DOI:10.16781/j.0258-879x.2017.05.0639

·综　述·

冠状动脉旁路移植术后静脉桥血管再狭窄的机制研究进展

乐士冠,肖　健,奚　望,李　伟,徐激斌*
第二军医大学长征医院胸心外科,上海 200003

［摘要］ 冠状动脉旁路移植术是治疗冠心病最有效的方法,其中大隐静脉是静脉桥血管的首选。但静脉桥血管10年再狭窄率超过60%,严重影响患者的预后和远期生存率。静脉桥血管再狭窄是多因素、多环节共同作用的结果,包括早期的内皮损伤、血栓形成、再内皮化、静脉桥血管的动脉化,中期的内膜增生以及晚期的粥样硬化及斑块破裂等。本文综述了静脉桥血管再狭窄机制的最新研究进展,并对未来预防静脉桥血管再狭窄的方法进行展望。

［关键词］ 冠状动脉旁路移植术;血管移植后狭窄;内皮损伤;炎症反应;动脉粥样硬化
［中图分类号］ R 654.33　［文献标志码］ A　［文章编号］ 0258-879X(2017)05-0639-07

Advance in mechanisms of vein graft restenosis after coronary bypass grafting

LE Shi-guan, XIAO Jian, XI Wang, LI Wei, XU Ji-bin*
Department of Cardiothoracic Surgery, Changzheng Hospital, Second Military Medical University, Shanghai 200003, China

［**Abstract**］ Coronary bypass grafting (CBG) is the most effective method of treating coronary artery disease and venae saphena magna is commonly used as vein graft for surgical revascularization; however, the incidence of vein graft restenosis is more than 60% in ten years after CBG, which threatens the prognosis and long-term survival of the patients. The vein graft restenosis has multiple factors and levels, including de-endothelialization, thrombosis, re-endothelialization and arterialization of vein graft in the early stage, intimal hyperplasia in the middle stage, and atherosclerosis and plaque rupture in the late stage. This review summarized the latest researches of the mechanisms of vein graft restenosis after coronary bypass grafting and discussed the prevention methods.

［**Key words**］ coronary artery bypass; vascular graft restenosis; endothelial injury; inflammatory response; atherosclerosis

［Acad J Sec Mil Med Univ, 2017, 38(5): 639-645］

冠状动脉旁路移植术是治疗冠心病最有效的方法。大隐静脉因取材方便、长度足够,是目前最常使用的移植静脉之一。但研究发现,超过20%的大隐静脉在移植后1年出现再狭窄,2年再狭窄率达40%,超过60%的静脉桥血管在移植后10年出现再狭窄[1]。再狭窄的静脉桥血管可能会造成心肌缺血、缺氧,甚至会导致心绞痛及心肌梗死[2]。研究表明,早期的内皮损伤、血栓形成、再内皮化、静脉桥血管的动脉化,中期的内膜增生以及晚期的粥样硬化与斑块破裂等,在静脉桥血管再狭窄的发生、发展中扮演了重要角色。本综述将对这一系列过程的内在机制进行阐述。

1　内皮损伤、血栓形成及再内皮化

在移植过程中大部分静脉会发生缺血再灌注损伤,从而引起氧化应激并激活细胞毒性反应,诱发内质网应激及凋亡,造成内皮细胞和平滑肌细胞的损伤[3]。Tseng等[4]发现在脊柱动物模型中,静脉桥血管内皮细胞中超氧化物生成增加,导致内皮细胞分泌一氧化氮减少,进一步引起血管舒缩功能障碍。

由于内皮损伤,细胞外基质蛋白暴露于血液,血小板和纤维蛋白聚集造成管腔内血栓形成,而血管收缩则加速这一病理过程。参与这一过程的相关因子还包括血小板源性生长因子(platelet-derived

［收稿日期］ 2016-10-06　［接受日期］ 2016-12-17
［作者简介］ 乐士冠,硕士生. E-mail: leshiguan@hotmail.com
*通信作者 (Corresponding author). Tel: 021-81885902, E-mail: jibinx@yahoo.com

growth factor，PDGF）、转化生长因子 β（transforming growth factor β，TGF-β）、vW 因子、JP‖纤维蛋白原等[5]，激活的血小板会分泌黏附分子等促使其黏附和渗透入损伤的血管壁[6]。有研究证实，通过调节内皮素、一氧化氮合酶等的活性可改善血管内皮功能，延缓内皮增生[7]；也有研究表明内皮损伤后 3 d 开始出现新生内皮细胞[8]。此外，研究发现 β3 依赖整合素相关祖细胞可能与再内皮化的发生相关[9]。

