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天然高分子材料在骨缺损修复中的研究进展

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摘　要

骨组织是为人体提供机械支撑的动态器官，炎症、肿瘤、外伤等诸多因素可导致骨缺损。自体骨移植、同种异体骨移植和异种骨移植受限于供体的可用性和供区并发症等问题。传统生物可降解材料，包括可降解金属和陶瓷等，面临耐腐蚀性不足、应力屏蔽效应及难以调控的降解速率等挑战。而天然高分子材料，如胶原蛋白、壳聚糖和丝素蛋白等，具备优异的生物相容性、可降解性及促进细胞增殖和迁移的特性，已被广泛用于骨缺损修复的研究。本文对此类天然高分子材料的来源、特性进行概述，介绍了它们常见的制备方法及应用形式，最后对其应用前景进行展望。

关键词

天然高分子材料，胶原蛋白，壳聚糖，丝素蛋白，明胶，藻酸盐，骨缺损修复

Research Progress of Natural Polymer Materials in Bone Defect Repair

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Abstract

Bone tissue is a dynamic organ that offers mechanical support for the human body. Numerous factors such as inflammation, tumors, trauma, and others can result in bone defects. Autologous bone grafting, allogeneic bone grafting, and xenogeneic bone grafting are restricted by issues such as the availability of donors and complications in the donor areas. Traditional biodegradable materials, including degradable metals and ceramics, encounter challenges like insufficient corrosion resistance, stress shielding effects, and difficult-to-regulate degradation rates. Natural polymeric materials,

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like collagen, chitosan, and silk fibroin, possess outstanding biocompatibility, biodegradability, and the property of promoting cell proliferation and migration, and have been extensively utilized in studies on bone defect repair. This paper summarizes the sources and characteristics of these natural polymeric materials, presents their common preparation methods and application forms, and finally looks forward to their application prospects.

Keywords

Natural Polymer Materials, Collagen, Chitosan, Fibroin, Gelatin, Alginate, Bone Defect Repair

1. 前言

骨组织由细胞、纤维和基质组成，负责支撑和保护其他组织器官。骨缺损通常由外伤、骨质疏松症、肿瘤等引起，大型骨缺损往往需要额外的修复手段[1]。自体骨移植是骨缺损修复的“金标准”，但受限于供体的可用性和供区并发症[2]。同种异体骨和异种骨存在免疫排斥和疾病传播风险[3]。此外，金属和生物陶瓷等传统材料存在抗腐蚀性差、生物毒性和应力屏蔽效应等问题[4]。鉴于天然高分子材料如胶原蛋白、壳聚糖、丝素蛋白和海藻酸盐等具有良好的生物相容性及促再生的特性，它们成为骨缺损修复领域的研究焦点。本文综述了天然高分子材料的来源、特性，并探讨了它们在骨缺损修复中的应用，包括常见制备方法和应用形式，最后对其应用前景进行展望。

2. 天然高分子材料的来源及特性

迄今为止，各种类型的天然聚合物已被用于骨组织工程，常用的天然聚合物包括胶原蛋白、壳聚糖、丝素蛋白、明胶、藻酸盐等。

2.1. 胶原蛋白

胶原蛋白可从多种生物体中提取，包括猪、牛、鱼类和水母等[5]。在骨形成过程中，羟基磷灰石沿着胶原纤维的长轴定向排列，形成高度有序的矿化胶原纤维，这是骨组织中有机与无机物质结合的核心结构。为模仿胶原纤维的有序排列，通过直接添加含有矿物的模拟体液或利用聚合物前体溶液诱导原位矿化来制备具有特定方向的纳米矿化胶原支架，取得了良好的仿生修复效果[6] [7]。矿化胶原纤维通过携带成骨相关细胞、生长因子、药物及无机金属元素，增强其促进骨再生、血管生成、免疫调节和抗感染的作用[8]。例如，通过体外仿生矿化技术，利用掺锶矿化胶原与聚乳酸混合，制备了具有类骨无机成分和孔隙均匀分布的纳米结构复合支架，能有效抑制破骨细胞分化，促进骨再生[9]。

