[文章编号] 1007-3949(2021)29-04-0359-05 ·文献综述·

颈动脉粥样硬化斑块内新生血管的研究现状及进展

齐炳才[1]，靳琦文[2]，胡 杰[1]，邢 淼[1]，袁 萌[1]，张智鑫[1]，董红霖[1]
(1. 山西医科大学第二医院血管外科，山西省太原市 030001；2. 北京大学中日友好临床医学院，北京市 100029)

[关键词] 脑卒中； 颈动脉粥样硬化； 易损斑块； 新生血管

[摘 要] 颈动脉粥样硬化斑块破裂是导致脑卒中的重要原因之一，大量研究证实颈动脉斑块内新生血管是导致斑块内出血、斑块破裂的重要因素。炎症因子及各类细胞通过斑块内新生血管进入斑块，导致斑块稳定性破坏，但影响斑块内新生血管形成的重要相关因子和主要机制目前尚未完全明确，因此识别斑块内新生血管、探索斑块内新生血管形成的相关因子及机制是研究斑块内新生血管致斑块不稳定性的关键。抑制斑块内新生血管生成，可能成为防治颈动脉斑块破裂、降低脑栓塞事件发生的新策略。本综述旨在探讨颈动脉斑块内新生血管形成的相关因子、机制以及检测成像的最新研究进展，为动脉粥样硬化的诊疗提供支持。

[中图分类号] R5；R654.3 [文献标识码] A

Research status and progress of carotid atherosclerotic intraplaque neovascularization

QI Bingcai[1], JIN Qiwen[2], HU Jie[1], XING Miao[1], YUAN Meng[1], ZHANG Zhixin[1], DONG Honglin[1]
(1. *Department of Vascular Surgery, the Second Hospital of Shanxi Medical University, Taiyuan, Shanxi* 030001, *China*; 2. *Peking University China-Japan Friendship School of Clinical Medical, Beijing* 100029, *China*)

[**KEY WORDS**] stroke; carotid atherosclerosis; unstable plaques; neovascularization

[**ABSTRACT**] Rupture of carotid atherosclerotic plaque is one of the important causes of stroke. A large number of studies have confirmed that carotid plaque neovascularization is an important factor leading to intraplaque hemorrhage and rupture. Inflammatory factors and all kinds of cells enter the plaque through intraplaque neovascularization, which leads to the destruction of plaque stability. But the important related factors and main mechanisms affecting the formation of intraplaque neovascularization are not completely clear. Therefore, to identify intraplaque neovascularization and explore the related factors and mechanism of intraplaque neovascularization is the key to study plaque instability caused by intraplaque neovascularization. Inhibition of intraplaque neovascularization may be a new strategy for prevention and treatment of carotid plaque rupture and reduction of cerebral embolism. The purpose of this review is to explore the related factors, mechanism and the latest research progress of detection and imaging of carotid intraplaque neovascularization, so as to provide support for the diagnosis and treatment of clinical diseases.

脑血管疾病的发病率在发展中国家逐年升高，是疾病致死和致残的主要原因之一[1-3]。其发病率随着年龄的增长而增加，而中国脑卒中的发病年龄明显趋于年轻化[4]。脑血管疾病中，80% 的脑卒中为缺血性脑卒中，其中动脉粥样硬化性颈动脉狭窄所致的缺血性脑卒中约占 25%～30%[4]。随着近年来实验研究和辅助检查手段的发展，越来越多的证据表明，颈动脉斑块的不稳定性是动脉粥样硬化性颈动脉狭窄导致缺血性脑卒中更危险的因素[5-8]。颈动脉狭窄的病理基础为动脉粥样硬化[4,9]，最近动脉粥样硬化病变的病理生理学研究为不稳定性斑块的形成提供了新的线索，一方面斑块周围炎症介质的增多有助于斑块不稳定发展；另一方面，巨噬细胞的聚集会增加斑块破裂的风险；再者血管内皮的功能障碍会促进斑块向不稳定性发展。近年来越来越多证据表明斑块内新生血管形成成为促进斑块不稳定性病变的重要因素，其可能通过促进斑块内出血、炎症介质或相关细胞的流

