血管周围脂肪组织与血管钙化关系的研究进展

吴冬雪, 徐 明*

(中国药科大学基础医学与临床药学学院, 江苏 南京 211100)

摘要: 血管钙化 (vascular calcification, VC) 是一种慢性全身性血管疾病, 其特征为羟基磷灰石矿物质在血管系统的异常沉积, 与衰老、糖尿病、动脉粥样硬化和慢性肾脏病等密切相关。血管周围脂肪组织 (perivascular adipose tissue, PVAT) 是血管周围包绕的一种特殊类型的脂肪组织, 被认为是血管结构的支撑成分, 并能够在血管舒张和收缩过程中发挥稳态调节的作用。目前, 越来越多的证据表明, PVAT作为内分泌和旁分泌器官, 与血管壁细胞成分之间作用紧密, 可能参与VC的发生发展。本文对PVAT在VC病理生理过程中的作用及其作为治疗干预靶标的潜力进行综述, 以期为VC的防治提供新思路。

关键词: 血管周围脂肪组织; 血管钙化; 脂肪因子; 炎症; 间充质干细胞; 褐变

中图分类号: R966 **文献标识码**: A **文章编号**: 0513-4870(2024)06-1527-11

Advances in the relationship between perivascular adipose tissue and vascular calcification

WU Dong-xue, XU Ming*

(*School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing 211100, China*)

Abstract: Vascular calcification (VC) is a chronic systemic vascular disease characterized by abnormal deposition of hydroxyapatite minerals in the vascular system and is closely associated with aging, diabetes, atherosclerosis, and chronic kidney disease. Perivascular adipose tissue (PVAT), a special type of adipose tissue that surrounds blood vessels, is thought to be a supportive component of the vascular structure and is capable of playing a role in homeostatic regulation during vasodilatation and contraction. Currently, there is growing evidence that perivascular adipose tissue acts as an endocrine and paracrine organ and interacts closely with cellular components of the vascular wall, which may be involved in the development of vascular calcification. This article reviews the role of perivascular adipose tissue in the pathophysiological process of vascular calcification and its potential as a target for therapeutic intervention, with the aim of providing new ideas for the prevention and treatment of vascular calcification.

Key words: perivascular adipose tissue; vascular calcification; adipokine; inflammation; mesenchymal stem cell; browning

血管钙化 (vascular calcification, VC) 曾被认为是钙、磷酸盐在血管壁被动沉积的一种退行性病理过程[1]。但近年来的研究结果发现, 血管平滑肌细胞 (vascular smooth muscle cells, VSMCs) 会向成骨细胞样表型分化[2]。同时, 在钙化血管中也检测到成骨相关转录因子如msh同源框2 (msh homeobox 2, Msx2)、SRY-盒转录因子9 (SRY-box transcription factor 9, Sox9)、Runt相关转录因子2 (Runt-related transcription factor 2, Runx2) 和osterix的表达, Runx2及osterix还会增加骨钙素 (osteocalcin, OCN)、核因子-κB受体活化因子配体 (receptor activator of nuclear factor-κB

收稿日期: 2023-12-05; 修回日期: 2024-02-27.
基金项目: 国家自然科学基金资助项目 (82373870).
*通讯作者 Tel: 15805195696, E-mail: mingxu2016@163.com
DOI: 10.16438/j.0513-4870.2023-1364

ligand, RANKL) 和碱性磷酸酶 (alkaline phosphatase, ALP) 等骨相关蛋白的表达[3]。表明VC是一种活跃的、可逆转的、与骨形成类似的主动调控过程。无定形磷酸钙是钙化早期的关键成分, 主要由Ca^{2+}和PO_4^{3-}离子组成, 随着疾病的进展转化为稳固的羟基磷灰石晶体[4]。在慢性肾脏病等病理条件下, VSMCs释放的外泌体能够促进磷脂酰丝氨酸表面暴露、钙化抑制剂的丢失等, 导致囊泡膜上形成Ca/P成核复合物, 从而介导羟基磷灰石晶体在血管壁上的沉积[4]。羟基磷灰石晶体同样会促进VSMCs成骨分化, 进一步增强钙化过程[5]。VC与衰老相关, 是动脉粥样硬化发生和发展的重要特征之一, 常见于2型糖尿病和晚期慢性肾脏病患者中, 特别是需要维持血液透析的患者, 是心血管疾病死亡率增加的独立危险因素[6]。VC具有隐匿性、持续性的特点, 胸主动脉钙化与致死性和非致死性心血管疾病及全因死亡率显著相关, 腹主动脉钙化与心血管疾病死亡率显著相关[7], 因此, 开发预防、早期识别及治疗VC的手段显得尤为重要。

血管周围脂肪组织 (perivascular adipose tissue, PVAT) 在解剖学上紧邻血管外膜, 不仅可以支撑、保护血管, 还可以通过旁分泌或自分泌方式参与血管稳态的调节。最近一项研究通过对过表达PR结构域蛋白16 (PR domain containing 16, PRDM16) 的VSMCs进行成脂诱导, 发现其表现出脂滴积累并增加了产热脂肪细胞标志物解偶联蛋白-1 (uncoupling protein 1, UCP-1) 的表达[8]。此外, 特异性敲除小鼠VSMCs中的脂肪转录因子过氧化物酶体增殖物激活受体γ (peroxisome proliferator-activated receptor γ, *PPARγ*) 后, 胸主动脉、腹主动脉及主动脉弓PVAT完全缺失[9]。这些研究表明, VSMCs与PVAT之间联系密切。进一步对成年小鼠胸主动脉基质细胞进行scRNA-seq分析及流式分选, 发现一种新的、有助于PVAT形成的具有成脂分化潜力的平滑肌细胞群CD200-SMCs (SMC-2), 其能够同时表达典型的平滑肌标志物 (Myh11、Acta2和Tagln2) 及脂肪细胞标志物 (Pparg、Lpl和Fabp4)。并且在人类PVAT中也发现与小鼠主动脉中SMC-2细胞相应的平滑肌样脂肪细胞祖细胞 (PPARγ^+ SMC样细胞)[10], 这表明VSMCs可能是PVAT中一些产热脂肪细胞的起源。

此外, 有研究表明胸主动脉PVAT与冠状动脉和腹主动脉钙化密切相关[11], 系统性红斑狼疮患者的胸主动脉PVAT的体积和密度更高, 且与VC的发生独立相关[12]。补体蛋白水平与中年女性动脉钙化显著相关, 而PVAT可能是补体蛋白的局部来源[13]。基于以上研究, PVAT与VC关系密切, 可能成为VC新的治疗干预靶点。

1 血管钙化概述

VC是多因素参与的、可调控的复杂病理过程。根据血管内受累部位不同, VC主要分为内膜钙化、中膜钙化和瓣膜钙化 (表1)[14-16]。

内膜钙化又称为动脉粥样硬化性钙化, 与脂质沉积、炎性细胞浸润、氧化应激等密切相关[17]。存在于斑块内的平滑肌细胞和巨噬细胞能够分泌基质囊泡 (matrix vesicles, MVs), 这些基质囊泡在胶原纤维之间聚集, 并作为血管壁异位矿化的起始位点, 形成微钙化, 增加斑块破裂的风险[18]。随后, 微钙化从坏死核心的深层区域延伸到周围的胶原基质, 最终形成大钙化, 大钙化通常被认为与厚纤维帽有关, 可以增加斑块稳定性, 防止斑块破裂, 但同时也增加了血栓形成的风险[19,20]。

中膜钙化又称为Mönckeberg钙化, 通常没有脂质积累或炎症细胞浸润。血管壁的中膜层主要由富含弹性蛋白的细胞外基质和VSMCs组成。在慢性肾脏病等疾病过程中, 弹性纤维断裂, 弹性蛋白发生降解并释

Table 1 Classification and characterization of vascular calcification[14-16]

