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靶向内皮功能:脑小血管病的潜在治疗策略与展望

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摘 要:脑小血管病(cerebral small vessel disease,CSVD)是一组以脑内微血管病变为特征的临床综合征,在老年人群中高发,是导致血管性认知障碍、步态异常、卒中及痴呆的重要病因。目前,CSVD的临床管理仍局限于控制传统血管危险因素,尚缺乏针对其核心病理机制的特异性疗法。内皮功能障碍作为CSVD发病的始动与核心环节,贯穿疾病全程,其表现包括血脑屏障破坏、血管调节功能失调、神经炎症及微血栓形成等,因而成为极具潜力的治疗靶点。本文系统综述了CSVD的临床特征和相关标志物,深入剖析了内皮功能障碍在CSVD中的病理机制,重点探讨了以改善内皮功能为靶点的潜在治疗策略,并对该领域未来的研究热点与挑战进行了展望,旨在为CSVD的临床治疗提供新的思路与理论依据。

关键词:脑小血管病;内皮功能;血脑屏障;病理机制
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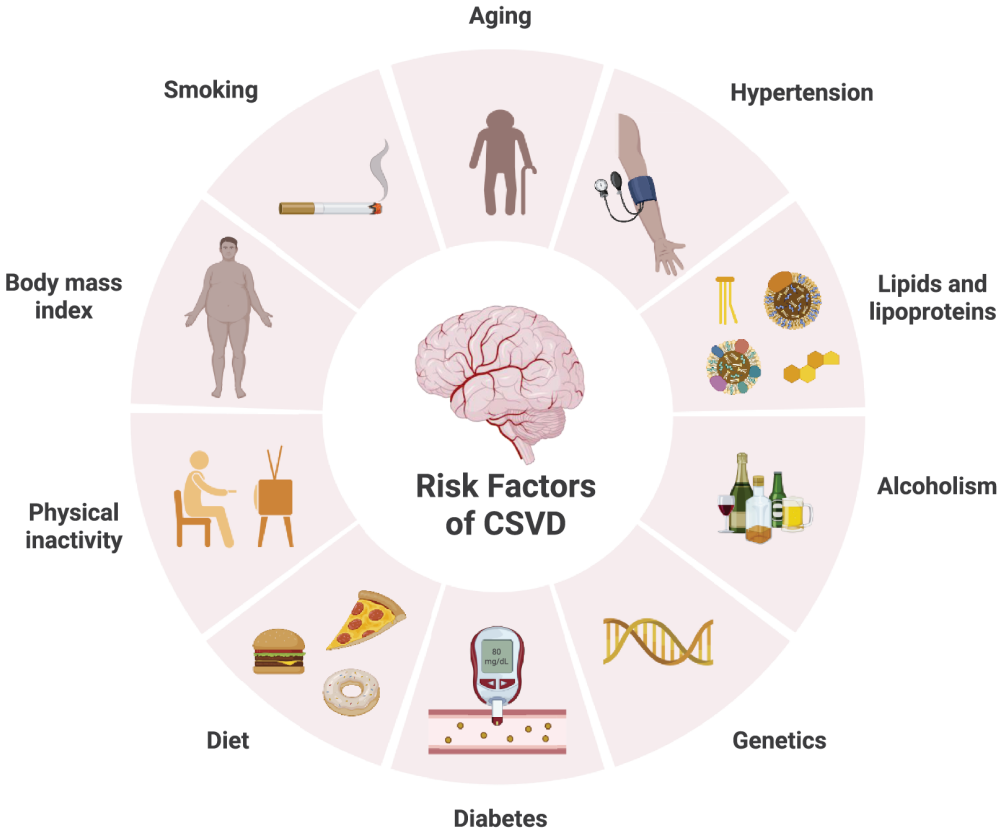
Progress in pathological mechanisms and targeted strategies for endothelial dysfunction-mediated cerebral small vessel disease

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Abstract: Cerebral small vessel disease (CSVD) encompasses a spectrum of disorders affecting the brain′s microvasculature, including small arteries, arterioles, capillaries, and venules. As a highly prevalent condition in aging populations and a major contributor to vascular cognitive impairment, stroke, and dementia, its clinical management remains predominantly supportive, focusing on controlling conventional vascular risk factors without addressing underlying core pathologies. Emerging evidence firmly establishes endothelial dysfunction as the pivotal initiating and perpetuating factor in CSVD. This dysfunction manifests as impaired vasoreactivity, blood-brain barrier (BBB) disruption, a pro-inflammatory and pro-thrombotic endothelial phenotype, and compromised neurovascular coupling, thereby serving as the critical mechanistic link between systemic risk factors and end-organ brain injury. This review provides a systematic synthesis of the current understanding of CSVD. We first outline its heterogeneous clinical presentations, from subtle executive deficits to overt dementia and gait disturbances, and detail the established neuroimaging hallmarks defined by STRIVE criteria, such as white matter hyperintensities, lacunes, and cerebral microbleeds. The discussion extends to promising fluid biomarkers reflecting endothelial activation, BBB leakage, and neuroinflammation. Subsequently, we delineate the essential physiological roles of cerebrovascular endothelial cells, emphasizing their central functions in orchestrating neurovascular coupling for dynamic cerebral blood flow control, in forming and maintaining the selective BBB, and in sustaining local anticoagulant and anti-inflammatory homeostasis. A central focus of this review is a detailed analysis of how endothelial dysfunction drives core pathological processes in CSVD: (1) structural vascular remodeling, evolving from adaptive wall thickening to maladaptive arteriolosclerosis and lumen stenosis; (2) hemodynamic failure, characterized by impaired cerebral autoregulation and vasoreactivity, leading to chronic hypoperfusion, capillary rarefaction, and heightened susceptibility to microhemorrhages; (3) neurovascular unit disintegration, wherein BBB breakdown precipitates vasogenic edema, neuroinflammation, excitotoxicity, and impaired clearance of metabolic waste

