·文献综述·

[文章编号] 1007-3949(2017)25-05-0536-05

祖细胞和干细胞与缺血性疾病的治疗

张 航[1]，王照飞[2]，张百灵[1]，何 晋[1]，郑昭芬[1]

(1.湖南省人民医院 湖南师范大学第一附属医院心内科，2.湖南省长沙市第一医院心内科，湖南省长沙市 410000)

[关键词] 祖细胞； 干细胞； 缺血性疾病

[摘 要] 缺血性疾病是严重危害人类健康的疾病之一，主要包括缺血性脑血管疾病、缺血性心血管疾病、下肢缺血性疾病等。祖细胞和干细胞都是具有自我复制能力的多潜能细胞，在一定条件下，它们可以分化成多种功能细胞。根据干细胞所处的发育阶段分为胚胎干细胞和成体干细胞，虽然胚胎干细胞具有万能分化型功能，但伦理学方面的争议使其研究困难重重，而成体干细胞相较胚胎干细胞，不仅避免了伦理学方面的争议问题，而且无移植后免疫排斥反应。本文主要讨论成体干细胞和祖细胞在缺血性疾病中的应用。近年来，关于祖细胞和干细胞在缺血性疾病中应用的研究日益增多，受到了广泛的关注，为我们提供了一条治疗缺血性疾病的新思路。

[中图分类号] R5 [文献标识码] A

Progenitor cells and stem cells in the treatment of ischemic disease

ZHANG Hang[1], WANG Zhao-Fei[2], ZHANG Bai-Ling[1], HE Jin[1], ZHENG Zhao-Fen[1]

(1. *Hunan Provincial People's Hospital & Department of Cardiology, the First Affiliated Hospital of Hunan Normal University*, 2. *Department of Cardiology, the First Hospital of Changsha, Changsha, Hunan* 410000, *China*)

[**KEY WORDS**] Progenitor cells; Stem cells; Ischemic disease

[**ABSTRACT**] Ischemic disease is one of the serious diseases that is harm to human health, which mainly includes ischemic cerebrovascular disease, ischemic heart disease, ischemic disease of lower extremities. Progenitor cells and stem cells are pluripotent cells with self-replicating ability. Under certain conditions, they are able to differentiate into a variety of cells. According to the developmental stages of stem cells, it is classified into embryonic stem cells and somatic stem cells. Although embryonic stem cells have abilities of differentiating into any cell, the ethics dispute makes its study difficult. Compared with embryonic stem cells, somatic stem cells can not only avoid the ethical controversy, but also have no immune rejection after transplanting. Therefore, this essay focuses on the application of stem cells and progenitor cells in ischemic disease. In recent years, the research on the application of progenitor cells and stem cells in this kind of disease has increased, and aroused wide attention, which provides us with a new approach to the treatment of ischemic diseases.

缺血性疾病严重危害人类健康，发病率逐渐升高。主要包括缺血性心血管疾病、缺血性脑血管疾病、下肢缺血性疾病等。缺血性疾病为全身血管性疾病，多因吸烟、肥胖、高血压、糖尿病等因素导致内皮细胞功能受损，最后发展为全身性动脉粥样硬化，导致血管狭窄，引发组织缺血。虽然药物治疗、介入手术、外科手术能减轻缺血性疾病症状、改善预后，但都有其局限性及风险性。祖细胞和干细胞都是具有自我修复和多向分化潜能的原始细胞，在一定条件下，它们可以分化成多种功能细胞。主要集中在内皮祖细胞(endothelial progenitor cells，EPC)、骨髓间充质干细胞(mesenchymal stem cells，MSC)、造血干细胞(hematopoietic stem cells，HSC)、脂肪干细胞(adipose tissue-derived mesenchymal stem cells，Ad-MSC)、神经干细胞(neural stem cells，NSC)五大类细胞。本文对这五大类细胞在缺血性疾病中的研究进展作一综述。

1 内皮祖细胞

内皮祖细胞是血管内皮细胞的前体细胞，亦称为成血管细胞，是一类能增殖、分化为血管的内皮

[收稿日期] 2016-12-17 [修回日期] 2017-03-07

[作者简介] 张航，住院医师，硕士研究生，主要研究方向为缺血性心肌再生，E-mail 为 602441000@qq.com。通讯作者郑昭芬，博士，主任医师，教授，主要研究方向为缺血性心肌再生，E-mail 为 zhaofenz@foxmail.com。