Item	Intimal calcification	Median calcification	Valve calcification
Prone areas	Intimal layer of large arteries such as coronary arteries and aorta	Smooth muscle layer of small and medium sized arterioles such as femoral artery and radial artery	Aortic valve, mitral valve
Distribution characteristics	Scattered punctate or plaque-like	Distributed in a linear pattern along the membrane of the blood vessels	Lobules are thickened and punctate calcifications may be present
Phenotypic changes	Contractile VSMCs transform into osteoblasts and foam cells	Contractile VSMCs transform into osteoblasts	Fibroblast-like phenotype transform into osteoblast-like phenotype
Pathologic manifestations	Intimal hyperplasia with lipid deposition and macrophage infiltration, luminal stenosis, and plaque rupture	Decreased vascular elasticity, compliance, and increased stiffness	Valve thickening, inflammatory cell infiltration, lipid plaque deposition
Risk factors	Hyperlipidemia, hypercholesterolemia	Aging, diabetes, chronic kidney disease	Aging, high blood pressure, diabetes, chronic kidney disease
Complication	Myocardial ischemia, myocardial infarction, stroke	Systolic hypertension, left ventricular hypertrophy, heart failure	Valvular stenosis, insufficiency, arrhythmias, heart failure, stroke

放被称为弹性蛋白因子的弹性蛋白衍生生物活性肽, 诱导VSMCs成骨分化[21]。同时, 胶原蛋白分泌增加, 能促进MVs的积累和释放, 并与MVs相互作用, 作为钙化的成核位点, 促进血管平滑肌细胞向骨/软骨样细胞转化, 加速VC的进展[22]。

瓣膜钙化被认为是慢性肾脏病患者 (尤其是透析患者) 死亡率增加的重要因素之一[23]。虽然瓣膜钙化与内膜、中膜钙化具有共同的危险因素[24], 但瓣膜和血管之间存在明显的解剖学、结构及细胞表型差异。研究表明, 主动脉血管平滑肌细胞比主动脉瓣膜间质细胞更易受到钙化刺激的影响从而发生钙化, 并且在同一群患者中瓣膜钙化的患病率显著低于血管钙化的患病率[25]。此外, 主动脉瓣膜间质细胞的钙化涉及由软骨生成mRNA (Bmp2、Sox9、Runx2和Pth1r)、阳性骨调节因子 (Comp、Ecm1、Ibsp) 与骨抑制剂Sost共同介导的骨/软骨生成分化过程, 而主动脉血管平滑肌细胞似乎并不经历这种骨/软骨生成分化过程[26], 表明主动脉瓣膜间质细胞与主动脉血管平滑肌细胞的钙化机制可能不同。

2 血管周围脂肪组织与血管钙化

PVAT是指围绕在血管周围并以旁分泌或自分泌方式释放各种因子以调节血管功能的脂肪组织, 包绕着除肺血管、脑血管外的大部分血管, 主要由脂肪细胞、前脂肪细胞、间充质干细胞、成纤维细胞、炎性细胞等组成[27]。在形态功能方面, PVAT中的脂肪细胞分化程度低, 细胞体积小, 更接近前脂肪细胞[28]。在结构上, PVAT在大血管周围与血管壁外膜紧密相连, 而在小血管和微血管中则被认为是血管壁的组成成分[29]。

PVAT具有显著的表型可塑性, 根据解剖位置不同可表现出白色、棕色和米色脂肪表型。研究表明, 啮齿动物胸主动脉PVAT在形态和功能方面类似于棕色脂肪表型, 具有多房脂滴, 富含线粒体及UCP-1[27,30]。来自人冠状动脉的PVAT表达棕色/米色特异性基因 (如UCP-1), 但人胸主动脉PVAT是否也是棕色脂肪表型仍有待研究[27]。啮齿动物和人腹主动脉周围的PVAT同时具有白色和棕色脂肪组织的特征, 提示腹部PVAT可能更类似于米色脂肪表型[27,31]。此外, 颈动脉、股动脉和肠系膜动脉等小动脉周围的PVAT大多为白色脂肪表型[32]。

在生理条件下, PVAT可以为血管提供结构支持。此外, PVAT是NO、瘦素和血管紧张素1～7等血管舒张因子的来源, 对动脉产生抗收缩作用, 从而减轻血管损伤[33]。在病理条件下 (如肥胖), PVAT功能受损, 能够通过旁分泌等方式导致血管平滑肌细胞、内皮细胞功能障碍, 以“由外而内”的方式引发血管病理生理改变[27]。

临床研究显示, 胸部PVAT体积与HIV感染患者的冠状动脉钙化相关[34]。系统性红斑狼疮患者的胸主动脉PVAT的体积和密度更高, 这与VC独立相关[12,35]。此外, 在系统性红斑狼疮小鼠中PVAT可以发生表型转换, 表现为UCP-1表达显著降低, 同时CD45阳性白细胞浸润增加, 并伴随促炎脂肪因子增多[36]。表明PVAT可能在VC的发生发展中发挥重要作用。

2.1 血管周围脂肪组织衍生的脂肪因子参与血管钙化

PVAT作为自分泌/旁分泌器官, 能够分泌脂肪因子等生物活性物质。脂肪因子被认为是PVAT和血管病变之间的桥梁, 能够靶向血管平滑肌细胞、内皮细胞介导脂肪组织和血管壁之间的串扰[37]。动脉粥样硬化、慢性肾脏病和糖尿病能够诱发PVAT慢性缺氧, 进而导致脂肪因子生成失衡, 失衡的脂肪因子能够通过调控细胞凋亡、VSMCs成骨分化、炎症等过程, 影响VC的发生发展 (表2)[38-62]。

2.2 血管周围脂肪组织白色变与褐变参与血管钙化

肥胖是心血管疾病重要的危险因素之一, 研究表明, 患者整体或腹部肥胖的程度、持续时间与冠状动脉钙化及其进展独立相关[63]。此外, 与维生素D缺乏症相关的肥胖可能会增加VC的风险[64]。同时, 肥胖也会诱导棕色脂肪组织和胸主动脉PVAT发生“白色变”, 表现为单房脂滴积聚、线粒体变性和产热能力下降等白色脂肪组织特征, 这主要与肥胖过程中的炎症、自噬、血管生成障碍等过程相关, 并且会进一步促进肥胖相关血管疾病[65]。此外, 衰老、糖尿病也会促进脂肪组织发生白色变[66,67]。

在刺激条件下, 白色脂肪组织中会出现棕色脂肪细胞样表型, 这种独特的现象称为“褐变”, 其能够减轻血管功能障碍过程中的炎症、氧化应激水平[68], 可能对VC发挥保护作用。研究发现, 诱导PVAT褐变可以改善内皮功能, 缓解高血压的进展[69]。促进PVAT褐变能够减弱血管损伤后的病理性血管重塑和促炎性巨噬细胞的积累, 从而在动脉粥样硬化过程中发挥保护作用[70]。通过移植胸主动脉PVAT至腹主动脉周围, 可有效防止磷酸钙诱导的腹主动脉瘤形成[71]。表明诱导PVAT褐变可能是一种有效的治疗策略。

既往研究表明, 主动脉不同区域的PVAT表现出明显的表型差异, 其中胸主动脉较腹主动脉钙化发生率更低[72]。胸主动脉PVAT富含棕色脂肪组织, 能够分泌大量软骨寡聚基质蛋白, 从而抑制VSMCs凋亡[71]。此外, 通过冷暴露诱导腹主动脉PVAT褐变能够降低促炎脂肪因子如TNF-α、IL-6的表达[73]。因此, 诱导PVAT褐变可能对VC具有治疗潜力, 但仍需大量

Table 2 Adipokines associated with vascular calcification (VC). TNF-*α*: Tumor necrosis factor-*α*; IL-6: Interleukin 6; CTRP3: C1q/TNF-related protein-3; MCP-1: Monocyte chemoattractant protein-1; OPN: Osteopontin; BMP2: Bone morphogenetic protein; ET-1: Endothelin-1; VCAM-1: Vascular cellular adhesion molecule-1; ICAM-1: Intercellular adhesion molecule-1; ROS: Reactive oxygen species; NF-*κ*B: Nuclear factor-kappa B; ANKH: Ankylosis protein homolog; PPi: Pyrophosphate; Runx2: Runt-related transcription factor 2; GPX1: Glutathione peroxidase 1; SOD1: Superoxide dismutases 1; SOD2: Superoxide dismutases 2; PRDX1: Peroxiredoxin-1; HSP70: Heat shock protein 70; MGP: Matrix Gla protein; OPG: Osteoprotegerin

