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血脑屏障的干预措施研究进展

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【摘要】 血脑屏障（BBB）是介于血液和脑组织之间的对物质通过有选择性阻碍作用的动态界面，对维持中枢神经系统（CNS）内环境稳定起着关键作用。近年来，研究发现BBB的调节机制涉及多种因素，包括细胞间紧密连接的动态变化、信号通路的激活、神经血管单元的相互作用等。本文综述了现阶段BBB的多种临床干预措施，包括药物治疗、基因治疗、中医药干预等及其未来可能的发展，以期为神经系统疾病的治疗提供新的思路和理论依据。

【关键词】 血脑屏障；神经系统疾病；干预措施；比较

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Research progress on intervention strategies for the blood-brain barrier

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【Abstract】 The blood-brain barrier（BBB）is a dynamic interface for selective molecular trafficking between blood and brain parenchyma，playing a pivotal role in maintaining central nervous system homeostasis. Recent investigations have uncovered intricate regulatory networks governing BBB function，involving dynamic intercellular tight junction remodeling，signaling cascade activation，and multicomponent interactions within the neurovascular unit. This review systematically integrates current mechanistic understanding of BBB regulation and provides a critical evaluation of emerging interventional strategies，including nanotechnology-based drug delivery systems，gene editing，and traditional Chinese medicine formula interventions，with emphasis on their translational potential in the future. By integrating bench-to-bedside perspectives，this work aims to provide novel theoretical frameworks for developing precision therapies targeting BBB dysfunction in neurological disorders.

【Keywords】 blood-brain barrier；neurological disorders；intervention measures；comparison

Conflicts of Interest：The authors declare no conflict of interest.

血脑屏障（blood-brain barrier，BBB）自19世纪末由德国科学家Paul Ehrlich发现以来，历经百余年研究，已成为神经科学的核心研究对象。这一高度特化的结构通过多层次防御体系阻挡外

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源性毒素、病原体及炎症因子，同时精准调控氧气、葡萄糖等营养物质的运输，维持离子浓度平衡与神经信号正常传导[1,2]。然而，其高度选择性也成为脑部疾病治疗的重大障碍——多数药物因无法穿透BBB，难以在脑内达到有效治疗浓度，严重制约治疗效果。

近年来，随着材料科学、基因工程及中医药现代化研究的推进，形成了药物递送优化、物理屏障开放、基因细胞修复及中医药多靶点调节等干预策略。本文围绕上述方向展开综述，旨在整合当前研究进展，探讨现有策略的优势与局限，为BBB靶向治疗的临床转化提供参考，并展望未来发展方向。

1　药物递送策略

药物递送策略通过优化载体设计或药物结构，提升药物自身的BBB穿透能力，是目前研究最成熟、临床转化最快的干预方向。其核心思路包括“载体介导转运”与“药物结构修饰”两类，具体涵盖纳米技术、鼻内给药系统及前药策略。

1.1　纳米技术

纳米技术与材料科学的结合促进了结构与功能可定制的纳米载体发展，在增强药物跨BBB能力中发挥关键作用[3-5]。其优化策略主要包括：（1）小尺寸依赖的被动穿透与胞吞作用：纳米粒子（通常<200 nm）有助于通过BBB内皮细胞的胞吞作用（如网格蛋白介导内吞、小窝蛋白依赖内化）进入脑部[6,7]，这一特性使其成为非侵入性递送药物的理想载体。然而，该方法的效率受限于纳米粒子的尺寸、形状和表面性质，以及内皮细胞的胞吞活性。对于药物浓度要求较高的疾病（如恶性脑肿瘤）需结合其他主动靶向策略。（2）表面修饰增强血液循环稳定性：未经修饰的纳米粒子易被网状内皮系统（reticuloendothelial system，RES）识别清除，半衰期通常不足1 h，通过聚乙二醇（polyethylene glycol，PEG）修饰可形成“隐形”纳米粒子，减少蛋白质吸附和免疫识别，显著延长其体内循环时间，提高BBB穿透效率[8,9]，例如，PEG化紫杉醇纳米颗粒能够利用增强渗透与滞留（enhanced permeability and retention，EPR）效应在脑肿瘤组织中特异性富集，显著提升脑内药物浓度[10]。但长期使用PEG可能引发“加速血液清除（accelerated blood clearance，ABC）”效应，因此，需探索PEG替代修饰材料（如透明质酸、壳聚糖）。（3）受体介导的主动靶向：通过纳米粒子表面偶联特异性配体（如转铁蛋白、血管肽-2等），可激活BBB内皮细胞上的受体（如转铁蛋白受体（transferrin receptor，TfR）、低密度脂蛋白受体1（low-density lipoprotein receptor-related protein 1，LRP1）），促进主动跨膜转运，从而实现药物的精准递送[11]。例如，转铁蛋白修饰的纳米颗粒通过TfR介导的内吞作用，可显著提升药物的脑内递送效率[12-14]。

