Recipient of 2011 Student Fellowship Award – SSF-ACR REF

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Project Title: Effects of FTY-720 on a murine model of Sjogren's syndrome

Abstract

Proposal
I am currently interested in studying the nature of lymphocyte circulation and infiltration in a mouse model of Sjögren’s syndrome. Previous studies in our lab have shown a decrease in the size of salivary infiltrates with the use of oral fingolimod (FTY720), an immunosuppressant drug that sequesters lymphocytes in secondary lymphoid organs thereby diminishing the numbers of circulating lymphocytes. This finding suggests that there is circulation of lymphocytes into and out of salivary glands of Sjögren’s mice. I am also interested in examining the therapeutic potential of oral fingolimod for Sjögren’s. With oral fingolimod having currently received FDA approval for treatment of multiple sclerosis, it is of importance to determine the efficacy of this drug for treatment of other lymphocytic infiltrative diseases, such as Sjögren’s.

Goals
After receiving funding the previous year from the ACR-SSF, Ms McCulloch has generated additional provocative data indicating that FTY-720 is effective in both reducing infiltrates and increasing salivary flow in SS mice. The current studies will extend this work in a mechanistic direction by characterizing the nature of the infiltrates in treated mice and will lay the groundwork for additional mechanistic studies.

Specific Aims
Sjögren’s syndrome (SS) is a systemic autoimmune disease characterized by lymphocyte infiltration into exocrine glands as well as loss of glandular structure and function. As a result, patients often present with dry eyes and dry mouth. Disease is diagnosed alone (primary Sjögren’s) or in conjunction with other rheumatic diseases (secondary Sjögren’s), most often systemic lupus erythematosus, rheumatoid arthritis, or scleroderma. Current thinking suggests that disease progresses in a series of phases. First, an initial insult occurs in the gland (injury or pathogen related). This activates apoptotic and/or necrotic pathways and results in cytokine and chemokine release as well as cell adhesion molecule upregulation. This attracts lymphocytes from circulation. Lymphocytes infiltrate the gland and contribute to the pro-inflammatory environment. Glandular dysfunction appears in the final stage of disease, perhaps as a result of the action of effector T cells on acinar cells and/or interruption of neural-acinar cell signaling by cytokines and autoantibodies.1
In our proposed study, we will use C57BL/6.NOD-Aec1Aec2 (hereafter, AEC) mice as our experimental SS model. By 16 weeks of age, AEC mice exhibit many of the hallmarks of Sjögren’s Syndrome, including xerostomia and xerophthalmia as well as autoantibody production. These mice have B6 genetic background but contain two genetic intervals from the NOD mouse: a 73.3cM region from chromosome 3 and 48.5cM genetic region from chromosomes 16. These loci were found to induce autoimmune exocrinopathy, but not insulin dependent diabetes mellitus (IDDM), in the normally healthy C57BL/6 mouse. These genetic regions were termed Aec1 and Aec2, respectively. In addition, replacement of Aec1 and Aec2 in the NOD mouse with genetic regions from C57BL/6 ameliorated autoimmune exocrinopathy.

To study lymphocyte circulation in these AEC mice, we will treat mice with a novel immunosuppressant, Oral Fingolimod (FTY720, Novartis Pharma). FTY720 recently received FDA approval for treatment of relapsing remitting multiple sclerosis. FTY720 resembles sphingosine, an 18-carbon amino alcohol with an unsaturated hydrocarbon chain that, in its phosphorylated form, plays an important role in lymphocyte egress from secondary lymphoid organs (spleen, lymph nodes) to blood. Once ingested, sphingosine kinases rapidly phosphorylate the drug. Phosphorylated FTY can bind spingosine receptor 1 on lymphocytes and induce internalization of the receptors, thereby helping to sequester lymphocytes in secondary lymphoid organs and to inhibit lymphocyte circulation.