2　静脉桥血管的动脉化

静脉桥血管会通过扩张来适应动脉血压，从而产生大量内皮细胞增殖、重构、管壁硬化及炎症反应，最终导致再狭窄[10]。动脉与静脉均由外模、中膜和内膜组成，但动、静脉管壁细胞的组成和数量存在明显差异，同时静脉内存在静脉瓣。因此，在生理上静脉能很好地适应血容量的改变，但对血流、血压的适应能力欠佳。将静脉移植到动脉系统后，高血压、高血流量、局部炎症反应均会导致平滑肌细胞的增殖和迁移，并造成静脉桥血管形态和结构的改变[11-12]。

静脉桥血管结构的变化主要包括管径变大、管壁厚度增加及内膜损伤面积扩大，其主要通过内膜的改变进行调节[13]，可在移植后 1 年内一定程度地延缓再狭窄的进程[14]。通过血管内超声（intravascular ultrasound，IVUS）技术观察移植后静脉，发现在移植后数周静脉血管壁即出现增厚与膨胀，其变化趋势在 6 个月后趋于稳定[15]。在动物模型及细胞学研究中，利用外支架减缓移植静脉早期扩张可减少平滑肌细胞增殖及内皮细胞增殖，最终降低再狭窄的发生率[16-17]，这已成为预防静脉桥血管再狭窄的方法之一。

3　内膜增生的形成

3.1　*平滑肌细胞*　在静脉桥血管中，中膜和内膜的平滑肌细胞会因缺血、缺氧而发生凋亡[8]。增殖、迁移以及凋亡的平滑肌细胞都是内膜增生的重要组成部分[6]，平滑肌细胞在此过程中由静默状态变为去分化、增殖状态。由于静脉血管壁缺乏弹性层，血管外膜成纤维细胞极易迁移进入静脉血管壁，并通过高度增殖及抑制超氧化物歧化酶等作用促进移植静脉平滑肌细胞的增殖[18]。趋化因子受体 Cxcr4 在平滑肌细胞的增殖中发挥重要作用，*Cxcr4* 敲除小鼠行静脉移植后，其静脉桥血管的增厚速度明显下降[19]。亦有研究发现，纤维细胞特异蛋白 1（fibroblast-specific protein 1，FSP-1）可通过激活 *Cxcr4* 促进平滑肌细胞增殖，而敲除 *FSP*-1 可预防内皮增生[20]。此外，研究发现细胞周期蛋白依赖性激酶抑制剂 CDKN1B（$p27^{Kip1}$）在维持平滑肌细胞静默状态中具有重要作用，*CDKN1B* 基因的缺失可导致内皮增生减少[21-22]，但针对 CDKN1B 的临床试验结果显示抑制其活性并无预防再狭窄的作用，尚需开展更进一步的研究[23]。

静脉桥血管内的平滑肌细胞会分泌血管内皮生长因子（vascular endothelium growth factor，VEGF）、PDGF 和 TGF-β 等生长因子，这些生长因子可促进平滑肌细胞的迁移、增殖和凋亡。丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）、细胞外调节蛋白激酶（extracellular regulated protein kinase，ERK）以及蛋白激酶 B（Akt）信号通路在细胞周期的调节过程中发挥重要作用，同时还可能直接影响平滑肌细胞和内皮细胞的增殖[24]。有研究发现静脉桥血管平滑肌细胞内 MAPK 和 Akt 的表达较动脉桥血管明显升高，表明 MAPK 和 Akt 的表达升高可能与静脉桥血管再狭窄率较高有关[25]。

3.2　*细胞外基质*　细胞外基质可促进平滑肌细胞的增殖和迁移。在发生重构的静脉桥血管中存在大量的基质金属蛋白酶（matrix metalloproteinase，MMP），常见的有 MMP-2 和 MMP-9[26]。MMP 可调控细胞外基质的产生。沉默体外培养大隐静脉的 *MMP*-2 和 *MMP*-9 基因后，平滑肌细胞迁移明显减少[27]。一项临床研究发现，静脉桥血管中膜MMP-2 的高表达与不良预后相关[28]。MMP 的组织内源性抑制物（tissue inhibitor of matrix metalloproteinase，TIMP）亦可通过抑制 MMP 的活性来减少平滑肌细胞的增殖和迁移，防止内皮增生[29]。在人再狭窄静脉桥血管内，血纤维蛋白溶酶原（plasminogen activator，PA）系统被激活[30]；激活的 PA 系统可分解细胞外基质中的基板糖蛋白和纤维连接蛋白，并激活细胞表面相关受体和 MMP[31]。PA 系统包括两类主要的纤溶酶激活物，即尿激酶型纤溶酶原激活物（urokinase plasminogen activator，uPA）和组织型纤溶酶原激活物（tissue plasminogen