除上述基于传统纳米粒子的策略外，超小尺寸的碳点（carbon dots，CDs，<10 nm）因生物相容性优异、表面可功能化及兼具载药与成像能力，成为近年研究热点。其可通过被动扩散（尺寸优势）或主动靶向修饰转铁蛋白（transferrin，Tf）、精氨酸-甘氨酸-天冬氨酸肽（arginine-glycine-aspartate peptide，RGD）高效入脑，例如载有姜黄素的CDs在阿尔茨海默病小鼠模型中，可同时实现β淀粉样蛋白清除与脑内荧光成像[15-17]。然而，CDs的长期毒性、代谢途径以及对神经系统的潜在影响仍需深入研究。

1.2　鼻内给药

鼻内给药作为非侵入性方式[18,19]，可通过嗅神经与三叉神经途径直接递送药物至中枢神经系统[20]，绕开BBB并降低外周副作用[21,22]。提高药物在鼻腔黏膜的滞留时间是增强效率的关键。近年来，鼻内给药系统不断优化中，纳米载体（纳米乳、脂质体等）因粒径小、生物相容性好，通过增强鼻黏膜渗透性促进吸收[23-25]；原位凝胶（*in situ* forming gel，ISG）系统在鼻腔内形成凝胶，延长药物与黏膜接触时间，如载有葛根素的温度敏感型原位凝胶与脂质纳米颗粒联用，可通过“凝胶滞留+纳米颗粒渗透”协同效应，提高药物脑内生物利用度[20,26-28]。壳聚糖等黏膜黏附性聚合物可延长药物作用时间，如合成胰岛素壳聚糖纳米颗粒（粒径165.3 nm）展现出良好的黏膜黏附性与生物相容性[21,29]。

此外，鼻内递送系统因能激活局部及系统免疫反应，在疫苗领域也具有广泛应用前景，研究表明，鼻内递送的RBD疫苗能够有效激发系统性和黏膜免疫，显示出良好的应用前景[22]。

1.3　前药策略

前药策略是通过化学修饰使药物进入体内后转化为活性形式，改善药代动力学性质与 BBB 通透性，实现靶向递送的新型给药策略[30-32]。

传统设计中，小分子配体修饰优势显著。首先靶向转运体介导，如多巴胺与氨基酸通过酰胺键连接的前药，可特异性结合 BBB 内皮细胞高表达的 L 型氨基酸转运 1（L-type amino acid transporter 1，LAT1），借助其跨膜功能跨越 BBB，在脑内特定酶系作用下释放活性成分，提升帕金森病治疗药物的脑内浓度[32-34]；其次抑制外排泵与结构优化，阿巴卡韦二聚体前药通过结构改造抑制 P-糖蛋白（P-glycoprotein，P-gp）外排，在细胞还原环境下裂解为单体，恢复抗病毒活性[35]；此外，MMP-9 抑制剂 ND-478 的体内代谢产物 ND-322 和 ND-364，因结构改变获得更优亲脂性与转运特性，从而实现在脑组织的有效分布[36]。

纳米前药与载体结合为脑部递送开辟了新方向，如 PLX038A（PEG 化 SN-38）通过 40 kDa PEG 与喜树碱衍生物偶联形成纳米复合物，该复合物能够利用 EPR 效应在脑肿瘤组织特异性积累，经酶促或非酶促反应释放活性药物，抑制颅内乳腺癌和胶质母细胞瘤生长[37,38]；此外，利用间充质干细胞（mesenchymal stem cells，MSCs）外泌体作为载体，携带 5-氟胞嘧啶（5-fluorocytosine，5-FC）并使其在肿瘤细胞内转化为细胞毒性 5-FU，也是实现靶向治疗的创新途径[39]。