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via the glymphatic system; and (4) compromised repair mechanisms, resulting from diminished secretion of neurotrophic factors and deficient angiogenic responses. We then critically evaluate emerging therapeutic strategies aimed at restoring endothelial function. Pharmacological approaches are categorized into agents designed to enhance endothelial vasodilation, suppress endothelial inflammation, reduce oxidative stress, and bolster BBB integrity. Innovative avenues, including endothelial progenitor cell transplantation and microRNA-based therapies, are also highlighted. Additionally, we summarize current methods for assessing endothelial dysfunction in CSVD, covering circulating biomarkers, advanced neuroimaging techniques, and retinal vascular analysis. In conclusion, while targeting endothelial dysfunction presents a highly promising strategy for CSVD treatment, significant translational challenges persist. These include the pathological heterogeneity of CSVD subtypes, the absence of specific biomarkers for patient stratification, the lack of sensitive and direct clinical trial endpoints, and the difficulty in achieving brain microvascular-selective drug delivery. Future research must prioritize the integration of multi-omics data to define endothelio-centric disease endotypes, the development of novel targeted therapeutics and delivery systems, the validation of composite dynamic endpoints, and the exploration of non-pharmacological interventions for early-stage disease modulation. A deeper mechanistic understanding coupled with advanced therapeutic targeting holds considerable potential to modify the disease trajectory and improve clinical outcomes for patients with CSVD.



Key words: cerebral small vessel disease; endothelial function; blood-brain barrier; pathological mechanisms

脑小血管病(cerebral small vessel disease, CSVD)是指各种病因影响脑内小动脉、微动脉、毛细血管、微静脉和小静脉所导致的一系列临床、影像、病理综合征。其发病率与年龄呈正相关,60岁以上人群患病率超50%;高血压、糖尿病、高脂血症患者为高危人群,患病率较普通人群高2~3倍;CSVD是导致约25%的缺血性卒中以及绝大部分脑出血的原因,更是血管性认知障碍和痴呆的首要病因[1]。此外,它还与步态障碍、排尿异常和抑郁等临床症状密切相关,是一种常见且危害大的神经系统疾病,严重影响老年人群的生活质量[2]。

尽管CSVD具有重要的临床与公共卫生意义,其发病机制仍未完全明晰[3]。既往研究多聚焦于血管壁的结构性病变,如动脉硬化、脂质透明变性等[4]。近年来,内皮功能紊乱被认为是CSVD病理级联反应的起始环节与核心驱动因素[5]。内皮功

能障碍是一个广义术语,指内皮细胞失去其正常的调节功能,表现为血管舒缩功能异常、促炎和促血栓状态,以及屏障功能破坏。在CSVD中,内皮功能障碍被认为是连接多种危险因素(如高血压、糖尿病、衰老)与最终脑组织损伤的关键桥梁[6]。因此,深入理解内皮功能障碍在CSVD中的作用机制,并开发针对性的治疗策略,具有重大的科学价值和临床意义。本综述将围绕这一核心主题,系统阐述其病理基础,并展望未来的治疗前景。

1 CSVD的临床特征和相关标志物

CSVD的临床特征具有多样性,且部分症状早期隐匿,随病情进展逐渐显现。多数患者早期表现为轻度认知功能下降,以执行功能受损和记忆力减退为主;随病情加重,可进展为血管性痴呆;也可出现平衡步态异常、精神情感障碍、尿失禁、生活能力下降,以及卒中相关事件等,严重影响日常生活能力[7]。其诊断和严重程度评估高度依赖于神经影像学,根据最新的STRIVE标准,其标志物包括:近期皮质下小梗死、假定血管源性的脑白质高信号(white matter hyperintensities,WMH)、腔隙灶、血管周围间隙扩大、脑微出血、脑萎缩等[8]。目前尚无诊断CSVD的特异性体液标志物,但部分生物分子可辅助判断病情,如脑脊液/血清白蛋白比率增高提示血脑屏障受损[9];炎症相关细胞因子如肿瘤坏死因子-α(tumor necrosis factor-α,TNF-α)和白介素-6(interleukin-6,IL-6),趋化因子如单核细胞趋化蛋白-1(monocyte chemoattractant protein-1,MCP-1)和趋化因子配体8(C-X-C motif chemokine ligand 8,CXCL8),血管细胞黏附分子-1(vascular cell adhesion molecule 1,VCAM-1),以及丝氨酸蛋白酶抑制因子3(serpin family A member 3,SERPINA3)等升高提示脑小血管存在炎症反应[10-12];血管内皮功能相关分子如血管内皮生长因子(vascular endothelial growth factor,VEGF)和血管性血友病因子(von Willebrand factor,vWF)等可反映内皮细胞功能状态[13];脑损伤相关蛋白(如神经丝轻链蛋白)可作为脑实质损伤的潜在标志物[14,15]。由于CSVD的病理、发病机制及临床表现均具有异质性,其相关研究进展缓慢。近年来,CSVD从基础到临床转化研究受到越来越多的关注,2013年发布CSVD国际影像标准STRIVE-1,并于2023年调整更新为STRIVE-2[8],国内专家组亦就CSVD形成诊疗指南[1],这些均为CSVD的临床诊疗提供了重要规范和参考。

