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生物活性玻璃在疾病治疗中的应用进展

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摘　要

生物活性玻璃是一种具有高度生物相容性和生物活性的非晶态材料，其主要成分通常包括二氧化硅、氧化钙、氧化钠和氧化磷等，能与生物体骨骼形成牢固的化学键或生物降解形成新骨骼，因此在疾病治疗方面已经取得了显著进展，特别是骨和软组织再生、口腔科修复以及特定慢性疾病的治疗等方面。近期的研究还聚焦于生物活性玻璃的多功能化，例如通过掺入金属离子或稀土元素赋予其抗炎抗菌、光热治疗、荧光监测等功能，为生物活性玻璃在疾病治疗中的应用提供了新的视角与策略。

关键词

生物活性玻璃，疾病治疗，生物成像，生物传感器，药物载体

Advances in the Application of Bioactive Glass in Disease Treatment

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Abstract

Bioactive glass is an amorphous material with high biocompatibility and bioactivity. Its main components typically include SiO_2, CaO, Na_2O and P_2O_5, which can form strong chemical bonds with the body's bones or biodegrade to form new bone tissue. Therefore, significant progress has been made in the treatment of diseases, especially in bone and soft tissue regeneration, dental restoration, and the treatment of specific chronic diseases. Recent research has also focused on the functionalization of bioactive glass, such as incorporating metal ions or rare earth elements to endow it with anti-inflammatory, antibacterial, photothermal therapy, and fluorescence monitoring capabilities. These advancements provide new perspectives and strategies for the application of bioactive glass in

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disease treatment.

Keywords

Bioactive Glass, Disease Treatment, Bioimaging, Biosensor, Drug Carrier

1. 引言

生物活性玻璃(Bioactive Glass, BG)，作为一种独特的生物材料，自 1969 年由 Larry Hench [1]发现以来，便以其卓越的生物相容性和生物活性在医学领域引起了广泛关注。其能够与生物体内的骨组织形成强有力的结合[2] [3]，促进新骨的再生与修复，已被广泛应用于骨科和口腔科等领域。近年来，BG 在疾病治疗中的潜力日益显现，不仅能够作为骨和软组织修复材料，还展现出在药物载体、组织工程支架以及抗菌涂层等方面的多重治疗功能[4]。此外，新型 BG 的开发，如离子掺杂和表面改性技术的应用，进一步增强了其在促进血管生成、调节生物活性等方面的能力，并赋予其抗炎抗菌[5]-[10]、光热治疗[11]-[15]、荧光监测[16]-[18]等额外功能。这些进展预示着 BG 在未来治疗中扮演更加重要的角色[19]。本文旨在探讨 BG 在疾病治疗方面的最新研究进展，评估其临床应用前景，并讨论如何通过材料设计和功能化策略进一步优化其治疗效果。

2. BG 的定义与特性

BG 是一种特殊的硅酸盐玻璃，能够与生物体组织发生直接的化学键合作用，促进骨组织的再生和修复。它由 SiO_2、Na_2O、CaO 和 P_2O_5 等基本成分组成，具有良好的生物相容性和生物活性[1]。BG 的显著特征是植入体内后，其表面能够迅速与生物体液发生离子交换，形成生物活性的羟基磷灰石(HA)层[20] [21]。这层保护膜不仅增强了材料的机械强度，还为组织提供了键合界面[22]，促进了细胞的附着和增殖。此外，BG 还能通过释放特定的离子如 Li、Mg、Cu、Sr、Tb 等[6] [9] [23]-[35]，刺激周围细胞的分化和骨形成。

2.1. 生物相容性和生物活性

BG 能够与宿主组织建立稳定的界面，不会引起免疫排斥反应[36]，且能够与骨和软组织形成稳定的结合[37]。BG 植入体内后，其表面能够与体液中的离子交换，形成羟基磷灰石层，模拟了自然骨的矿化过程，从而与骨组织形成牢固键合，促进骨组织的再生和修复。BG 的生物活性还体现在其能够持续释放有利于骨再生的离子或离子基团如 Ca、Si、P 等，这些离子或离子基团的释放可以激活生长因子表达吸引骨祖细胞并诱导其往成骨方向分化，促进骨组织的再生和修复，同时也有助于改善骨整合性能，使 BG 与宿主骨骼紧密连接[38]。

2.2. 可控的降解性

BG 的可控降解主要依赖于其化学组成和微观结构。通过调整玻璃中的 SiO_2、Na_2O、CaO 和 P_2O_5 等组分的比例，可以调控玻璃网络结构，从而影响其降解速率。例如，增加 CaO 的含量通常会提高 BG 的生物活性，加快降解速率；相反，增加 P_2O_5 的含量则会增加玻璃网格的稳定性，降低降解速率[39]。此

