

专家共识

血管钙化研究进展和临床实践的共识与争议

黄辉^{1,*}, 张爱华^{2,*}, 陈靖^{3,*}, 袁凌青^{4,*}

¹中山大学附属第八医院, 深圳 518033; ²首都医科大学宣武医院, 北京 100053; ³复旦大学附属华山医院, 上海 200040; ⁴中南大学湘雅二医院, 长沙 410011

摘要: 血管钙化是一个主动的、活跃的, 由众多因子参与调控的复杂病理过程。血管钙化可累及多个器官、系统, 与心血管疾病、慢性肾脏病等疾病的发生率和死亡率升高密切相关, 严重影响人民健康, 因此日益受到重视。目前, 血管钙化的发病机制学说及临床实践不断完善, 主要包括钙磷失衡学说、血管平滑肌细胞转分化学说、骨稳态失衡学说、表观遗传学调控学说、炎症学说、细胞外基质学说、新细胞命运学说等, 但仍存在许多未解之谜。由于血管钙化发生和发展涉及多个器官、系统, 为总结近年来有关血管钙化的多个学科进展, 本专家共识由国内从事血管钙化研究的临床医生和基础研究专家集体撰写, 旨在从流行病学、发病机制以及防治方面系统阐述血管钙化的最新研究进展、治疗共识与争议, 从而为此领域的深入研究提供理论依据和临床启示。

关键词: 血管钙化; 流行病学; 机制进展; 临床实践共识与争议

Consensus and controversy on research progress and clinical practice of vascular calcification

HUANG Hui^{1,*}, ZHANG Ai-Hua^{2,*}, CHEN Jing^{3,*}, YUAN Ling-Qing^{4,*}

¹The Eight Affiliated Hospital, Sun Yat-sen University, Shenzhen 518033, China; ²Xuanwu Hospital of Capital Medical University, Beijing 100053, China; ³Huashan Hospital, Fudan University, Shanghai 200040, China; ⁴The Second Xiangya Hospital of Central South University, Changsha 410011, China

Abstract: Vascular calcification is an active and complex pathological process regulated by several factors. Vascular calcification is closely related to the incidence and mortality of the cardiovascular disease, chronic kidney disease and other diseases, which affects multiple organs and systems, thus affecting people's health. Therefore, more and more attention is paid to vascular calcification. At present, the pathogenesis and clinical practice of vascular calcification have been continuously improved, which mainly includes calcium and phosphorus imbalance theory, vascular smooth muscle cell transdifferentiation theory, bone homeostasis imbalance theory, epigenetic regulation theory, inflammation theory, extracellular matrix theory, new cell fate theory and so on. However, there are still many unsolved problems. Since the occurrence and development of vascular calcification affect multiple organs and systems, this expert consensus gathered clinicians and basic research experts engaged in the study of vascular calcification in order to summarize the progress of various disciplines related to vascular calcification in recent years. The purpose of this consensus is to systematically summarize the latest research progress, treatment consensus and controversy of vascular calcification from the aspects of epidemiology, pathogenesis, prevention and treatment, so as to provide theoretical basis and clinical enlightenment for in-depth research in this field.

Key words: vascular calcification; epidemiology; mechanism progress; consensus and controversy in clinical practice

*Corresponding authors. HUANG Hui: Tel: +86-755-83982222, E-mail: huangh8@mail.sysu.edu.cn; ZHANG Ai-Hua: E-mail: zhangaihua0982@sina.com; CHEN Jing: E-mail: chenjing1998@fudan.edu.cn; YUAN Ling-Qing: +86-731-85295146, E-mail: allenylq@csu.edu.cn

前言

血管钙化是一种系统性血管疾病,其特征是以羟基磷灰石等形态和化学成分上不均匀的矿物沉积等一系列病理改变为特征的动态血管病变,所有血管内膜、中膜等组分都可以发生异常矿化^[1]。除了血管平滑肌细胞 (vascular smooth muscle cells, VSMCs)、内皮细胞、周细胞、巨噬细胞、骨髓来源的间充质干细胞等可以参与血管钙化以外,细胞外基质同样参与了血管钙化的发生和发展。最新研究表明,基底膜蛋白 Nidogen-2 作为血管细胞外基质微环境的重要组成部分,参与了 VSMCs 转分化和血管钙化^[2]。总之,这些细胞及非细胞成分之间的相互作用,诱发钙化物在血管壁沉积,导致血管壁弹性下降、血管结构完整性受损,进而引发一系列不良临床事件的发生。

血管系统由各种血管(动脉、静脉和毛细血管)组成,由于瓣膜活动受损对心血管功能影响较大,故瓣膜也常被认为是血管系统的一个组成部分。随着人口老龄化和代谢性疾病患病率的增加,血管钙化患病率越来越高,对社会、家庭和患者的影响也越来越大。因此积极探索血管钙化的发病机制,寻找有效的诊疗手段是亟待解决的重要临床问题。

近年来,国内外有关血管钙化的研究层出不穷,相关学说及机制研究也在不断快速更新,这为进一步深入探索血管钙化的发病机制、更新对血管钙化的认识以及寻找新的治疗靶点提供了一定的理论依据和实践基础。

目前,血管钙化的患病率呈逐年增高趋势。同时,随着对血管钙化机制研究的深入认识,以及影像学技术发展使检出率增加,人们逐渐意识到血管钙化不仅与心血管残余风险密切相关,也同时涉及多个器官和组织的疾病谱。因此,针对此领域内亟待解决的问题,本文联合了国内多位来自不同学科从事血管钙化研究的临床和基础的知名专家,共同探讨血管钙化基础和临床研究的最新进展与争议,旨在组织多学科的力量,从不同的维度更新对血管钙化的认识,进而为血管钙化基础研究提供客观临床实践反馈,从而推动血管钙化基础研究和临床防治的相互促进。

一、血管钙化的概述

血管钙化主要是由羟基磷灰石在血管壁上异位沉积而产生的病理过程。血管钙化在动脉粥样硬化、

高血压、糖尿病、老年及慢性肾脏病 (chronic kidney disease, CKD) 人群中普遍存在。几乎所有动脉的中膜和内膜均可发生血管钙化,其中冠状动脉钙化最为常见。血管钙化导致心血管疾病、CKD、脑卒中等疾病的发生风险增加。因此,血管钙化在全球范围内日益受到越来越多的关注。

1 血管钙化的危险因素

血管钙化的危险因素主要包括年龄、性别、种族、病变部位等。血管钙化的患病率随年龄增长而增加,被认为是增龄性改变,男女患病率因年龄不同各异。其中增龄、体重指数增加和舒张压升高是男性血管钙化的独立危险因素;而体重指数增加、尿酸升高、高密度脂蛋白降低和缺乏锻炼是女性血管钙化的独立危险因素^[3,4]。动脉粥样硬化多种族研究(The Multi-Ethnic Study of Atherosclerosis, MESA)显示,白人冠状动脉钙化量最大,然后依次是中国人、西班牙裔、黑人^[5]。不同部位血管钙化的患病率也存在差异:冠状动脉钙化患病率最高,腹主动脉次之,颈动脉钙化患病率最低^[6]。

2 血管钙化的分类

血管钙化根据病因不同有多种分类方法。临床常根据血管钙化发生部位的不同分为内膜钙化、中膜钙化、外膜钙化、钙化防御、瓣膜钙化 5 种类型^[7]。不同部位血管钙化的发病机制不同,其临床危害也不尽相同。(1) 内膜钙化:内膜钙化主要发生在动脉粥样硬化病变中,与内皮细胞、VSMCs 和巨噬细胞有关^[8],是脂质积累、平滑肌细胞增殖、巨噬细胞侵袭和细胞外基质蛋白功能障碍的结果^[9]。内膜钙化不仅容易引起血管腔狭窄,还可能导致动脉粥样硬化斑块负荷增加以及急性心肌梗死和卒中等不良事件的发生^[8]。血管内膜钙化是冠状动脉钙化的主要类型。冠状动脉钙化是心血管事件和总死亡风险增加的重要因素之一。(2) 中膜钙化:中膜钙化主要发生在血管壁中膜,与胶原、弹性蛋白纤维和 VSMCs 有关。中膜钙化发病机制涉及血管钙化抑制因子的缺失、成/破骨细胞标志分子的增加、细胞外基质和基质水解酶的成分以及含量变化、自噬等^[10]。中膜钙化会导致心血管疾病患病率和死亡率增加,常存在于衰老、糖尿病、CKD 等疾病的发展进程中^[11-14]。(3) 外膜钙化:外膜钙化可以发生在不同的动脉。周细胞作为微血管系统的组成部

