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Short Review Paper

A review of obstacles facing reversal of vascular calcification

Karl Rybka and Nasim Nosoudi*
Department of Biomedical, Industrial and Human Factors Engineering, Wright State University,Dayton, OH 45435 USA
nosoudi.nasim@wright.edu

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Abstract

Cardiovascular disease (CVD) refers to several types of conditions that affect the heart and blood vessels.CVD is the leading cause of death in the world and is often characterized by pathological vascular calcification, which has been recognized as a major risk factor for various cardiovascular events including heart failure, pulmonary hypertension (PTH), and death in chronic kidney disease (CKD) patients. To date, there are no therapies to reverse medial or intimal calcification. In this mini-review we aim to shed light on the relationship between macrophages, osteoclasts, and vascular calcification.

Keywords: Vascular calcification, cardiovascular disease (CVD), chronic kidney disease (CKD), macrophages, osteoclasts.

Introduction

Despite the clinical relevance of calcification in vascular tissue, limited research and treatment options exist. The pathophysiological process of vascular calcification is characterized by the buildup of mineral deposits throughout blood vessels in a process similar to that of osteogenesis[1]. Within the skeletal system, osteoblasts function as the main synthesizer of bone. To mediate this action, specialized multinucleated cells known as osteoclasts resorb bone to perform periodic repairs and regulate calcium levels. In healthy individuals, osteoclast activity remains in equilibrium with the bone formation performed by osteoblasts so that no net change in bone mass occurs[2]. Hyperactivity of osteoclasts can lead to pathobiological processes with severe clinical implications such as rheumatoid arthritis and osteoporosis[3]. It is hypothesized that this mechanism works in reverse fashion throughout vascular tissue, with the decreased activity of cells possessing resorption capabilities, known asosteoclast-like cells (OLCs), inducing vascular calcification[4]. While a substantial amount of research exists regarding the overall formation of osteoclasts from hemopoietic progenitors in bone, there is a lack of information available concerning the mechanism of macrophage differentiation to osteoclasts in the setting of blood vessels. Therefore, the purpose of this review paper is to outline current knowledge of the specific pathway of the differentiation of macrophages to osteoclasts and investigate the possible utilization of this differentiation to treat vascular calcification.

Osteoclastogenesis in Skeletal Bone Setting

Osteoclasts are derived from hemopoietic cells, a classification which encompasses macrophages. Consequently, the differentiation process requires two hematopoietic factors necessary for osteoclastogenesis, the tumor necrosis factor RANKL and macrophage colony-stimulating factor (M-CSF)[5]. In a skeletal setting, direct interaction of the RANKL ligand found on the surface of osteoblasts with the RANK receptor of osteoclast progenitors not only initiates differentiation, but also activates osteoclast resorption function by inducing structural changes such as act in cytoskeleton rearrangement and the formation of a sealed compartment around the area of bone to be eroded[5]. In addition to osteoblasts, Kong et al.[6] discovered that activated T-cells express RANKL and contribute to bone resorption through stimulation of osteoclastogenesis. Consequently, local inflammation in skeletal structures attracts activated T-cells which couldinitiate and act as a positive feedback to bone remodeling. Also, studies done with mice possessing an inactivating mutation in the M-CSF gene have shown M-CSF to directly affect macrophage production and their differentiation to osteoclasts[7]. Lastly, osteoprotegerin (OPG) operates as the main regulator of osteoclastogenesis by acting asa soluble decoy receptor for RANKL[5]. At each step of the process from macrophage to activated osteoclast, OPG retains the ability to directly inhibit the RANK/RANKL signaling pathway in bone.

