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·文献综述·

大隐静脉源性血管平滑肌细胞表型转化的研究进展

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摘 要 血管平滑肌细胞（VSMCs）表型转化是血管重塑的细胞学基础。收缩表型和合成表型VSMCs反映不同的功能，且两者之间可相互转化。笔者就大隐静脉源性VSMCs表型转化的概念及特点、表型标记物、细胞增殖和迁移，以及基质金属蛋白酶及其抑制物、细胞凋亡、表观遗传学与其表型转化的关系等研究进展进行归纳叙述，旨在为寻找防治静脉曲张相关的药物作用靶点提供理论基础。

关键词 肌，平滑，血管；隐静脉；表型；静脉曲张；综述文献

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Research progress in phenotypic transformation of vascular smooth muscle cells from great saphenous vein

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Abstract Phenotypic transformation of the vascular smooth muscle cells (VSMCs) is considered the cytological basis of vascular remodeling. VSMCs with contractile phenotype and synthesis phenotype exhibit different functions, and they can transform to each other reciprocally. Here, the authors review and extract the research progress in terms of the concept and characteristics of phenotypic transformation, phenotype markers, and proliferation and migration of the VSMCs derived from the great saphenous vein, as well as the relation of the matrix metalloproteinases and their inhibitors, apoptosis, and epigenetic factors with their phenotypic transformation, so as to provide a theoretical foundation for screening the drug targets associated with prevention and treatment of varicose veins.

Key words Muscle, Smooth, Vascular; Saphenous Vein; Phenotype; Varicose Veins; Review

CLC number: R654.3

大隐静脉曲张（great saphenous varicose vein，GSVV）是下肢常见疾病之一，以静脉瓣功能不全、静脉反流、静脉扩张和迂曲、管腔内静脉压力增高为主要临床特征，可并发静脉血栓形成、浅表血栓性静脉炎和静脉性溃疡[1-2]。大隐静脉曲张发生率为20%~40%，老年人为高发人群[3]。多年来，尽管许多学者[4-5]致力于大隐静脉曲张发病机制的研究，但一直尚无定论。研究[6-7]显示，静脉壁中细胞和细胞外基质成分的改变，包括内膜增生、平滑肌细胞功能失调、胶原和弹力纤维比例的变化、基质金属蛋白酶（matrix metalloproteinases，MMPs）及其组织抑制剂（tissue inhibitor of metalloproteinase，TIMPs）

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的失衡，可能是导致静脉壁松弛、薄弱，继而静脉膨张、静脉瓣关闭不全和反流的主要因素。生物组织中含有多种具有特定表型的细胞群，在组织稳态中依据各自的作用相互间调节，通过细胞微环境中的信号维持这些细胞静息与激活之间的平衡。近年来，在控制细胞命运和功能的微环境刺激中，机械力的重要性逐渐受到关注[8]。现已明确，外部压力（如流体静力压、拉伸张力或鞘压）和细胞内细胞骨架张力能驱动转录调节改变[9]。此外，血管平滑肌细胞（vascular smooth muscle cells，VSMCs）的相对动态环境，还涉及多种细胞内外生物化学分子以及机械力的变化：包括生长因子、炎症因子、血管活性因子、血流机械力以及活性氧等因素。鉴于静脉高压是静脉曲张形成的一个重要因素，研究机械力在静脉曲张病理形成中所起的作用已成为热门课题。本文就大隐静脉源性VSMCs表型转化研究进行归纳叙述，旨在为寻找防治静脉曲张相关的药物作用靶点奠定理论基础。