Adipokine	Mechanism	Effect
Leptin	↑ TNF-*α*, IL-6, MCP-1[38-40]	Promote VC
	↑ ALP, OPN, osteocalcin, activate of ERK1/2 signaling promotes VSMCs osteogenic differentiation[41]	
	↑ RANKL, BMP2, activate ERK1/2 and PI3K/Akt signaling pathways to promote the osteogenic differentiation of VSMCs[42]	
Resistin	↑ ET-1, VCAM-1, ICAM-1 and MCP-1, regulates inflammation levels[43-45]	Promote VC
	↑ ROS, IL-6, TNF-*α*, promote the proliferation, migration and dedifferentiation of VSMCs[46]	
TNF-*α*	↑ NF-*κ*B signaling promotes Msx2/Wnt signaling, which in turn promotes high expression of ALP, Runx2 and osterix[47]	Promote VC
	↑ Msx2, Wnt3a, Wnt7a and ALP, enhances Msx2/Wnt signaling and promotes calcification[48]	
	↑ NF-*κ*B signaling pathway, reduce ANKH expression, and reduce extracellular PPi levels[49]	
	↓ AMPK/PI3K/Akt signaling pathway, promote apoptosis of VSMCs[50]	
	↑ ROS, ↓ GPX1, SOD1, SOD2, PRDX1, the level of oxidative stress increases, promoting the osteogenic differentiation of VSMCs[51]	
IL-6	↑ HSP70, binds MGP and enhances BMP activity, thereby promoting vascular calcification[52]	Promote VC
	↑ BMP2, to induce osteogenic differentiation of VSMCs[53]	
Adiponectin	↑ the expression of AMPK-dependent Gas6 and inhibits the apoptosis of VSMCs[50]	Inhibit VC
	↓ endoplasmic reticulum stress, reduces apoptosis of VSMCs[54]	
	↑ AMPK phosphorylation and inhibit the osteogenic differentiation of VSMCs through the AMPK/mTOR pathway[55]	
	↓ STAT3 phosphorylation and nuclear transport, ↓ osterix, inhibit the osteogenic differentiation of VSMCs[56]	
	↓ ALP activity, osteocalcin secretion, Runx2 protein expression, inhibit the osteogenic differentiation of VSMCs through the AdipoR1/p38 signaling pathway[57]	
CTRP3	↓ TTP phosphorylation and promotes TTP binding to Runx2, accelerating Runx2 mRNA destabilization and degradation[58]	Inhibit VC
	↓ *β*-catenin nuclear translocation, inhibits the osteogenic differentiation of VSMCs[59]	
Omentin-1	↓ ALP activity, osteocalcin secretion, Runx2 expression, attenuates arterial calcification by promoting AMPK and Akt activation[60]	Inhibit VC
	↑ OPG, inhibits RANKL production through the PI3K/Akt pathway, improving arterial calcification[61]	
	↓ ALP, osteocalcin, inhibits the osteogenic differentiation of VSMCs through the PI3K/Akt pathway[62]	

研究进一步证实。

2.3 血管周围脂肪组织来源的间充质干细胞参与血管钙化 间充质干细胞 (MSCs) 是一种非造血干细胞亚群, 具有高度增殖和多谱系分化能力, 可以协调组织修复机制, 但其在VC过程中的作用仍未明确。有研究表明, 骨髓间充质干细胞来源的外泌体可以减轻慢性肾病中的VC[74], 骨髓来源间充质干细胞的条件培养基通过介导BMP2-Smad1/5/8信号通路减轻*β*-甘油磷酸钠诱导的VSMCs钙化[75]。但也有研究表明, 位于动脉外膜的Gli1$^+$ MSC类细胞是VSMCs的祖细胞, 是患有慢性肾病的*ApoE*$^{-/-}$小鼠内膜和中膜钙化中成骨细胞样细胞的主要来源[76]。

脂肪组织是MSCs的丰富来源, 有研究表明, 脂肪来源的间充质干细胞移植可以减轻腺嘌呤诱导的肾损伤并延缓VC的进展[77]。但对于PVAT而言, 单细胞RNA测序表明, miR-378a-3p可以调节PVAT衍生的间充质干细胞向平滑肌谱系分化[78]。血管周围脂肪来源的干细胞 (PV-ADSC) 中Clec11a$^+$亚群可能参与并调节PV-ADSC向平滑肌细胞表型的分化, 并参与血管重塑[79]。基质Gla蛋白 (MGP) 可以通过BMP2/SMAD途径调节PV-ADSC向平滑肌细胞分化, 增强新生内膜形成[80]。此外, 人PVAT的基质血管部分具有成软骨分化的潜力[81]。上述研究表明, PVAT来源的间充质干细胞可能直接分化为成骨细胞样细胞参与VC, 或首先向VSMCs谱系分化, 随后在慢性肾脏病等疾病条件下, 炎症、氧化应激、高磷酸盐水平等诱导其去分化并失去VSMCs标志物的表达。因此, PVAT来源的间充质干细胞可能是治疗VC的新靶点。

2.4 血管周围脂肪组织中肾素−血管紧张素−醛固酮系统异常激活参与血管钙化 肾素−血管紧张素−醛固酮系统 (renin-angiotensin-aldosterone system, RAAS) 异常激活在心血管疾病的进展中发挥重要作用, 阻断RAAS可以降低高血压、动脉粥样硬化、糖尿病和慢性肾脏病的发病率和死亡率。除肾素外, 所有RAAS成

分均在脂肪组织中表达[82]。研究表明, PVAT能够通过ACE2/Ang II途径生成大量血管紧张素1～7 (Ang 1～7), Ang 1～7能够激活Mas受体, 抑制ROS依赖性PI3K/Akt信号通路, 拮抗Ang II诱导的VSMCs增殖、迁移及炎症[83]。此外, Ang 1～7还能延缓VSMCs的成骨转变[84], 并抑制体内外醛固酮分泌[85]。脂肪细胞释放的瘦素能够上调肾上腺合成醛固酮的水平[86], 醛固酮是RAAS活化的代谢产物, 能够增强血管氧化应激, 促进血管炎症和细胞凋亡, 并且可以抑制AMP活化蛋白激酶 (AMPK) 介导的自噬, 从而促进高磷酸盐诱导的钙化[87]。此外, PVAT表达大量血管紧张素II-1型受体, 能将巨噬细胞转变为促炎表型, 参与局部炎症和基质金属蛋白酶活化[88], 升高局部Ang II水平[89]。同时, PVAT中局部RAAS的过度激活会诱发炎症反应, 改变PVAT分泌的脂肪因子水平[82]。因此, PVAT中RAAS可能在VC过程中发挥关键作用 (图1)。

3 基于PVAT的血管钙化药物治疗

3.1 PPARγ激动剂 PPARγ激动剂常用于治疗心血管疾病, 同时也是调节脂肪生成的关键因素。PPARγ缺乏会增加巨噬细胞中的TNF-α、IL-1β和IL-6分泌[90], 而PPARγ活化使单核细胞经历向M2抗炎巨噬细胞的转变[91]。研究表明, 低密度脂蛋白受体缺陷小鼠VSMCs选择性缺失核受体PPARγ后, 通过高胆固醇饮食致动脉粥样硬化, 会加速VC[92]。脂联素是PPARγ已知的下游靶标[93], 可通过TLR4信号通路抑制巨噬细胞活化从而减少脂肪组织炎症[94], 并能通过抑制JAK2/STAT3信号通路下调转录因子osterix的表达, 从而减轻β-甘油磷酸钠诱导的VSMCs钙化[56]。

