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“Role of Act1 in development of Sjögren’s syndrome”

Recipient of Research Grant Award

LAY ABSTRACT:

Autoimmune diseases, including Sjögren's Syndrome, arise when B-cells (cell of the immune system) produce antibodies that attack the body's own tissues. In Sjögren's Syndrome glands that produce saliva and tears are the main organs targeted by these B-cells. The origin of autoreactive B-cells is unknown, but studies have suggested that defects in the mechanisms that control their survival and elimination may lead to autoimmunity. We have identified a molecule, called Act1 that regulates the survival the B-cells. Modified mice that lack Act1 expression develop symptoms that very closely resemble human Sjögren's Syndrome. In our investigations we want to define whether defects in Act1 contribute to the development of the disease in patients. Also, further studies on Act1-deficient mice will help our understanding of the pathology of Sjögren's Syndrome and it is our hope that these studies will result in the development of new effective therapeutic to treat the disease.

SCIENTIFIC ABSTRACT AND RESEARCH PROPOSAL:

Sjögrens Syndrome (SjS) is a relatively frequent (~ 1.5% of the population) systemic autoimmune disease in which the salivary and lachrymal glands become infiltrated by especially B lymphocytes leading to the development of xerostomia and xerophthalmia (dry mouth and dry eye). The diagnosis of SjS is dependent on the presence of elevated levels of specific autoantibodies against SSA/Ro and SSB/La and thus B lymphocytes are thought to play a major role in the disease development. Although multiple factors, including environmental stress, infections and genetic background have been proposed, the etiology of the disease is largely unknown.

We have developed a new mouse model of SjS by targeted the expression of an adapter molecule, Act1, involved in B cell activation and survival. