脑动静脉畸形发病机制相关信号通路研究进展

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摘 要：脑动静脉畸形（brain arteriovenous malformations，bAVM）是神经外科常见的血管性疾病，其组织病理学表现为动静脉之间缺乏常见的毛细血管，血液从动脉直接分流到静脉，由动脉化静脉和静脉化动脉组成的异常血管团。破裂出血是bAVM最为常见的临床表现，严重者影响神经功能甚至危及生命。尽管大多数bAVM病例是散发性的，没有家族史，但有些病例是有家族性的。大多数家族性bAVM病例与一种称为遗传性毛细血管扩张症（hereditary hemorrhagic telangiectasia，HHT）的疾病有关。本文综述了近年来bAVM研究的最新进展，并对bAVM发病机制中的一些重要信号通路途径进行了总结。

关键词：脑动静脉畸形；发病机制；信号通路

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RESEARCH PROGRESS OF SIGNAL PATHWAY RELATED TO PATHOGENESIS OF CEREBRAL ARTERIOVENOUS MALFORMATION

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Abstract: Brain arteriovenous malformations (bAVM) is a common vascular disease in neurosurgery. Its histopathological manifestations are the lack of common capillaries between the arteriovenous, and the blood flows directly from the artery to the vein, which is an abnormal vascular mass composed of arterialized vein and venous artery. Rupture and hemorrhage is the most common clinical manifestation of BAVM, which seriously affects the nerve function and even endangers life. Although most of the cases are sporadic and have no family history, some cases are familial. Most cases of familial balavm are associated with a disease called hereditary telangiectasia (HHT). This paper reviews the latest progress in the study of BAVM in recent years, and summarizes some important signaling pathways in the pathogenesis of BAVM.

Key words: cerebral arteriovenous malformation; pathogenesis; signal pathway

脑动静脉畸形是一种异常血管团，容易破裂，导致危及生命的颅内出血（ICH）[1]。正常人中bAVM患病率大约为0.05%[2]。bAVM患者可能无症状或出现癫痫发作、局灶性神经功能缺损或脑出血，这些并发症的出现也是治疗的主要原因。总体而言，bAVM占50岁以下成人出血性中风的25%[3]，高达40%的bAVM患者在脑出血后一年内死亡或功能受损[4]。尽管不同医院的死亡率不同，但现有的每种治疗方式都有与手术相关的并发症，且发生率不低[5-7]。近年来随着影像学技术的进步，越来越多的无症状bAVM患者被诊断出来。而无症状患者的治疗越来越有争议，因为一项关于未破裂bAVM（ARUBA）的随机试验结果表明，随机接受保守治疗的未破裂bAVM患者的中风和死亡率低于接受任何介入治疗的患者[5,6,8~11]。揭示bAVM的发病机制对于寻找特异性治疗方法，以减少对侵入性手术的

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需求至关重要。

尽管bAVM的发病机制与许多途径和修饰基因有关，但本综述中主要介绍了RAS-MAPK-ERK、TGFβ、血小板源性生长因子b(Pdgfb)途径和非编码RNA在bAVM研究中的最新发现。

1 RAS-MAPK-ERK信号转导通路

95%以上的bAVM是无明确家族史的散发病例。散发性bAVM的致病基因尚不清楚。最近的研究通过对从患者AVM病变中分离的DNA进行下一代测序[12,13]，确定了散发性bAVM和外周AVM中RAS-MAPK途径基因的体细胞突变。RAS通路包括不同的信号级联，如RAF-MEK-MAPK/ERK。这条通路调节一些关键的细胞功能，包括增值、生长、存活和衰老[14]。有研究者[15]在72例患者中的45例bAVM病变中发现了体细胞激活KRAS突变，而在21例配对血样中没有发现。突变包括KRAS p.Gly12Val和KRAS p.Gly12Asp突变。进一步研究下游信号通路，发现在人bAVM的内皮细胞培养中，MAPK-ERK和PI3K-AKT通路被KRAS激活突变激活。与正常脑血管内皮细胞相比，bAVM内皮细胞ERK1/2磷酸化水平升高。他们发现突变增加了与血管生成和Notch信号相关的基因的表达。将KRAS p.Gly12Val导入培养的内皮细胞，能增强其迁移行为。有趣的是，抑制了MAPK-ERK通路则逆转了内皮细胞中的VEGF基因信号[12]。随后的研究表明，在bAVM和脊髓AVM中KARS/BRAF突变的患病率分别为81%和100%[16]。这些均表明KRAS的体细胞突变可能参与了bAVM的发病机制。