activator, tPA)。上调猪静脉桥血管内 tPA 的水平可减少静脉桥血管早期血栓的发生[32]。纤溶酶原激活物抑制剂 1 (plasminogen activator inhibitor 1, PAI-1)可通过抑制 PA 的激活调控平滑肌细胞与内皮细胞的增殖、迁移以及凋亡[33];而 PAI-1 缺乏小鼠的内皮增生明显增加[34]。

3.3 炎症介质 炎症介质的释放对静脉桥血管病理生理改变具有重要作用[35]。静脉移植后早期出现扩张,导致内生损伤相关分子模式(damage-associated molecular patterns, DAMPs)增加,并激活 Toll 样受体(TLR),进一步引起血管内皮细胞、血管平滑肌细胞的增殖和重构[36-37]。在 TLR4 缺乏小鼠模型中,静脉桥血管炎症反应明显抑制,内膜增生及血管重构减少[36]。磷酸胆碱为 TLR4 配体,在高胆固醇血症小鼠模型中给予抗磷酸胆碱抗体可有效预防静脉桥血管粥样硬化,提示磷酸胆碱可能与桥血管再狭窄有关[38]。除 TLR3 外,所有 TLR 均可通过 MYD88-NFκB 信号通路激活单核细胞趋化蛋白 1(CCL-2)和 TNF-α 等下游促炎因子,促进移植静脉发生重构[39]。在高脂饮食小鼠模型中,CCL-2显性受体抑制剂可减少移植静脉粥样硬化及单核细胞浸润,而 CCL-2 受体 RNA 沉默的平滑肌细胞的增殖和迁移水平明显下降,内膜增生停止[40]。移植静脉早期 TLR 的激活上调其下游 TNF-α 的表达,在 TNF 受体 1 抑制小鼠模型中,CCL-2 的表达下降,平滑肌细胞的增殖减少,最终减缓静脉桥血管内膜增生[41];而在 TNF 受体 2 抑制小鼠模型中,因内皮细胞凋亡,静脉桥血管内膜增生过程停止[42]。

TLR 作为模式识别受体的中心环节,可激活多种炎症细胞和补体系统。与 TLR 类似,补体系统也广泛分布于静脉桥血管壁,并调节固有免疫系统。在小鼠静脉桥血管中,补体系统可通过干扰补体 C3 的功能旁路激活补体 C1 和 C5, 最终减轻炎性反应与内膜增生,降低内皮细胞损伤并抑制平滑肌细胞增殖[43-44]。一项前瞻性研究表明静脉内使用补体 C5 抗体培克珠单抗(pexelizumab)可明显降低接受冠状动脉旁路移植术的高风险患者的病死率[45]。

炎症细胞侵入血管壁后会定植于特定位置并发挥作用。巨噬细胞是血管内膜及中层最主要的炎症细胞,而自然杀伤细胞(NK 细胞)和肥大细胞多见于血管外膜[46]。Koga 等[47]发现,在动物模型中通过抑制巨噬细胞激活因子抑制巨噬细胞的产生,可预防炎症反应和静脉桥血管再狭窄。亦有研究发现,移植术后早期,肥大细胞可迅速侵入静脉,在静脉桥血管周围也同时发现激活和静息状态的肥大细胞[44,48];研究发现,肥大细胞激活可能造成静脉桥血管破裂,而抑制其激活可显著减轻静脉桥血管内皮增生[44]。NK 细胞也被发现通过调节炎症细胞和干扰素 γ(IFN-γ)表达,在桥血管再狭窄中具有重要作用。对 NK 细胞基因复合体缺乏的 C57BL/6 小鼠行旁路移植术后,其静脉桥血管内皮增生情况较 NK 细胞基因复合体正常的 C57BL/6 小鼠降低约 43%[48]。固有免疫系统可加速内膜增生及再狭窄过程,但获得性免疫在此过程中的作用仍不明确。有研究发现在静脉桥血管中存在 T 细胞和 B 细胞以及 T 细胞共刺激因子 CD40,提示获得性免疫可能与血管疾病、粥样硬化及再狭窄有关[49],但 T 细胞和 B 细胞在静脉再狭窄中的作用仍需进一步研究。

