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·生物材料专栏 综述·

石墨烯基纳米材料在神经再生中的生物学基础与应用策略

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【摘要】 在外伤、肿瘤切除术后颌面部软组织缺损及大面积骨缺损中常伴有神经组织的损伤,而神经再生是神经组织损伤修复的重要生物学基础。随着纳米技术的发展,石墨烯基纳米材料(GBMs)因其独特的生物相容性与理化性能,在神经再生领域展现出巨大优势。本文综述了含GBMs的神经导管、复合水凝胶和药物递送系统,通过调控其表面形貌、化学修饰和生物因子,这些材料可显著促进神经组织的再生。进一步分析其内在机制,发现GBMs可利用导电微环境引导轴突生长;模拟细胞外基质构建仿生拓扑结构;调控干细胞诱导神经分化;结合抗菌、抗氧化和抗炎特性改善损伤微环境。因此,GBMs在促进轴突定向生长、髓鞘形成及神经功能恢复中具有重要作用。然而,其在临床转化、靶向定位、生物安全性等领域仍存在一定的挑战。

【关键词】 石墨烯基纳米材料；　神经再生；　生物相容性；　复合水凝胶；　神经导管；　药物递送；　导电微环境；　仿生拓扑结构；　干细胞分化；　免疫微环境
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The biological basis and application strategies of graphene-based nanomaterials in neural regeneration

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【Abstract】 In cases of trauma, soft tissue defects and large bone defects in the maxillofacial region after tumor resection surgery, nerve tissue damage often happens. Thus, nerve regeneration is a crucial biological basis for the repair of nerve tissue damage. With the development of nanotechnology, graphene-based nanomaterials (GBMs) have shown great advantages in the field of nerve regeneration due to their unique biocompatibility and physicochemical properties. This review systematically summarizes nerve conduits, composite hydrogels, and drug delivery systems containing GBMs. By regulating their surface morphology, chemical modification, and biological factors, GBMs can significantly promote the regeneration of nerve tissue. Further analysis of the underlying mechanisms reveals that GBMs can guide axonal growth by creating a conductive microenvironment; simulate the extracellular matrix to construct biomimetic topological structures; regulate stem cell-induced neural differentiation; and improve the damaged microenvironment by combining antibacterial, antioxidant, and anti-inflammatory properties. Therefore, GBMs play an important role in promoting axonal directional growth, myelin formation, and neural function recovery.

【Key words】 graphene-based nanomaterials; nerve regeneration; biocompatibility; composite hydrogels; nerve conduits; drug delivery; conductive microenvironment; biomimetic topological structure; stem cell differentia-

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在外伤、肿瘤切除术后颌面部软组织缺损及大面积骨缺损等情况下，神经组织常受到破坏，而神经再生是神经组织损伤修复的重要生物学基础。面对神经损伤这一常见临床难题，自体神经移植作为外周神经损伤修复的金标准，存在着供体有限、功能恢复不佳等局限[1]，而中枢神经几乎不能再生。随着再生医学和纳米技术的发展，人工生物材料支架成为核心替代策略，但其电活性不足、微环境调控能力弱等问题制约了修复效果。石墨烯基纳米材料（graphene based nanomaterials，GBMs），由sp^2杂化碳原子组成的单层或少层蜂窝状晶格构成，包括石墨烯、氧化石墨烯（graphene oxide，GO）、还原氧化石墨烯（reduced graphene oxide，rGO）和石墨烯量子点（graphene quantum dots，GQDs）等[2-5]。GBMs作为新兴纳米材料，凭借高比表面积、优越导电性、仿生结构特性及可调控表面化学特性，在神经再生领域受到学者们的广泛关注[6-11]。近年来越来越多的研究揭示，GBMs不仅能模拟神经组织的生理微环境，还能通过多重生物学机制加速神经损伤修复的进程，如促进雪旺细胞（schwann cell，SCs）增殖、引导轴突定向生长、调控免疫反应等。