1　VSMCs表型转化的概念及特点

1989年，Baumbach等[10]提出“血管重塑”的概念，由此人们逐渐认识到静脉疾病的病理生理过程不仅是管壁形态结构的改变，VSMCs表型转化才是血管重塑的细胞学基础和关键环节。与骨骼肌和心肌细胞不同，静脉源性VSMCs表型具有分化可逆性和多样性的特点。在胚胎发育过程中，VSMCs由未分化表型逐渐转化为具有成熟特征的分化表型。当血管受损或VSMCs受到生长因子、机械作用、血管活性物质以及血流动力学等因素刺激时，VSMCs又从分化型转化为去分化型，并获得增殖能力，对这一演变过程称之为表型转化（phenotypic transformation）。VSMCs是一种高度特异性细胞，其主要功能为收缩和血管张力调节，以控制血压和血流[11]。根据细胞结构和功能的不同，VSMCs有两种表型，即收缩型（分化型）和合成型（去分化型或未分化型）。收缩型VSMCs，分化程度高，呈纺锤状，胞浆内肌丝丰富，高尔基复合体和线粒体较少，增殖和迁移能力差，其主要功能是维持血管壁的弹性和收缩血管。合成型VSMCs内含大量的高尔基复合体、粗面内质网，肌丝含量少，合成和分泌功能旺盛，增殖和迁移能力强，并能产生大量的细胞外基质，其主要功能是合成分泌基质蛋白，并参与到血管壁重塑和损伤修复[12]。

2　VSMCs表型转化标志物

当VSMCs受到外界刺激后，可通过激活多种信号通路来激发VSMCs表型转化，以适应静脉高压和缺氧对血管壁的影响。检测VSMCs表型转化的标记物种类繁多，一般可分为收缩型标记物和合成型标记物，收缩性标记物主要有平滑肌α–肌动蛋白（α-SM-actin，α-SMA）、平滑肌22α（smooth muscle 22α，SM22α）、平滑肌肌球蛋白重链（smooth muscle-myosin heavy chain，SMMHC）、平滑肌蛋白（smoothelin）、以及H–钙调素结合蛋白（caldesmon），合成型标记物主要有骨桥蛋白（osteopontin，OPN）、上皮调节蛋白（epiregulin）等[13-18]。

2.1　收缩型表型标志物

α-SMA是一种维持VSMCs形态和收缩的重要细胞骨架蛋白，在收缩型VSMCs中优势表达，是VSMC分化早期特异性标志物；SM22α属细胞骨架的结构成分，但不是控制VSMCs收缩的必需蛋白；SM-MHC则是在胚胎形成时期VSMCs特异性表达的一种标志蛋白，且SM–MHC在非SMCs细胞中不表达[19]。因此，SM-MHC被认为是鉴别收缩型VSMCs的最常用标志物之一。Smoothelin表达下调则提示收缩型VSMCs向合成型VSMCs转化，常用于协同SM-MHC区分收缩型VSMCs和合成型VSMCs[20]。

2.2　合成型表型标志物

合成型VSMCs的标志物包括OPN和Epiregulin。OPN是一种富含唾液酸磷酸化和糖基化修饰的基质糖蛋白。OPN是VSMCs表型转化的起始促进因子，其表达与VSMCs的增殖密和迁移密切相关。Epiregulin是表皮生长因子家族的成员之一，可促进VSMCs的增殖。Takahashi等[21]研究显示，Epiregulin是VSMCs去分化的主要自分泌和旁分泌因子，可通过趋化因子以及ERK和p38MAPK等信号通路来调控VSMCs的增殖和表型转化，从而影响到“血管重塑”的病理生理过程。

VSMCs具有高度可塑性，并能在不同的表型状态下生存[22]。VSMCs由收缩型调节至合成型依赖于环境改变，即增殖和迁移活性增加，收缩性丧失，细胞外基质异常[23-24]。此外，VSMCs不同表型标志物的表达受多种因素的调节如转化生长因子β（transforming growth factor β，TGF-β）、

血小板衍生生长因子（platelet derived growth factor，PDGF）、miRNA等。Ha等[25]观察大鼠胸主动脉VSMCs表型转化，发现收缩型VSMCs α-SMA和SM22α呈阳性表达。Hao等[26]研究发现，SM-MHC表达受TGF-β1信号通路的促进，维持平滑肌收缩表型，Gareri等[27]则通过PDGF刺激VSMCs表型转化，使得SM-MHC表达大量下降。Feng等[28]研究显示，在体外血管收缩素（angiotensin II，Ang-II）可诱导VSMCs骨源性表型转化和钙化，同时发现α-SMA和SM22α标记物下调，OPN标记物上调。由此可见，在生理和病理状态下，SMCs参与血管重塑，不同的标记物反映不同的VSMCs表型，且表型变异和可逆性转化是一个复杂和动态的过程[29-31]。

