·综 述·

血管外膜成纤维细胞在血管重构中的作用

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[摘 要] 血管重构促进心血管病病程进展,是导致心血管事件和影响预后的关键因素,阻止病理性血管重构是防治心血管病并发症和改善预后的重要策略。传统观点认为血管外膜对血管起支持保护作用,而现在认为血管外膜是血管的信号分析处理中心,直接调控血管的结构和功能,在心血管病的血管重构特别是病程进展和转归中起关键作用。血管外膜成纤维细胞是血管外膜的主要细胞成分,在血管重构发生发展中的作用尤为突出。本文主要论述血管外膜成纤维细胞在血管重构中的作用与机制,特别是其在高血压、动脉粥样硬化、主动脉瘤和主动脉夹层血管重构中的作用。

[关键词] 成纤维细胞;血管重构;高血压;动脉粥样硬化;主动脉瘤

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Roles of vascular adventitial fibroblasts in vascular remodeling

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[**Abstract**] Vascular remodeling promotes the progression of cardiovascular disease and is crucial for cardiovascular events and influencing prognosis. Intervention of pathological vascular remodeling is an important strategy for preventing and treating complications of cardiovascular disease and improving prognosis. Vascular adventitia has been regarded as a supportive and protective tissue for blood vessels for a long time, but now it is believed that the adventitia is the signal analysis and processing center of the blood vessels. It directly modulates the structure and function of blood vessels, and plays a key role in vascular remodeling, especially in the progression and prognosis of cardiovascular diseases. Adventitial fibroblasts are the main cellular component of the adventitia, and play a particularly prominent role in the occurrence and development of vascular remodeling. This review is focused to show the role and mechanism of the adventitial fibroblasts in vascular remodeling, especially in the research progress of hypertension, atherosclerosis, aortic aneurysm and aortic dissection.

[**Key words**] fibroblasts; vascular remodeling; hypertension; atherosclerosis; aortic aneurysm

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血管重构是指血管壁出现的一系列结构和功能异常,包括血管壁中细胞的增殖、迁移、凋亡和基质成分变化,血管的结构变化如管壁增厚、管壁/管腔比值增大和纤维化,并伴有血管功能异常[1-2]。血管重构在早期往往是一种适应性保护机制,但随着病程进展而转变为失代偿,并促进心血管病的病程进展和并发症,干预血管重构是预防和减轻心血管病的并发症和改善预后的重要策略[3-5]。

动脉壁由血管外膜、中膜和内膜3层组成,传统观点认为血管外膜对血管起支持保护作用,而现在认为血管外膜是血管的信号分析处理中心,调控血管的结构和功能,在高血压、动脉粥样硬化、主动脉瘤和主动脉夹层等心血管病的血管重构中起重要作用,影响心血管病的病程进展、转归和预后[4,6]。血管外膜成纤维细胞(adventitial fibroblast, AF)是血管外膜的主要细胞成分,作为血管重构中的“前哨细胞”,是血管重构的第一反应者和启动者,对各种刺激产

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生反应。一旦AF被激活，将发生增殖、迁移和分化等表型变化，进而通过多种信号机制调控血管中膜和内膜的功能和结构，特别是对血管中膜的血管平滑肌细胞（vascular smooth muscle cell，VSMC）有重要调节作用，引起血管重构[7-8]。

1　血管外膜的细胞成分、滋养血管和神经支配

血管外膜包含多种细胞成分，包括AF、微血管内皮细胞、驻留巨噬细胞、T淋巴细胞、B淋巴细胞、肥大细胞和树突状细胞，并受交感神经支配[9-12]。血管外膜的主要细胞成分是AF，可产生细胞外基质，包括Ⅰ型和Ⅲ型胶原蛋白、蛋白多糖和纤维连接蛋白[6]。在一定病理条件下AF发生表型转换，分化为肌成纤维细胞（myofibroblast cell，MF），这是一种可收缩的成纤维细胞，其特征是存在应力纤维和细胞骨架蛋白，能从外膜迁移到中膜并参与新内膜的形成[1,13]。α-平滑肌肌动蛋白（α-smooth muscle actin，α-SMA）是MF的特征性标志蛋白，表达于MF，而不表达于AF。