分,在血管钙化尤其是外膜钙化中发挥了重要作用^[15]。外膜钙化一般不会影响血流,但如果大的动脉发生外膜钙化,可能导致血管的膨出、形成动脉瘤;而发生在中动脉、小动脉的外膜钙化,则对机体无显著不良影响。(4)钙化防御:钙化防御也称作钙化性小动脉病,常发生于糖尿病肾病和终末期肾脏病长期透析患者,以全身多部位持续性疼痛、溃疡或坏死性皮肤损害为临床特征,病情进展迅速,治疗棘手。(5)瓣膜钙化:瓣膜钙化最常见的发生部位是主动脉瓣和二尖瓣,可导致心血管事件和卒中的发生风险增加^[3,5,14,15]。主动脉瓣钙化是最常见的一种瓣膜性心脏病,其次是二尖瓣钙化。高龄、高血压、糖尿病、CKD等是主动脉瓣和二尖瓣钙化的危险因素^[16-24],其特征是成纤维细胞样细胞表型转变为成骨细胞样细胞表型^[25]。但瓣膜钙化与血管钙化并不同步发生,血管钙化也并非同步伴随有瓣膜钙化,二者在不同患者中的共患率及钙化的严重程度上均有显著差异,提示瓣膜钙化与血管钙化两者发生机制可能不同^[24,26]。

3 血管钙化的评估

目前,评估血管钙化常用影像学钙化评分体系,主要包括 Agatston 评分、Kauppila 钙化积分和 Adragao 评分^[27]。此外,冠状动脉钙化早期无症状患者可进行 CT 扫描,对 5 年绝对心血管风险为低风险者和中风险者以及不愿接受治疗的高风险者适合采用冠状动脉钙化评分评估血管钙化情况。冠状动脉钙化评分是评估血管钙化等不良心血管事件的最强个体预测因子之一。冠状动脉钙化评分越高,不良心血管事件和全因死亡率越高^[28]。

4 原发性疾病与血管钙化

4.1 CKD与血管钙化

在透析患者和未进入透析的 CKD1~5 期的患者中,血管钙化均有很高的发生率^[22,29-32],同时血管钙化也是导致 CKD 患者心血管疾病发生的关键因素。CKD 患者的冠状动脉钙化评分越高,肾功能下降越快,进展至终末期肾病的风险越高^[33,34]。高龄、肾功能失代偿及合并高脂血症为 CKD 患者出现心血管疾病的独立危险因素。高龄、低蛋白血症及双瓣膜钙化为 CKD 患者全因死亡的独立危险因素^[35]。并且,即使评估血管钙化的方式不同,结果亦均提示血液透析患者血管钙化的患病率高于腹膜

透析患者^[22,36]。相比于终末期肾病合并血管内膜钙化的患者,终末期肾病合并血管中膜钙化的患者年龄更小,钙磷紊乱的患病率更高,透析时间更长^[12]。

尽管钙化防御可在非 CKD 患者中出现,但大多数病例发生于 CKD 透析患者。透析患者钙化防御发病率约为 0.04%~4%,并在过去 10 年中逐渐上升^[37-39]。多因素分析显示,体重指数升高、透析时间延长、华法林治疗、甲状旁腺功能亢进、糖尿病、肿瘤、低蛋白血症、血清碱性磷酸酶水平升高是发生钙化防御的高危因素^[40]。

虽然静脉钙化并不常见,但透析患者的自体动静脉内瘘却常常发生钙化,并且血管通路发生严重钙化病变是内瘘失效的重要原因^[41,42],被视为血液透析患者独立的死亡预测因子^[42]。

4.2 糖尿病和血管钙化

糖尿病患者血管钙化的患病率远远高于非糖尿病患者^[11,43-47],即使在空腹血糖受损和糖尿病前期的患者中,冠状动脉钙化发生和进展的风险也高于非糖尿病患者^[48]。血管钙化增加糖尿病患者心血管病风险:相较于非糖尿病患者,糖尿病会增加冠状动脉钙化评分等级,并增加终身心血管疾病的风险^[49]。在无症状糖尿病患者中,冠状动脉钙化评分的增加与全因死亡率和/或致死性和非致死性心血管事件风险的增加密切相关^[50]。最新研究提示,在 2 型糖尿病患者中,血磷水平升高会增加全因死亡风险,可能与高磷诱导血管钙化有关^[51]。多项临床研究表明,不同的降糖药物对血管钙化影响并不一致,其中二甲双胍被证实可以降低糖尿病患者的冠状动脉钙化评分^[52-54]。一项前瞻性研究发现胎球蛋白 A (Fetuin-A) 与糖尿病微血管并发症发生率呈线性负相关^[55]。此外,补充维生素 K1 对糖尿病患者的主动脉和冠状动脉钙化有保护作用^[56]。

4.3 其他原发性疾病和血管钙化

除了以上容易合并血管钙化的疾病外,高血压使冠状动脉钙化的患病率增加 10%~23%^[5]。同时,原发性醛固酮增多症患者较非原发性醛固酮增多症患者的腹主动脉钙化发生率几乎高出 1 倍,提示醛固酮可能在血管钙化的进程中发挥关键作用^[57,58]。

衰老过程中累积了众多血管损伤因素^[59],是血管钙化的重要原因。血管钙化是老年人群的标志性血管病理损害,从 20 岁到 90 岁,血管钙化发病率可增加 30%^[60]。

5 饮食与血管钙化

MESA 数据显示, 增加全脂牛奶摄入可以减轻冠状动脉钙化, 可能具有心血管保护作用, 其发挥有益作用可能与其富含短链脂肪酸有关^[61]。另外, 研究发现与冠状动脉钙化进展的风险增加有关的是膳食中高镁锌比例, 而非单一矿物质摄入量, 摄入较多的锌和较少的镁对心血管有保护作用^[62]。对 2 万多名参与者进行筛查发现, 与不饮用含糖碳酸饮料的参与者相比, 每周饮用 ≥ 5 种含糖碳酸饮料的参与者的多变量校正冠状动脉钙化相对风险增加 70%, 且含糖饮料的摄入与心血管疾病风险的增加呈剂量依赖性^[63]。在 CKD 患者中, 过量的钙磷摄入, 包括含钙的磷酸盐结合剂, 均会增加 CKD 患者血管钙化的风险^[64]。地中海饮食虽不能降低冠状动脉钙化评分, 但能降低心包脂肪。在成人中, 较高的的心包脂肪与冠状动脉钙化的发展相关, 因而地中海饮食可以降低冠状动脉疾病发生率^[65]。

综上所述, 血管钙化患病率随年龄增长和衰老而显著增加, 男性和女性的血管钙化患病率也存在差异。此外, 不同部位的血管钙化患病率不同, 冠状动脉钙化最常见, 主动脉钙化次之; 瓣膜钙化以主动脉瓣和二尖瓣最为常见。钙化防御最常见于 CKD 患者。CKD、糖尿病、高血压等疾病显著增加血管钙化的发生风险。血管钙化的严重程度(冠状动脉钙化评分)与心血管疾病的发生及预后显著相关。吸烟、缺乏锻炼、含糖饮料摄入增加、肥胖、高胆固醇血症等增加血管钙化风险。而调整微量元素摄入和饮用全脂牛奶则可能减少血管钙化风险。

二、血管钙化的发生机制与临床实践

迄今为止, 血管钙化发生机制的相关研究不断探索和完善, 给临床带来了重要启示, 但在临床实践中仍存在有争议的地方。血管钙化发生机制主要包括钙磷失衡学说、VSMCs 转分化学说、骨稳态失衡学说、表观遗传学调控学说、炎症学说、细胞外基质学说以及新细胞命运学说等。目前, 临床上尚无针对血管钙化的特效治疗药物。因此, 根据血管钙化相关机制的研究, 提出包括磷酸盐结合剂或拟钙剂、硫代硫酸钠(sodium thiosulfate, STS)、SNF472 等用于血管钙化的治疗与预防。

1 钙磷失衡学说

钙磷失衡学说作为经典学说在 CKD 患者血管

钙化的进程中发挥重要作用。本文主要从以下几方面进行阐述。

1.1 高血钙和高血磷

1.1.1 机制进展

高血钙可促进 VSMCs 向成骨细胞转分化及随后的基质矿化。阻断钙离子通道或者激活钙感受体(calcium-sensing receptor, CaSR)均可以显著缓解 VSMCs 钙化^[66, 67]。相较于高血钙, 越来越多的研究证实长期高血磷是导致软组织和血管钙化的主要危险因素, 显著增加 CKD 患者心血管疾病的发生率和死亡率^[68–70]。目前, 高血磷促进血管钙化的确切机制尚不明确, 可能包括以下几种: (1) 诱导 VSMCs 发生转分化: 高磷促进 VSMCs 中骨钙素、核心结合因子 α -1 及成骨细胞分化标记物的表达, 以剂量依赖的方式导致钙化增加^[71, 72], III 型钠磷协同转运子 Pit-1 可能介导了高磷诱导的 VSMCs 转分化^[71, 73]。(2) 促进矿化基质的形成: 高磷或高钙导致 $[Ca] \times [Pi]$ 乘积增加, 从而促进羟磷灰石结晶通过热动力学机制在细胞外基质中增长和沉积, 增加基质矿化程度^[74]。此外, 高磷血症还会导致细胞外基质重塑。高磷刺激 VSMCs 合成基质金属蛋白酶(matrix metalloproteinases, MMPs), 降解胶原蛋白和其他细胞外基质蛋白, 促进钙磷沉积和中膜钙化^[75–77]。(3) 促使 VSMCs 凋亡: 高磷诱导 VSMCs 发生凋亡, 细胞降解产生基质囊泡, 后者与胞外基质蛋白结合进而启动血管壁钙化^[78, 79]。(4) 抑制单核细胞/巨噬细胞分化为破骨细胞样细胞: 高磷除了导致 VSMCs 转分化外, 还可抑制单核细胞/巨噬细胞分化为破骨细胞样细胞, 进一步促进 CKD 血管钙化的发生^[71, 80, 81]。因此, 高磷在钙磷失衡所致血管钙化中发挥着核心作用。

1.1.2 临床共识与争议

磷代谢稳态是控制血管钙化的重要抓手之一, 为血管钙化的防治提供有效的治疗靶点。磷主要来源于饮食摄入, 参与机体新陈代谢, 再经肾脏排泄维持磷平衡。当肾功能下降, 如老年人群、肾病人群, 磷稳态容易失衡。不同磷饮食的生理代谢研究表明, 每日 1 500 mg 及以上饮食磷摄入尽管不造成显性血磷升高, 却可增加体内磷负荷^[82, 83]。定期评估饮食磷负荷、24 h 尿磷、控制每日磷摄入量为 800~1 000 mg 是血管钙化的早期防控策略^[82, 84, 85]。

磷结合剂是控制肠道磷吸收的药物, 可分为抑制肠道磷转运的药物以及单纯的磷螯合剂。磷在肠

道的吸收通过两种途径：(1) 非钠依赖的细胞旁途径，是磷吸收的主要途径，占总磷吸收的 70%^[86]；(2) 钠依赖的主动跨细胞途径，是磷吸收的次要途径，占总磷吸收的 30%，主要由钠磷协同转运子 IIb (sodium-dependent phosphate cotransporter type IIb, Npt2b) 介导。近期有 3 项随机对照试验 (randomized controlled trial, RCT) 发现，透析患者使用 Npt2b 抑制剂 (DS-2330b、ASP3325) 均无显著降血磷作用^[87, 88]。影响磷细胞旁途径吸收的药物钠 / 氢交换子 3 (sodium-hydrogen exchanger type 3, NHE3) 抑制剂 Tenapanor 治疗 8 周，可使血透患者血磷下降 1.0~1.2 mg/dL^[86]。推测 NHE3 抑制剂可改善血管钙化这一硬终点，期待后续临床研究进一步证实。

单纯磷螯合剂根据是否含钙分为含钙磷结合剂、非含钙磷结合剂。应用含钙磷结合剂易导致正钙平衡，加速血管钙化^[89]。血管钙化的高危人群 (如糖尿病、心血管疾病基础人群) 应当限制含钙磷结合剂的使用，以减少发生血管钙化风险^[90]。

此外，终末期肾病患者高磷血症的治疗还应当关注残余肾功能保护、充分透析、肾性骨病的预防和治疗。新入透析患者的残余肾功能是决定血磷的重要独立因素，推荐采用递增式透析方案保护残余肾功能^[91, 92]。当患者进入维持性透析阶段，影响单个时间点血磷的因素依据权重分别为骨病 (57%)、饮食摄入 (17%)、透析充分性 (16%)、磷结合剂 (11%)。因此，避免严重高转化、低转化或无动力性骨病是透析人群高磷管理的首要要素^[93]，充分透析对降低血磷也有着重要意义^[94]。

1.2 继发性甲状旁腺功能亢进症 (secondary hyperparathyroidism, SHPT)

1.2.1 机制进展

SHPT 的主要特征是甲状旁腺增生和甲状旁腺素 (parathyroid hormone, PTH) 过度合成和分泌，可以导致 CKD 患者骨代谢紊乱和心血管并发症，增加患者病死率^[95, 96]。多项临床研究发现透析患者血管钙化与 SHPT 导致的高 PTH 血症密切相关^[30, 97]。大多数学者认为，高 PTH 血症相关的钙磷代谢紊乱是 CKD 患者血管钙化的主要原因。在 CKD 早期，尽管血磷尚未升高，但由于肾单位减少，体内已经出现磷潴留，机体代偿性增加 PTH 和成纤维细胞生长因子 23 (fibroblastic growth factor 23, FGF23) 的分泌，共同诱导了近端小管上皮细胞刷状缘 Npt2a/Npt2c 内吞降解，进而抑制近端肾小管对磷的重吸

收，促进尿磷排泄，维持体内磷平衡^[98, 99]。随着 CKD 的进展，机体代偿机制难以抗衡肾功能减退导致的磷潴留和活性维生素 D [1,25(OH)₂D₃, 1,25D] 水平下降，体内出现明显的血磷升高，进一步刺激骨骼 FGF23 和甲状旁腺 PTH 大量分泌^[100]；同时，SHPT 所致的高转化骨病将促进骨钙磷动员，使血钙、血磷进一步增加，形成恶性循环^[101]。另外，越来越多的证据支持 PTH 对血管钙化的直接作用，PTH 可促进 VSMCs 的转分化和钙化^[102]，也可直接诱导血管内皮细胞表达软骨标志物，促使内皮细胞 - 软骨细胞转分化^[103]，从而参与血管钙化。

1.2.2 临床共识与争议

目前，使用维生素 D 受体激动剂 (vitamin D receptor activators, VDRA) 和 CaSR 激动剂 (即拟钙剂) 是 SHPT 的关键治疗策略。

自上世纪 70 年代至今，1,25D 及其类似物 VDRA 已成为 SHPT 治疗策略中最核心的治疗药物，一方面可与甲状旁腺细胞内 VDR 结合，通过与 PTH 基因启动子中维生素 D 反应元件作用而直接抑制 PTH 基因转录与蛋白合成；另一方面通过促进胃肠道钙的吸收，升高血钙来间接抑制 PTH 分泌^[104]。然而，1,25D 对血管钙化的作用是双重的，1,25D 的过量和缺乏都与血管钙化相关。1,25D 过量可以通过增加血钙、血磷水平或 [Ca] × [Pi] 乘积、上调 FGF23 水平、促进 MMPs 表达、下调钙化抑制蛋白水平等多种途径促进血管钙化；1,25D 缺乏可以通过激活炎症、刺激 PTH 合成、引起内皮功能障碍等途径促进血管钙化^[105]。此外，不同类型的 VDRA 对血管钙化有着不同作用。骨化三醇和度骨化醇可明显增加尿毒症大鼠的 [Ca] × [Pi] 乘积和主动脉钙含量，而帕立骨化醇不会诱导这些作用^[106]。因此，目前认为 1,25D 对血管钙化的作用是一把双刃剑，需要进一步研究以确定维持血管健康的最佳 VDRA 类型及最佳剂量。

拟钙剂是另一类 SHPT 治疗药物，通过增强甲状旁腺细胞 CaSR 对胞外钙离子的敏感性，快速抑制 PTH 释放，降低血清 PTH 水平，使增生的甲状旁腺体积缩小^[107]。在其他器官中，拟钙剂可以增加肾脏尿钙排泄，减少骨转换，降低肠道钙吸收，导致血钙进一步降低^[108]。目前，多数研究显示拟钙剂在治疗 SHPT 的过程中可以明显改善血管钙化^[109, 110]。CKD 伴 SHPT 的大鼠模型中，西那卡塞和维拉卡肽可显著抑制血管钙化的进展，并降低血

清 FGF23、钙和磷水平^[111, 112]。体外研究显示拟钙剂可促进人 VSMCs 的 CaSR 表达, 减少基质胶原分泌和矿物质沉积^[113]。因此, 拟钙剂可间接通过降低血 PTH、钙和磷水平或直接作用于 VSMCs 来缓解钙化。由于拟钙剂具有低钙血症、胃肠道反应等副作用, 而 VDRA 有高钙血症、高磷血症等副作用, 因而联合应用这两类药物对于控制 SHPT 更为理想^[114]。

甲状旁腺切除术 (parathyroidectomy, PTX) 可以明显纠正 CKD 患者的高 PTH 血症及钙磷代谢紊乱, 适用于内科治疗无效的 SHPT^[115, 116], 但能否缓解血管钙化目前结论不一。有小样本研究显示 PTX 可以明显延缓透析患者的动脉钙化, 改善动脉硬化^[117, 118]。也有研究发现尽管 PTX 显著改善透析患者的钙磷代谢紊乱, 但并未改善冠脉钙化积分进展^[119]。此外, 不少患者在 PTX 后出现严重的甲状旁腺功能减退, 过低的 PTH 造成低动力性骨病, 导致钙、磷无法沉积入骨, 反而促进了血管钙化的发展^[120]。因此, PTX 对血管钙化的影响还需进一步研究。

