DOI:10.16781/j.0258-879x.2016.08.0992

·综 述·

主动脉疾病中血管平滑肌细胞表型转化调控机制研究进展

安 朝,徐志云*
第二军医大学长海医院胸心外科,上海 200433

[摘要] 主动脉疾病(aortic disease, AD)指由于主动脉壁病变所致的一类疾病,往往高度致命。目前非遗传性AD的发病机制尚未完全阐明。血管平滑肌细胞(vascular smooth muscle cells, VSMC)是主动脉壁中层的主要细胞成分,通常认为其存在收缩型与合成型两种表型,且可相互转化。VSMC由收缩型向合成型的过度转化在AD的发生发展过程起重要作用。尽管关于VSMC表型转化研究较多,但众多调控机制如何协调运作以及相互之间的关系仍然有待阐明。本文就目前已知的VSMC表型转化调控机制作一综述。

[关键词] 主动脉疾病;血管平滑肌;平滑肌肌细胞;表型转化;表观遗传学
[中图分类号] R 543.1 [文献标志码] A [文章编号] 0258-879X(2016)08-0992-04

Regulatory mechanism of vascular smooth muscle cell phenotype switch in aortic disease: an update

AN Zhao, XU Zhi-yun*
Department of Cardiothoracic Surgery, Changhai Hospital, Second Military Medical University, Shanghai 200433, China

[**Abstract**] Aortic disease(AD) consists of a series of life-threatening diseases caused by aortic wall lesions. Up to now little has been known about the etiology of non-hereditary AD. Vascular smooth muscle cells(VSMC) are the major components of the medial aortic wall and can toggle between a contractile phenotype and a synthetic phenotype. The excessive transformation of VSMC from contractile state to synthetic state plays an important role in the development and progression of AD. Although there are many researches on the regulation of VSMS phenotype switch, how these regulatory pathways operate harmoniously and the what relationship between them remain to be elucidated. Here in this paper we reviewed the existing regulatory mechanisms of VSMC phenotype switch.

[**Key words**] aortic diseases; vascular smooth muscle; smooth muscle myocytes; phenotype switch; epigenetics
[Acad J Sec Mil Med Univ, 2016, 37(8): 992-995]

主动脉疾病(aortic disease,AD)包括急性主动脉综合征(acute aortic syndrome,AAS)、主动脉动脉瘤(aortic aneurysm,AA)等,是一类起病隐匿、高度致死性疾病[1]。除Marchesani综合征、Loeys-Dietz综合征等遗传性病因外,目前这类疾病的具体发病机制尚未完全阐明。主动脉壁中层血管平滑肌细胞(vascular smooth muscle cell,VSMC)数量减少及过度表型转化在AD的发生过程中扮演重要角色[2],VSMC过度表型转化直接导致主动脉壁中层细胞外基质(extracellular matrix,ECM)成分构成发生改变,并促进AD发生、发展。本文就目前AD中VSMC表型转化机制方面的研究进展进行综述。

1 VSMC表型转化与AD

主动脉中VSMC主要定位于主动脉壁中层,是主动脉壁中层的主要细胞成分[3]。不同于骨骼肌与心肌细胞,成人主动脉壁VSMC仍具有增殖分化能力。VSMC表型主要为收缩型与合成型:生理情况下VSMC表型主要为收缩型,主要特征为细胞内肌丝丰富,收缩功能较强,含α平滑肌肌动蛋白(α-SMA)、平滑肌肌球蛋白重链(SM-MHC)、平滑肌22α(SM22α)等特征性蛋白,几乎无分裂增殖能力,主要功能为参与维持主动脉壁的机械性能;当收缩型VSMC受内外因素刺激时可转化为合成型,主要特征为分裂增殖能力强,合成分泌功能旺盛,肌丝含量少,收缩功能弱或缺如,含骨桥蛋白(OPN)等特征性蛋白,主要功能为参与受损血管壁的修复[4]。Kimura等[5]报道,在胸主动脉夹层(thoracic aortic dissection,TAD)小鼠模型中,TAD组主动脉壁中层VSMC合成型较对照组明显增多,而收缩型减少、同时伴随细胞外弹性膜层数减少,断裂以及排列紊乱。Wang等[6]报道,在TAD患者中发现类似现

[收稿日期] 2015-09-17 [接受日期] 2016-03-11
[作者简介] 安 朝,博士. E-mail:341757207@qq.com
*通信作者 (Corresponding author). Tel:021-31161765, E-mail:zhiyunxu@hotmail.com

象,并发现 VSMC 数量减少,同时由收缩型向合成型过度转化并大量分泌胶原与基质金属蛋白酶 2(matrix metalloproteinase-2,MMP2),导致胶原沉积与细胞外弹性膜降解,最终导致 AD 发生。Blunder 等[7]发现,主动脉壁中层 VSMC 减少及 ECM 构成异常与动脉瘤发生相关。这些研究提示 VSMC 的表型转化与 AD 的发生发展密切相关。

2　VSMC 表型转化机制

2.1　多条信号通路参与 VSMC 表型转化调控　血小板衍生因子(platelet-derived growth factor,PDGF)可促进 VSMC 由收缩型向合成型转化,其广泛存在,正常血管壁表达 PDGF 及其受体水平较低,但当血管壁受损、高血压等病理情况下其表达可显著上调[8]。PDGF 为二聚体,其二聚体可由两条高度同源的 A 链与 B 链构成,包括 PDGF-AA、PDGF-BB、PDGF-AB。有研究表明,在大鼠颈动脉中灌注 PDGF 可促进 VSMC 迁移增殖并向合成型转化[9]。PDGF 可以通过激活 VSMC 的 PDGF 受体,进而激活 PI3K-Akt 通路、ERK 信号通路促进 VSMC 的表型转化[10]。Ishigaki 等[11]在体外细胞研究中证明,PDGF 可促进 VSMC 由收缩型向合成型转化。Owens 等[12]报道,在小鼠的高血压模型中检测到 *PDGF* mRNA 表达水平较对照高 2 倍,并且这一差异在血压纠正后消失。

表皮生长因子(epidermal growth factor,EGF)可通过促进 VSMC 由收缩型向合成型转化[13]。VSMC 表面分布 EGF 受体(epidermal growth factor receptor,EGFR)并可分泌 EGF[14],EGF 与 EGFR 结合后,EGFR 发生构象变化形成二聚体,激活 EGFR 胞质内酪氨酸激酶结构域,发生自身磷酸化[15]。Igura 等[16]报道,EGF 在大鼠颈动脉血管受球囊损伤 2 h 后表达可较正常状态下升高 12 倍以上。VSMC 中 EGFR 的自身磷酸化可激活多条通路,被激活的通路包括 PI3K-Akt 通路[16]、MAPK 通路[17]、JAK-STAT 通路[18]。这些通路的激活可使 VSMC 向合成型转化,其增殖、分泌、迁移能力均增强。Fiebeler 等[19]报道,高血压时 VSMC 中 EGFR 的反式激活促进了 VSMC 向合成型转化,导致血压水平进一步升高,而高血压是 AD 的重要危险因素。

Notch 通路参与调控了 VSMC 表型转化。Notch 受体被周围细胞细胞膜表面的 Notch 配体激活后可通过 CBF-1/RBP-Jκ 依赖与非依赖两种途径激活下游 bHLH 转录因子,进而调控 VSMC 表型转化[20]。Notch 通路对 VSMC 表型的调节表现为双向性,Notch 通路被激活后 Notch 受体的胞内部分可通过直接结合于 α-SMA 的启动子部分并促进其转录以维持 VSMC 的收缩表型,同时被激活的下游 bHLH 转录因子通过上调 KLF4、抑制心肌素表达等途径在转录水平抑制 α-SMA 表达并促进 VSMC 向合成表型转化[21]。

已证实转化生长因子 β1(transforming growth factor-β1,TGF-β1)可维持 VSMC 的收缩表型,在体外 TGF-β1 可抑制由血清、PDGF、EGF 等引起的 VSMC 表型转化与分裂增殖并促进 α-SMA 、SM-MHC、SM22α 等收缩型 VSMC 标志物表达[22-24]。TGF-β1 与 AD 的发生密切相关,有研究表明在大鼠受损的主动脉血管壁中层中 TGF-β1 含量下降同时伴随 VSMC 收缩型标志物表达下降[25];Kimura 等[5]报道在小鼠的 TAD 模型中观察到发生 TAD 的小鼠中 TGF-β1 通路下游信号转导蛋白 Smad2 表达下降,同时伴 VSMC 合成型异常增多,ECM 构成改变,主动脉壁中层弹性膜层数减少,结构异常。