外，BG 的降解性能还可以通过添加特定的元素或化合物来进一步调控。例如，Sr 和 B 的添加可以改变玻璃的网络结构稳定性，从而影响离子的释放速度和降解速率[40] [41]。最新的研究表明，中国科学院过程工程研究所的研究团队开发了一种新型的生物分子玻璃，这种玻璃由氨基酸或肽制成[42]，具有优异的生物相容性和生物可降解性。这些玻璃在实验室测试中表现出与商业玻璃和塑料相比更高的降解速率，能够在堆肥中被微生物分解，且在小鼠模型中显示出体内无害的生物降解性。通过这一性质控制降解速率，不仅提高了其在医疗领域的适用性和安全性，还有助于实现生态环境的可持续发展。

2.3. 可塑性

BG 的可塑性是指其能够通过调整成分和处理工艺来改变其物理和化学性质，以适应不同的临床需求[43]。高可塑性的 BG 可以通过不同的制造技术，如电纺、3D 打印等[44] [45]，被加工成具有复杂形状和精细结构的支架，这些支架能够更好地模拟自然骨组织的微观环境，提供必要的细胞附着点和营养物质传递通道。例如，基于热挤压的 3D 打印技术能够制造出具有分层孔隙结构的 MBG/PCL 复合支架[45]，这种结构有利于细胞的增殖和成骨分化。此外，生物活性玻璃的可塑性还允许其与其他生物材料如聚合物结合，形成复合材料，这些复合材料可以展现出改良的生物相容性和机械性能[46]，从而更适合特定的骨组织工程应用。例如，静电增强的生物聚合物水凝胶通过引入氨基官能化的 BG，改善了界面相容性，促进了巨噬细胞的 M2 表型转变并上调干细胞的成骨基因表达，加速了新骨形成[47]。因此，利用这种性质，可以通过化学组分的设计和调控来获得新的治疗功能。

2.4. 抗菌性

BG 的抗菌性主要源于其释放出的金属离子，如 Ag、Cu、Zn 等，这些离子具有强烈的抗菌作用，能够破坏细菌的细胞壁，导致细菌死亡或失去分裂增殖能力[48]-[50]。研究表明，BG 的抗菌性能与其成分及溶出离子的种类密切相关，不同的金属离子掺杂可以赋予 BG 不同的抗菌特性[50]。例如，含有 Ag 的 BG 具有广谱抗菌活性，能够有效抑制多种细菌生长；含有 Cu 和 Zn 的 BG 则对大肠杆菌具有更强的抑菌性能；而含有 Co 的 BG 在短时间内就能有效消灭多种细菌，在抗菌性能上表现出色。此外，还可以利用金属离子的协同作用进一步提高 BG 的抗菌性能[51]。在实际应用中，金属离子的释放速率和浓度对生物活性玻璃的抗菌性能至关重要，不同金属离子的释放动力学可能会影响其抗菌效果的持续时间和强度。

3. BG 的发展历程

BG 首次以成品的形式出现要追溯到一种名为 45S5 的生物玻璃[52] (SiO_2-CaO-Na_2O-P_2O_5，45Wt% SiO_2，24.5Wt% Na_2O，24.5Wt% CaO 以及 6Wt% P_2O_5)的出现。1971 年，Larry Hench 研制出了这种具有优秀生物活性的 45S5 玻璃，并发现作为材料植入体内后其表面没有被纤维组织包裹，自此 BG 开始走进人们的视线。随着研究的深入，多种不同类型的生物活性玻璃被开发出来，包括 Ceravital 生物微晶玻璃[53]、磷灰石－硅灰石活性玻璃[54] (Apatite/Wollastonite Bioactive Glass Ceramic, A/WGC)、可切削生物活性玻璃[55] (Machinable Bioactive Glass Ceramic, MBGC)、溶胶－凝胶生物活性玻璃[56] (Sol-Gel Bioactive Glass, SGBG)以及离子掺杂生物活性玻璃[57] (Ion-Doped Bioactive Blass, IDBG)等。进入 21 世纪，生物活性玻璃的研究进入了新的阶段，研究者们开始开发新型的生物活性玻璃材料，如介孔生物活性玻璃[58] [59] (Mesoporous Bioactive Glass, MBG)，这种材料具有更高的比表面积和孔容，以及可控的介孔和介观结构，能够提供更佳的生物性能。近年来，BG 的研究继续深化，科学家们探索了新型 BG 的合成，如具有光热效应和荧光特性的 Nd-Ca-Si 基 BG，这些新型材料不仅可以用于肿瘤光热治疗，还能在治疗过程中通过荧光监测肿瘤原位温度，并修复过高光热对肿瘤周边正常组织的烫伤[18]。