目前GBMs在神经再生领域的研究，已不只是对其理化性质与生物学特性的单纯探索，而是进一步转向对其应用策略的实践创新[12-14]。本文旨在综述GBMs在神经再生中的生物学基础与应用进展：首先解析其生物相容性的决定因素与优化策略；继而深入探究其电学特性、拓扑引导、干细胞调控及微环境重塑等核心机制；最后总结并探讨GBMs在神经导管、复合水凝胶、药物递送系统等应用中的设计策略。本篇综述为GBMs在神经再生领域的研究提供理论依据，有助于为未来研究提供指导。

1　GBMs的生物相容性

GBMs被识别并进入细胞内，是其能够与神经细胞发生生物学作用的前提。内吞途径是GBMs进入细胞的主要方式[15]，例如直径约40 nm的GO可通过笼蛋白介导的内吞途径进入细胞[16]。GBMs的生物相容性受材料类型、横向尺寸的影响[17-18]。研究者发现石墨烯纳米片（graphene nanoplatelet，GNPs）具有较好的生物安全性，这可能是因为其表面官能团密度较低、缺陷较少且边缘较钝，不易引起氧化应激或造成细胞膜损伤。部分GBMs因其较大的横向尺寸能减少细胞内吞从而显著降低膜损伤风险。此外，GBMs比表面积不低于200 m^2/g时，材料诱导氧化应激风险显著降低[19]。因为GBMs生物安全性受其表面结构影响，对材料进行表面修饰成为提高生物安全性的重要策略。聚乙二醇（polyethylene glycol，PEG）化是最有效的方法之一。在多种人类细胞系中，PEG化原始石墨烯几乎不发生聚集[20]。类似地，PEG修饰的羧基化GO在1 mg/mL的高浓度下仍保持溶血率<5%，且几乎无毒性，证明其具备临床级血液与细胞相容性[21]。壳聚糖-GO-肝素多层涂层显著降低溶血和血小板黏附，改善了材料的生物相容性[22]。虽然研究结论有略微差异，但总体上学者们认为浓度也是影响GBMs生物相容性的因素之一[23-24]。定向GO支架在GO含量≤0.5%时对原代SCs无显著毒性；壳聚糖-GO复合支架在3%～6%GO时显著促进神经细胞存活与黏附[22]。在石墨烯/丝素蛋白纳米纤维膜中，10%石墨烯含量可最大化促进SCs增殖[25]。GBMs的生物相容性由材料类型、横向尺寸和浓度共同决定[26]。通过对材料进行表面修饰，可以将生物安全风险降至最低。尽管已有多项体外实验证明了由GBMs合成的生物支架材料能显著促进鼠的坐骨神经再生[27-28]，并且有多项研究指出GBMs的抗菌抗炎特性有利于形成促进神经生长的微环境[29-31]，关于GBMs发生生物学作用机理的研究仍不够充分。

2　GBMs促进神经再生的原理和特性

GBMs通过重建导电微环境、仿生拓扑引导、调控神经干细胞、抗菌防护以及抗炎抗氧化微环境重塑五大机制的协同作用，为神经再生提供安全适配的理想环境，最终有效促进轴突生长、髓鞘形成与神经功能恢复（图1）。

2.1　优异的电学特性：促进神经电功能重建

神经组织本身具有电活性，且神经系统依赖动作电位和突触传递实现生物电信号的传递。因

此构建与生理电环境适配的导电微环境成为重建神经功能的核心[32-33]。石墨烯及其衍生物如GO和、rGO凭借高电子迁移率[34-35]，能有效弥补受损神经间隙的电信号中断[36-38]。