滋养血管是位于血管外膜的微血管网络，为外膜和中膜提供氧气和营养。在高血压和动脉粥样硬化等病理情况下，滋养血管数量增加，通常从外膜延伸到中膜，参与血管重构[14-16]。Li等[17]发现，在大鼠球囊损伤模型中，血管损伤后第14天，滋养血管数量增加，与AF分泌的血管内皮生长因子（vascular endothelial growth factor，VEGF）促血管生成作用有关。AF作为血管损伤中的“前哨细胞”，通常第一个迁移到伤口部位，分泌细胞因子和促血管生成生长因子，促进滋养血管的生成[18]。

血管外膜受交感神经支配[19]。肺动脉高压和动脉粥样硬化等病理情况下，血管外膜的交感神经支配增加[20]。交感神经系统过度激活引起血管收缩和氧化低密度脂蛋白增多，引起氧化应激和血管重构，促进动脉粥样硬化的发生发展[21]。

2　AF的激活与血管重构

生理状态下的AF通常处于静止的未分化状态，但在激素、炎症、缺氧/缺血等应激条件下，AF往往是血管壁内最先被激活的细胞，发生表型转换，产生细胞因子，合成和分泌趋化因子，激活白细胞，启动炎症反应[6,22]。活化的AF引起某些细胞黏附分子如细胞间黏附分子-1（intercellular adhesion molecule-1，ICAM-1）和血管黏附分子（vascular adhesion molecules，VCAM）上调，以及刺激生长因子的分泌，影响血管壁内细胞的表型[23]。AF具有高度的可塑性，多种刺激可引起AF分化、增殖和迁移。在N-硝基-L-精氨酸甲酯诱导的高血压模型中，血管外膜的细胞数量和厚度显著增加，早于并超过血管内皮细胞和VSMC的增殖[24]；在猪冠状动脉成形术模型中，外膜重构的发生要早于内皮功能障碍[25]。这些研究表明某些病理情况下AF比血管内皮细胞和VSMC更早发生变化，且变化更为显著。血管外膜AF是血管重构的风向标，很可能存在重要的标志分子和早期干预血管重构的关键靶点。

Irisin是2012年新发现的蛋白类激素，其前体是Ⅲ型纤连蛋白域蛋白5（fibronectin type Ⅲ domain containing 5，FNDC5），FNDC5/Irisin能减轻高脂饮食引起的高血脂、高血糖、胰岛素抵抗、糖尿病和脂肪肝[26-27]，本课题组发现FNDC5减少高血压大鼠的AF表型转换，过表达FNDC5可减轻血管重构[28]。交感神经末梢释放的去甲肾上腺素（norepinephrine，NE）通过激活α受体促进AF表型转换，并促进AF释放细胞外囊泡（extracellular vesicle，EV），包括增加EV数量、直径以及增加EV中血管紧张素转化酶（angiotensin converting enzyme，ACE）的含量，从而促进VSMC增殖，参与高血压的血管重构[8]。Qian等[29]发现白三烯B4（leukotriene B4，LTB4）除引起肺动脉内皮细胞凋亡和平滑肌细胞生长外，还通过p38 MAPK信号通路激活血管AF，促进肺动脉高压。瞬变感受器电位蛋白V4（transient receptor potential protein V4，TRPV4）通道介导肺动脉高压模型的血管外膜AF活化和血管重构[30]。抑制血管外膜AF的热休克蛋白90（heat shock protein 90，HSP90）表达，可减弱血管紧张素Ⅱ诱导的AF表型转换和外膜重构[31]。MicroRNA-122通过调节SIRT6-elabela-ACE2信号通路，加重血管紧张素Ⅱ介导的AF凋亡、自噬、氧化应激和炎症[32]。这些研究表明多种信号分子调控血管外膜AF，参与血管重构。

3　血管外膜与高血压的血管重构

自发性高血压大鼠主动脉血管外膜中FNDC5下调，且NOD样受体热蛋白结构域相关蛋白3（NOD-like receptor thermal protein domain associated protein 3，NLRP3）炎症小体激活。过表达FNDC5或补充外源性的FNDC5可抑制自发性高血压大鼠的AF表型转化、基质成分的过度合成和分泌、NLRP3炎症小体的激活和炎症，并抑制AF中NADPH氧化酶2（NADPH oxidase 2，NOX2）表达和活性氧（reactive