骨形态发生蛋白 4(bone morphogenetic protein 4,BMP4)通路可通过上调心肌蛋白相关转录因子(myocd-related transcription factor,MRTF)进而下调 KLF4 来维持 VSMC 的收缩表型[26]。Chaterji 等[27]报道 CD138 参与维持 VSMC 的收缩表型,敲减 CD138 的小鼠 VSMC 收缩型标志物α-SMA等表达显著下降,分裂增殖与合成能力增强,其认为 CD138 通过整合素 αvδ3 与 αvδ5 途径维持了 VSMC 的收缩表型。

2.2　ECM 中多种成分参与 VSMC 表型调控　ECM 中成分可通过整合素介导的多条信号通路参与细胞功能调控,层黏连蛋白可通过 P38-MAKP 信号通路维持 VSMC 的收缩表型,而纤连蛋白可通过 ERK-MAKP 信号通路促进 VSMC 向合成表型转化[28]。Qin 等[29]报道,层粘连蛋白可使 VSMC 收缩型标志物 SM22α 等表达下调,并且可使 VSMC 由收缩型向合成型转化。Arcucci 等[30]报道 ECM 中超氧化物歧化酶 3(superoxide dismutase 3,SOD3)与 Akt 含量降低导致细胞外信号调节激酶 1/2(extracellular signal regulated kinase 1/2,Erk1/2)磷酸化下降、MMP9 含量升高,最终导致 VSMC 凋亡、弹性蛋白与胶原蛋白裂解,动脉瘤生成。Blunder 等[7]报道,Ⅳ型胶原可促进 VSMC 收缩型标志物如 α-SMA、SM-MHC 表达,而Ⅰ型胶原则通过激活 VCAM-1 蛋白、转录因子 NFAT 等促进 VSMC 向合成型转化。

2.3　microRNA（miR）参与 VSMC 的表型调控　Cordes 等[31]报道，miR-143 与 miR-145 参与调控了干细胞向成熟 VSMC 分化的过程，其受血清应答因子（serum response factor，SRF）、心肌素、Nkx2.5 调控，并且 miR-143/145 的高表达可维持 VSMC 的收缩表型，抑制 VSMC 向合成型分化。Davis-Dusenbery 等[26]报道，TGF-β 通路与 BMP4 通路均可调控下游的 miR-143/145 上调表达，进而下调 KLF4，维持 VSMC 的收缩表型。miR-21 在大鼠颈动脉损伤后的血管壁中高表达，并且细胞实验证实其促进 VSMC 向合成型转化[32]。TGF-β 下游心肌素亦受 miR-9 调节，miR-9 可协同 KLF4 抑制心肌素表达从而促进 VSMC 向合成型转化[33]。

2.4　VSMC 表型转化受表观遗传学机制调控　DNA 甲基化与脱甲基化、组蛋白修饰等表观遗传学方面调节机制参与了 VSMC 表型转化的调控。Liu 等[34]发现，TET2 蛋白通过上调 MYOCD 与 SRF 启动子区域 5-羟甲基胞嘧啶（5-hydroxymethylcytosine，5-hmC）水平促进 MYOCD 与 SRF 表达进而维持 VSMC 的收缩表型，同时 VSMC 合成型的促进因素 KLF4 则被抑制；敲除 TET2 则可促进 VSMC 向合成型转化。Qiu 等[35]则报道 TGF-β1 通过上调 P300/CBP 蛋白促进 SM22α 基因所在区域组蛋白的乙酰化水平上调 SM22α 表达；过表达组蛋白乙酰化抑制蛋白如 Twist1、E1A 则抑制 TGF-β1 通路。

3　展　望

VSMC 是主动脉壁中的主要细胞成分，主动脉壁中 VSMC 由收缩型向合成型过度转化可导致主动脉壁 VSMC 功能相关蛋白减少，进而影响 VSMC 行使正常功能，最终可能导致主动脉壁弹性膜受损，ECM 构成改变。这一过程可能在 AD 的发生、发展中起重要作用。目前已知多种机制共同导致了 AD 时 VSMC 的表型转化，但这些调控机制所构成的调控网络如何运作、是否有尚未阐明的其他机制作用于 VSMC、VSMC 的表型转化与 AD 发生的确切因果关系等仍有待进一步深入研究。明确 VSMC 表型转化的调控机制有助于寻找 AD 相关的治疗靶点，预防 AD 的发生，巩固 AD 的手术疗效。

[参考文献]

[1] KOCHANEK K D, KIRMEYER S E, MARTIN J A, STROBINO D M, GUYER B. Annual summary of vital statistics: 2009 [J]. Pediatrics, 2012, 129: 338-348.

