Traditional Chinese Medicine 中医学, 2025, 14(9), 3805-3813
Published Online September 2025 in Hans. https://www.hanspub.org/journal/tcm
https://doi.org/10.12677/tcm.2025.149555

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基于壳聚糖的纳米载体在特应性疾病治疗中的研究进展

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收稿日期：2025年7月31日；录用日期：2025年8月25日；发布日期：2025年9月8日

摘　要

壳聚糖及其衍生物具有优异的生物相容性、可降解性和低免疫原性，兼具抗氧化、免疫调节和抗菌等多种生物活性。在药物递送领域，纳米载体技术显著改善了药物的水溶性、靶向性和安全性。目前研究的壳聚糖纳米递送系统主要包括：纳米颗粒(良好的亲水性和生物相容性)、静电纺纳米纤维(提升药物溶解度和渗透性)、纳米凝胶(高持水性)以及壳聚糖修饰脂质体(增强靶向性和组织穿透力)。这些载体系统凭借其显著的抗炎、抗过敏特性和高生物利用度，为哮喘、变应性鼻炎等特应性疾病的治疗提供了高效低毒的新策略，展现出广阔的临床应用前景。本文重点探讨壳聚糖纳米载体在特应性疾病治疗中的应用机制。

关键词

壳聚糖，纳米载体，特应性疾病，综述

Advances in Chitosan-Based Nanocarriers in the Treatment of Atopic Diseases

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Received: Jul. 31st, 2025; accepted: Aug. 25th, 2025; published: Sep. 8th, 2025

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文章引用: 李璇, 张蓉, 邓思瑶, 唐维康, 易欣, 刘慧霞. 基于壳聚糖的纳米载体在特应性疾病治疗中的研究进展[J]. 中医学, 2025, 14(9): 3805-3813. DOI: 10.12677/tcm.2025.149555

Abstract

Chitosan and its derivatives have excellent biocompatibility, degradability, and low immunogenicity, and combine a variety of biological activities, such as antioxidant, immunomodulatory, and antibacterial. In the field of drug delivery, nanocarrier technology has significantly improved the water solubility, targeting and safety of drugs. The chitosan nanodelivery systems studied so far mainly include: nanoparticles (good hydrophilicity and biocompatibility), electrostatically spun nanofibers (enhanced drug solubility and permeability), nanogels (high water-holding capacity), and chitosan-modified liposomes (enhanced targeting and tissue penetration). With their remarkable anti-inflammatory and anti-allergic properties and high bioavailability, these carrier systems provide a new strategy of high efficiency and low toxicity for the treatment of atopic diseases, such as asthma and allergic rhinitis, and show broad prospects for clinical applications. This paper focuses on the application mechanism of chitosan nanocarriers in the treatment of atopic diseases.

Keywords

Chitosan, Nanocarrier, Atopic Diseases, Review

1. 引言

壳聚糖(CS)作为天然碱性多糖，因其独特的理化特性在医药领域具有重要应用价值。研究表明，CS表现出优异的水溶性、流变特性和抗凝血功能[1]，其分子结构中的氨基使其具有 pH 响应特性，显著影响载体的稳定性和体内滞留时间[2]。这些特性使其成为理想的药物递送材料。CS 最显著的特点是优异的生物粘附性和广谱抗菌活性，这使其在伤口敷料领域获得成功应用[3]。随着纳米技术的发展，目前已开发出多种 CS 基递送系统，包括纳米颗粒、微球和纳米纤维等新型制剂。这些纳米载体系统通过尺寸效应和表面修饰，显著提高了药物的水溶性、靶向性和控释性能。在药物递送领域，CS 纳米载体因其良好的生物相容性和可降解性而备受关注。与传统载体相比，CS 基纳米载体不仅能克服传统递送系统的局限性，还能实现药物的精准递送和可控释放。这种独特的优势使其成为当前生物医学研究的热点之一。

