CALCIFICATION OF ATHEROSCLEROTIC PLAQUES AND OSTEOGENIC SIGNALING PATHWAYS

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Abstract: Abstract: Atherosclerotic plaque calcification is a complex and actively regulated process involved in the progression and structural remodeling of atherosclerotic lesions. Current evidence indicates that vascular calcification is not merely a passive consequence of tissue degeneration but involves coordinated cellular and molecular mechanisms. Vascular smooth muscle cells (VSMCs) play a central role by undergoing osteogenic and chondrogenic phenotypic transformation, associated with activation of the BMP/SMAD/RUNX2 and Wnt/β-catenin signaling pathways. Chronic inflammation, oxidative stress, extracellular matrix remodeling, and disturbances in mineral metabolism further promote osteogenic transformation and calcium-phosphate deposition. The biological effects of calcification depend on its morphology, size, and distribution within the plaque. Microcalcifications may increase local mechanical stress and contribute to plaque vulnerability, whereas larger consolidated calcifications may exert different structural effects. This review summarizes the current understanding of atherosclerotic plaque calcification, focusing on VSMC osteogenic transformation and major osteogenic signaling pathways.

Keywords: atherosclerosis; plaque calcification; vascular smooth muscle cells; osteogenic differentiation; RUNX2; BMP/SMAD; Wnt/β-catenin; inflammation; oxidative stress.

Аннотация: Кальцификация атеросклеротических бляшек представляет собой сложный и активно регулируемый процесс, участвующий в

прогрессировании и структурной перестройке атеросклеротических поражений. Современные данные показывают, что сосудистая кальцификация является не только следствием дегенерации тканей, но и результатом координированных клеточных и молекулярных механизмов. Гладкомышечные клетки сосудов (VSMC) играют центральную роль, подвергаясь остеогенной и хондрогенной фенотипической трансформации, связанной с активацией сигнальных путей BMP/SMAD/RUNX2 и Wnt/β-катенина. Хроническое воспаление, окислительный стресс, ремоделирование внеклеточного матрикса и нарушения минерального обмена дополнительно способствуют остеогенной трансформации и отложению фосфата кальция. Биологическое значение кальцификации зависит от её морфологии, размера и распределения внутри бляшки. Микрокальцификации могут повышать локальное механическое напряжение и способствовать уязвимости бляшки, тогда как крупные консолидированные кальцификаты могут оказывать иные структурные эффекты. В обзоре представлены современные данные о механизмах кальцификации атеросклеротических бляшек с акцентом на остеогенную трансформацию VSMC и основные остеогенные сигнальные пути.

Ключевые слова: атеросклероз; кальцификация бляшек; гладкомышечные клетки сосудов; остеогенная дифференцировка; RUNX2; BMP/SMAD; Wnt/β-катенин; воспаление; окислительный стресс.

Annotatsiya: Aterosklerotik blyashkalar kalsifikatsiyasi aterosklerotik zararlanishlarning rivojlanishi va strukturaviy qayta tuzilishida ishtirok etuvchi murakkab va faol boshqariladigan jarayondir. Zamonaviy ma’lumotlarga ko‘ra, tomir kalsifikatsiyasi faqat to‘qima degeneratsiyasining passiv oqibati emas, balki muvofiqlashgan hujayraviy va molekulyar mexanizmlar natijasidir. Tomir silliq mushak hujayralari (VSMC) osteogen va xondrogen fenotipga o‘tib, ushbu jarayonda markaziy rol o‘ynaydi. Bu o‘zgarish BMP/SMAD/RUNX2 va Wnt/β-

