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基于壳聚糖的纳米药物在脑部疾病治疗中的应用

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摘要 血脑屏障作为中枢神经系统和外周血液循环之间的生理屏障, 严格阻挡微生物、毒素、炎症因子和抗体等异物通过血液循环进入大脑, 充当大脑的“安全卫士”, 对维持中枢神经系统正常生理状态具有重要的生物学意义. 然而, 血脑屏障的存在也限制了小分子药物、大分子物质等治疗性药物的通过, 阻碍了脑部疾病的治疗. 研究发现, 纳米材料因具有尺寸小、比表面积大、易于修饰等独特优势, 容易透过血脑屏障, 常被应用于脑部药物递送. 壳聚糖作为最常见的多糖聚合物, 具有生物可降解性、生物相容性、低免疫原性、无毒、黏膜黏附性等生物学特性, 常被用来作为纳米药物递送载体. 然而, 壳聚糖不溶于水和大多数有机溶剂, 限制了其应用范围. 对壳聚糖进行磷酸化、羧甲基化、季铵化等不同修饰, 不仅可以改变其溶解性, 还赋予其止血、抗菌等新性能, 进而扩展了其应用范围. 本文主要综述了基于壳聚糖及其衍生物的纳米载体在神经胶质瘤、阿尔茨海默病、帕金森综合征、缺血性脑中风、创伤性脑损伤疾病治疗中的应用, 为脑部疾病治疗的药物递送方案提供了思路.

关键词 壳聚糖, 壳聚糖衍生物, 血脑屏障, 纳米药物, 脑部疾病

血脑屏障(blood brain barrier, BBB)是大脑实质与外周循环系统间的一道天然保护屏障, 主要由脑微血管内皮细胞(brain microvascular endothelial cell, BMEC)、周细胞、星形胶质细胞和基底膜组成[1]. BMEC之间形成的紧密连接仅允许特定类型的小分子从血流进入大脑神经元和其他周围细胞, 限制病原体、亲水性大分子等物质的通过, 在维持脑组织内微环境稳态中发挥了重要作用[2]. 然而, BBB的存在也限制了大多数小分子药物和大分子(例如肽、蛋白质和基于基因的药物)的通过, 严重阻碍了脑部疾病(例如神经退行性疾病、脑肿瘤、脑部感染和缺血性脑中风等)的治疗[3]. 近年来, 纳米技术的发展为脑部疾病带来了有效的诊断和治疗方法. 在协助治疗性生物分子向大脑的转运方面, 已经广泛探索了多种纳米材料, 例如多糖纳米材料、无机纳米材料和生物膜纳米材料等[4,5]. 这些纳米材料因具有尺寸小、比表面积大、可穿透BBB、易于修饰、吸附能力强、可控释放等独特优势而被广泛应用于脑部药物递送体系[6,7]. 目前应用于脑部疾病治疗的纳米载体有很多种, 如聚乳酸-羟基乙酸共聚物(poly(lactic-co-glycolic acid), PLGA)、脂质体, 虽然它们可以穿透血脑屏障, 但其同时又具有炎症风险高、修饰过程复杂等局限性, 限制了它们在临床治疗中的应用[8,9].

壳聚糖(chitosan, CS)是由甲壳素脱乙酰化得到的天然多糖聚合物, 由N-乙酰氨基葡萄糖和D-氨基葡萄糖随机排列, 并通过β-1,4-糖苷键连接而成, 具有生物可降解性好、生物相容性高、免疫原性低、无毒等生物学特性, 常被用于药物递送载体[10]. 不仅如此, 与

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PLGA、脂质体等纳米载体相比, 壳聚糖化学结构中的三种活性基团: 氨基、C-3和C-6位置的伯羟基和仲羟基的存在, 使化学修饰更为简单, 扩大了其应用范围[11]. 例如, 吴德成等人[12]基于磷酸化壳聚糖开发的一种新型原位注射和自愈合止血水凝胶, 能够显著增强红细胞黏附/聚集和凝血能力, 从而加速止血. 季铵化的壳聚糖水溶性大幅提高, 通过席夫碱反应和氧化葡聚糖交联形成的水凝胶骨架常被用于抗菌治疗, 还赋予了其对抗耐药细菌的能力[13]. 羧甲基化壳聚糖和氧化海藻酸钠交联制备的双组分原位水凝胶可以应用于促进黏膜修复和伤口闭合方面[14]. 化学改性不仅可以改善壳聚糖的理化性质, 还赋予其独特性能, 扩大了壳聚糖在生物医学中的应用范围[15].

作为一种阳离子多糖, 壳聚糖可以通过带正电荷的氨基与血管内皮细胞表面和BBB基底膜处的阴离子发生静电相互作用, 从而依靠吸附介导的胞吞作用(adsorptive-mediated transcytosis, AMT)穿透BBB并进入脑实质[16]. 同时, 壳聚糖还可以通过瞬时打开上皮细胞中的紧密连接来影响膜的通透性[17]. 壳聚糖的黏膜特性、打开紧密连接的能力及在壳聚糖表面进行修饰如RVG肽化、转铁蛋白修饰等, 都可以使基于壳聚糖的纳米药物高效透过BBB[16,18]. 本文主要综述了基于壳聚糖的纳米药物在脑部疾病—神经胶质瘤、阿尔茨海默病、帕金森综合征、缺血性脑中风、创伤性脑损伤治疗中的应用, 并讨论了未来需要解决的问题及研究方向.

1 壳聚糖及其衍生物在神经胶质瘤治疗中的应用

神经胶质瘤是颅内最常见的原发脑肿瘤, 具有侵袭性高、易复发、死亡率高等特点, 严重危害人类生命健康[19]. 目前, 神经胶质瘤的发病机制尚不明确, 传统的手术治疗、化疗和放疗虽然部分缓解胶质瘤的症状, 但治疗效果不尽如人意, 同时存在不良耐药性、复发和转移等风险[20]. 此外, BBB的存在也限制了多种胶质瘤化疗药物深入肿瘤病灶部位发挥作用. 因此, 研究可穿透BBB且可以将药物高效、稳定地递送至胶质瘤细胞的方法对神经胶质瘤的治疗和缓解尤为重要.