2.2. 壳聚糖

甲壳素和壳聚糖都来源于自然界中的甲壳类动物的外壳，以及某些真菌和藻类的细胞壁。壳聚糖是甲壳素经过脱乙酰基处理得到的产物，由葡糖胺和 N-乙酰基葡糖胺构成线性结构，由于含有游离氨基和 N-乙酰基，脱乙酰壳聚糖具有阳离子性质，能与糖胺聚糖和蛋白聚糖相互作用[10]。壳聚糖的提取方式包括化学水解甲壳类动物壳或酶解真菌细胞壁。在体外可被溶菌酶和壳聚糖酶等酶降解，而在体内主要依靠溶菌酶降解，降解速度与结晶度和乙酰化程度成反比[10]。壳聚糖分子量常在 10 至 1000 kDa [11]，超

过 1000 kDa 的为超高分子量[12]。分子量影响壳聚糖生物材料的制备方法、孔隙率、力学性能、降解速率、抗菌性以及官能团的性质[13] [14]。分子量越高，壳聚糖支架的机械强度越大，降解越慢，分子量还直接影响壳聚糖支架的表面特性，进而间接影响细胞粘附[13]。分子量增加会导致溶液粘度升高，低分子量壳聚糖适合用于药物传递和关节润滑剂[14]。在 3D 打印中，低分子量壳聚糖因粘度不足难以保持打印形状,而中等分子量壳聚糖因其合适的粘度和打印精度应用广泛[13]。高分子量壳聚糖则因粘度过高和强阳离子特性难以进行电纺[15]。

2.3. 丝素蛋白

丝素蛋白是一种从家蚕、蜘蛛和苍蝇等生物中提取的活性聚合物。蚕茧中的天然丝主要由丝胶蛋白和丝素蛋白组成。丝素蛋白由一条轻链(约 25 kDa)和重链(约 390 kDa)组成，两条链通过二硫键连接，轻链具有亲水性，重链富含疏水性甘氨酸。丝素蛋白在骨修复领域有多种应用形式，包括薄膜、纳米颗粒、水凝胶、海绵、块体螺钉和三维支架等[16]。纯丝素蛋白的力学性能有限，常通过与其他生物材料结合制成复合支架来增强其物理性能。例如，近期的研究，Kim 等人利用 γ 射线辐照技术制备了含有羟基磷灰石纳米颗粒的丝素蛋白复合水凝胶，具有优异的机械性能，能激活骨髓间充质干细胞的分化，促进骨再生[17]。

2.4. 明胶

明胶，源自猪皮、猪骨和牛骨等的天然蛋白质，通常由胶原蛋白水解而来，分为 I 型(酸处理，等电点 8~9)和 II 型(碱处理，等电点 4~5) [18]。通过控制加工过程中的温度，可以使三螺旋胶原蛋白分解成不同分子量和机械强度的明胶，明胶中含有的精氨酸－甘氨酸－天冬氨酸序列能够促进细胞的粘附、增殖和分化，可制成组织工程支架、水凝胶和纳米颗粒等[19]。明胶还可与天然或合成高分子材料、生物活性陶瓷和无机金属/非金属材料复合，制备出具有优异机械性能和骨诱导活性的明胶基复合材料[20]。

2.5. 藻酸盐

藻酸盐，主要从棕色海藻和转基因细菌中提取，以海藻酸钠应用最为广泛。海藻酸钠，一种天然亲水阴离子多糖，化学式为$(C_6H_7O_6Na)_n$，相对分子质量在 32,000 到 400,000 之间[21]，基本结构单元理论摩尔质量为 198.11 g/mol [22]。因其具有良好的生物相容性、低免疫原性、低成本和增稠性等特性，海藻酸钠在骨组织工程中广泛应用[23]。单一的海藻酸钠水凝胶作为支架材料存在力学性能不足、易在生理环境中崩解、缺乏细胞特异性识别位点等缺点。为提高其生物适用性，常通过添加一种或多种材料制备海藻酸盐复合水凝胶，包括添加聚合物、生物活性蛋白或多肽、生物陶瓷等[24]。