然而，前药的非特异性分布、长期毒性及代谢调控仍是临床转化的难点。未来需结合化学生物学与纳米技术，优化药物设计以提升效率、降低不良反应。

2　物理干预方法

药物递送策略通过“载体优化”提升药物跨 BBB 能力，而物理干预方法则通过“可逆性开放屏障”为药物入脑创造通道，主要包括超声介导、磁共振引导聚焦超声、渗透压冲击等。

2.1　超声介导的 BBB 开放

该技术基于机械效应，通过低频超声（0.2~2 MHz）使细胞间紧密连接短暂解离，形成药物通道[40]。聚焦超声（focused ultrasound，FUS）作为一种非侵入性的技术，近年来在 BBB 开放领域备受瞩目[41,42]，高强度聚焦超声（high-intensity focused ultrasound，HIFU）利用热效应或空化效应消融肿瘤[43]；低强度 FUS 联合微泡技术通过微泡振荡、膨胀与破裂增强空化效应，促使紧密连接蛋白短暂分离，实现非损伤性、可逆性开放[44-47]。

该技术时空可控，可局部靶向开放 BBB，对脑组织损伤小。动物实验已证实，其可使 BBB 通透性提高数倍，有效促进 siRNA 递送和肿瘤部位药物蓄积[48]；临床研究也表明，该技术能有效增加脑肿瘤组织化疗药物浓度，且未观察到明显的长期副作用[44,49,50]。但超声参数（频率、强度等）与微泡特性（浓度、粒径等）对效果与安全性影响显著，需系统优化。

2.2　磁共振引导的聚焦超声

磁共振引导的聚焦超声（magnetic resonance-guided focused ultrasound，MRgFUS）整合了磁共振成像（magnetic resonance imaging，MRI）的高分辨率定位与 FUS 的非侵入性开放优势[51,52]。与非引导性超声技术相比，MRgFUS 的优点在于通过 MRI 能够实时监测超声能量在脑内的分布、BBB 的开放程度以及药物的递送过程，从而实现对整个治疗过程的精准调控[53,54]，这使得 MRgFUS 能够靶向脑部特定区域，将亲水性药物特异性地输送至靶组织，显著提升了药物递送的精准度和效率，并有效降低非靶向效应和潜在的副作用[55]。然而，该技术设备成本高、操作复杂，且 MRI 环境对超声设备存在兼容性限制，制约临床普及。

2.3　渗透压冲击

渗透压冲击方法通过静脉注射高渗溶液（如甘露醇）升高血液渗透压，使 BBB 内皮细胞脱水皱缩，紧密连接短暂扩张，形成药物通道[56,57]。该方法操作简便，曾用于辅助治疗脑部疾病，但开放 BBB 缺乏靶向性，可能引发全身性渗透压改变与水电解质失衡，反复使用易损伤内皮细胞，仅适用于特定情况，且需密切监测患者的全身状况，目前临床应用减少。

2.4　电穿孔技术

电穿孔技术通过脑部电极施加短暂高电场脉冲，使 BBB 内皮细胞膜产生可逆性纳米孔洞，增加通透性，促进药物跨膜运输[58,59]。其可精准控制开放区域，适用于小分子药物与基因治疗载

体递送,近年研究在参数优化上取得进展,例如采用高频不可逆电穿孔(high-frequency irreversible electroporation,H-FIRE)模式(如 500 ns 脉冲,600 V/cm)可显著减轻组织肌肉收缩与热损伤,同时通过调节细胞骨架重塑和紧密连接蛋白(tight junction proteins,TJPs)的再分布,实现更可控的 BBB 开放[60],但电场参数控制不当可能导致热损伤或不可逆电损伤[61],目前仍处于临床前研究阶段。

2.5　磁场引导

磁场引导是一种利用纳米粒子表面修饰磁性材料,在外加磁场作用下,引导药物跨越 BBB 进入脑内特定靶组织的新型药物递送技术[62]。该方法通过将治疗药物(如抗肿瘤药物多柔比星)装载到磁性纳米粒子(如磁性氧化石墨烯纳米粒)上,利用外部磁场精准控制纳米粒子的运动轨迹,使其在脑内靶区富集,从而显著提高局部药物浓度,减少全身暴露及副作用。动物实验显示,该技术可提升脑内药物浓度,并显著延长胶质瘤模型大鼠的生存期[62]。然而,该技术仍面临磁性纳米粒子生物相容性、长期安全性、跨膜效率等科学问题,磁场强度与分布的优化也存在挑战,其临床转化仍面临严峻挑战。