[收稿日期] 2020-03-18 [修回日期] 2020-05-09
[基金项目] 国家自然科学基金项目(81870354)
[作者简介] 齐炳才，硕士研究生，E-mail 为 15235356554@163.com。通信作者董红霖，教授，博士研究生导师，研究方向为颈动脉易损斑块，E-mail 为 honglindong@sxmu.edu.cn。

入破坏斑块稳定性[10-12]，但具体机制尚不明确。本文拟对颈动脉粥样硬化斑块内新生血管形成的相关研究现状及进展作一综述。

1 新生血管概述

新生血管生成是指从现有的微血管中形成新的毛细血管，同时相关支持细胞向不同节段血管系统的募集。在肿瘤、糖尿病视网膜病变、动脉粥样硬化等病理条件下，持续上调的新生血管成为疾病发展的关键因素[13-14]。Paterson 等[15]在 1936 年发现了动脉粥样硬化斑块内的小血管。斑块内小血管形成过程中新的内皮细胞从内皮前体细胞分化成初级血管丛，经过萌芽、微血管生成、迁移、增殖或者经过血管重塑形成新生血管[16]。正常血管壁中的微血管结构通常局限于血管中膜和外膜之间[17-18]，而动脉硬化病变中，颈动脉内膜会发生血管化，在内膜层形成许多薄壁血管，这些新生血管为炎性细胞、巨噬细胞、红细胞或坏死物质等向斑块的浸润提供了通道，加上新生血管结构上不稳定，最终为斑块破裂提供了基础[19]。

2 调节斑块内新生血管的相关因子

新生血管形成对肿瘤病理生理机制的研究报道比较多，动脉粥样硬化斑块内新生血管形成机制比较复杂，研究报道相对缺乏[20]。目前研究证实缺氧和炎症反应是斑块内新生血管形成的重要诱因，进一步通过调节相关因子在动脉粥样硬化斑块区域的表达，可发挥抑制斑块失稳的重要作用[21-22]。斑块形成早期，血管内膜损害以及氧扩散障碍，导致缺氧状态，进一步通过 Toll 样受体（Toll-like receptor，TLR）、肿瘤坏死因子（tumor necrosis factor，TNF）、白细胞介素 1（interleukin-1，IL-1）、核因子 κB（nuclear factor-κB，NF-κB）和其他生长因子如胰岛素样生长因子 1/2（insulin like growth factor-1/2，IGF-1/2）、成纤维生长因子 2（fibroblast growth factor-2，FGF-2）、转化生长因子 1（transforming growth factor-1，TGF-1）等激活缺氧诱导因子（hypoxia inducible factor，HIF），触发斑块内新生血管形成[16,23]。

很多内皮生长因子参与斑块内新生血管的形成，其中血管内皮生长因子（vascular endothelial growth factor，VEGF）被普遍认为是斑块内新生血管的诱导剂。VEGF 家族有 VEGF-A、B、C、D 和胎盘生长因子五个成员；VEGF-A 是新生血管形成的有效因子，其可由内皮细胞、平滑肌细胞、星形胶质细胞和巨噬细胞等释放，并通过激活其受体 VEGFR-2 促进血管内皮细胞存活、成熟、迁移和增殖[24]。研究发现大量 VEGF 存在晚期颈动脉粥样硬化斑块中，有助于斑块内新生血管形成，抑制其受体可减少斑块内新生血管形成，从而使动脉粥样硬化病变减小或趋于稳定[25-28]。