1.3 FGF23和Klotho

1.3.1 机制进展

FGF23 主要由骨细胞合成和分泌, 通过促进尿磷的排泄和抑制 1,25D 合成调节钙磷稳态。FGF23 过量与 CKD 的不良预后相关, 但它与血管钙化的关系尚不清楚, 且多项研究得出的结果相互矛盾。因此, FGF23 在血管钙化中的确切作用有待进一步阐明^[121]。

Klotho 基因是高表达于肾脏的一种抗衰老基因, 其编码产物 Klotho 蛋白对肾脏组织的炎症反应、氧化应激损伤及细胞凋亡等具有抑制作用。目前各项研究均支持 Klotho 在血管钙化中的保护作用。临床研究显示 Klotho 基因突变的患者存在明显的异位钙化^[122], 动物研究发现 Klotho 基因敲除的小鼠出现明显的血管钙化, 过表达 Klotho 基因或注射重组 Klotho 后钙化显著减轻^[123]。Klotho 可直接抑制 VSMCs 中钠磷转运子活性, 并阻止随后高磷诱导的成骨转分化和钙磷沉积^[124]。此外, Klotho 还可能影响血管内皮细胞的功能, 通过增加内皮一氧化氮的产生对抗高磷引起的潜在有害作用^[125]。

1.3.2 临床启示

在 CKD 的早期阶段, 血液和尿中 Klotho 减少, 伴随血液中 FGF23 升高。这种变化可作为肾功能

不全的早期生物学标记, 同时可作为 CKD 患者和普通人群血管钙化和死亡的预测因子^[126]。

预防 Klotho 减少, 促进内源性 Klotho 产生, 或补充外源性 Klotho, 能否成为血管钙化的治疗手段, 需要更多的研究来证实。

1.4 钙化防御

1.4.1 机制进展

钙化防御是由于微血管钙化、真皮及皮下脂肪组织中血栓形成, 导致极度疼痛的缺血性皮肤及软组织改变。病理表现为系统性小动脉中膜钙化、钙化相关的内膜纤维化、继发性血栓性血管闭塞^[127]。目前钙化防御的发病机制尚不清楚。

1.4.2 临床启示与争议

钙化防御目前的诊断主要依靠临床表现及皮肤活检病理, 然而传统的病理染色方法只能显示血管内粗大钙化, 对于早期微钙化诊断困难。有研究发现钙敏荧光染料 Fluo-3AM 可作为一种快速、敏感可靠的皮肤微钙化染色方法^[128]。

钙化防御目前缺乏有效的治疗手段, 目前已开展临床试验的药物主要包括 STS 和 SNF472。STS 是一种钙螯合剂, 在治疗钙化防御中具有一定的疗效, 但其用于钙化防御治疗属于一种超说明书使用, 作用机制尚不明确, 可能通过抗氧化、溶解沉积在组织的钙、扩张血管等发挥作用。目前支持使用 STS 的证据主要来自回顾性研究和病例系列研究^[127]。三项关于 STS 治疗钙化防御的随机临床试验 (NCT03150420、NCT02527213 和 ISR-CTN73380053) 已终止, 但目前无任何研究结果发表。SNF472 是一种新型羟磷灰石结晶螯合剂, 能够抑制羟磷灰石结晶生成和聚集, 减少羟基磷灰石沉积至动脉, 从而抑制终末期肾病透析患者血管钙化的进展^[129]。目前该药尚在进行 III 期临床试验^[130], 其 IIb 期临床试验 (CaLIPSO 研究) 证实 SNF472 可延缓血液透析患者冠状动脉和主动脉瓣钙化进展^[131]。

亦有研究者运用人羊膜间充质干细胞静脉及局部注射成功治疗钙化防御的案例报道^[132], 但缺乏大规模 RCT 研究验证。

综上所述, 血管钙化是一个复杂且受到多种因素调控的过程, 血磷与各种调磷激素相互影响, 形成调节网络, 共同参与血管钙化。目前我们对磷调控网络与血管钙化发生和发展的机制认识远远不够, 有待深入探索。

2 VSMCs转分化学说

VSMCs转分化学说认为, 血管钙化的关键是VSMCs向成骨细胞样表型转化。转化过程以细胞凋亡和基质小泡为始动环节, 以胶原为细胞外基质的骨架, 同时受多种骨分化相关蛋白和信号转导通路的调控。

2.1 机制进展

当VSMCs发生成骨型或软骨型分化时, 其收缩型标志蛋白(如平滑肌22 α 、 α 平滑肌肌动蛋白、钙调节蛋白1)表达降低, 成骨相关转录因子2(Runt-related transcription factor 2, Runx2)、SRY-Box转录因子9、Osterix(OSX或Sp7 transcription factor, SP7)、肌节同源盒蛋白同系物2(muscle segment homeobox homolog of 2, Msx2)、骨桥蛋白(osteopontin, OPN)表达上调, 并促进钙化的碱性磷酸酶活性上升和骨形态发生蛋白2(bone morphogenetic protein 2, BMP-2)表达增加, 钙化的血管壁上的VSMCs可以向成骨样细胞转分化, 并通过细胞内信号转导介导骨基质在管壁上沉积^[9, 75, 133, 134]。其中, BMP-2、Runx2和Osterix是VSMCs发生表型转化较为显著的特异性转录因子。近年来, 该学说研究成果丰硕。多项研究发现, 在致骨化因子(如BMP-2)和炎症介质[如肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)]作用下, Msx2和Wnt信号通路被激活, 导致Runx2和Osterix表达增多^[135-138]。上调Runx2可以促进下游骨相关蛋白[如骨钙蛋白(osteocalcin, OCN)、硬化蛋白]以及NF- κ B受体激活因子配体(receptor activator of NF- κ B ligand, RANKL)表达增多。Runx2的下游靶点Osterix也可以增强骨涎蛋白和碱性磷酸酶的表达。最近研究发现, 吡啶胺2,3-双加氧酶1缺失导致的犬尿氨酸不足会促进Runx2介导的VSMCs成骨重编程和体内钙化^[139]。醛固酮也可能通过该机制促进血管钙化, 引起原发性醛固酮增多症患者的腹主动脉钙化增加^[57]。此外, 磷酸钙晶体通过BMP-2/Smad信号通路诱导人主动脉平滑肌细胞成骨转分化和钙化^[140]。

2.2 临床启示

当人体内的血管钙化抑制因子表达减少或活性降低时, 会引起血管的钙化。然而, 局部和循环钙化抑制剂或相关因子可以抑制血管钙化的进程。基质Gla蛋白(matrix Gla protein, MGP)是一种维生素K依赖性蛋白, 主要由软骨细胞和VSMCs分泌。研究发现, MGP抑制BMP-2与其受体的结合, 降

低BMP-2的表达, 从而抑制VSMCs转分化和血管钙化。在118例糖尿病肾病患者的队列中, 随访7年, 发现MGP T-138C多态性是血管钙化和心血管疾病死亡率的一个强大的独立预测因子^[141]。此外, 研究发现MGP G-7A多态性是内膜和中膜钙化的独立预测因子^[142]。尽管在体外和体内研究中都取得了良好的结果, 但基于人群的研究未能显示关于MGP与血管钙化和心血管疾病关联的明确结果^[143-146], 并且有研究表明补充外源性的MGP并不能逆转血管钙化进展。Fetuin-A是一种由肝脏分泌的糖蛋白, 通过限制凋亡小体在细胞外基质形成碱性磷酸核位点的矿化能力, 从而抑制血管钙化^[147-149]。临床研究发现, 在970例无严重肾脏疾病的冠心病患者中, Fetuin-A与二尖瓣环钙化呈负相关。在没有糖尿病的参与者中, Fetuin-A和主动脉狭窄之间也呈负相关。因此, Fetuin-A可能是冠心病患者营养不良钙化的重要抑制剂^[150]。这些发现为未来血管钙化的临床治疗提供了一定的研究基础和启发。

综上, 以上研究表明, VSMCs转分化在血管钙化的发病机制中居于中心环节, 有效逆转或延缓VSMCs转分化是减缓血管钙化进程的关键。

3 骨稳态失衡学说

骨稳态失衡学说认为, 因骨稳态因子在终末期肾病、衰老和糖尿病等状态下在血管壁表达失调, 导致体内的成骨与破骨作用失衡, 从而在血管内形成异位钙化。

3.1 机制进展

3.1.1 成骨作用异常

多种骨稳态因子可通过影响成骨分化从而促进或抑制血管钙化的发生和进展。BMP是转化生长因子 β 配体的家族成员, 在成骨分化中发挥重要作用^[151]。BMP-2通过上调Runx2、Osterix等参与VSMCs的转分化从而促进血管钙化的发生^[152]。通过激活NF- κ B信号通路, RANKL可增加VSMCs中BMP-4的表达进而促进血管钙化^[153]。BMP-6可上调Runx2和Msx2, 诱导血管内皮细胞的成骨分化^[154]。BMP-9可通过激活素受体样激酶1、Smad和碱性磷酸酶依赖性机制, 也可以通过Wnt/ β -catenin途径诱导VSMCs转分化和钙化^[155, 156]。另一方面, BMP也有抑制血管钙化的作用, BMP-7被证明通过上调抑制性的Smad6和7有效抑制血管钙化^[157]。