特应性疾病是由 IgE 介导的过敏反应性疾病，主要包括变应性鼻炎(AR)、特应性皮炎(AD)和哮喘等[4]。流行病学调查显示，这类疾病的全球发病率持续攀升，给公共卫生系统带来沉重负担[5]-[8]。虽然现有免疫治疗手段取得一定疗效，但传统药物治疗仍存在生物利用度低、靶向性差和代谢过快等瓶颈问题。近年来，纳米载体技术为解决这些问题提供了新思路。研究表明，基于壳聚糖(CS)的纳米递送系统具有显著优势：1) 改善药物溶解度和稳定性；2) 增强黏膜渗透性；3) 实现靶向递送；4) 延长药物作用时间[9]。特别是 CS 纳米载体与特应性疾病的病理特征高度匹配，在调节 Th1/Th2 免疫平衡、抑制肥大细胞活化等方面展现出独特价值[10]。

特应性疾病(如 AR、AD 和哮喘)以黏膜过敏性炎症为主要特征。研究发现，壳聚糖纳米载体因其独特的理化特性，能有效针对这些疾病的病理特点发挥作用。尽管这类新型递药系统前景广阔，但目前仍缺乏对其作用机制的系统性总结。本文系统评述：1) CS 的基本特性及其功能机制；2) CS 基纳米载体(包括微球、纳米粒等)在特应性疾病治疗中的应用进展；3) 药物–载体相互作用的关键影响因素。通过整合

最新研究进展，为开发新型治疗方案提供理论依据。

2. CS 纳米载体现状

2.1. CS 的结构

壳聚糖自 1859 年被发现以来，其独特的分子结构特征备受关注。作为由 N-乙酰基-D-葡萄糖胺和 D-葡萄糖胺通过 β-(1→4)糖苷键连接而成的线性多糖[11]，CS 的每个 D-葡萄糖胺单元含有 1 个氨基和 2 个羟基，这一特殊结构赋予其显著的正电荷特性，使其能与带负电的生物分子形成稳定复合物[11]。研究表明 CS 的游离氨基不仅增强了其水溶性[12]，更为化学修饰提供了重要位点。

CS 的关键特性参数包括：1) 脱乙酰度(DD)：直接影响电荷分布、粘度和溶解度，DD 越高则化学修饰潜力越大[13]；2) 乙酰化度(DA = 100% − DD)：通常低于 50% [14]，显著影响分子间相互作用和材料性能[15]-[17]；3) 分子量(MW)：研究显示 MW 为 540 kDa 时基因表达最优[18] [19]，而低 MW CS 通常表现出更高的生物活性[20]。高 MW CS 则显示出更好的载药性能[21] [22]，这可能与小分子在界面的容纳能力有关[23]。

除上述特性外，CS 还具有多种卓越性能：在理化特性方面表现出优异的黏膜粘附性、可控药物释放能力和渗透增强作用[24] [25]；在生物活性方面则具有抗菌、抗氧化、免疫调节和促进组织修复等功能[26]，这些特性使 CS 成为药物递送领域的理想材料。

2.2. 基于 CS 的衍生物

CS 的化学修饰显著拓展了其应用潜力，通过硫醇化、硫酸化、羧甲基化和季铵化等修饰策略[27]-[32]，可有效改善 CS 的溶解性并扩展其 pH 适用范围。这些衍生物在保留 CS 原有生物相容性和抗菌性的基础上，赋予材料新的功能特性：硫醇化 CS 通过硫醇基团与黏膜糖蛋白形成二硫键，显著增强黏膜黏附性[27] [28]；硫酸化 CS 不仅提高水溶性，还能结合生长因子促进神经分化[29] [30]；羧甲基化修饰使 CS 获得 pH 响应性溶解特性[31]；季铵化则同步提升了材料的抗菌性和渗透性[32]，这些功能化修饰为 CS 在药物递送和医用敷料等领域的应用创造了更多可能性。