3 细胞增殖、迁移与表型转化

VSMCs表型转化是血管重塑的细胞学基础。成熟的VSMCs为收缩和分化表型，细胞的增生和合成能力低下，可表达多种收缩蛋白、离子通路、细胞收缩功能分子信号[32-33]。在病理状态下，VSMCs由收缩表型转化为合成和去分化表型，其特征是收缩能力丧失，细胞增生、迁移和基质分泌异常[34]。动物实验[35-36]表明，移植大隐静脉管腔狭窄的主要原因是中膜和外膜的SMCs迁移至内膜，导致新生内膜增生。机械力和炎症的协调可导致VSMCs增殖和迁移，其中炎性介子可通过白介素1β（interleukin 1β，IL-1β）和白介素18（interleukin 18，IL-18）信号通路诱导增殖和迁移[37]。Zhang等[38-39]研究发现，肿瘤坏死因子α（tumor necrosis factor α，TNF-α）可抑制丝裂素活化蛋白激酶磷酸酶（mitogen-activated protein kinase phosphatase，MAKP）炎性通路，降低炎性反应。在刺激过程中，VSMCs表型由静止收缩型转化为促炎反应型，SMCs向内膜迁移，提示VSMCs增殖和迁移与炎症相关。动物实验显示，血管细胞黏附分子1（vascular cell adhesion molecule-1，VCAM-1）或VCAM-1 siRNA表达能阻止单核/巨噬细胞募集反应，抑制VSMCs增殖、迁移和新生内膜形成[40-41]。在血管重塑过程中，VSMCs收缩表型和合成表型存在本质性差异（即标记物表达、细胞形态和活性）。合成型VSMCs源于中膜去分化收缩型VSMCs和外膜分化成纤维细胞及未分化间质干细胞。合成型VSMCs收缩器（肌丝，致密体和斑）少，合成器（粗面内质网，高尔基体）增多[42]。诸多因素（物理、机械、缺氧、激素、氧化应激、基因、钙离子等）影响VSMCs表型，而VSMCs的增殖和迁移改变取决于VSMCs表型。李源等[43]发现，源于曲张静脉的VSMCs增殖和迁移能力比正常静脉增加，提示VSMCs表型转化影响细胞功能。有学者[44-45]认为，VSMCs在分化和去分化之间表型转化是一种可逆性变化，并伴随着细胞与细胞、细胞基质黏附网络形态和功能的改变。因此，如何在分子水平调节VSMCs的增殖与迁移，控制细胞表型的转化，可视为分子通路靶标研究的发展趋势[46-51]。

4 MMPs与表型转化

MMPs是一种依赖于锌离子的内肽酶，具有降解细胞外基质（extracellular matrix，ECM）蛋白作用。MMPs可与细胞膜上的生物活性分子相互作用，并能调节偶联G蛋白受体和细胞信号。MMPs参与多种生理过程，并影响细胞增殖、迁移、变异。MMPs还涉及细胞凋亡、免疫反应、组织修复、血管生成[52]。MMPs家族依据消化底物的不同分为胶原酶类，明胶酶类，基质溶解素类、膜型金属蛋白酶类和未分类[53]。MMPs有助于VSMCs增殖和迁移，迁移可促进血管新生内膜增生（即内皮细胞和SMCs通过MAPK信号激活，刺激生长因子、细胞因子和MMPs的分泌）[54]。VSMCs表型变化决定MMPs代谢异常。合成表型收缩型丧失，ECM产生异常，VSMCs迁移增加；收缩表型低蛋白含量和增殖率，具有独特的收缩蛋白和信号分子[55]。动物实验表明，MMP-2和MMP-9在不同静脉层表达有所差异。MMP-2表达主要位于外膜，MMP-9表达则位于内皮细胞、中膜SMCs、外膜微血管。与此同时，炎症可促进MMP-2和MMP-9表达[56-57]。人体外细胞培养显示，异常VSMCs其MMP-2和MMP-9呈高表达[55,58]。研究[59]发现，抵抗素可诱导MMP-2和MMP-9表达（mRNA和蛋白水平），抗MMP-2和MMP-9 IgG可抑制抵抗素诱导VSMCs迁移。TIMP-1优先结合MMP-9，TIMP-2优先结合MMP-2，抵抗素抑制TIMPs表达；WNT1诱导信号通道蛋白1（WNT1 inducible signaling pathway protein 1，WISPI）可促进SMCs内MMPs和TIMPs高表达[60]；氢可降低p38MAPK活性导致移植静脉MMP-2和MMP-9低表达，抑制VSMCs迁移[61]；在增生的血管内膜中，MMP-3 mRNA和蛋白呈高表达[62]；OPN和MMPs具有密切的关联

