(学位論文のタイトル) Title
Suppression of Systemic Lupus Erythematosus in NZBWF1 mice infected with Hymenolepis microstoma
腸管寄生性蠕虫Hymenolepis microstomaによるNZBWF1マウスでの自然発症全身性エリテマトーデスの抑制
(学位論文の要旨) 2,000字程度、A4判 (approx. 800 Words in English /A4 size)

The decline in the incidence of infectious diseases in western countries and recently in developing countries has led to the increase in the incidence of autoimmune and allergic diseases, which is known as hygiene hypothesis. Based on epidemiological findings, there is an inverse relationship between autoimmune diseases and helminths infestations, supporting the hypothesis. Thus, helminthic infections are supposed to suppress autoimmunity. Intestinal helminths induce immune suppressive responses thought to regulate inflammatory diseases including allergies and autoimmune diseases. For instance, a rodent intestinal nematode, Heligmosomoides polygyrus, suppresses bronchial asthma and drug-induced type 1 diabetes, Schistosoma mansoni reduces the severity of chemical-induced colitis, and experimental autoimmune encephalitis, a model of multiple sclerosis. Furthermore, a swine whipworm, Trichuris suis, and a human hookworm Necator americanus has been used to treat inflammatory bowel diseases and multiple sclerosis.

SLE is a systemic autoimmune disease characterized by a circulating immune complex consisting of autoantibodies directed to a diverse array of cellular components. The disease can involve almost all organs and tissues with a wide range of clinical manifestations including arthritis, pericarditis, skin rash, and life-threatening neuropsychiatric symptoms. One of the most affected organs is the kidney, which contains a complicated vascular system called the glomerulus. Lupus nephritis develops in more
than 70% of patients with SLE. The etiological abnormality in SLE is uncontrolled production of autoantibodies mainly due to impaired self-tolerance, immune complex deposition and immune-mediated injury to the kidney, resulting in increased cell proliferation, apoptosis, and induction of inflammatory and fibrotic processes that destroy normal nephrons. This study was therefore designed to evaluate whether helminthic infections suppress the natural development of systemic lupus erythematosus (SLE) in NZBWFI mice.

NZBWFI, a mouse model for natural development of SLE were infected with helminths. Autoantibody development was monitored by measuring serum IgG with ELISA. Proteinuria was measured semi quantitatively by Urine dipstick assay, and Albumin concentration was quantitated by ELISA. Mice were sacrificed between 6 to 10 months. Spleen and kidney were removed to investigate splenomegaly and glomerular pathology respectively. Changes in cell population was analyzed by flow cytometry.

Infection of NZBWFI SLE-prone mice with two nematodes *Heligmosomoides polygyrous* (Hp) and *Trichuris muris* (Tm) failed to establish long-lasting settlement. However, the *Hymenolepis microstoma* (Hm) rodent tapeworm successfully established long-term parasitization of NZBWFI mice and was used to evaluate the suppressive effects of helminth infection. Ten-month-old NZBWFI mice developed symptoms including autoantibody generation, proteinuria, glomerular histopathology, and splenomegaly, but mice infected with Hm at 2 months of age did not show any clinical signs and lived longer than uninfected mice. Furthermore, infection with Hm reduced lymphocyte activation including B-lymphocytes, T-follicular helper cells, and increased regulatory T cells in the spleen and mesenteric lymph nodes. These results indicate that infection with Hm protects NZBWFI mice from naturally developing SLE and suggest that pathological immunity is attenuated, presumably because of the induction of regulatory T cells.