·国家“十二五”时期神经科学成果·

缺血性卒中基础与临床研究进展

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【摘要】 脑卒中是临床最常见的脑血管病，严重影响患者生活质量，给家庭和社会带来沉重负担。临床治疗方面，除重组组织型纤溶酶原激活物静脉溶栓外，血管内机械取栓的出现是近年缺血性卒中治疗的重大突破。许多新药业已进入临床试验阶段，为缺血性卒中的治疗带来新的希望。本文拟就我国国民经济和社会发展第十二个五年规划（简称“十二五”）时期取得的缺血性卒中基础与临床研究进展进行概述，包括组学技术、基因治疗、微小RNA治疗研究和干细胞治疗，特别是干细胞治疗已进入临床试验阶段并展现出良好发展前景。基础研究向临床积极转化为脑血管病的精准治疗提供有价值的信息。

【关键词】 卒中； 脑缺血； 中国； 综述

Basic and clinical research advances in ischemic stroke

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【Abstract】 Stroke is the most common cerebrovascular disease worldwide, which seriously affects life quality of survivals and results in huge economic burden of families and society. In terms of clinical treatment for ischemic stroke, apart from thrombolytic therapy with recombinant tissue-type plasminogen activator (rt-PA), the occurrence and successful application of endovascular thrombectomy in patients of ischemic stroke is a major breakthrough. Meanwhile, many novel clinical drugs for ischemic stroke therapy have entered into clinical trials. Most of basic and clinical researches have showed promising results in ischemic stroke therapy. This review mainly summarizes the progress of research during the period of Twelfth Five-Year Plan for National Economic and Social Development on treatment of ischemic stroke, including omics technologies, gene therapy, microRNA (miRNA) interference and stem cell therapy. Stem cell therapy has shown great potential since many clinical trials have been completed or are ongoing. The development and mutual transformation of basic and clinical research will provide valuable and comprehensive information for the precise treatment of ischemic stroke.

【Key words】 Stroke; Brain ischemia; China; Review

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脑卒中系各种原因引起的脑血管病变致局灶性神经功能缺损或中枢神经系统损伤[1]。脑卒中是目前导致全球人类死亡的第2位疾病，是导致成人永久性病残的首要病因[2-3]。美国每40秒即有1例罹患脑卒中[4]。2013年，全球有103×10^6例发生脑卒中，65×10^6例死于脑卒中，达11.30×10^6/残疾调整生命年（DALY）[5]。由于不发达国家脑卒中危险因素增加，其造成的经济负担仍有增加趋势。预计截至2030年，脑卒中病死例数将达120×10^6例，达0.20×10^9/残疾调整生命年[6]。我国是脑卒中负担最重的国家之一，过去30年间脑卒中负担增加，特

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别是农村地区[7-8]，2013年我国脑卒中患病率、发病率和病死率分别为1114.80/10万、246.80/10万和114.80/10万[9]。

脑卒中包括缺血性卒中（约占87%[10]）和出血性卒中。既往数十年，脑卒中的临床治疗取得新的进展，特别是血管内机械取栓的出现，开启缺血性卒中治疗的新篇章。对于梗死灶小且有良好侧支循环的患者，血管内机械取栓可以显著改善临床症状[11-12]。随机对照临床试验显示，缺血性卒中8小时内予血管内机械取栓治疗可以有效改善临床症状[13]。英国国家卫生与临床优化研究所（NICE）制定指南，只要条件允许，静脉溶栓和血管内机械取栓是缺血性卒中治疗的“金标准”[1]。目前，缺血性卒中的治疗策略主要分为三步：建立卒中单元；对符合条件的患者进行静脉溶栓；血管内机械取栓重新开通堵塞的血管[14-18]。但是由于严格的治疗时间窗（脑卒中后4.50小时内）或存在严重的并发症风险，仅不足5%的患者予以重组组织型纤溶酶原激活物（rt-PA）静脉溶栓，部分行rt-PA静脉溶栓治疗的患者可同时行血管内机械取栓治疗，大多数缺血性卒中患者仅行对症支持治疗[19]。有研究显示，行rt-PA静脉溶栓的患者中仅10%临床预后较好，行血管内机械取栓的患者中71%实现血管再通、仅50%实现缺血-再灌注[20-22]。因此，积极寻找改善缺血性卒中预后的方法即显得尤为重要。尽管缺血性卒中病理生理学机制复杂，临床治疗进展缓慢，尚待大量动物实验和临床前试验以加快临床转化进程，但是目前已有众多临床前或临床治疗策略显示出较好的治疗潜能。本文拟就我国国民经济和社会发展第十二个五年规划（以下简称“十二五”）时期取得的缺血性卒中基础与临床研究进展进行概述。

一、组学技术进展

无论是静脉溶栓，还是快速有效促进组织修复或减少损伤均需要有特定方向，多组学技术的出现为缺血性卒中提供新的特异性治疗靶点。多组学技术包括基因组学、二代基因测序、转录组学、蛋白质组学和代谢组学。通过上述组学技术，不仅可以发现脑卒中损伤或修复相关病理生理学机制，同时还可以为临床药物试验提供快速评价药物毒性和治疗效果的分子学标志物。全基因组相关性研究（GWAS）业已发现众多与脑卒中发生与发展相关的重要遗传学标志物，如定位于12q24的*ALDH2*基因与所有类型缺血性卒中密切相关，而某些基因如*HDAC9*基因和定位于1p13.2的*TSPAN2*基因与大动脉粥样硬化型（LAA型）密切相关，*PITX2*和*ZFHX3*基因与心源性栓塞型（CE型）密切相关[23]，某种单核苷酸多态性（SNP）与冠心病密切相关[24]。最近研究显示，髓过氧化物酶（*MPO*）基因表达上调与腔隙性梗死密切相关，由于该基因不受环境因素的影响，提示*MPO*基因是脑血管病的致病基因[25]。基因组学的进展为早期采取有效措施干预脑卒中高危人群生活方式和针对性治疗提供可能。

蛋白质组学和代谢组学的快速发展有利于脑卒中的诊断、治疗和预后评价。蛋白质组学技术发现，rt-PA静脉溶栓可以引起脑卒中患者血浆蛋白酶如基质金属蛋白酶（MMPs）表达变化，提示rt-PA可能通过改变相关蛋白质表达水平或调节蛋白酶活性发挥治疗作用或引起颅内出血等并发症[26]。蛋白质组学技术有助于发现脑卒中后血-脑屏障（BBB）破坏相关关键靶分子，从而拓宽rt-PA静脉溶栓的治疗范围。蛋白质组学技术显示，血清淀粉样蛋白A（SAA）水平升高与脑卒中后感染密切相关，提示可以通过检测血清淀粉样蛋白A表达变化以预测并预防脑卒中后感染的发生[27]。临床前实验方面，通过蛋白质组学技术发现，与缺血性卒中组和缺血预处理组小鼠相比，缺血性卒中耐受组小鼠脑组织转录抑制蛋白特别是多梳家族（PcG）水平升高，介导脑卒中后神经保护的表观遗传学机制[28]。亦有研究显示，缺血性卒中患者移植骨髓间充质干细胞（BMSCs）后，一些蛋白质如Abca1、Grb2、Ptgds等水平升高，提示其可能是骨髓间充质干细胞发挥治疗作用的关键[29]。因此，蛋白质组学技术可以提供更多有价值的信息，有助于研究人员更好地探讨缺血性卒中的病理生理学机制，为临床治疗缺血性卒中提供新的靶点。代谢组学通过检测体液中小分子代谢物，一方面可以增加影像学检查的敏感性，另一方面可以有助于预测短暂性脑缺血发作（TIA）患者发生脑卒中的可能[30-31]。有学者采集脑卒中患者体液包括血浆、尿液和粪便进行代谢组学分析，发现血浆和尿液同型半胱氨酸（Hcy）、叶酸、支链氨基酸和脂质代谢物水平可以预测脑卒中复发风险[32]。此外，血浆支链氨基酸和脂质代谢物水平降低与脑卒中后抑郁（PSD）和脑卒中后认知功能障碍（PSCI）相关[33]。根据脑卒中特殊病理生理学变化，联合代谢组学技术可以将脑卒中分为不同亚组，以进行更加精准的治疗[34]。更重要的是，代谢