2 TGFβ信号转导通路

大约5%的bAVM与一种遗传性疾病HHT有关，HHT是一种常染色体显性遗传性血管疾病，全世界约有1/5000的人受到影响[17~19]。HHT的主要临床特征是AVM在多个器官(包括大脑)出血[20]。三个基因已经被鉴定出导致HHT：ENG[21]、ALK或ACVRL1[22]和SMAD4[23]。HHT根据致病基因突变分为HHT1、HHT2和JP(青少年息肉病)-HHT。HHT1(ENG突变)和HHT2(ALK1突变)占所有HHT病例的90%以上[24]。虽然HHT1和HHT2之间的临床表现无法区分，但基因型-表型相关研究表明，HHT1在脑和肺中的AVM患病率较高，而HHT2在肝脏和胃肠道的AVM患病率较高[18,25]。10.4%的HHT患者存在脑动静脉畸形。HHT1患者的bAVM患病率(13.4%)明显高于HHT2患者(2.4%)。大多数与HHT相关的bAVM较小(小于3cm)，Spetzler-Martin等级为2或更低，而在散发bAVM人群中，bAVM病灶的平均大小约为3cm，Spetzler-Martin评分中位数为3。虽然约20%的这些HHT相关bAVM伴有破裂，但近50%的bAVM无症状。

所有与HHT相关的基因都是TGF-β家族成员信号转导的组成部分。因此，HHT被认为是由TGF-β家族成员的信号转导缺陷引起的疾病。然而，关于与AVM发育相关的ENG-ALK1信号的配体、Ⅱ型受体和下游效应基因的特性大多不清楚。

3 Pdgfb/pdgf受体β(pdgfrβ)信号通路

血管壁的结构缺陷和不成熟提示bAVM血管发育不良。在小鼠模型的bAVM血管中也发现了异常的血管壁结构。与正常脑血管生成灶相比，bAVM小鼠模型病变血管直径大于15μm，缺乏平滑肌。

血管由内皮细胞和壁细胞组成，包括血管平滑肌细胞和周细胞。周细胞包裹毛细血管和小静脉的内皮细胞。它们对血管的稳定性起着至关重要的作用。血管周细胞减少会损害血管完整性。最近的研究表明，与正常脑血管相比，人和小鼠的bAVM血管壁细胞覆盖率都减低，这表明bAVM血管重构异常。血管平滑肌细胞和周细胞覆盖率降低与血管通透性增加和bAVM出血有关。

PDGF-B和PDGFR-β在血管生成过程中参与周细胞和血管平滑肌细胞的募集。敲除小鼠Pdgfb或pdgfrβ，导致微血管周细胞的丢失。周细胞的缺失也导致内皮增生和内皮管腔膜过度折叠。在啮齿类动物模型和患者的bAVM中，PDGF-B和PDGFR-β的异常表达已被描述。pdgfβ在Alk1缺陷小鼠bAVM病变中表达降低，这与平滑肌细胞和周细胞覆盖率的降低有关，这表明Alk1和PDGF-B和PDGFR-β信号通路之间可能存在联系。然而，目前尚不清楚bAVM中PDGFR-β表达的降低是周细胞减少的原因还是结果。有趣的是，有Alk1缺陷型bAVM中PDGF-β的过度表达增加了bAVM血管上的周细胞覆盖率并减少了bAVM出血。提示PDGF-B和PDGFR-β信号通路在bAVM血管完整性中起重要作用。

4 非编码RNA

近年来的研究表明，非编码RNA也可能在bAVM的发病机制中发挥作用。Li等人发现4个长的非编码RNA在AVM病灶中异常表达。可能与bAVM患者的癫痫发作有关。通过对bAVM患者血液中小RNA的深度测序，Chen等发现了新的调控失调的miRNA，其中一个靶向VEGF通路。已经观察到miRNA-137和miRNA-196*抑制培养的AVM平滑肌细胞的异常生物学特性。此外，最近的一项研究表明，Drosha的失活突变导致了与小鼠HHT相似的血管异常。Drosha变异体（P100L和R279L）已在缺乏已知致病性突变的HHT患者中检测到。这些表明microRNA处理可能在AVM的发病机制中起作用。

