DOI: 10.11844/cjcb.2026.03.0021
中国细胞生物学学报 Chinese Journal of Cell Biology 2026, 48(3): 802–808 CSTR: 32200.14.cjcb.2026.03.0021

· 综述 ·

细胞外基质硬度调控血管平滑肌细胞功能的研究进展

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摘要　血管平滑肌细胞(vascular smooth muscle cells, VSMCs)是血管壁的主要细胞成分, 其功能与血管生理病理密切相关。细胞外基质(extracellular matrix, ECM)是决定血管力学特性的关键结构, 其硬度随血管的病理状态的加重而增加。变硬的ECM通过影响VSMC的功能, 进一步加快血管疾病的发生发展。因此, 该文对ECM硬度调控VSMC的功能及相关机制进行综述, 以期为阐明血管疾病发生发展的机制提供依据。

关键词　血管平滑肌细胞; 增殖迁移; 细胞外基质硬度; 力学信号转导; 血管疾病

Research Advances in the Regulation of Vascular Smooth Muscle Cell Function by Extracellular Matrix Stiffness

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Abstract　VSMCs (vascular smooth muscle cells) are the main cellular components of the blood vessel walls, and their functions are tightly associated with vascular physiopathology. The ECM (extracellular matrix) is a key structure determining the mechanical properties of blood vessels, and its stiffness is increased with the progression of vascular pathology. The stiffer ECM accelerates the onset and progress of vascular diseases. Herein, this review has outlined recent research on how ECM stiffness impacts VSMC function and the underlying mechanisms, aiming to offer a better understanding of the mechanisms underlying the occurrence and progression of vascular diseases.

Keywords　vascular smooth muscle cells; proliferation and migration; extracellular matrix stiffness; mechanotransduction signaling; vascular diseases

1　血管ECM硬度

细胞外基质(extracellular matrix, ECM)是由胶原蛋白、弹性蛋白、糖胺聚糖链及其核心蛋白(蛋白聚糖)以及层粘连蛋白等复合糖蛋白组成的非细胞结构[1-2]。就血管系统而言, ECM除了为血管提供结构支撑、维持血管的完整性外, 还介导细胞外物理因素如硬度对血管细胞功能的调控[3-5]。

ECM硬度(stiffness)是量化血管壁ECM抵抗形变的宏观能力。在生物力学研究中, 其可量化的核心参数是杨氏弹性模量(Young's modulus), 即刚度, 它特指材料在弹性形变范围内抵抗形变的能力[6]。ECM硬度由弹性蛋白、胶原等成分的固有弹性、相对含量及交联程度共同决定[7]。体外检测ECM硬度一般通过原子力显微镜(atomic force microscope, AFM)等方法进行, 通过测量其应力–应变曲线进行计算, 以单位kPa/MPa表征。在体外研究中, 常使用

收稿日期: 2025-10-20　接受日期: 2025-12-25
国家自然科学基金(批准号: 12272031)资助的课题
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Received: October 20, 2025　Accepted: December 25, 2025
This work was supported by the National Natural Science Foundation of China (Grant No.12273031)
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表1 常见疾病中ECM硬度增加的原因

Table 1 Causes of increased ECM stiffness in common diseases

疾病 Disease	ECM硬度增加的原因 Causes of increased ECM stiffness
Atherosclerosis	Proteoglycan accumulation and collagen deposition, lipoprotein and inflammation[26-27]
Thoracic aortic aneurysm	Abnormal collagen cross-linking and stiffness due to genetic defects[28]
Diabetic vascular complications	Macro/microvascular basement membrane thickening (collagen IV and laminin deposition), AGEs cross-linking of collagen, and increased stiffness[5]
Osteoarthritis	Abnormal collagen cross-linking, mitophagy activation, and enhanced TGF-β signaling[29]
Liver fibrosis	Activated hepatic stellate cells secrete excessive ECM components and reduce MMP production[30]