卡莫司汀是一种亚硝基脲类药物, 可以使细胞内的DNA烷基化从而造成细胞死亡. 与游离的卡莫司汀相比, 壳聚糖包被的PLGA纳米颗粒(PLGA-chitosan nanoparticle, PLGA-CS NP)可以显著提高卡莫司汀的入脑效率, 增强对神经胶质瘤细胞的杀伤作用[21]. PLGA-CS NP还可以负载紫杉醇和R-氟比洛芬, 对神经胶质瘤表现出更高的治疗活性[22]. 脯氨酰4-羟化酶亚基α1 (prolyl 4-hydroxylase subunit alpha 1, P4HA1)通过调节上皮-间质转化促进神经胶质瘤侵袭. 壳聚糖-明胶纳米微球通过静电相互作用包载P4HA1 siRNA, 显著抑制胶质瘤细胞的增殖、迁移、侵袭和促进血管再生[23]. 在C6神经胶质瘤细胞中, 负载水飞蓟宾的壳聚糖纳米颗粒(silibinin chitosan nanoparticle, SCNP)通过增加caspase3和bax促凋亡基因的表达, 诱导神经胶质瘤细胞凋亡(图1)[24]. 此外, 壳聚糖不溶于水的特性限制了其生物学应用范围. 将壳聚糖溶于HCl溶液并通过透析、冻干等步骤获得的水溶性壳聚糖, 通过包载具有强大抗氧化特性和促进神经元再生能力的葫芦巴碱制备的纳米颗粒(Trigonelline chitosan nanoparticle, Trigo-WSCS-NP), 显著抑制C6神经胶质瘤细胞的生长, 促进PC12细胞的神经突生长[25]. 基于聚酰胺树枝状聚合物和壳聚糖组成的纳米制剂可将替莫唑胺递送至胶质瘤细胞. 这种递送方法使药物在大脑中的浓度比单独使用替莫唑胺增加了一倍[26,27]. 基于壳聚糖的纳米载体还可以向神经胶质瘤细胞递送具有神经保护作用的生物活性化合物丁香酚. 负载丁香酚的壳聚糖纳米颗粒能够抑制NF-κB的表达, 减少基质金属蛋白酶表达, 降低血管内皮生长因子表达, 对C6神经胶质瘤细胞表现出促凋亡、自噬和抗转移作用[27,28].

多种神经胶质瘤化疗药物如DNA烷基化药物、siRNA等通过负载到壳聚糖纳米载体中, 获得更高的入脑效率, 表现出更高的细胞毒性作用, 为脑胶质瘤治疗提供潜在方法. 然而, 目前这些研究仍存在一些局限性. 多数研究集中在体外细胞实验和动物模型阶段, 临床转化面临挑战. 药物在肿瘤组织中的分布均匀性和深度穿透性仍有待提高, 且不同药物负载的壳聚糖纳米颗粒的最佳配方和给药方案尚未完全明确. 未来需要进一步开展大样本、多中心的临床研究, 优化纳米药物的设计, 以推动其向临床应用的转化.

2 壳聚糖及其衍生物在阿尔茨海默病治疗中的应用

阿尔茨海默病(Alzheimer's disease, AD)是一种起病隐匿、呈进行性发展的神经退行性疾病, 其主要特征是进行性记忆丧失和认知能力缺陷. 2019年, 全球有超过5000万人受到AD的影响, 预计到2050年将达到

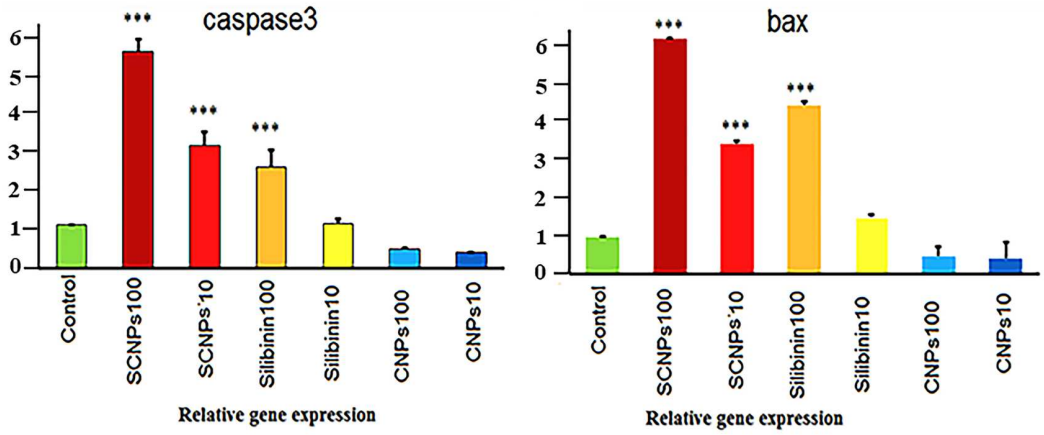

图 1 (网络版彩色)SCNPs增加caspase3和bax促凋亡基因的表达, 诱导神经胶质瘤细胞凋亡[24]
Figure 1 (Color online) SCNPs increase the expression of bax and caspase3 pro-apoptosis genes, and induce the apoptosis of glioma cells[24]

1.52亿[29]. AD的病理特征主要是β-淀粉样蛋白(amyloid β-protein, Aβ)组成的神经炎性斑块堆积、微管相关蛋白tau蛋白的过度磷酸化导致的细胞内神经元纤维缠结, 以及神经元丢失[30,31]. 因此, 抑制Aβ的沉积和降低tau蛋白的磷酸化水平是AD的潜在治疗方法.

据报道, 壳聚糖自身具有抗神经炎症、抗氧化活性、抑制Aβ分泌酶和神经保护等作用[32]. 作为药物载体, 壳聚糖可以在分子水平上透过BBB将生物活性物质转运到神经细胞. AD中超磷酸化tau蛋白的积累会导致线粒体功能障碍和活性氧ROS产生[33]. 黑磷(black phosphorus, BP)常被用作药物载体和抗氧化剂, 与tau聚集抑制剂亚甲基蓝(methylthionine, MB)结合, 制备的BP-MB可以减少ROS的产生和tau蛋白的聚集. Liu等人[34]通过交联羧甲基壳聚糖和醛基Pluronic F127微胶束, 制备了一种热敏水凝胶. 将BP-MB纳米复合物纳入水凝胶中, 得到了BP-MB@Gel(图2). BP-MB@Gel可有效抑制tau蛋白的病理性聚集、恢复线粒体功能以及减轻神经炎症, 最终改善认知功能. 这一研究为构建用于治疗具有复杂病理的AD的脑靶向药物递送系统提供了一个新的策略.

白藜芦醇(resveratrol, Res)是一种常见的天然多酚, 具有抗氧化、抗炎、抗糖尿病等特性, 表明它可能会有效对抗AD中的炎症和氧化应激[35]. 然而, Res几乎不溶于水, 且在胃肠道中不稳定, 导致其具有较差的吸收效率和较低的体内生物活性. 硒纳米颗粒(selenium nanoparticles, SeNP)可以提高Res的生物活性, 但是其BBB转运效率较差, 限制了Res在体内的应用[36,37]. 壳聚糖中带正电荷的氨基与带负电荷的三聚磷酸钠交联形成的纳米颗粒, 封装Res可以增强药物的稳定性和入脑效率, 通过JNK/AKT/GSK3β信号通路进一步抑制Aβ聚集和Tau蛋白磷酸化, 显著增强了AD小鼠的认知能力[38].