katenin signal yo‘llarining faollashuvi bilan bog‘liq. Surunkali yallig‘lanish, oksidlovchi stress, ekstrasellyulyar matriksning qayta tuzilishi va mineral almashinuvining buzilishi osteogen transformatsiya hamda kalsiy-fosfat birikmalarining to‘planishini kuchaytiradi. Kalsifikatsiyaning biologik ta’siri uning morfologiyasi, hajmi va blyashka ichidagi joylashuviga bog‘liq. Mikro-kalsifikatsiyalar mahalliy mexanik zo‘riqishni oshirib, blyashka beqarorligiga hissa qo‘shishi mumkin, yirik birlashgan kalsifikatsiyalar esa boshqa strukturaviy ta’sir ko‘rsatishi mumkin. Ushbu sharhda aterosklerotik blyashkalar kalsifikatsiyasining zamonaviy mexanizmlari, ayniqsa VSMC osteogen transformatsiyasi va asosiy osteogen signal yo‘llari ko‘rib chiqiladi.

Kalit so‘zlar: ateroskleroz; blyashka kalsifikatsiyasi; tomir silliq mushak hujayralari; osteogen differensiallanish; RUNX2; BMP/SMAD; Wnt/β-katenin; yallig‘lanish; oksidlovchi stress.

Introduction:

Introduction: Atherosclerosis is a chronic vascular disease characterized by lipid accumulation, inflammation, extracellular matrix remodeling, and progressive structural changes in the arterial wall. As lesions progress, calcium-phosphate deposits may develop within the intima, leading to plaque calcification. Current evidence indicates that vascular calcification is an actively regulated process involving cellular phenotypic changes, extracellular vesicles, matrix remodeling, mineral metabolism, and intracellular signaling pathways.

Calcification is particularly common in advanced atherosclerotic lesions and may occur as small microcalcifications or larger, confluent deposits. Its biological effects depend not only on the presence of calcium but also on the size, morphology, location, and distribution of mineralized regions. Microcalcifications may increase local mechanical stress and contribute to plaque vulnerability, whereas larger areas of consolidated calcification may have different structural and biomechanical effects.

Vascular smooth muscle cells (VSMCs) are key cellular mediators of plaque calcification. Under physiological conditions, VSMCs maintain a contractile phenotype that supports vascular integrity. However, inflammatory mediators, oxidative stress, altered mechanical forces, lipid accumulation, and extracellular matrix changes can induce phenotypic switching. VSMCs may lose contractile characteristics and acquire osteogenic or chondrogenic properties, thereby contributing directly to extracellular mineralization.A central regulator of this transformation is runt-related transcription factor 2 (RUNX2), which promotes the expression of osteogenic genes and is associated with suppression of the contractile VSMC phenotype. Its activity is regulated by several interconnected pathways, including bone morphogenetic protein (BMP)/SMAD and Wnt/β-catenin signaling. Other regulators, such as MSX2, SOX9, and KLF5, also contribute to osteogenic or osteochondrogenic differentiation.

Inflammation and oxidative stress further promote calcification by inducing cellular dysfunction, apoptosis, extracellular vesicle release, and osteogenic signaling. Apoptotic bodies and extracellular vesicles can serve as nucleation sites for calcium-phosphate deposition, while extracellular matrix remodeling may facilitate crystal formation. Thus, VSMC phenotypic plasticity, inflammation, oxidative stress, apoptosis, and matrix remodeling form an interconnected network that drives vascular mineralization.

Despite significant progress, the mechanisms linking these processes and determining different patterns of plaque calcification remain incompletely understood. Therefore, this review summarizes the cellular and molecular mechanisms of atherosclerotic plaque calcification, with particular emphasis on VSMC osteogenic transformation and the major signaling pathways involved.

Conclusion: Atherosclerotic plaque calcification is a complex and actively regulated process involving interactions between vascular smooth muscle cells, inflammatory mediators, oxidative stress, extracellular matrix remodeling, and

mineral metabolism. VSMC phenotypic transformation toward an osteogenic state represents a central mechanism in this process, with RUNX2 serving as an important regulator of osteogenic gene expression.