Runx2 是成骨细胞分化的主要调节因子。Runx2 在血管钙化时显著上调。VSMCs 中 Runx2 可响应 AKT、MAPK 和 BMP-2 等信号而上调, 从而诱导 VSMCs 转分化和钙化^[158, 159]。除此之外, VSMCs 中 Runx2 的上调抑制 VSMCs 特异性标记基因的表达, 增强 VSMCs 表型转换^[160]。OCN 是一种骨细胞分泌和维生素 K 依赖性蛋白质, 是 VSMCs 转分化的晚期标志物。动物实验和人体标本均表明, 钙化组织中的 OCN 水平高于非钙化组织^[161, 162]。OCN 通过改变 Wnt 信号通路和增加缺氧诱导因子-1 α 依赖性葡萄糖代谢来促进 VSMCs 的转分化, 进而促进血管钙化^[163, 164]。碱性磷酸酶是成骨细胞的生物标志物之一, 骨型组织非特异性碱性磷酸酶可水解无机焦磷酸盐并产生无机磷酸盐, 从而导致血管钙化^[165]。

3.1.2 破骨作用异常

骨稳态因子也可以影响破骨作用。骨保护素 (osteoprotegerin, OPG) 主要通过 OPG/RANKL/NF- κ B 受体激活因子 (receptor activator of NF- κ B, RANK) 信号通路抑制破骨细胞的成熟分化, 从而抑制骨吸收, 抑制骨组织中钙磷的释放, 最终抑制血管钙化的发生和发展^[166, 167]。OPG 还可以通过增加胰岛素样生长因子-1 受体的数量抑制血管钙化^[168]。Runx2 还可以通过促进巨噬细胞浸润和血管炎症, 诱导血管破骨细胞样细胞的形成^[169]。

3.2 临床启示与争议

目前已有临床试验研究抗骨质疏松药物对血管钙化的作用, 包括双膦酸盐和地舒单抗。

双膦酸盐是目前临床常用的治疗骨质疏松症药物。双膦酸盐与骨矿物质结合, 并且主要通过骨吸收部位被破骨细胞吸收来抑制破骨细胞功能。双膦酸盐既对骨质中的羟磷灰石有强大的结合能力, 抑制钙化的发生; 同时还对破骨细胞的前体具有抑制作用, 从而抑制骨质吸收。2013 年的一项 RCT 表明, 绝经后妇女接受双膦酸盐治疗后, 内皮祖细胞中成骨基因的表达下降, 并且 OCN 的表达也有下降的趋势, 因此双膦酸盐可能抑制血管钙化的发生^[170]。给弹性假黄瘤患者使用依替膦酸盐治疗一年后, 发现依替膦酸盐显著阻止了除冠状动脉以外的所有血管床的钙化进展^[171]。

地舒单抗已被美国食品药品监督管理局 (Food and Drug Administration, FDA) 批准用于骨质疏松的治疗。地舒单抗通过靶向 RANKL, 阻止 RANKL 与

其受体 RANK 结合, 从而抑制破骨细胞的发育、活化和存活, 减少骨吸收。在一项针对血液透析患者的观察性研究中发现, 使用地舒单抗治疗 30 个月患者的主动脉弓钙化下降^[172]。地舒单抗还可以抑制 SHPT 和骨量减少患者血管钙化的进展^[173]。

然而, 也有一些临床研究表明, 双膦酸盐及地舒单抗对血管钙化没有影响。地舒单抗和阿仑膦酸 (二膦酸类) 均不影响钙化性主动脉瓣狭窄患者的主动脉瓣钙化进展^[174], 冠状动脉钙化评分与治疗前无显著差异^[175]。骨稳态因子和血管钙化的关系见图 1 和表 1。

4 表观遗传学调控学说

表观遗传学调控学说认为, 表观遗传学调控异常引起与血管钙化相关的基因表达失衡, 导致 VSMCs 表型和心功能的改变。目前已经有证据表明, 表观遗传学修饰中 DNA 甲基化和去甲基化、组蛋白修饰、非编码 RNA 等的关键分子, 可能通过其对血管钙化相关病理生理通路的影响而调控血管钙化的发生和发展^[176]。

4.1 DNA 甲基化和去甲基化

4.1.1 机制进展

DNA 甲基化在血管钙化中起着重要作用。近年来, 人们发现与血管钙化关键调控基因的表达与 DNA 甲基化有关。部分研究显示, 去甲基化修饰可能激活血管钙化关键调控基因的表达, 促进血管钙化发生, 例如 DNA 甲基化关键酶 DNA 甲基转移酶 3a (DNA methyltransferase 3a, DNMT3a) 可以促进血管钙化的发生^[177]。但是, 不同的 DNMT 亚型作用并不一致, 例如 DNMT1 和 DNMT3b 在血管钙化中发挥负性调控的作用^[178, 179]。此外, 最新研究发现, 腺相关病毒编码 alkB 同源物 1 介导的 DNA N6-甲基腺嘌呤 (N6-methyladenine, 6mA) 去甲基化修饰促进血管钙化^[180]。维持性血液透析患者全血 Runx2 甲基化水平与血管钙化呈负相关。因此, 全血 Runx2 甲基化水平可能有望成为维持性血液透析患者血管钙化的诊断指标^[181]。上述系列研究表明, DNA 甲基化和去甲基化是调控血管钙化的重要机制之一。

4.1.2 临床启示

DNA 甲基转移酶抑制剂可能在预防或治疗血管钙化的进程中发挥潜在作用。研究证实, DNA 甲基转移酶抑制剂地西他滨可能通过去甲基化 KLF2

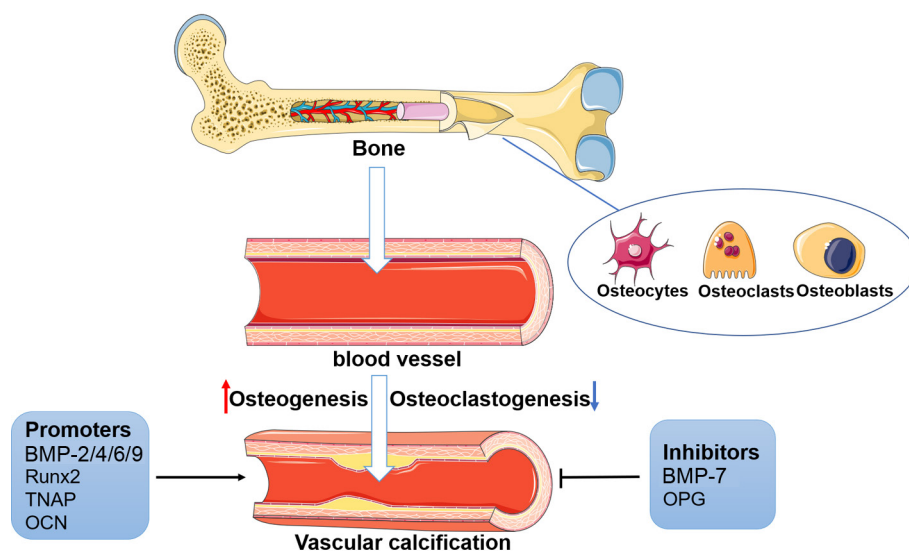


图 1. 骨稳态因子与血管钙化。OPG：骨保护素；BMP：骨形态发生蛋白；Runx2：成骨相关转录因子2；TNAP：骨型组织非特异性碱性磷酸酶；OCN：骨钙蛋白。该图在 Servier Medical Art (<https://smart.servier.com>)帮助下完成。

Fig. 1. Bone homeostasis factors and vascular calcification. OPG: osteoprotegerin; BMP: bone morphogenetic protein; Runx2: Runt-related transcription factor 2; TNAP: tissue nonspecific alkaline phosphatase; OCN: osteocalcin. This figure was created with the aid of Servier Medical Art (<https://smart.servier.com>).

