World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Check for updates

Bony Heart: Myocardial and pericardial calcification, the yet unrevealed mechanism

Jayeeta Samanta [1,*] and Saswata Manna [2]

[1] *Department of Zoology, Vedanta College, Kolkata, India.*
[2] *Department of Zoology, University of Calcutta, Kolkata, India.*

World Journal of Advanced Research and Reviews, 2026, 31(01), 501–511

Publication history: Received on 30 May 2026; revised on 04 July 2026; accepted on 06 July 2026

Article DOI: https://doi.org/10.30574/wjarr.2026.31.1.1852

Abstract

The pulsatile organ, heart consists of cells possessing different functions during developmental stages and in adult, lack of which causes pathological condition. Previous studies show increased alkaline phosphatase (ALP), osteopontin expression in atherosclerosis and vascular calcification, increased reactive oxygen species (ROS) generation and Runt-related transcription factor-2 (Runx2), osteocalcin during aortic valve calcification, increased Runx2, osteopontin in cardiac fibroblasts upon osteogenic induction. Recent findings indicate that cardiomyocytes too take osteoblastic phenotype during hypertrophy. Cardiac injuries including hypertrophy, oxidative stress make the cells prone to calcification. This review mainly focusses on the current knowledge of the osteoblastic modification of cardiac cells with special emphasis on the rare cases of myocardial, pericardial and fetal cardiac calcification. Since cardiomyocyte and pericardial calcification are rare but gradually increasing phenomenon, better understanding of the associated molecular mechanism is needed for therapeutic intervention and in targeting specific molecules for treating or slowing down the calcification process.

Keywords: Fibroblasts; Cardiomyocytes; Pericardial; Calcification; Osteoblastic Modification.

1. Introduction

Heart development is an important event which occurs through 3 main stages, the cardiac progenitor, cardiac crescent and looped heart stage. Cells of the cardiac crescent form the first heart field (FHF) whereas the second heart field (SHF) is formed by the progenitor cells occupying the medial position of the cardiac crescent. The heart is mesodermal in origin but presence of some cells from neuroectodermal and endodermal origin is also evident. Out of the two cell lineages of myocardium, FHF cells form one lineage, forming left ventricle while cells of the SHF form another lineage resulting in the outflow tract and right ventricle formation [1]. In mouse, cardiac crescent formation occurs at embryonic day E7.5, looped heart stage at E8.5 and the fetal heart at E14.5 [1]. After E7.5, the cells start expressing different genes which leads to the differentiation of progenitor cells into cardiomyocytes, fibroblasts, smooth muscle cells (SMCs) and endocardial cells [2]. Each of these cell types performs their specific functions that are required for proper heart development and functioning. Figure 1 gives a brief idea about the various types of cells in heart, the marker genes expressed by them and the functions of the cells. Plethora of studies reveal that these various cell types of heart have the potential to take osteoblastic fate upon different modes of injuries like myocardial infraction (MI), cardiomyopathy, diabetes, renal disorders. Thus, in this review, we will discuss about the osteoblastic potential of the different cell types of heart with special emphasis on two very rare phenomenon of calcification, myocardial and pericardial calcification. Several recent researches have been focused on cardiac calcification, but the mechanism of transformation and entry into osteogenic lineage by the cells needs more studies.

* Corresponding author: Jayeeta Samanta.

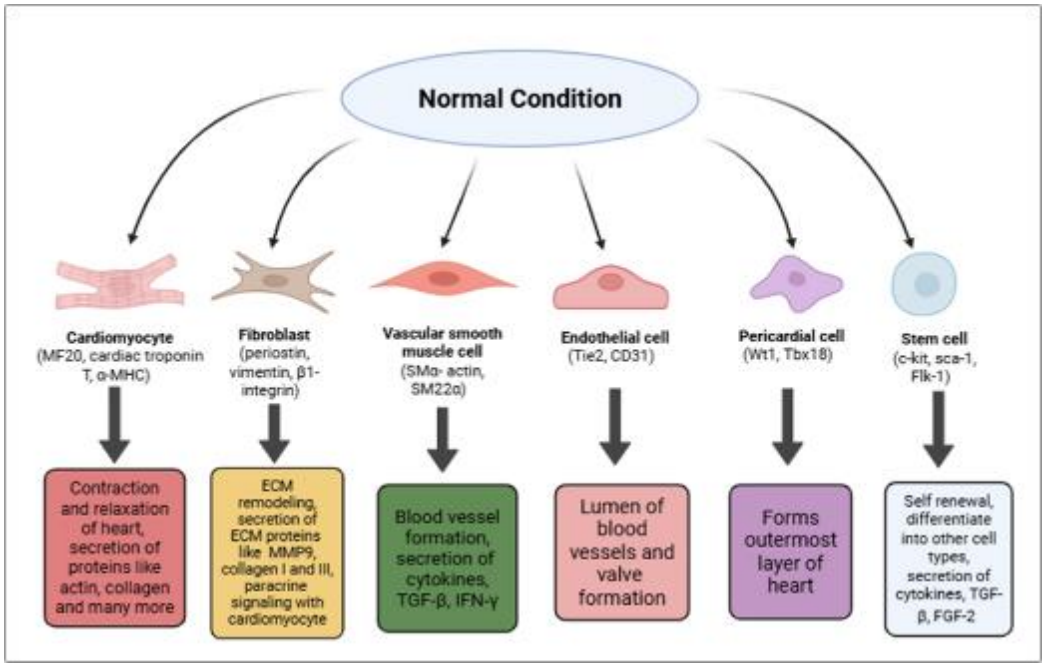

Figure 1 Schematic diagram of the different types of cells in the adult heart in normal condition.

