Two strategies to maintain the intestinal homeostasis: anion-exchange resin to avoid antibiotic-induced dysbiosis and mannan-coated antigen nanoparticles for allergy treatment

李, 順怡

（様式３）

氏　　名　：李　順怡

論 文 名　：Two strategies to maintain the intestinal homeostasis: anion-exchange resin to avoid antibiotic-induced dysbiosis and mannan-coated antigen nanoparticles for allergy treatment
（腸管恒常性の維持戦略：アニオン交換樹脂を用いた抗生物質によるディスバイオシスの回避とマンナン-抗原ナノ粒子を用いたアレルギーの治療）

区　　分　：甲

論　文　内　容　の　要　旨

In the intestine, there is the largest lymphoid tissue in the body. At every moment, immune cells are influenced by the commensal microbiota. These immune cells play a key role in maintaining immune homeostasis by inhibiting the response to antigens from commensal bacteria as well as food. At the same time, gut commensal bacteria also modulate the immune system through metabolites. Imbalance of the gut microbiota, termed dysbiosis, can trigger some immune diseases such as allergy by affecting the activities of immune cells near or far from the site of dysbiosis. One risk factor to induce dysbiosis is administration of antibiotics. To prevent dysbiosis, it need to administrate antibiotics without destroying gut microbiota. To treat the allergy which has developed, allergen immunotherapy (AIT) is used to induce antigen-specific immune tolerance. Nanoparticles (NPs) such as emulsions and liposomes have been used into pre-clinical allergy treatment in recent years, but preparation method of these NPs are complicated. In this thesis, I prevented antibiotic-induced dysbiosis by an anion-exchange resin (AER), and developed two NPs to treat allergy.

In Chapter 2, I used an AER for adsorbing the ß-lactam antibiotic cefoperazone (CEF). The AER was used to adsorb CEF through electrostatic and π-π interactions. The AER was specific for CEF over biological molecules in the intestine and protected Escherichia coli from CEF in vitro. Furthermore, oral administration of the AER reduced the fecal free CEF concentration, and protected the gut microbiota from CEF-induced dysbiosis.

In Chapter 3, I developed a simple approach for preparing disulfide bond crosslinked mannoprotein (MAN)-ovalbumin (OVA) NPs (MDO), in order to induce OVA-specific immune tolerance via dendritic cells (DCs). DCs play a crucial role in the antigen-specific immunotherapy which could induce regulatory T (Treg) cells to maintain tolerance. Mannan on the surface of MDO enhance uptake efficiency of DCs and antigen presentation efficiency of MDO on DCs was high. MDO showed low reactivity with anti-OVA antibodies and did not induce anaphylaxis in allergic mice, which demonstrated high safety of MDO. In mouse allergic asthma model, MDO showed great prevention effect and therapeutic effect through both oral and subcutaneous administration. Thus, based on the therapeutic efficiency and safety of MDO, I believe that MDO could act as a new approach for allergy treatment.

In Chapter 4, I followed the strategy in Chapter 3 which used disulfide bond to crosslink MAN and protein for DC targeting. In this chapter, I used human serum albumin (HSA) as matrix to prepare MAN-coated NP to delivery antigens and drugs which is suitable for precious antigen delivery. HSA-based matrix could delivery antigens which have similar denaturation temperature with HSA and low tendency of self-aggregation. I demonstrated that MAN-coated HSA-OVA NP (MHO) could target DCs, enhanced uptake efficiency, antigen presentation efficiency and inhibited activation of DCs. Thus, antigen-HSA NPs are possible to treat allergy effectively and safety.

The new approaches in this thesis may provide a fresh perspective into the development of more straightforward methods to utilize the materials to maintain immune homeostasis via the intestine. These approaches maybe more effective, safer and lower cost to treat several diseases.