研究表明，通过控制rGO的还原程度及其在聚合物基质中的含量，如聚己内酯（polycaprolactone，PCL）、丙交酯-己内酯共聚物[poly（lactic acid-co-caprolactone），PLCL]、丝素蛋白，可以精准调节支架的电导率，使其达到甚至超过人类神经的生理电导率，以支持动作电位的顺畅传播[33，36，39]。在细胞层面，GBMs的电学特性通过影响细胞膜电位激活离子通道，可直接引导和加速神经元的生长与分化。当施加电刺激时，导电的GBMs引起细胞膜去极化，激活电压门控Ca^{2+}通道，促使Ca^{2+}内流，能启动下游信号级联反应，促进神经轴突生长延伸以及细胞骨架蛋白的组装[36]。一种具有优异导电性的GBMs支架，凭借其优异的电活性和高表面电荷密度，使得大鼠肾上腺嗜铬细胞瘤细胞（PC12细胞）活性加强，其细胞神经突长度可比对照组增长47%[40]。聚苯胺功能化石墨烯可通过电刺激诱导PC12再生并促进轴突延长，为神经损伤修复提供了应用前景[41]。此外，GBMs的导电特性与拓扑结构相结合，还能有效引导SCs的定向排列。进一步探索其内在机制，GBMs电导性之所以能促进神经再生，是因为电信号能激活关键信号通路。一方面，电刺激通过GBMs提升细胞内环磷酸腺苷水平，激活环磷酸腺苷-蛋白激酶A（cyclic adenosine monophosphate-protein kinase A，cAMP-PKA）通路，进而上调包括Ⅲ型β微管蛋白（β（Ⅲ）-tubulin）、肌动蛋白、生长相关蛋白-43（growth associated protein 43，GAP-43）在内的一系列再生蛋白表达[36]。另一方面，GBMs介导的电学信号能促进脑源性神经营养因子（brain-derived neurotrophic factor，BDNF）及其受体原肌球蛋白激酶受体B（tropomyosin receptor kinase B，TrkB）的表达，通过环磷酸腺苷（cyclic adenosine monophosphate，cAMP）通路增强神经元的存活、分化和突触可塑性[37]。同时，导电微环境还能通过激活磷脂酰肌醇3-激酶/蛋白激酶B（phosphatidylinositol 3-kinase/protein kinase B，PI3K/Akt）等信号通路，促进SCs的增殖，引导再生轴突准确长回目标位置[42]。

2.2　仿生结构特性：拓扑结构仿生细胞外基质

GBMs能够通过其表面特殊的拓扑结构，仿生细胞外基质（extra cellular matrix，ECM），以重构损伤神经部位的微环境。GBMs在二维和三维空间层面都可提供物理支撑与拓扑引导，促进轴突生长和神经功能恢复。

研究发现，以石墨烯作为二维仿生ECM基底，背根结神经元的黏附性提升且轴突延伸速度加快，轴突延伸长度较玻璃基底提高约70%～80%[43]。石墨烯还通过静电相互作用和表面纳米拓扑重塑轴突骨架结构，使微管间距减少约19%、抑制膜相关周期性骨架的径向扩张，从而诱导神经生长因子（nerve growth factor，NGF）在局部发生停滞，强化生长锥附近的促生长信号[43]。在三维层面，GBMs通过与聚合物复合构建高度仿生的ECM框架，将这种拓扑调控从平面拓展至空间尺度。将还原rGO应用于PCL/壳聚糖纳米纤维体系，构建工程化灰质与白质结构，其多孔定向纤维网络在力学性能上匹配脊髓组织，同时在拓扑上模拟天然神经束排列，从而在体内引导轴突纵向生长，实现脊髓损伤后的结构性再生[36]。类似地，将GO引入3D打印聚乳酸-羟基乙酸共聚物神经导管，通过提高表面粗糙度，为间充质干细胞和再生轴突提供稳定的仿生黏附界面，体内表现为β（Ⅲ）-tubulin和髓鞘碱性蛋白（myelin basic protein，MBP）表达上调，进而加速坐骨神经功能恢复[36]。GBMs的导电性与仿生拓扑结构形成协同效应，更好地模拟损伤部位的ECM，为后续修复创造生物学条件。rGO-PCL-褪黑素多层纳米纤维支架在结