转化生长因子 β（transforming growth factor-β，TGF-β）作为血小板活性因子在动脉粥样硬化及斑块内新生血管调节中起重要作用[29]。TGF-β1 被普遍认为是一种促血管生成因子。研究证实，TGF-β1 存在双向功能，其作用依赖于不同的信号通路，ALK1/SMAD1/5 通路激活可以促进内皮迁移，促进血管生成，而 ALK5/SMAD2/3 激活抑制血管生成。通过靶向调控 TGF-β1 的下游通路，可有效地减少斑块内新生血管形成，降低颈动脉斑块易损风险[30]。

此外，FGF-2 已被证明有促进斑块内新生血管形成作用[31]，是斑块内新生血管生成的重要调节剂[32]。有研究发现血管生成素（angiogenin，Ang）在动脉粥样硬化中的表达增加，且与斑块内新生血管密度呈正相关。其他血管生成因子如肝素结合表皮生长因子（heparin-binding epidermal growth factor，HB-EGF）、肝细胞生长因子（hepatocyte growth factor，HGF）等也被证实与斑块内新生血管形相关，这为研究斑块内新生血管形成与斑块稳定性提供潜在靶点。

3 斑块内新生血管的检测

动脉粥样硬化不稳定性斑块的检测是心脑血管栓塞疾病研究领域的一大挑战。明确颈动脉粥样硬化斑块的形态及性质，不仅可以辅助早期诊断，同时为内、外科干预计划提供了指导依据[33]。斑块内新生血管是易损斑块的关键特征之一，检测斑块内新生血管形成可早期识别和预防动脉硬化易损斑块，推动急性脑缺血事件的诊断和预防[34-35]。一直以来，组织病理学分析是准确显示不稳定性斑块内新生血管的方法[36]，多用于实验研究，对临床诊断有一定的局限性。因此非侵入性成像检测方法是目前临床诊断动脉内斑块的主要手段。

目前，对动脉硬化斑块诊断的常用方法有 CT 血管造影（computed tomography angiography，CTA）、

血管超声、磁共振血管造影(magnetic resonance angiography,MRA)、血管造影等。但是,对斑块内新生血管的非侵入成像仍然具有一定的挑战,只有少数检查方法可以详细显示斑块内新生血管。磁共振成像(magnetic resonance imaging,MRI)是检查斑块内出血的重要手段,但对斑块内新生血管不敏感[35,37]。正电子发射计算机断层显像(positron emission tomography,PET-CT)是目前临床斑块内新生血管检测的先进手段,通过静脉注射 18F-氟代脱氧葡萄糖(2-fluoro-2-deoxy-D-glucose,FDG)后,通过监测斑块内新生血管 18F-FDG 的摄取率来进行评估[38-39],但 PET-CT 不能呈现完整的斑块组织结构,需结合 CT 和 MRI 来评估;超声造影结合传统超声和造影技术提供了高时空分辨率的优势,特殊靶向标记微泡造影剂可有效显示斑块内新生血管,而不破坏循环微环境的稳态。后期通过颈动脉斑块内新生血管量化软件进一步对超声造影(contrast-enhanced ultrasound,CEUS)图像中的新生血管进行量化,无论动物还是临床研究均已证实 CEUS 造影强度与新生血管密度直接相关[40-41]。此外,近红外荧光(near infrared fluorescence,NIRF)以斑块内血管形成过程中以插入纤维连接蛋白外区 B 为目标,识别斑块内新生血管[42-43]。该技术结合光学相干断层扫描(optical coherence tomography,OCT),利用 OCT 高空间精度的优点更好地显示斑块内新生血管结构,除此还可通过显示斑块内钙化结节、纤维帽厚度以及脂质沉积的量来识别易损斑块[44]。虽然目前没有完美的成像技术,但通过互补识别高危斑块,为临床疾病预防治疗以及实验研究提供了强有力的帮助。

4　斑块内新生血管的防治

动脉粥样硬化斑块内新生血管成为近年来斑块不稳定因素的研究热点之一,阻止斑块内新生血管形成也成为了预防颈动脉狭窄所致脑卒中的新举措。Koutouzis 等[28]通过临床调查统计研究证明他汀类药物对抑制颈动脉斑块内新生血管的形成有积极作用;随后在兔动脉粥样硬化模型中也证明他汀药物治疗后斑块内新生血管减少,斑块趋于稳定[45]。动物模型体内亦证实依维莫司和阿西替尼分别通过抑制雷帕霉素受体和 VEGF 受体信号转导,抑制斑块新生血管形成,并稳定动脉粥样硬化斑块[27,46]。目前结合斑块内新生血管的相关研究通路及相关因子,对动物模型的研究较多,但临床研究仍相对较少,针对性药物研究也相对较少。如何抑制斑块内新生血管,并尽早应用于动脉粥样硬化性疾病的治疗,有待进一步探索。

5　小结与展望

对于动脉硬化斑块内新生血管的研究,近年来发现了很多与斑块内新生血管相关的促进和抑制因子,如 VEGF、TGF-β、血管生成素 1/2、成纤维生长因子、血小板源性生长因子、HIF 等。目前相关研究领域对影响斑块内新生血管形成的促进和抑制因子的研究仍非常有限,而且具体形成机制尚未完全明确;其次,虽然目前的研究成果为斑块内新生血管的形成提供了很多治疗靶点,但在临床治疗技术和新药研制方面仍存在巨大挑战;此外,大量研究证实斑块内新生血管形成与易损斑块中斑块内出血和斑块破裂密切相关,但对于新生血管形成与斑块形成的时间关系目前尚无定论,仅有个别研究说明斑块内血管形成早于斑块发展,但证据不足,仍需进一步探索。通过有效成像技术或多技术结合识别斑块内新生血管,可有效识别早期或晚期不稳定性斑块,在辅助预防和治疗颈动脉疾病降低脑缺血事件发生中发挥作用。随着进一步深入研究,斑块内新生血管的干预在抑制颈动脉粥样硬化斑块发展、降低斑块破裂风险有广泛前景,并且有可能成为防治动脉粥样硬化的新举措。

[参考文献]

[1] 陈 竺. 全国第三次死因回顾抽样调查报告[M]. 北京: 中国协和医科大学出版社, 2008: 10-17.

[2] Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association [J]. Stroke, 2014, 45(12): 3754-3832.

[3] Pelisek J, Eckstein HH, Zernecke A. Pathophysiological mechanisms of carotid plaque vulnerability: impact on ischemic stroke[J]. Arch Immunol Ther Exp (Warsz), 2012, 60(6): 431-442.

[4] 中华医学会外科学分会血管外科学组. 颈动脉狭窄诊治指南[J]. 中华血管外科杂志, 2017, 2(2): 78-79.

[5] Howard DP, van Lammeren GW, Redgrave JN, et al. Histological features of carotid plaque in patients with ocular ischemia versus cerebral events[J]. Stroke, 2013, 44(3): 734-739.

[6] Gorgui J, Gasbarrino K, Georgakis MK, et al. Circulating adiponectin levels in relation to carotid atherosclerotic plaque presence, ischemic stroke risk, and mortality: a systematic review and Meta-analyses[J]. Metabolism, 2017, 69: 51-66.

[7] Abbott AL, Paraskevas KI, Kakkos SK, et al. Systematic review of guidelines for the management of asymptomatic and symptomatic ca-