组学技术不仅可以弥补蛋白质组学不能快速诊断的缺陷，而且可以将蛋白质组学和基因组学信息相联系。有学者采用代谢组学技术研究白藜芦醇治疗缺血性卒中的作用机制，发现神经元沉默信息调节因子1（*SIRT1*）基因可以调节葡萄糖代谢和糖酵解过程，影响实验动物对缺血性卒中的耐受程度，提示代谢组学可以作为研究缺血性卒中发病机制和药物作用机制的新方法[35]。未来有望通过上述组学技术、多学科合作，更好地研究脑卒中发病机制和损伤机制[1]。

二、基因治疗进展

脑卒中后数小时至数周，脑组织损伤仍在继续，为基因治疗提供可能。目前，基因治疗的主要措施是通过外源性导入具有抗凋亡、增加细胞存活、靶向引导干细胞、促进血管再生和神经再生等作用的基因，最大程度地促进组织恢复、减轻脑组织损伤[36]。抗凋亡基因主要是B细胞淋巴瘤/白血病-2（Bcl-2）家族成员，包括Bcl-2、Bcl-xL和Bcl-2l2或Bcl-w，可以调节细胞凋亡、促进神经再生[37]。基础研究显示，多种病毒载体，如单纯疱疹病毒（HSV）[38]、腺病毒[39]、腺相关病毒（AAV）[40]和慢病毒[41]等均可介导缺血性卒中后Bcl-2过表达，且发挥良好治疗作用。通过单纯疱疹病毒载体在脑组织中过表达Bcl-2，可以减少梗死灶体积、减轻神经胶质细胞增生，可能是通过抑制骨形态发生蛋白4（BMP-4）表达上调以促进脑缺血后纹状体区神经再生[42]。过表达Bcl-2可以抑制脑卒中后脑组织凋亡诱导因子（AIF）的核转位，增加神经元存活[43]。亦有研究显示，缺血性卒中患者脑组织过表达热休克蛋白（HSP）家族成员HSP72和谷胱甘肽过氧化物酶（GSH-Px），通过上调Bcl-2表达以发挥减少脑缺血后神经元损伤、促进长期功能恢复的作用[44-45]。

神经营养因子具有调节神经细胞生长、发育、增殖、分化，并在生理和病理环境下促进神经细胞存活，维持神经细胞稳态的作用。目前，多项研究采用不同病毒载体在脑组织过表达神经营养因子相关基因，如血管内皮生长因子（*VEGF*）[46]、脑源性神经营养因子（*BDNF*）[47]、胶质细胞源性神经营养因子（*GDNF*）[48-50]、睫状神经营养因子（*CNTF*）[48]、脑多巴胺源性神经营养因子（*CDNF*）[51]和类肝素结合样表皮生长因子（*HB-EGF*）[52]，可以不同程度减小梗死灶体积和抑制凋亡通路激活，从而减轻脑组织损伤。除直接过表达神经营养因子相关基因以发挥神经保护作用外，亦可以过表达增加内源性干细胞活性的基因和促内源性修复的基因，如趋化因子*CXCL12*，又称基质细胞衍生因子-1（*SDF-1*），于缺血性卒中后表达上调[53]。研究显示，缺血性卒中前3天预过表达或脑卒中后1周过表达CXCL12，可以减轻脑萎缩，促进血管新生和神经再生，促进少突前体细胞迁移、分化、髓鞘再生，从而加速脑组织修复[54-56]。另一种神经生长因子——轴突导向因子-1（netrin-1）在生理状态下可以促进神经轴突生长、发育和成熟，发生缺血性卒中时表达上调。研究显示，缺血性卒中小鼠脑组织过表达轴突导向因子-1，可以促进脑缺血后少突胶质前体细胞增殖和成熟，减轻白质损害，改善脑卒中后运动功能、肢体协调能力和探索能力[57-58]。在既往研究中，过表达基因的时间点从预处理至脑卒中后即刻、数小时、1周，治疗时间窗广泛，为不同类型脑卒中的治疗提供理论基础。