4. BG 的临床应用

作为玻璃界的“医疗兵”，BG 活跃在骨科、口腔科、神经外科、组织工程等领域，为疾病治疗做贡献。随着临床需求的不断提高，拥有良好生物相容性的 BG 已经不再是简单的 45S5 Bioglass，而是如今的从单一功能到多功能改性，从熔融法到纳米颗粒，从硬组织到软组织的新型组织修复材料，已被广泛应用于骨和软组织修复[60]-[64]、创面修复[14] [31] [65]-[69]、肿瘤治疗[14] [15] [55] [70] [71]、药物递送[72]-[75]、支架涂层[76]-[80]、免疫调节[26] [81] [82]等多方面的生物活性材料。最新的研究表明，BG 还具有生物成像的功能，同时还展现出其作为光学元件的应用潜力[83]。

4.1. 在生物成像领域的应用

在生物成像领域，BG 的应用主要集中在利用其光致发光特性进行成像。研究表明，含有 Ce、Ga 和 V 氧化物的硼酸盐基 BG 粉末在模拟体液中表现出增强的光致发光和双指数衰减特性[84]，这些特性使得这些材料在生物医学应用中具有很大的潜力，尤其是在生物成像方面。此外，单分散超小生物活性玻璃纳米体系的研究显示了其在干细胞行为调控和成像基础研究中的应用潜力。这些纳米体系通过模板技术和乳化技术合成，能够实现小尺寸、单分散性高度可控的生物活性玻璃纳米粒，利用稀土元素掺杂实现材料可调光致发光和细胞成像应用。BG 成像的核心原理在于稀土元素的电子能级跃迁效应，当 BG 受到特定波长的光激发时，其内部的发光中心会吸收光能并跃迁到激发态，随后在返回基态的过程中释放出光子，产生荧光，荧光强度和波长取决于其成分和结构。相较于传统荧光探针，BG 体系具有三大独特优势：通过组分调节可精准控制发射波长；玻璃基质对稀土离子的包裹作用有效降低荧光淬灭效应；表面丰富的羟基基团便于功能化修饰。然而，硅酸盐基 BG 的量子产率普遍较低，这限制了其在深层组织成像中的应用。

复旦大学张凡团队开发的近红外二区(NIR-II)比率荧光生物支架实现了原位监测骨修复过程中的早期炎症反应、血管生成和植入物降解情况[17]。这种支架利用稀土纳米颗粒和荧光染料的组合并通过 3D 打印技术制备得到，其空间分辨率达到 25 μm，穿透深度超过 8 mm，可以避免组织肿胀所引起的荧光信号波动，从而准确监测骨修复过程中的炎症过程。与之相比，西安交通大学雷波课题组开发的多功能可注射聚柠檬酸酯水凝胶(FPRC) [85]，具有生物降解的可视化荧光跟踪检测能力以及肿瘤微环境响应性降解和药物释放的功能，并可安全有效地实现对皮肤肿瘤的局部治疗以及材料降解的可视化无损示踪。其采用有机荧光基团标记，虽在肿瘤微环境响应性方面表现优异，但存在光稳定性差和发射波长受限等缺陷。值得关注的是以色列特拉维夫大学 Ehud Gazit 教授团队开发的新型超分子无定形玻璃材料[83]。该材料通过 π-π 堆积形成的非晶结构展现出独特的光子晶体特性，其反射光谱可随降解程度发生动态偏移。研究人员发现，由多个重复酪氨酸单元构成的短肽 YYY 易溶于水，并能通过水溶液蒸发而自发组装成无定形玻璃，这种由天然氨基酸组成的简单生物有机肽玻璃材料展现出非凡的机械性能和自愈能力，其独特的光学性质也许能够表现出与生物光子晶体[86]类似的功能：通过精确控制光子的传播和反射特性来实现药物的定向递送与释放，提高治疗效果并减少副作用；用于检测血液中的代谢产物和特定细胞标志物等成分的变化情况从而帮助医生实现更早更精确的疾病诊断。三类技术路线对比显示：无机 BG 体系在成像深度和稳定性方面占优，而有机 BG 体系在生物响应性和代谢安全性上更具潜力。