Cardiomyocytes, fibroblasts, vascular smooth muscle cells, endothelial cells, pericardial cells, stem cells express a variety of marker genes. Each cell type performs specific functions mentioned in the figure

α-MHC: α-myosin heavy chain; ECM: extracellular matrix; FGF-2: fibroblast growth factor-2; IFN-γ: interferon-γ; MMP9: matrix metalloproteinase 9; TGF-β: transforming growth factor-β.

2. Calcification, a crosstalk on passive and active process

Cardiac calcification being a problem for many human beings worldwide since many years, several studies regarding the process have been done so far and are also ongoing. However, there is a major difference between the previous and present concept of calcification in different regions of the heart. Atherosclerotic lesions being prone to calcification, according to previous concept, it was thought that the mode of calcification is passive involving precipitation of calcium [3,4]. Many years ago, Virchow examined vascular calcification during atherosclerosis and noted that the process is not merely calcification but similar to ossification and bone formation [3]. But recent studies challenge this concept. Cases of ectopic calcification in blood vessels reveal that the cells of the vessels take osteoblast like character producing a bony matrix. Calcification of the aortic valve is also one of the most common calcification phenomena in heart. It was previously believed to be an age-related damage process besides wear and tear of the valve [5]. Many studies are being done now which indicate that the process of calcification of different regions of heart is active, the mechanism of which will be discussed in this review.

3. Osteogenic transformation of different cells upon cardiac injury

Several studies have indicated the alteration of cellular and physiological activities of different cell types of heart following cardiac injury. Increased ECM deposition, cell death, hypertrophy, dedifferentiation of cells along with reactivation of fetal genes are some common alteration that has been identified post cardiac injuries [6,7,8,9,10]. Very interestingly, recent studies identified that different cell types of heart including valvular interstitial cells (VICs), cardiomyocytes, fibroblasts, SMCs, and even pericardial cells are prone to undergo differentiation into osteogenic lineage which leads to overall compromised function of heart. Transformation to the osteogenic lineage in extreme cases leads to calcific nodule deposition. Calcification can be seen in valve defects, like Calcific Aortic Valve Disease (CAVD), a major problem in many countries nowadays. Apart from calcification of valvular interstitial cells (VICs), calcification also occurs in fibroblasts, cardiomyocytes, SMCs, pericardial cells. However, very few studies have been done on understanding the molecular mechanisms of calcification in cardiomyocytes, fibroblasts and pericardial cells upon different modes of cardiac injury such as myocardial infarction, diabetes, obesity, atherosclerosis, increased ROS generation due to aging. Analysis of the mechanism of calcification of these different types of cells is necessary to find

out new medicines that will manipulate the signaling pathways and help in attenuating the diseased state. Moreover, the known signaling pathways involved in calcification of SMCs, VICs may also be analysed in case of calcification of cardiomyocytes and pericardial cells to understand whether the same mechanism is followed in these cases. Here, we will focus on the various signaling pathways that trigger the different types of cells to enter into the osteogenic lineage with detailed discussion of various rare cases of myocardial and pericardial calcification (Table 1).

Table 1 Signaling pathways involved and the therapeutic strategies in osteoblastic transformation of the various cardiac cell types.

Cell type	Signaling pathway/molecules affected	Probable therapeutic approach	Selected references
Cardiomyocyte	CD73-TNAP signaling	Suppression of TNAP.	Gan *et al.* (2014)
Fibroblast	ENPP1-PPi-Pi axis	Etidronate targets the pathway and prevents calcification.	Pillai *et al.* (2017)
	TNAP	Studies on TNAP inhibitors and TNAP knockdown/knockout studies required.	Schuetze *et al.* (2015)
Smooth muscle cell	Notch	Notch inhibitor reduces osteogenic differentiation in vitro.	Shimizu *et al.* (2009)
		Some studies show the role of Notch in reducing calcification.	Sciaudone *et al.* (2003) Hilton *et al.* (2008) Engin *et al.* (2008) Tezuka *et al.* (2002) Nobta *et al.* (2005)
	Marix GLA protein	Activation of this protein may be a therapeutic approach.	Hruska *et al.* (2005) Chen *et al.* (2008) Reynolds *et al.* (2004) Luo *et al.* (1997)
	TGF-β, ELR-1, ALK-5 protein kinase C signaling	Blocking these pathways in diabetic condition may reduce osteogenesis.	Sinha and Vyavahare (2003)
	BMP-2 signaling	TGF-β administration reduces BMP activity and phosphate induced osteogenesis.	Guerrero *et al.* (2014)
	p38 and ERK pathway	Downregulation of these two pathways will be important therapeutic target in vascular calcification.	Vickers *et al.* (2010)
Aortic valve cell	Wnt signaling	Inhibition of Wnt may reduce valve pathogenesis.	Alfieri *et al.* (2010)
	Notch	Complementary to Wnt signaling, thus Notch may help in controlling osteoblastic transformation.	Rusanescu *et al.* (2008)
	TGF-β	More studies needed to understand the VICs mediated inhibition of EndMT and osteoblastic changes in VECs involving TGF-β.	Hjortnaes *et al.* (2015)

Pericardial cell	Case reports available, mechanism yet unknown	Therapeutic strategies to be found out.	Nguyen *et al.* (2014) Isaacs *et al.* (2003)
Stem cell	Unknown	Regenerative potential of stem cells in reducing calcification may be studied.	

3.1. Cardiomyocyte calcification:

Many case studies have been done which shows different instances of myocardial calcific depositions. However, cases of myocardial calcific deposits are usually rare. Two types of calcification cases are detected. One is the dystrophic calcification which occurs in abnormal tissues as a result of wear and tear, detected in the myocardium and other regions when the heart has been subjected to several injuries during surgeries, congenital defects and others. It has been detected that there is a positive relationship between the myocardial infarct size and chondro-osteogenic mass deposition [11]. The other one is metastatic calcification showing calcific granule deposits in the undamaged cardiomyocytes. The following are several cases of myocardial calcification [12].