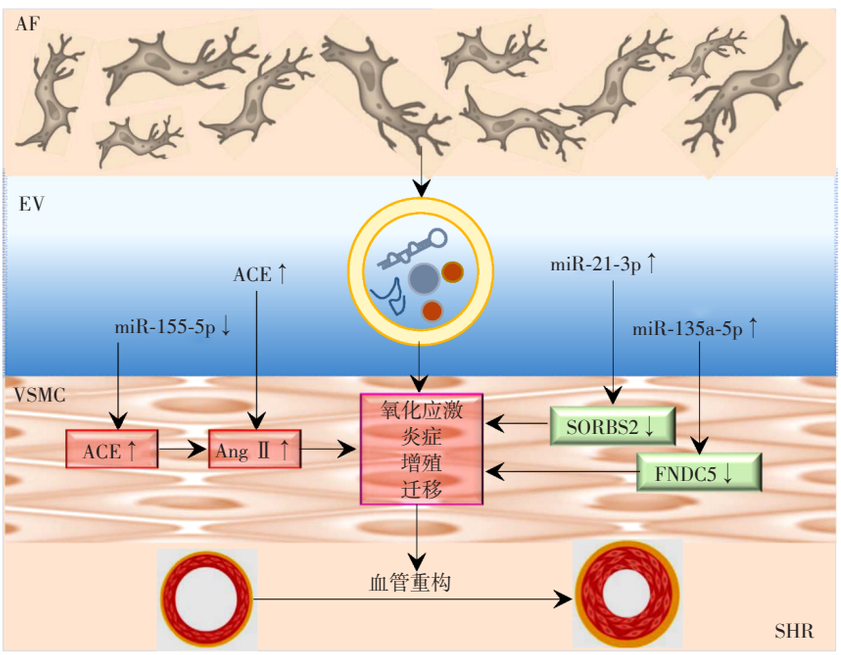
oxygen species,ROS)生成,降低高血压和减轻血管重构,提示血管外膜AF的FNDC5在减轻高血压和血管重构方面发挥有益作用[28]。

AF通过释放EV调控VSMC表型,在高血压血管重构中起重要作用[33](图1)。Tong等[34]首次从AF分离出EV,发现自发性高血压大鼠AF分泌的EV促进VSMC迁移,其机制与EV中ACE水平增高有关,敲低AF中的ACE可阻止高血压大鼠EV中的ACE水平升高,进而消除EV的促VSMC迁移效应。正常大鼠AF生成的EV可抑制高血压大鼠VSMC增殖,其机制主要与正常大鼠EV中miR-155-5p水平较高有关;而高血压大鼠AF生成的EV促进正常大鼠和高血压大鼠的VSMC增殖,其机制与高血压大鼠EV中ACE水平较高有关。因此,尾静脉多次重复注射正常大鼠的EV减轻高血压和血管重构,而注射高血压大鼠的EV加重高血压和血管重构[7]。高血压大鼠AF的EV中,miR-135a-5p和miR-21-3p水平升高,分别通过抑制FNDC5表达和精氨酸结合蛋白2(sorbin and SH3 domain containing 2,SORBS2)表达促进血管重构[35-36],抑制高血压大鼠的miR135a-5p表达可减轻高血压和血管重构[37]。血管外膜受交感神经支配,交感神经兴奋时通过神经末梢释放NE调节血管活动。Ye等[8]发现NE通过激活α受体促进AF的表型转化和增殖,进而促进EV释放,并增加EV中ACE的含量。敲低AF的ACE表达可使EV中ACE含量减少,并消除EV的促VSMC增殖作用,干预AF来源的EV释放和相关信号分子可能是减轻交感神经过度激活相关血管重构的有效策略。

血管外膜的滋养血管与血管重构密切相关。Kuwahara等[38]发现高血压大鼠血管外膜的滋养血管增多,提示在高血压血管重构过程中,增加的滋养血管起维持动脉壁血液供应的作用。在缺氧引起的肺动脉高压模型中,缺氧使肺动脉血管的滋养血管密度增加[39]。