壳聚糖包被PLGA纳米颗粒与抗Aβ抗体偶联制备的免疫纳米载体, 可靶向沉积的Aβ蛋白以缓解AD进展. 相较于裸露的PLGA-NPs, 壳聚糖包被修饰提升了免疫纳米材料穿透BBB和被神经细胞摄取的效率. 此外, 冻干虽可延长纳米载体制剂保质期, 但无冷冻保护剂时, 会使纳米载体表面偶联的抗体变性, 引发纳米载体聚集与药物泄漏. 而壳聚糖可充当冷冻保护剂, 有效地保留了与免疫纳米载体表面偶联的抗Aβ抗体的完整性[39].

姜黄素具有抗淀粉样变性、抗炎、抗氧化、金属螯合特性, 具有潜在的神经保护作用[40,41]. 然而, 姜黄素的稳定性和生物利用度差以及BBB的存在限制了姜黄素在AD治疗中的应用[42,43]. 研究发现, 以壳聚糖和牛血清蛋白(bovine serum albumin, BSA)制备的CS-BSA纳米载体提高了姜黄素的BBB渗透能力, 并且通过抑制M1型巨噬细胞极化和阻断TLR4-MAPK/NF-κB信号通路表现出抗炎和神经保护作用[44]. 除姜黄素外, 还有多种抗炎、抗氧化、抗胆碱酯酶类发挥神经保护作用的小分子药物如胡椒碱、藏红花素、氢溴酸加兰他敏等, 可经壳聚糖递送至大脑, 用于缓解神经炎症、延缓AD进展[45~47].

基因疗法在AD治疗方面也崭露头角. 有研究提出

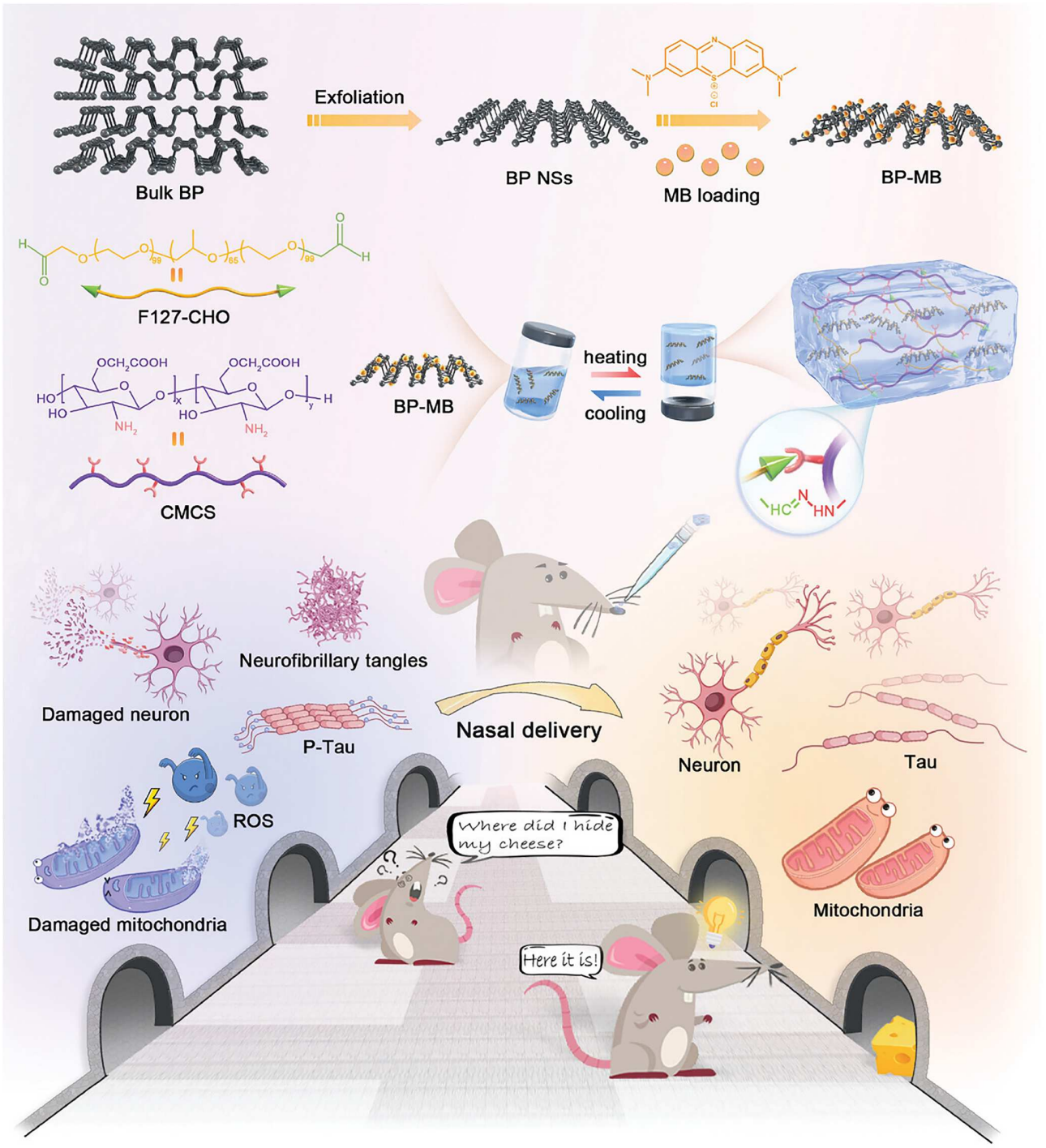

图 2 (网络版彩色)BP-MB@Gel制备及其改善AD病理学中应用的示意图[34]

Figure 2 (Color online) Schematic overview of the preparation of BP-MB@Gel and its application for improving AD pathology[34]

改变参与AD病理生理学特定蛋白的表达水平，可能有助于神经发生和神经保护，最终阻止AD的进展[48,49]. 神经内分泌调节多肽VGF (nerve growth factor inducible)作为一种神经营养蛋白，在维持突触正常功能和神经发生中起重要作用[50]. 基于壳聚糖的纳米胶束作为非病毒载体通过递送pVGF，可以降低Aβ蛋白毒性和神

经炎症, 有助于减缓AD进展[51].