2.3. 基于 CS 的纳米载体

近年来，基于 CS 的纳米递送系统因其独特的优势获得广泛研究。主要类型包括：1) CS 纳米颗粒(NPs)：具有优良的生物相容性和可降解性，通过调控 CS 分子量和浓度可获得理想粒径，增强靶向性[33]；2) CS 纳米纤维(NFs)：通过静电纺丝技术制备，其多孔结构模拟细胞外基质，显著提升药物溶解度和渗透性[34] [35]；3) CS 纳米凝胶(NGs)：通过交联形成三维网络结构，具有高持水性和稳定性[36]；4) CS 修饰脂质体(LPs)：兼具脂质体和 CS 的优点，可改善药代动力学并增强组织靶向性[37]。这些纳米载体系统有效克服了传统递药系统的局限性，在提高药物生物利用度、降低毒副作用方面展现出显著优势。不同类型的 CS 纳米载体在针对特应性疾病的不同给药场景中各具特点：对于特应性皮炎等需要经皮肤给药的场景，CS 纳米凝胶凭借其优异的持水性和生物黏附性，能在皮肤表面形成持续给药的凝胶层，减少药物因皮肤屏障作用导致的损失，更适合局部长期治疗；而在肺部吸入给药治疗过敏性哮喘时，CS 纳米颗粒因粒径可控，且具有良好的分散性，能随气流深入肺部并快速释放药物，发挥速效作用；CS 纳米纤维由于其多孔结构模拟细胞外基质，在皮肤创面修复相关的特应性疾病辅助治疗中，可促进药物渗透并为细胞生长提供支撑，展现出独特优势；CS 修饰脂质体则因兼具脂质体的膜融合特性和 CS 的靶向性，在系统性特应性疾病治疗中，能通过改善药代动力学特性，延长药物循环时间，提高对病变组织的靶向递送效率，减少对正常组织的毒副作用。

3. CS 纳米载体的作用

3.1. 抗氧化

CS 纳米颗粒(NPs)作为抗氧化递送系统具有多方面优势[38]。实验证据表明：1) 基础抗氧化性能：CSNPs 能有效清除 DPPH、ABTS+等自由基[39]，抑制脂质过氧化[38]；2) 复合系统增效：Murugesan 等开发的离子凝胶化 CSNPs 显著提升自由基清除能力[40]，Musa 团队构建的疝素/氧化石墨烯-CS 系统对人肺 A549 细胞显示强抗氧化作用[41]；3) 分子机制：葛梅丽等证实硫酸化 β-葡聚糖-CSNPs 通过抑制 NO 和 TNF-α 分泌发挥抗氧化效果[42]，其作用涉及 Nrf2/HO-1 信号通路激活[42]。这些研究系统论证了 CSNPs 通过直接清除自由基、调控氧化应激通路等多重机制增强抗氧化活性的特点。

3.2. 免疫调节

CS 基纳米系统通过多途径调节免疫反应的研究取得重要进展。在免疫激活方面：1) Zhang 等开发的甘露糖修饰 CS 胶束通过 cGAS-STING 通路促进 DC 成熟[43]；2) N-2-HACC/CMCS NPs 可增强 Th1 应答，上调 cGAS/TBK1/IRF3 信号[44]。在抗炎作用方面：1) Feihong D 团队证实 MTC-miR146b NPs 通过 TLR4/NF-κB 通路抑制 M1 巨噬细胞活化[45]；2) 植物提取物-CS 复合物能显著降低 TNF-α、IL-6 等炎性因子[46] [47]；3) 冯艳霞等发现多肽-CS NPs 可抑制 iNOS 和促炎细胞因子基因表达[48]。其他免疫调节机制包括：1) Xiao-Yan H 报道的双靶向 NPs 通过激活 PI3K/Akt 和 MAPK 通路增强免疫应答[49]；2) 黑磷-CS 水凝胶调控 p-p38/Snail1 信号促进上皮修复[50]；3) Soojin S 研究的 CS NPs 可激活 NALT 免疫，诱导 IgG/IgA 产生[51]；4) Latexin-CS NPs 抑制 Treg 细胞分化[52]。这些研究系统阐明了 CS 纳米载体在免疫调控中的多重作用机制。

4. CS 纳米载体的应用

CS 基纳米载体凭借其生物可降解性、组织相容性和低免疫原性，成为特应性疾病靶向治疗的理想选择。其优势体现在：增强药物稳定性、提高黏膜黏附性和实现可控缓释[53]，显著提升临床疗效。