三、微小RNA治疗进展

微小RNA（miRNA）是小序列非编码RNA，转录后可以调节多种蛋白质表达。1993年，Lee等[59]首先在秀丽线虫体内发现miRNA。迄今已在200余种物种中发现30×10^3余种miRNA[60]。过去10年间，关于miRNA结构、功能、生物学特性和病理生理学作用机制的研究发展迅速[61]。在病理条件下，血浆和体液miRNA含量迅速变化，通过调节下游靶蛋白表达加速或延缓疾病进程[62]。多种miRNA均与缺血性卒中高危因素如高血压、糖尿病和动脉粥样硬化等相关（表1），研究显示，与正常对照者相比，高血压患者血清miRNA-7-5p和miRNA-26b-5p水平升高[63]，推测miRNA可能与高血压的发生与发展相关；过表达miRNA-21可以通过抑制Bcl-2表达而诱导胰腺β细胞凋亡[64]，提示miRNA-21高表达可能加速糖尿病的发生；人动脉粥样硬化血管组织中，miRNA-206水平降低[65]；体外实验结果显示，过表达miRNA-206可以抑制血管平滑肌增殖，诱导其凋亡[66]，提示miRNA-206可能是动脉粥硬化的治疗靶点。缺血性卒中急性期，miRNA表达变化与脑卒中病理生理学机制如兴奋性毒性、炎症反应、氧化应激、细胞凋亡、血-脑屏障破坏等相关（表1），例如，缺血性卒中急性期血浆miRNA-181c水平降低，与血小板计数呈正相关[67]；缺血性卒中模型小鼠急性期脑组织过表达miRNA-181c，可以增加神经元和小胶质细胞凋亡及梗死灶体积[67]；缺血性卒中恢复

表1 脑卒中相关miRNA

Table 1. miRNAs associated with ischemic stroke

Stroke	miRNA
Risk factor	
Hypertension	miRNA-7-5p, miRNA-26b-5p, miRNA-155, miRNA-204, miRNA-487b, miRNA-103a-2-5p, miRNA-585-5p, miRNA-125a/b-5p, miRNA-22, miRNA-122
Diabetes	miRNA-21, miRNA-146a, miRNA-499a, miRNA-466a/d-3p, miRNA-204, miRNA-146a, miRNA-144, Let-7p, miRNA-30c
Arteriosclerosis	miRNA-206, miRNA-320a, miRNA-30c-5p, miRNA-19a, miRNA-143/145, miRNA-92a, miRNA-181a, miRNA-362-3p, miRNA-33, miRNA-155, miRNA-214-3p, miRNA-221, miRNA-222
Acute phase	
Excitotoxicity	miRNA-233, miRNA-503, miRNA-107, miRNA-181a, miRNA-124, miRNA-125b, miRNA-29a
Inflammatory response	Let-7a, miRNA-15a/16-1, miRNA-181c, miRNA-22, miRNA-210, miRNA-203, miRNA-124, miRNA-9, miRNA-375, miRNA-424, miRNA-132, miRNA-491-5p, miRNA-106a, miRNA-7c-5p
Oxidative stress	miRNA-424, miRNA-93, miRNA-204, miRNA-23a-3p, miRNA-99a, miRNA-210, miRNA-106b-5p, miRNA-145, miRNA-101, miRNA-146a
Cell apoptosis	Let-7a, miRNA-124, miRNA-21, miRNA-25, miRNA-200c, miRNA-134, miRNA-106b-5p, miRNA-181c, miRNA-15, miRNA-494, miRNA-497, miRNA-181a, miRNA-29b, miRNA-99a, miRNA-204
BBB disruption	miRNA-130b, miRNA-29b, miRNA-210, miRNA-124, miRNA-143, miRNA-9, miRNA-375, miRNA-424, miRNA-154, miRNA-15a, miRNA-21, miRNA-130a, miRNA-320, miRNA-145, miRNA-150, miRNA-155
Recovery phase	
Neurogenesis	miRNA-9, miRNA-107, miRNA-134, miRNA-17-92, miRNA-210, miRNA-148b, miRNA-124, miRNA-124a, miRNA-376b-5p, miRNA-155
Angiogenesis	miRNA-17-92, miRNA-377, miRNA-150, miRNA-9, miRNA-210, miRNA-124, miRNA-493, miRNA-107, miRNA-376b-5p, miRNA-296, miRNA-140-5p