虽然将基因治疗药物、神经保护药物、抗炎药物等负载到壳聚糖纳米载体中显著提高了药物的生物活性、利用度、稳定性和入脑效率, 进而降低了Aβ斑块聚集、减轻了tau蛋白磷酸化、缓解了AD的进展, 但是目前只在动物水平取得了一定的治疗效果, 而在临床试验中的有效性和安全性仍需验证. 鉴于阿尔茨海默病多因素致病机制, 未来可设计多功能壳聚糖纳米药物, 同时针对多个病理靶点进行干预. 例如, 开发集抗氧化、抗炎、抑制Aβ和tau蛋白聚集等多种功能于一体的纳米药物, 通过协同作用来提高治疗效果.

3 壳聚糖及其衍生物在帕金森综合征治疗中的应用

帕金森综合征(Parkinson's disease, PD)是目前发病率仅次于AD的神经退行性疾病, 全球发病人数已超过600万人[52]. PD是一种与神经元丢失和黑质中神经元α-突触核蛋白(α-synuclein, α-Syn)聚集(形成路易体和路易神经突)相关的临床病理综合征, 表现为进行性不对称运动迟缓、强直、震颤和步态障碍[53]. 目前PD的治疗策略主要集中在增加中枢神经系统内的多巴胺(dopamine, DA)水平或刺激多巴胺受体来缓解运动症状[54]. PD治疗药物的药效常受到不可预测的吸收能力和外周代谢的影响. 基于壳聚糖的纳米药物递送系统可以克服传统疗法的药代动力学局限性, 保护药物免于降解, 提供持续释放, 并将药物递送至特定细胞, 以靶向特定的细胞内途径[55].

羧甲基壳聚糖(carboxymethyl chitosan, CMCS)的羧基与多巴胺的氨基结合, 可获得羧甲基壳聚糖多巴胺偶联物(CMCS-DA), 并通过鼻腔给药提高脑内多巴胺水平[56]. 季铵化壳聚糖和明胶交联制备的可注射水凝胶作为药物载体, 能够通过持续释放多巴胺和抗炎药物甲硝唑以补充脑内多巴胺并降低炎症反应(图3(a))[57]. 基于壳聚糖的纳米载体还可以递送多巴胺受体激动剂(如罗替高汀、罗匹尼罗等)以提高药物入脑效率、改善脑内多巴胺水平[58,59]. 脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)对大脑神经元的发育、存活和维持具有积极作用, 然而其作用常受到半衰期短、非神经元细胞摄取高等因素的限制. 利用壳聚糖微球负载BDNF相较等量游离的BDNF具有更强的促神经细胞分化和轴突生长能力(图3(b))[60]. 蛋白磷酸酶2激活剂FTY720可以使α-Syn去磷酸化来减缓PD进展, 负载FTY720的壳聚糖纳米颗粒(FTY720 chitosan nanoparticles, FCsNPs)增加了FTY720的生物利用度和神经保护作用, 有助于预防和缓解PD进展[61]. 此外, 一些天然物质如绿茶提取物(green tea extract, GTE)、柚皮素等作为抗氧化剂在神经保护方面具有显著作用[62,63]. 研究发现, 壳聚糖-明胶-绿茶提取物(chitosan gelatin green tea extract, CS-Gel-GTE)复合颗粒具有抗氧化性能, CS-Gel-GTE复合颗粒的正电荷表面可以黏附PC12细胞并被内化, 表现出抑制ROS形成、增加酪氨酸羟化酶表达和降低α-Syn蛋白表达的潜力[62].

多巴胺、多巴胺受体激动剂、神经营养因子、抗氧化剂等治疗PD的药物和壳聚糖基纳米载体偶联可以提高入脑效率、延长半衰期. 通过静脉注射或者鼻腔给药途径, 基于壳聚糖的纳米药物可以到达受损的脑

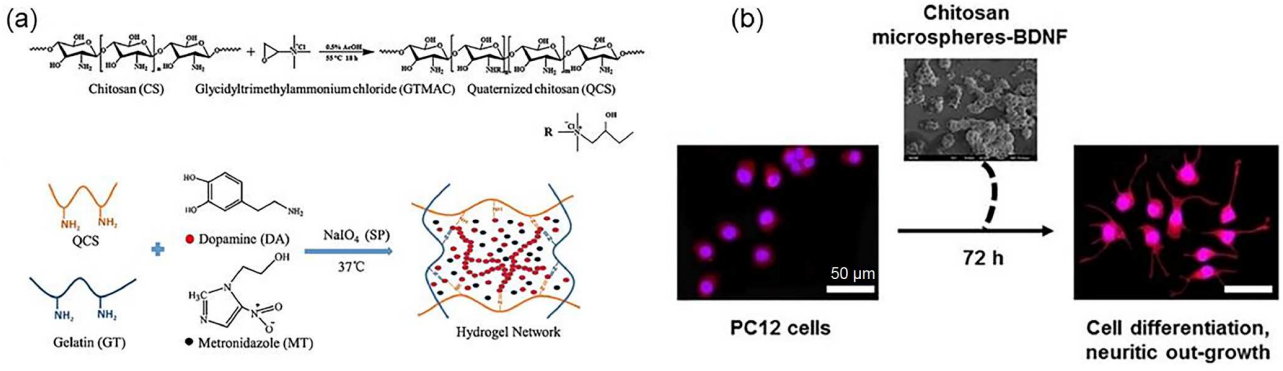

图 3 (网络版彩色)基于壳聚糖及其衍生物的纳米药物在帕金森综合征治疗中的应用. (a) 季铵化壳聚糖和明胶交联制备可注射水凝胶[57]. Copyright © 2017, Elsevier. (b) 负载BDNF的壳聚糖微球促进神经细胞分化和轴突生长能力[60]

Figure 3 (Color online) Application of nano-drugs based on chitosan and its derivatives in the treatment of Parkinson's syndrome. (a) Preparation of injectable hydrogel by cross-linking quaternized chitosan and gelatin[57]. Copyright © 2017, Elsevier. (b) The ability of chitosan microspheres loaded with BDNF to promote nerve cell differentiation and axon growth[60]

区，进一步补充脑内多巴胺水平、降低神经炎症、发挥抗氧化性能、降低α-Syn蛋白水平，从而缓解PD进展.

4 壳聚糖及其衍生物在缺血性脑中风治疗中的应用

脑中风是仅次于心血管疾病的全球第二大死因[64]. 在各种中风类型中，缺血性脑中风最为常见，约占所有脑中风病例的87%左右[65]. 大脑缺血缺氧导致细胞代谢紊乱，从而引起一系列病理生理变化，包括BBB破坏、神经元死亡、氧化应激、线粒体障碍和神经炎症等[66]. 缺血性卒中的常见临床治疗包括组织型纤溶酶原激活剂的快速溶栓治疗和黄金时间内通过外科手术进行机械血栓切除术[67]. 但是这些治疗方案的时间窗狭窄，常需要在脑中风发生4~6小时内进行干预，并伴随出血风险与缺血再灌注损伤等反应. 因此，针对缺血性脑中风的治疗药物仍亟待研究.