聚丙烯酰胺水凝胶(polyacrylamide hydrogel, PA)和聚二甲基硅氧烷(polydimethylsiloxane, PDMS)等材料构建不同的刚度模型以模拟生理或病理状态的血管ECM硬度, 并用以研究ECM硬度对细胞功能的影响及机制[8-10]。然而, 需注意这些方法与模型的局限性。AFM测量反映的是ECM的局部硬度, 而体内血管ECM具有力学异质性, 因此局部测量值可能与组织的整体硬度存在偏差[11]。此外, PA水凝胶等模型虽能精确控制刚度这一单一变量, 但难以完全模拟体内ECM复杂的生化组成、三维拓扑结构及动态重塑过程[12]。因此, 在解读体外实验结果并推论至体内病理过程时, 需充分考虑这些差异。从体内生理与病理状态来看, 健康哺乳动物血管的动脉硬度(以弹性模量表征)范围为2~5 kPa[13], 而在动脉粥样硬化、高血压等病理状态下, 其硬度显著增加并随病理进程其硬度增加不一[14]。

在不同的血管疾病如慢性肾病(chronic kidney disease, CKD)、高血压和血管老化等疾病中, 这些疾病导致ECM硬度增加的共同原因是I型胶原(type I collagen, Col I)含量增加、交联沉积, 并且弹性蛋白含量降低。例如, 在CKD中肾脏损伤肾功能下降导致机体代谢紊乱, Col I和基质金属蛋白酶(matrix metalloproteinases, MMPs)等炎症相关酶类分泌增加, 后者降解弹性蛋白并促进胶原沉积, 进而增加ECM硬度[15,17-18]。在高血压中, 长期高压力负荷使动脉壁ECM反复拉伸, 导致弹性蛋白损伤, 失去缓冲功能, 肾上腺素–血管紧张素–醛固酮系统被过度激活, 血管紧张素II刺激VSMCs(vascular smooth muscle cells)合成Col I, 醛固酮则促进胶原交联, 从而使ECM硬度增加[16,19-21]。在血管老化中, 血管壁Col I含量增多且血液中晚期糖基化终末产物(advanced glycation end-products, AGEs)的累积使得胶原纤维排列异常、不可逆交联, 弹性蛋白因合成减少并因MMPs介导其降解而减少, 导致胶原/弹性蛋白二者比例失衡从而使得ECM硬度增加[22-25]。其他血管疾病或并发症ECM硬度增加的原因如表1所示。

2 ECM硬度调控VSMCs的功能

血管壁由内膜、中膜及外膜三层结构组成[28]。其中VSMCs是中膜的核心组成成分, 作为维持血管张力与正常生理功能的主要细胞, 在血管疾病发生发展过程中也发挥关键作用[31]。VSMCs具有表型可塑性, 其形态与功能会随微环境变化而动态调整。在生理状态下, 分化成熟的VSMCs呈纺锤形, 高表达如平滑肌肌球蛋白重链(smooth muscle myosin heavy chain, SMMHC)等收缩相关蛋白, 核心功能是通过收缩与舒张的动态平衡调节血管张力, 进而维持局部组织的血流稳定[32-33]。在病理状态下, VSMCs中如周期蛋白A(CyclinA)表达水平升高, VSMCs会向合成表型转化, 形态变为上皮样或多边形, 通过异常增殖迁移及参与ECM重塑, 推动血管壁结构重构[34]。ECM硬度是血管微环境的关键物理调节因子, 但其在体内并非独立作用, 病理状态下硬度的改变, 始终伴随着ECM成分异质性(如I型与III型胶原比例变化、弹性蛋白降解)和结构拓扑性(如胶原纤维从有序变为无序排列)的重塑。这些物理与生化信号协同耦合, 共同构成决定VSMCs命运的复杂微环境[6,15]。尽管存在这种耦合, 但体外研究已明确证实, ECM硬度本身的变化对VSMCs功能具有独立且重要的调控作用[35-38]。