3.4 粥样硬化及斑块破裂 粥样硬化损伤常出现于静脉桥血管再狭窄晚期。尸检发现冠状动脉旁路移植术后静脉桥血管粥样硬化以中心性为主,较冠状动脉粥样硬化更弥漫,也更易出现血栓和破裂[50]。

静脉桥血管在术后 1 年即可出现泡沫细胞,术后 2～5 年可出现坏死中心且往往同时存在斑块内出血[51]。有研究发现冠状动脉旁路移植术后静脉桥血管损伤处会出现薄的纤维帽,其内含有大量出血性坏死中心,这些坏死中心使斑块更容易破裂[51]。De Vries 等[52]在高胆固醇饮食小鼠模型中发现晚期静脉桥血管斑块形成与动脉粥样硬化斑块形成具有明显的不同,前者具有斑块内新生血管以及斑块内出血等特征。在该研究中,研究人员通过上调 TIMP1,产生稳定斑块的作用[52]。同时,亦有研究发现,调节膜联蛋白 A5、肥大细胞以及补体 C5a 不但可减少内膜增生,还可以减少粥样硬化及斑块破裂,起到保护静脉桥血管的作用[44,53]。

4 影像学诊断

4.1 血管内超声(intravascular ultrasound, IVUS) IVUS 已广泛应用于冠状动脉造影术中,通过 IVUS 检查冠状动脉旁路移植术后的静脉桥血

管可直观了解其病变情况。有研究通过 IVUS 测量静脉桥血管壁、斑块等面积，发现其病变情况与既往研究相符[54]。但亦有研究通过对冠状动脉旁路移植术后 9 个月、24 个月及 6 年患者行静脉桥血管 IVUS 检查，发现静脉桥血管再狭窄受个体差异影响较大[55]。研究发现，部分患者静脉桥血管内粥样硬化及斑块形成明显[55]。IVUS 可以通过很小的创伤直观描述静脉桥血管病变情况，同时 IVUS 的检查路径也可作为局部用药的自然通道[54]，因此 IVUS 有望成为检查、预防及治疗桥血管再狭窄的新方法。

4.2　光学相干断层成像（optical coherence tomography，OCT）　OCT 最早用于眼科检查，近年来被用于冠状动脉检查。有研究比较传统冠状动脉造影、IVUS 和 OCT 检查，发现 OCT 检查可清晰地显示血管腔内粥样斑块，包括内膜增生、纤维帽和附着血栓的形成[56-57]，分辨率明显高于传统冠状动脉造影以及 IVUS。OCT 具有组织相关性、高分辨率等特点，可对特定组织形态进行迅速、直接的成像，在冠状动脉旁路移植术后早期即可发现病变的发展，可为早期预防静脉桥血管再狭窄提供依据。相较于 IVUS，OCT 导管更细、操作更简单，有效减少了对患者的创伤。目前因其成像原理的局限，OCT 扫描深度仅1～2 mm，相信随着技术的发展，其成像质量将会进一步提升。

5　小结与展望

静脉桥血管是桥血管的最常用选择之一，但在多种因素作用下，静脉桥血管再狭窄发生率较高，已严重影响手术远期预后。目前通过抑制炎症反应、降低血清胆固醇含量、调节血脂、稳定斑块等治疗可在一定程度上延缓部分患者静脉桥血管再狭窄的发展进程，但并不能预防再狭窄的发生[58-59]，且一旦发生再狭窄，除放置支架或再次手术外，亦无有效的治疗方法。通过基因治疗、转录因子 E2F 寡核苷酸诱饵等预防内皮细胞损伤、激活内皮细胞生长、抑制平滑肌细胞增殖和迁移是目前研究的热点，有些药物已进入临床试验阶段[60-61]，但试验结果多为阴性，还需要更深入的研究。此外，通过更先进的影像学手段实现早期诊断静脉桥血管再狭窄已成为可能，这为探索静脉桥血管再狭窄的机制提供了新方法，为其治疗及预防提供了更可靠的依据。

[参 考 文 献]

[1] DE VRIES M R, SIMONS K H, JUKEMA J W, BRAUN J, QUAX P H. Vein graft failure: from pathophysiology to clinical outcomes [J]. Nat Rev Cardiol, 2016, 13: 451-470.