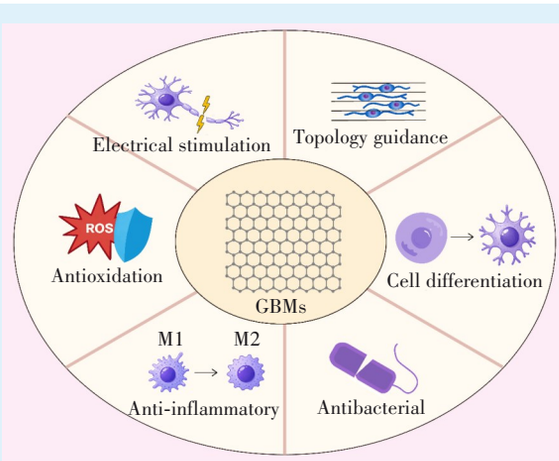


Figure was created with Microsoft Adobe Illustrator 29.5. GBMs: graphene based nanomaterials

Figure 1　The principles and characteristics of GBMs promoting neural regeneration

图1　GBMs促进神经再生的原理和特性

构上提供定向纳米拓扑，并通过rGO赋予支架导电性。这一结构与电学协同作用的“双仿生”环境显著增强S100钙结合蛋白β（S100β）、MBP和GAP-43等再生标志物表达，在坐骨神经缺损模型中实现接近金标准的修复效果[44]。此外，Diana等[45]总结了GBMs在口腔再生领域促进神经再生的机制，GBMs的纳米拓扑结构模拟天然ECM，通过机械信号传导引导牙髓干细胞（dental pulp stem cells，DPSCs）向神经细胞分化。由此可见，GBMs作为仿生ECM的重要因素，通过拓扑结构与电信号协同重塑损伤神经微环境，可调控细胞黏附、迁移、排列，进而促进轴突再生与功能恢复[32, 46]。

2.3　调控神经干细胞：促进神经分化

GBMs凭借独特的理化性能，在诱导神经干细胞（neural stem cells，NSCs）定向分化为功能性神经元方面表现出重要作用[18, 36, 47]。

首先，GBMs的纳米级拓扑结构为NSCs提供了仿生ECM的物理诱导信号。研究发现，具有各向异性结构的GBMs支架能够通过机械力转导激活细胞表面的整合素受体，进而触发黏着斑激酶（focal adhesion kinase，FAK）信号通路，引导NSCs沿支架定向迁移与增殖[18, 36]。进一步研究发现，在转录组分析中，GO可显著激活Ras相关蛋白1（Ras-related protein 1，Rap1）信号通路，进而上调的蛋白表达[48]。这一过程进一步诱导下游PI3K/Akt轴的磷酸化，使NSCs倾向于向神经元细胞分化[47-48]。同时，3D石墨烯泡沫结构还能诱导细胞发生代谢重构，为NSCs的快速增殖和轴突生长提供能量[47]。此外，GBMs优越的导电性能可以模拟神经组织的电生理微环境，改变干细胞的静息膜电位，触发电压门控离子通道开放，产生Ca^{2+}内流[32, 40]，启动细胞内信号级联反应，显著上调β(Ⅲ)-tubulin和微管相关蛋白2（microtubule-associated protein 2，MAP2）等神经特异性标志物的表达[18, 48]。综上，GBMs通过多条路径调控NSCs实现神经修复。

2.4　抗菌特性：优化损伤生物微环境

细菌感染是破坏神经再生进程的重要因素。炎症反应会损伤神经细胞，阻碍轴突延伸和SCs的迁移。GBMs具有多种抗菌特性，通过物理破坏与化学氧化应激协同作用，为神经再生提供安全的微环境[49-54]。