细胞。在某些生理或病理因素的刺激下,从骨髓动员到外周血参与损伤血管的修复。1997 年,Asahara 等[1]在成人外周血中发现 $CD34^+$ 细胞、$Flk\text{-}1^+$ 细胞在体外分离培养可以分化为内皮祖细胞。内皮祖细胞参与新生血管的形成,不仅因为直接参与内皮再生及修复[2],所分泌的血管生长因子也发挥重要作用[3]。前者与内皮祖细胞的动员、迁移相关,如基质细胞衍生因子 1(stromal cell-derived factor-1, SDF-1)/基质细胞衍生因子受体 4(stromal cell derived factor receptor 4,CXCR4)信号轴在此过程中发挥了重要作用;后者与内皮祖细胞分泌的多种血管生长因子相关,如血管内皮生长因子(vascular endothelial growth factor,VEGF)、成纤维细胞生长因子(fibroblast growth factor, FGF)等,最重要的是 VEGF。循环内皮祖细胞已被证明与血管内皮功能障碍和心血管危险因素呈负相关[4]。他汀类药物能显著增加内皮祖细胞的数量以及改善内皮祖细胞的功能[5-7]。罗国君等[8]研究分析了 206 例缺血性脑血管病患者,包括 82 例急性脑梗死、46 例短暂性脑缺血发作及 78 例颈动脉硬化患者,与 90 例同期健康体检者对照,显示内皮祖细胞数量与缺血性脑血管病患者颈动脉硬化程度呈负相关。Teraa 等[9]研究发现炎症反应因子白细胞介素 6(interleukin-6,IL-6)能大量刺激骨髓中内皮祖细胞动员至外周血,从而促进血管生长,增加缺血区血流量,加快缺血肢体伤口的愈合。在一项内皮祖细胞移植治疗小鼠后肢缺血模型的研究中,过表达 VEGF 的内皮祖细胞能更有效地参与血管新生[10]。Tanaka 等[11]应用肌内注射自体骨髓单核细胞可显著缓解下肢疼痛、缩小溃疡面积和提高无肢体疼痛的步行距离,随访 3 年显示明显降低截肢率。甲状旁腺素可增加 CXCR4 表达,促进骨髓干细胞转移至缺血心肌,促进梗死部位的心肌细胞的再生和修复[12]。心肌缺血时植入药物洗脱支架(DES)虽然减少了病变血管再狭窄率,但也同时延缓了内膜修复,从而出现支架内晚期血栓形成,造成心肌梗死[13]。Fernández 等[14]研究发现中度到高强度的体能耐力训练可提高内皮祖细胞的再生能力,并对代谢综合症患者起到积极作用。

2　骨髓间充质干细胞

骨髓间充质干细胞是多能细胞,源于发育早期的中胚层和外胚层,在体内或体外特定的诱导条件下,可以分化成脂肪、骨、软骨、肌肉、肌腱、韧带、神经、肝、心肌、内皮等多种组织细胞[15]。1997 年 Prockop 等[16]成功地从外周血中分离出骨髓间充质干细胞。G 蛋白偶联受体 APJ 的内源性配体多肽 Apelin-13 通过阻断 MAPK/ERK1/2 和 PI3K/Akt 的信号通路发挥抗凋亡作用,提高缺血组织中移植的骨髓间充质干细胞的存活率[17]。SDF-1/CXCR4 通路在动员骨髓间充质干细胞迁移中发挥着重要作用,但 Wang 等[18]最新研究表明,SDF-1/CXCR7 通路同样可以动员骨髓间充质干细胞的迁移,且 CXCR7 的效果比 CXCR4 的更强。骨髓干细胞表面受体 CXCR4 的拮抗剂 AMD3100 可以抑制白细胞的迁移和浸润。粒细胞集落刺激因子(granulocyte colony-stimulating factor,G-CSF)与 CXCR4 联合作用动员骨髓间充质干细胞可显著抑制脑缺血后的中枢神经系统炎症和损害,保护血脑屏障的完整性[19]。梗死后心肌重塑导致心力衰竭与心律失常,临床治疗困难。细胞移植疗法在急性心肌梗死中的应用受到关注。由于骨髓间充质干细胞向缺血组织靶向迁移的能力较弱,单纯骨髓间充质干细胞移植疗法难以取得预期效果。Mu 等[20]设计骨髓间充质干细胞与整合素连接激酶(integrin linked kinase,ILK)及多效性蛋白结合,经严密调控细胞活性、增殖、分化和血管生成,与空载质粒修饰的骨髓间充质干细胞相比,ILK 转染的骨髓间充质干细胞显著减少细胞凋亡、增加细胞增殖、增加局部灌注、减少梗死面积、改善左心室收缩功能。Honma 等[21]给短暂性大脑中动脉闭塞的大鼠静脉输注人端粒酶基因修饰的骨髓间充质干细胞($SH2^+$、$SH3^+$、$CD34^-$ 和 $CD45^-$),发现高纯度的骨髓间充质干细胞可减少脑梗死面积,促进脑功能的恢复,且静脉输注骨髓间充质干细胞的细胞数量与病灶面积的减少和功能的改善程度呈正相关。Yang 等[22]给予因动脉粥样硬化闭塞症或血栓闭塞性脉管炎所致严重肢体缺血病终末期的患者移植骨髓间充质干细胞有效。但 Jonsson 等[23]报道使用干细胞移植治疗 9 名下肢缺血患者,其中有 4 名患者出现严重并发症,2 名与骨髓刺激有关,并被认为由骨髓动员引起。因而,提醒干细胞移植患者需密切观察,减少并发症。