Osteoclastogenesis in Vascular Setting

Similar toa skeletal environment, a fine balance exists between the osteoclast-like cellsand osteoblast-like cells found in vascular tissue. In arteries especially, an imbalance of this homeostasis leads to mineral depositionin the intimal and medial layers of blood vessel walls as part of a pathological process known as vascular calcification[8]. It is hypothesized that this condition is caused by a localized lack of OLC activity rather than an active deposition of calcium[4]. A study done by Qiao et al.[9] supports this by showing increased development of calcium deposits in arteries of mice with a point mutation in the gene encoding M-CSF. Additionally, mice lacking the carbonic

anhydrase enzyme necessary for osteoclast resorption functionality exhibited extensive vascular calcinosis[10]. While the osteoclast differentiation processes in bone and vascular tissue share similarities, the rarity of osteoclasts in calcified arteries casts some doubt on the feasibility of the use of OLCs in resorbing vascular mineral deposits[11].

The introduction of OPG, the competitive inhibitor of RANKL, yields arterial calcification results contrary to those achieved in a skeletal bone-based model. Mice lacking in OPG exhibited both osteoporosis and arterial calcification. The presence of these drastically opposite conditions simultaneously leads to what is known as the calcification paradox[12]. In a murine model of arterial calcification, the addition of OPG reduced calcification. The results obtained from the calcium deposits of OPG-deficient mice indicate the presence of multinucleated cells displaying the lysosomal hydrolases characteristic of functional osteoclasts (tartrate-resistant acid phosphatase (TRAP) and cathepsin K (CTSK)) and lacking the distinguishing antigens (F4/80) of macrophages[4]. Additionally, warfarin induced calcification in mice was significantly reduced by treatment with OPG[13].

Recent findings have demonstrated the capability of RANKL to stimulate calcification. One study displayed increased vascular calcification in vascular smooth muscle cells (VSMC) by way of a RANK dependent pathway yielding increased levels of BMP4, a morphogenic protein involved in bone formation[14]. As shown by another study, RANKL activation of macrophage paracrine activity in a phosphate-rich environment increased calcification levels in smooth muscle cells through increased expression of IL-6 and TNF-α[15]. While the similarity between the formation of bone and the calcification of vascular tissue is undeniable, these findings suggest that perhaps a key differentiation step exists in the vascular osteoclastogenesis process.

Other factors have been shown to affect resorption activity in vascular calcification. N-acetylglucosamine-1-phosphate transferase containing alpha and beta subunits (GNPTAB) is a transmembrane transferase that regulates the transport of lysosomal hydrolases necessary for osteoclast function[16]. A study done by Lei et al.[16] found levels of GNPTAB to be significantly elevated, and the level of lysosomal hydrolases to be depressed in localized areas of calcium deposits within human carotid arteries. Using a human macrophage to osteoclast differentiation model, the study silenced expression of the GNPTAB gene to show increased functional osteoclast formation and activity.

Because vascular calcification is often expressed in patients with chronic kidney disease (CKD), it comes as no surprise that the two conditions are likely related. Researchers have shown that the high levels of inorganic phosphate resulting from CKD decrease osteoclast differentiation by down-regulating the RANK/RANKL signaling pathway[17]. This most likely holds true for vascular tissue, as shown by a study in which human aortic smooth muscle cells cultured in elevated levels of inorganic phosphate displayed increased calcium deposition[18].

Conclusion

In conclusion, evidence seems to indicate that the problem with harnessing the resorption ability of osteoclasts to combat vascular calcification lies with the suppressed functionality of osteoclasts present in calcified plaques and that activating these osteoclasts may hold the key to reducing calcification.

References

1. Moe S.M. and Chen N.X. (2008). Mechanisms of vascular calcification in chronic kidney disease. *Journal of the American Society of Nephrology,* 19(2), 213-216.

2. Blair H.C. (1998). How the osteoclast degrades bone. *BioEssays : news and reviews in molecular, cellular and developmental biology,* 20(10), 837-846. doi:10.1002/(sici)1521-1878(199810)20:10<837::aid-bies9>3.0.co;2-d.

3. Sato K. and Takayanagi H. (2006). Osteoclasts, rheumatoid arthritis, and osteoimmunology. *Current opinion in rheumatology*, 18(4), 419-426. doi:10.1097/01.bor.0000231912.24740.a5.

