contents lists available at ScienceDirect

Materials Science and Engineering B

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

Review

Vascular calcification: Inducers and inhibitors

Donghyun Lee*

Department of Biomedical Engineering, Division of Integrative Engineering, Chung-Ang University, 221 Heukseok-Dong, Dongjak-Gu, Seoul 156-756, Republic of Korea

ARTICLE INFO

Article history:
Received 23 December 2010
Received in revised form 26 May 2011
Accepted 13 June 2011
Available online 29 June 2011

Keywords:
Mineralization
Vascular calcification
Atherosclerosis
Pathogenesis

ABSTRACT

Unlike the traditional beliefs, there are mounting evidences suggesting that ectopic mineral depositions, including vascular calcification are mostly active processes, many times resembling that of the bone mineralization. Numbers of agents are involved in the differentiation of certain subpopulation of smooth muscle cells (SMCs) into the osteoblast-like entity, and the activation and initiation of extracellular matrix ossification process. On the other hand, there are factors as well, that prevent such differentiation and ectopic calcium phosphate formation. In normal physiological environments, activities of such procalcific and anticalcific regulatory factors are in harmony, prohibiting abnormal calcification from occurring. However, in certain pathophysiological conditions, such as atherosclerosis, chronic kidney disease (CKD), and diabetes, such balances are altered, resulting in abnormal ectopic mineral deposition. Understanding the factors that regulate the formation and inhibition of ectopic mineral formation would be beneficial in the development of tissue engineering strategies for prevention and/or treatment of such soft-tissue calcification. Current review focuses on the factors that seem to be clinically relevant and/or could be useful in developing future tissue regeneration strategies. Clinical utilities and implications of such factors are also discussed.

© 2011 Elsevier B.V. All rights reserved.

Contents

1. Introduction

Ectopic calcification often leads to devastating clinical consequences when it is present in joints, blood vessels, heart valves, etc. [1]. It often occurs as a local tissue response to different kinds of stimuli such as soft-tissue injury, free fat transplantation, infection, trauma, systemic mineral imbalance, endocrine disorders and organ malfunction [1,2]. It is commonly believed that matrix mineralization in any tissue/organ is normally controlled by a balance between procalcific and anticalcific regulatory proteins, prohibiting abnormal ossification from occurring [1]. However, stimuli described above often times result in the alter-

* Tel.: +82 2 820 5782.
E-mail address: dhlee@cau.ac.kr

0921-5107/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.mseb.2011.06.011

ations in such balance, leading to ectopic mineral deposition [1]. It is also believed that the process of calcification that occurs in the atherosclerotic lesion many times resembles that of the bone mineralization [3]. Recent evidence suggests that vascular smooth muscle cells (VSMCs) express a number of bone matrix proteins that facilitate and regulate the calcification process [4–6].

2. Types of vascular calcification process

In general, vascular calcification (a well-known major risk factor for the development of cardiovascular diseases) can be categorized into four different types: intimal (atherosclerotic) calcification, medial calcification (calcification in tunica media), valvular calcification and vascular calciphylaxis [6,7].

Atherosclerotic calcification is a type of dystrophic calcification which can be characterized by cellular necrosis, inflammation, and lipoprotein/phospholipid complexes [6,8–10]. In association with atherosclerotic plaques and old myocardial infarcts, lipid complexes, which are derived from cellular membranes, adluminal thrombo-fibronoid complexes, and serum lipoproteins nucleate calcium deposition [6,8]. Endothelial cell dysfunction drives additional lipid deposition through providing a thrombogenic surface which in turn provides fibrin and platelet derived phospholipids [6,8]. Following the degenerative tissue calcification, calcified cartilage forms via a vascular remodeling process through endochondral ossification process [6].

Cardiac valve calcification is known to be induced by mechanical stressors and inflammation, which is followed by dystrophic mineralization and intramembranous ossification in association with endochondral ossification (although to a lesser extent compared to that of the atherosclerotic calcification) [6,11,12]. It is believed that aortic valve calcification is strongly related to aging in many cases where degenerative calcification, which is the most common cause of aortic stenosis in patients older than 70 years, is observed [12,13].

Medial calcification usually occurs in the absence of lipid, and is associated with α-smooth muscle actin-positive VSMCs [7]. It is an intramembranous ossification process of the arterial tunica media, which resembles calvarial bone formation and odontogenesis [6]. It does not require any cartilaginous precursor, and BMP2 (bone morphogenic protein-2)/Msx2 (muscle segment homeobox 2) dependent signaling is a central feature of the mineral formation [6,14–16]. Moreover, it has been reported by multiple researchers that vascular calcification is initially triggered by matrix vesicles in association with fibrillar collagen extracellular matrix (ECM) [17–19].