性，这与动脉压对移植静脉刺激的适应性有关[63]。VSMCs释放MMPs降解ECM，并产生TIMPs，因此，MMPs和TIMPs的平衡决定ECM的动态平衡[64-65]。动物实验显示，小鼠移植静脉TIMP-1呈高表达。这一结果提示，TIMP-1可抑制MMPs，阻止斑块发展，并增加其稳定性[66]。结缔组织生长因子是一种异常的纤维化介质，它能通过结缔组织生长因子信号通道调节ECM的合成，从而改变静脉管壁纤维化的进程[67]。可见，MMPs与SMCs表型转化关系密切，在VSMCs发生重构过程中，MMPs和TIMPs通过分子信号通道调节发挥重要的生理和病理生理功能。

5　细胞凋亡与表型转化

细胞凋亡是细胞内有规律的自我消亡过程，细胞死亡的一种生理形式，受诱导基因（p53、bcl-xs、bax）、抑制基因（Bcl-2、bcl-xl、mcl-1）及参与基因（c-myc、c-fos）的调控[68]。细胞凋亡的作用是维持组织内环境的稳定性，以减少细胞的更新。细胞凋亡包括内源性和外源性两条通道。内源性通道又称线粒体通道，调节细胞凋亡启动蛋白（bax或Bcl-2）及特异胱门蛋白酶（caspase）刺激线粒体释放细胞色素C进入胞浆与凋亡蛋白酶活化因子1（APAF-1）结合引发细胞凋亡。外源性通道又称跨膜通道，在细胞凋亡信号的刺激下，FasL和TNF-α作用相应的受体导致细胞凋亡[69]。Whiteley等[70]获取人曲张大隐静脉标本，采用免疫组化和免疫荧光法标记p53，发现曲张静脉SMCs凋亡上调，并与炎性标记物呈正相关。研究发现，膜联蛋白A2过表达和IncRNA低表达可促进SMCs增殖与迁移，并减少SMCs凋亡[50]。诱导VSMCs缺氧模型显示，VSMCs增殖与迁移增加，但与细胞凋亡无相关性[71]。在缺氧状态下，金属硫蛋白可阻止VSMCs凋亡，这一结果有可能为静脉曲张的靶标治疗提供理论依据[72]。许多学者[1, 73]认为，VSMCs凋亡与年龄和性别密切相关。>50岁和女性细胞凋亡明显增加，故研究VSMCs凋亡与表型转化应考虑年龄和性别因素。文献[74]报道，炎性因子可增加VSMCs增殖与迁移，并经p38MAPK-HSPS27分子通道诱导细胞凋亡。同源异型盒蛋白过表达可促进VSMCs增殖与迁移及抗凋亡能力，上调OPN可有利于VSMCs表型转化[30]。细胞自体吞噬作用可抑制肌饿诱导VSMCs凋亡，而异常自体吞噬作用可调节VSMCs的功能[75]。小窝蛋白3能调节VSMCs收缩和合成型的转型，抑制细胞凋亡[76]。由此可见，VSMCs凋亡的变化是建立在表型变化的基础上，表型的异常必定影响细胞的凋亡。