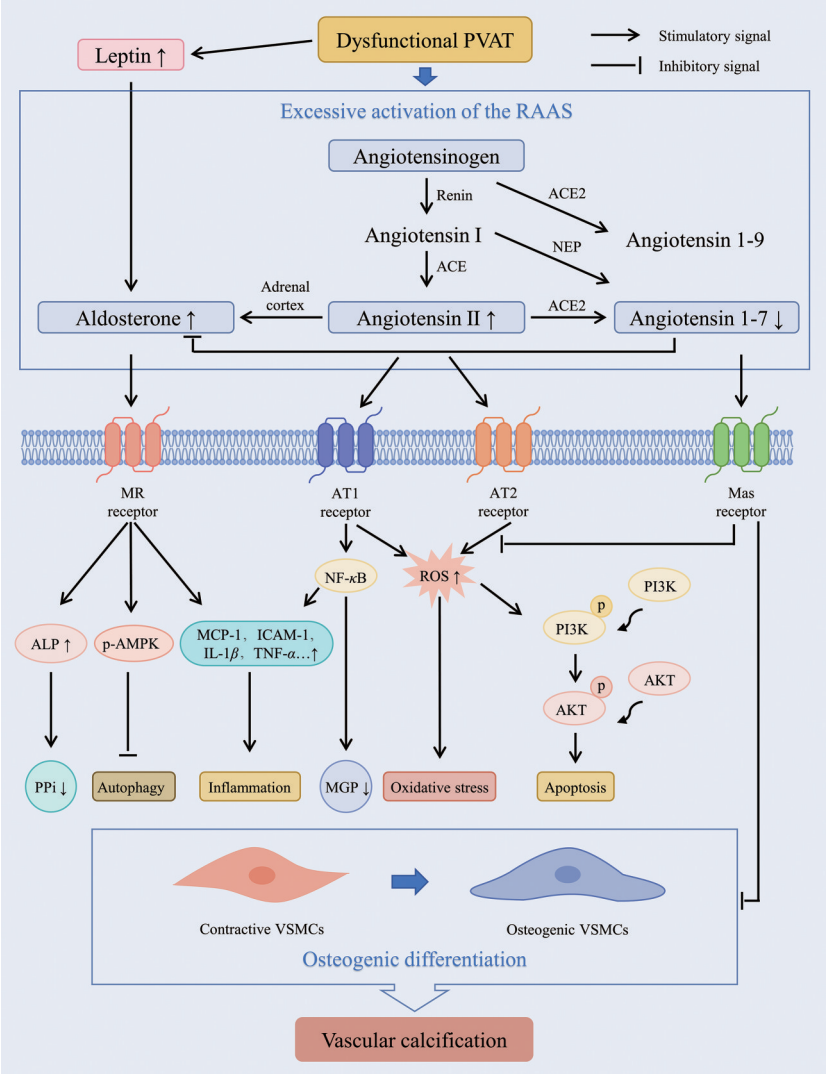

Figure 1 Excessive activation of the renin angiotensin aldosterone system in dysfunctional perivascular adipose tissue (PVAT) plays an important role in the progression of vascular calcification. ACE: Angiotensin-converting enzyme; NEP: Neutral endopeptidase; MR receptor: Mineralocorticoid receptor; AT1 receptor: Angiotensin II receptor type 1; AT2 receptor: Angiotensin II receptor type 2; p-AMPK: Phosphorylated AMP-activated protein kinase; PI3K: Phosphoinositide 3-kinase; Akt: Protein kinase B

噻唑烷二酮类药物吡格列酮和罗格列酮是临床常用的PPARγ激动剂。研究表明, 在高磷诱导的VSMCs钙化过程中, PPARγ表达下调, 而吡格列酮能通过PPARγ依赖性途径减少细胞外钙积累, 并增强VSMCs中Klotho的表达, 从而抑制VC[95]。罗格列酮可以通过PPARγ依赖性途径增强Klotho的表达, 来抑制Pi诱导的牛主动脉VSMCs钙化, 但其并不能减弱沉默Klotho及Klotho缺陷小鼠主动脉环的钙化[95,96]。因此, 需要进一步探索PPARγ信号传导在钙化过程中的作用。

3.2 AMPK激活剂 AMPK是一种丝氨酸/苏氨酸蛋白激酶, 可以通过上调IL-10和下调TNF-α、IL-6发挥抗炎作用, 而AMPKα1的缺失会减弱PVAT的抗收缩作用并减少脂联素的释放[97]。其中, 脂联素是PVAT通过AMPK对血管产生调节作用的主要介质[98]。二甲双胍是一线口服抗糖尿病药物, 可以在体内外以剂量和时间依赖性方式激活AMPK。在2型糖尿病患者中, 二甲双胍的使用与较低的冠状动脉及膝下动脉钙化评分独立相关[99,100]。长期二甲双胍治疗可以通过激活AMPKα1下调*ApoE*$^{-/-}$小鼠中的Runx2水平防止VC的进展[101]。恩格列净是一种钠−葡萄糖共转运蛋白2 (SGLT2)抑制剂, 能够激活AMPK调节NFR2/HO-1信号通路, 减少高磷酸盐诱导的VSMCs钙化, 并且抑制成骨标志物 (如Runx2)的表达, 从而减轻慢性肾脏病小鼠的VC[102]。

3.3 GLP-1受体激动剂 据报道, 脂肪组织分泌低水平的胰高血糖素样多肽1 (glucagon-like peptide-1, GLP-1), 从而减少脂质积累[103], 增加脂联素的表达[104], 并促进M2巨噬细胞极化[105]。GLP-1类似物也能抑制巨噬细胞和脂肪细胞的促炎活化[106]。研究表明, 利拉鲁肽可以通过抑制PCSK9/LDLR阻断同型半胱氨酸诱导的VSMCs增殖、迁移和表型转换[107], 并且能够抑制VSMCs中NF-κB的表达, 减弱晚期糖基化终产物诱导的冠状动脉平滑肌细胞表型转化[108]。艾塞那肽是一种用于治疗2型糖尿病的哺乳动物GLP-1受体激动剂, 可通过NF-κB/RANKL信号通路抑制人VSMCs的成骨分化和钙化[109]。

3.4 DPP-4抑制剂 二肽基肽酶-4 (dipeptidyl peptidase-4, DPP-4)与脂肪细胞炎症和胰岛素抵抗相关[110], 能够抑制VSMC的增殖和迁移, 并防止单核巨噬细胞浸润[111]。DPP-4抑制剂替格利汀可抑制动脉粥样硬化形成, 改变PVAT中的炎症表型[33,106]。一项随机对照试验显示, 吉格列汀能够降低VC标志物水平和肾损伤生物标志物水平[112]。此外, 吉格列汀通过下调Pit-1表达、抑制ROS生成、磷酸化PI3K/Akt和Wnt信号通路等途径减弱VC和VSMCs成骨分化[113]。西他列汀可以通过PI3K/Akt通路调节糖尿病大鼠脂肪组织中脂肪细胞因子的表达[114], 并且抑制NADPH氧化酶和NF-κB的活化, 降低RAGE的表达, 从而抑制动脉钙化的发生发展[115]。

3.5 褐变诱导剂 儿茶酚胺或冷暴露已被证明可以使白色脂肪组织发生褐变, 表达UCP-1并且在形态上类似于棕色脂肪组织[116,117]。但有研究报道, 儿茶酚胺在动物和人类中加剧动脉粥样硬化, 并且导致VSMCs异常增殖[118], 长期或间歇性暴露于寒冷会导致高血压、心脏肥大[119]。此外, 乳酸、肠道微生物群、甲状腺激素、鸢尾素、成纤维细胞生长因子21等也能够通过褐变将白色脂肪组织转换为棕色/米色脂肪组织[120], 但需考虑如何消除不良反应, 改善不良代谢结局。

白藜芦醇是在虎杖、葡萄等植物表皮中发现的一种天然多酚, 在改善能量代谢及相关代谢疾病中作用显著。据报道, 白藜芦醇是NAD依赖性脱乙酰酶沉默信息调节因子1 (Sirt1)激活剂, 能以Sirt1依赖性的方式促进白色脂肪发生褐变[121]。同时, 白藜芦醇还能通过调节Wnt/β-catenin信号传导, 改善高磷酸盐诱导的VSMCs对成骨细胞样细胞的转分化和动脉中膜钙化[122]。因此, 白藜芦醇可能是通过诱导PVAT褐变治疗VC有潜力的候选药物之一。

3.6 RAAS抑制剂 RAAS抑制剂可以靶向脂肪组织, 对代谢和心血管系统发挥有益作用。研究表明, 低剂量螺内酯可以改善脂肪组织炎症和细胞凋亡[123], 并且能通过下调Pit-1抑制VSMCs的成骨转化[124], 减轻慢性肾脏病小鼠VC及高磷血症, 改善血液透析患者的钙化倾向[125]。血管紧张素II受体阻滞剂氯沙坦通过增加PVAT中棕榈酸甲酯的生物合成发挥抗高血压作用[126]。此外, 氯沙坦还能够抑制VC大鼠BMP2、Runx2表达及主动脉VSMCs凋亡, 从而减轻VC[127]。