4 血管外膜与动脉粥样硬化的血管重构

动脉粥样硬化是一种慢性炎症性疾病,以内皮损伤、脂质沉积、炎症细胞浸润、VSMC表型转化、泡沫细胞形成、斑块形成和血管重构为主要特征[40-41]。虽然动脉粥样硬化的研究主要集中在血管内膜病变上,但血管外膜在动脉粥样硬化发病中的重要作用也已引起关注[6,42]。在载脂蛋白E(apolipoprotein E,ApoE)敲除的小鼠动脉粥样硬化模型的早期阶段,血管外膜的AF就被激活[43],引发炎症反应[22,44],促进动脉粥样硬化的发生发展。Zhou等[45]发现,



ACE:血管紧张素转换酶;AF:成纤维细胞;Ang Ⅱ:血管紧张素Ⅱ;EV:细胞外囊泡;FNDC5:Ⅲ型纤连蛋白域蛋白5;SHR:自发性高血压大鼠;VSMC:血管平滑肌细胞。

图1 血管外膜AF释放的EV促进自发性高血压大鼠血管重构示意图

Figure 1 Schematic diagram of AF promoting vascular remodeling in spontaneously hypertensive rats by releasing EV from the adventitia of blood vessels

NLRP3炎性小体的表达与动脉粥样硬化程度呈正相关。Sharma等[46]发现NLRP3炎性小体抑制剂MCC950可以减轻糖尿病的动脉粥样硬化病变。

FNDC5可抑制血管外膜AF的NOX2来源的ROS生成，并抑制NLRP3炎性小体激活，从而减轻血管炎症[28]。泡沫细胞的形成和单核细胞黏附是动脉粥样硬化发病的重要环节[47-48]，FNDC5主要通过抑制VSMC中NF-κB的激活和上调NLRP3来抑制氧化低密度脂蛋白诱导的泡沫细胞形成和单核细胞黏附[49]，提示FNDC5可能对动脉粥样硬化患者具有保护作用。Irisin是FNDC5的裂解产物，循环Irisin水平与血管动脉粥样硬化病程进展相关，是亚临床阶段动脉粥样硬化的独立预测因子[12,50]。

血管外膜滋养血管在动脉粥样硬化的发展中起重要作用。滋养血管为动脉管壁提供氧气和营养物质，从而为动脉粥样硬化斑块的形成提供合适的环境，并作为把常驻细胞和祖细胞运送到中膜和内膜的通道，参与动脉粥样硬化的血管重构[51]。

5　血管外膜与主动脉瘤和主动脉夹层的血管重构

主动脉瘤和主动脉夹层是主动脉的常见病变，有较多相似之处，均以主动脉进行性扩张或破裂、主动脉壁结构异常的病理改变为主要特征，病死率非常高。血管外膜在主动脉瘤和主动脉夹层的发生发展中起重要作用[52-53]。

主动脉瘤包括腹主动脉瘤和胸主动脉瘤，其中腹主动脉瘤的发病率是胸主动脉瘤的3倍[54-55]。主动脉瘤的主要特征是主动脉扩张或膨出，表现为血管炎性浸润、细胞外基质降解、弹性蛋白断裂、VSMC耗竭和胶原沉积[56]。血管外膜AF合成的细胞外基质参与主动脉瘤的发病机制。当主动脉壁受损时，AF迁移到主动脉中膜内，并转化为VSMC，进而参与主动脉重构。研究者发现，在人腹主动脉瘤组织中可见血管外膜有巨噬细胞、T淋巴细胞和B淋巴细胞浸润[57-58]，在$CaCl_2$诱导的小鼠主动脉瘤模型中，Tsuruda等[59]发现血管外膜肥大细胞促进主动脉瘤的发生发展和主动脉瘤破裂。

主动脉夹层指主动脉内的血液从主动脉内膜的撕裂处进入主动脉的中膜，使中膜分离，并沿着主动脉的长轴方向扩展，形成主动脉壁的真假两腔分离状态[60-61]。对主动脉夹层发病机制的研究主要集中在内膜和中膜上，但实际上血管外膜在主动脉夹层发病中也起重要作用。Wang等[62]发现主动脉夹层患者主动脉外膜的ERK1/2磷酸化水平和α-SMA表达增加，且外膜中表达α-SMA的MF数量增加，提示AF发生表型转换，AF可能通过增强分化、增殖和迁移以及分泌炎性因子、基质金属蛋白酶促进主动脉血管重构和主动脉夹层的形成。