Vascular calciphylaxis, also known as calcific uremic arteriolopathy, usually occurs in patients with secondary hyperparathyroidism and renal insufficiency, especially those with end-stage renal hemodialysis [20–22]. From a biochemical point of view, it occurs when the physiological calcium-phosphate solubility ($60\ mg^2/dl^2$) level is exceeded, exhibiting widespread deposition of amorphous calcium phosphate [6,23,24]. However, certain case reports describe the occurrence of the syndrome in patients with normal renal and parathyroid function, and no abnormalities in calcium and phosphorous level [20,22].

3. Inducers of vascular calcification

As is briefly mentioned in the previous section, vascular calcification is an active process, involving cell activity where a number of bone matrix proteins are expressed by vascular smooth muscle cells (VSMCs); the process resembles that of the bone mineralization process [3,4,25]. This goes the same for many other pathological soft-tissue calcifications (STCs) and multiple clinical and pathological features of STC including tumoral calcinosis have been discussed by numerous authors [26–32].

Table 1
Inducers of vascular calcification, and their roles in vascular calcification formation.

Inducers of vascular calcification	Role in vascular calcification
Elevated calcium and phosphate level	Pi enters human smooth muscle cells by the mediation of Pit-1, and upregulates the osteogenic gene expression. Pit-1 is upregulated by calcium ions.
BMP-2 and BMP-4	BMP-2 upregulates the expression of Pit-1. BMP-4 signals and induces promineralizing activity of VSMCs in conjunction with VEGF.
Cellular senescence of VSMC	Enhanced expression of Cbfa1. Reduced expression of osterix.
TGF-β1 and 25-hydroxycholesterol	Induce CVCs in atherosclerotic plaques to express osteoblastic characteristic features and form mineralized nodules.
FGF-23	There are positive correlation between FGF-23 level and carotid artery intima-media thickness (CIMT).

Although the precise mechanisms of vascular calcification are not completely understood, it is generally agreed that the calcification process involves differentiation of VSMCs into phenotypically distinct cells that generate calcification in vitro [10,33]. It has been demonstrated that a subpopulation of VSMCs from the artery wall and cardiac valves, termed calcifying vascular cells (CVC), have the ability to undergo osteoblastic differentiation and mineralization, including the capacity for chondrogenic, leiomyogenic (smooth muscle), and stromogenic (marrow stromal) lineages [10,34–38]. It has been shown that lineage determination in mesenchymal progenitor cells in vitro and vascular calcification in vivo are regulated by Msx2 (developmental homeobox-related transcription factors) [14,15,34].

Levels of calcium and phosphate are known to be one of the factors that have potential role in VSMC differentiation into osteoblast-like cells. It has been demonstrated that exposure of human VSMCs to increased level of phosphate and/or calcium concentration resulted in matrix mineralization [33,39,40]. Elevated phosphate level may initiate calcification by enhancing the activation of Cbfa1, which is a factor known to stimulate the differentiation of mesenchymal stem cells into osteoblasts [33,41]. Differentiated VSMCs subsequently release membrane-bound matrix vesicles, and synergistically, along with the presence of apoptotic bodies, mineralization takes place [33,40]. Moreover, cell death provides phospholipid-rich membranous debris that may serve as nucleation site for mineral formation, which is the case in diseases where necrosis and apoptosis are prevalent, such as arterial sclerosis [42–44]. In addition, VSMCs synthesize collagen-rich extracellular matrix, and secrete bone-associated proteins, such as alkaline phosphatase, osteocalcin and osteopontin [33,45–47]. Summary of the inducers of the vascular calcification is listed in Table 1.

3.1. Elevated calcium and phosphate level

Although phosphate levels were long thought to induce mineralization through mere physic-chemical means, recent studies revealed that phosphate regulates and coordinates cell signaling and gene expression via dynamic transport processes [34]. The expression of Cbfa1, which is an absolute requirement for osteoblast differentiation, and osteocalcin is strongly induced in the presence of elevated phosphate [41,45,48]. In cell culture studies, such osteogenic markers were induced as early as 24 h after the

Download English Version:

https://daneshyari.com/en/article/1529710

Download Persian Version:

https://daneshyari.com/article/1529710

Daneshyari.com