[2] VELAZQUEZ E J, LEE K L, JONES R H, AL-KHALIDI H R, HILL J A, PANZA J A, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy [J]. N Engl J Med, 2016, 374: 1511-1520.

[3] OSGOOD M J, HOCKING K M, VOSKRESENSKY I V, LI F D, KOMALAVILAS P, CHEUNG-FLYNN J, et al. Surgical vein graft preparation promotes cellular dysfunction, oxidative stress, and intimal hyperplasia in human saphenous vein [J]. J Vasc Surg, 2014, 60: 202-211.

[4] TSENG C N, KARLÖF E, CHANG Y T, LENGQUIST M, ROTZIUS P, BERGGREN P O, et al. Contribution of endothelial injury and inflammation in early phase to vein graft failure: the causal factors impact on the development of intimal hyperplasia in murine models [J/OL]. PLoS One, 2014, 9: e98904. doi: 10.1371/journal.pone.0098904.

[5] WEAVER H, SHUKLA N, ELLINSWORTH D, JEREMY J Y. Oxidative stress and vein graft failure: a focus on NADH oxidase, nitric oxide and eicosanoids [J]. Curr Opin Pharmacol, 2012, 12: 160-165.

[6] HILBERT T, DUERR G D, HAMIKO M, FREDE S, ROGERS L, BAUMGARTEN G, et al. Endothelial permeability following coronary artery bypass grafting: an observational study on the possible role of angiopoietin imbalance [J]. Crit Care, 2016, 20: 51.

[7] HATTORI K, YAMANOUCHI D, BANNO H, KOBAYASHI M, YAMAMOTO K, KAJIKURI J, et al. Celiprolol reduces the intimal thickening of autogenous vein grafts via an enhancement of nitric oxide function through an inhibition of superoxide production[J]. J Vasc Surg, 2007, 46: 116-123.

[8] BORIN T F, MIYAKAWA A A, CARDOSO L, DE FIGUEIREDO BORGES L, GONCALVES G A, KRIEGER J E. Apoptosis, cell proliferation and modulation of cyclin-dependent kinase inhibitor $p21^{cip1}$

in vascular remodelling during vein arterialization in the rat[J]. Int J Exp Patho, 2009, 90: 328-337.

[9] LIANG M, WANG Y, LIANG A, DONG J F, DU J, CHENG J. Impaired integrin β3 delays endothelial cell regeneration and contributes to arteriovenous graft failure in mice[J]. Arterioscler Thromb Vasc Biol, 2015, 35: 607-615.

[10] SCHNOOR M, ALCAIDE P, VOISIN M B, VAN BUUL J D. Crossing the vascular wall: common and unique mechanisms exploited by different leukocyte subsets during extravasation [J]. Mediators Inflamm, 2015, 2015: 946509.

[11] NOLTE A, SECKER S, WALKER T, GREINER T O, NEUMANN B, SIMON P, et al. Veins are no arteries: even moderate arterial pressure induces significant adhesion molecule expression of vein grafts in an *ex vivo* circulation model [J]. J Cardiovasc Surg (Torino), 2011, 52: 251-259.

[12] OWENS C D. Adaptive changes in autogenous vein grafts for arterial reconstruction: clinical implications [J]. J Vasc Surg, 2010, 51: 736-746.

[13] DASHWOOD M R, TSUI J C. 'No-touch' saphenous vein harvesting improves graft performance in patients undergoing coronary artery bypass surgery: a journey from bedside to bench[J]. Vascul Pharmacol, 2013, 58: 240-250.

[14] LAU G T, RIDLEY L J, BANNON P G, WONG L A, TRIEU J, BRIEGER D B, et al. Lumen loss in the first year in saphenous vein grafts is predominantly a result of negative remodeling of the whole vessel rather than a result of changes in wall thickness [J]. Circulation, 2006, 114(1 Suppl): I435-I440.

[15] WONG A P, NILI N, JACKSON Z S, QIANG B, LEONG-POI H, JAFFE R, et al. Expansive remodeling in venous bypass grafts: novel implications for vein graft disease[J]. Atherosclerosis, 2008, 196: 580-589.

