Development of nanoparticles to induce immunosuppression in the gut-liver chronic inflammation

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論 文 名　：　Development of nanoparticles to induce immunosuppression in the gut-liver chronic inflammation
（慢性炎症に対する免疫抑制の誘導のためのナノ粒子製剤の開発）

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論　文　内　容　の　要　旨

Thanks to the characteristics of nanomedicine that polymer-based nanoparticle and lipid-based nanoparticle have, nanoparticles' strategies to induce anti-inflammatory response to treat chronic inflammatory diseases have been extensively evolved. Nanoparticle has been designed to passively or actively target the site of inflammation and have been shown to be more beneficial than conventional formulations, better bioavailability at inflamed tissues and reduced systemic adverse effects. Oral delivery by using nanoparticles has been recognized as the most attractive method due to ease of administration and intensified immune response. However, the functional outcome of oral nanoparticles depends on many intrinsic particle factors and also is interfered by external factor such as the biological barriers. To address this tissue and to utilize the potential of nanoparticle, development of an inert and simpler nano-delivery system is required. In this thesis, I approached this goal through two methods.

In chapter 2, I established successfully the new oral drug delivery system of butyrate by using the polyvinyl butyrate (PVBu) to the lower part of intestine for the treatment of colitis induced by dextran sulfate sodium (DSS). PVBu nanoparticle (NP) suppressed the activation of macrophage in vitro, indicating that PVBu was hydrolyzed to release butyrate and raise the intracellular concentration of butyrate. Although oral administration of NP did not raise the concentration of butyrate in cecum, NP showed the therapeutic effect on the colitis model indicating that NP may target immune cells like the residential macrophage and raise the intracellular butyrate concentration. This characteristic may be suitable to avoid the side effect brought by the high concentration of butyrate. I also demonstrated that PVBu nanoparticles can be a carrier of vitamin D_3 and showed the synergy on the therapeutic effect with butyrate derived from PVBu. Thus, PVBu may be a novel carrier of butyrate to treat inflammatory bowel diseases (IBD) with reduced butyrate concentration in lumen.

In chapter 3, I utilized nanostructured lipid carriers (NLC) containing active vitamin D_3 to target the intestine and liver for treatment of non-alcoholic steatohepatitis (NASH) model mice. At a safe dose at which free vitamin D_3 did not show a therapeutic effect, NLC suppressed intestinal permeability and ameliorated NASH symptoms. This simple formulation of vitamin D_3 prepared from approved materials and could be a practical therapeutic agent that act on the liver and intestine for NASH therapy via the gut–liver

axis.

The novel approaches and findings in this research may provide new insights into the development of more straightforward methods to utilize the unique advantages of nanoparticles in the anti-inflammatory therapy. In a broader sense, they can lead realizing of more efficient, safer and cheaper medications for severe diseases associated with chronic inflammation.