3　造血干细胞

造血干细胞指尚未发育成熟的造血细胞,是所有造血细胞和免疫细胞的起源细胞,具有两个重要的特征:其一,高度的自我更新或自我复制能力;其二,可分化成所有类型的血细胞。G-CSF 能通过减

少骨髓 SDF-1 的分泌、上调 CXCR4 的表达从而增强诱导的造血干细胞动员，控制造血干细胞在骨髓和外周循环间的运输[24]。Huang 等[25]研究表明 GSK-3抑制剂在器官移植时可改善造血干细胞归巢、分化、自我更新能力。Losordo 等[26]应用冠状动脉内输注造血干细胞-$CD34^+$治疗顽固性心绞痛，可显著减少心绞痛发作频率并提高运动耐力。缺血性脑卒中还可通过增加交感紧张启动造血干细胞，使缺血区域的中性粒细胞和单核细胞数量增加而淋巴系祖细胞数量减少，促进脑卒中恢复和减少再次脑卒中[27]。研究发现，使用 G-CSF 动员造血干细胞时，35%的患者不能动员足够数量的 CD34 细胞入外周血，导致缺血症状改善不明显[28]。因此，需探索更多造血干细胞动员剂并联合应用以改善治疗效果。此外，小鼠睡眠剥夺可减少造血干细胞移植治疗的疗效，与睡眠剥夺下调 miR-19b、抑制造血干细胞迁移和归巢的细胞因子信号抑制基因负调节子的表达有关，使造血干细胞迁移和归巢能力下降[29]。

4 脂肪干细胞

脂肪干细胞是从脂肪组织中分离得到的一种具有多向分化潜能的干细胞，2001 年由 Zuk 等[30]在人体脂肪组织中首先发现。Karpov 等[31]在缺血性心力衰竭大鼠模型中比较骨髓来源的间充质干细胞（bone marrow-derived mesenchymal stem cells，BMSC）与脂肪组织来源的间充质干细胞（adipose tissue-derived mesenchymal stem cells，ADSC）移植对坏死面积缩小和左心室功能改善的作用。虽然 BMSC 具有更好的心肌保护作用，但从人体外周血中分离和培养骨髓间充质干细胞耗时、效率低，而 ADSC 来源广泛、取材方便[32]。ADSC 与 BMSC 有相似的生物学特性及分化潜能，因而具有更好的应用前景。心肌梗死后，炎性细胞如嗜中性粒细胞、单核细胞、巨噬细胞可渗透和吞噬坏死组织并分泌多种炎症细胞因子，但过度的炎症反应会导致心室重塑[33]，导致心力衰竭的发生[34]。ADSC 抑制核因子 κB（nuclear factor-κB，NF-κB）蛋白的表达，降低白细胞介素 1 受体、白细胞介素 10 受体、肿瘤坏死因子 α 和其它促炎细胞因子的水平[35]，从而调控炎症反应，减轻心室重塑、改善心功能。