The BMP–SMAD–RUNX2 and Wnt/β-catenin pathways play major roles in regulating VSMC osteogenic differentiation, while inflammatory and oxidative signaling pathways further amplify these responses. Other regulatory mechanisms, including Notch, PI3K/AKT, MAPK, and PPARγ signaling, contribute to the complex molecular network underlying vascular mineralization.

The clinical consequences of calcification depend on its morphology, size, and distribution within the atherosclerotic plaque. In particular, microcalcification may have different effects on plaque stability compared with larger, consolidated calcified regions. A better understanding of these molecular and structural mechanisms may facilitate the identification of biomarkers and therapeutic targets for the prevention or modulation of pathological vascular calcification.Further research integrating molecular mechanisms, advanced imaging, and clinical investigations is needed to clarify how osteogenic signaling can be safely targeted and how this may influence the progression and clinical consequences of calcified atherosclerotic plaques.

References

1. Chen NX, Moe SM. Pathophysiology of vascular calcification. Curr Osteoporos Rep. 2015;13(6):372-380. doi:10.1007/s11914-015-0293-9. PMID:26409849.
2. Leopold JA. Vascular calcification: mechanisms of vascular smooth muscle cell calcification. Trends Cardiovasc Med. 2015;25(4):267-274. doi:10.1016/j.tcm.2014.10.021. PMID:25435520.
3. Durham AL, Speer MY, Scatena M, Giachelli CM, Shanahan CM. Role of smooth muscle cells in vascular calcification: implications in atherosclerosis

and arterial stiffness. Cardiovasc Res. 2018;114(4):590-600. doi:10.1093/cvr/cvy010. PMID:29514202.

4. Tyson J, Bundy K, Roach C, Douglas H, Ventura V, Segars MF, et al. Mechanisms of the osteogenic switch of smooth muscle cells in vascular calcification: WNT signaling, BMPs, mechanotransduction, and EndMT. Bioengineering (Basel). 2020;7(3):88. doi:10.3390/bioengineering7030088. PMID:32781528.
5. Chen Y, Zhao X, Wu H. Transcriptional programming in arteriosclerotic disease: a multifaceted function of the Runx2 (Runt-related transcription factor 2). Arterioscler Thromb Vasc Biol. 2021;41(1):20-34. doi:10.1161/ATVBAHA.120.313791. PMID:33115268.
6. Li X, Yang HY, Giachelli CM. BMP-2 promotes phosphate uptake, phenotypic modulation, and calcification of human vascular smooth muscle cells. Atherosclerosis. 2008;199(2):271-277. doi:10.1016/j.atherosclerosis.2007.11.031. PMID:18179800.
7. Cai T, Sun D, Duan Y, Wen P, Dai C, Yang J, et al. WNT/β-catenin signaling promotes VSMCs to osteogenic transdifferentiation and calcification through directly modulating Runx2 gene expression. Exp Cell Res. 2016;345(2):206-217. doi:10.1016/j.yexcr.2016.06.007. PMID:27321958.
8. Rong S, Zhao X, Jin X, Zhang Z, Chen L, Zhu Y, et al. Vascular calcification in chronic kidney disease is induced by bone morphogenetic protein-2 via a mechanism involving the Wnt/β-catenin pathway. Cell Physiol Biochem. 2014;34(6):2049-2060. doi:10.1159/000366400. PMID:25562153.
9. Bundy K, Boone J, Simpson CL. Wnt signaling in vascular calcification. Front Cardiovasc Med. 2021;8:708470. doi:10.3389/fcvm.2021.708470. PMID:34595218.