[2] SHEN Y H, ZHANG L, REN P, NGUYEN M T, ZOU S, WU D, et al. AKT2 confers protection against aortic aneurysms and dissections[J]. Circ Res, 2013, 112: 618-632.

[3] WAGENSEIL J E, MECHAM R P. Vascular extracellular matrix and arterial mechanics[J]. Physiol Rev, 2009, 89: 957-989.

[4] SHI N, CHEN S Y. Mechanisms simultaneously regulate smooth muscle proliferation and differentiation [J]. J Biomed Res, 2014, 28: 40-46.

[5] KIMURA T, SHIRAISHI K, FURUSHO A, ITO S, HIRAKATA S, NISHIDA N, et al. Tenascin C protects aorta from acute dissection in mice [J]. Sci Rep, 2014, 4: 4051.

[6] WANG L, ZHANG J, FU W, GUO D, JIANG J, WANG Y. Association of smooth muscle cell phenotypes with extracellular matrix disorders in thoracic aortic dissection[J]. J Vasc Surg, 2012, 56: 1698-1709.

[7] BLUNDER S, MESSNER B, ASCHACHER T, ZELLER I, TÜRKCAN A, WIEDEMANN D, et al. Characteristics of TAV- and BAV-associated thoracic aortic aneurysms-smooth muscle cell biology, expression profiling, and histological analyses [J]. Atherosclerosis, 2012: 355-361.

[8] RAINES E W. PDGF and cardiovascular disease[J]. Cytokine Growth Factor Rev, 2004, 15: 237-254.

[9] JAWIEN A, BOWEN-POPE D F, LINDNER V, SCHWARTZ S M, CLOWES A W. Platelet-derived growth factor promotes smooth muscle migration and intimal thickening in a rat model of balloon angioplasty [J]. J Clin Invest, 1992, 89: 507-511.

[10] LI H, LUO K, HOU J. Inhibitory effect of Puerariae radix flavones on platelet-derived growth factor-BB-induced proliferation of vascular smooth muscle cells via PI3K and ERK pathways [J]. Exp Ther Med, 2015, 9:257-261.

[11] ISHIGAKI T, IMANAKA-YOSHIDA K, SHIMOJO N, MATSUSHIMA S, TAKI W, YOSHIDA T. Tenascin-C enhances crosstalk signaling of integrin αvβ3/PDGFR-β complex by SRC recruitment promoting PDGF-induced proliferation and migration in smooth muscle cells [J]. J Cell Physiol, 2011, 226: 2617-2624.

[12] OWENS G K, SCHWARTZ S M. Alterations in vascular smooth muscle mass in the spontaneously hypertensive rat. Role of cellular hypertrophy, hyperploidy, and hyperplasia[J]. Circ Res, 1982, 51: 280-289.

[13] MITSUMATA M, GAMOU S, SHIMIZU N, YOSHIDA Y. Response of atherosclerotic intimal smooth muscle cells to epidermal growth factor *in vitro*