2 脑血管内皮细胞的生理功能

2.1 神经血管耦合与脑血流调节

内皮细胞是脑小血管壁的单层扁平上皮,控制着大脑与全身循环间的物质和信息交换,对维持脑内环境稳态和正常神经功能至关重要[16]。神经血管耦合(neurovascular coupling,NVC)是指局部脑血流量随神经元活动而动态变化的生理现象,这一功能由神经元、神经胶质细胞、血管内皮细胞及周细胞等多种细胞构成的功能单元共同调节[17]。其基本机制是,当脑内神经元被激活时,会释放谷氨酸等神经递质,激活邻近星形胶质细胞终足的代谢型受体,引发胞内Ca^{2+}升高。Ca^{2+}激活磷脂酶A_2,产生花生四烯酸,经细胞色素P450表氧化酶催化为环氧-二十碳三烯酸(epoxyeicosatrienoic acids,EETs)[18]。花生四烯酸代谢产物EETs和ATP等血管活性物质,直接作用于邻近的脑血管内皮细胞[19]。脑血管内皮细胞感知上述信号后,激活一氧化氮合成酶(endothelial nitric oxide synthase,eNOS),生成并释放一氧化氮(nitric oxide,NO);同时,内皮细胞还会释放前列环素(prostacyclin I_2,PGI_2)等舒张因子。这些因子作用于血管平滑肌细胞,使其松弛,导致局部脑小动脉扩张,进而增加该区域的脑血流量[20]。周细胞是嵌在脑微血管基底膜内、直接包裹内皮细胞的壁细胞。周细胞表达多种神经递质和血管活性物质的受体,如谷氨酸受体、嘌呤能受体;并且富含α-平滑肌肌动蛋白,其突起通过黏着斑与内皮紧密连接。当周细胞激活,胞内Ca^{2+}升高时,周细胞体及其突起可发生快速、局灶性的收缩或舒张,直接改变毛细血管管径,在数百毫秒内调节其所在毛细血管节段的血流[21]。而内皮细胞持续分泌的血小板源性生长因子(platelet-derived growth factor-BB,PDGF-BB)是周细胞存活、增殖和迁移的关键信号。在CSVD中,内皮功能障碍导致PDGF-BB分泌减少或信号转导受损,致使周细胞从血管壁脱落,是CSVD的标志性病理改变[22]。新近研究提示,隧道纳米管(tunneling nanotubes,TNTs)是周细胞与内皮细胞间直接双向运输细胞器(如线粒体、溶酶体)、囊泡、离子(如Ca^{2+})和信号分子的长距离、膜包裹的细胞质通道[23]。周细胞可以通过TNTs将功能性线粒体转

移至线粒体受损的内皮细胞。这种转移能直接恢复内皮细胞的ATP水平、减少活性氧(reactive oxygen species,ROS)产生、稳定紧密连接,从而抵抗血脑屏障的破坏[24]。此外,神经元兴奋导致胞外K^+浓度瞬时升高(1~3 mmol/L)。内皮细胞上的内向整流钾通道(inward rectifier potassium channel subtype 2.1,Kir2.1)可感知此变化,引发内皮细胞超极化。该电信号通过缝隙连接,在血管壁内快速传导,导致血管舒张。而Kir2.1通道功能易受氧化应激影响,在CSVD早期即可受损,是NVC反应延迟的早期电生理基础[25]。因此,神经活动增强时,局部脑组织代谢产物浓度升高也可直接刺激内皮细胞,进一步促进血管舒张,强化血流增加效应,形成"神经信号-内皮响应-血流匹配"的完整闭环[26,27]。有研究也提示脑动脉内皮细胞的缝隙连接耦合,直接决定了神经活动诱发的血管舒张传播的速度与空间范围,进而灵活高效地分配有限能量资源,以维持大脑的正常功能运转[28]。NVC是脑功能正常运行的基础,当脑血管内皮细胞功能障碍时,NVC会出现异常,也是CSVD相关认知功能降低的早期机制。

2.2 血脑屏障的构成与功能

血脑屏障(blood brain barrier,BBB)是脑组织与外周血液间的选择性通透屏障,而相邻内皮细胞之间通过Claudin、Occludin等蛋白形成连续的、犹如"拉链"般的紧密连接,彻底封堵了细胞间的缝隙,阻止血液中的物质通过旁细胞途径自由扩散入脑。同时,内皮细胞极低的胞饮活性,大大限制了非特异性的大分子物质通过跨细胞途径转运[29]。内皮细胞具有特定的转运系统,一方面通过特异性载体转运葡萄糖、氨基酸、核苷、乳酸等营养物质,另一方面,通过P-糖蛋白(P-glycoprotein,P-gp)、乳腺癌耐药蛋白等外排泵,将潜在的神经毒性物质、代谢废物和药物主动"泵回"血液中,保护脑组织[30]。脑血管内皮细胞的特异转运蛋白是维持BBB和脑内环境稳定的分子基础。主要促进因子超家族成员2a(major facilitator superfamily domain containing 2a,Mfsd2a)是一种钠依赖性溶血磷脂酰胆碱同向跨膜转运蛋白,负责运输二十二碳六烯酸入脑,维持BBB的低通透性[31]。*Mfsd2a*基因敲除的小鼠在早期胚胎阶段表现出BBB渗漏,并发展出小头畸形、认知障碍和焦虑等表型[31,32]。Mfsd2a转运的脂质形成了一个独特的脂质环境,可抑制脑血管内皮细胞中的小窝囊泡形成,从而抑制转胞吞作用并确保BBB完整性[33]。葡萄糖转运体1(glucose transporter 1,GLUT1)介导葡萄糖从血液到大脑的跨内皮细胞易化扩散,是脑细胞几乎唯一的能量来源通道。GLUT1在脑毛细血管内皮细胞上表达水平最高,其功能对维持大脑高能耗至关重要。在CSVD中,GLUT1功能障碍是缺血损伤的核心分子基础[34]。脑内皮细胞并非简单地阻止所有转胞吞,而是存在一个精密的分选系统。其中决定货物是被转运还是被降解的关键,在于能否进入一种称为"分类管"的细胞结构。Ras超家族小GTP酶Rab17特异性地定位于脑内皮细胞内的分类管,是促进分类管形成和特异性转胞吞的关键调节因子[35]。因此,脑内皮细胞的转运系统是一个高度特异、精细调控的功能单元。

2.3 抗凝血与抗炎功能

正常的内皮细胞表面具有抗凝血特性,通过表达硫酸肝素蛋白多糖、血栓调节蛋白和分泌组织型纤溶酶原激活物(tissue plasminogen activator,t-PA)等,抑制血小板聚集和凝血因子激活,防止脑内微血栓形成。当内皮受损时,这一平衡被打破,转变为促凝状态[36]。在静息状态下,内皮细胞不表达或低表达黏附分子,阻止白细胞黏附和迁移。当感知到炎症信号时,内皮细胞被激活,上调E-选择素、P-选择素、VCAM-1和细胞间黏附分子-1(intercellular adhesion molecule 1,ICAM-1)等的表达,引导免疫细胞(如淋巴细胞、单核细胞)有序地黏附、变形并穿越内皮层进入脑实质,参与免疫监视或炎症反应,控制神经炎症的进展[37]。此外,在发育和某些病理条件下,内皮细胞通过产生VEGF、血管生成素等信号分子,驱动新血管的形成;同时,通过与周细胞和星形胶质细胞终足的相互作用,共同维持血管结构的成熟和稳定[38]。基于BBB的结构特殊性和中枢免疫特权,与外周血管内皮相比,脑内血管内皮细胞的抗凝血与抗炎机制具有一定独特模式。例如,脑内皮细胞表面富含硫酸乙酰肝素(heparan sulfate,HS),且HS含多个N-硫酸化位点,糖链结构复杂,对抗凝血酶(antithrombin,AT)的结合亲和力较外周血管内皮更强,抗凝血效率更高[39]。脑内皮细胞是中枢神经系统t-PA的主要来源之一,其分泌过程具有极性特征,主要通过面向血管腔的顶端膜定向释放[40]。这种高亲和力HS-AT系统和极性分泌t-PA,可优先阻断血栓形成,同时避免过度抗凝导致脑出血。此外,与