2.1 ECM硬度调控VSMCs细胞骨架结构

ECM硬度是决定VSMCs细胞骨架组装与稳定性的关键因素。研究表明, 与软的ECM相比, 硬的ECM更有利于细胞骨架的稳定与聚合[39-41]。例如,

人主动脉VSMCs微管数量在72 kPa上显著高于其在12 kPa上, 表明硬度增加能有效稳定微管结构, 防止其解聚[41]。同样地, 对VSMC细胞系A7r5细胞的研究也发现, 微丝(F-actin)的数量(组装)在130 kPa上远多于1 kPa[41]。这些结果提示硬度增加通过促进微管和微丝的组装, 为VSMCs提供了更强的内部力学支撑。这种骨架重塑是细胞感知、传递和响应ECM硬度的结构基础, 其进一步影响了VSMC的铺展、迁移、增殖等细胞行为。

2.2 ECM硬度调控VSMCs表型转变

ECM硬度的增加促进了VSMCs向合成/成骨表型转变[38,42-44]。研究表明, 当ECM硬度从生理水平(5 kPa)增至病理水平(50~100 kPa)时, VSMCs中成骨关键转录因子Runt相关转录因子2(Runt-related transcription factor 2, Runx2)的表达呈现梯度性上调[43]。与之相一致, 另一研究显示, 在较硬的16.75 kPa上, 人脐动脉VSMCs的收缩标志物表达下调, 而成骨及增殖标志物表达上调[38]。在细胞形态与功能上, 硬度增加导致VSMCs从细长梭形转变为扁平多角形, 同时伴随收缩能力下降和钙化倾向增强[38,44]。这些研究结果证明了ECM硬度增加通过调控基因表达、细胞形态和功能的多维改变, 进而促进VSMCs向病理表型转分化。

2.3 ECM硬度调控VSMCs增殖

ECM硬度增加是驱动VSMCs异常增殖的核心物理因素[41,45-46]。研究表明, 硬度增加能显著加速VSMCs的细胞周期进程。例如, 在模拟病理硬度的ECM上, A7r5细胞的增殖速率在多个时间点均显著快于其在生理硬度上[41]。更重要的是, 硬的ECM通过促进抗凋亡蛋白(Survivin)的表达, 进而上调CyclinD1、CyclinA等关键周期蛋白的水平, 从而推动VSMCs从G_0/G_1期向S期转换, 最终导致细胞总数显著增加[46]。这些证据表明, ECM硬度可直接通过调控细胞周期核心蛋白的表达, 启动VSMCs的病理性增殖程序。

2.4 ECM硬度调控VSMCs迁移

ECM硬度增加促进细胞迁移[47-49]。ALEX等[48]在纤粘连蛋白(fibronectin, FN)包被的3.5 kPa、28 kPa、103 kPa的PA胶上接种大鼠VSMCs。使用JuLI Stage活细胞成像系统记录了VSMC的运动轨迹, 其结果表明ECM硬度的增加显著增加了VSMCs的迁移距离、提升了VSMCs的迁移速度、减少了停顿次数, 同时增加了细胞的随机运动系数。THOMAS等[49]用FN包被8 kPa和16 kPa的PA并在其上接种人VSMCs, 延时视频显微镜检查发现细胞在16 kPa上的迁移距离与速度显著高于其在8 kPa上的水平, 轨迹更直、方向性更强。这些研究结果表明, ECM硬度通过调控VSMC的运动轨迹、位移和频率影响细胞的迁移。

2.5 ECM硬度调控VSMCs的炎症反应

ECM硬度增加促进VSMCs向促炎表型转变并发生炎症反应[13,44,50]。WANG等[13]发现与19.66 kPa的PA胶相比, 3.24 kPa的PA胶显著诱导VSMCs促炎因子MCP-1与IL-6的表达/分泌, 增强其对巨噬细胞的趋化, 使细胞邻近ECM进一步变硬, 导致ECM硬度的恶性循环性增加, 加剧动脉硬化。LI等[44]将大鼠VSMCs分别接种于2.6 kPa、10.6 kPa、19.7 kPa的PA胶上, 检查了不同硬度上VSMCs中MCP-1、IL-6、IL-1β和IL-18等炎症因子的表达水平, 发现随着硬度的增加, 19.7 kPa以时间依赖的方式促进了VSMCs的炎症反应。这些研究表明, ECM硬度调控VSMCs的炎症反应, 在动脉粥样硬化等血管炎症相关疾病中发挥了重要作用。