4.2. 应用挑战

当前 BG 在生物成像领域面临的核心矛盾在于“功能－安全”的权衡。在技术层面，BG 的生物相容性与成像对比度的平衡、光学性质优化、稳定性与降解速率匹配以及多功能化等问题仍需解决。生物相容性与成像对比度的平衡：BG 需要具有良好的生物相容性以便在生物体内部安全使用，同时还要提供足

够的成像对比度以便清晰观察[87]，这两者之间的平衡是一个技术难题；光学性质的优化：BG 的光学性质，如透光率、折射率和荧光发射特性，需要根据不同的成像技术进行优化。例如，NIR-II [17]荧光成像要求材料具有在这个区域的强发射能力和低生物组织吸收，以实现深组织成像；稳定性与降解速率：BG 的稳定性必须与其在体内的降解速率相匹配，以确保长期稳定的成像信号和适时的生物响应，过快或过慢的降解都会影响成像效果和治疗效果；多功能化：将 BG 与其他功能化材料(如药物载体、荧光标记物等)结合，可以实现多重生物医学功能，尽管如此，BG 的研究与应用存在易团聚、缺乏修饰位点等困难与挑战，需要克服材料兼容性和功能集成的技术难题[88] [89]。

在临床转化层面，除技术挑战外还存在伦理问题和成本效益等方面的挑战。在伦理层面，由于患者可能会暴露于一定的辐射或化学物质中，为了确保 BG 的使用不会对人体造成伤害，同时要保证成像效果的准确性和可靠性，这需要在研发和应用过程中进行严格的安全性评估和有效性验证，同时在临床应用中进行严格的伦理审查和监管。此外，在使用 BG 时需要获得受试者的知情同意并确保其隐私得到保护。在成本效益方面，BG 的制备成本较高，需要考虑治疗效果与成本的平衡，限制了其大规模的生产和应用。

针对这些挑战，建议采取以下策略：开发基于机器学习的光学性质预测模型，利用计算机模拟技术，在分子水平上设计 BG 的成分和结构，预测其生物相容性和成像对比度，筛选出具有潜力的候选材料，同时也可减少实验筛选成本；将 BG 与具有特定光学性质的纳米材料复合如量子点或碳纳米管，利用它们的光学优势互补，使复合体系满足不同成像技术的光学需求；在体外建立模拟体内生理环境的模型如含有多种生物分子和细胞的三维培养体系，深入研究 BG 在其中的稳定性和降解行为，为体内应用提供更准确的依据；利用生物分子识别原理，设计特异性的生物分子－材料相互作用界面，提高材料兼容性，实现 BG 与药物载体、荧光标记物等的有效结合；组建跨学科团队，包括材料科学家、生物医学工程师、临床医生和监管专家等，共同开展研究，全面评估 BG 的生物安全性、制定合理的临床研究方案，并应对监管审批流程；建立产学研合作模式，促进 BG 的产业化发展，通过规模生产降低成本，同时提高产品质量和稳定性，以满足临床应用的要求。

5. 展望

利用 BG 的生物相容性和生物活性，使其能够与宿主细胞和生物分子有效互动及作用，我们可以开发一种具有高灵敏度与高选择性且性质较稳定的生物传感器，用于治疗糖尿病等疾病：可以用具有高比表面积和可调节孔道结构的 MBG 作为该生物传感器的基底材料，通过表面改性和功能化技术使其与生物分子及药物进行有效结合，最终实现生物分子的监测和药物的精准释放。下面我将以针对糖尿病治疗的生物传感器为例展开介绍。

首先，糖尿病主要是由于人体不能正常分泌调节血糖的胰岛素而导致的，因此可以考虑利用固定化酶技术将搭载胰岛素的 MBG 与葡萄糖氧化酶等生物分子结合，通过检测葡萄糖氧化酶催化葡萄糖氧化反应产生的电信号来监测血糖水平，提高传感器准确性的同时也有助于保护酶免受外界影响，从而延长传感器的使用寿命，为糖尿病患者提供了长期实时监测血糖浓度的可能。当血糖浓度达到一定阈值时，作为药物载体的 MBG 可实现胰岛素的控制释放，而当血糖水平回归稳定时，胰岛素释放减少。至于这一功能的实现，或许可以利用日本名古屋大学和东京医科齿科大学的研究人员开发出的新型材料[90]，该材料由苯硼酸和高分子凝胶结合而成，能够在葡萄糖浓度低时形成薄膜，在葡萄糖浓度升高时薄膜消失。将该材料置于 MBG 的固态纳米孔内，从而实现控制胰岛素释放的功能。

然而随着科技的进步，势必会有更先进的智能控释载体出现，有助于构建长效递药系统，为更多慢性疾病患者带来更大的福祉。

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