将血管内皮生长因子和碱性成纤维生长因子(basic fibroblast growth factor, bFGF)等神经营养因子递送至中风腔或半影区，能够显著提高该区域受损神经细胞的修复成效[66]. 然而，这些可溶性因子的半衰期极短，极大地限制了它们穿透BBB的能力以及在卒中腔内的续存时间，导致临床治疗效果欠佳. 研究发现，将bFGF封装到壳聚糖凝胶中可以弥补游离bFGF的缺陷，在中风7天后给予bFGF-壳聚糖，有效促进了血管生成，并刺激了神经干/祖细胞增殖、迁移和分化为神经元. 该凝胶还促进了中风腔内新生神经元的存活和成熟，进一步增强了功能恢复[68].

鉴于缺血性卒中大脑ROS释放增加，一些ROS响应型纳米药物应运而生. 研究报道，用ROS响应性硼酸酯修饰硫酸化壳聚糖外壳递送神经保护剂雷帕霉素(rapamycin，RAPA)可促进小胶质细胞极化，并且维持BBB的完整性，减少脑梗塞面积，促进脑神经血管重塑[69]. 此外，单宁酸通过氢键和壳聚糖交联形成的可注射水凝胶也可以通过NF-κB通路促进小胶质细胞的抗炎极化，促进突触可塑性、恢复中风小鼠的运动能力([图4])[70]. 乙酰基-11-酮-β-乳香酸(acetyl-11-keto-β-boswellic acid，AKBA)作为锯齿乳香树脂的主要活性成分，是治疗脑缺血再灌注损伤的新型候选药物[71]. 然而，该化合物水溶性差、生物利用度低，体内循环时间短、清除速度快，严重限制了其疗效. 将AKBA负载到邻羧甲基壳聚糖纳米颗粒(AKBA nanoparticles，AKBA-NPs)可以显著增加药代动力学和入脑效率，延长半衰期. 与游离AKBA相比，AKBA-NPs具有更好的

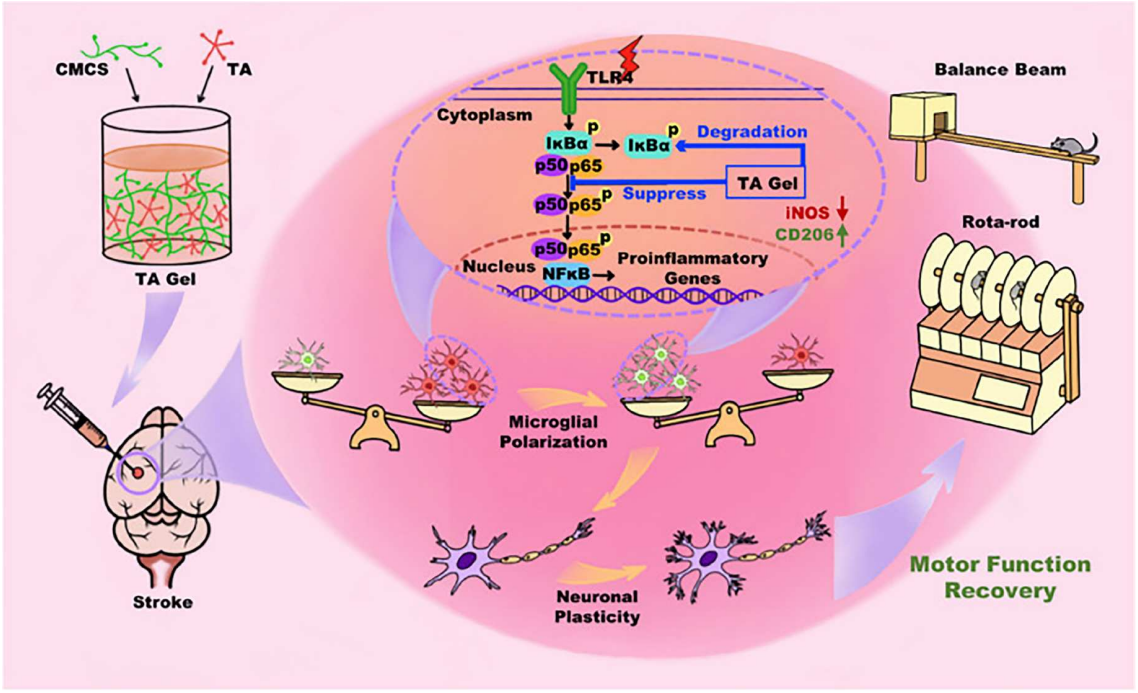

图 4 (网络版彩色)负载单宁酸的壳聚糖可注射水凝胶治疗中风机制图[70]
Figure 4 (Color online) Mechanism diagram of chitosan injectable hydrogel loaded with tannic acid in treating stroke[70]

脑递送功效. 在氧-葡萄糖剥夺的原代神经元模型和大脑中动脉闭塞的动物模型中, 与游离的AKBA相比, AKBA-NP具有更好的神经保护作用. AKBA-NPs还可以通过增加核红细胞相关因子-2和血红素加氧酶-1表达, 以及降低NF-κB和5-脂氧合酶表达, 更有效地调节抗氧化和抗炎途径[72]. 此外, 将没食子酸负载到邻羧甲基壳聚糖纳米颗粒中也可以改善没食子酸吸收率低、生物利用度差等缺陷, 发挥更高效的神经保护作用[73].

综上所述, 一些神经营养因子、神经保护药物负载到壳聚糖纳米载体中, 可以显著提高入脑效率, 进而恢复缺血性脑中风BBB的完整性、减少梗死面积、降低再灌注造成的损伤风险, 改善中风大鼠的运动功能障碍, 具有积极的神经保护作用.

5 壳聚糖及其衍生物在创伤性脑损伤治疗中的应用

创伤性脑损伤(traumatic brain injury, TBI)是由头部受到外力重击或震动而引起脑功能改变的神经系统疾病, 具有病情急、变化快、病死率高、致残率高、预后差等特点, 严重危害人类生命健康[74,75]. 由机械损伤造成的原发性损伤易诱发包括氧化应激、神经炎症、细胞凋亡、神经退化等继发性损伤, 进而导致脑神经功能障碍[76~78]. 此外, TBI还会增加患有癫痫、脑水肿、中风、AD等神经疾病的风险, 加重病情进展[79~81]. 目前关于TBI治疗的研究集中在直接递送细胞因子或移植细胞[82,83]; 然而, 细胞因子的半衰期短和移植细胞的存活率极低, 限制了这些方法的持久治疗效果. 研究发现, 基于壳聚糖的纳米载体可以延长TBI治疗药物的半衰期和提高移植细胞的存活率[84].