miRNA, microRNA, 微小RNA; BBB, blood-brain barrier, 血-脑屏障

期，miRNA通过调节神经再生和血管再生促进脑组织修复[61]（表1）。鉴于miRNA在缺血性卒中病理生理学机制中的重要作用，多项研究采用miRNA治疗缺血性卒中，侧脑室过表达miRNA-148b可通过调节Wnt/β-连环蛋白（β-catenin）信号转导通路，促进缺血性卒中后神经干细胞（NSCs）分化为成熟神经元和星形胶质细胞，从而促进神经功能恢复[68]；脑组织过表达miRNA-1906可通过下调Toll样受体4（TLR-4）水平以发挥减小梗死灶体积、促进功能恢复的作用[69]；过表达miRNA-29b可减轻血-脑屏障破坏、减小梗死灶体积，可能与抑制水通道蛋白4（AQP4）表达有关[70]。由于miRNA在体液中稳定存在且具有组织特异性，有多项研究检测血浆miRNA表达变化，旨在探讨可以有效预测缺血性卒中和评价预后的新型miRNA，以填补临床尚无针对缺血性卒中血浆分子生物学标志物的空白。最新研究显示，脑卒中后抑郁患者血浆miRNA-92a-3p水平升高，与抑郁程度和前脑白质高信号相关[71]，提示miRNA-92a-3p可能介导脑卒中后抑郁。另一项研究对缺血性卒中患者和正常对照者进行miRNA组学分析，证实缺血性卒中后血浆miRNA-125a-5p、miRNA-125b-5p和miRNA-143-3p水平升高，提示这3种miRNA有望成为缺血性卒中早期诊断的分子标志物。尽管关于miRNA作为缺血性卒中分子标志物的研究较多，但目前临床进展仍较缓慢，主要是由于既往miRNA检测存在异质性，且后续验证缺乏科学严谨的实验设计[72]，尚待更多研究加速miRNA作为缺血性卒中分子标志物的临床转化过程[73]。

四、干细胞治疗进展

目前，除rt-PA静脉溶栓和血管内机械取栓外，干细胞治疗是最有可能从根本上促进缺血性卒中治疗进展的方法[14]。干细胞治疗包括胚胎干细胞（ESCs）[74-75]、诱导型多能干细胞（iPSCs）[76]、神经干细胞[77-79]、骨髓间充质干细胞[80-83]、造血干细胞（HSCs）[84]、内皮祖细胞（EPCs）[85-86]、脂肪间充质干细胞（ADSCs）[87]，可以改善缺血性卒中预后（表2）。具体作用机制尚待进一步研究，但目前实验研究结果显示，干细胞通过抑制炎症反应、调节免疫应答、分化为成熟神经元或内皮细胞、促进神经突触重塑、促进神经再生和血管再生、分泌神经营养因子等多种途径发挥治疗作用[88-91]。干细胞治疗缺血性卒中的基础研究成果显著，过去15年间有多项干细胞治疗缺血性卒中的早期临床试验，其中一项多中心随机双盲Ⅱ期临床试验显示，缺血性卒中急性期（24～48小时）静脉移植异体多能干细胞（MultiStem®，美国Athersys公司）安全，能够改善脑卒中后1年的神经功能[91]。干细胞治疗的最常见不良反应是头痛和发热，但多呈自限性，主要与移植途径有关，头痛主要出现在接受立体定位注射移植的患者[82,92-93]。最新的研究采用新的移植方式——经鼻内途径移植。研究显示，经鼻内途径移植骨髓间充质干细胞治疗缺血性卒中可以促进神经血管再生，改善神经功能[94-95]。与其他移植方式如动脉注射移植、静脉注射移植和立体定位注射移植相比，经鼻内途径移植的优势在于简单、无创且移植细胞可以快速通过鼻黏膜进入脑实质。因此，经鼻内途径移植有可能成为临床干细胞移植途径的新选择[91,96]。多项研究证实，干细胞治疗缺血性卒中

表2 干细胞治疗缺血性卒中临床试验

Table 2. Clinical trials of stem cell therapy for ischemic stroke

Registration number	Phase	Type of stem cells	Route	Observation	Primary end point	Secondary end point	Result
NCT01436487	Ⅱ	Stem cells	Vein injection	1.50 years	Safety and function	Function	Safe, no improvement of function
NCT01151124	Ⅰ	NSCs (CTX0E03)	Transcranial injection	2 years	Safety	Function	—
NCT02117635	Ⅱ	NSCs	Transcranial injection	1 year	Function	Safety	—
NCT01327768	Ⅰ	NSCs (CTX0E03)	Transcranial injection	2 years	Safety	—	—
*	Ⅰ/Ⅱa	BMSCs	Vein injection	1–6 months	Safety	—	Safe, no improvement of function
NCT00859014	Ⅰ/Ⅱa	Autogenous BMSCs	Vein injection	1–3 d	Safety and feasibility	Function	—
NCT02178657	Ⅱ	BMSCs	Artery injection	0.50 year	mRS	NIHSS and BI	Safe, no improvement of function
NCT01518231	Ⅱ	BMSCs	Artery injection	2 years	Function	Function	—
NCT01501773	Ⅱ	BMSCs	Vein injection	3–12 months	BI	Function	—
NCT00875654	Ⅰ/Ⅱa	Autogenous BMSCs	Vein injection	6 weeks	Safety and feasibility	Function	—
NCT01287936	Ⅰ/Ⅱa	BMSCs (SB623)	Transcranial injection	1 year	Safety and function	—	Safe, no improvement of function
NCT01389453	Ⅰ	Umbilical cord blood MSCs	Vein/transcranial injection	7–14 d	Function	Function	—
NCT00535197	Ⅰ/Ⅱ	Autogenous bone marrow CD34 stem cells	Artery injection	7 d	Safety	Function	—
NCT00950521	Ⅱ	Autogenous peripheral blood-derived CD34 stem cells	Transcranial injection	0.50–5.00 years	Function	Function	—
NCT01468064	Recruitment	EPCs	Vein injection	1 year	Number of adverse events	Function	—

*, no registration number, 无试验编号；—, not mentioned, 未提及。NSCs, neural stem cells, 神经干细胞；BMSCs, bone marrow-derived mesenchymal stem cells, 骨髓间充质干细胞；MSCs, mesenchymal stem cells, 间充质干细胞；EPCs, endothelial progenitor cells, 内皮祖细胞；mRS, modified Rankin Scale, 改良Rankin量表；BI, Barthel Index, Barthel指数；NIHSS, National Institutes of Health Stroke Scale, 美国国立卫生研究院卒中量表

安全、有效，关于其最佳治疗时间窗和最佳移植途径的临床试验仍在进行中[91,97]。移植的干细胞主要是外源性神经干细胞、自体骨髓来源的间充质干细胞（MSCs）、单核细胞和$CD34^+$干细胞；移植途径包括静脉注射移植、动脉注射移植、鞘内注射移植和立体定位注射移植；治疗效果评价的最短时间是移植后24小时（https://www.clinicaltrials.gov/ct2/results?cond=&term=NCT00859014&cntry1=&state1=&recrs=，试验编号：NCT00859014）、最长时间是移植后5年（https://www.clinicaltrials.gov/ct2/results?cond=&term=NCT01151124&cntry1=&state1=&Search=Search，试验编号：NCT01151124）。干细胞治疗缺血性卒中业已展现出巨大潜能，未来需要解决的问题主要有：（1）移植干细胞的来源。（2）干细胞治疗的最佳时间窗。（3）最大程度发挥和维持移植干细胞促组织修复的功能特性有待突破。（4）移植时导致肺栓塞或脑栓塞及移植后成瘤（胚胎干细胞或诱导型多能干细胞）[92,98]有待解决。因此，尚待更多试验设计科学、合理的大规模随机对照临床试验以验证干细胞治疗的安全性和有效性，以及实验设计科学、合理的基础研究，以阐明干细胞生物学特性、提高干细胞治疗效果。

五、药物治疗进展

脑卒中是一种由包括环境因素和遗传因素在内的多因素共同导致的疾病，其病理生理学过程复杂，多种生物学分子、细胞和信号转导通路激活，给临床治疗带来巨大挑战，也同时提供多个可干预的治疗靶点。缺血性卒中治疗的首要目标是恢复脑组织灌注且不加重脑组织损伤，同时对加重缺血-再灌注损伤的因素进行调节，促进脑组织修复[1]。过去20年间有450种药物应用于缺血性卒中的治疗研究。迄今仅40种药物进入临床试验阶段，19种药物在不同国家批准上市。目前，处于缺血性卒中临床试验阶段或已应用于临床的药物主要包括溶栓药、抗血小板药、神经保护药和促组织修复药[99-100]（表3）。