rotid stenosis[J]. Stroke, 2015, 46(11): 3288-3301.
[8] Brinjikji W, Huston IJ, Rabinstein AA, et al. Contemporary carotid imaging: from degree of stenosis to plaque vulnerability[J]. J Neurosurg, 2016, 124(1): 27-42.
[9] Madden JA. Role of the vascular endothelium and plaque in acute ischemic stroke[J]. Neurology, 2012, 79(13 Suppl 1): S58-S62.
[10] Michel JB, Virmani R, Arbustini E, et al. Intraplaque haemorrhages as the trigger of plaque vulnerability[J]. Eur Heart J, 2011, 32(16): 1977-1985.
[11] de Vries MR, Quax PH. Plaque angiogenesis and its relation to inflammation and atherosclerotic plaque destabilization[J]. Curr Opin Lipidol, 2016, 27(5): 499-506.
[12] Haasdijk RA, den Dekker WK, Cheng C, et al. THSD1 preserves vascular integrity and protects against intraplaque haemorrhaging in ApoE$^{-/-}$ mice[J]. Cardiovasc Res, 2016, 110(1): 129-139.
[13] Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease[J]. Nat Med, 1995, 1(1): 27-31.
[14] Pandya NM, Dhalla NS, Santani DD. Angiogenesis--a new target for future therapy[J]. Vascul Pharmacol, 2006, 44(5): 265-274.
[15] Paterson JC. Vascularization and hemorrhage of the intima of arteriosclerotic coronary arteries[J]. Arch. Path, 1936, 13(1): 313-324.
[16] Shoeibi S, Mozdziak P, Mohammadi S. Important signals regulating coronary artery angiogenesis[J]. Microvasc Res, 2018, 117: 1-9.
[17] Kazemi-Bajestani SM, Ghayour-Mobarhan M. Concept of atherosclerosis velocity: is it a better measure of cardiovascular risk[J]. Iran J Med Sci, 2013, 38(3): 210-220.
[18] Lu J, Duan W, Qiao A. Finite element analysis of mechanics of neovessels with intraplaque hemorrhage in carotid atherosclerosis[J]. Biomed Eng Online, 2015, 14(Suppl 1): S3.
[19] Mofidi R, Rigden, B. Carotid plaque morphology: plaque instability and correllation with development of ischaemic neurological events[J]. Carotid Artery Disease, 2014: 85-104.
[20] Potente M, Gerhardt H, Carmeliet P. Basic and therapeutic aspects of angiogenesis[J]. Cell, 2011, 146(6): 873-887.
[21] Ogata A, Kawashima M, Wakamiya T, et al. Carotid artery stenosis with a high-intensity signal plaque on time-of-flight magnetic resonance angiography and association with evidence of intraplaque hypoxia[J]. J Neurosurg, 2017, 126(6): 1873-1878.
[22] Chistiakov DA, Orekhov AN, Bobryshev YV. Contribution of neovascularization and intraplaque haemorrhage to atherosclerotic plaque progression and instability[J]. Acta Physiol (Oxf), 2015, 213(3): 539-553.
[23] Basic J, Stojkovic S, Assadian A, et al. The relevance of vascular endothelial growth factor, hypoxia inducible factor-1 alpha, and clusterin in carotid plaque instability[J]. J Stroke Cerebrovasc Dis, 2019, 28(6): 1540-1545.
[24] Simons M, Gordon E, Claesson-Welsh L. Mechanisms and regulation of endothelial VEGF receptor signalling[J]. Nat Rev Mol Cell Biol, 2016, 17(10): 611-625.