2.6. 其他

其他天然高分子材料如硫酸软骨素、纤维素、角蛋白、透明质酸、甲壳素和淀粉等在骨缺损修复领域的研究也不断增加。其中，硫酸软骨素作为一种糖胺聚糖，存在于人和动物的结缔组织中，具有抗氧化和降解特性，可以多孔支架、水凝胶、表面涂层、以及微球等形式用于骨修复[25]-[27]。纤维素主要来源于植物、细菌和海藻，羟乙基纤维素与脱矿骨基质结合的骨水泥在动物模型中显示出良好的机械性能和成骨能力[28]。角蛋白是动物皮肤附属物中的纤维结构蛋白，具有优异的生物相容性，同时因存在二硫键、氢键和离子键而具有较高拉伸强度和弹性模量，在骨缺损修复中的应用日益增多[29]。

3. 天然高分子材料用于骨缺损修复材料的制备方法

天然高分子材料在骨缺损修复应用中的常见制备方法分为传统方法和增材制造。

3.1. 传统方法

颗粒浸出技术通常与溶剂浇铸法结合使用，该方法成本低，但使用的有机溶剂可能有毒，常用于制备天然聚合物骨再生支架[30]。乳化冷冻干燥技术结合乳化和冷冻干燥可制造出孔隙率超过 95%、孔径约 200 微米的支架[31]。气体发泡技术则涉及将惰性气体(如二氧化碳或氮气)在一定压力下溶解于材料，压力降至大气压使惰性气体释放，产生孔洞，结合 3D 打印技术，可制造具有微孔的定制组织工程支架[32]。此外，静电纺丝技术常用于制造纳米纤维支架，通过调整电流、流速、电压及收集器与注射器间距离，可控制孔径大小[33]。

3.2. 增材制造

增材制造也常被称为 3D 打印，它通过计算机辅助设计数据，逐层添加材料的方式来构建三维物体。光固化成型技术利用特定波长的光固化光敏树脂，逐层堆叠形成三维物体，擅长制造高精度和复杂结构的部件[34] [35]。熔融沉积成型通过加热使材料熔化，并通过移动喷头逐层挤出这些熔融材料，以此堆叠形成三维结构，它的优点包括易于操作和成本较低，缺点则包括打印速度慢、表面不够光滑，以及可用材料种类有限等[36]。而选择性激光烧结技术核心则在于利用移动的激光束有选择地烧结粉末状的聚合物或金属材料，逐层构建 3D 部件[37]。此外，生物打印使用计算机辅助技术，以“生物墨水”为原料，通过生物打印机结合 3D 打印技术(如挤出式、喷墨式等)，完成骨组织工程支架的构建[38]。

4. 天然高分子材料在骨缺损修复中的应用

天然高分子材料可制备成多种形式用于骨缺损修复，而主要应用形式为骨组织工程支架，水凝胶、骨替代物和微球。

4.1. 骨组织工程支架

在早期的报道中，通过用不同的丝素蛋白结构如脱胶纤维和丝素蛋白颗粒来改善丝素蛋白支架的力学性能[16]。丝素蛋白、壳聚糖和藻酸盐等均可与其他天然及合成聚合物、陶瓷生物材料等结合制备成复合支架，如 3D 打印的丝素蛋白/羟基磷灰石/海藻酸钠复合支架[39]和壳聚糖/*β*-磷酸三钙复合丝素蛋白支架[40]等。甲壳素、角蛋白和纤维素在骨缺损修复中应用日益广泛，例如通过 3D 打印技术制造聚乳酸/甲壳素纳米晶微孔支架[41]，以及开发由人发角蛋白、水母胶原蛋白和纳米羟基磷灰石组成的骨诱导性复合支架[42]。在骨给药和再生领域，纤维素基支架分为有机、无机和有机/无机复合三种类型，这些复合方式会影响支架的物理化学属性、机械性能和生物相容性[43]。临床试验表明，电纺壳聚糖/聚乙烯醇纳米纤维支架可减少拔牙后牙槽骨吸收并促进骨再生[44]。此外，胶原蛋白与透明质酸、明胶、藻酸盐、金属、生物活性玻璃和一些新型碳基材料复合已用于骨组织工程[8]。临床试验表明，磷酸八钙－胶原蛋白复合材料能有效促进人下颌骨大型缺损的骨再生，术后伤口愈合良好，未出现感染或过敏[45]。胶原蛋白以多种形态(肽、基质、膜)在临床试验研究中均表明可促进骨缺损修复，但也可能引起过敏反应、感染等风险[46]-[48]。