1.溶栓药 主要包括rt-PA、瑞替普酶和替奈普酶[101]。一项Ⅰ期临床试验结果显示,急性缺血性卒中3~6小时联合应用瑞替普酶和阿昔单抗可以改善脑缺血症状[102]。另一项Ⅱ期临床试验比较瑞替普酶与替奈普酶的治疗效果,结果显示,急性缺血性卒中3~4小时,替奈普酶组患者脑组织再灌注和神经功能均优于瑞替普酶组,认为替奈普酶有望进入Ⅲ期临床试验阶段[103]。最近一项临床试验比较瑞替普酶和替奈普酶(相同时间点和相同治疗剂量)的治疗效果,结果显示,二者对挽救缺血脑组织并无明显差异[104],提示两种药物的治疗效果尚待大规模随机对照临床试验的验证。

2.抗血小板药 主要包括阿司匹林、氯吡格雷和西洛他唑。阿司匹林通过抑制环氧合酶、氯吡格雷通过抑制ADP和嘌呤受体抗血小板聚集。阿司匹林是目前最主要的缺血性卒中二级预防药物,氯吡格雷可用于阿司匹林过敏的脑卒中患者二级预防。由于可以增加颅内出血风险,不推荐长期联合应用阿司匹林和氯吡格雷[105]。研究显示,缺血性卒中初期,与单纯应用阿司匹林相比,更换另一种抗血小板药或联合应用其他抗血小板药,发生心血管并发症和脑卒中复发风险降低[106]。因此,阿司匹林和氯吡格雷的最佳临床治疗策略尚待进一步基础与临床研究。西洛他唑是新一代抗血小板药,通过抑制磷酸二酯酶3(PDE3)抗血小板聚集。动物实验显示,在全脑缺血模型小鼠中,西洛他唑通过抑制C-Jun氨基末端激酶3(JNK3)/Caspase-3信号转导通路以发挥减少神经元凋亡和预防脑卒中后认知功能障碍的作用[107]。此外,西洛他唑还可以通过抑制细胞间粘附分子-1(ICAM-1)表达和激活小胶质细胞,改善长期预后[108]。目前,西洛他唑主要用于治疗血栓闭塞性脉管炎,未推荐用于缺血性卒中的治疗,尚待进一步在缺血性卒中动物模型中进行研究,以为西洛他唑治疗缺血性卒中提供理论证据。

3.神经保护药 包括中成药银杏叶和芹菜提取物丁苯酞(NBP)、甲磺酸法舒地尔、胞二磷胆碱、尤瑞克林、洛伐他汀、多奈哌齐、依达拉奉[109]、格列本脲、重组人活化蛋白C、Caffeinol等。临床药物主要针对缺血性卒中后介导脑组织损伤的不同病理生理学应激过程发挥作用,包括扩血管和增加脑血流量(CBF)[110-113]、抗氧化应激[114]、抗细胞凋亡[115-117]、抑制兴奋性毒性[118-119]和抑制炎症反应[99-100,120-121]等,其中,丁苯酞已进入Ⅳ期临床试验[99]。尽管临床药物治疗研究取得一定进展,但某些药物的临床效果仍缺乏足够证据,尚待高质量的大规模随机对照临床试验进一步验证[122-124]。

表3 缺血性卒中治疗药物分类及作用机制

Table 3. Classification and therapeutic mechanism of drugs for clinical treatment of ischemic stroke

Stroke	Action of drugs	Classification of drugs
Acute phase	Restoration	Thrombolytic drugs: rt-PA, reteplase, tenecteplase
		Antiplatelet drugs: aspirin, clopidogrel, cilodiazol
		Vascular dilation drugs: fasudil mesylate, 3-N-butylphthalide
	Regulation of harmful factors	Antioxidants: edaravone, gingko mihuan, lovastatin, citicoline
		Anti-apoptotic drugs: urinary kallidinogenase
		Anti-inflammation drugs: 3K3A-APC, lovastatin, glyburide (RP-1127), G-CSF
		Inhibiting excitatory toxicity drugs: caffeinol, donepezil
Chronic phase	Promotion of neuro-repair	Promoting angiogenetic drugs: 3-N-butylphthalide, G-CSF
		Promoting neurogenic drugs: G-CSF

rt-PA, recombinant tissue-type plasminogen activator, 重组组织型纤溶酶原激活物; APC, activated protein C, 活化蛋白C; G-CSF, granulocyte colony-stimulating factor, 粒细胞集落刺激因子