4. Doherty T.M., Uzui H., Fitzpatrick L.A., Tripathi P.V., Dunstan C.R., Asotra K. and Rajavashisth T.B. (2002). Rationale for the role of osteoclast-like cells in arterial calcification. *The FASEB journal*, 16(6), 577-582.

5. Boyle W.J., Simonet W.S. and Lacey D.L. (2003). Osteoclast differentiation and activation. *Nature*, 423(6937), 337. doi:10.1038/nature01658.

6. Kong Y.Y., Yoshida H., Sarosi I., Tan H.L., Timms E., Capparelli C. and Khoo W. (1999). OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. *Nature*, 397(6717), 315-323. doi:10.1038/16852.

7. Stanley E.R., Berg K.L., Einstein D.B., Lee P.S., Pixley F. J., Wang Y. and Yeung Y.G. (1997). Biology and action of colony-stimulating factor-1. *Molecular Reproduction and Development: Incorporating Gamete Research*, 46(1), 4-10. doi:10.1002/(sici)1098-2795(199701)46:1<4::aid-mrd2>3.0.co;2-v.

8. Wu M., Rementer C. and Giachelli C.M. (2013). Vascular calcification: an update on mechanisms and challenges in treatment. *Calcified tissue international*, 93(4), 365-373. doi:10.1007/s00223-013-9712-z.

9. Qiao J.H., Tripathi J., Mishra N.K., Cai Y., Tripathi S., Wang X.P. and Lusis A.J. (1997). Role of macrophage colony-stimulating factor in atherosclerosis: studies of osteopetrotic mice. *The American journal of pathology,* 150, 1687-1699.

10. Spicer S.S., Lewis S.E., Tashian R.E. and Schulte B.A. (1989). Mice carrying a CAR-2 null allele lack carbonic anhydrase II immunohistochemically and show vascular calcification. *The American journal of pathology,* 134(4), 947-954.

11. Han K.H., Hennigar R.A. and O'neill W.C. (2015). The association of bone and osteoclasts with vascular calcification. *Vascular Medicine*, 20(6), 527-533. doi:10.1177/1358863x15597076.

12. Sage A.P., Tintut Y. and Demer L.L. (2010). Regulatory mechanisms in vascular calcification. *Nature reviews. Cardiology,* 7, 528-536. doi:10.1038/nrcardio.2010.115.

13. Price P.A., June H.H., Buckley J.R. and Williamson M.K. (2001). Osteoprotegerin inhibits artery calcification induced by warfarin and by vitamin D. *Arteriosclerosis, thrombosis, and vascular biology*, 21(10), 1610-1616.

14. Panizo S., Cardus A., Encinas M., Parisi E., Valcheva P., López-Ongil S. and Valdivielso J.M. (2009). RANKL increases vascular smooth muscle cell calcification through a RANK-BMP4–dependent pathway. *Circulation research*, 104(9), 1041-1048.

15. Deuell K.A., Callegari A., Giachelli C.M., Rosenfeld M.E. and Scatena M. (2012). RANKL enhances macrophage paracrine pro-calcific activity in high phosphate-treated smooth muscle cells: dependence on IL-6 and TNF-α. *Journal of vascular research*, 49(6), 510-521. doi:10.1159/000341216.

16. Lei Y., Iwashita M., Choi J., Aikawa M. and Aikawa E. (2015). N-acetylglucosamine-1-Phosphate Transferase Suppresses Lysosomal Hydrolases in Dysfunctional Osteoclasts: A Potential Mechanism for Vascular Calcification. *Journal of cardiovascular development and disease,* 2, 31-47. doi:10.3390/jcdd2020031.

17. Mozar A., Haren N., Chasseraud M., Louvet L., Mazière C., Wattel A. and Mazière J.C. (2008). High extracellular inorganic phosphate concentration inhibits RANK-RANKL signaling in osteoclast-like cells. *Journal of cellular physiology,* 215, 47-54. doi:10.1002/jcp.21283.

18. Giachelli C.M., Jono S., Shioi A., Nishizawa Y., Mori K. and Morii H. (2001). Vascular calcification and inorganic phosphate. *American journal of kidney diseases*, 38(4), S34-S37.