GO/醋酸纤维素复合材料处理后，可见细菌出现膜破裂[30]。GO因其独特的物理形态而具备抗菌能力。研究发现，GO的二维片层具有锋利的边缘，能像“纳米刀”一样接触并切割细菌细胞膜，导致细胞死亡[55]。这种抗菌方式不诱发细菌耐药性，并能高效清除病原体。诱导氧化应激是GO发挥抗菌作用的另一重要机制。GO表面丰富的含氧官能团能刺激诱导活性氧（reactive oxygen species，ROS）产生，进而攻击细菌内的脂质、蛋白质和核酸，造成氧化损伤，破坏细菌的正常代谢功能，最终导致细菌死亡[30]。这一机制在与其它功能纳米复合材料作用时效果显著增强[56-57]。例如，胺化还原氧化石墨烯（aminated reduced graphene oxide，NH_2-rGO）与二氧化钛纳米管协同作用时，在可见光下能大幅提升ROS的含量，实现对病原体的光催化杀菌，该途径能有效清除病原体，减轻由感染引发的过度炎症反应，从而避免对神经细胞造成二次伤害[58]。在AgNPs@Gelatin@GO复合材料中，GO的物理切割与银纳米颗粒（silver nanoparticles，AgNPs）中Ag^+协同作用，可破坏细菌细胞膜结构，实现广谱抗菌功能[59]。一种新型镀锡钢板所用涂层基体包含还原氧化石墨烯（rGO）、壳聚糖以及钛酸锡（$SnTiO_3$），其将功能化钛酸锡纳米颗粒锚定在rGO表面，再掺入环氧树脂基体中，制备得到的纳米复合材料表现出优异的抗菌效果，对革兰氏阳性菌、革兰氏阴性菌的抑菌效果均优于纯环氧树脂及各单一组分材料[60]。这些协同策略极大地提升了抗菌效率，确保了神经再生微环境的稳定性。

GBMs主要通过“膜切割”和“氧化攻击”破坏细菌的结构，进而提升神经元的存活率、促进轴突的定向生长以及改善细胞的功能，最终促进神经组织的再生[61-62]。

2.5　抗氧化与抗炎特性：改善损伤微环境

神经损伤后通常伴随剧烈的氧化应激与持续性炎症，两者相互强化使神经再生陷入“ROS—炎症”的恶性循环。而GBMs可发挥抗氧化与抗炎协同调控作用，从而重塑有利于神经再生的微环境[63-72]。

首先，在氧化应激方面，GO/rGO本身就具有ROS清除能力，其表面含氧官能团作为电子供体可直接中和·OH、O_2·$^-$等自由基，降低细胞内ROS水平[32]。这一效应与其他抗氧化效应协同效果更加显著，在rGO/褪黑素支架中，rGO高效负载可实现褪黑素的局部缓释[44]，在GO导电水凝胶中，GO协同抗氧化分子清除ROS从而减少细胞凋亡[73]。透明质酸-壳聚糖/改性GO导电水凝胶的GO表面

官能团可清除ROS并下调肿瘤坏死因子-α(tumor necrosis factor-α,TNF-α)[74]。

在炎症调控方面,GBMs主动重塑神经免疫微环境。GO可负载抗炎生物活性分子,延长其局部作用时间。聚乳酸/GO复合支架中,GO显著提高抗体递送效率并促进巨噬细胞由促炎M1型向促修复M2型极化,同时激活Rap1/PI3K/Akt通路以增强神经干细胞的存活与抗应激能力[48]。石墨烯功能化支架在体内可抑制小胶质细胞过度激活和星形胶质细胞瘢痕化,降低胶质纤维酸性蛋白表达并避免胶质瘢痕形成[31]。鞣花酸改性的羧甲基壳聚糖/GO复合纳米纤维膜通过抑制核因子-κB(nuclear factor-κB,NF-κB)通路、促进M2极化而发挥抗炎抗氧化作用[75]。

抗氧化与抗炎作用具有明确的协同性:通过降低ROS水平可减弱NF-κB等炎症通路激活,而炎症抑制又反过来减少ROS产生,GBMs在炎症与氧化应激两端同时发挥作用,有效抑制了"ROS—炎症"的恶性循环[32]。