脑动静脉畸形是一种非静止性先天性疾病。目前还没有针对bAVM的药物治疗。贝伐单抗、丝裂原活化蛋白激酶（MEK）抑制剂、雷帕霉素和沙利度胺等都曾用于非中枢神经系统AVM患者，其疗效不同。bAVM的治疗理念应该是稳定血管组织，从而降低自发性脑出血的风险。因此，除了确定参与AVM发生的途径外，了解AVM血管重构、维持血管完整性和破裂的机制和因素，对于制定稳定AVM血管壁和防止AVM破裂的策略至关重要。

参考文献

[1]Kim H., Su H., Weinsheimer S., et al. Brain arteriovenous malformation pathogenesis: A response-to-injury paradigm. Acta Neurochir. Suppl. 2011;111:83-92

[2]Shaligram SS, Winkler E, Cooke D, et al. Risk factors for hemorrhage of brain arteriovenous malformation. CNS Neurosci Ther. 2019;**25**(10):1085-1095

[3]Shtaya A, Millar J, Sparrow O. Multimodality management and outcomes of brain arterio-venous malformations (AVMs) in children: personal experience and review of the literature, with specific emphasis on age at first AVM bleed. Childs Nerv Syst. 2017 ;**33**(4):573-581

[4]Goldberg J, Raabe A, Bervini D. Natural history of brain arteriovenous malformations: systematic review. J Neurosurg Sci. 2018;**62**(4):437-443

[5]Feghali J, Huang J. Updates in arteriovenous malformation management: the post-ARUBA era. Stroke Vasc Neurol. 2019;**215**(1):34-39

[6]Mohr J.P., Parides M.K., Stapf C., et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): A multicentre, non-blinded, randomised trial. Lancet. 2014;383:614-621

[7]Reynolds AS, Chen ML, Merkler AE, et al. Effect of A Randomized trial of Unruptured Brain Arteriovenous Malformation on Interventional Treatment Rates for Unruptured Arteriovenous Malformations. Cerebrovasc Dis. 2019;**47**(5-6):299-302

[8]Matsumaru Y, Ishikawa E, Yamamoto T, et al. Recent Trends in Neuro-endovascular Treatment for Acute Ischemic Stroke, Cerebral Aneurysms, Carotid Stenosis, and Brain Arteriovenous Malformations. Neurol Med Chir (Tokyo). 2017; **57** (6): 253-260

[9]Iyer A, D'souza M, Steinberg GK. Embolization before stereotactic radiosurgery for the treatment of brain arteriovenous malformations. J Neurosurg Sci. 2018;**62**(4):514-518

[10]Ryu B, Ishikawa T, Kawamata T. Multimodal Treatment Strategy for Spetzler-Martin Grade III Arteriovenous Malformations of the Brain. Neurol Med Chir (Tokyo). 2017;**57**(2):73-81

[11]Derdeyn C.P., Zipfel G.J., Albuquerque F.C., et al.On behalf of the American Heart Association Stroke Council Management of Brain Arteriovenous Malformations: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2017;48:e200-e224

[12]Nikolaev S.I., Vetiska S., Bonilla X., et al. Somatic Activating KRAS Mutations in Arteriovenous Malformations of the Brain. N. Engl. J. Med. 2018;378:250-261

[13]Couto J.A., Huang A.Y., Konczyk D.J., et al. Somatic MAP2K1 Mutations Are Associated with Extracranial Arteriovenous Malformation. Am. J. Hum. Genet. 2017;100:546-554

[14]McCubrey J.A., Steelman L.S., Chappell W.H., et al. Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. Biochim. Biophys. Acta. 2007;1773:1263-1284

[15]Barbosa Do Prado L, Han C, Oh SP, et al. Recent Advances in Basic Research for Brain Arteriovenous Malformation. Int J Mol Sci. 2019;**20**(21):5324

[16]Hong T., Yan Y., Li J., et al. High prevalence of KRAS/BRAF somatic mutations in brain and spinal cord arteriovenous malformations. Brain. 2019;142:23-34

[17] Jackson SB, Villano NP, Benhammou JN, et al. Gastrointestinal Manifestations of Hereditary Hemorrhagic Telangiectasia (HHT): A Systematic Review of the Literature. Dig Dis Sci. 2017;**62**(10):2623-2630

[18]Shovlin CL, Patel T, Jackson JE. Embolisation of PAVMs reported to improve nosebleeds by a subgroup of patients with hereditary haemorrhagic telangiectasia. ERJ Open Res. 2016;**2**(2):0035-2016