3.1.1. Case studies:

Case study 1

A 6 year old Caucasian boy with congenital cyanotic heart disease underwent several surgical procedures and later on was detected with various complications, one of them was calcific deposits in the ventricular chamber and its wall.

Case study 2

An 84 year old Caucasian with renal disease and other previous problems like hypertension and MI was detected with white calcific deposits in the left ventricular wall.

Case study 3

A calcified thrombus was detected in the right ventricular apex in a 45 year old Caucasian female suffering from renal disease and other complications.

Case study 4

An 82 year old female with chronic lymphocytic leukemia was detected with calcification in the left ventricular myocardium. However, the calcium level in blood serum was normal and she did not suffer from any MI [13].

Case study 5

A 48 year old man without any previous history of cardiac disease was examined with patchy calcifications in the myocardium after he was detected with signs of heart failure and other problems like fever, dyspnoea. He was also diagnosed with pneumonia. Cytochemical studies showed that in normal cardiomyocytes, calcium deposition occurred in the inner leaflets of sarcolemma, T-tubules, mitochondria but in necrotic cardiomyocytes, extensive calcium deposition was observed in the mitochondria along with loss of calcium from the sarcolemma. This case indicates that calcium overload occurs in viable cardiomyocytes and is not a mere case of secondary and passive deposition of calcium after cardiomyocyte death [14].

Case study 6

A 66 year old man with acute myocardial infarction died from clinical complications and septic shock was detected with intracellular and extracellular myocardial calcium deposition at the periphery of the infarct. According to some authors, calcific deposition is deleterious since it hampers the normal repair process and disrupts the balance in the calcium in the body. Others consider the calcification phenomenon to be a process of cardiac remodeling [15].

Case study 7-18

Case study 7- A 78 year old man was detected with calcification in the ventricular region. The person had previous history of MI. *Case study 8*- A very rare case of infant heart calcification was observed after delivery complications due to enterovirus myocarditis. Calcification was mainly detected in the left ventricle. However, the baby did not survive. *Case study 9:* Several calcific depositions were detected not only in heart but also in other organs like lungs, kidneys in

a 49 year old man suffering from renal disorder. Fibrosis was detected along with calcification in the myocardium. *Case study 10:* Calcific deposits in the ventricular myocardium were detected in a 62 year old woman having oxalosis. *Case study 11:* A 46 year old man with congenital heart disease was detected with patchy calcification throughout the left atrium, left ventricle and papillary muscles. Several cardiac complications may be the cause of extensive calcification. *Case study 12:* Chalky calcification was detected in a 2 year old girl in right and left ventricle. Studies showed that the girl suffered from renal failure. *Case study 13:* A 61 year old man suffering from acute renal failure was initially not detected with cardiac calcification but gradually developed epicardial calcification**.** *Case study 14:* A 51 year old woman underwent heart transplant due to nonischemic cardiomyopathy. She was also suffering from chronic renal insufficiency. The woman was detected with extensive calcification along with fibrosis in the left ventricle. *Case study 15:* Calcification was detected in the septum of a 76 year old man who had a history of MI. *Case study 16:* Calcifications were also detected in a 52 year old man having chronic renal insufficiency. *Case study 17:* In an 80 year old woman, calcification occurred in the papillary muscle. The woman was a patient of coronary artery disease. *Case study 18:* Calcification was also detected in the papillary muscle of a 4 year old girl with tetralogy of Fallot [16].

Case study 19

A 55 year old woman was having dyspnea and had a history of type 1 multiple endocrine neoplasia and hyperparathyroidism. Several examinations showed that the person had extensive myocardial calcifications. She also showed extensive subepicardial calcifications [17].

Case study 20

A 46 year old woman was reported with extensive calcification in the left ventricle, interatrial and interventricular septae. This caused coronary artery obstruction. The patient had no other previous causes that have led to myocardial calcification [18].

Case study 21

A 56 year old man without any previous medical history had a septic shock after suffering from diarrhoea. Though he was improving from the condition after treatment, he was further detected with respiratory failure and cardiac dysfunction. He showed signs of cardiac calcification in the left ventricle [19].

Case study 22

A patient with end-stage renal failure was kept on dialysis. Several clinical examinations showed that the patient had left ventricular hypertrophy, myocardial fibrosis, cardiac arrhythmia. Autopsy after death of the patient from ventricular arrhythmia revealed microcalcification and fibrosis of the left ventricular myocardium [20].

Case study 23

A 62 year old woman showed subendocardial calcification as well as calcification of the lateral wall and apex of left ventricle. The woman had a history of hypertension and pulmonary embolism [21].

These are so far the recorded and rare incidents of myocardial calcification, although there are no proper records of the causes of such cases.

3.1.2. Molecular mechanism of myocardial / cardiomyocyte calcification:

Osteogenic transformation of the myocardium can be detected in various diseased conditions. Recent studies indicate that phenylephrine (PE), a hypertrophy inducer of cardiomyocytes can also promote cardiomyocyte calcification [7]. However, much more detailed studies are to be done on cardiomyocyte calcification in order to understand the mechanism of this phenomenon and to ameliorate it. Studies reveal that in normal state, cluster of differentiation 73 (CD-73) is high and converts adenosine monophosphate (AMP) to adenosine (Ado). Adequate amount of Ado inhibits tissue nonspecific alkaline phosphatase (TNAP) which regulates calcification. Since TNAP is less in normal condition, there is less amount of inorganic phosphate (Pi) produced from pyrophosphate (PPi). The crosstalk between CD73 and TNAP has been found to play a role in cardiomyocyte calcification (Figure 2a). In PE induced cardiomyocyte calcification, decreased expression of CD-73 results in increased TNAP expression which leads to increased amount of Pi from PPi resulting in increased intracellular calcification [7]. Studies have shown that H9c2 cardiomyocytes shows calcification which involves the role of Forkhead box transcription factor FoxO1 and nuclear factor of activated T-cells NFATc3 through FoxO1/NFATc3/Runx2 signaling pathway [22]. Thus, drugs designed to target this signaling pathway may reduce cardiomyocyte calcification. Apart from the mentioned mechanism, many other signaling pathways may be involved in myocardial calcification that needs to be explored. Very few studies have been done till date on

cardiomyocyte calcification which is a gradually increasing phenomenon, understanding the mechanism of which will help us to find out new ways in treating the less studied phenomenon of cardiomyocyte calcification.