3　GBMs在神经再生中的应用形式

近年来,诸多研究致力于将GBMs与其他材料复合,构建出包括神经导管、复合水凝胶、药物递送系统在内的多种纳米复合材料。这些材料在神经再生修复领域展现出优于传统材料的显著优势,是具有潜力的修复方案。

3.1　神经导管

周围神经缺损修复中,传统修复材料的神经导管缺乏电活性,主要起到"引导桥梁"与"保护屏障"的作用。而GBMs的引入,使导管从简单的辅助支架转变为具备电活性的功能材料,既能提供物理引导,又可利用电导性引导SCs迁移与轴突定向生长,实现了支架材料辅助的"电引导",成为辅助神经再生的新方法[76-77]。

早期研究以赋予材料电学特性为目标。研究者们构建了具备导电性的GBMs复合导管,并发现由GBMs协助产生的电刺激可促进细胞定向迁移、黏附及SCs的神经元表达[28],促进轴突与髓鞘修复,证明了GBMs促进神经修复的有效性并为后续的功能拓展奠定基础。随着研究进一步深入,研究者们将电信号引导与物理拓扑、化学因子等结合,形成了更具潜力的协同促修复策略。导电性与纵向微结构或微通道相结合,可增强SCs活动,协同引导轴突生长[27-28, 36]。更进一步的研究则以电信号与物理拓扑为基础,引入神经生长因子NGF或化学趋化因子Netrin-1等,实现了多重线索引导的神经再生策略[78]。GBMs导管的作用不仅限于宏观引导,还可深入细胞与基因层面。GBMs制备的导电导管可上调Nestin和MAP2等神经特异性基因的表达,促进神经元分化[36]。GBMs与二硫化钨(tungsten disulfide, WS_2)可通过形成中性粒细胞外陷阱(neutrophil extracellular traps,NETs),调控免疫微环境,有助于提高生物相容性[79]。

目前研究致力于将GBMs导管与先进的医学技术相结合,以提供精准医疗服务。在神经导管内,脂肪来源的干细胞可主动组装含rGO的纳米纤维碎片,形成活性的、导电的三维网络,发挥干细胞的旁分泌作用[36]。将负载骨髓间充质干细胞外囊泡的rGO导管植入体内,可通过高效促进血管生成来增强神经再生[36]。针对糖尿病患者神经损伤难以愈合的难题,研究者们开发了利用神经营养因子梯度促进神经再生的非缝合胶带导管,展示了GBMs神经导管在精准医疗领域的高效应用[80]。3D打印与复合材料技术也在不断优化导管性能[81-83]。向3D打印聚丙烯腈导管中填充SCs、纤维蛋白水凝胶和GQDs,能显著提升感觉功能恢复,增加轴突数量并促进再髓鞘化[81]。

值得特别提及的是,在口腔颌面部神经损伤修复中,石墨烯/壳聚糖导管(graphene/chitosan,G/CST)与牙髓干细胞(dental pulp stem cells,DPSCs)相容性良好,能促进DPSCs的黏附、增殖和神经向分化。在兔面神经缺损模型中,G/CST桥接神经断端并联合DPSCs移植,DPSCs分化为雪旺样细胞,分泌神经营养因子Nestin和S100,从而促进轴突再生、髓鞘形成,实现组织和功能的神经再生[84]。

综上所述,GBMs神经导管经历了从建立基础电活性,到与拓扑、化学信号协同的发展历程,实现了细胞基因层面的调控,最终融合先进生物策略,展现了GBMs神经导管在神经修复领域的卓越能力。

3.2　复合水凝胶

GBMs复合水凝胶通过模拟ECM三维微环境,并利用GBMs优异的导电性、抗菌抗炎等特性,构建了可高效促进神经再生的微环境[85-86]。其核心在于构建兼具物理支撑和导电性能的仿生微环境。水凝胶提供类似ECM的物理支架结构,GBMs的引入则建立了电信号传导通路[87]。将GBMs纳入双网络水凝胶体系制备导电复合水凝胶,实现