3 ECM硬度调控VSMCs功能的作用机制

目前研究表明, VSMCs首先由细胞表面力感受器如整合素、酪氨酸激酶受体1(discoidin domain receptor 1, DDR1)、机械敏感离子通道等感知ECM硬度, 经黏着斑与骨架进行信号转导, 将外界机械信号转化、放大为胞内化学信号, 随后引发相应激酶激活、基因表达改变和表观遗传重编程等, 最终实现对VSMC功能的调控(图1)[51]。

3.1 ECM硬度通过DNA甲基转移酶1(DNA methyltransferase 1, DNMT1)介导VSMCs表型转变

ECM硬度对VSMCs表型的调控涉及深刻的表观遗传改变。其中, DDR1-DNMT1轴是一条关键通路。研究表明, ECM硬度增加通过激活DDR1, 抑制DNMT1的表达, 导致细胞整体DNA甲基化水平下降, 这种DNA甲基化水平下降使得VSMCs收缩型基因如*SM22α*和*α-SMA*沉默, 而合成/成骨型基因如*BMP2*(bone morphogenetic protein 2)和*RunX2*的mRNA水平升高、*Cyclin A*的mRNA水平升高, 最终驱动VSMCs向合成/成骨表型转化, 并促进血管钙化[38]。

3.2 ECM硬度通过中电导钙激活钾通道(IKCa通道)和Survivin调控VSMC增殖

在表型转变的基础上, ECM硬度进一步通过

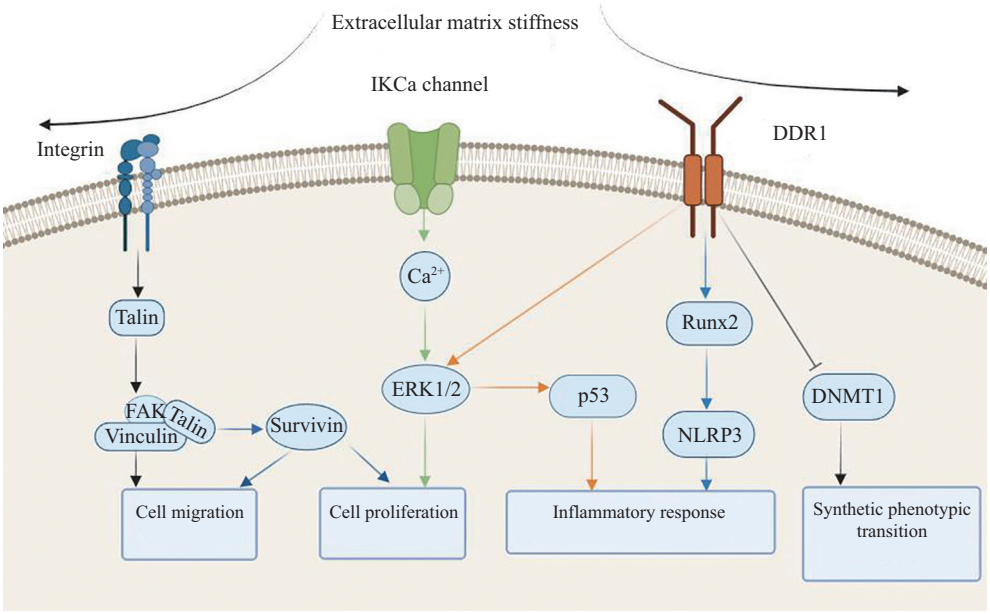

图1 ECM硬度调控VSMCs功能的机制示意图

Fig.1 Schematic diagram illustrating the mechanisms by which ECM stiffness regulates VSMC functions

激活特定的信号通路, 直接驱动细胞周期进程。一方面, ECM硬度增加可上调IKCa通道相关蛋白的表达; IKCa通道激活引发细胞膜超极化, Ca^{2+}内流增强, 胞内Ca^{2+}浓度升高; Ca^{2+}浓度升高进一步激活ERK(extracellular signal regulated kinase)通路, ERK激活推动细胞周期G_0/G_1期细胞向S期转变, 从而促使VSMCs增殖[41]。