3.1.3. Cardiac calcification and renal failure:

From the above discussed and known cases of cardiac/cardiomyocyte calcification so far, it seems that there is a relation between renal problems and cardiovascular calcification. It has been observed that the cases of cardiac calcification are more prominent in patients suffering from renal failure/problems. Calcified plaques are detected more in coronary heart patients with uremic disease compared to the nonuremic patients [23]. Inappropriate metabolism of calcium and phosphate in end stage renal disease is thought to be a cause for myocardial calcification in most of the cases [24]. Fibroblast growth factor 23 (FGF23), a hormone synthesised by bone osteocytes and osteoblasts regulates the phosphate level and vitamin D metabolism. Klotho protein helps in the balance of calcium, phosphate and magnesium by forming a receptor complex with FGF23 in proximal renal tubules. At the time of renal failure, the level of klotho protein decreases which increases vascular calcification [25]. Although it is argued that there is no direct relationship among the levels of calcium, phosphorus or parathyroid hormone, yet it has been detected that chronic renal failure patients with secondary hyperparathyroidism are more prone to calcium deposition in the heart due to increased phosphate level.

3.1.4. Particular chromosome locus determining myocardial calcification:

Calcification of the myocardium can be detected in case of age-related cardiomyopathy and this is called dystrophic cardiac calcinosis (DCC). Studies were done to find out the locus responsible for DCC but no detailed studies have been done to detect the mechanism of cardiomyocyte/myocardial calcification. Gene mapping studies revealed that *Dyscalc* gene on chromosome 7 in mouse is the responsible gene for DCC [26]. Finding out the gene/genes involved in cardiomyocyte calcification in future will be helpful in getting an idea of cardiomyocyte injury and calcification and its treatment.

3.2. Pericardial calcification

Apart from myocardial calcification, another unusual event of cardiac calcification is pericardial calcification. Calcification in the outer covering of the heart is not commonly detected. Pericardial calcification is rare and often asymptomatic. Thus, the molecular mechanisms of calcification of the cells forming the pericardium are not yet understood. A recent case report demonstrated that a middle-aged Caucasian man without any history of cardiac problems like palpitation or dyspnea, surprisingly showed bradycardia by electrocardiographic analysis. Further studies revealed that patient had mild pericardial calcification [27]. By computed tomography (CT), pericardial calcification was also detected in cases of patients who have undergone cardiac surgery, tuberculosis, trauma [28]. Fibrotic change is associated to pericardial calcification causing pericardial constriction though all patients do not show pericardial constriction [28]. Extensive research in this area is required on this rare phenomenon to know whether the mechanism is similar to the known calcification processes that occur in other regions of the heart.

4. Fetal cardiac calcification in myocardium and epicardium:

Cardiac calcification is generally an age-related process. Since paediatric calcification is a rare event, detailed studies have not been done. Whether the mechanism of fetal calcification is the same as that of adult cardiac calcification is unknown. Several reports are there from the past few years on fetal myocardial calcification. Histopathological studies revealed that the maximum calcification occurred in the myocardium and epicardium at the base of the heart [29].

Echocardiographic results showed myoepicardial calcification along with other complications like right ventricular outflow obstruction, tachycardia at 18 weeks' of gestation. There was no viral infection or autoimmune disease. The epicardium became thick due to calcium deposition and fibrosis. In another instance, at 21 weeks' gestation, atrial calcification and fibrosis were detected along with calcific deposits at the base of the heart. In a case study, at 20 weeks' gestation, the mother gave birth to a stillborn foetus although there was no infection or autoimmune disorder. Although the fetal heart was found to be anatomically normal, there was fibrosis along with epicardial and myocardial calcification. An infant male born at 37 weeks' of gestation showed calcification in the ventricle and many other problems like hydrocephalus [29]. From all these observations, it is quite clear that there are several evidences of rare cardiac calcification events not only in adults but also in infants, a huge area of which is yet undiscovered in depth.

So far, we have mentioned about the very unusual cases of fetal and adult myocardial and epicardial calcification. Now, we will look into the well-known mechanisms of cardiac calcification in other cell types in brief.

5. Some well-known calcification mechanisms in other regions/cells of heart:

Mechanism of calcification in cardiac SMCs, VICs, fibroblasts has been studied well. The following brief discussion about these well-known calcification mechanisms will give us ideas to correlate or find out the unknown calcification mechanisms in cardiomyocyte and pericardial cells.

5.1. Cardiac fibroblast/aortic valve fibroblast calcification:

Although the most common type of calcification seen in mammalian heart is valve calcification, recent findings indicate that upon injury induction, cardiac fibroblasts undergo mineralization by upregulating ectonucleotide pyrophosphatase/ phosphodiesterase-1 (ENPP1), the enzyme involved in bone mineralization (Figure 2a). ENPP1 generates PPi which upon hydrolysis produces Pi resulting in calcification [30]. Calcium hydroxyapatite deposition can be seen upon osteogenic induction of the cardiac fibroblasts for 21 days along with increased expression of different osteoblast genes like osterix, osteopontin, Runx2 [30].