了对神经组织微环境的仿生模拟[78, 88]。另外，水凝胶的三维多孔结构是递送细胞的理想载体，相关研究已将其用作“生物墨水”负载干细胞或SCs[89]。

在具备基础功能之后，研究进一步赋予材料主动调控局部微环境的能力。将神经生长因子NGF或化学趋化因子Netrin-1等与导电性结合，可实现多重线索引导的神经再生[78, 80]。负载药物或调控免疫微环境是实现治疗的另一重要方向。GO/玉米醇溶蛋白/果胶水凝胶能够持续释放小檗碱和褪黑素，发挥抗炎和抗氧化作用，清除再生障碍[73]。GO掺杂右旋手性水凝胶可诱导巨噬细胞从促炎的M1型向修复性的M2型极化[36]。将GBMs水凝胶应用于光响应复合材料是重要的研究方向。GBMs水凝胶光响应复合材料可实现非接触精准治疗，红光响应材料可产生微电流用于无创电刺激[90]；近红外光响应水凝胶则可程序化协同实现抗菌、免疫调节与促血管生成[91]。面对骨缺损伴神经损伤的临床难题，3D打印的还原氧化石墨烯-甲基丙烯酰化明胶（reduced graphene oxide-gelatin methacryloyl，rGO-GelMA）水凝胶支架，可通过rGO增强细胞黏附与信号传导，SCs和骨髓间充质干细胞（bone marrow mesenchymal stem cells，BMSCs）协同实现了骨与神经的同步再生。展现了GBMs水凝胶在解决多种组织缺损情况下协同修复的独特优势[36]。

GBMs复合水凝胶在神经修复中的应用，从提供基础的物理支撑与电学引导，到主动进行化学免疫调控，再到响应外部刺激实现智能治疗，展现着其在神经损伤修复领域的优越性能。

3.3　药物递送系统

GBMs的高比表面积和丰富的表面官能团是其能构建神经再生载药系统的重要基础[92]。通过π－π堆积、静电作用和共价功能化，GBMs可高效负载神经营养因子、神经保护药物、信号分子或抗炎药物，实现可控释放[93]。研究指出GBMs通过化学功能化，能够更高效地实现载药[94]。

以此为基础，优化载药系统结构并将其与外源刺激协同，载药系统的神经修复效能可得到进一步增强。利用GO通过π-π堆积与共价键负载7，8-二羟基黄酮，形成氧化石墨烯-聚3，4-乙烯二氧噻吩[graphene oxide-poly（3，4-ethylenedioxythiophene），GO-PEDOT]复合薄膜，可在电刺激下触发药物控释[95]。类似地，构建以对齐石墨烯网格为骨架的双网络水凝胶载药系统，可有效负载Netrin-1等关键趋化因子[38, 78]。此外，梯度化载药可进一步提升神经再生效率。通过定向冻干和原位还原技术，在GO基多通道水凝胶导管内构建NGF浓度梯度，实现物理引导、电刺激与生化刺激的三重调控，可显著促进轴突定向延伸、髓鞘再生及功能恢复[80]。在可控释放层面，将GO纳米片引入甲基丙烯酸化水凝胶中，构建依赖电刺激响应的NGF载药系统，可以实现对生长因子释放的精确调控，显著延长生物活性窗口，以满足神经再生的需要[96]。除神经营养因子外，GBMs载药系统亦可整合抗炎、抗氧化或抗菌药物。多功能神经导管同时负载小檗碱和褪黑素，通过药物抑制炎症反应、清除氧化应激，显著促进轴突生长和髓鞘修复[73]。利用rGO的光热效应实现抗生素的可控释放，可显著抑制感染，最终实现神经感觉功能恢复[91]。