另一方面, JOHN等[46]揭示了“FAK(focal adhesion kinase)-E2F1-Survivin-周期蛋白”信号轴在ECM硬度调控VSMCs增殖中的重要作用。ECM硬度增加促使整合素聚集在VSMCs的黏着斑处, 诱导黏着斑形成并激活FAK; 激活的FAK调控下游Rac1, 促进转录因子E2F1核转位并增强其转录活性, E2F1上调Survivin mRNA与蛋白的表达; Survivin通过解除p21对CyclinD1/Cdk4复合物的抑制, 促使CyclinA和B等周期蛋白高表达, 推动细胞周期进程(促进DNA合成与细胞分裂), 从而导致VSMCs过度增殖。Survivin在此过程中扮演了枢纽角色, 它不仅调控增殖, 如下所述它也参与了ECM硬度对VSMCs迁移的调控。

3.3 ECM硬度通过ECM蛋白和Survivin调控VSMC迁移

除了影响增殖外, ECM硬度也显著增强VSMCs的迁移能力。其机制涉及细胞–基质黏附动力学的改变。在硬度增加的ECM上, 因整合素与FN结合亲和力低, 整合素与FN形成的黏着斑表现出“快速形成–快速解离”的特性, 这种特性结合硬度增加所激活的RhoA(ras homologous member A)/ROCK(rho-associated protein kinase)通路, 共同提升细胞前端牵引力, 促进微丝重组, 提升细胞迁移灵活性, 最终增加VSMCs迁移距离和速度[48]。进一步的研究揭示了Survivin在这一过程中也发挥作用。THOMAS等[49]发现, 在模拟病变硬度的环境中, VSMCs内Survivin的表达上调, 促进FAK在其第397位酪氨酸(Tyr397)位点的磷酸化, 并将活化的FAK招募至黏着斑, 推动细胞骨架有序化及应力纤维形成, 使VSMCs形成定向板状伪足, 减少迁移过程中的停滞现象, 最终提升迁移距离与速度。

3.4 ECM硬度通过DDR1-DNMT1机械转导轴激活VSMCs的促炎反应

ECM硬度不仅是血管炎症的结果, 更是其持续恶化的重要驱动因素, 且与表型转变机制存在交汇。研究至少揭示了两条信号通路。其一是ECM硬度增加可通过激活VSMCs表面的DDR1, 进一步激活细胞内ERK-p53信号通路; 核内p53结合*DNMT1*启动子抑制其转录, DNMT1下调导致DNA甲基化水平降低, 引发VSMCs从收缩型向促炎型转化, 使其分泌促炎因子; 招募单核细胞/巨噬细胞浸润血管壁, 形成恶性循环[13]。

其二是LI等[44]发现ECM硬度增加可上调并激活转录因子Runx2; 活化的Runx2转录激活炎症小

体NLRP3的表达; 激活的NLRP3促进IL-1β、IL-18等炎症因子的成熟与释放。这些炎症信号与增殖、迁移信号网络相互交织, 共同加剧血管损伤。

3.5 机制网络整合与交叉对话

综上所述, ECM硬度调控VSMCs功能的分子机制构成了一个多层次、相互交汇的信号网络。上游感受器(如整合素、DDR1)存在感知分工: 整合素介导快速的黏附与骨架重组, 而DDR1更倾向于触发持久的表观遗传与炎症重编程。下游通路则通过关键节点交叉互联: DNMT1的下调是核心的表观遗传开关, 为收缩表型丢失和病理性基因激活奠定了基础; Survivin作为功能协同的枢纽, 同时调控增殖与迁移。ERK则作为共享信号中转站。这些通路共同形成了一个“从机械信号到表观遗传重编程到多功能输出导致ECM进一步硬化”的恶性循环, 持续推动血管疾病的进展。