6　表观遗传学调控与表型转化

VSMCs的表型转化受多种因素影响，其中，表观遗传学调控机制在VSMCs表型转化中所起到的重要作用日益受到人们重视。表观遗传通常被定义为不涉及DNA核苷酸序列改变的基因表达和调控的可遗传修饰，通常是由于环境因素而引发改变，主要包括DNA甲基化、组蛋白修饰、非编码RNA以及染色质重塑等。研究表明，表观遗传对VSMCs表型转化的调控主要是通过对其表型标志基因（例如：α-SMA、SM22α、SM-MHC、OPN等）表达的调控来实现[34, 77-78]。Hiltunen等[79]的早期研究通过高效液相色谱法检测体内VSMCs染色体5-甲基胞嘧啶含量发现，动脉粥样硬化模型VSMCs表型转化过程中呈现全基因组的低甲基化状态；同样在体外实验，细胞增殖过程中collagen type VX α1基因的低甲基化诱导相应基因高表达进而调控VSMCs的表型转化并影响动脉粥样硬化的发展[80]。近年来，更多的实验研究发现，DNA的异常甲基化可通过特定的基因修饰来调控VSMCs的表型转化并影响到相关血管疾病进程。Jiang等[34]研究发现静脉曲张VSMCs中OPN基因启动子的低甲基化可能是诱导OPN高表达的重要因素，提示异常的表观遗传修饰参与了VSMCs的表型转化并导致新生血管内膜增厚进而影响静脉曲张的发生与发展。Ali等[81]证实肿瘤坏死因子α（tumor necrosis factor-α，TNT-α）可诱导SMCs收缩型基因（α-SMA、SM-MHC）启动子甲基化并通过Krupper样因子4（Krupper like factor-4，KLF-4）调节通路来诱导大鼠脑SMCs表型变化。组蛋白修饰多发生于细胞生长发育期，通过调控血清反应因子（serum response factor，SRF）及其辅助因子与染色质模板的结合来改变外环境，从而影响VSMCs分化过程[82-83]。由于组蛋白修饰的VSMCs限制性位点位于VSMCs基因染色质的CArG box序列，SRF及其辅助因子与VSMCs染色质启动子CArG box DNA序列相互反应是引起VSMCs在生长发育和表型转化过程中的信号通路关键环节。此外，有研究[84]表明，高脂饮食可诱导DNA甲基转移酶1（DNA methyltransferase 1，

DNMT-1）负性调控因子miR-152下调，进而导致主动脉VSMCs雌激素受体α基因（Estrogen receptor α gene，ER-α）高甲基化，而染色质重塑亦被发现在VSMCs分化过程中起到关键作用[77]。与此同时，一些新的调控靶点如TET-2（ten-eleven translocation 2）以及YAP（yes-associated protein）相关研究的出现进一步完善了VSMCs表型转化与血管性疾病发生发展的机制探索[85-86]。由此可见，VSMCs的可塑性与细胞外部环境和表观遗传调控机制密切相关，然而，不同于DNA序列的改变，许多表观遗传的改变是可逆的，因此，如何从表观遗传调控水平去调节并控制VSMCs表型转化，可作为相应血管类疾病靶向治疗的研究思考方向。

7 结 语

综上所述，大隐静脉源性VSMCs表型转化是血管重塑的细胞学基础。VSMCs表型转化除了与其基因表达谱改变有关外，还受细胞骨架结构与功能的影响。设想建立人正常静脉VSMCs和曲张静脉VSMCs细胞单层培养系统，从VSMCs增殖、迁移、黏附、衰老、骨架、MMPs和TIMPs分泌和细胞凋亡方面研究曲张大隐静脉来源VSMCs的生物学变化特征，有助于初步证实曲张大隐静脉、浅表血栓性静脉炎及缺氧诱导正常静脉VSMCs从收缩型向合成型转化并获得增生、迁移和分泌大量细胞外基质的能力。

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