表 1. 骨稳态因子与血管钙化

Table 1. Bone homeostasis factors and vascular calcification

骨稳态因子	对血管钙化的作用	作用方式	参考文献
OPG	抑制	OPG/RANKL/RANK信号通路或者增加IGF1R的数量	[166-168]
BMP-7	抑制	上调抑制性的Smad6和7	[157]
BMP-2	促进	上调Runx2、Osterix	[152]
BMP-4	促进	RANKL激活替代的NF- κ B信号通路	[153]
BMP-6	促进	上调Runx2和Msx2	[154]
BMP-9	促进	ALK1, Smad和ALP依赖性机制或Wnt/ β -catenin途径	[155, 156]
Runx2	促进	诱导VSMCs转分化和钙化；诱导血管破骨细胞样细胞的形成；增强VSMCs表型转换	[158-160, 169]
TNAP	促进	水解PPi并产生Pi	[165]
OCN	促进	改变Wnt信号和增加 HIF-1 α 依赖性葡萄糖代谢	[163, 164]

OPG：骨保护素；BMP：骨形态发生蛋白；Runx2：成骨相关转录因子2；TNAP：骨型组织非特异性碱性磷酸酶；OCN：骨钙蛋白；RANKL：核因子 κ B受体激活因子配体；RANK：核因子 κ B受体激活因子；VSMCs：血管平滑肌细胞；IGF1R：胰岛素样生长因子-1；Msx2：肌节同源盒蛋白同系物2；ALK1：激活素受体样激酶1；ALP：碱性磷酸酶；PPi：焦磷酸盐；Pi：无机磷酸盐；HIF-1 α ：缺氧诱导因子-1 α

基因增强 Krüppel 样因子 -2 (Krüppel-like factor 2, KLF2) mRNA 和蛋白的表达。KLF2 过表达增强白介素 10 (interleukin 10, IL-10) 和转化生长因子 β 1 基因的转录，抑制破骨细胞分化，并与 Runx2 相互作用诱导成骨分化和钙化^[182]。未来更多靶向血管钙化的 DNA 甲基化的相关药物尚需进一步探索，以更好地应用于临床的诊治过程中。

4.2 组蛋白修饰

4.2.1 机制进展

组蛋白修饰是表观遗传学中重要的调控机制之一。有研究证明组蛋白甲基化和组蛋白乙酰化在血管钙化进展中发挥着关键作用。研究报道，*transgelin* (TAGLN)/平滑肌 22 α 的表达在表观遗传水平上受到组蛋白甲基转移酶 EZH2 的调控，从而可能

参与血管钙化的进程^[183]。在 Sirtuin 家族中, 研究最多的 Sirtuin1、Sirtuin3 和 Sirtuin6 通过调控 Runx2 等相关因子减少 VSMCs 的转分化, 抑制血管钙化, 可作为血管钙化进程的负性调控因子^[184–187]。然而, 目前组蛋白去乙酰化酶 (histone deacetylase, HDAC) 在血管钙化进程中的作用和机制尚不完全清楚, 其很有可能作为转录因子调控下游靶基因表达, 从而参与血管钙化病理进程。研究表明, HDAC4 和 HDAC9 可以促进血管钙化的发生^[188, 189]。综上所述, 组蛋白修饰相关基因有望未来成为血管钙化的预测和诊断指标。

4.2.2 临床启示

组蛋白修饰相关研究和策略在血管钙化治疗进展中具有重要意义。组蛋白乙酰转移酶 P300 是一种参与基因表达调控和蛋白质乙酰化的转录辅激活子。研究报道在人主动脉瓣钙化中乙酰化组蛋白 3 和 4 水平升高。组蛋白乙酰转移酶 P300 抑制剂抑制乙酰化组蛋白 3 和 4, 减轻体外高钙 / 高磷处理引起的主动脉瓣钙化^[190]。研究发现 C646 (P300 抑制剂) 可下调骨钙素基因和蛋白表达。抑制 P300 可能通过下调组蛋白乙酰转移酶活性来调节 Klotho 表达, 并减弱瓣膜间质细胞的成骨转分化和钙化。因此, 抑制 P300 可能是血管钙化的潜在治疗靶点^[191]。此外, HDAC 抑制剂 vorinostat 通过 P38 和 ERK1/2 磷酸化抑制 IL-1 β 诱导的 MMPs 表达, 从而减弱 VSMCs 转分化和钙化。因此, HDAC 抑制剂 vorinostat 可能有望成为未来治疗血管钙化的重要药物^[192]。今后, 组蛋白修饰相关血管钙化的药物和临床试验还需广泛深入的研究, 此领域可成为未来研究的热点。

4.3 非编码 RNA

4.3.1 机制进展

近年来, 许多非编码 RNA, 包括微小 (microRNA, miRNA)、长链非编码 RNA (long non-coding RNA, lncRNA) 和环状 (circular RNA, circRNA) 在血管钙化中的重要作用被相继发现。miRNA 是研究最为深入的非编码 RNA。不同的 miRNA 在血管钙化中发挥正性或负性的作用。研究发现, miRNA-30b 可以抑制血管钙化的病理进程^[193, 194]。然而, miRNA-128-3p 和 miRNA-19A-3p 促进血管钙化的发展^[195, 196]。此外, lncRNA 在血管钙化的发生过程中至关重要。LncRNATUG1 是血管钙化的正性调控因子^[197]。Lrrc75a-as1 和 LncRNA-SNHG29 在血管钙化中起

到负性调节的作用^[198, 199]。二肽基肽酶 4 抑制 LincRNA ENST00000540293 表达, 进而加速 VSMCs 钙化的进程^[200]。CircRNA 不仅是血管钙化的诊断指标, 而且也是血管钙化发病机制中的关键因素。CDR1as 和 CircRNA-vgl3 加速成骨分化和钙化的进程^[201, 202]。然而, CircRNA TGFBR2 发挥抑制钙化的作用^[203]。总之, 这些发现不仅为非编码 RNA 在血管钙化中的研究提供了一个新的视角, 还对寻找新的防治血管钙化的潜在药物靶点具有重要的意义。

4.3.2 临床启示

许多研究显示, 非编码 RNA 可能将成为血管钙化的新型治疗基因。临床研究发现, 透析患者血液的细胞外囊泡中 miRNA-223 下降, 同时 VSMCs 钙化减少。因此, miRNA-223 可能是治疗血管钙化的重要靶标^[204]。研究证实 lncRNA-ANCR 是调控成骨细胞分化的重要因子。LncRNA-ANCR 可能通过激活 β -甘油磷酸钠 (β -glycerophosphate, β -GP) 诱导的 VSMCs 自噬, 显著降低 Runx2 和 BMP-2 的表达和矿化结节的形成, 并减弱 VSMCs 的转分化, 从而保护血管钙化。因此, LncRNA-ANCR 可能是治疗血管钙化的关键策略^[205]。此外, 研究发现 lncRNA H19 通过激活 Wnt/ β -catenin 通路, 显著增强人肾间质成纤维细胞中 Runx2、骨钙素、碱性磷酸酶和 β -catenin 的表达水平和矿化结节的形成, 从而加速人肾间质成纤维细胞的成骨分化和钙化过程。XAV939 (Wnt/ β -catenin 信号通路抑制剂) 抑制 H19 诱导的人肾间质成纤维细胞成骨分化, 这可能成为未来治疗血管钙化的潜在药物^[206]。临床研究显示, 与健康对照组相比, 骨质疏松患者的外泌体 hsa_cirRNA_0006859 表达上调。Hsa_cirRNA_0006859 过表达通过抑制 miRNA-431-5p 上调 miRNA-431-5p 的靶基因 ROCK1, 显著降低人骨髓间充质干细胞中骨钙素和碱性磷酸酶蛋白的水平, 减少矿化结节的形成, 从而抑制成骨细胞分化。因此, hsa_cirRNA_0006859 可能是预防血管钙化的重要基因之一^[207]。综上, 目前还未发现可应用于临床治疗血管钙化的非编码 RNA 相关药物。这些研究表明, RNA 疗法是一种很有前途的治疗血管钙化的策略。未来我们期待将这些发现应用到血管钙化的临床治疗中。

5 炎症学说

炎症学说认为, 机体通过炎症介质的监督和干

预,可以有效地管控体内炎症反应,维持生理平衡。然而,异常的细胞因子与代谢毒物累积可使机体产生大量炎症介质,刺激免疫系统过度活化,引起炎症反应失衡。持续低强度免疫炎症激活是血管钙化发生和发展的重要环节,主要表现为白介素(interleukins, ILs)、TNF- α 等炎症因子释放和单核巨噬细胞、T细胞等免疫炎症细胞激活。炎症反应失衡是介导促钙化危险因素与血管钙化发生的重要媒介。