[J]. Arterioscler Thromb, 1994, 14: 1364-1371.
[14] SCHREIER B, GEKLE M, GROSSMANN C. Role of epidermal growth factor receptor in vascular structure and function[J]. Curr Opin Nephrol Hypertens, 2014, 23: 113-121.
[15] BURGESS A W, CHO H S, EIGENBROT C, FERGUSON K M, GARRETT T P, LEAHY D J, et al. An open-and-shut case? Recent insights into the activation of EGF/ErbB receptors[J]. Mol Cell, 2003, 12: 541-552.
[16] IGURA T, KAWATA S, MIYAGAWA J, INUI Y, TAMURA S, FUKUDA K, et al. Expression of heparin-binding epidermal growth factor-like growth factor in neointimal cells induced by balloon injury in rat carotid arteries[J]. Arterioscler Thromb Vasc Biol, 1996, 16: 1524-1531.
[17] REYNOLDS C M, EGUCHI S, FRANK G D, MOTLEY E D. Signaling mechanisms of heparin-binding epidermal growth factor-like growth factor in vascular smooth muscle cells[J]. Hypertension, 2002, 39(2 Pt 2): 525-529.
[18] LEE K S, PARK J H, LEE S, LIM H J, CHOI H E, PARK H Y. HB-EGF induces delayed STAT3 activation via NF-kappaB mediated IL-6 secretion in vascular smooth muscle cell[J]. Biochim Biophys Acta, 2007,1773:1637-1644.
[19] FIEBELER A, LUFT FC. The mineralocorticoid receptor and oxidative stress[J]. Heart Fail Rev, 2005, 10: 47-52.
[20] MORROW D, GUHA S, SWEENEY C, BIRNEY Y, WALSHE T, O'BRIEN C, et al. Notch and vascular smooth muscle cell phenotype[J]. Circ Res, 2008, 103: 1370-1382.
[21] TANG Y, URS S, LIAW L. Hairy-related transcription factors inhibit Notch-induced smooth muscle alpha-actin expression by interfering with Notch intracellular domain/CBF-1 complex interaction with the CBF-1-binding site[J]. Circ Res, 2008, 102: 661-668.
[22] BJÖRKERUD S. Effects of transforming growth factor-beta 1 on human arterial smooth muscle cells *in vitro*[J]. Arterioscler Thromb, 1991, 11: 892-902.
[23] OWENS G K, GEISTERFER A A, YANG Y W, KOMORIYA A. Transforming growth factor-beta-induced growth inhibition and cellular hypertrophy in cultured vascular smooth muscle cells[J]. J Cell Biol, 1988, 107: 771-780.
[24] DEATON R A, SU C, VALENCIA T G, GRANT S R. Transforming growth factor-beta1-induced expression of smooth muscle marker genes involves activation of PKN and p38 MAPK[J]. J Biol Chem, 2005, 280: 31172-31181.
[25] GRAINGER D J, METCALFE J C, GRACE A A, MOSEDALE D E. Transforming growth factor-beta dynamically regulates vascular smooth muscle differentiation *in vivo*[J]. J Cell Sci, 1998, 111 (Pt 19): 2977-2988.
[26] DAVIS-DUSENBERY B N, CHAN M C, RENO K E, WEISMAN A S, LAYNE M D, LAGNA G, et al. down-regulation of Kruppel-like factor-4 (KLF4) by microRNA-143/145 is critical for modulation of vascular smooth muscle cell phenotype by transforming growth factor-beta and bone morphogenetic protein 4[J]. J Biol Chem, 2011, 286: 28097-28110.
[27] CHATERJI S, LAM C H, HO D S, PROSKE D C, BAKER A B. Syndecan-1 regulates vascular smooth muscle cell phenotype[J]. PLoS One, 2014, 9: e89824.
[28] STEGEMANN J P, HONG H, NEREM R M. Mechanical, biochemical, and extracellular matrix effects on vascular smooth muscle cell phenotype[J]. J Appl Physiol, 2005, 98: 2321-2327.
[29] QIN H, ISHIWATA T, WANG R, KUDO M, YOKOYAMA M, NAITO Z, et al. Effects of extracellular matrix on phenotype modulation and MAPK transduction of rat aortic smooth muscle cells *in vitro*[J]. Exp Mol Pathol, 2000, 69: 79-90.
[30] ARCUCCI A, RUOCCO M R, ALBANO F, GRANATO G, ROMANO V, CORSO G, et al. Analysis of extracellular superoxide dismutase and Akt in ascending aortic aneurysm with tricuspid or bicuspid aortic valve[J]. Eur J Histochem, 2014, 58: 2383.
[31] CORDES K R, SHEEHY N T, WHITE M P, BERRY E C, MORTON S U, MUTH A N, et al. miR-145 and miR-143 regulate smooth muscle cell fate and plasticity[J]. Nature, 2009, 460: 705-710.
[32] JI R, CHENG Y, YUE J, YANG J, LIU X, CHEN H, et al. MicroRNA expression signature and antisense-mediated depletion reveal an essential role of microRNA in vascular neointimal lesion formation[J]. Circ Res, 2007, 100: 1579-1588.
[33] WANG K, LONG B, ZHOU J, LI P F. MiR-9 and NFATc3 regulate myocardin in cardiac hypertrophy[J]. J Biol Chem, 2010, 285: 11903-11912.
[34] LIU R, JIN Y, TANG W H, QIN L, ZHANG X, TELLIDES G, et al. Ten-eleven translocation-2 (TET2) is a master regulator of smooth muscle cell plasticity[J]. Circulation, 2013, 128: 2047-2057.
[35] QIU P, RITCHIE R P, GONG X Q, HAMAMORI Y, LI L. Dynamic changes in chromatin acetylation and the expression of histone acetyltransferases and histone deacetylases regulate the SM22alpha transcription in response to Smad3-mediated TGFbeta1 signaling[J]. Biochem Biophys Res Commun, 2006, 348: 351-358.

[本文编辑] 魏学丽