综上，将GBMs用于兼具结构引导与刺激响应效能的载药系统，可通过负载不同药物，为神经再生提供高度可调控的应用策略，在周围神经损伤修复中展现出显著优势。

4　小结与展望

本文综述了GBMs在神经再生领域的生物学基础与应用策略。研究表明，GBMs并非简单的被动支架材料，而是具备了生物学功能的主动修复材料。多重机制协同作用是其促进神经修复的核心优势。GBMs优异的电学性能可重建损伤神经的导电微环境，通过激活Ca^{2+}信号通路引导轴突生长与髓鞘形成；GBMs独特的仿生拓扑结构通过模拟ECM，为细胞黏附、迁移和定向排列提供拓扑引导，并与电、化学信号协同，形成“双仿生”甚至“三重提示”的协同效应；GBMs对NSCs调控能力使其能精准诱导神经分化；此外，GBMs的抗菌、抗氧化及抗炎特性能有效清除病原体，调控免疫微环境，为神经再生创造有利的生物学微环境。在应用层面，GBMs通过神经导管、复合水凝胶、药物递送系统等多种应用形式发挥神经修复效能，展现出从单一功能向集成化多功能的发展趋势。

虽然GBMs在神经组织再生应用中已展现诸多优势，但其作用机制仍有待深入揭示。比如，GBMs介导电学信号向细胞内信号通路的转导机制尚不明确，以及其调控巨噬细胞向特定功能表型极化的精确路径仍存在空白[97]，需要更多的后续研究进行补充。尽管前景广阔，GBMs的临床转化仍面临一系列关键挑战。有研究认为GBMs的

生物毒性极低。然而另一部分研究指出其生物学毒性依赖于材料的物理化学参数。有研究指出GBMs具有极高的化学稳定性,是可用于修复的理想材料。仍有观点认为GBMs在生理环境中的稳定性仍存在挑战,包括材料的团聚倾向、表面修饰的稳定性以及其促再生性能受时间变化的影响。建立精确的定量构效关系,并通过表面修饰(如PEG化、蛋白或脂质包裹)调控其生物安全性仍是未来研究的重要方向。GBMs在体内的代谢途径仍有部分尚未明确[98-99],目前研究中酶促氧化降解的分子机制证据最为充分[100-101]。有研究提出可通过提高氧化程度(如增加羧基、羟基、环氧基等)增加缺陷密度,以此提高氧化与酶攻击的敏感性,从而加快GBMs降解。但过度氧化会增加ROS风险,关于GBMs可控降解的研究仍存在部分空白。目前GBMs促神经再生的研究仍然处于实验阶段,以验证其有效性。进一步明确GBMs促神经再生的信号通路转导机制,通过修饰手段调控GBMs的稳定性和生物毒性,探索GBMs的可控降解途径,将为GBMs从实验阶段向临床转化提供重要依据。材料的标准化与规模化制备是保障研究成果可重复性与临床转化的基础,稳定可控的合成体系亟待建立。

GBMs在神经再生领域展现出巨大的应用潜力,其中GQDs在神经再生中的生物成像与示踪被认为极具发展前景。GQDs具有卓越的光致发光特性、高生物相容性以及能够穿越血脑屏障的能力,已有研究将其设计成可实时追踪细胞迁移路径和分化情况的纳米探针。应用在神经再生领域,GQDs能够动态监测干细胞迁移、神经元分化和轴突生长,从而进一步阐明材料促神经再生的机理。对于GBMs未来的整体发展,一方面,研究将更注重个性化精准医疗,例如针对糖尿病神经病变、脊髓损伤等特定疾病设计解决方案[36, 102-103];另一方面,与干细胞疗法、基因治疗及外泌体技术等先进生物策略的深度融合,将进一步提升GBMs促神经修复的效能。最终,通过材料科学、生物学、医学与工程学的多学科交叉创新,推动GBMs修复策略从被动的"保护支撑"向主动的"微环境重塑与功能重建"转变,为神经损伤修复治疗开辟了新的途径。

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【Generative AI statement】 Figure in this manuscript was created with Adobe Illustrator 29.5. The authors reviewed and edited the output and take full responsibility for the figure. No other generative AI technology was used in the creation of this manuscript.

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