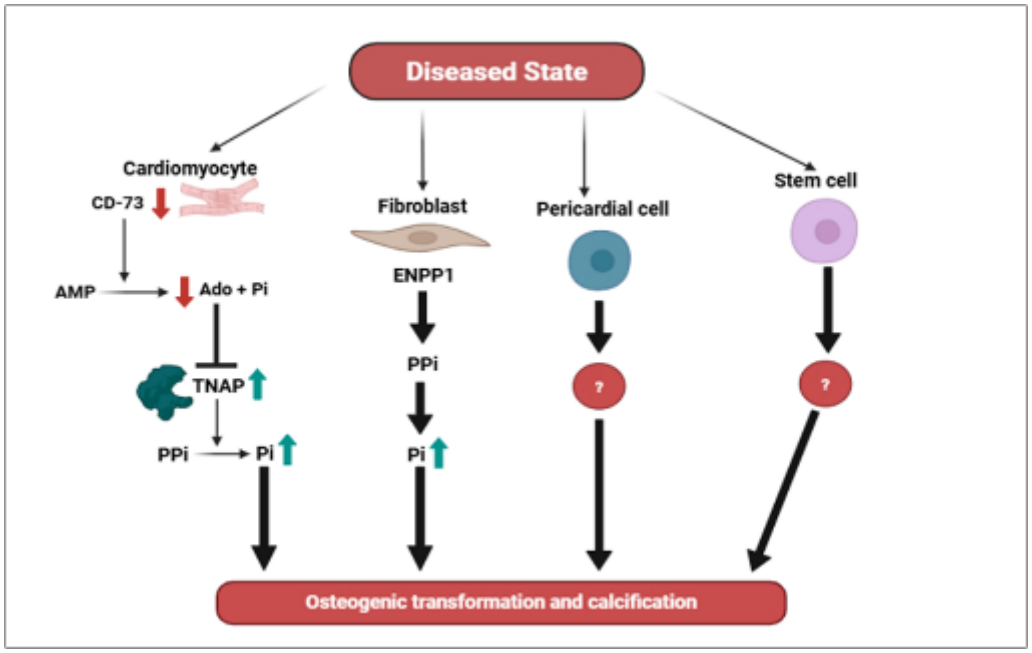

Figure 2a Signaling pathways activated in diseased state in cardiomyocytes, fibroblasts, pericardial cells, stem cells during osteogenesis.

CD-73 and TNAP are major players in cardiomyocyte calcification. ENPP1-PPi-Pi axis is involved in osteogenic transformation of fibroblast. Calcification mechanism in pericardial cells and stem cells is yet to be studied in detail. Upward and downward green arrows indicate upregulation and downregulation respectively

Ado: adenosine; AMP: adenosine monophosphate; ENPP1: ectonucleotidepyrophosphatase/ phosphodiesterase-1; Pi: inorganic phosphate; PPi: pyrophosphate; TNAP: tissue nonspecific alkaline phosphatase.

Few studies demonstrated that glutaraldehyde (GA) causes calcification of fibroblasts in porcine and canine aortic valve [31]. Evidences show that calcification occurs in the cases where stenotic valves have been replaced with glutaraldehyde-fixed valvular prostheses (GFVPs) [31]. TNAP also mediates fibroblast calcification similar to its role in cardiomyocyte calcification.

5.2. Calcification of Smooth muscle cell (SMC)

SMC calcification, particularly vascular calcification is one of the most prevalent problems worldwide. SMC calcification is mostly seen in cases of atherosclerosis, with increasing age, diabetes, high blood pressure and in renal disorders. A lot of studies on SMC calcification indicate that many signaling molecules like Notch, transforming growth factor-β (TGF-β), protein kinase C, p-38, extracellular signal regulated kinases (ERK) are involved. BMP2 and Msx2 are upregulated in vascular calcification too. Figure 2b summarizes various signaling pathways involved in SMC calcification. Evidences suggest that overexpression of intracellular domain of Notch in human aortic SMCs induces increased expression of

Msx2 and ALP activity and also osteogenic differentiation in vitro although there are some controversies [32,33,34,35,36]. Previous studies show that matrix GLA protein (MGP) is expressed by the SMCs of the arterial walls in normal state and reduction in MGP expression leads to arterial calcification [37]. High glucose containing culture media mimicking diabetic condition along with TGF-β and elastin shows osteogenesis of SMCs. High glucose mediated increased protein kinase C signaling along with osteogenesis was detected in vascular smooth muscle cells (VSMCs). Two other important signaling pathways associated with osteogenesis of VSMCs are ELR-1 and ALK-5 signalling [38]. Another mechanism for VSMC calcification in human is p38 and ERK pathway that is activated upon lyso-phosphatidylcholine (LPC) induced calcification [39].