然而, 这一核心网络在不同血管病理背景下呈现出显著的疾病特异性。ECM硬度的升高往往与疾病特有的生化微环境(如代谢异常、脂质堆积、特定炎症因子)协同作用, 从而塑造出差异化的VSMCs反应与疾病表型。在动脉粥样硬化中, 斑块内ECM硬度的改变与氧化型低密度脂蛋白(oxidized low-density lipoprotein, ox-LDL)堆积等生物微环境有关。研究表明, 1~10 kPa的ECM更易驱动VSMCs向巨噬细胞样泡沫细胞转化, 形成脂质核心; 而超过80 kPa的ECM则通过激活Piezo1等机械感应通道, 协同ox-LDL加剧细胞内脂质蓄积并促使其向成骨样细胞分化, 加速钙化[6]。在高血压中, 除静态ECM硬度增加外, 周期性机械牵张也是持续存在的刺激。研究表明, 高幅度的循环牵张可通过整合素等机械感受器, 激活包括RhoA、MAPK(mitogen-activated protein kinase)在内的多条信号通路, 驱动VSMCs向合成表型转换[33]。当前研究多将二者分开探讨, 但该领域综述明确指出, 开发能整合硬度与牵张信号的复杂体外模型是未来的关键方向, 这提示在高血压环境下, 牵张信号与改变的ECM微环境很可能通过整合素–细胞骨架系统产生协同效应, 进一步激活上述信号通路, 诱导VSMCs肥厚性生长并促进ECM过度合成, 最终导致血管壁的结构重塑[16,52]。因此, 尽管存在如DNMT1、Survivin等共同节点, 但上游触发环境(代谢异常、炎症、压力)的差异, 决定了下游信号通路的权重与组合方式。

4 展望

现有研究已证实ECM硬度调控VSMCs的功能, 但其在血管病变复杂病理环境中的特异性机制与靶向干预策略仍面临严峻挑战。其一, ECM硬度常与炎症等信号共存, 二者协同调控VSMCs功能的交叉网络尚不明确。其二, 针对ECM硬度的干预手段, 如调控胶原交联的赖氨酰氧化酶(lysyl oxidase, LOX)抑制剂, 虽在体外实验中能降低ECM硬度, 但研发因其亚型丰富, 抑制剂泛毒性及单一亚型抑制剂疗效局限等存在困难[53]。例如, 首个不可逆抑制剂β-氨基丙腈(β-aminopropionitrile, BAPN)在临床试验中出现了骨质疏松和组织脆性增加等严重副作用。在结直肠癌中LOXL1扮演抑癌角色, 而在胆管癌中却促进癌症发展。靶向LOXL2的单克隆抗体Simtuzumab在II期临床试验中未能减轻患者肺纤维化, 深刻揭示了靶向ECM单个组分在复杂人体环境中的挑战。目前尚无LOX小分子抑制剂作为抗纤维化及抗癌药物上市, 但不断有新的LOX小分子抑制剂进入临床试验。其三, 在不同血管疾病(如动脉粥样硬化、糖尿病血管病变等)中, ECM硬度升高所处的病理微环境(脂质、高糖等)存在显著异质性, 这些异质性如何塑造ECM硬度调控VSMCs功能的特异性机制网络, 目前缺乏系统阐释。

未来研究可从以下方面推进。一方面, 需构建更仿生的多细胞培养体系(VSMCs、内皮细胞与巨噬细胞或外膜成纤维细胞共培养)或疾病和硬度的耦合模型体系, 结合单细胞转录组学或空间转录组技术, 在模拟氧化型低密度脂蛋白、高糖等特征性病理刺激的环境中, 系统解析硬度信号如何通过与疾病特异性通路的交叉对话, 差异化驱动VSMCs的表型转化[54-55]。另一方面, 未来的干预思路可以转向靶向其下游的核心机械信号节点。其中, 整合素-YAP(Yes-associated protein)/TAZ(transcriptional coactivator with PDZ-binding motif)机械信号转导轴作为枢纽, 极具潜力。研究已证实, 在VSMCs中特异性敲除*YAP/TAZ*会引发类似动脉粥样硬化的转录程序, 导致细胞收缩表型丧失, 并转向促炎症、促硬化的状态。研发精准调控特定整合素亚型或YAP/TAZ的激动剂/拮抗剂, 有望实现对病理性机械信号的“精准干预”, 在抑制VSMC有害表型转化的同时, 最大限度地保留其正常功能[56]。

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郭莹莹负责论文设计与文章撰写；门俊琦负责文稿修改；贾潇凌负责论文设计、评阅与指导。

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