Developing Polymeric Nanoparticles for Controlled Drug Delivery in Anti-inflammatory Therapies

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（抗炎症治療における薬物送達を制御可能な高分子ナノ粒子の開発）

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論　文　内　容　の　要　旨

The immune system is a complex and delicate system in living organisms that contributes to the homeostasis of life in the form of signaling, cell-to-cell interactions, and biological responses. Within this complex network, the natural balance of the immune system is essential for maintaining health. However, sometimes the balance can be disturbed, triggering immune dysregulation such as inflammatory bowel disease (IBD) and allergy. In response to these challenges, nanoparticles have emerged as a promising platform. In-depth exploration and understanding of nanoparticles in the immune system will provide us with new avenues to manage the immune response and thus have a significant impact on health and disease. In this thesis, I have designed three nanoparticles to restore immune homeostasis to treat intestinal disorders or allergic diseases through different routes of administration.

In Chapter 2, I designed polyvinyl butyrate nanoparticles (PVBu NP) that could be orally administered and delivered to the intestine to release anti-inflammatory butyrate. To evaluate the size effect of the therapeutic efficacy on colitis model mice, I prepared two sizes of NPs (NP1:100 nm and NP2:200 nm). Both NP1 and NP2 showed suppressed release of butyrate and inhibited the inflammatory response of macrophages. NP2 showed better therapeutic effects on colitis mice compared to NP1. NP2 containing all-trans retinoic acid (ATRA) showed an enhanced ability to ameliorate colitis compared to NP2, despite reports that ATRA alone exacerbates inflammation. In conclusion, PVBu NPs are a promising therapeutic approach for the treatment of IBD.

In Chapter 3, I prepared the PLGA nanoparticles (NPs) to incorporate OVA and tolerance agents (rapamycin, bexarotene, and suberoylanilide hydroxamic acid) by the W/O/W double emulsion method for allergy treatment. I evaluated the stability of NPs in the gastrointestinal (GI) tract mimic solution. The NPs demonstrated stability after incubation in the GI tract mimic solution without size changes and significant content release except for NP-rapamycin. To summarize, the NPs exhibited stability in the GI tract environment, suggesting the potential for oral administration.

In Chapter 4, I designed a gelatin-based nanoparticle loaded with the antigen OVA (G) to treat allergic diseases. To fabricate safer, more efficient nanoparticles, I developed heated G (hG) and mannan-coated G(MG). Heated OVA could alleviate allergy symptoms and also suppress IgE binding ability. Mannan is known to be a DCs targeting molecule, and mannan-modified particles could induce immune tolerance. hG and MG showed more prolonged release of OVA. MG showed significant DC uptake efficiency and enhanced the ability of DCs to secrete IL-10. Regarding safety, both hG and MG significantly reduced the binding capacity to IgE and suppressed the risk of anaphylaxis. Besides, G did not produce anti-drug antibodies (IgG, IgM) during repeated injections, indicating low immunogenicity. In allergic mice, both hG and MG showed therapeutic effects by decreasing anti-OVA IgE and IgG1 and eosinophils. Thus, gelatin nanoparticle is a suitable therapeutic method for allergy treatment.