外周血管内皮相比，脑内皮细胞在生理状态下几乎不表达细胞黏附的关键分子E-选择素和P-选择素，以及低表达ICAM-1和VCAM-1，仅在严重脑损伤时才少量诱导表达，避免中性粒细胞过度浸润[41]。脑内皮细胞的紧密连接，也阻止外周炎症细胞和促炎因子进入脑实质。这种选择性细胞黏附和紧密连接结构，严格限制了外周炎症因子和细胞入脑，是脑部小血管的独有特性。

3　内皮功能障碍驱动的CSVD关键病理环节

3.1　脑小血管结构重塑：从“适应性”到“破坏性”改变

CSVD的核心病理改变是脑小血管的结构重塑，主要表现为血管壁增厚、管腔狭窄、血管迂曲以及功能异常。越来越多的证据表明，内皮功能障碍是这一重塑过程的始动环节和核心驱动因素[42]。如图1所示，在高血压、衰老、糖尿病等多种危险因素作用下，早期内皮功能障碍引发的血管舒缩失衡，会启动血管壁的血管平滑肌细胞增殖、胶原沉积等适应性重塑过程，以维持血管张力；但长期失衡会导致破坏性血管结构改变[43]。危险因素损伤内皮细胞后，内皮的屏障功能丧失，血浆有害物质渗漏到血管壁周围，激活周细胞和血管平滑肌细胞[43]。周细胞的活化和血管平滑肌细胞表型转换，使细胞外基质沉积和血管壁增厚、硬化，失去弹性，形成“玻璃样变”，导致血管壁增厚、管腔狭窄。这种改变常见于基底节区、丘脑的穿支动脉，是腔隙性梗死的主要病理基础[44,45]。此外，内皮功能障碍介导微血栓形成、血管壁重塑，最终引发微动脉闭塞，形成直径3~15 mm的腔隙性梗死；若闭塞时间短、侧支循环代偿不足，还会导致脑微梗死（直径<2 mm）。研究证实，CSVD患者脑内微梗死数量与认知功能下降速度显著相关，每增加1个微梗死，执行功能评分下降0.8[46,47]。

3.2　脑血流动力学异常：灌注不足与自动调节失效

脑血流动力学异常主要包括脑血流自动调节功

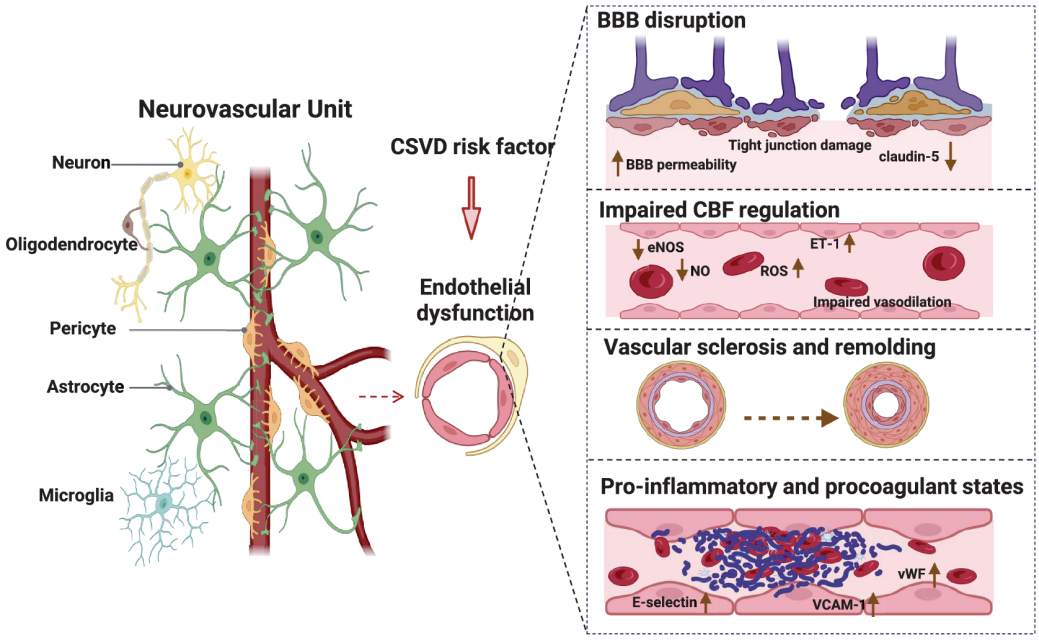


图1　内皮功能障碍驱动脑小血管病的关键病理环节

CSVD：脑小血管病；CBF：脑血流；NO：一氧化氮；ROS：活性氧；ET-1：内皮素-1；vWF：血管性血友病因子；VCAM-1：血管细胞黏附分子-1。

Figure 1　Endothelial dysfunction mediates key pathological processes in cerebral small vessel disease

CSVD: cerebral small vessel disease; CBF: cerebral blood flow; NO: nitric oxide; ROS: reactive oxygen species; ET-1: endothelin-1; vWF: von willebrand factor; VCAM-1: vascular cell adhesion molecule-1.