4 总结与展望

由于VC形成机制复杂且尚未完全阐明, 尽管目前已经出现一些VC的治疗药物, 如他汀类药物、磷酸盐结合剂、拟钙剂、肌醇六磷酸酯等, 但疗效不佳[128]。

PVAT在血管结构和功能的调节中发挥重要作用, 其功能障碍是心血管疾病的主要危险因素之一, 与VC的发生发展密切相关。在生理条件下, PVAT具有抗收缩、抗炎和抗氧化功能, 参与维持血管稳态。在慢性肾脏病、糖尿病等病理条件下, PVAT可以通过释放脂肪因子, 发生表型转换及RAAS异常激活等, 参与VC过程, 因此有望成为VC的防治靶点 (图2)。此外, 一些药物在体外和动物实验中已被证明对PVAT发挥作用, 如二甲双胍通过抑制PVAT炎症调节脂肪因子的表达, 从而改善内皮功能障碍[129]; 阿托伐他汀能够减

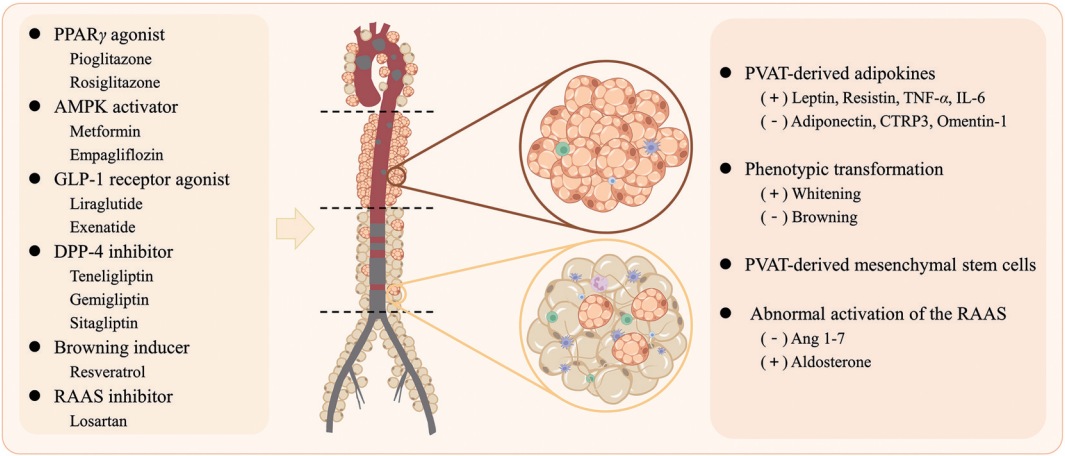

Figure 2 The role of perivascular adipose tissue (PVAT) in the regulation of vascular calcification

轻PVAT炎症, 通过促进PVAT释放血管松弛因子恢复高血压模型中丧失的有益的抗收缩特性[130], 且均有助于缓解VC[131,132], 但仍需要更大规模的临床试验加以证实。

作者贡献: 吴冬雪负责整体写作; 徐明负责修改。
利益冲突: 本文所有作者声明不存在利益冲突关系。

References

[1] Johnson RC, Leopold JA, Loscalzo J. Vascular calcification: pathobiological mechanisms and clinical implications [J]. Circ Res, 2006, 99: 1044-1059.

[2] Leopold JA. Vascular calcification: mechanisms of vascular smooth muscle cell calcification [J]. Trends Cardiovasc Med, 2015, 25: 267-274.

[3] Hruska KA, Mathew S, Saab G. Bone morphogenetic proteins in vascular calcification [J]. Circ Res, 2005, 97: 105-114.

[4] Millan A, Lanzer P, Sorribas V. The thermodynamics of medial vascular calcification [J]. Front Cell Dev Biol, 2021, 9: 633465.

[5] Lei Y, Sinha A, Nosoudi N, et al. Hydroxyapatite and calcified elastin induce osteoblast-like differentiation in rat aortic smooth muscle cells [J]. Exp Cell Res, 2014, 323: 198-208.

[6] Villa-Bellosta R, O'Neill WC. Pyrophosphate deficiency in vascular calcification [J]. Kidney Int, 2018, 93: 1293-1297.

[7] Wilson PW, Kauppila LI, O'Donnell CJ, et al. Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality [J]. Circulation, 2001, 103: 1529-1534.

[8] Long JZ, Svensson KJ, Tsai L, et al. A smooth muscle-like origin for beige adipocytes [J]. Cell Metab, 2014, 19: 810-820.

[9] Chang L, Villacorta L, Li R, et al. Loss of perivascular adipose tissue on peroxisome proliferator-activated receptor-gamma deletion in smooth muscle cells impairs intravascular thermoregulation and enhances atherosclerosis [J]. Circulation, 2012, 126: 1067-1078.

[10] Angueira AR, Sakers AP, Holman CD, et al. Defining the lineage of thermogenic perivascular adipose tissue [J]. Nat Metab, 2021, 3: 469-484.

[11] Lehman SJ, Massaro JM, Schlett CL, et al. Peri-aortic fat, cardiovascular disease risk factors, and aortic calcification: the Framingham Heart Study [J]. Atherosclerosis, 2010, 210: 656-661.

[12] Shields KJ, El Khoudary SR, Ahearn JM, et al. Association of aortic perivascular adipose tissue density with aortic calcification in women with systemic lupus erythematosus [J]. Atherosclerosis, 2017, 262: 55-61.

[13] Nagaraj N, Matthews KA, Shields KJ, et al. Complement proteins and arterial calcification in middle aged women: cross-sectional effect of cardiovascular fat. The SWAN Cardiovascular Fat Ancillary Study [J]. Atherosclerosis, 2015, 243: 533-539.

[14] Kaur R, Singh R. Mechanistic insights into CKD-MBD-related vascular calcification and its clinical implications [J]. Life Sci, 2022, 311: 121148.

[15] Henaut L, Sanchez-Nino MD, Aldamiz-Echevarria Castillo G, et al. Targeting local vascular and systemic consequences of inflammation on vascular and cardiac valve calcification [J]. Expert Opin Ther Targets, 2016, 20: 89-105.

[16] Leopold JA. Cellular mechanisms of aortic valve calcification [J]. Circ Cardiovasc Interv, 2012, 5: 605-614.

[17] Qian Y, Li L, Sun Z, et al. A multi-omics view of the complex mechanism of vascular calcification [J]. Biomed Pharmacother, 2021, 135: 111192.

[18] Buffolo F, Monticone S, Camussi G, et al. Role of extracellular vesicles in the pathogenesis of vascular damage [J]. Hypertension, 2022, 79: 863-873.

[19] Shi X, Gao J, Lv Q, et al. Calcification in atherosclerotic plaque vulnerability: friend or foe? [J]. Front Physiol, 2020, 11: 56.

[20] Hutcheson JD, Goettsch C, Bertazzo S, et al. Genesis and growth of extracellular-vesicle-derived microcalcification in atherosclerotic

plaques [J]. Nat Mater, 2016, 15: 335-343.

[21] Ribeiro-Silva JC, Nolasco P, Krieger JE, et al. Dynamic crosstalk between vascular smooth muscle cells and the aged extracellular matrix [J]. Int J Mol Sci, 2021, 22: 10175.

[22] Zhao Y, Sun Z, Li L, et al. Role of collagen in vascular calcification [J]. J Cardiovasc Pharmacol, 2022, 80: 769-778.

[23] Bellasi A, Ferramosca E, Ratti C, et al. Cardiac valve calcification is a marker of vascular disease in prevalent hemodialysis patients [J]. J Nephrol, 2012, 25: 211-218.

[24] Chen HY, Engert JC, Thanassoulis G. Risk factors for valvular calcification [J]. Curr Opin Endocrinol Diabetes Obes, 2019, 26: 96-102.

[25] Vieceli Dalla Sega F, Fortini F, Severi P, et al. Cardiac calcifications: phenotypes, mechanisms, clinical and prognostic implications [J]. Biology (Basel), 2022, 11: 414.

[26] Kessler JR, Bluemn TS, DeCero SA, et al. Exploring molecular profiles of calcification in aortic vascular smooth muscle cells and aortic valvular interstitial cells [J]. J Mol Cell Cardiol, 2023, 183: 1-13.