5 神经干细胞

神经干细胞具有分化为神经元、星形胶质细胞和少突胶质细胞的能力，是一类具有分裂潜能和自我更新能力的母细胞，通过不对等的分裂方式产生神经组织的各类细胞，是胚胎脑发育和神经再生的细胞基础。Xiao 等[36]研究显示 VEGF 上调 Flk-1 的表达从而通过 ERK1/2 途径促进神经干细胞增殖。神经干细胞移植疗法可改善脑缺血后大脑损伤，但受供体细胞存活不良的限制，血肿和随后的铁超载明显降低神经干细胞的存活率。一氧化碳释放分子 2（carbonic oxide releasing molecule-2，CORM-2）可干扰 NF-κB 信号通路，包括抑制核转运和下调 NF-κB p65 的表达，从而提高神经干细胞移植后的存活率[37]。Jiang 等[38]将神经干细胞移植到大脑中动脉梗塞大鼠模型的缺血区侧脑室中，4 周后 MRI 检测到缺血区有新生血管生成，神经干细胞移植组较非移植组神经功能恢复更好，推测神经干细胞可选择性向缺血区域迁移。Muneton-Gomez 等[39]发现神经干细胞能分化成不同的细胞类型，如神经元、星形胶质细胞，在腔隙性脑梗死时发挥神经元替代治疗和营养神经作用。中脑星形胶质细胞源性神经营养因子减轻神经干细胞在治疗神经变性疾病时的炎症反应，有利于神经干细胞发挥其功能[40]。神经系统受损疾病，包括如帕金森、亨廷顿病和脑卒中等其它病症移植神经干细胞有效[41]。动物实验显示针刺疗法通过促进脑缺血损伤大鼠神经干细胞增殖、分化、迁移，而发挥治疗作用[42]。

6 结 语

近年来，祖细胞和干细胞移植在缺血性疾病中的应用研究日益增多。虽然其有效性及安全性仍需大量的临床试验验证，但这无疑是不同于传统治疗方法的一种崭新的领域。随着研究深入，祖细胞和干细胞应用于临床仍有许多问题需要解决。目前，祖细胞和干细胞来源的不确定性、鉴定的不统一以及临床因素对其功能的影响，限制其临床应用。因此如何使祖细胞和干细胞的功能进一步提升，以适应患者复杂的临床因素是其关键。基因治疗技术的发展，基因治疗与祖细胞和干细胞的结合很可能是突破点。

[参考文献]

[1] Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis[J]. Science, 1997, 275(5302): 964-967.

[2] Asahara T, Masuda H, Takahashi T, et al. Bone marrow

origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization[J]. Circ Res, 1999, 85(3): 221-228.

[3] Seebach C, Henrich D, Wilhelm, K, et al. Endothelial progenitor cells improve directly and indirectly early vascularization of mesenchymal stem cell-driven bone regeneration in a critical bone defect in rats[J]. Cell Transplant, 2012, 21(8): 1 667-677.

[4] Ye L, KK Poh. Enhancing endothelial progenitor cell for clinical use[J]. World J Stem Cells, 2015, 7(6): 894-898.

[5] Oikonomou E, Siasos G, Zaromitidou M, et al. Atorvastatin treatment improves endothelial function through endothelial progenitor cells mobilization in ischemic heart failure patients[J]. Atherosclerosis, 2015, 238(2): 159-164.

[6] Khan S, Chuturgoon AA, Naidoo DP. Telomeres and atherosclerosis[J]. Cardiovasc J Afr, 2012, 23(10): 563-571.

[7] Liu HF, Qi XW, Ma LL, et al. Atorvastatin improves endothelial progenitor cell function and reduces pulmonary hypertension in patients with chronic pulmonary heart disease [J]. Exp Clin Cardiol, 2013, 18(1): e 40-43.

[8] 罗国君, 艾志兵, 唐春雷, 等. 循环内皮祖细胞水平与缺血性脑血管患者颈动脉粥样硬化程度的相关性[J]. 中国老年学杂志, 2014, 18: 5 117-118.

[9] Teraa M, Sprengers RW, Westerweel PE, et al. Bone marrow alterations and lower endothelial progenitor cell numbers in critical limb ischemia patients[J]. PLoS One, 2013, 8(1): e55592.

[10] Yang HN, Park JS, Woo DG, et al. Transfection of VEGF (165) genes into endothelial progenitor cells and in vivo imaging using quantum dots in an ischemia hind limb model[J]. Biomaterials, 2012, 33(33): 8 670-684.

[11] Tanaka R, Masud H, Kato S, et al. Autologous G-CSF-mobilized peripheral blood $CD34^+$ cell therapy for diabetic patients with chronic nonhealing ulcer[J]. Cell Transplant, 2014, 23(2): 167-179.