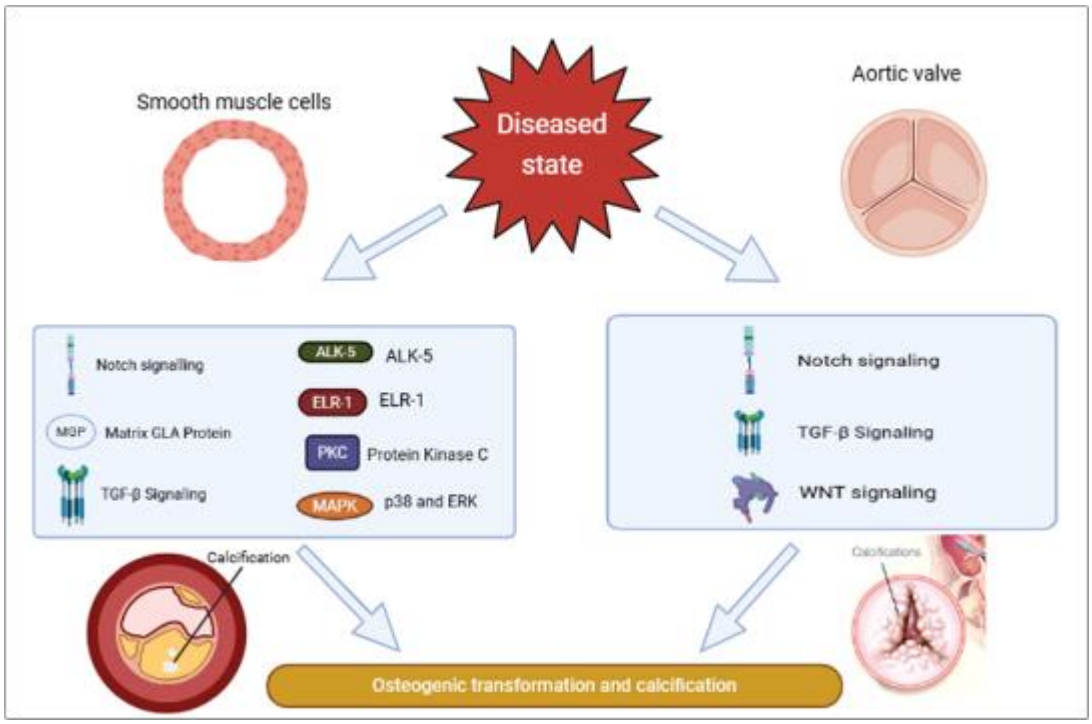

Figure 2b Various signaling pathways in smooth muscle cells and aortic valve cells during calcification.

Calcific nodule deposition is quite common in case of smooth muscle cells and aortic valve cells which occurs through various signaling pathways like Notch, Wnt and many more. Increased expression of Notch, TGF-β, ELR-1, ALK-5, Protein kinase C, p38, ERK and reduced expression of matrix GLA protein induces calcification os smooth muscle cells. Whereas, increased TGF-β and Wnt and reduced expression of Notch induces aortic valve calcification.

ERK: extracellular signal regulated kinases; TGF-β: transforming growth factor-β.

5.3. Calcification of aortic/mitral valve:

CAVD is one of the major reasons for mortality worldwide in the developed countries. Different osteoblast specific genes are upregulated in cases of valve calcification like osteocalcin, Runx2, Cbfa1, osteopontin, ALP [40]. Several signaling pathways are involved in CAVD (Figure 2b). Wnt signaling enhances the expression of osteogenic genes like periostin, Runx2 in VICs treated with osteogenic media [41]. Reduced Notch signaling makes the valve cells prone to calcification leading to aortic valve stenosis [41]. Apart from the aortic valve cells, the mitral valve cells also undergo calcification in some cases. Reduced Notch signaling makes the valve cells prone to calcification leading to aortic valve stenosis [42]. The mitral valve cells showed increased expression of osteopontin upon treatment with TGF-β1 for 5 days and osteogenic media for 2 weeks consecutively [43].

6. Therapeutic approaches

There are several evidences of cardiomyocyte/myocardial and pericardial calcification till date but very few studies have been done on this phenomenon. As a result, we have very less knowledge on the molecular mechanism of cardiomyocyte and pericardial calcification. From the studies so far, we can say that if we can identify the agents that can promote CD73 or inhibit TNAP with least side effects, it may help in reducing cardiomyocyte calcification (Table 1).

Two factors that are to be considered during the studies on therapeutics of calcification are, whether the strategies are preventive or they completely cure calcification. Another factor is whether reduction of calcification affects the normal calcification process in bone and teeth. Thus, the difference in the mode of calcification in bone or teeth and calcification of myocardium/pericardium is to be understood to specifically target the calcification process in the heart to inhibit it. There are some potent calcification inhibitors in vitro as also in vivo. PPi is one of them, which prevents hydroxyapatite deposition. Bisphosphonates work well in case of patients with ENPP1 deficiency, the enzyme involved in PPi synthesis. One of the bisphosphonates is etidronate which prevents fibroblast calcification if administered before osteogenic induction **[30]**. Thus, its potency in reducing calcification in cardiomyocytes or pericardial cells can be examined. However, bisphosphonates have some side effects, it is accumulated in the kidneys of chronic kidney disease (CKD) patients and also inhibits bone formation. Previous reports showed that another agent, thiosulfate inhibits vascular calcification [44]. However, side effects on bone formation were not analyzed. Whether thiosulfate has any role in reducing myocardial/pericardial calcification has not been investigated. For treatment of CAVD, different pathways like TGF-β, Notch signaling are specifically targeted but there is yet no ultimate solution discovered [45]. One of the common drugs is statins, which reduces the effects seen in CAVD. However, if excessive calcification has already occurred, then it is difficult to revert back by statins. Pioglitazone is another agent that reduces osteogenic markers expression in heart valve. Thus, these agents involved in reducing heart valve calcification can also be focussed on to find out their potency in reducing myocardial and pericardial calcification as well.

7. Conclusion

More case study analysis is needed with special emphasis on the cases of ectopic calcification in cardiomyocytes and pericardial cells that are very less studied. Since very few drugs are available for these cases, the known drugs for treating vascular or heart valve calcification can be considered in these cases to study their potency. Moreover, different natural products having least side effects that reduce oxidative stress can also be considered since oxidative stress is one of the major causes that induces cardiac calcification. The potency of some of the natural agents like resveratrol [46], salvianolic acid [47], *Zanthoxylum alatum* extracts [48], extract of edible herb *Enhydra fluctuans* [49] and other such agents may be examined in reducing cardiac calcification.