能受损和脑血管反应性降低。内皮功能障碍是该过程的始动和核心环节,它直接导致脑血流动力学异常,后者又加剧脑组织低灌注和损伤,进一步损害内皮功能,形成正反馈循环,最终导致CSVD的影像学和临床表现。脑血流自动调节是指脑血流在动脉血压波动时维持稳定的能力,内皮细胞主要通过NO释放调控该过程。内皮细胞功能障碍时,eNOS解耦联,NO生物利用度降低,结合ROS增加,脑血流自动调节失效,可引发脑灌注不足和血流动力学应激与微出血两大血流动力学问题[48]。NO生成减少导致脑小血管舒张功能下降,即使血压正常,脑深部白质、基底节区的脑血流量仍会降低15%~20%[49]。长期灌注不足导致脑组织缺血缺氧,引发胶质细胞活化、神经元凋亡,进而形成WMH。影像学研究显示,WMH区域的脑血流量每降低10 mL/(100 g·min),WMH体积每年增加1.2 mL[50,51]。脑血管反应性降低是指大脑血管在受到化学刺激(如CO_2)或神经功能活动刺激时,其舒张和相应增强血流量的能力下降。该过程直接反映了内皮依赖性血管舒张功能受损,其在白质区域(特别是额叶和顶叶深部白质)比灰质更明显,这与CSVD的病灶分布一致[52]。此外,脑血流自动调节失效后,血压波动会直接传递至脑小血管,导致血管壁承受过高压力。对于已有内皮损伤、基底膜变薄的血管,这种应激易引发血管破裂,形成脑微出血。脑微出血常见于高血压相关CSVD(基底节区为主)与脑淀粉样血管病,其数量与脑出血风险正相关,≥5个脑微出血的患者脑出血风险增加5倍[53,54]。功能障碍的内皮细胞PDGF-BB分泌异常,导致周细胞上的PDGFR-β信号减弱,周细胞变性、凋亡和丢失,参与微出血的形成[55]。另外,衰老的内皮细胞进入不可逆的细胞周期停滞,并分泌促炎、促凋亡的衰老相关分泌表型因子(IL-6、IL-1α/β等),促进局部炎症和基质降解,形成自我延续的破坏性微环境,加速血管壁的脆弱化,在脑血流波动下促成微出血[56]。

内皮细胞eNOS是脑血流动力学异常调节的关键分子。研究证实,CSVD患者脑微血管内皮细胞中的eNOS活性较健康人群降低30%~50%,NO生成量减少40%以上,且eNOS基因多态性与CSVD的影像学标志物WMH体积显著相关[57,58]。而eNOS缺陷小鼠在幼年时出现脑低灌注和BBB渗漏,并随年龄增长而逐渐恶化,被用作自发性CSVD动物模型[59]。CSVD中各类危险因素通过两种途径抑制eNOS活性:(1)氧化应激诱导eNOS解偶联,生成无活性的非耦合eNOS,减少NO生成;(2)炎症因子抑制eNOS基因转录,降低蛋白表达[59]。eNOS活性不仅由内皮细胞自主决定,而且也受到脑内其他细胞的调控。神经元-星形胶质细胞信号通过花生四烯酸代谢产物,作用于邻近微血管内皮细胞,激活eNOS,舒张局部血管[18]。在CSVD的病理状态下,该信号传递受损,导致eNOS无法被正确激活,表现为NVC功能障碍。此外,在慢性低灌注刺激下,小胶质细胞被激活为促炎表型,以及星形胶质细胞被活化,释放ROS和炎症因子,抑制eNOS表达和活性,并加剧其解耦联[60]。此外,CSVD患者脑微血管中β位点淀粉样前体蛋白切割酶1(beta-site APP cleaving enzyme 1,BACE1)表达显著升高。BACE1会促使细胞膜上小窝蛋白1积累,进而与eNOS过度结合,同时其产生的循环Aβ也会进一步抑制eNOS活性[61]。因此,BACE1异常介导的eNOS功能抑制会直接导致内皮功能障碍,进而引发脑血流量减少、BBB渗漏等一系列CSVD相关病理改变。

3.3 神经微环境紊乱:从支持内皮到毒性损伤转变

正常的神经微环境是神经元正常运作的基础,依赖于稳定的离子平衡、充足的营养供应、及时的废物清除以及适度的炎症反应。内皮细胞通过BBB维持神经微环境的稳定,内皮功能障碍导致BBB破坏后,引发系列连锁反应,最终形成神经微环境的全面紊乱[62]。其中,内皮细胞间的紧密连接(tight junction,TJ)蛋白降解导致血脑屏障通透性增加,血浆中的白蛋白、纤维蛋白原、免疫球蛋白等大分子物质渗漏到血管周围的脑组织,形成血管源性水肿,尤其在扩散能力较差的脑白质区最为明显,在MRI上表现为白质高信号[63]。脑微血管内皮细胞的紧密连接是一个高度动态的蛋白质复合体,主要由跨膜蛋白(如Claudin-5、Occludin、JAMs)和胞质支架蛋白(如ZO-1、ZO-2、AF-6)构成。在CSVD中,多种病理因素共同导致该复合物分解,涉及的分子信号机制主要有以下几方面。(1)氧化应激直接氧化或修饰TJ蛋白(如Occludin、ZO-1)的特定氨基酸残基,导致TJ蛋白错误折叠、功能丧失,诱导其内吞[64]。(2)基质金属蛋白酶(matrix metalloproteinases,MMPs)的降解作用:MMP-2和MMP-9的表达和活性在CSVD中被显著上调,其可直接切割降解Occludin和Claudin-5

的胞外结构域，并降解血管基底膜的主要成分Ⅳ型胶原和层粘连蛋白，摧毁TJ赖以锚定的外骨架，形成双重破坏[65]。(3)RhoA/MLC通路激活：在CSVD中，被激活的免疫细胞释放IL-1β、TNF-α等炎症因子，持续激活内皮细胞的Rho激酶/MLC通路，导致肌动蛋白细胞骨架重排和收缩，破坏TJ蛋白在细胞膜上的定位与组装[66]。(4)非编码RNA的调控作用：miR-150通过靶向血管生成素受体Tie-2来调节Claudin-5的表达和内皮细胞存活，从而影响血脑屏障的通透性[67]；miR-501-3p也被证实可直接靶向抑制ZO-1的翻译[68]。(5)BACE1介导的特异性剪切通路：CSVD患者脑小血管内皮细胞中的BACE1被发现异常上调，而紧密连接核心蛋白Occludin是其新型作用底物，BACE1特异性剪切Occludin，导致该蛋白结构断裂、功能丧失[61]。