4.促组织修复药 目前临床应用相对较少,基础和临床研究较多的主要是粒细胞集落刺激因子(G-CSF),可以促进造血干细胞动员和分化[125-126],广泛应用于遗传性或获得性粒细胞减少症以及促进移植干细胞增殖[127]。近年动物实验显示,除用于造血系统疾病的治疗外,粒细胞集落刺激因子还可以通过抑制细胞凋亡和炎症反应,促进血管新生和神经再生,促进脑组织修复,改善缺血性卒中小鼠长期预后[128-131]。小规模临床试验显示,缺血性卒中24~48小时内应用粒细胞集落刺激因子是安全的,但并未起到改善神经功能的效果[132-135]。因此,粒细胞集落刺激因子治疗缺血性卒中的效果尚待进一步基础研究和大规模随机对照临床试验的验证。

六、展望

脑卒中是全球性疾病,病理生理学机制复杂,多种基础研究有效的治疗方法在临床实践中效果欠佳,提示基础研究策略与临床实际应用仍然存在较大差距,需要科研工作者和广大临床医师之间加强交流与合作。一方面,科研工作者在设计实验时尽可能遵循脑卒中临床发作规律,如选择高龄、有多个基础疾病的实验动物,选择患者易接受的治疗方法如静脉滴注或口服,不仅应重视急性期治疗效果,而且应重视长期预后;另一方面,临床医师应对

进入临床试验阶段的药物进行科学严谨的大规模随机对照临床试验，以明确药物治疗效果。国家“十二五”时期，我们课题组通过药物治疗、基因治疗、miRNA治疗、干细胞治疗等方法对缺血性卒中治疗效果及作用机制进行较为深入的研究，主要在调节缺血性卒中后血管功能、促进血管新生和神经再生方面取得一些成果。未来在我国国民经济和社会发展第十三个五年规划（简称“十三五”）时期，我们课题组将加强再生医学的前沿研究，注重学科交叉与转化，在基因治疗、组织工程、干细胞技术、生物医学材料等方面进行新理论指导下的技术提升。此外，将重点针对缺血性卒中病理生理学过程中涉及炎症反应调控机制、神经免疫调节机制及移植干细胞和其他神经细胞的相互调节机制进行研究，以期为个体化精准治疗提供新方法和新策略。总之，脑卒中基础研究与临床治疗是一项艰巨且需长期坚持的任务，只有加强多方面人才、多学科交叉与合作，方能加快基础研究向临床转化的进展。

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·小词典·

中英文对照名词词汇（一）

阿尔茨海默病 Alzheimer's disease（AD）

γ-氨基丁酸受体 γ-aminobutyric acid receptor（GABAR）

C-Jun氨基末端激酶 C-Jun N-terminal kinase（JNK）

白天过度嗜睡 excessive daytime sleepiness（EDS）

伴中央-颞区棘波的儿童良性癫痫
benign epilepsy of childhood with centrotemporal spikes（BECT）

胞嘧啶-腺嘌呤-鸟嘌呤 cytosine-adenine-guanine（CAG）

表皮生长因子 epidermal growth factor（EGF）

丙氨酸转氨酶 alanine aminotranferase（ALT）

Whipple病 Whipple's disease（WD）

EB病毒 Epstein-Barr virus（EBV）

哺乳动物雷帕霉素靶蛋白1
mammalian target of rapamycin complex 1（mTORC1）

不宁腿综合征 restless legs syndrome（RLS）

部分各向异性 fractional anisotropy（FA）

残疾调整生命年 disability adjusted life year（DALY）

常染色体显性遗传性脑动脉病伴皮质下脑梗死和白质脑病
cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy（CADASIL）

超氧化物歧化酶1 superoxide dismutase 1（SOD1）

齿状核红核苍白球路易体萎缩
dentatorubral-pallidoluysian atrophy（DRPLA）

重复时间 repetition time（TR）

重组组织型纤溶酶原激活物
recombinant tissue-type plasminogen activator（rt-PA）

磁共振帕金森综合征指数
magnetic resonance parkinsonism index（MRPI）