[27] Queiroz M, Sena CM. Perivascular adipose tissue in age-related vascular disease [J]. Ageing Res Rev, 2020, 59: 101040.

[28] Chatterjee TK, Stoll LL, Denning GM, et al. Proinflammatory phenotype of perivascular adipocytes: influence of high-fat feeding [J]. Circ Res, 2009, 104: 541-549.

[29] Gil-Ortega M, Somoza B, Huang Y, et al. Regional differences in perivascular adipose tissue impacting vascular homeostasis [J]. Trends Endocrinol Metab, 2015, 26: 367-375.

[30] Fitzgibbons TP, Kogan S, Aouadi M, et al. Similarity of mouse perivascular and brown adipose tissues and their resistance to diet-induced inflammation [J]. Am J Physiol Heart Circ Physiol, 2011, 301: H1425-H1437.

[31] Hu H, Garcia-Barrio M, Jiang ZS, et al. Roles of perivascular adipose tissue in hypertension and atherosclerosis [J]. Antioxid Redox Signal, 2021, 34: 736-749.

[32] Horimatsu T, Kim HW, Weintraub NL. The role of perivascular adipose tissue in non-atherosclerotic vascular disease [J]. Front Physiol, 2017, 8: 969.

[33] Galvez-Prieto B, Somoza B, Gil-Ortega M, et al. Anticontractile effect of perivascular adipose tissue and leptin are reduced in hypertension [J]. Front Pharmacol, 2012, 3: 103.

[34] Longenecker CT, Jiang Y, Yun CH, et al. Perivascular fat, inflammation, and cardiovascular risk in HIV-infected patients on antiretroviral therapy [J]. Int J Cardiol, 2013, 168: 4039-4045.

[35] Hanley C, Shields KJ, Matthews KA, et al. Associations of cardiovascular fat radiodensity and vascular calcification in midlife women: the SWAN cardiovascular fat ancillary study [J]. Atherosclerosis, 2018, 279: 114-121.

[36] Shi H, Goo B, Kim D, et al. Perivascular adipose tissue promotes vascular dysfunction in murine lupus [J]. Front Immunol, 2023, 14: 1095034.

[37] Sowka A, Dobrzyn P. Role of perivascular adipose tissue-derived adiponectin in vascular homeostasis [J]. Cells, 2021, 10: 1485.

[38] Loffreda S, Yang SQ, Lin HZ, et al. Leptin regulates proinflammatory immune responses [J]. FASEB J, 1998, 12: 57-65.

[39] Santos-Alvarez J, Goberna R, Sanchez-Margalet V. Human leptin stimulates proliferation and activation of human circulating monocytes [J]. Cell Immunol, 1999, 194: 6-11.

[40] Bouloumie A, Marumo T, Lafontan M, et al. Leptin induces oxidative stress in human endothelial cells [J]. FASEB J, 1999, 13: 1231-1238.

[41] Zeadin M, Butcher M, Werstuck G, et al. Effect of leptin on vascular calcification in apolipoprotein E-deficient mice [J]. Arterioscler Thromb Vasc Biol, 2009, 29: 2069-2075.

[42] Liu GY, Liang QH, Cui RR, et al. Leptin promotes the osteoblastic differentiation of vascular smooth muscle cells from female mice by increasing RANKL expression [J]. Endocrinology, 2014, 155: 558-567.

[43] Jung HS, Park KH, Cho YM, et al. Resistin is secreted from macrophages in atheromas and promotes atherosclerosis [J]. Cardiovasc Res, 2006, 69: 76-85.

[44] Verma S, Li SH, Wang CH, et al. Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction [J]. Circulation, 2003, 108: 736-740.

[45] Kawanami D, Maemura K, Takeda N, et al. Direct reciprocal effects of resistin and adiponectin on vascular endothelial cells: a new insight into adipocytokine-endothelial cell interactions [J]. Biochem Biophys Res Commun, 2004, 314: 415-419.

[46] Raghuraman G, Zuniga MC, Yuan H, et al. PKCepsilon mediates resistin-induced NADPH oxidase activation and inflammation leading to smooth muscle cell dysfunction and intimal hyperplasia [J]. Atherosclerosis, 2016, 253: 29-37.

[47] Lee HL, Woo KM, Ryoo HM, et al. Tumor necrosis factor-alpha increases alkaline phosphatase expression in vascular smooth muscle cells *via* MSX2 induction [J]. Biochem Biophys Res Commun, 2010, 391: 1087-1092.

[48] Al-Aly Z, Shao JS, Lai CF, et al. Aortic Msx2-Wnt calcification cascade is regulated by TNF-alpha-dependent signals in diabetic $Ldlr^{-/-}$ mice [J]. Arterioscler Thromb Vasc Biol, 2007, 27: 2589-2596.

[49] Zhao G, Xu MJ, Zhao MM, et al. Activation of nuclear factor-kappa B accelerates vascular calcification by inhibiting ankylosis protein homolog expression [J]. Kidney Int, 2012, 82: 34-44.

[50] Son BK, Akishita M, Iijima K, et al. Adiponectin antagonizes stimulatory effect of tumor necrosis factor-alpha on vascular smooth muscle cell calcification: regulation of growth arrest-specific gene 6-mediated survival pathway by adenosine 5'-monophosphate-activated protein kinase [J]. Endocrinology, 2008, 149: 1646-1653.

[51] Agharazii M, St-Louis R, Gautier-Bastien A, et al. Inflammatory

cytokines and reactive oxygen species as mediators of chronic kidney disease-related vascular calcification [J]. Am J Hypertens, 2015, 28: 746-755.

[52] Yao Y, Watson AD, Ji S, et al. Heat shock protein 70 enhances vascular bone morphogenetic protein-4 signaling by binding matrix Gla protein [J]. Circ Res, 2009, 105: 575-584.

[53] Sun M, Chang Q, Xin M, et al. Endogenous bone morphogenetic protein 2 plays a role in vascular smooth muscle cell calcification induced by interleukin 6 *in vitro* [J]. Int J Immunopathol Pharmacol, 2017, 30: 227-237.

[54] Lu Y, Bian Y, Wang Y, et al. Globular adiponectin reduces vascular calcification *via* inhibition of ER-stress-mediated smooth muscle cell apoptosis [J]. Int J Clin Exp Pathol, 2015, 8: 2545-2554.

[55] Zhan JK, Wang YJ, Wang Y, et al. Adiponectin attenuates the osteoblastic differentiation of vascular smooth muscle cells through the AMPK/mTOR pathway [J]. Exp Cell Res, 2014, 323: 352-358.

[56] Lu Y, Ma Y, Wang R, et al. Adiponectin inhibits vascular smooth muscle cell calcification induced by beta-glycerophosphate through JAK2/STAT3 signaling pathway [J]. J Biosci, 2019, 44: 86.

[57] Luo XH, Zhao LL, Yuan LQ, et al. Development of arterial calcification in adiponectin-deficient mice: adiponectin regulates arterial calcification [J]. J Bone Miner Res, 2009, 24: 1461-1468.

[58] Li Y, Wang W, Chao Y, et al. CTRP13 attenuates vascular calcification by regulating Runx2 [J]. FASEB J, 2019, 33: 9627-9637.

[59] Liu D, Cui X, Lu R, et al. CTRP3 is a coronary artery calcification biomarker and protects against vascular calcification by inhibiting beta-catenin nuclear translocation to prevent vascular smooth muscle cell osteogenic differentiation [J]. J Cardiol, 2022, 79: 551-558.

[60] Xu F, Li FX, Lin X, et al. Adipose tissue-derived omentin-1 attenuates arterial calcification *via* AMPK/Akt signaling pathway [J]. Aging (Albany NY), 2019, 11: 8760-8776.

[61] Xie H, Xie PL, Wu XP, et al. Omentin-1 attenuates arterial calcification and bone loss in osteoprotegerin-deficient mice by inhibition of RANKL expression [J]. Cardiovasc Res, 2011, 92: 296-306.

[62] Duan XY, Xie PL, Ma YL, et al. Omentin inhibits osteoblastic differentiation of calcifying vascular smooth muscle cells through the PI3K/Akt pathway [J]. Amino Acids, 2011, 41: 1223-1231.