5.1 机制进展

事实上,血管钙化与免疫炎症应答各组分的激活密不可分,炎症因子及炎症相关转录因子NF- κ B可通过直接作用促进VSMCs转分化及钙化,也可通过降低钙化抑制剂水平发挥间接促钙化作用。TNF- α 和TNF样凋亡弱诱导因子(TNF-like weak inducer of apoptosis, TWEAK)通过NF- κ B上调成骨基因表达,促进VSMCs转分化和钙化^[208,209]。RANKL/RANK轴可激活NF- κ B促进成骨基因BMP-4、Runx2及碱性磷酸酶表达,抑制钙化抑制基因MGP表达,从而促进VSMCs转分化及钙化^[153,210]。Toll样受体2介导的NF- κ B活化抑制OPG的表达,导致动脉粥样硬化中血管钙化的发展^[211]。此外,研究表明NLRP3炎症小体复合物各组分在钙化组织中上调。高磷诱导NLRP3活化促进细胞焦亡,IL-1 β 及乳酸脱氢酶释放增加,加重VSMCs钙化^[212]。研究发现巨噬细胞激活T细胞产生细胞因子如干扰素 γ 可增强血管钙化发生,然而另一项研究则表明干扰素 γ 可抑制高磷诱导的VSMCs转分化和钙化^[213]。C反应蛋白和转化生长因子 β 可通过加速VSMCs转分化进程参与血管钙化发生。此外,C反应蛋白还可通过炎症刺激IL-6等释放促进血管钙化^[214,215]。

各种促炎/抑炎ILs也在血管钙化中发挥作用。IL-1 β 可以与TNF- α 共同诱导人主动脉内皮细胞-间充质转化,下调BMP受体2从而加重血管钙化^[216]。IL-1 β 还可激活p53/p21通路促进VSMCs衰老,参与血管钙化发展^[217]。此外,其他促炎性ILs也广泛参与血管钙化的发生。IL-6与可溶性IL-6受体结合可激活p-STAT3进而提高RUNX2、碱性磷酸酶及OPN的表达,促进VSMCs转分化及钙化^[218]。而IL-8则通过阻断OPN表达并以浓度依赖的方式增强VSMCs钙化^[219]。IL-18可促进VSMCs成骨转录因子表达,显著增强高磷诱导的人VSMCs钙化^[220]。血清IL-18水平也与冠状动脉钙化正相关,其可激活M型瞬时受体电位通道,促进高磷诱导

的大鼠VSMCs转分化及钙化^[221]。然而,有研究表明IL-18对人VSMCs转分化无促进作用,而是通过抑制OPN的表达促进主动脉钙化的发生^[222]。早期研究表明抑炎因子IL-24通过激活Wnt/ β -catenin通路抑制 β -GP诱导的VSMCs钙化^[223],然而近期研究发现IL-24可促进BMP-2的表达从而刺激VSMCs钙化^[224]。IL-37通过抑制IL-18和TNF- α 等促炎因子表达,增强抗炎因子IL-10活性参与血管钙化过程中炎症的调节,从而发挥抑制血管钙化的作用^[225],除此之外,其钙化保护作用部分依赖于OPG^[226]。由此可见,诸多抑炎因子也参与了血管钙化的调节(如IL-24)^[224,227]。虽然目前研究结果尚存一定争议,但为血管钙化研究提供了新的思路。

免疫炎症细胞异常激活,抗炎与促炎细胞比例失调是血管钙化免疫炎症失衡的重要环节。自微钙化到骨组织样化生,单核细胞来源的巨噬细胞广泛参与血管钙化的整个进程,其产生促炎因子,诱导氧化应激损伤介导血管及心脏瓣膜细胞成骨样转化和钙化。值得注意的是,不同环境下巨噬细胞表型的高度可塑性使这一过程变得复杂。钙磷结晶促进M0巨噬细胞向M1型极化,提示在钙化过程中炎症免疫细胞向钙化部位募集^[228]。活化巨噬细胞可释放炎症因子诱导VSMCs转分化。而钙化的VSMCs可通过RANKL刺激巨噬细胞向成骨样细胞迁移和活化,二者形成正反馈,促进血管钙化发展^[169,229-231]。调节性T细胞与辅助性T细胞17比例失衡与透析患者血管钙化独立相关^[232]。近期研究表明,衰老T细胞(CD4⁺CD28^{null})也与CKD血管钙化相关。随着研究的进展,免疫细胞分型被不断细化,不同亚型在病变部位募集,细胞因子分泌,抗原提呈或吞噬功能存在差异性,其对血管钙化的作用是复杂的,亟待进一步探索。

炎症不仅促进血管钙化的发展,还可能是其始发因素。现已证实:磷超载可诱导血管炎症反应和钙化的发生,高磷诱导VSMCs炎症因子TNF- α 表达且先于骨/软骨标志物增加^[233]。临床研究也表明动脉局部炎症信号的增加先于相应动脉节段钙化的发生^[234]。上述研究表明炎症是触发和驱动血管钙化的关键,与血管钙化存在因果关系。

慢性免疫炎症是血管钙化的关键环节。促钙化内环境刺激免疫细胞活化释放多种炎症因子,这些炎症因子通过其受体及下游信号通路广泛参与氧化应激损伤、细胞衰老、焦亡、凋亡、钙化抑制剂分泌、

VSMCs 转分化等血管钙化的多个过程。由此可见，控制体内慢性炎症状态可能是治疗血管钙化的关键。炎症因子和血管钙化的关系见图 2 和表 2。

5.2 临床启示

既往研究中由于疾病模型及种属差异往往导致

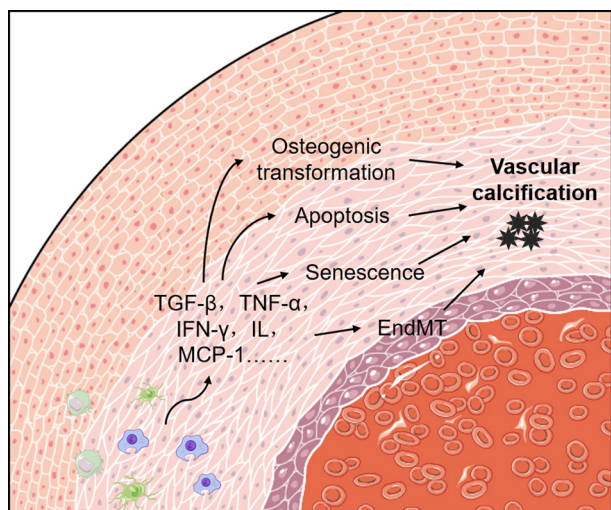


图 2. 炎症与血管钙化。TGF- β : 转化生长因子- β ; TNF- α : 肿瘤坏死因子- α ; IFN- γ : 干扰素- γ ; IL: 白介素; MCP-1: 单核细胞趋化因子1; EndMT: 内皮细胞-间充质转化。该图在 Servier Medical Art (<https://smart.servier.com>)帮助下完成。
Fig. 2. Inflammation and vascular calcification. TGF- β : transforming growth factor- β ; TNF- α : tumor necrosis factor- α ; IFN- γ : interferon- γ ; IL: interleukins; MCP-1: monocyte chemoattractant protein-1; EndMT: endothelial-to-mesenchymal transition. This figure was created with the aid of Servier Medical Art (<https://smart.servier.com>).

研究结果的不同，而参与免疫炎症反应的细胞和介质的复杂性也为探索血管钙化与炎症之间的确切机制带来巨大挑战，临床转化也是困难重重。尽管目前尚无有效抑制血管钙化相关炎症状态的临床干预手段，但近期研究表明丹参酮 IIa 可通过下调 NF- κ B 信号抑制 VSMCs 转分化和钙化^[235]。靶向 RANKL 的地诺单抗可恢复骨质疏松大鼠 OPG 水平，抑制血管钙化，增加骨密度^[236]，此外，来自肝脏和肾脏的循环钙化抑制剂 Fetuin-A 和 Klotho 的分泌抑制也与炎症因子活化相关^[237, 238]。这些发现为以炎症为靶点的血管钙化干预带来了曙光。此外，寻找能够有效预测血管钙化的炎症标志物对于血管钙化患者的管理也十分必要。

6 细胞外基质学说

细胞外基质学说认为，细胞外基质是血管壁的重要组成部分，也是血管钙化发生的主要场所。

6.1 机制进展

细胞外基质是维持血管壁完整结构和血管正常功能的重要保证。细胞外基质与血管壁细胞间相互作用，影响其粘附、增殖、迁移、分化等功能，因此细胞外基质的合成或降解的动态变化影响血管的形态和功能。细胞外基质重塑改变了血管壁的力学性质，是导致血管钙化发生的重要机制。细胞外基质各组分在血管钙化过程中发生动态变化，同时这些组分又能反过来影响血管钙化的发生和发展^[239]。除此之外，细胞外基质重塑和基质成分发生改变也