骨髓间充质干细胞(bone marrow mesenchymal stem cells, BMSC)的多向分化潜能使其可作为多种器官改建或损伤后修复的细胞源[85]. BMSC分泌的多种激素和神经营养因子可以促进内源性神经元前体细胞的生长、分化, 对神经损伤修复和再生产生积极作用[86]. 在TBI的细胞移植治疗中, 细胞分布和存活率在神经功能的整体恢复中起着至关重要的作用[87]. Ji等人[84]研究发现, 采用BMSCs复合壳聚糖多孔支架移植治疗能显著提高TBI大鼠的认知功能, 其治疗效果明显优于单纯的BMSCs或壳聚糖多孔支架移植治疗. 壳聚糖多孔支架能为BMSCs提供三维结构的生长环境, BMSCs能在脑局部微环境刺激下分化为神经细胞, 并与正常脑组织建立联系, 从而促进了TBI大鼠神经功能的修复(图5(a)). 基于壳聚糖的多孔支架还可以装载人脐带内皮细胞或用IGF-1/IFN-γ预处理的神经干细胞外泌体, 它们促进了TBI大鼠的神经再生、血管生成并抑制了脑部炎症和细胞凋亡(图5(b)~6(b))[88~90].

李晓光及其团队开发出一种具备可降解特性的活性生物材料, 即神经营养因子3 (NT3)与壳聚糖的组合体[91]. 这种独特的活性材料支架能够实现对NT3的精准控释, 有力地驱动内源性神经干细胞的动员, 促使其不断增殖并向脑损伤区域定向迁移, 随后逐步分化为具有完备功能的神经元, 逐步修复受损的神经网络, 最终改善脑损伤大鼠的认知功能. 相较于传统的外源性细胞移植手段, 它巧妙地规避了免疫排斥反应以及各类伦理争议等诸多难题, 为脑损伤治疗领域开拓出一条前所未有的创新路径, 有望成为脑损伤治疗策略中的新突破点并引发更多相关研究与应用的探索. 此外, 将BDNF包载到壳聚糖纳米颗粒中, 也可以延长其半衰期, 更好地发挥抗炎、促血管再生、改善TBI后运动功能障碍等神经保护作用[60]. TBI后丝氨酸蛋白酶抑制剂(serpin protease inhibitor, Serp)也参与多种病理生理过程, 包括调节炎症反应, 保护神经细胞. 将Serp装载到壳聚糖-胶原水凝胶支架中显著提高了Serp的半衰期和稳定性, 有助于进一步减轻炎症反应, 同时有效抑制了神经胶质细胞的凋亡进程, 多方面协同发挥显著的神经保护作用, 为脑损伤后的神经修复与功能恢复提供了极具潜力的治疗策略与途径[92].

综上所述, 目前已有的文献报道了骨髓间充质干细胞、人脐带内皮细胞、外泌体或细胞因子负载到壳聚糖纳米载体中可以显著提高药物半衰期和稳定性. 与常规治疗手段相比, 基于壳聚糖的纳米药物可以更高效地发挥神经保护作用, 抑制神经细胞凋亡, 缓解TBI进展. 未来可以设计响应性释放壳聚糖纳米药物系统. 例如, 设计能够响应创伤性脑损伤部位特定生物标志物或环境信号(如pH变化、酶活性变化等)的纳米药物, 有望实现药物的精准释放, 提高治疗效果并减少副作用. 同时, 结合生物打印技术, 构建个性化的壳聚糖纳米药物-细胞复合支架, 根据患者的创伤部位和程度进行定制化治疗, 从而实现“因病施药”.

6 总结与展望

BBB的存在可以阻止有害物质进入大脑, 但也限制了大多数治疗药物进入脑部, 因此脑部疾病的靶向

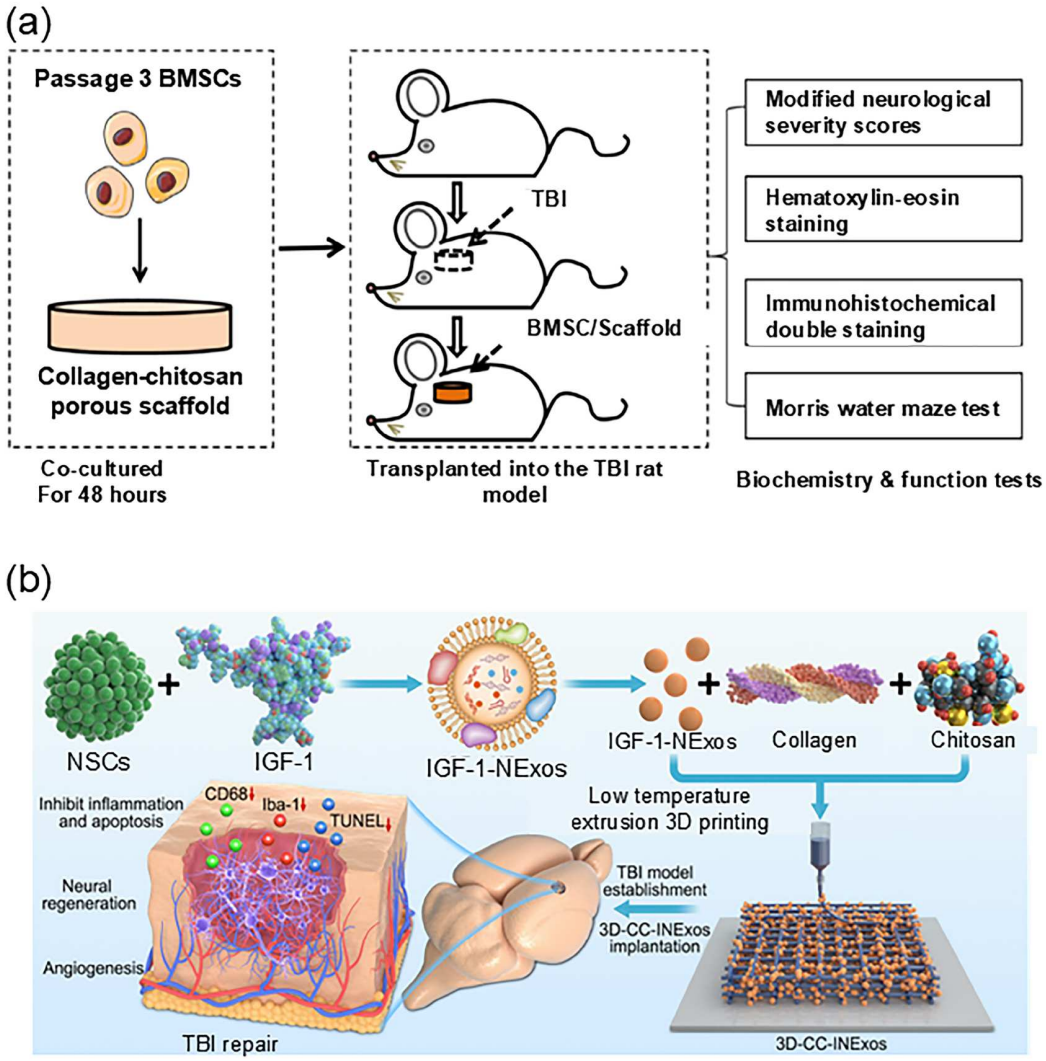

图 5 (网络版彩色)基于壳聚糖及其衍生物的纳米药物在创伤性脑损伤治疗中的应用. (a) 经实际治疗效果验证的骨髓间充质干细胞胶原-壳聚糖支架治疗TBI的有效性[84]. (b) 植入3D-CC-INExos可改善大鼠TBI后的神经再生、改善血管生成并抑制炎症和细胞凋亡[88]