[63] Reis JP, Loria CM, Lewis CE, et al. Association between duration of overall and abdominal obesity beginning in young adulthood and coronary artery calcification in middle age [J]. JAMA, 2013, 310: 280-288.

[64] Kim JK, Park MJ, Song YR, et al. Vitamin D: a possible modifying factor linking obesity to vascular calcification in hemodialysis patients [J]. Nutr Metab (Lond), 2017, 14: 27.

[65] Boucher JM, Ryzhova L, Harrington A, et al. Pathological conversion of mouse perivascular adipose tissue by Notch activation [J]. Arterioscler Thromb Vasc Biol, 2020, 40: 2227-2243.

[66] Pan XX, Yao KL, Yang YF, et al. Senescent T cell induces brown adipose tissue "whitening" *via* secreting IFN-gamma [J]. Front Cell Dev Biol, 2021, 9: 637424.

[67] Lapa C, Arias-Loza P, Hayakawa N, et al. Whitening and impaired glucose utilization of brown adipose tissue in a rat model of type 2 diabetes mellitus [J]. Sci Rep, 2017, 7: 16795.

[68] Cheng CK, Ding H, Jiang M, et al. Perivascular adipose tissue: fine-tuner of vascular redox status and inflammation [J]. Redox Biol, 2023, 62: 102683.

[69] Persson P, Marchetti M, Friederich-Persson M. Browning of perivascular adipose tissue prevents vascular dysfunction and reduces hypertension in angiotensin II-infused mice [J]. Am J Physiol Regul Integr Comp Physiol, 2023, 325: R290-R298.

[70] Adachi Y, Ueda K, Nomura S, et al. Beiging of perivascular adipose tissue regulates its inflammation and vascular remodeling [J]. Nat Commun, 2022, 13: 5117.

[71] Huang CL, Huang YN, Yao L, et al. Thoracic perivascular adipose tissue inhibits VSMC apoptosis and aortic aneurysm formation in mice *via* the secretome of browning adipocytes [J]. Acta Pharmacol Sin, 2023, 44: 345-355.

[72] Jadidi M, Poulson W, Aylward P, et al. Calcification prevalence in different vascular zones and its association with demographics, risk factors, and morphometry [J]. Am J Physiol Heart Circ Physiol, 2021, 320: H2313-H2323.

[73] Li RM, Chen SQ, Zeng NX, et al. Browning of abdominal aorta perivascular adipose tissue inhibits adipose tissue inflammation [J]. Metab Syndr Relat Disord, 2017, 15: 450-457.

[74] Liu Y, Guo Y, Bao S, et al. Bone marrow mesenchymal stem cell-derived exosomal microRNA-381-3p alleviates vascular calcification in chronic kidney disease by targeting NFAT5 [J]. Cell Death Dis, 2022, 13: 278.

[75] Wang S, Hu S, Wang J, et al. Conditioned medium from bone marrow-derived mesenchymal stem cells inhibits vascular calcification through blockade of the BMP2-Smad1/5/8 signaling pathway [J]. Stem Cell Res Ther, 2018, 9: 160.

[76] Kramann R, Goettsch C, Wongboonsin J, et al. Adventitial MSC-like cells are progenitors of vascular smooth muscle cells and drive vascular calcification in chronic kidney disease [J]. Cell Stem Cell, 2016, 19: 628-642.

[77] Yokote S, Katsuoka Y, Yamada A, et al. Effect of adipose-derived mesenchymal stem cell transplantation on vascular calcification in rats with adenine-induced kidney disease [J]. Sci Rep, 2017, 7: 14036.

[78] Gu W, Nowak WN, Xie Y, et al. Single-cell RNA-sequencing and metabolomics analyses reveal the contribution of perivascular adipose tissue stem cells to vascular remodeling [J]. Arterioscler Thromb Vasc Biol, 2019, 39: 2049-2066.

[79] Xie Y, Ji Y, Lu Y, et al. Distinct characteristics between perivascular and subcutaneous adipose-derived stem cells [J]. Diabetes, 2022, 71: 321-328.

[80] Ni H, Liu C, Chen Y, et al. MGP regulates perivascular adipose-derived stem cells differentiation toward smooth muscle cells *via* BMP2/SMAD pathway enhancing neointimal formation [J]. Cell Transplant, 2022, 31: 9636897221075747.

[81] Scott SS, Yang X, Robich M, et al. Differentiation capacity of human aortic perivascular adipose progenitor cells [J]. J Vis Exp, 2019, (145): 10.3791/59337.

[82] Balakumar P, Alqahtani A, Khan NA, et al. The physiologic and physiopathologic roles of perivascular adipose tissue and its interactions with blood vessels and the renin-angiotensin system [J]. Pharmacol Res, 2021, 173: 105890.

[83] Zhang F, Ren X, Zhao M, et al. Angiotensin-(1-7) abrogates angiotensin II-induced proliferation, migration and inflammation in VSMCs through inactivation of ROS-mediated PI3K/Akt and MAPK/ERK signaling pathways [J]. Sci Rep, 2016, 6: 34621.

[84] Sui YB, Chang JR, Chen WJ, et al. Angiotensin-(1-7) inhibits vascular calcification in rats [J]. Peptides, 2013, 42: 25-34.

[85] Shefer G, Marcus Y, Knoll E, et al. Angiotensin 1-7 is a negative modulator of aldosterone secretion *in vitro* and *in vivo* [J]. Hypertension, 2016, 68: 378-384.

[86] Huby AC, Antonova G, Groenendyk J, et al. Adipocyte-derived hormone leptin is a direct regulator of aldosterone secretion, which promotes endothelial dysfunction and cardiac fibrosis [J]. Circulation, 2015, 132: 2134-2145.

[87] Gao JW, He WB, Xie CM, et al. Aldosterone enhances high phosphate-induced vascular calcification through inhibition of AMPK-mediated autophagy [J]. J Cell Mol Med, 2020, 24: 13648-13659.

[88] Barp CG, Bonaventura D, Assreuy J. NO, ROS, RAS, and PVAT: more than a soup of letters [J]. Front Physiol, 2021, 12: 640021.

[89] Galvez-Prieto B, Bolbrinker J, Stucchi P, et al. Comparative expression analysis of the renin-angiotensin system components between white and brown perivascular adipose tissue [J]. J Endocrinol, 2008, 197: 55-64.

[90] Heming M, Gran S, Jauch SL, et al. Peroxisome proliferator-activated receptor-gamma modulates the response of macrophages to lipopolysaccharide and glucocorticoids [J]. Front Immunol, 2018, 9: 893.

[91] Daniel B, Nagy G, Czimmerer Z, et al. The nuclear receptor PPARgamma controls progressive macrophage polarization as a ligand-insensitive epigenomic ratchet of transcriptional memory [J]. Immunity, 2018, 49: 615-626.e6.

[92] Woldt E, Terrand J, Mlih M, et al. The nuclear hormone receptor PPARgamma counteracts vascular calcification by inhibiting Wnt5a signalling in vascular smooth muscle cells [J]. Nat Commun, 2012, 3: 1077.

[93] Antonopoulos AS, Margaritis M, Coutinho P, et al. Reciprocal effects of systemic inflammation and brain natriuretic peptide on adiponectin biosynthesis in adipose tissue of patients with ischemic heart disease [J]. Arterioscler Thromb Vasc Biol, 2014, 34: 2151-2159.

[94] Abe M, Matsuda M, Kobayashi H, et al. Effects of statins on adipose tissue inflammation: their inhibitory effect on MyD88-independent IRF3/IFN-beta pathway in macrophages [J]. Arterioscler Thromb Vasc Biol, 2008, 28: 871-877.

[95] Cheng L, Zhang L, Yang J, et al. Activation of peroxisome proliferator-activated receptor gamma inhibits vascular calcification by upregulating Klotho [J]. Exp Ther Med, 2017, 13: 467-474.

[96] Liu L, Liu Y, Zhang Y, et al. High phosphate-induced downregulation of PPARgamma contributes to CKD-associated vascular calcification [J]. J Mol Cell Cardiol, 2018, 114: 264-275.

[97] Almabrouk TAM, Ugusman AB, Katwan OJ, et al. Deletion of AMPKalpha1 attenuates the anticontractile effect of perivascular adipose tissue (PVAT) and reduces adiponectin release [J]. Br J Pharmacol, 2017, 174: 3398-3410.