[12] Brunner S, Weinberger T, Huber BC, et al. The cardioprotective effects of parathyroid hormone are independent of endogenous granulocyte-colony stimulating factor release [J]. Cardiovasc Res, 2012, 93(2): 330-339.

[13] Chaabane C, Otsuka F, Virmani R, et al. Biological responses in stented arteries[J]. Cardiovasc Res, 2013, 99(2): 353-363.

[14] Fernández JM, Rosado-Álvarez D, Da Silva Grigoletto ME, et al. Moderate-to-high-intensity training and a hypocaloric mediterranean diet enhance endothelial progenitor cells and fitness in subjects with the metabolic syndrome[J]. Clin Sci (Lond), 2012, 123(6): 361-373.

[15] Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells[J]. Science, 1999, 284(5411): 143-147.

[16] Prockop DJ. Marrow stromal cells as stem cells for nonhematopoietic tissues [J]. Science, 1997, 276 (5309): 71-74.

[17] Zeng X, Yu SP, Taylor T, et al. Protective effect of apelin on cultured rat bone marrow mesenchymal stem cells against apoptosis[J]. Stem Cell Res, 2012, 8(3): 357-367.

[18] Wang Y, Fu W, Zhang S, et al. CXCR-7 receptor promotes SDF-1alpha-induced migration of bone marrow mesenchymal stem cells in the transient cerebral ischemia/reperfusion rat hippocampus[J]. Brain Res, 2014, 1575: 78-86.

[19] Huang J, Li Y, Tang Y, et al. CXCR4 antagonist AMD3100 protects blood-brain barrier integrity and reduces inflammatory response after focal ischemia in mice [J]. Stroke, 2013, 44(1): 190-197.

[20] Mu D, Zhang XL, Xie J, et al. Intracoronary transplantation of mesenchymal stem cells with overexpressed integrin-linked kinase improves cardiac function in porcine myocardial infarction[J]. Sci Rep, 2016, 6: 19155.

[21] Honma T, Honmou O, Iihoshi S, et al. Intravenous infusion of immortalized human mesenchymal stem cells protects against injury in a cerebral ischemia model in adult rat[J]. Exp Neurol, 2006, 199(1): 56-66.

[22] Yang SS, Kim NR, Park KB, et al. A phase I study of human cord blood-derived mesenchymal stem cell therapy in patients with peripheral arterial occlusive disease[J]. Int J Stem Cells, 2013, 6(1): 37-44.

[23] Jonsson TB, Larzon T, Arfvidsson B, et al. Adverse events during treatment of critical limb ischemia with autologous peripheral blood mononuclear cell implant [J]. Int Angiol, 2012, 31(1): 77-84.

[24] Petit I, Szyper-Kravitz M, Nagler A, et al. G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4 [J]. Nat Immunol, 2002, 3(7): 687-694.

[25] Huang J, Nguyen-McCarty M, Hexner EO, et al. Maintenance of hematopoietic stem cells through regulation of Wnt and mTOR pathways[J]. Nat Med, 2012, 18(12): 1 778-785.

[26] Losordo DW, Henry TD, Davidson C, et al. Intramyocardial, autologous $CD34^+$ cell therapy for refractory angina [J]. Circ Res, 2011, 109(4): 428-436.

[27] Courties G, Herisson F, Sager HB, et al. Ischemic stroke activates hematopoietic bone marrow stem cells[J]. Circ Res, 2015, 116(3): 407-417.

[28] Hopman RK, DiPersio JF. Advances in stem cell mobilization[J]. Blood Rev, 2014, 28(1): 31-40.