4.2. 水凝胶

纯丝素蛋白和纯藻酸盐水凝胶因机械性能限制主要用于非承重部位的骨损伤，通过与其他材料复合，如与羟基磷灰石结合，可以提高其机械性能[49]。对于腔隙骨缺损的修复常制备可注射水凝胶，如最近有研究制备了丝素蛋白/介孔生物玻璃/海藻酸钠复合水凝胶具有优异的可注入性和可成形性，可有效促进腔隙骨缺损再生[50]。甲基丙烯酸酐改性的明胶水凝胶也适用于骨缺损修复[51]。改性透明质酸具有免疫调

节、抗菌、抗氧化特性，较多临床试验表明，透明质酸可促进骨缺损修复[52]。然而，也有少数临床研究显示透明质酸与骨侵蚀相关，可引起颏骨吸收等并发症[53]。此外，甲壳素晶须/壳聚糖液晶水凝胶通过模拟骨细胞外基质微环境，展现出卓越的成骨效果、血管生成能力及抗菌特性[54]。壳聚糖基水凝胶可以纳米、微球和金属凝胶三种形态用于修复骨缺损，主要分为温敏、pH 敏和活性氧响应型[49]。壳聚糖可通过交联调整机械特性，结合生物材料或干细胞促进再生，并通过药物释放和响应性成分实现靶向治疗[49]。

4.3. 骨替代物的开发

天然高分子聚合物骨替代物在植入骨缺损部位后，能够释放信号分子，促进细胞分化，随着聚合物逐渐降解，新骨取而代之。丝素蛋白、壳聚糖和海藻酸盐等天然高分子材料已被广泛研究，用于开发骨替代品。例如，通过壳聚糖低温改性聚乳酸制备的骨替代品，展现出高亲水性和类似松质骨的结构，有利于骨细胞的生长[55]。研究人员还在丝素蛋白膜上培养骨髓间充质干细胞和内皮祖细胞，并与管状丝素蛋白支架结合，开发出一种仿生骨膜－骨干替代品，动物实验表明其能有效促进骨形成和血管生成[56]。最新研究还发现，丝素蛋白分子通过热压方式，以脱胶丝织物为增强体，再生丝为基体，制备出丝素蛋白骨替代物，展现出优异的机械性能，性能更接近人骨，避免了金属和合金人工骨的应力屏蔽效应以及陶瓷人工骨的脆性问题[57]。

4.4. 微球及纳米球

目前，各种天然聚合物，脱乙酰壳聚糖、藻酸盐和明胶等已用于生产微球和纳米球结构，它们可以通过聚合、相分离、溶剂萃取等方法制备，已广泛用于骨组织工程[58]。在骨组织工程中，微球及纳米球作为生长因子、药物及细胞的载体，由于它们是小而球形的，可以直接注射到治疗部位[59]。藻酸盐、壳聚糖及其他类似的天然聚合物与电流体动力喷雾相容，都可以用于产生受控尺寸的载有细胞的微球[60]，例如，利用高速剪切阳离子乳化技术，模仿自然骨的结构与密度，成功制备了聚乳酸/胶原/纳米羟基磷灰石的复合微球，通过调整胶原蛋白的含量，可使纳米羟基磷灰石的降解速度与人体骨组织的生长和愈合周期相匹配，从而发挥优异的成骨效果[61]。

5. 结论与展望

天然高分子材料在骨组织缺损修复领域已取得显著的研究进展。这些材料包括胶原蛋白、壳聚糖、丝素蛋白等，因其良好的生物相容性、可降解性和成骨诱导能力，以支架、水凝胶、骨移植替代品、微球和纳米球等形式被广泛使用。结合不同材料之间的优势来制备复合材料，已成为骨缺损修复材料的发展趋势。然而，为实现临床转化的目标，在制备高度仿生的材料、调控细胞行为、精确控制生长因子的表达与释放，以及验证临床应用安全性等方面，仍是未来研究需要深入探讨的问题，我们期待这些材料能够为骨缺损修复带来更多突破性的解决方案。

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