BBB渗漏也可导致血液中兴奋性氨基酸进入脑组织，引发神经元的兴奋性毒性损伤[69]。内皮功能障碍介导的脑血流低灌注和毛细血管稀疏化，导致向神经元和胶质细胞的氧气和葡萄糖输送减少，使脑组织能量代谢紊乱，神经元突触功能受损，直接影响学习和记忆[70]。少突胶质细胞对能量短缺极其敏感，导致髓鞘生成和维护障碍，表现为髓鞘脱失[71]。此外，内皮细胞受损使促炎表型激活，黏附分子VCAM-1、ICAM-1等表达上调，招募外周单核细胞、中性粒细胞浸润脑实质。同时，内皮细胞自身分泌IL-6、TNF-α等炎症因子增强，进一步激活小胶质细胞极化至M1促炎表型，形成内皮炎症-胶质激活的级联反应[72]。孟德尔随机化研究已证实，循环中促炎蛋白CXCL8、IL-1β水平与CSVD发病风险存在因果关系，且这类蛋白的表达异常可通过内皮-免疫轴加重神经损伤[73]。近来研究显示，类淋巴系统和血管周围间隙是清除脑内代谢废物的关键通路，而CSVD中血管壁僵硬、舒缩功能异常，导致动脉搏动减弱或异常，损害类淋巴系统功能。这使得Aβ、tau等毒性蛋白在脑间质中积聚，不仅加剧了神经损伤，也构成了CSVD与阿尔茨海默病共病的重要病理基础[74]。

3.4 神经修复障碍：内皮-神经交互作用缺失

内皮细胞不仅是屏障细胞，还是神经支持细胞，通过分泌神经营养因子、调控血管生成，参与神经修复。而内皮功能障碍可导致这种内皮-神经交互作用缺失[75]。内皮细胞分泌的BDNF是神经元存活与突触形成的关键因子，CSVD患者脑微血管内皮细胞中BDNF表达降低50%以上，导致神经元突触密度下降、树突分支缩短[76]。此外，内皮细胞增殖与迁移是血管生成的基础，氧化应激与炎症因子抑制内皮细胞增殖，同时降低血管内皮生长因子受体VEGFR2表达，导致缺血区域的血管新生不足，无法代偿灌注缺陷[77]。内皮细胞通过分泌TGF-β、PDGF等因子，调控少突胶质前体细胞的迁移与成熟[46]。在CSVD中，内皮功能障碍导致这些因子分泌失衡，少突胶质前体细胞成熟受阻，髓鞘合成减少，进而加剧脑白质损伤[78]。

4 靶向内皮功能的CSVD治疗策略

4.1 改善内皮舒张功能的治疗策略

近年来，以硝酸甘油、单硝酸异山梨酯为代表的硝酸酯类药物在CSVD治疗中的应用逐渐受到关注。多项临床研究数据表明，长期使用单硝酸异山梨酯能够显著改善CSVD患者的脑血流灌注水平，并有效减缓脑白质疏松的病理进程[79]。然而，鉴于现有研究样本量及随访周期的局限性，其长期治疗效果及安全性仍需通过多中心、大样本的随机对照临床试验进行系统性验证。此外，eNOS激活剂的研究亦备受关注。在CSVD动物模型研究中，外源性补充四氢生物蝶呤(tetrahydrobiopterin，BH4)可显著上调eNOS磷酸化水平，增强NO生物利用度，有效改善脑小动脉内皮依赖性舒张功能，并通过抑制氧化应激与炎症级联反应，减轻白质脱髓鞘及轴索损伤[80]。目前，基于BH4通路的药物主要有沙丙蝶呤和墨蝶呤。沙丙蝶呤可改善肺血管内皮eNOS功能，已获批用于治疗肺动脉高压，但在CSVD中的应用面临血脑屏障挑战[81]。墨蝶呤是BH4前体，可经内源性还原酶高效还原为BH4，维持eNOS耦合。一项名为APHENITY的Ⅲ期随机双盲对照临床试验显示，口服墨蝶呤可显著降低苯丙酮尿症患者血液中的苯丙氨酸，同时具有良好的安全性[82]。另一项在健康人群中的临床研究发现，口服墨蝶呤可显著增加脑内BH4水平[83]。墨蝶呤是治疗CSVD和脑血管病的候选分子，其生物学机制明确，临床前疗效显著，并具有良好的临床安全性[84]，有望成为修复内皮功能障碍、治疗CSVD的一种全新对因治疗策略。但截至当前，尚无以CSVD、卒中后认知障碍等为主要终点的大规模墨蝶呤临床Ⅱ和Ⅲ期试验。未来的

突破将取决于药物递送技术的创新和精准患者分层的实现。

可溶性鸟苷酸环化酶(soluble guanylate cyclase, sGC)作为内皮NO信号通路中关键的下游效应器和放大器,其激动剂为治疗CSVD提供了一种潜在新策略。目前sGC激动剂主要用于肺高压和心衰,但基础研究显示其能改善老龄小鼠的脑微循环和认知功能,是未来CSVD药物开发的潜在方向[85]。瞬时受体电位香草酸受体4(transient receptor potential vanilloid 4,TRPV4)是内皮细胞感知剪切力、触发Ca^{2+}信号和内皮舒张的关键信号分子,可通过激活eNOS和中间电导钙激活钾通道,引起血管舒张。在多种CSVD相关动物模型中,特异性TRPV4调节剂显著减轻BBB破坏、改善白质病变和部分恢复脑血管反应性[86]。但由于TRPV4广泛表达于多种组织,全身性给药可能引起副作用。利用药物化学手段设计对脑血管内皮TRPV4具有更高选择性的变构调节剂,可能是未来新的转化方向。