[29] Rolls A, Pang WW, Ibarra I, et al. Sleep disruption impairs haematopoietic stem cell transplantation in mice[J]. Nat Commu, 2015, 6(6): 8516.
[30] Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies [J]. Tissue Eng, 2001, 7(2): 211-228.
[31] Karpov AA, Uspenskaya YK, Minasian SM, et al. The effect of bone marrow-and adipose tissue-derived mesenchymal stem cell transplantation on myocardial remodelling in the rat model of ischaemic heart failure[J]. Int J Exp Pathol, 2013, 94(3): 169-177.
[32] Ahern BJ, Schaer TP, Terkhorn SP, et al. Evaluation of equine peripheral blood apheresis product, bone marrow, and adipose tissue as sources of mesenchymal stem cells and their differentation potential[J]. Am J Vet Res, 2011, 72(1): 127-133.
[33] Anzai T. Post-infarction inflammation and left ventricular remodeling: a double-edged sword[J]. Circ J, 2013, 77 (3): 580-587.
[34] Hofmann U, Frantz S. How can we cure a heart "in flame" A translational view on inflammation in heart failure[J]. Basic Res Cardiol, 2013, 108(4): 356.
[35] Prockop DJ, Youn Oh J. Mesenchymal stem/stromal cells (MSCs): role as guardians of inflammation[J]. Mol Ther, 2012, 20(1): 14-20.
[36] Xiao Z, Kong Y, Yang S, et al. Upregulation of Flk-1 by bFGF via the ERK pathway is essential for VEGF-mediated promotion of neural stem cell proliferation[J]. Cell Res, 2007, 17(1): 73-9.
[37] Xie Z, Han P, Cui Z, et al. Pretreatment of mouse neural stem cells with carbon monoxide-releasing molecule-2 interferes with NF-kappaB p65 signaling and suppresses iron overload-induced apoptosis [J]. Cell Mol Neurobiol, 2016, 36(8): 1 343-351.
[38] Jiang Q, Zhang ZG, Ding GL, et al. Investigation of neural progenitor cell induced angiogenesis after embolic stroke in rat using MRI[J]. Neuroimage, 2005, 28(3): 698-707.
[39] Muneton-Gomez VC, Doncel-Perez E, Fernandez AP, et al. Neural differentiation of transplanted neural stem cells in a rat model of striatal lacunar infarction: light and electron microscopic observations[J]. Front Cell Neurosci, 2012, 6: 30.
[40] Zhu W, Li J, Liu Y, et al. Mesencephalic astrocyte-derived neurotrophic factor attenuates inflammatory responses in lipopolysaccharide-induced neural stem cells by regulating NF-kappaB and phosphorylation of p38-MAPKs pathways[J]. Immunopharmacol Immunotoxicol, 2016, 38 (3): 205-213.
[41] Bonnamain V, Neveu I, Naveilhan P. Neural stem/progenitor cells as a promising candidate for regenerative therapy of the central nervous system[J]. Front Cell Neurosci, 2012, 6: 17.
[42] 焦 洋, 孟智宏, 樊小农, 等. 针刺治疗缺血性中风对神经干细胞增殖分化作用的最新实验研究进展[J]. 辽宁中医杂志, 2014, 39(8): 1 654-657.

(此文编辑 文玉珊)

(上接第 494 页)

[7] Hou X, Shi J, Sun H. Gene polymorphism of cytochrome P450 2C19 * 2 and clopidogrel resistance reflected by platelet function assays: a meta-analysis [J]. Eur J Clin Pharmacol, 2014, 70 (9): 1 041-047.
[8] Dogan A, Kahraman S, Usta E, et al. Effect of obesity and serum leptin level on clopidogrel resistance [J]. Turk Kardiyol Dern Ars, 2016, 44(7): 548-553.
[9] Hobson AR, Qureshi Z, Banks P, et al. Gender and responses to aspirin and clopidogrel: insights using short thrombelastography[J]. Cardiovasc Ther, 2009, 27(4): 246-252.
[10] Akturk IF, Caglar FN, Erturk M, et al. Hypertension as a risk factor for aspirin and clopidogrel resistance in patients with stable coronary artery disease [J]. Clin Appl Thromb Hemost, 2014, 20 (7): 749-754.
[11] Motovska Z, Widimsky P, Petr R, et al. Factors influencing clopidogrel efficacy in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention: statin's advantage and the smoking "paradox"[J]. J Cardiovasc Pharmacol, 2009, 53(5): 368-372.
[12] 张春英, 侯旭敏, 仇兴标, 等. 冠心病 PCI 术后发生氯吡格雷抵抗的影响因素[J]. 上海交通大学学报:医学版, 2012, 32(6): 792-795.
[13] Angiolillo DJ, Bernardo E, Ramirez C, et al. Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment[J]. J Am Coll Cardiol, 2006, 48(2): 298-304.
[14] Liu XL, Wang ZJ, Yang Q, et al. Impact of CYP2C19 polymorphism and smoking on response to clopidogrel in patients with stable coronary artery disease[J]. Chin Med J(Engl), 2010, 123(22): 3 178-183.
[15] 张 优, 传 玉, 洪 智, 等. 早期应用替罗非班对行介入治疗的中高危急性冠脉综合征患者血小板聚集率和临床结果的影响[J]. 中国急救医学, 2010, 30(1): 69-72.

(此文编辑 朱雯霞)