[25] Pelisek J, Well G, Reeps C, et al. Neovascularization and angiogenic factors in advanced human carotid artery stenosis[J]. Circ J, 2012, 76(5): 1274-1282.
[26] Stefanadis C, Toutouzas K, Stefanadi E, et al. Inhibition of plaque neovascularization and intimal hyperplasia by specific targeting vascular endothelial growth factor with bevacizumab-eluting stent: an experimental study[J]. Atherosclerosis, 2007, 195(2): 269-276.
[27] Bieke van der Veken, Guido RM, Wim M. Axitinib attenuates intraplaque angiogenesis, haemorrhages and plaque destabilization in mice[J]. Vascul Pharmacol, 2018, 100: 34-40.
[28] Koutouzis M, Nomikos A, Nikolidakis S, et al. Statin treated patients have reduced intraplaque angiogenesis in carotid endarterectomy specimens[J]. Atherosclerosis, 2007, 192(2): 457-463.
[29] Bertolino P, Deckers M, Lebrin F, et al. Transforming growth factor-beta signal transduction in angiogenesis and vascular disorders[J]. Chest, 2005, 128(6 Suppl): 585S-590S.
[30] Nanda V, Downing KP, Ye J, et al. CDKN2B regulates TGFβ signaling and smooth muscle cell investment of hypoxic neovessels[J]. Circ Res, 2016, 118(2): 230-240.
[31] Doyle B, Caplice N. Plaque neovascularization and antiangiogenic therapy for atherosclerosis[J]. J Am Coll Cardiol, 2007, 49(21): 2073-2080.
[32] Mao Y, Liu X, Song Y, et al. VEGF-A/VEGFR-2 and FGF-2/FGFR-1 but not PDGF-BB/PDGFR-beta play important roles in promoting immature and inflammatory intraplaque angiogenesis[J]. PLoS One, 2018, 13(8): e0201395.
[33] Gonçalves I, Den RH, Nahrendorf M, et al. Detecting the vulnerable plaque in patients[J]. J Intern Med, 2015, 278(5): 520-530.
[34] Parma L, Baganha F, Quax PH, et al. Plaque angiogenesis and intraplaque hemorrhage in atherosclerosis[J]. Eur J Pharmacol, 2017, 816: 107-115.
[35] Bieke Van der Veken, Guido RM, Wim M. Intraplaque neovascularization as a novel therapeutic target in advanced atherosclerosis[J]. Expert Opin Ther Targets, 2016, 20(10): 1247-1257.
[36] Kodama T, Narula N, Agozzino M, et al. Pathology of plaque haemorrhage and neovascularization of coronary artery[J]. J Cardiovasc Med (Hagerstown), 2012, 13(10): 620-627.
[37] Taqueti VR, Di Carli MF, Jerosch-Herold M, et al. Increased microvascularization and vessel permeability associate with active inflammation in human atheromata[J]. Circ Cardiovasc Imaging, 2014, 7(6): 920-929.
[38] Calcagno C, Mulder WJ, Nahrendorf M, et al. Systems biology and noninvasive imaging of atherosclerosis[J]. Arterioscler Thromb Vasc Biol, 2016, 36(2): e1-e8.
[39] Pérez-Medina C, Binderup T, Lobatto ME, et al. In vivo PET imaging of HDL in multiple atherosclerosis models[J]. JACC Cardiovasc Imaging, 2016, 9(8): 950-961.
[40] Akkus Z, Van Burken G, van den Oord SC, et al. Carotid intraplaque neovascularization quantification software (CINQS)[J]. IEEE J Biomed Health Inform, 2015, 19(1): 332-338.