Compliance with ethical standards

Disclosure of conflict of interest

The authors have no conflicts of interest to declare.

Funding

The authors declare that no funds, grants and any other support were received during preparation of the manuscript.

References

[1] Meilhac SM, Lescroart F, Blanpain C, Buckingham ME. Cardiac Cell Lineages that Form the Heart. Cold Spring Harbor Perspectives in Medicine. 2014 Sep 1;4(9):a013888–8.

[2] Brade T, Pane LS, Moretti A, Chien KR, Laugwitz KL. Embryonic heart progenitors and cardiogenesis. Cold Spring Harbor perspectives in medicine. 2013;3(10):a013847

[3] Doherty TM, Detrano RC. Coronary arterial calcification as an active process: A new perspective on an old problem. Calcified Tissue International. 1994 Mar 1;54(3):224–30.

[4] Schinke T, Karsenty G. Vascular calcification—a passive process in need of inhibitors. Nephrology Dialysis Transplantation [Internet]. 2000 Sep 1;15(9):1272–4.

[5] Hughes BR, Chahoud G, Mehta JL. Aortic stenosis: Is it simply a degenerative process or an active atherosclerotic process? Clinical Cardiology. 2005 Mar 1;28(3):111–4.

[6] Fan D, Takawale A, Lee J, Kassiri Z. Cardiac fibroblasts, fibrosis and extracellular matrix remodeling in heart disease. Fibrogenesis & Tissue Repair. 2012 Sep 3;5(1):15.

[7] Gan XT, Taniai S, Zhao G, Huang CX, Velenosi TJ, Xue J, et al. CD73-TNAP crosstalk regulates the hypertrophic response and cardiomyocyte calcification due to α1 adrenoceptor activation. Molecular and Cellular Biochemistry. 2014 Jun 3;394(1–2):237–46.

[8] Krenning G, Zeisberg EM, Kalluri R. The origin of fibroblasts and mechanism of cardiac fibrosis. Journal of Cellular Physiology [Internet]. 2010 Jul 15;225(3):631–7.

[9] Manabe I, Shindo T, Nagai R. Gene expression in fibroblasts and fibrosis. Circulation Research [Internet]. 2002 Dec 13;91(12):1103–13.

[10] Pathak M, Sarkar S, Vellaichamy E, Sen S. Role of myocytes in myocardial collagen production. Hypertension. 2001 Mar 1;37(3):833–40.

[11] Delo DM, Guan X, Wang Z, Groban L, Callahan M, Smith T, et al. Calcification after myocardial infarction is independent of amniotic fluid stem cell injection. Cardiovascular Pathology. 2010 Apr 10;20(2):e69–78.

[12] Catellier MJ, Chua GT, Youmans G, Waller BF. Calcific deposits in the heart. Clinical Cardiology. 1990 Apr 1;13(4):287–94.

[13] Lasser A. Calcification of the myocardium. Human Pathology. 1983 Sep 1;14(9):824–6.

[14] Olbrich H G, Herrmann G, Vandeplassche G et al: Calcium overload in human giant cell myocarditis. J Clin Pathol 1990; 43:650-653

[15] Rios E, Mancio J, Rodrigues-Pereira P, Magalhães D, Bartosch C. Large myocardial infarction with myocardium calcium deposits associated with reperfusion injury. Cardiovascular Pathology. 2014 Jul 15;23(6):379–80.

[16] Nance JW, Crane GM, Halushka MK, Fishman EK, Zimmerman SL. Myocardial calcifications: Pathophysiology, etiologies, differential diagnoses, and imaging findings. Journal of Cardiovascular Computed Tomography. 2014 Oct 22;9(1):58–67.

[17] Mana M, Sanguineti F, Unterseeh T, Bouvier E, Garot J. Petrified myocardium. Circulation. 2012 Aug 27;126(9):1139–42.

[18] Aras D, Topaloglu S, Demirkan B, Deveci B, Ozeke O, Korkmaz S. Porcelain heart: a case of massive myocardial calcification. International Journal of Cardiac Imaging. 2005 Jul 22;22(1):123–6.

[19] Van Kruijsdijk RCM, Van Der Heijden JJ, Uijlings R, Otterspoor LC. Sepsis-Related myocardial calcification. Circulation Heart Failure. 2011 Sep 1;4(5):e16-8

[20] Lee CJ, Ramirez C, Thomson LEJ. A stone heart: fatal cardiac microcalcification. European Heart Journal. 2007 May 4;28(19):2312.

[21] Ionescu CN, Marcu CB. Unexpected massive myocardial calcification. Netherlands Heart Journal. 2009 Dec 1;17(12):491.

[22] Samanta J, Mondal A, Das S, Chakraborty S, Sengupta A. Induction of cardiomyocyte calcification is dependent on FoxO1/NFATc3/Runx2 signaling. In Vitro Cellular & Developmental Biology - Animal. 2021 Nov 29;57(10):973–86.

[23] Ketteler M, Gross ML, Ritz E. Calcification and cardiovascular problems in renal failure. Kidney International. 2005 Mar 4;67(94):S120–7.

[24] Saremi F. Myocardial calcinosis in chronic renal failure. Journal of Radiology Case Reports. 2009 Feb 1;3(2):16–9.

[25] Primc D, Peršić V, Španjol J, Divković D, Kovačević M, Pećanić S, et al. Vaskularna kalcifikacija regulirana Klotho proteinom tijekom fiziološkog i patofiziološkog starenja. Hrčak Portal of Scientific Journals of Croatia (University Computing Centre). 2026 Jan 1.

[26] Ivandic BT, Qiao JH, Machleder D, Liao F, Drake TA, Lusis AJ. A locus on chromosome 7 determines myocardial cell necrosis and calcification (dystrophic cardiac calcinosis) in mice. Proceedings of the National Academy of Sciences. 1996 May 28;93(11):5483–8.