血管外膜炎症在主动脉瘤和主动脉夹层发病中起重要作用。Tieu等[63]发现内皮的白细胞介素-6（interleukin-6，IL-6）和单核细胞趋化因子-1（monocyte chemokine-1，MCP1）加速巨噬细胞介导的血管炎症并导致小鼠主动脉夹层。Anzai等[64]发现血管外膜的CXC趋化因子配体1（CXC chemokine ligand 1，CXCL1）和粒细胞集落刺激因子（granulocyte colony stimulating factor，G-CSF）触发局部中性粒细胞募集和激活，通过IL-6生成增多引起血管外膜炎症，导致急性主动脉夹层破裂。这些结果提示，恢复血管外膜功能很可能是预防和治疗主动脉瘤和主动脉夹层的有效途径。

6　总结与展望

血管外膜是血管的信号分析处理中心，调控血管的结构和功能，在血管重构中起重要作用，直接影响高血压、动脉粥样硬化、主动脉瘤和主动脉夹层等发生发展和心血管事件的发生。AF是血管外膜的主要细胞成分，在血管重构发生发展中的作用尤为突出，其在血管重构中的作用与机制需要深入研究。某些AF相关的信号分子可能是心血管病的重要标志分子，干预AF的表型转换及其与VSMC的交互作用可能是防治血管重构的重要靶点，值得深入探讨。

[参考文献]

[1] LIN S G，LIN R R，ZHANG H K，et al. Peripheral vascular remodeling during ischemia [J]. Front Pharmacol，2022，13：1078047

[2] 伍雪橙，李　南，黄　文，等. 吸入CDDO-NO对野百合碱诱导的大鼠肺动脉高压的作用[J]. 南京医科大学学报（自然科学版），2022，42（9）：1201-1208

[3] ZOU F D，LI Y，ZHANG S J，et al. DP1（prostaglandin D（2）receptor 1）activation protects against vascular remodeling and vascular smooth muscle cell transition to myofibroblasts in angiotensin Ⅱ - induced hypertension in mice[J]. Hypertension，2022，79（6）：1203-1215

[4] HUMPHREY J D. Mechanisms of vascular remodeling in hypertension[J]. Am J Hypertens，2021，34（5）：432-441

[5] BROWN I A M，DIEDERICH L，GOOD M E，et al. Vascular smooth muscle remodeling in conductive and resistance arteries in hypertension [J]. Arterioscler Thromb