(下转第 368 页)

[J]. Inflamm Res, 2014, 63(10): 885-893.
[22] Hertle E, Arts I, van der Kallen C, et al. Classical pathway of complement activation: longitudinal associations of C1q and C1-INH with cardiovascular outcomes: the CODAM study (cohort on diabetes and atherosclerosis Maastricht)-brief report[J]. Arterioscler Thromb Vasc Biol, 2018, 38(5): 1242-1244.
[23] Ursini F, Abenavoli L. The emerging role of complement C3 as a biomarker of insulin resistance and cardiometabolic diseases: preclinical and clinical evidence[J]. Rev Recent Clin Trials, 2018, 13(1): 61-68.
[24] Nilsson B, Hamad OA, Ahlstrom H, et al. C3 and C4 are strongly related to adipose tissue variables and cardiovascular risk factors[J]. Eur J Clin Invest, 2014, 44(6): 587-596.
[25] Qi X, Qu S, Xiong W, et al. Perivascular adipose tissue (PVAT) in atherosclerosis: a double-edged sword[J]. Cardiovasc Diabetol, 2018, 17(1): 134.
[26] Sereflican B, Bugdayci G. Components of the alternative complement pathway in patients with psoriasis[J]. Acta Dermatovenerol Alp Pannonica Adriat, 2017, 26(2): 37-40.
[27] Hertle E, van Greevenbroek MM, Arts IC, et al. Distinct associations of complement C3a and its precursor C3 with atherosclerosis and cardiovascular disease: the CODAM study[J]. Thromb Haemost, 2014, 111(6): 1102-1111.
[28] Stellos K, Gawaz M. Platelets and stromal cell-derived factor-1 in progenitor cell recruitment[J]. Semin Thromb Hemost, 2007, 33(2): 159-164.
[29] Wezel A, de Vries MR, Lagraauw HM, et al. Complement factor C5a induces atherosclerotic plaque disruptions[J]. J Cell Mol Med, 2014, 18(10): 2020-2030.
[30] Lu X, Xia M, Endresz V, et al. Immunization with a combination of 2 peptides derived from the C5a receptor significantly reduces early atherosclerotic lesion in Ldlr (tm1Her) Apob (tm2Sgy) J mice[J]. Arterioscler Thromb Vasc Biol, 2012, 32(10): 2358-2371.
[31] Vijayan S, Asare Y, Grommes J, et al. High expression of C5L2 correlates with high proinflammatory cytokine expression in advanced human atherosclerotic plaques[J]. Am J Pathol, 2014, 184(7): 2123-2133.
[32] Selle J, Asare Y, Kohncke J, et al. Atheroprotective role of C5ar2 deficiency in apolipoprotein E-deficient mice[J]. Thromb Haemost, 2015, 114(4): 848-858.
[33] Arbore G, West EE, Spolski R, et al. T helper 1 immunity requires complement-driven NLRP3 inflammasome activity in $CD4^+$ T cells[J]. Science, 2016, 352(6292): aad1210.
[34] Gimbrone MJ, Garcia-Cardena G. Endothelial cell dysfunction and the pathobiology of atherosclerosis[J]. Circ Res, 2016, 118(4): 620-636.
[35] Vlaicu SI, Tatomir A, Boodhoo D, et al. RGC-32 is expressed in the human atherosclerotic arterial wall: role in C5b-9-induced cell proliferation and migration[J]. Exp Mol Pathol, 2016, 101(2): 221-230.

(此文编辑 曾学清)

(上接第 362 页)

[41] Van Den Oord SC, Akkus Z, Renaud G, et al. Assessment of carotid atherosclerosis, intraplaque neovascularization, and plaque ulceration using quantitative contrast-enhanced ultrasound in asymptomatic patients with diabetes mellitus[J]. Eur Heart J Cardiovasc Imaging, 2014, 15(11): 1213-1218.
[42] Matter CM, Schuler PK, Alessi P, et al. Molecular imaging of atherosclerotic plaques using a human antibody against the extra-domain B of fibronectin[J]. Circ Res, 2004, 95(12): 1225-1233.
[43] Bourantas CV, Garcia-Garcia HM, Torii R, et al. Vulnerable plaque detection: an unrealistic quest or a feasible objective with a clinical value[J]. Heart, 2016, 102(8): 581-589.
[44] Bourantas CV, Jaffer FA, Gijsen FJ, et al. Hybrid intravascular imaging: recent advances, technical considerations, and current applications in the study of plaque pathophysiology[J]. Eur Heart J, 2017, 38(6): 400-412.
[45] Liu HY, Zhou J, Tong H, et al. Quantitative evaluation of atherosclerotic plaques and intraplaque neovascularization using contrast-enhanced ultrasound after treatment with atorvastatin in rabbits[J]. Biomed Pharmacother, 2017, 92: 277-284.
[46] Kurdi A, Roth L, van der Veken B, et al. Everolimus depletes plaque macrophages, abolishes intraplaque neovascularization and improves survival in mice with advanced atherosclerosis[J]. Vascul Pharmacol, 2019, 113: 70-76.

(此文编辑 秦旭平)