[27] Nguyen T. Incidental findings of pericardial calcification. World Journal of Clinical Cases. 2014 Jan 1;2(9):455.

[28] Isaacs, D; Stark, P; Nichols, Cl; Antevil, J; Shabetai, R. Post-Traumatic pericardial calcification. Journal of Thoracic Imaging. 2003 Oct;18(4):250–3.

[29] Simchen MJ, Toi A, Silver M, Smith CR, Hornberger LK, Taylor G, et al. Fetal cardiac calcifications: report of four prenatally diagnosed cases and review of the literature. Ultrasound in Obstetrics and Gynecology. 2006 Feb 16;27(3):325–30

[30] Pillai ICL, Li S, Romay M, Lam L, Lu Y, Huang J, et al. Cardiac fibroblasts adopt osteogenic fates and can be targeted to attenuate pathological heart calcification. Cell Stem Cell. 2016 Nov 17;20(2):218-232.e5

[31] Kim KM, Herrera GA, Battarbee HD. Role of glutaraldehyde in calcification of porcine aortic valve fibroblasts. American Journal of Pathology. 1999 Mar 1;154(3):843–52.

[32] Engin F, Yao Z, Yang T, Zhou G, Bertin T, Jiang MM, et al. Dimorphic effects of Notch signaling in bone homeostasis. Nature Medicine. 2008 Feb 24;14(3):299–305.

[33] Hilton MJ, Tu X, Wu X, Bai S, Zhao H, Kobayashi T, et al. Notch signaling maintains bone marrow mesenchymal progenitors by suppressing osteoblast differentiation. Nature Medicine. 2008 Feb 24;14(3):306–14.

[34] Nobta M, Tsukazaki T, Shibata Y, Xin C, Moriishi T, Sakano S, et al. Critical regulation of bone morphogenetic protein-induced osteoblastic differentiation by Delta1/Jagged1-activated Notch1 signaling. Journal of Biological Chemistry. 2005 Feb 5;280(16):15842–8.

[35] Sciaudone M, Gazzerro E, Priest L, Delany AM, Canalis E. Notch 1 impairs osteoblastic cell differentiation. Endocrinology. 2003 Sep 9;144(12):5631–9.

[36] Tezuka KI, Yasuda M, Watanabe N, Morimura N, Kuroda K, Miyatani S, et al. Stimulation of osteoblastic cell differentiation by notch. Journal of Bone and Mineral Research. 2002 Feb 1;17(2):231–9.

[37] Luo G, Ducy P, McKee MD, Pinero GJ, Loyer E, Behringer RR, et al. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Nature. 1997 Mar 1;386(6620):78–81.

[38] Sinha A, Vyavahare NR. High-glucose levels and elastin degradation products accelerate osteogenesis in vascular smooth muscle cells. Diabetes and Vascular Disease Research. 2013 Jun 10;10(5):410–9.

[39] Vickers KC, Castro-Chavez F, Morrisett JD. Lyso-phosphatidylcholine induces osteogenic gene expression and phenotype in vascular smooth muscle cells. Atherosclerosis. 2010 Apr 15;211(1):122–9.

[40] Hirao M, Tamai N, Tsumaki N, Yoshikawa H, Myoui A. Oxygen Tension Regulates Chondrocyte Differentiation and Function during Endochondral Ossification. Journal of Biological Chemistry. 2006 Aug 12;281(41):31079–92.

[41] Alfieri CM, Cheek J, Chakraborty S, Yutzey KE. Wnt signaling in heart valve development and osteogenic gene induction. Developmental Biology. 2009 Dec 3;338(2):127–35.

[42] Rusanescu G, Weissleder R, Aikawa E. Notch signaling in cardiovascular disease and calcification. Current Cardiology Reviews. 2008 Aug 1;4(3):148–56.

[43] Wylie-Sears J, Aikawa E, Levine RA, Yang JH, Bischoff J. Mitral valve endothelial cells with osteogenic differentiation potential. Arteriosclerosis Thrombosis and Vascular Biology. 2010 Dec 17;31(3):598–607.

[44] O'Neill WC, Hardcastle KI. The chemistry of thiosulfate and vascular calcification. Nephrology Dialysis Transplantation. 2011 Jul 7;27(2):521–6.

[45] Hutcheson JD, Aikawa E, Merryman WD. Potential drug targets for calcific aortic valve disease. Nature Reviews Cardiology. 2014 Jan 21;11(4):218–31.

[46] Zhao X, Li G, Liu Y, Chai L, Chen J, Zhang Y, et al. Resveratrol protects against arsenic trioxide-induced cardiotoxicity in vitro and in vivo. British Journal of Pharmacology. 2008 Mar 10;154(1):105–13.

[47] Wang M, Sun GB, Sun X, Sun X, Wang HW, Meng XB, et al. Cardioprotective effect of salvianolic acid B against arsenic trioxide-induced injury in cardiac H9c2 cells via the PI3K/Akt signal pathway. Toxicology Letters. 2012 Nov 30;216(2–3):100–7.

[48] Karmakar I, Haldar S, Chakraborty M, Dewanjee S, Haldar PK. Antioxidant and cytotoxic activity of different extracts of zanthoxylum alatum. Free Radicals and Antioxidants. 2015 Feb 16;5(1):21–8.

[49] Dua TK, Dewanjee S, Khanra R, Joardar S, Barma S, Das S, et al. Cytoprotective and Antioxidant Effects of an Edible Herb, Enhydra fluctuans Lour. (Asteraceae), against Experimentally Induced Lead Acetate Intoxication. PLoS ONE. 2016 Feb 9;11(2):e0148757.