Vasc Biol,2018,38(9):1969-1985
[6] TINAJERO M G,GOTLIEB A I. Recent developments in vascular adventitial pathobiology:the dynamic adventitia as a complex regulator of vascular disease[J]. Am J Pathol,2020,190(3):520-534
[7] REN X S,TONG Y,QIU Y,et al. MiR155-5p in adventitial fibroblasts-derived extracellular vesicles inhibits vascular smooth muscle cell proliferation via suppressing angiotensin-converting enzyme expression[J]. J Extracell Vesicles,2020,9(1):1698795
[8] YE C,ZHENG F,XU T,et al. Norepinephrine acting on adventitial fibroblasts stimulates vascular smooth muscle cell proliferation via promoting small extracellular vesicle release[J]. Theranostics,2022,12(10):4718-4733
[9] MAJESKY M W,WEISER-EVANS M C M. The adventitia in arterial development,remodeling,and hypertension[J].Biochem Pharmacol,2022,205:115259
[10] CRAIG D J,JAMES A W,WANG Y Y,et al. Blood vessel resident human stem cells in health and disease[J]. Stem Cells Transl Med,2022,11(1):35-43
[11] REUSTLE A,TORZEWSKI M. Role of p38 MAPK in atherosclerosis and aortic valve sclerosis[J]. Int J Mol Sci,2018,19(12):3761
[12] BYUN K,LEE S. The potential role of irisin in vascular function and atherosclerosis:a review[J]. Int J Mol Sci,2020,21(19):7184
[13] DOROTHEOU D,BOCHATON-PIALLAT M L,GIANNOPOULOU C,et al. Expression of α-smooth muscle actin in the periodontal ligament during post-emergent tooth eruption[J]. J Int Med Res,2018,46(6):2423-2435
[14] ZHENG L,YANG W J,NIU C B,et al. Correlation of adventitial Vasa vasorum with intracranial atherosclerosis:a postmortem study[J]. J Stroke,2018,20(3):342-349
[15] JOO S P,LEE S W,CHO Y H,et al. Vasa vasorum densities in human carotid atherosclerosis is associated with plaque development and vulnerability[J]. J Korean Neurosurg Soc,2020,63(2):178-187
[16] GYCHKA S G,SHULTS N V,NIKOLAIENKO S I,et al. Vasa vasorum lumen narrowing in brain vascular hyalinosis in systemic hypertension patients who died of ischemic stroke[J]. Int J Mol Sci,2020,21(24):9611
[17] LI X D,HONG M N,CHEN J,et al. Adventitial fibroblast-derived vascular endothelial growth factor promotes Vasa vasorum-associated neointima formation and macrophage recruitment[J]. Cardiovasc Res,2020,116(3):708-720
[18] TALBOTT H E,MASCHARAK S,GRIFFIN M,et al. Wound healing,fibroblast heterogeneity,and fibrosis[J]. Cell Stem Cell,2022,29(8):1161-1180
[19] HIRST G D,EDWARDS F R. Sympathetic neuroeffector transmission in arteries and arterioles[J]. Physiol Rev,1989,69(2):546-604
[20] NOLLER C M,MENDEZ A J,SZETO A,et al. Structural remodeling of sympathetic innervation in atherosclerotic blood vessels:role of atherosclerotic disease progression and chronic social stress[J]. Psychosom Med,2017,79(1):59-70
[21] ZORC-PLESKOVIČ R,ZORC M,ŠUPUT D,et al. Inflammatory cells in perivascular adipose tissue and the integrity of the tunica media in atherosclerotic coronary arteries[J]. Bosn J Basic Med Sci,2020,20(2):183-187
[22] HUERTAS A,TU L,HUMBERT M,et al. Chronic inflammation within the vascular wall in pulmonary arterial hypertension:more than a spectator[J]. Cardiovasc Res,2020,116(5):885-893
[23] FU C H,LIU P,LI P L,et al. FSP1 promotes the biofunctions of adventitial fibroblast through the crosstalk among RAGE,JAK2/STAT3 and Wnt3a/β-catenin signalling pathways[J]. J Cell Mol Med,2019,23(11):7246-7260
[24] ARRIBAS S M,GONZÁLEZ C,GRAHAM D,et al. Cellular changes induced by chronic nitric oxide inhibition in intact rat basilar arteries revealed by confocal microscopy[J]. J Hypertens,1997,15(12 Pt 2):1685-1693
[25] MALIK N,FRANCIS S E,HOLT C M,et al. Apoptosis and cell proliferation after porcine coronary angioplasty[J].Circulation,1998,98(16):1657-1665
[26] LIU T Y,SHI C X,GAO R,et al. Irisin inhibits hepatic gluconeogenesis and increases glycogen synthesis via the PI3K/Akt pathway in type 2 diabetic mice and hepatocytes[J]. Clin Sci,2015,129(10):839-850
[27] LIU T Y,XIONG X Q,REN X S,et al. FNDC5 alleviates hepatosteatosis by restoring AMPK/mTOR-mediated autophagy,fatty acid oxidation,and lipogenesis in mice[J]. Diabetes,2016,65(11):3262-3275
[28] LING L,CHEN D,TONG Y,et al. Fibronectin type Ⅲ domain containing 5 attenuates NLRP3 inflammasome activation and phenotypic transformation of adventitial fibroblasts in spontaneously hypertensive rats[J]. J Hypertens,2018,36(5):1104-1114
[29] QIAN J,TIAN W,JIANG X G,et al. Leukotriene B4 activates pulmonary artery adventitial fibroblasts in pulmonary hypertension[J]. Hypertension,2015,66(6):1227-1239
[30] CUSSAC L A,CARDOUAT G,TIRUCHELLVAM P N,et al. TRPV4 channel mediates adventitial fibroblast activation and adventitial remodeling in pulmonary hypertension[J]. Am J Physiol Lung Cell Mol Physiol,2020,318(1):L135-L146

[31] HUANG G J, CONG Z L, WANG X Y, et al. Targeting HSP90 attenuates angiotensin Ⅱ-induced adventitial remodelling via suppression of mitochondrial fission [J]. Cardiovasc Res, 2020, 116(5): 1071-1084

[32] SONG J J, YANG M, LIU Y, et al. MicroRNA-122 aggravates angiotensin Ⅱ-mediated apoptosis and autophagy imbalance in rat aortic adventitial fibroblasts via the modulation of SIRT6-elabela-ACE2 signaling[J]. Eur J Pharmacol, 2020, 883: 173374