[16] LONGCHAMP A, ALONSO F, DUBUIS C, ALLAGNAT F, BERARD X, MEDA P, et al. The use of external mesh reinforcement to reduce intimal hyperplasia and preserve the structure of human saphenous veins[J]. Biomaterials, 2014, 35: 2588-2599.

[17] TAGGART D P, BEN GAL Y, LEES B, PATEL N, WEBB C, REHMAN S M, et al. A randomized trial of external stenting for saphenous vein grafts in coronary artery bypass grafting [J]. Ann Thorac Surg, 2015, 99: 2039-2045.

[18] SHI Y, PATEL S, DAVENPECK K L, NICULESCU R, RODRIGUEZ E, MAGNO M G, et al. Oxidative stress and lipid retention in vascular grafts: comparison between venous and arterial conduits [J]. Circulation, 2001, 103: 2408-2413.

[19] ZHANG L, BRIAN L, FREEDMAN N J. Vein graft neointimal hyperplasia is exacerbated by CXCR4 signaling in vein graft-extrinsic cells [J]. J Vasc Surg, 2012, 56: 1390-1397.

[20] CHENG J, WANG Y, LIANG A, JIA L, DU J. *FSP*-1 silencing in bone marrow cells suppresses neointima formation in vein graft [J]. Circ Res, 2012, 110: 230-240.

[21] DESART K M, BUTLER K, O'MALLEY K A, JIANG Z, BERCELI S A. Time and flow-dependent changes in the $p27^{kip1}$ gene network drive maladaptive vascular remodeling[J]. Ann Thorac Surg, 2015, 62: 1296-1302.

[22] CONTE M S, OWENS C D, BELKIN M, CREAGER M A, EDWARDS K L, GASPER W J, et al. A single nucleotide polymorphism in the $p27^{kip1}$ gene is associated with primary patency of lower extremity vein bypass grafts[J]. J Vasc Surg, 2013, 57: 1179-1185.

[23] HARSKAMP R E, ALEXANDER J H, SCHULTE P J, BROPHY C M, MACK M J, PETERSON E D, et al. Vein graft preservation solutions, patency, and outcomes after coronary artery bypass graft surgery: follow-up from the PREVENT Ⅳ randomized clinical trial[J]. JAMA surgery, 2014, 149: 798-805.

[24] CHANAKIRA A, KIR D, BARKE R A, SANTILLI S M, RAMAKRISHNAN S, ROY S. Hypoxia differentially regulates arterial and venous smooth muscle cell migration[J/OL]. PLoS One, 2015, 10: e0138587. doi: 10.1371/journal.pone.0138587.

[25] FRISCHKNECHT K, GREUTERT H, WEISSHAUPT C, KASPAR M, YANG Z, LUSCHER T F, et al. Different vascular smooth muscle cell apoptosis in the human internal mammary artery and the saphenous vein. Implications for bypass graft disease[J]. J Vasc Res, 2006, 43: 338-346.

[26] SHARONY R, PINTUCCI G, SAUNDERS P C, GROSSI E A, BAUMANN F G, GALLOWAY A C,

et al. Matrix metalloproteinase expression in vein grafts: role of inflammatory mediators and extracellular signal-regulated kinases-1 and -2[J]. Am J Physiol Heart Circ Physiol, 2006, 290: H1651-H1659.

[27] TURNER N A, HALL K T, BALL S G, PORTER K E. Selective gene silencing of either MMP-2 or MMP-9 inhibits invasion of human saphenous vein smooth muscle cells[J]. Atherosclerosis, 2007, 193: 36-43.

[28] PEREK B, MALINSKA A, MISTERSKI M, OSTALSKANOWICKA D, ZABEL M, PEREK A, et al. Preexisting high expression of matrix metalloproteinase-2 in tunica media of saphenous vein conduits is associated with unfavorable long-term outcomes after coronary artery bypass grafting[J]. BioMed Research International, 2013, 2013: 730721.

[29] GEORGE S J, WAN S, HU J, MACDONALD R, JOHNSON J L, BAKER A H. Sustained reduction of vein graft neointima formation by *ex vivo TIMP*-3 gene therapy[J]. Circulation, 2011, 124(11 Suppl): S135-S142.

[30] FARRIS S D, HU J H, KRISHNAN R, EMERY I, CHU T, DU L, et al. Mechanisms of urokinase plasminogen activator (uPA)-mediated atherosclerosis: role of the uPA receptor and S100A8/A9 proteins[J]. J Biol Chem, 2011, 286: 22665-22677.