10. Reinhold S, Blankesteijn WM, Foulquier S. The interplay of WNT and PPARγ signaling in vascular calcification. Cells. 2020;9(12):2658. doi:10.3390/cells9122658. PMID:33322009.
11. Byon CH, Javed A, Dai Q, Kappes JC, Clemens TL, Darley-Usmar VM, et al. Oxidative stress induces vascular calcification through modulation of the osteogenic transcription factor Runx2 by AKT signaling. J Biol Chem. 2008;283(22):15319-15327. doi:10.1074/jbc.M800021200. PMID:18378684.
12. Liu Y, Shanahan CM. Signalling pathways and vascular calcification. Front Biosci (Landmark Ed). 2011;16(4):1302-1314. doi:10.2741/3790. PMID:21196233.
13. Wang D, Zhang X, Li Y, et al. Activation of nuclear factor-kappa B accelerates vascular calcification by inhibiting progressive ankylosis protein homolog expression. [Journal details should be retained according to the final PubMed record used for citation]. PMID: available through PubMed record.
14. Proudfoot D, Skepper JN, Hegyi L, Bennett MR, Shanahan CM, Weissberg PL. Apoptosis regulates human vascular calcification in vitro: evidence for initiation of vascular calcification by apoptotic bodies. Circ Res. 2000;87(10):e10-e17. PMID:11090552.
15. Reynolds JL, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, Proudfoot D, et al. Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: a potential mechanism for accelerated vascular calcification in ESRD. J Am Soc Nephrol. 2004;15(11):2857-2867. PMID:15504939.
16. Liu Y, Drozdov I, Shroff R, Beltran LE, Shanahan CM. Prelamin A accelerates vascular calcification via activation of the DNA damage response and inhibition of autophagy. Circ Res. 2013;113(8):e1-e12. [Use only if this mechanism is retained in the final text].

17. Wang M, et al. Vascular calcification is coupled with phenotypic conversion of vascular smooth muscle cells through Klf5-mediated transactivation of the Runx2 promoter. Biosci Rep. 2014;34(4):e00103. doi:10.1042/BSR20140103. PMID:25205373.
18. Augstein A, Mierke J, Poitz DM, Strasser RH. Sox9 is increased in arterial plaque and stenosis, associated with synthetic phenotype of vascular smooth muscle cells and causes alterations in extracellular matrix and calcification. Biochim Biophys Acta Mol Basis Dis. 2018;1864(8):2526-2537. doi:10.1016/j.bbadis.2018.05.009. PMID:29777903.
19. Shioi A, Mori K, Jono S, Koyama H, Hosoi M, Nishizawa Y. Mechanism of atherosclerotic calcification. J Atheroscler Thromb. 2006;13(6):278-285. [Use as background for osteogenic and mineralization mechanisms].
20. Shioi A, Ikari Y. Cardiovascular calcification during atherosclerosis and chronic kidney disease. J Atheroscler Thromb. 2018;25(4):256-263. [Use for clinical/pathophysiological background where appropriate].
21. Lin ME, Chen TM, Wallingford MC, Nguyen NB, Yamada S, Sawangmake C, et al. Runx2 deletion in smooth muscle cells protects against vascular calcification. Circ Res. 2016;119(10):1062-1074. [Use for the functional role of VSMC-derived RUNX2].
22. Hosaka N, Mizobuchi M, Ogata H, Kumata C, Kondo F, Koiwa F, et al. Inhibition of bone morphogenetic protein signaling suppresses vascular calcification in chronic kidney disease. [Verify final bibliographic details before submission].
23. Shioi A, Morioka T, Shoji T, Emoto M. The inhibitory roles of vitamin K in progression of vascular calcification. Nutrients. 2020;12(2):583. doi:10.3390/nu12020583.
24. Maldonado N, Kelly-Arnold A, Vengrenyuk Y, Laudier D, Fallon JT, Virmani R, et al. A mechanistic analysis of the role of microcalcifications in

atherosclerotic plaque stability: potential implications for plaque rupture. Am J Physiol Heart Circ Physiol. 2012;303(5):H619-H628. doi:10.1152/ajpheart.00036.2012. PMID:22777419.

25. Zhao Y, Li H, Guo Y. Interleukin family in vascular calcification: molecular mechanisms and therapeutic perspectives. Front Cardiovasc Med. 2025;12:1619018. doi:10.3389/fcvm.2025.1619018. PMID:40959491.