表 2. 炎症因子与血管钙化

Table 2. Inflammatory factors and vascular calcification

炎症因子	来源	性质	与血管钙化关系	参与机制	参考文献
TNF- α	单核巨噬细胞	促炎	促进	促进VSMCs转分化；促内皮细胞间充质转化；抑制焦磷酸分泌	[208, 209, 216]
IFN- γ	T细胞	促炎	尚存争议		[213]
TGF- β	多种细胞	多效性	促进	促VSMCs转分化	[215]
CRP	肝细胞	促炎	促进	促VSMCs转分化；刺激其他炎症因子(如IL-6, 内皮素)释放	[214]
IL-6	单核巨噬细胞	促炎	促进	促VSMCs转分化，抑制OPG，促CRP	[218]
IL-8	巨噬细胞	促炎	促进	阻断钙化抑制因子(OPN)表达	[219]
IL-18	巨噬细胞	促炎	促进	促VSMCs转分化	[220, 222]
IL-1 β	多种细胞	促炎	促进	促内皮细胞间充质转化；促VSMCs转分化及衰老	[216, 217]
IL-24	多种细胞	抑炎	尚存争议		[224, 227]
IL-37	多种细胞	抑炎	抑制	减少促炎因子释放，黏附分子表达，抑制巨噬细胞浸润；促进抑炎因子(IL-10)	[225]

TNF- α : 肿瘤坏死因子- α ; IFN- γ : 干扰素- γ ; TGF- β : 转化生长因子- β ; CRP: C反应蛋白; IL: 白介素; VSMCs: 血管平滑肌细胞; OPG: 骨保护素; OPN: 骨桥蛋白

会引发心脏瓣膜细胞类型的转化，从而影响瓣膜钙化^[240]。

6.2 临床启示

MMPs 是降解细胞外基质成分的最重要的酶。它不仅参与血管钙化的发生，MMPs 的上调也是瓣膜重塑和钙化的必要条件^[241]。MMPs 的蛋白水解活性主要由 MMPs 组织抑制剂 (tissue inhibitors of MMPs, TIMPs) 调节。衰老、炎症刺激等也可以调节 MMPs 及其抑制剂 TIMPs 的表达^[242, 243]。TIMPs 通过负向调节 MMPs 来控制细胞外基质成分的分解，并参与血管钙化的调控^[244]。除 MMPs 外，还有很多细胞外基质蛋白参与血管钙化：对钙化主动脉瓣与相对邻近的正常组织进行蛋白质组学分析发现，钙化的主动脉组织中，细胞外基质蛋白 X 的表达降低，提示其与细胞外基质重塑有关^[245]。软骨寡聚基质蛋白是一种血管细胞外基质蛋白，被认为是血管衰老相关过程包括动脉粥样硬化和血管钙化的负调控因子^[246]。基底膜蛋白 Nidogen-2 是细胞外基质微环境的重要组成成分，研究表明其对于维持 VSMCs 收缩表型至关重要，而 VSMCs 由收缩表型转换为合成表型被认为是动脉重塑的一个关键机制^[247]。同时 Nidogen-2 是富含亮氨酸重复序列的 G 蛋白耦联受体 4 (leucine-rich repeat G-protein-coupled receptor 4, LGR4) 的高亲和内源性配体，对 Gαq- $\text{PKC}\alpha$ -AMPK α 1 有偏向性激活作用，是血管钙化的内源性保护因子^[2]。研究发现，钙粘蛋白 -11 通过诱导细胞外基质重塑，引起主动脉瓣钙化，也是治疗主动脉瓣钙化的潜在分子靶点^[248]。因此，细胞外基质在血管钙化的发生和发展中起着重要作用，其相关研究可能为血管钙化的治疗寻找到新的靶点。

7 新细胞命运学说——铁死亡和细胞焦亡

新细胞命运学说认为，铁死亡和细胞焦亡加速血管钙化的进程，从而发挥正性调控的作用。

7.1 机制进展

在铁死亡和细胞焦亡的形成过程中会释放大量的促炎症因子^[249]。持续刺激炎症导致内皮细胞损伤，氧化应激反应增强，VSMCs 增殖和转分化，从而促进血管钙化。最新研究发现，高磷高钙下调了谷胱甘肽过氧化物酶 4 的表达，导致脂质过氧化物的积累，引发铁死亡，最终增强血管钙化的发展，而抑制铁死亡可以减轻 CKD 血管钙化^[250]。研究显示，铁刺激 VSMCs 通过 Fenton 反应产生活性氧应

激，增加 IL-24 基因的表达水平，从而介导 VSMCs 的转分化和钙化^[251]。骨膜蛋白通过下调 p53 抑制 SLC7A11 的表达，从而降低谷胱甘肽 / 氧化型谷胱甘肽比值，最终导致 VSMCs 的铁死亡^[252]。

7.2 临床启示

目前，在新细胞命运学说机制研究中尚未发现有效的可以治疗血管钙化的药物。但有研究报道，二甲双胍可通过抗铁死亡作用抑制高脂血症相关的血管钙化。研究结果显示，棕榈酸处理促进了细胞外基质蛋白骨膜蛋白的表达和向细胞外环境的分泌，而二甲双胍则减弱了这一作用。机制研究表明，骨膜蛋白通过下调 p53 抑制 SLC7A11 表达，导致谷胱甘肽 / 氧化型谷胱甘肽比值降低，从而引发 VSMCs 的铁死亡。无论是用重组大鼠骨膜蛋白补充 VSMCs，还是敲低 p53，二甲双胍的抗铁死亡作用均被取消。因此，这些发现提示了二甲双胍在铁死亡中的信号转导和调控机制。铁死亡调节可能是抗钙化干预的一个新的治疗靶点^[253]。

靶向细胞焦亡机制的研究在血管钙化的治疗中扮演重要的角色。研究发现，血浆氧化三甲胺和葛根素通过靶向经典 NF- κ B/NLRP3 炎症通路抑制钙化^[254, 255]。研究表明，磷酸盐刺激可上调炎性小体的活性，促进 Caspase-1 和 IL-1 β 的表达，从而增强 VSMCs 的钙化^[256]。此外，新近研究发现，鸢尾素通过诱导 CKD 中的自噬和抑制 VSMCs 焦亡防止血管钙化^[212]。白藜芦醇通过抑制 NLRP3/Caspase-1 信号通路抑制 VSMCs 焦亡，从而对血管钙化发挥保护作用^[257]。因此，葛根素、鸢尾素和白藜芦醇等未来有望成为 CKD 相关血管钙化的有效治疗剂。

总之，在 VSMCs 钙化中，大多数编程性细胞死亡（如铁死亡和细胞焦亡）伴随着炎症反应和氧化应激的增加而增强，进而导致促钙化微环境的形成。因此，铁死亡和细胞焦亡可能是激活血管钙化相关信号通路的关键机制，进而加速血管钙化的进程。未来开发靶向铁死亡和细胞焦亡等相关机制治疗血管钙化的药物将是该领域的研究热点。

三、结论与展望

综上所述，近年来逐步完善的血管钙化的发生机制涌现了一系列学说，包括钙磷失衡学说、VSMCs 转分化学说、骨稳态失衡学说、表观遗传学调控学说、炎症学说、细胞外基质学说以及新细胞命运学说等，而部分学说在临床实践中仍存在争

议。血管钙化病变在心血管疾病、CKD 和糖尿病等多系统疾病中发挥重要作用，是临床治疗的难题。因此，积极开展血管钙化的基础和临床研究对于改善心血管、CKD 和糖尿病等疾病的并发症和预后具有重要意义。然而，迄今为止，血管钙化尚无有效的临床治疗药物。尽管目前血管钙化研究进展和临床实践仍存在诸多争议，但基础研究的逐步深入必将带来治疗领域的革新，其中正在开展临床试验的血管钙化治疗药物包括 STS 和 SNF472 等已经带来了曙光，相信在不久的将来，有望成为临床治疗血管钙化的潜在药物。未来尚需进一步探索调控血管钙化的分子机制以及治疗血管钙化的药物，为血管钙化的防治寻找更多的策略，从而更好地指导临床治疗。

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写作组成员：黄辉(中山大学附属第八医院)，张爱华(首都医科大学宣武医院)，陈靖(复旦大学附属华山医院)，袁凌青(中南大学湘雅二医院)

资深专家组成员：唐朝枢(北京大学基础医学院)，廖二元(中南大学湘雅二医院)，葛均波(复旦大学附属中山医院)，徐清波(浙江大学附属第一医院)

专家组成员(按姓氏汉语拼音排序)：郝丽荣(南方科技大学医院)，黄聿(香港中文大学)，孔炜(北京大学基础医学院)，李贵森(四川省人民医院)，廖晓波(中南大学湘雅二医院)，刘建民(上海交通大学附属瑞金医院)，刘江华(南华大学附属第一医院)，孙伟(南京医科大学附属第一医院)，夏维波(北京协和医院)，谢辉(中南大学湘雅医院)，颜建云(南方医科大学珠江医院)，赵景宏(陆军军医大学新桥医院)，张澄(山东大学齐鲁医院)，张晓良(东南大学附属中大医院)，章振林(上海交通大学附属第六人民医院)

秘书组成员：史云聪(中山大学附属第八医院)，吴彦霖(中南大学湘雅二医院)，倪丽(复旦大学附属华山医院)，许为佳(湖北省十堰市太和医院，首都医科大学宣武医院)，王佩文(北京协和医院)

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