3　基因治疗与细胞治疗

基因与细胞治疗作为前沿技术,在 BBB 干预中展现独特优势,全球已有数千项基因治疗临床试验,多项基因和细胞治疗产品已获 FDA 及其他监管机构批准上市,标志其正加速向临床转化[63]。

3.1　病毒载体基因治疗

腺相关病毒(adeno-associated virus,AAV)、腺病毒和慢病毒经改造后可作为外源基因载体[64]。其中 AAV 因低免疫原性与优异 BBB 穿透能力,成为神经系统疾病首选工具[65,66]。例如,AAV 递送 CRISPR/Cas9 系统可编辑 BBB 相关基因,改善屏障功能[67];携带脆性 X 智力低下蛋白亚型的单链 AAV 载体,可纠正脆性 X 综合征小鼠的行为异常[68]。

但免疫毒性、脱靶效应与肝毒性制约病毒载体发展[69]。CRISPR/Cas9 对 PAM 位点的非特异性识别可能导致基因组意外切割;病毒载体引发的免疫反应不仅影响疗效,还可能损伤肝功能[70]。目前研究正聚焦高特异性载体(如高保真 Cas9 变体 eSpCas9)与新型纳米递送系统,通过优化给药方案提升安全性与有效性。

3.2　干细胞移植

干细胞可在微环境诱导下分化为血管内皮细胞、神经胶质细胞等,参与 BBB 修复与重建。MSCs 因来源广泛(骨髓、脐带等)、低免疫原性及多向分化能力成为研究焦点。卒中动物模型与初步临床试验显示,动脉内给药的 MSCs 可靶向迁移至缺血脑组织,分化为血管内皮细胞修复 BBB,改善神经功能[71,72];人羊膜间充质干细胞(human amniotic mesenchymal stem cells,hAMSCs)静脉注射可剂量依赖性减轻脑梗死小鼠神经功能缺损,机制涉及抑制促炎因子释放、减少 BBB 破坏及凋亡[73]。

为提升干细胞脑内滞留效率,研究将聚焦超声介导的 BBB 破坏(blood-brain barrier disruption,BBBD)与磁靶向结合,通过超顺磁性氧化铁纳米颗粒(superparamagnetic iron oxide nanoparticles,SPIONs)负载人神经祖细胞(human neural progenitor cells,hNPCs),在 FUS 开放 BBB 后,外部磁场可有效吸引细胞,提高其在脑内的富集[74]。但 MSCs 治疗机制、移植细胞命运及与 BBB 的动态互作仍需深入研究,以推动临床转化。

3.3　外泌体

外泌体作为纳米级细胞外囊泡,通过携带核酸、蛋白质等信号分子调控靶细胞行为,为改善 BBB 损伤提供新思路[75,76]。当前研究重点已转向“工程化外泌体”,通过表面修饰靶向配体(如 RGD 肽、TfR 抗体)可显著提升其脑内递送效率。例如,装载 siRNA 的 RVG 肽(靶向乙酰胆碱受体)修饰的外泌体,在阿尔茨海默病小鼠模型中显示出高效的基因沉默效应[77];缺血性脑卒中研究中,健康大鼠血清外泌体可减轻 BBB 损伤[78];人参来源的外泌体样纳米颗粒(ginseng-derived exosome-like nanoparticles,GELNs)可靶向 BBB 与肿瘤组织,募集 M1 型巨噬细胞,抑制神经胶质瘤生长[79]。此外,外泌体因高生物屏障穿透性,成为极具潜力的药物递送载体,有望突破 BBB 实现胶质母细胞瘤高效治疗[80]。