肾素-血管紧张素系统抑制剂除降压作用外,亦被证实可改善内皮依赖性血管舒张功能。循证医学研究显示,此类药物能显著优化CSVD患者的脑血流动力学,延缓WMH进展,并减轻微出血负荷[87]。一项5年期多中心前瞻性研究显示,培哚普利干预组CSVD患者脑白质疏松体积增长速率较对照组显著减缓,MoCA评分的年度递减幅度下降23.7%[88]。缬沙坦和氯沙坦被发现可抑制氧化应激、减轻神经炎症、维持BBB结构完整[89]。目前,肾素-血管紧张素系统抑制剂已成为CSVD合并高血压患者一线用药,对于血压正常的CSVD人群,其神经保护效应虽在观察性研究中得到初步验证,但仍需临床随机对照试验提供更高级别的循证证据。

西洛他唑是一种磷酸二酯酶Ⅲ抑制剂,通过增加细胞内cAMP浓度,不仅能抑制血小板聚集,还可激活eNOS,促进NO生成,从而改善内皮功能[90]。LACI-2试验发现,西洛他唑和单硝酸异山梨酯联合用于症状性CSVD患者显示出安全性和潜在疗效,为靶向血管功能的治疗理念提供了重要支持[91]。

4.2 抑制内皮炎症反应的治疗策略

除了改善血管舒张功能,抑制CSVD中活跃的内皮炎症反应也是重要的治疗方向。内皮细胞NF-κB信号通路是炎症级联核心元件,临床前研究证实抑制NF-κB通路可降低TNF-α、IL-6等炎症介质水平,改善内皮功能、减轻脑白质炎性损伤并提升神经行为表现[92]。不过,该类药物目前仍处于基础研究阶段,其长期疗效与安全性尚待大规模临床试验验证。

他汀类药物可通过抑制TNF-α、IL-6等炎症因子及ICAM-1、VCAM-1等黏附分子表达,减轻内皮炎症。随机对照试验显示,40 mg/d 阿托伐他汀治疗2年能抑制CSVD患者WMH进展,改善认知评分并优化脑灌注[93]。系统评价证实,他汀类药物可降低CSVD患者脑卒中发生率,其神经保护作用获广泛认可[94]。

4.3 减轻氧化应激的治疗策略

烟酰胺腺嘌呤二核苷酸磷酸氧化酶(nicotinamide adenine dinucleotide phosphate oxidase,NADPH)作为内皮细胞中活性氧(ROS)生成的关键催化酶系,在CSVD病理进程中扮演重要角色。在CSVD患者及动物模型中,NADPH氧化酶活性均显著上调,驱动ROS的过度产生,进而加剧氧化应激损伤。鉴于此,靶向抑制NADPH氧化酶活性已成为干预CSVD氧化应激损伤的重要策略。芹菜素作为经典的NADPH氧化酶抑制剂,通过竞争性结合催化亚基或调控相关信号通路,有效阻断ROS的生物合成。在CSVD实验动物模型研究中,芹菜素干预可显著降低脑组织内ROS水平,修复受损的内皮细胞功能,同时减轻脑白质疏松及微出血等病理改变[95]。目前,该药物已进入临床Ⅰ/Ⅱ期试验阶段,其在CSVD患者中的治疗有效性及安全性正在多中心临床研究中进行系统性评估。

4.4 保护BBB完整性的治疗策略

体内外实验研究证据显示,通过靶向干预手段激活Claudin-5或Occludin蛋白功能,能够有效促进紧密连接蛋白的生物合成,并优化其在细胞膜上的空间分布,进而显著增强BBB的结构稳定性与屏障功能[96]。在CSVD动物模型研究中,给予Claudin-5特异性激动剂干预后,经定量分析证实,该处理能够显著降低BBB通透性系数,伴随脑组织含水量的显著减少与炎症因子表达水平的下调,最终表现为神经功能评分的显著改善[97]。值得关注的是,尽管当前针对紧密连接蛋白调节剂的研究已在细胞与动物模型层面取得系列进展,但该类干预策略仍处于临床前研究阶段。

4.5 新型潜在疗法

近年来,新型靶向内皮功能的方法不断涌现,其中内皮祖细胞(endothelial progenitor cells,EPCs)移植呈现较好潜力。CSVD患者外周血中EPCs的数量和功能显著降低[98],而输注EPCs可改善CSVD动物模型的内皮功能,减轻脑白质损伤[99]。目前,EPCs移植治疗CSVD已进入临床试验阶段,初步结果显示,EPCs移植可显著提高CSVD患者的脑血流灌注,改善认知功能,但该治疗方法的长期疗效和安全性仍需进一步研究。

此外,多种miRNA在CSVD患者中表达异常,且与内皮功能障碍密切相关。其中,miR-126可通过靶向调节血管内皮生长因子信号通路,促进内皮细胞增殖和迁移,改善内皮功能。在CSVD动物模型中,过表达miR-126可显著改善内皮舒张功能,减轻脑白质疏松程度[100]。因此,miRNA模拟物或抑制剂成为CSVD治疗的潜在药物,相关研究已进入临床前阶段,有望在未来为CSVD治疗提供新的方向[101]。

5 脑小血管内皮功能障碍的评估方法

5.1 循环生物标志物

由于脑小血管直径极小且位于颅内,直接评估其内皮功能极具挑战性。通过血液或脑脊液的相关分子检测,可反映内皮细胞激活、损伤或功能障碍,主要包括黏附分子ICAM-1、VCAM-1和E-选择素,止血与血栓因子vWF、纤溶酶原激活物抑制剂-1和血栓调节蛋白,NO通路相关分子不对称二甲基精氨酸,BBB损伤标志物脑脊液/血清白蛋白比率和S100钙结合蛋白B,以及内皮微粒。这些标志物采样方便,可高通量检测,有助于早期CSVD筛查。但不足之处在于缺乏特异性,全身任何部位炎症或血管损伤均可使其升高,不仅限于脑,而且易受药物、感染、代谢状态干扰[15]。近来有研究聚焦于内皮来源的外泌体,相比于游离蛋白,外泌体携带的microRNA或蛋白质更能反映内皮细胞的特定状态,且更能抵抗血液中的降解,有望成为新兴的特异性标志物[102]。