4.1. 特应性皮炎

CS 纳米载体在特应性皮炎(AD)治疗中展现出显著优势。研究表明，负载氢化可的松(HC)和羟基酪氨酸(HT)的 CSNPs (100~250 nm)通过延长药物滞留和增强皮肤渗透[54] [55]，可显著改善 AD 症状(降低经表皮水分流失、红斑强度等) [56]，同时减少不良反应[57]。机制研究显示，氢化可的松-CSNPs 能有效抑制 IL-4、IL-6、TNF-α 等炎症因子表达[58]。此外，中药-CS 复合系统(如没食子酸/白藜芦醇-CSNPs)通过抑制 ROS 产生和氧化损伤，为 AD 治疗提供了新思路[59]。

4.2. 哮喘

CS 纳米载体为哮喘治疗提供了新策略。研究表明，多种 CS 递药系统展现出良好效果：1) CS/果胶复合纳米颗粒增强特布他林鼻内递送[60]；2) 透明质酸-FA-CSNPs 通过雾化给药有效控制症状[61]；3) 泼尼松龙-CSNPs 口服片改善儿童用药依从性[62]；4) 孟鲁司特-CSNPs 实现肺部深度沉积[63]。其治疗机制包括：调节 Th1/Th2 和 Th17/Treg 平衡[64]，抑制 IL-4、IL-17 等炎症因子；CS-肝素复合物阻止肥大细胞脱颗粒[65] [66]；吲哚醌-CSNPs 调控 NPRA 信号通路[67]；pH 敏感型 CSNPs 实现胃肠道靶向释放[68]。这些系统显著缓解气道炎症和支气管收缩，为哮喘治疗提供更安全有效的选择。

4.3. 过敏性鼻炎

CS 纳米载体为过敏性鼻炎(AR)治疗提供了创新解决方案。研究表明：1) 色甘酸钠-CS 纳米颗粒显著

延长鼻腔滞留时间，提高患者依从性[69]；2) pVAX1-Derp1/CSNPs 有效保护 DNA 免受降解，增强基因治疗效果[70]；3) 槲皮素-CSNPs 通过调节 INF-γ/IL-4 平衡减轻炎症反应[71]；4) 苍耳子油-CS 纳米系统通过调控 Th1/Th2 免疫平衡和抑制肥大细胞活化发挥治疗作用。这些 CS 基递药系统展现出靶向性强、控释性能好和毒副作用低等优势[69]-[72]，为 AR 治疗提供了更安全有效的选择。

5. 小结

壳聚糖基纳米载体凭借优异的生物相容性与低免疫原性，在特应性疾病治疗领域展现出独特优势。其作用机制主要包括：1) 延长药物滞留时间并增强黏膜渗透能力；2) 激活 cGAS-STING 通路以强化免疫应答；3) 调控 TLR4/MAPK/NF-κB 信号通路实现炎症抑制；4) 调节 Th1/Th2 及 Th17/Treg 平衡以减轻炎症反应。在过敏性鼻炎(AR)、特应性皮炎(AD)、哮喘等黏膜炎症性疾病中，CS 载体通过提升氢化可的松、倍他米松等药物的生物利用度，可达成高效低毒的治疗效果。尽管 CS 纳米药物的研究已取得重要进展，但在分子机制解析与临床转化层面仍需深化探索。当前研究存在三方面局限性：一是机制研究多依赖小鼠等动物模型，其生理结构与人类存在差异，可能导致部分实验结果难以直接转化；二是临床前研究多为小样本量探索，缺乏大样本验证数据；三是长期毒性评估(如慢性给药后的器官蓄积效应)尚未完全明确，这些因素均可能影响其临床应用进程。现有研究证实，CS 基纳米载体具备显著的抗炎、抗氧化及免疫调节作用，为特应性疾病的治疗提供了创新策略，其应用前景值得期待。

基金项目

新疆塔里木大学胡杨英才－引进人才科研启动金(博士)项目(TDZKBS202574)、(TDZKBS202576)。

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