4　中医药干预策略

中医药在神经系统疾病防治中历史悠久,其干预 BBB 的策略日益受关注,包括活血化瘀、补益、芳香开窍类中药及针灸等方法。

4.1　活血化瘀类中药对 BBB 功能的调控

丹参、川芎等活血化瘀中药的活性成分(丹参酮、川芎嗪等)可改善脑循环,调节 BBB 通透性[81,82]。川芎嗪通过抑制 BBB 内皮细胞 P-gp 的表达与功能,减少药物外排,提高脑内浓度[83],其分子机制研究揭示,川芎嗪可下调 NF-κB 信号通路的活化,减少 P-gp 的转录,同时可能影响蛋白激酶 C(protein kinase C,PKC)的活性,从而在转运体层面改善 BBB 的通透性。纳米技术也为活血化瘀中药干预 BBB 提供了新的策略,研究显示纳米中药可以将活性成分递送到靶向脑区,提高疗效[84]。

4.2　补益类中药对 BBB 功能的保护

研究表明,某些补气养血类中药可能通过改善脑部微循环,增强脑组织供氧,间接维护 BBB 的完整性。如人参、黄芪等,能够通过调节神经内分泌免疫网络,增强 BBB 的稳定性和功能[85]。人参皂苷 Rg1 可促进 BBB 内皮细胞的增殖和迁移,增强细胞间的紧密连接,研究证实此作用与激活 Akt/ERK 信号通路,进而上调闭锁小带蛋白-1(zonula occludens-1,ZO-1)和 Occludin 的表达密切相关。同时调节相关信号通路,提高 BBB 对营养物质的转运能力[86],为神经细胞提供良好的微环境[87]。虽然直接针对补益类中药影响 BBB 的深入研究相对较少,但现有证据表明,它们可能通过改善脑部整体环境,间接发挥保护 BBB 的作用。研究提示,中医药可能通过多靶点、多途径的方式,对包括 BBB 在内的复杂生理系统产生积极影响[88]。

4.3　芳香开窍类中药对 BBB 的双向调控

芳香开窍类中药具有双向调控 BBB 的潜力[89]。一方面,某些芳香开窍类中药能够增强药物透过 BBB 的能力,提高药物的脑部利用率,例如冰片可打开紧密连接增强 BBB 通透性,与脑缺血治疗药物联用,可增加药物脑内分布[90];另一方面,芳香开窍类中药可通过调节紧密连接蛋白的表达和功能,发挥保护 BBB 的作用,例如芳香开窍类中药能够上调紧密连接蛋白 Claudin-5 和 Occludin 的表达,增强 BBB 的紧密连接,从而在一定程度上保护 BBB 的完整性[91]。但其分子机制(如靶点、信号通路、剂量-效应关系)仍需深入研究。

此外,一些复方中药也被发现对 BBB 具有调节作用。补阳还五汤可促进血管内皮细胞增殖修复,增加紧密连接蛋白表达,调节细胞因子水平以抑制炎症、减少 BBB 破坏[92],临床用于缺血性脑卒中改善神经功能,但复方成分复杂,作用机制、有效成分鉴定及质量控制仍面临挑战。

4.4　针灸对 BBB 的动态调控

除了中药单体和复方,针灸作为中医药的另一重要组成部分,近年来在 BBB 干预方面也展现出潜力。动物实验显示,针灸可以通过调节多种信号通路和分子机制来影响 BBB 的通透性及功能[93-95]。

针对脑出血等急性脑损伤,针灸可靶向抑制关键损伤信号通路。脑出血大鼠接受“百会”透“曲鬓”头皮针治疗后,通过抑制 RhoA/ROCK Ⅱ/MLC 2 通路,上调紧密连接蛋白表达,降低 BBB 通透性,促进神经功能恢复[96];醒脑开窍针刺疗法可通过调节自噬-凋亡平衡,有效抑制 BBB 破坏,延长缺血性卒中溶栓治疗的时间窗[97]。在脑缺血再灌注(cerebral ischemia-reperfusion,I/R)损伤模型中,针灸展现出显著的抗氧化应激与抗炎特性,电针预处理通过双重机制减轻氧化应激损伤:一方面抑制 NADPH 氧化酶 4(NADPH oxidase 4,NOX4)表达,减少活性氧(reactive oxygen species,ROS)生成;另一方面降低炎症因子 TNF-α 和 IL-1β 水平,减轻 I/R 后的 BBB 破坏和脑水肿[98]。值得注意的是,电针百会、人中穴位可选择性增加 BBB 通透性而不诱发脑水肿,这种可控性开放效应为神经生长因子等靶向药物递送提供了新思路[99]。