[33] YE C, ZHENG F, WU N, et al. Extracellular vesicles in vascular remodeling [J]. Acta Pharmacol Sin, 2022, 43(9): 2191-2201

[34] TONG Y, YE C, REN X S, et al. Exosome-mediated transfer of ACE (angiotensin-converting enzyme) from adventitial fibroblasts of spontaneously hypertensive rats promotes vascular smooth muscle cell migration [J]. Hypertension, 2018, 72(4): 881-888

[35] TONG Y, YE C, ZHENG F, et al. Extracellular vesicle-mediated miR135a-5p transfer in hypertensive rat contributes to vascular smooth muscle cell proliferation via targeting FNDC5[J]. Vascul Pharmacol, 2021, 140: 106864

[36] ZHENG F, YE C, GE R, et al. MiR-21-3p in extracellular vesicles from vascular fibroblasts of spontaneously hypertensive rat promotes proliferation and migration of vascular smooth muscle cells[J]. Life Sci, 2023, 330: 122023

[37] YE C, TONG Y, WU N, et al. Inhibition of miR-135a-5p attenuates vascular smooth muscle cell proliferation and vascular remodeling in hypertensive rats [J]. Acta Pharmacol Sin, 2021, 42(11): 1798-1807

[38] KUWAHARA F, KAI H, TOKUDA K, et al. Hypoxia-inducible factor-1alpha/vascular endothelial growth factor pathway for adventitial Vasa vasorum formation in hypertensive rat aorta[J]. Hypertension, 2002, 39(1): 46-50

[39] DAVIE N J, CROSSNO J T, FRID M G, et al. Hypoxia-induced pulmonary artery adventitial remodeling and neovascularization: contribution of progenitor cells [J]. Am J Physiol Lung Cell Mol Physiol, 2004, 286(4): L668-L678

[40] LIBBY P. The changing landscape of atherosclerosis [J]. Nature, 2021, 592(7855): 524-533

[41] KONG P, CUI Z Y, HUANG X F, et al. Inflammation and atherosclerosis: signaling pathways and therapeutic intervention[J]. Signal Transduct Target Ther, 2022, 7(1): 131

[42] CHEN J, WEI J Q, HONG M N, et al. Mitogen-activated protein kinases mediate adventitial fibroblast activation and neointima formation via GATA4/cyclin D1 axis [J/OL]. Cardiovasc Drugs Ther, 2023 (2023-01-18) [2023-01-09]. DOI: 10.1007/s10557-10.1007/s10023-07428-1

[43] XU F, JI J, LI L, et al. Activation of adventitial fibroblasts contributes to the early development of atherosclerosis: a novel hypothesis that complements the "response-to-injury hypothesis" and the "inflammation hypothesis" [J]. Med Hypotheses, 2007, 69(4): 908-912

[44] KUMAR S, FRID M G, ZHANG H, et al. Complement-containing small extracellular vesicles from adventitial fibroblasts induce proinflammatory and metabolic reprogramming in macrophages[J]. JCI Insight, 2021, 6(21): e148382

[45] ZHOU Y Q, ZHOU H X, HUA L, et al. Verification of ferroptosis and pyroptosis and identification of PTGS2 as the hub gene in human coronary artery atherosclerosis [J]. Free Radic Biol Med, 2021, 171: 55-68

[46] SHARMA A, CHOI J S Y, STEFANOVIC N, et al. Specific NLRP3 inhibition protects against diabetes-associated atherosclerosis[J]. Diabetes, 2021, 70(3): 772-787

[47] BONETTI J, CORTI A, LEROUGE L, et al. Phenotypic modulation of macrophages and vascular smooth muscle cells in atherosclerosis-nitro-redox interconnections [J]. Antioxidants, 2021, 10(4): 516

[48] MAGUIRE E M, PEARCE S W A, XIAO Q Z. Foam cell formation: a new target for fighting atherosclerosis and cardiovascular disease [J]. Vascul Pharmacol, 2019, 112: 54-71

[49] ZANG Y H, CHEN D, ZHOU B, et al. FNDC5 inhibits foam cell formation and monocyte adhesion in vascular smooth muscle cells via suppressing NF-κB-mediated NLRP3 upregulation [J]. Vascul Pharmacol, 2019, 121: 106579