[31] FAY W P, GARG N, SUNKAR M. Vascular functions of the plasminogen activation system[J]. Arterioscler Thromb Vasc Biol, 2007, 27: 1231-1237.

[32] THOMAS A C, WYATT M J, NEWBY A C. Reduction of early vein graft thrombosis by tissue plasminogen activator gene transfer[J]. Thromb Haemost, 2009, 102: 145-152.

[33] DIEBOLD I, KRAICUN D, BONELLO S, GORLACH A. The 'PAI-1 paradox' in vascular remodeling[J]. Thromb Haemost, 2008, 100: 984-991.

[34] JI Y, STRAWN T L, GRUNZ E A, STEVENSON M J, LOHMAN A W, LAWRENCE D A, et al. Multifaceted role of plasminogen activator inhibitor-1 in regulating early remodeling of vein bypass grafts[J]. Arterioscler Thromb Vasc Biol, 2011, 31: 1781-1787.

[35] OZAKI C K. Cytokines and the early vein graft: strategies to enhance durability[J]. J Vasc Surg, 2007, 45 (Suppl A): A92-A98.

[36] KARPER J C, DE VRIES M R, VAN DEN BRAND B T, HOEFER I E, FISCHER J W, JUKEMA J W, et al. Toll-like receptor 4 is involved in human and mouse vein graft remodeling, and local gene silencing reduces vein graft disease in hypercholesterolemic APOE * 3Leiden mice[J]. Arterioscler Thromb Vasc Biol, 2011, 31: 1033-1040.

[37] KHALEEL M S, DORHEIM T A, DURYEE M J, DURBIN H E Jr, BUSSEY W D, GARVIN R P, et al. High-pressure distention of the saphenous vein during preparation results in increased markers of inflammation: a potential mechanism for graft failure[J]. Ann Thorac Surg, 2012, 93: 552-558.

[38] SOBEL M, MORENO K I, YAGI M, KOHLER T R, TANG G L, CLOWES A W, et al. Low levels of a natural IgM antibody are associated with vein graft stenosis and failure[J]. J Vasc Surg, 2013, 58: 997-1005.

[39] KAWAI T, AKIRA S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors[J]. Nat Immunology, 2010, 11: 373-384.

[40] SCHEPERS A, EEFTING D, BONTA P I, GRIMBERGEN J M, DE VRIES M R, VAN WEEL V, et al. Anti-MCP-1 gene therapy inhibits vascular smooth muscle cells proliferation and attenuates vein graft thickening both *in vitro* and *in vivo*[J]. Arterioscler Thromb Vasc Biol, 2006, 26: 2063-2069.

[41] ZHANG L, PEPPEL K, BRIAN L, CHIEN L, FREEDMAN N J. Vein graft neointimal hyperplasia is exacerbated by tumor necrosis factor receptor-1 signaling in graft-intrinsic cells[J]. Arterioscler Thromb Vasc Biol, 2004, 24: 2277-2283.

[42] ZHANG L, SIVASHANMUGAM P, WU J H, BRIAN L, EXUM S T, FREEDMAN N J, et al. Tumor necrosis factor receptor-2 signaling attenuates vein graft neointima formation by promoting endothelial recovery[J]. Arterioscler Thromb Vasc Biol, 2008, 28: 284-289.

[43] KRIJNEN P A, KUPREISHVILI K, DE VRIES M R, SCHEPERS A, STOOKER W, VONK A B, et al. C1-esterase inhibitor protects against early vein graft remodeling under arterial blood pressure[J]. Atherosclerosis, 2012, 220: 86-92.

[44] DE VRIES M R, WEZEL A, SCHEPERS A, VAN SANTBRINK P J, WOODRUFF T M, NIESSEN H W, et al. Complement factor C5a as mast cell activator

mediates vascular remodelling in vein graft disease[J]. Cardiovasc Res, 2013, 97: 311-320.

[45] SMITH P K, SHERNAN S K, CHEN J C, CARRIER M, VERRIER E D, ADAMS P X, et al. Effects of C5 complement inhibitor pexelizumab on outcome in high-risk coronary artery bypass grafting: combined results from the PRIMO-CABG Ⅰ and Ⅱ trials [J]. J Thorac Cardiovasc Surg, 2011, 142: 89-98.

[46] MALINSKA A, PEREK B, BUCZKOWSKI P, KOWALSKA K, OSTALSKA-NOWICKA D, WITKIEWICZ W, et al. CD68 expression in aortocoronary saphenous vein bypass grafts [J]. Histochem Cell Biol, 2013, 140: 183-188.