[98] Almabrouk TA, Ewart MA, Salt IP, et al. Perivascular fat, AMP-activated protein kinase and vascular diseases [J]. Br J Pharmacol, 2014, 171: 595-617.

[99] Lu Y, Wang Y, Weng T, et al. Association between metformin use and coronary artery calcification in type 2 diabetic patients [J]. J Diabetes Res, 2019, 2019: 9484717.

[100] Mary A, Hartemann A, Liabeuf S, et al. Association between metformin use and below-the-knee arterial calcification score in type 2 diabetic patients [J]. Cardiovasc Diabetol, 2017, 16: 24.

[101] Cai Z, Ding Y, Zhang M, et al. Ablation of adenosine monophosphate-activated protein kinase alpha1 in vascular smooth muscle cells promotes diet-induced atherosclerotic calcification *in vivo* [J]. Circ Res, 2016, 119: 422-433.

[102] Lu CW, Lee CJ, Hsieh YJ, et al. Empagliflozin attenuates vascular calcification in mice with chronic kidney disease by regulating the NFR2/HO-1 anti-inflammatory pathway through AMPK activation [J]. Int J Mol Sci, 2023, 24: 10016.

[103] Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus [J]. Nat Rev Endocrinol, 2012, 8: 728-742.

[104] Xiong X, Lu W, Qin X, et al. Downregulation of the GLP-1/CREB/adiponectin pathway is partially responsible for diabetes-induced dysregulated vascular tone and VSMC dysfunction [J]. Biomed Pharmacother, 2020, 127: 110218.

[105] Qi XY, Qu SL, Xiong WH, et al. Perivascular adipose tissue (PVAT) in atherosclerosis: a double-edged sword [J]. Cardiovasc Diabetol, 2018, 17: 134.

[106] Salim HM, Fukuda D, Higashikuni Y, et al. Teneligliptin, a dipeptidyl peptidase-4 inhibitor, attenuated pro-inflammatory phenotype of perivascular adipose tissue and inhibited

atherogenesis in normoglycemic apolipoprotein-E-deficient mice [J]. Vascul Pharmacol, 2017, 96-98: 19-25.

[107] Ji J, Feng M, Niu X, et al. Liraglutide blocks the proliferation, migration and phenotypic switching of Homocysteine (Hcy) -induced vascular smooth muscle cells (VSMCs) by suppressing proprotein convertase subtilisin kexin9 (PCSK9)/low-density lipoprotein receptor (LDLR) [J]. Bioengineered, 2021, 12: 8057-8066.

[108] Horton JD, Cohen JC, Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism [J]. J Lipid Res, 2009, 50 Suppl: S172-S177.

[109] Zhan JK, Tan P, Wang YJ, et al. Exenatide can inhibit calcification of human VSMCs through the NF-kappaB/RANKL signaling pathway [J]. Cardiovasc Diabetol, 2014, 13: 153.

[110] Shin J, Fukuhara A, Onodera T, et al. Regulation of dipeptidyl peptidase-4, its substrate chemokines, and their receptors in adipose tissue of *ob*/*ob* mice [J]. Horm Metab Res, 2017, 49: 380-387.

[111] Cao F, Wu K, Zhu YZ, et al. Roles and mechanisms of dipeptidyl peptidase 4 inhibitors in vascular aging [J]. Front Endocrinol (Lausanne), 2021, 12: 731273.

[112] Trakarnvanich T, Satirapoj B, Suraamornkul S, et al. Effect of dipeptidyl peptidase-4 (DPP-4) inhibition on biomarkers of kidney injury and vascular calcification in diabetic kidney disease: a randomized controlled trial [J]. J Diabetes Res, 2021, 2021: 7382620.

[113] Choi SY, Ryu HM, Oh EJ, et al. Dipeptidyl peptidase-4 inhibitor gemigliptin protects against vascular calcification in an experimental chronic kidney disease and vascular smooth muscle cells [J]. PLoS One, 2017, 12: e0180393.

[114] Wu QM, Ni HX, Lu X. Changes of adipocytokine expression after diabetic rats received sitagliptin and the molecular mechanism [J]. Asian Pac J Trop Med, 2016, 9: 893-897.

[115] Lin CP, Huang PH, Chen CY, et al. Sitagliptin attenuates arterial calcification by downregulating oxidative stress-induced receptor for advanced glycation end products in LDLR knockout mice [J]. Sci Rep, 2021, 11: 17851.

[116] Sidossis L, Kajimura S. Brown and beige fat in humans: thermogenic adipocytes that control energy and glucose homeostasis [J]. J Clin Invest, 2015, 125: 478-486.

[117] Lim S, Honek J, Xue Y, et al. Cold-induced activation of brown adipose tissue and adipose angiogenesis in mice [J]. Nat Protoc, 2012, 7: 606-615.

[118] Wu D, Yang CM, Lau YT, et al. Mechanism of catecholamine-induced proliferation of vascular smooth muscle cells [J]. Circulation, 1998, 98: 94.

[119] Sun Z. Cardiovascular responses to cold exposure [J]. Front Biosci (Elite Ed), 2010, 2: 495-503.

[120] Ghesmati Z, Rashid M, Fayezi S, et al. An update on the secretory functions of brown, white, and beige adipose tissue: towards therapeutic applications [J]. Rev Endocr Metab Disord, 2024, 25: 279-308.

[121] Li Z, Zhang Z, Ke L, et al. Resveratrol promotes white adipocytes browning and improves metabolic disorders in Sirt1-dependent manner in mice [J]. FASEB J, 2020, 34: 4527-4539.

[122] Huang X, Wang Y, Qiu Y, et al. Resveratrol ameliorates high-phosphate-induced VSMCs to osteoblast-like cells transdifferentiation and arterial medial calcification in CKD through regulating Wnt/beta-catenin signaling [J]. Eur J Pharmacol, 2022, 925: 174953.

[123] Areloegbe SE, Peter MU, Oyeleke MB, et al. Low-dose spironolactone ameliorates adipose tissue inflammation and apoptosis in letrozole-induced PCOS rat model [J]. BMC Endocr Disord, 2022, 22: 224.

[124] Wang P, Quan Z, Luo D, et al. Spironolactone dose-dependently alleviates the calcification of aortic rings cultured in hyperphosphatemic medium with or without hyperglycemia by suppressing phenotypic transition of VSMCs through downregulation of Pit-1 [J]. Mol Med Rep, 2019, 19: 3622-3632.

[125] Hammer F, Buehling SS, Masyout J, et al. Protective effects of spironolactone on vascular calcification in chronic kidney disease [J]. Biochem Biophys Res Commun, 2021, 582: 28-34.

[126] Liu CH, Hsu HJ, Tseng TL, et al. COMT-catalyzed palmitic acid methyl ester biosynthesis in perivascular adipose tissue and its potential role against hypertension [J]. J Pharmacol Exp Ther, 2020, 373: 175-183.

[127] Li M, Wu P, Shao J, et al. Losartan inhibits vascular calcification by suppressing the BMP2 and Runx2 expression in rats *in vivo* [J]. Cardiovasc Toxicol, 2016, 16: 172-181.

[128] Singh A, Tandon S, Tandon C. An update on vascular calcification and potential therapeutics [J]. Mol Biol Rep, 2021, 48: 887-896.

[129] Sun Y, Li J, Xiao N, et al. Pharmacological activation of AMPK ameliorates perivascular adipose/endothelial dysfunction in a manner interdependent on AMPK and SIRT1 [J]. Pharmacol Res, 2014, 89: 19-28.

[130] Sanna F, Margaritis M, Antoniades C. Perivascular adipose tissue as an endocrine organ: the role of statins [J]. Curr Pharm Des, 2017. DOI: 10.2174/1381612823666170926133843.

[131] Phadwal K, Koo E, Jones RA, et al. Metformin protects against vascular calcification through the selective degradation of Runx2 by the p62 autophagy receptor [J]. J Cell Physiol, 2022, 237: 4303-4316.

[132] Li H, Tao HR, Hu T, et al. Atorvastatin reduces calcification in rat arteries and vascular smooth muscle cells [J]. Basic Clin Pharmacol Toxicol, 2010, 107: 798-802.