Development of nanoparticles for induction of immunotolerance towards the therapy of inflammation and allergic diseases

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論 文 名　：Development of nanoparticle for induction of immunotolerance towards the therapy of inflammation and allergic diseases
（炎症およびアレルギー疾患の治療のための免疫寛容誘導ナノ粒子の開発）

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論　文　内　容　の　要　旨

Thanks to the nanomedicine properties and characteristics that lipid-based nanoparticle and protein-based nanoparticle have, developing strategies to design tolerogenic nanoparticle have been extensively evolved. Whether encapsulation or conjugation of immunomodulatory molecules with nanoparticles is achieved through covalent, chemical, or physical interaction, the ultimate purposes are to improve efficacy of existing drugs and develop new therapeutic systems. Nanoparticle therapies are growing and used in the understanding of the underlying pathogenesis of immune-mediated diseases. Nanoparticles also have potential to restore peripheral immune tolerance or to regulate aberrant monocyte activities during severe inflammation. However, the functional outcome of nanoparticles depends on many intrinsic factors of nanoparticle and also is interfered by external factor such as route of administration. To address this issue and to utilize the potential of nanoparticle, development of an inert and simpler nanoparticle is required. In this thesis, I approached this goal through two methods.

Following is the content of this thesis.

In chapter 1, I explained the function of vitamins on the regulation of immune system and introduced previous works about induction of immunotolerance by nanoparticles.

In chapter 2, I could successfully prepare effective formulation of nanostructured lipid carrier (NLC) for delivery of $1,25(OH)_2D_3$ to colonic inflammatory lesions via oral

administration. NLC as lipid-based nanoparticle is suitable for incorporation of hydrophobic molecules. NLC orally delivered $1,25(OH)_2D_3$ to the colon in mice and maintained a high concentration of $1,25(OH)_2D_3$ in the colonic tissue for at least 12 h. The NLC showed multiple effects on the suppression of symptoms of colitis induced by dextran sodium sulfate, namely maintaining crypt structure, reducing the tissue concentration of inflammatory cytokines, suppressing the infiltration of polymorphonuclear leukocytes, and augmenting anti-inflammatory CX_3CR1^{high} macrophages. My NLCs containing $1,25(OH)_2D_3$ may be an alternative treatment for IBD therapy.

In chapter 3, I followed first strategy which used NLC as carrier for regulation inflammation. I used same formulation of NLC for incorporation and delivery of all-trans retinoic acid (ATRA). NLC containing ATRA (NLC-RA) thus obtained was taken up by macrophages and induced anti-inflammatory response via suppressing NF-κB signaling as well as via enhancing the production of anti-inflammatory cytokines. Moreover, NLC-RA enhanced differentiation of naïve T cells to regulatory T cells in the co-culture system with dendritic cells. These results suggest that NLC-RA is a promising alternative therapy for the autoimmune diseases especially intestinal bowel disease.

In chapter 4, I proposed a simple formulation of ovalbumin nanoparticles complexed with all-trans retinoic acid (OVA/RA NPs) induced phenotype of tolerogenic dendritic cells (tDCs). tDCs play a crucial role in the immunotolerance therapy because they induce anergic response for auto-reactive helper T cells and also enhance differentiation to regulatory T cells to maintain tolerance against auto-antigens. ATRA is one of the representative molecules to induce tDCs. As a result, OVA/RA NPs were taken up by DCs and successfully induced phenotype of tolerogenic dendritic cells (tDCs). These promising features of OVA/RA NPs will be suited for immunotolerance therapy and may be applicable to pulmonary delivery via inhalation to treat allergic asthma.

In chapter 5, I described the summary of this paper as well as the future prospect of this research.