[50] REMUZGO-MARTÍNEZ S, RUEDA-GOTOR J, PULITO-CUETO V, et al. Irisin as a novel biomarker of subclinical atherosclerosis, cardiovascular risk and severe disease in axial spondyloarthritis [J]. Front Immunol, 2022, 13: 894171

[51] TARBELL J, MAHMOUD M, CORTI A, et al. The role of oxygen transport in atherosclerosis and vascular disease [J]. J R Soc Interface, 2020, 17(165): 20190732

[52] MACKAY C D A, JADLI A S, FEDAK P W M, et al. Adventitial fibroblasts in aortic aneurysm: unraveling pathogenic contributions to vascular disease [J]. Diagnostics, 2022, 12(4): 871

[53] BOSSONE E, EAGLE K A. Epidemiology and management of aortic disease: aortic aneurysms and acute aortic syndromes[J]. Nat Rev Cardiol, 2021, 18(5): 331-348

[54] WANG Y D, LIU Z J, REN J, et al. Pharmacological therapy of abdominal aortic aneurysm: an update [J]. Curr Vasc Pharmacol, 2018, 16(2): 114-124

[55] SAKALIHASAN N, MICHEL J B, KATSARGYRIS A, et al. Abdominal aortic aneurysms[J]. Nat Rev Dis Primers,

(下转第1595页)

[47] RITMAN E L, LERMAN A. The dynamic Vasa vasorum [J]. Cardiovasc Res, 2007, 75(4): 649-658
[48] MICHEL J B, THAUNAT O, HOUARD X, et al. Topological determinants and consequences of adventitial responses to arterial wall injury [J]. Arterioscler Thromb Vasc Biol, 2007, 27(6): 1259-1268
[49] TINAJERO M G, GOTLIEB A I. Recent developments in vascular adventitial pathobiology: the dynamic adventitia as a complex regulator of vascular disease [J]. Am J Pathol, 2020, 190(3): 520-534
[50] CHEN J, WEI J Q, HONG M N, et al. Mitogen-activated protein kinases mediate adventitial fibroblast activation and neointima formation via GATA4/Cyclin D1 axis [J]. Cardiovasc Drugs Ther, 2023, 10: 1007

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2018, 4(1): 34
[56] GOLLEDGE J. Abdominal aortic aneurysm: update on pathogenesis and medical treatments [J]. Nat Rev Cardiol, 2019, 16(4): 225-242
[57] ERHART P, CAKMAK S, GROND-GINSBACH C, et al. Inflammasome activity in leucocytes decreases with abdominal aortic aneurysm progression [J]. Int J Mol Med, 2019, 44(4): 1299-1308
[58] MÁRQUEZ-SÁNCHEZ A C, KOLTSOVA E K. Immune and inflammatory mechanisms of abdominal aortic aneurysm [J]. Front Immunol, 2022, 13: 989933
[59] TSURUDA T, KATO J, HATAKEYAMA K, et al. Adventitial mast cells contribute to pathogenesis in the progression of abdominal aortic aneurysm [J]. Circ Res, 2008, 102(11): 1368-1377
[60] CARREL T, SUNDT T M, VON KODOLITSCH Y, et al. Acute aortic dissection [J]. Lancet, 2023, 401(10378): 773-788
[61] JURASZEK A, CZERNY M, RYLSKI B. Update in aortic dissection [J]. Trends Cardiovasc Med, 2022, 32(7): 456-461
[62] WANG Z W, REN Z L, HU Z P, et al. Angiotensin-Ⅱ induces phosphorylation of ERK1/2 and promotes aortic adventitial fibroblasts differentiating into myofibroblasts during aortic dissection formation [J]. J Mol Histol, 2014, 45(4): 401-412
[63] TIEU B C, LEE C, SUN H, et al. An adventitial IL-6/MCP1 amplification loop accelerates macrophage-mediated vascular inflammation leading to aortic dissection in mice [J]. J Clin Invest, 2009, 119(12): 3637-3651
[64] ANZAI A, SHIMODA M, ENDO J, et al. Adventitial CXCL1/G-CSF expression in response to acute aortic dissection triggers local neutrophil recruitment and activation leading to aortic rupture [J]. Circ Res, 2015, 116(4): 612-623

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