Figure 5 (Color online) Application of nano-drugs based on chitosan and its derivatives in the treatment of traumatic brain injury. (a) The effectiveness of collagen-chitosan scaffold of bone marrow mesenchymal stem cells in the treatment of TBI[84]. (b) Implantation of 3D-CC-INExos can improve nerve regeneration and angiogenesis, and inhibit inflammation and apoptosis after TBI in rats[88]

给药成为治疗的难点. 近年来, 壳聚糖及其衍生物具有生物相容性、可降解性、低免疫原性、黏膜黏附性等生物学特性, 常被用作药物递送载体. 壳聚糖表面的正电荷及其作为阳离子聚电解质的特性为大脑药物递送提供了三个优势: 首先, 壳聚糖的黏膜黏附特性可以与BBB中糖萼上的负电荷产生静电相互作用的界面[93]; 其次, 通过打开紧密连接来增强渗透[94]; 第三, 它能够覆盖表面并增强其他材料的性能, 例如产生正电位, 从而提高纳米材料在生理条件下的稳定性[18]. 基于壳聚糖的纳米药物可以穿透BBB将内容物递送至大脑, 用来治疗神经胶质瘤、阿尔茨海默病、帕金森综合征、缺血性脑中风、创伤性脑损伤等脑部疾病(表1). 此外, 壳聚糖基纳米载体负载小分子药物、细胞因子、治疗细胞等弥补了药物半衰期短、稳定性差、细胞存活率低、药效低等缺陷, 使得壳聚糖基纳米载体在脑部疾病治疗中具有广阔的发展前景和应用潜力.

然而, 目前基于壳聚糖及其衍生物的纳米药物研究仅处于初步探究阶段, 还存在许多问题亟待解决. 壳聚糖纳米载体在药物包封率方面还有较大的提升空间. 此外, 带正电荷的壳聚糖进入体内后会通过静电相互

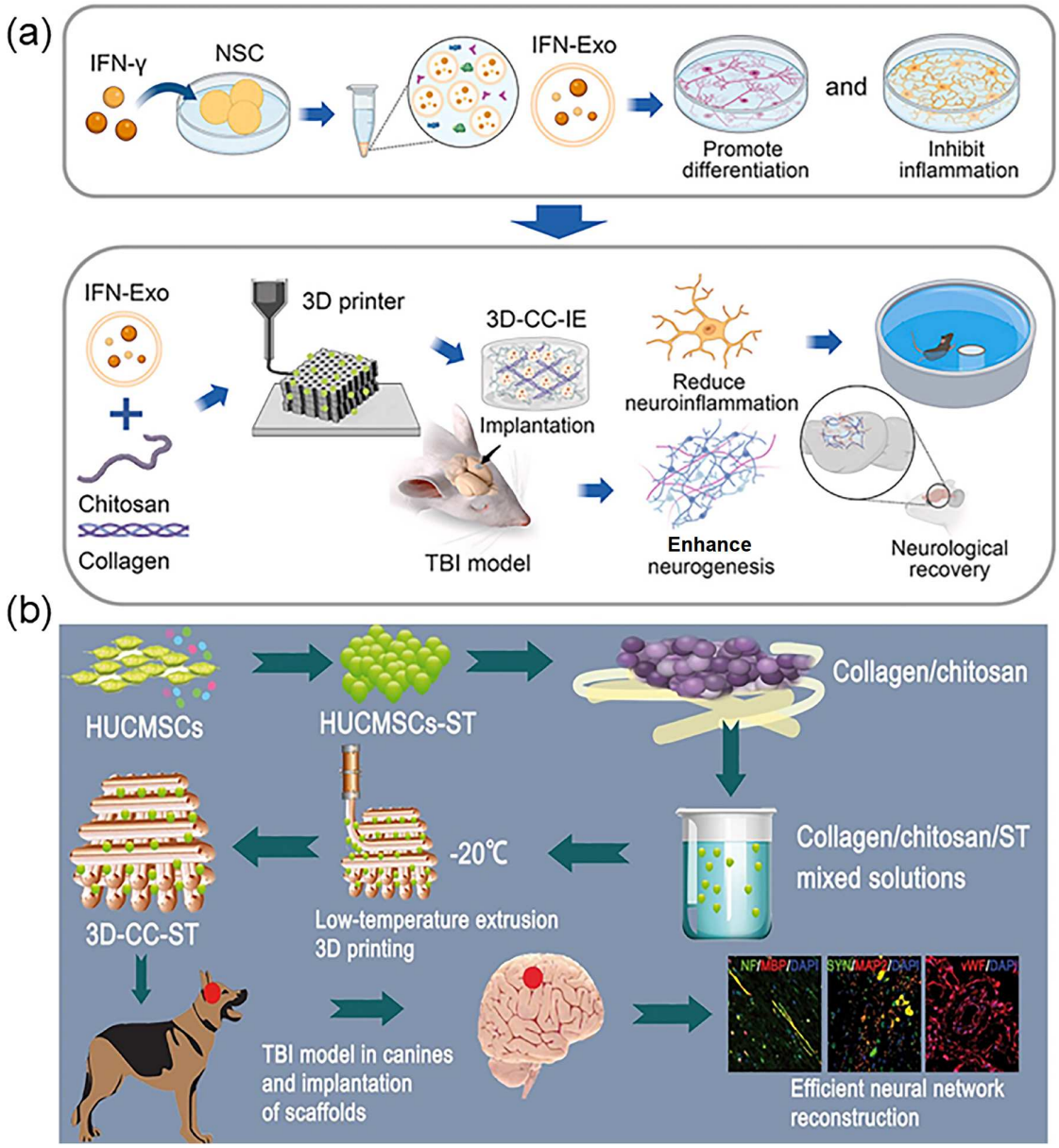

图 6 (网络版彩色)基于壳聚糖及其衍生物的纳米药物在创伤性脑损伤治疗中的应用. (a) 3D-CC-IE支架促进TBI后的神经修复[89]. (b) 源自HUCMSC支架的三维打印胶原蛋白/壳聚糖/分泌蛋白组支架可减少大型犬TBI后细胞凋亡并调节全身炎症因子水平[90]