针灸对 BBB 的调节作用还延伸至肠-脑轴,针灸可通过调节肠道菌群(如增加双歧杆菌、减少大肠杆菌等),从而减少脂多糖(lipopolysaccharide,LPS)的生成。LPS 作为一种病原相关分子模式,可通过激活 BBB 内皮细胞上的 Toll 样受体 4(Toll-like receptor 4,TLR4),进一步活化 NF-κB 信号通路,诱导炎症因子释放并破

坏紧密连接进而破坏 BBB 功能,针灸通过上述机制可减轻阿尔茨海默病模型小鼠的 BBB 功能障碍[100]。

综上,针灸对 BBB 的调节呈现多通路、动态化的特点,其既可通过抑制损伤信号通路、抗氧化抗炎减轻病理状态下的 BBB 破坏,又能通过调节肠-脑轴实现系统性功能改善;同时,在疾病恢复期还可适度提升 BBB 通透性,辅助靶向药物递送。这种兼具治疗与辅助给药双重潜力的特性,为中枢神经系统疾病的综合治疗提供了新思路,也彰显了针灸在现代神经医学领域的应用前景。

5　不同干预措施的比较

各种干预措施并非孤立,其在靶向性、药物类型、临床转化阶段、成本与可操作性等方面各有优劣,为临床选择提供依据(表 1)。

首先,在靶向性方面,药物递送策略和物理干预方法均可实现高度局部化的药物释放,从而在靶向性上优于传统的全身给药方法。纳米技术结合受体介导的主动靶向策略,可针对特定脑

表 1　血脑屏障主要干预措施比较

Table 1　Comparison of major intervention strategies for the blood-brain barrier

干预类别 Category	核心机制 Core mechanism	靶向性 Targeting	主要适用药物类型 Major applicable drug types	临床转化阶段 Clinical translation stage	优势 Advantages	风险与挑战 Risks & challenges
纳米技术 Nanotechnology	胞吞、受体介导转运 Endocytosis, receptor-mediated transcytosis	中-高(取决于修饰) Medium-high (depends on modification)	小分子、核酸、蛋白 Small molecules, nucleic acids, proteins	临床前/早期临床 Preclinical /early clinical	载药多样,可多功能化 Versatile drug loading, multi-functionalization	长期生物安全性、潜在毒性 Long-term biosafety, potential toxicity
鼻内给药 Intranasal administration	沿神经通路绕过 BBB Bypassing BBB via neural pathways	低(嗅球/脑干富集) Low (enriched in olfactory bulb/brainstem)	小分子、肽类 Small molecules, peptides	临床阶段 Clinical stage	非侵入、便捷、起效相对快 Non-invasive, convenient, relatively rapid onset	剂量受限、黏膜清除 Limited dosage, mucosal clearance
聚焦超声联合微泡 FUS+MB	声空化效应暂时开放紧密连接 Transient tight junction opening via sonoporation	高(可精准定位) High (precise localization possible)	大分子、抗体、核酸 Macromolecules, antibodies, nucleic acids	临床阶段 Clinical stage	时空可控、可逆、开放程度强 Spatiotemporally controllable, reversible, strong opening effect	设备昂贵,需精确参数控制 Expensive equipment, requires precise parameter control
磁共振引导的聚焦超声 MRgFUS	同聚焦超声联合微泡,但由 MRI 实时引导 Same as FUS + MB, but guided by real-time MRI	极高 Very high	大分子、抗体、核酸 Macromolecules, antibodies, nucleic acids	临床阶段 Clinical stage	精准度最高,可实时监控 Highest precision, real-time monitoring	成本极高,操作复杂 Extremely high cost, complex operation
针灸 Acupuncture	多通路调节(抗炎、抗氧化等) Multi-pathway regulation (anti-inflammatory, antioxidant, etc.)	中(穴位特异性) Medium (acupoint-specific)	辅助增强其他药物 Adjuvant enhancement of other drugs	临床实践/机制探索 Clinical practice/ mechanism exploration	整体调节、安全性高 Holistic regulation, high safety	机制复杂,标准化难 Complex mechanisms, difficult standardization
外泌体 Exosomes	天然/工程化靶向递送 Natural/engineered targeted delivery	高(可工程化) High (engineerable)	核酸、小分子、蛋白 Nucleic acids, small molecules, proteins	临床前 Preclinical	生物相容性好,天然归巢能力 Excellent biocompatibility, natural homing ability	规模化生产、质量控制 Scalable production, quality control