[19]Sabba C., Pasculli G., Lenato G.M.,et al. Hereditary hemorragic telangiectasia: Clinical features in ENG and ALK1 mutation carriers. J. Thromb. Haemost. 2007;5:1149-1157

[20]de Gussem EM, Edwards CP, Hosman AE, et al. Life expectancy of parents with Hereditary Haemorrhagic Telangiectasia. Orphanet J Rare Dis. 2016;11:46

[21]McAllister K.A., Grogg K.M., Johnson D.W, et al. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. Nat. Genet. 1994; 8:345-351
[22]Johnson D., Berg J., Baldwin M., et al. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. Nat. Genet. 1996;13:189-195
[23]Gallione C.J., Repetto G.M., Legius E., et al. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4) Lancet. 2004;363:852-859
[24]McDonald J., Wooderchak-Donahue W., Webb C.V., et al. Hereditary hemorrhagic telangiectasia: Genetics and molecular diagnostics in a new era. Front. Genet. 2015;6:1
[25]Tual- Chalot S., Oh S.P., Arthur H.M. Mouse models of hereditary hemorrhagic telangiectasia: Recent advances and future challenges. Front. Genet. 2015;6:25

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[18]朱军伟,李印.肺部分切除术后胸腔引流管拔除时机的现状及进展[J].中国微创外科杂志,2015;**15**(04):373-375
[19]Fu R, Zhang JT, Dong S, et al.Drainage tube hole suture improvement: removal-free stitches. Thorac Cancer, 2019;**10**(9):1827-1833
[20]Cooke DT, David EA.Large-bore and small-bore chest tubes: types, function, and placement. Thorac Surg Clin, 2013;**23**(1): 17-24
[21]Yokoyama Y, Nakagomi T, Shikata D, et al. A novel technique forchest drain removal using a two layer method with triclosan-coated sutures. J Thorac Dis, 2017;**9**(1):211-213
[22]张晔,李辉,胡滨,等.肺叶切除术后早期拔除胸腔引流管的前瞻性随机对照研究[J].中华外科杂志,2013;(06): 533-537
[23]褚翔鹏,贺猛,薛原,等.单孔胸腔镜术后留置超细引流管在普胸手术中的应用[J].中国社区医师,2017;**33**(23):28+30
[24] Brown SG, Ball EL, Macdonald SP, et al. Spontaneous pneu mothorax; A multicentre retrospective analysis of emergency treatment, complications and outcomes[J]. Intern Med J, 2014; **44**(5):450-457
[25]杨于钢,张汝,卢佳.胸腔闭式引流术后常见并发症原因及治疗方法.临床医学,2016;**29**(32):256

(上接第213页)

[15]Nitin, Arora, Yoel, et al. Microbial Vertical Transmission during Human Pregnancy[J]. cell host & microbe, 2017; 21 (5):561
[16]Gilden D, Nagel M A, Cohrs R J. Varicella-zoster[J]. Handb Clin Neurol.2020:265-283
[17]Peter G E, Kennedy, Anne A, et al. Clinical Features of Varicella-Zoster Virus Infection[J]. Viruses, 2018; **41**(04): 251-253
[18]Nagel M A, Gilden D. Update on Varicella Zoster Virus Vasculopathy[J]. Curr Infect Dis Rep, 2014;**16**(6):1-8
[19]Smith, F P. Pathological studies of spinal nerve ganglia in relation to intractable intercostal pain[J]. Surg Neurol, 1978; **10**(1):50-53
[20]Watson C P N, Watt V R, Chipman M, et al. The prognosis with postherpetic neuralgia[J]. Pain, 1991;**46**(2):195-199
[21]Shinjoh M, Takahashi T. Varicella zoster exposure on paediatric wards between 2000 and 2007: safe and effective post-exposure prophylaxis with oral aciclovir[J]. J Hosp Infect, 2009;**72**(2):163-168
[22]Hope-Simpson R E . The Nature of Herpes Zoster.[J]. Practi tioner, 1964;193:217-219
[23] Dooling K L, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines[J]. Am J Transplant, 2018; **18**(3): 756-762
[24] Cunningham AL, Lal H, Kovac M, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older[J]. N Engl J Med. 2016;**375**(11):1019-1032
[25] Dendouga N, Fochesato M, Lockman L, et al. Cell-mediated immune responses to a varicella- zoster virus glycoprotein E vaccine using both a TLR agonist and QS21 in mice[J]. Vaccine, 2012;**30**(20):3126-3135