Figure 6 (Color online) Application of nano-drugs based on chitosan and its derivatives in the treatment of traumatic brain injury. (a) 3D-CC-IE stent promotes nerve repair after TBI[89]. (b) Three-dimensional printed collagen/chitosan/secretory protein scaffold derived from HUCMSC scaffold can reduce cell apoptosis and regulate the level of systemic inflammatory factors in large dogs after TBI[90]

作用吸附周围带负电的血清蛋白, 这会影响纳米载体与周围环境的相互作用以及后续的生物分布. 因此, 提升壳聚糖基纳米药物在血液循环中的稳定性, 探索合适的化学修饰方法来减少壳聚糖与血清蛋白的相互作用是未来的重点研究方向之一. 虽然一些壳聚糖基纳米药物可以透过BBB, 但其具体转运机制还尚不明确, 未来可通过使用不同转运途径的抑制剂来探究壳聚糖基纳米药物的具体转运途径. 此外, 其精准释放机制亟待深入探索与完善, 未来需要专注于开发刺激响应型壳聚糖基纳米载体, 使其能在靶部位以可控方式释放药物. 最后, 未来也需探索壳聚糖基纳米药物与其他手段的联合应用, 如在不同脑部疾病中与放疗、免疫治

表 1 基于壳聚糖的纳米药物在脑部疾病治疗中的应用汇总

Table 1 Summary of the application of chitosan-based nano-drugs in the treatment of brain diseases

载体	递送药物	疾病类型	文献
PLGA-CS	卡莫司汀	神经胶质瘤	[21]
PLGA-CS	紫杉醇		[22]
PLGA-CS	R-氟比洛芬		[22]
CS-Gel	P4HA1 siRNA		[23]
CS	水飞蓟宾		[24]
CS	葫芦巴碱		[25]
PAMAM-CS	替莫唑胺		[26]
CS	丁香酚		[28]
CMCS	BP-MB	阿尔茨海默病	[34]
CS-TPP	Res		[38]
PLGA-CS	抗Aβ抗体		[39]
CS-BSA	姜黄素		[44]
CSC	pVGF		[50]
CMCS	DA	帕金森综合征	[56]
QCS-Gel	甲硝唑		[57]
CS	多巴胺受体激动剂		[58,59]
CS	BDNF		[60]
CS	FTY720		[61]
CS-Gel	GTE		[62]
CS	bFGF	缺血性脑中风	[68]
TA-CS	RAPA		[69]
CMCS	AKBA		[72]
CMCS	没食子酸		[73]
CS	BMSC	创伤性脑损伤	[84]
CS	Exosome		[88]
CS	HUCMSCs		[90]
CS	NT3		[91]
CS	BDNF		[60]
CS-collagen	Serp		[92]

疗、基因治疗等相结合, 进一步增强治疗效果. 这些问题无疑都应当成为未来研究重点聚焦的核心方向, 以便充分挖掘壳聚糖纳米载体在药物递送领域的潜力, 为高效、安全的脑部疾病药物治疗开辟新的路径.

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Summary for “基于壳聚糖的纳米药物在脑部疾病治疗中的应用”

Application of chitosan-based nano-drugs in the treatment of brain diseases

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The blood-brain barrier (BBB), an exquisitely selective semipermeable interface, operates as a potent safeguard, vigilantly shielding the central nervous system (CNS) from deleterious substances within the bloodstream. This intricate physiological bulwark, constituted by brain capillary endothelial cells, astrocytes, pericytes, and a basal lamina, stringently governs the molecular flux, thereby preserving the homeostasis of the CNS. However, paradoxically, this protective role of the BBB has inadvertently metamorphosed into a substantial encumbrance within the purview of brain disease therapeutics. The BBB curtails the ingress of numerous therapeutic agents, spanning from small molecule pharmaceuticals to large biomolecular entities, into the brain, thereby gravely impeding the efficacy of treatment regimens for a broad spectrum of neurological maladies, including gliomas, neurodegenerative afflictions (Alzheimer’s and Parkinson’s diseases), ischemic stroke, and traumatic brain injury.

In recent epochs, nanotechnology has surfaced as a formidable arsenal in the quest to surmount the BBB conundrum. Chitosan, a naturally sourced polysaccharide derived from chitin, has amassed considerable intrigue within the domain of drug delivery, attributable to its exceptional biodegradability, biocompatibility, low immunogenicity, and mucoadhesive attributes. This review undertakes an exhaustive exploration of the application of chitosan-based nanomedicines in the amelioration of diverse brain disorders.

Chitosan-based nanocarriers proffer several distinctive merits in the realm of drug conveyance. Their diminutive size and augmented surface area-to-volume ratio capacitate them to engage with the BBB in a more efficacious manner. Chemical modifications of chitosan, such as phosphorylation, carboxymethylation, and quaternization, not only augment its solubility but also endow it with supplementary advantageous characteristics, encompassing enhanced drug loading capacity and regulated release kinetics. These nanocarriers can be further embellished with an array of ligands, including peptides and antibodies, to actualize active targeting to specific brain regions or cellular entities.

In the context of glioma treatment, chitosan nanoparticles have been adroitly exploited to encapsulate and ferry chemotherapeutic agents, augmenting their cytotoxic potency against cancer cells while concomitantly attenuating systemic side effects. In the arena of neurodegenerative diseases, chitosan-based nanomedicines have evinced promise in transporting drugs and genetic materials to modulate the pathophysiological processes associated with Alzheimer’s and Parkinson’s diseases, such as amyloid-beta deposition and alpha-synuclein aggregation. For ischemic stroke and traumatic brain injury, chitosan carriers have been enlisted to deliver neurotrophic factors and stem cells, thereby fostering tissue repair, angiogenesis, and functional restitution.

Notwithstanding the remarkable strides accomplished hitherto, several hurdles still await resolution. The stability of chitosan-based nanocarriers within the complex physiological milieu of the bloodstream mandates further refinement to guarantee efficient drug delivery. The precise mechanistic underpinnings governing the translocation of chitosan nanoparticles across the BBB and their interactions with brain cells remain only partially elucidated and necessitate in-depth scrutiny. Additionally, the evolution of more refined and stimuli-responsive nanocarriers for controlled drug release at the target locus represents an active area of research inquiry.

chitosan, chitosan derivatives, blood-brain barrier, nano-drugs, brain diseases

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