区进行精准药物递送。

在适用药物类型方面,药物递送策略尤其适用于小分子药物,并通过前药策略改善其药代动力学特征及 BBB 通透性。物理干预方法如 FUS 和电穿孔技术,能有效提升多种药物(包括基因治疗载体)的跨膜效率。基因治疗与细胞治疗技术则更适用于大分子生物制剂,利用病毒载体和干细胞实现特定基因组的编辑或促进 BBB 修复。

在临床转化阶段,各策略的发展程度不尽相同。纳米递送技术已在临床前实验中取得积极成果,但尚需克服长期毒性与代谢相关问题,而物理干预方法如 FUS 已进入临床试验,其设备成本和操作复杂性在一定程度上阻碍了广泛应用。基因和细胞治疗策略虽然展现良好前景,但免疫毒性与脱靶效应仍须进一步优化。

在设备成本和定位精度方面,MRgFUS 和 FUS 占据优势,可根据实时成像调整治疗范围,但设备昂贵且操作复杂,可能限制其在资源有限医疗环境中的普及。电穿孔技术设备简单,成本较低,但其风险控制仍是发展瓶颈。

对于适用疾病,药物递送策略适合慢性疾病的长期治疗,且在恶性脑肿瘤等高浓度药物需求的病况中表现出色。而物理干预和基因、细胞治疗方法更适合急性或进行性疾病的干预,比如缺血性卒中或神经退行性疾病中的 BBB 功能恢复。

在可逆性和安全性评估中,物理干预方法中的电穿孔和高渗透压冲击存在安全隐患,可能引发组织损伤或全身性电解质失衡,仅适用于特定场景。而 FUS 联合微泡技术则显示出良好的可逆性和安全性,具有进一步临床探索的价值。

6　总结与展望

尽管目前在 BBB 的调节机制与干预措施方面取得了一定研究进展,但仍面临诸多挑战。现有体外细胞模型、离体灌注模型以及动物模型均存在局限性,难以完全模拟体内 BBB 的复杂结构和生理功能。此外,许多干预措施的安全性和有效性仍有待进一步提高。一些物理干预方法,如聚焦超声联合微泡技术(microbubble-enhanced focused ultrasound,FUS+MB)、电穿孔技术等,虽然能够暂时打开 BBB,促进药物递送,但可能对脑组织造成一定损伤,引起局部炎症反应、神经细胞凋亡等。在药物递送策略中,纳米粒子等载体虽然能够提高药物的脑内递送效率,但其长期安全性和潜在毒性仍不明确,部分纳米粒子可能会在体内蓄积,对肝、脾等器官造成损害。基因治疗和细胞治疗在 BBB 调节中具有广阔的应用前景,但目前仍面临基因编辑的脱靶效应、免疫原性以及干细胞的分化调控等问题,影响其治疗效果。

针对上述挑战,未来研究应分阶段推进:在基础研究层面,应致力于优化 BBB 模型,使其更贴近体内生理环境;在临床转化层面,则需着重提升现有干预措施的安全性和有效性。具体而言,在干预措施研究方面,未来可从以下方向突破:首先,优化纳米技术是重要方向,通过对纳米粒子的表面修饰和结构设计,降低其免疫原性和毒性,提高靶向性和稳定性;其次,改进基因编辑技术,减少脱靶效应,提高基因编辑的准确性和安全性。基于单细胞测序技术,解析 BBB 细胞亚群在疾病中的特异性变化,开发条件性基因编辑策略。此外,加强对干细胞分化调控的研究,提高干细胞治疗的效果和安全性。将药物递送策略与物理干预方法相结合,或者将基因治疗与细胞治疗相结合,以实现对 BBB 的精准调控和疾病的有效治疗,形成联合治疗策略。综合运用现代生物技术、纳米技术、影像学技术等,有望在 BBB 研究领域取得更大的突破,为治疗脑部疾病带来新的希望,改善患者的预后和生活质量,推动神经科学和医学的发展。

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