[47] KOGA J, NAKANO T, DAHLMAN J E, FIGUEIREDO J L, ZHANG H, DECANO J, et al. Macrophage Notch ligand Delta-like 4 promotes vein graft lesion development: implications for the treatment of vein graft failure[J]. Arterioscler Thromb Vasc Biol, 2015, 35: 2343-2353.

[48] DE VRIES M R, SEGHERS L, VAN BERGEN J, PETERS H A, DE JONG R C, HAMMING J F, et al. C57BL/6 NK cell gene complex is crucially involved in vascular remodeling[J]. J Mol Cell Cardiol, 2013, 64: 51-58.

[49] EWING M M, KARPER J C, ABDUL S, DE JONG R C, PETERS H A, DE VRIES M R, et al. T-cell co-stimulation by CD28-CD80/86 and its negative regulator CTLA-4 strongly influence accelerated atherosclerosis development[J]. Int J Cardiol, 2013, 168: 1965-1974.

[50] YAHAGI K, KOLODGIE F D, OTSUKA F, FINN A V, DAVIS H R, JONER M, et al. Pathophysiology of native coronary, vein graft, and in-stent atherosclerosis [J]. Nat Rev Cardiol, 2016, 13: 79-98.

[51] YAZDANI S K, FARB A, NAKANO M, VORPAHL M, LADICH E, FINN A V, et al. Pathology of drug-eluting versus bare-metal stents in saphenous vein bypass graft lesions [J]. JACC Cardiovascular interventions, 2012, 5: 666-674.

[52] DE VRIES M R, NIESSEN H W, LOWIK C W, HAMMING J F, JUKEMA J W, QUAX P H. Plaque rupture complications in murine atherosclerotic vein grafts can be prevented by TIMP-1 overexpression[J/OL]. PLoS One, 2012, 7: e47134. doi: 10.1371/journal.pone.0047134.

[53] WEZEL A, DE VRIES M R, LAGRAAUW H M, FOKS A C, KUIPER J, QUAX P H, et al. Complement factor C5a induces atherosclerotic plaque disruptions[J]. J Cell Mol Med, 2014, 18: 2020-2030.

[54] MURPHY G J, ANGELINI G D. Insights into the pathogenesis of vein graft disease: lessons from intravascular ultrasound[J]. Cardiovasc Ultrasound, 2004, 2: 8.

[55] WANG B, YAMAMOTO M H, NAND P, STEWART J, WEBSTER M, GONZALES H, et al. Long-term changes in plaque burden and vessel remodeling in saphenous vein grafts: insights from serial intravascular ultrasound [J]. Coronary artery disease, 2016, 27: 523-527.

[56] ADLAM D, ANTONIADES C, LEE R, DIESCH J, SHIRODARIA C, TAGGART D, et al. OCT characteristics of saphenous vein graft atherosclerosis [J]. JACC Cardiovasc Imaging, 2011, 4: 807-809.

[57] KOTSIA A, MICHAEL T, RANGAN B, PAPAYANNIS A, DIMAIO M, PELTZ M, et al. Serial optical coherence tomography imaging for the evaluation of aortocoronary saphenous vein graft disease. Insights from the Cardiac Catheterization for Bypass Graft Patency Rate Optimization (CABG-PRO) study [J]. J American College Cardiol, 2014, 63: A1781.

[58] BOMB R, OLIPHANT C S, KHOUZAM R N. Dual antiplatelet therapy after coronary artery bypass grafting in the setting of acute coronary syndrome[J]. Am J Cardiol, 2015, 116: 148-154.

[59] AMICO F, AMICO A, MAZZONI J, MOSHIYAKHOV M, TAMPARO W. The evolution of dual antiplatelet therapy in the setting of acute coronary syndrome: ticagrelor versus clopidogrel[J]. Postgrad Med, 2016, 128: 159-163.

[60] HESS C N, LOPES R D, GIBSON C M, HAGER R, WOJDYLA D M, ENGLUM B R, et al. Saphenous vein graft failure after coronary artery bypass surgery: insights from PREVENT Ⅳ[J]. Circulation, 2014, 130: 1445-1451.

[61] WANG X W, ZHAO X J, XIANG X Y. Gene therapy for vein graft failure[J]. J Card Surg, 2013, 28: 144-147.

[本文编辑] 曾奇峰