5.2 神经影像学评估

利用MRI技术间接评估脑血管内皮的调节能力和屏障完整性。(1)脑血管反应性(cerebrovascular reactivity,CVR):利用BOLD-fMRI或ASL-MRI,配合CO_2吸入、屏气、呼吸调控等刺激,评估小血管对血管活性刺激的扩张能力。CVR直接反映脑血管储备能力,可定位受损脑区。CVR下降代表内皮依赖性舒张功能受损,其与WMH增加、皮层下梗死、步态和认知功能下降显著相关[103]。(2)BBB通透性成像:利用动态对比增强MRI(dynamic contrast enhanced MRI,DCE-MRI),测量顺磁性对比剂从血管内渗漏到血管外间隙的速率(Ktrans),是量化评估BBB内皮渗漏的金标准。CSVD患者即使在看似正常的脑白质区域,Ktrans值也已升高,提示内皮渗漏早于结构性损伤[104]。虽然DCE-MRI和CVR成像非常精准,但耗时且昂贵,难以作为大规模筛查手段。(3)多模态影像融合技术:目前研究倾向于结合CVR图谱和基于弥散张量成像的白质微结构完整性量化参数(例如各向异性分数FA及平均弥散率MD),在WMH出现之前检测内皮功能调节异常的“外观正常白质”区域[105]。

5.3 视网膜血管成像

视网膜血管与脑小血管同源。视网膜动静脉管径比、微血管瘤等改变可间接反映脑内皮状况,主要分析血管管径、分形维数、血管弯曲度,该方法快速、无创和廉价,但白内障、青光眼等眼部疾病易影响成像质量[106]。利用深度学习算法分析视网膜血管图像,预测CSVD的WMH体积、微出血和内皮功能状态,准确率正在显著提高。

6 讨论与展望

6.1 当前研究面临的主要挑战

尽管当前已明确内皮功能障碍在CSVD发病机制中居于核心地位,但由于CSVD的异质性,其发病机制仍存在诸多未知领域。如虽已知年龄增长、炎症反应、过量盐摄入、淀粉样蛋白沉积等因素可致内皮细胞损伤,然而这些因素之间的相互作用以及它们协同引发内皮细胞功能障碍的具体过程,尚未全面阐明。在CSVD的发生与发展进程中,内皮细胞与周细胞、星形胶质细胞、少突胶质细胞等神经血管单元其他组成部分之间复杂的交互作用机制,亦亟待深入探究。对发病机制认识的不足,致使难以制定出更为精准有效的治疗策略[4,5]。

此外,在不同类型的CSVD中,内皮功能障碍的表现形式和主导机制可能截然不同。如在高血压性CSVD中,血流动力学应激和氧化应激可能是主因;而在淀粉样脑血管病中,Aβ的直接毒性作用及清除障碍则更为关键。这种高度的异质性会让一

种旨在普遍修复内皮的治疗方法，可能仅对某一亚组患者有效。目前，缺乏可靠的生物标志物来精确区分这些亚型并对患者进行分层，因而难以实现精准医疗[107]。

除病理机制的复杂和异质性外，评估靶向内皮治疗的有效性也缺乏敏感且特异的终点指标。虽然MRI影像上的白质高信号体积、腔隙灶数目等是CSVD临床试验常用的替代终点，但其变化缓慢，对短期治疗干预不敏感，且与临床功能改善的关联性并非绝对。此外，临床终点如认知功能衰退、步态恶化等变化同样缓慢，且易受多种混杂因素影响。对于内皮功能本身的评价，目前尚缺乏能够直接、无创、定量评估活体人脑微血管内皮功能的技术。而外周血管的内皮功能检测能否准确反映脑微循环状态，仍存疑问[108]。

在现有的以内皮细胞相关靶点开展的治疗研究中，如何实现治疗靶点的精准性，是一个亟待解决的关键问题。一方面，由于脑小血管分布广泛且管径细小，使得药物难以精准地作用于病变部位，从而影响治疗效果。另一方面，目前的治疗靶点往往缺乏高度的特异性，在作用于病变内皮细胞的同时，可能会对正常的内皮细胞或其他组织器官产生不良影响，引发一系列副作用，严重限制了治疗药物的临床应用[109]。

6.2 未来研究方向与展望

为克服上述挑战，未来的研究应聚焦于以下几个方向。(1)多组学联合解析发病机制和定义内皮功能障碍亚型，通过整合分析基因组学、蛋白质组学、代谢组学和神经影像等多组学数据，探索靶向内皮细胞的新型致病基因、信号通路以及生物标志物，并将CSVD患者划分为基于内皮功能障碍机制的亚型，如“血脑屏障渗漏主导型”“脑血管调节失调型”“神经血管炎症亢进型”，从而为靶向疗法选择最合适的患者群体，为精准治疗提供理论支持。(2)研发高特异性、低副作用的新型内皮细胞靶向药物是未来治疗CSVD的重要方向。一方面，基于对内皮细胞功能和发病机制的深入理解，运用计算机辅助药物设计、高通量药物筛选等先进技术，筛选和设计出能够精准作用于病变内皮细胞的药物分子。另一方面，借助纳米技术、基因编辑技术等前沿科技，提高药物的疗效和安全性[110]。(3)开发复合终点与动态监测技术，将传统的影像学指标与血脑屏障通透性定量成像、脑血流灌注储备测量等更敏感的先进影像技术，以及数字化、高频次的临床评估相结合，形成能够快速、全面反映治疗效果的复合终点和多模态评估体系。探索研发新型MRI或PET探针，用于直接、无创地评估活体人脑微循环的NO生物利用度、氧化应激水平或炎症状态，为疗效评估提供最直接的证据[111]。(4)拓展非药物干预与早期预防，在出现明显影像学病变或临床症状前，对中年高血压、糖尿病患者等高危人群，前移防治关口，进行早期内皮功能筛查和干预。探索有氧运动、特定饮食模式改善脑内皮功能的具体模式，并制定出针对CSVD不同阶段的个性化、可执行的生活方式处方[112]。

以内皮细胞为目标的CSVD治疗研究至关重要。虽目前在发病机制、治疗靶点精准性和临床转化等方面面临挑战，但随着多组学联合分析、新型靶向药物研发及整合医学模式探索等不断推进，有望揭示CSVD发病的深层奥秘，开发更高效、精准、安全的治疗方法，改善患者生活质量，减轻家庭和社会负担。

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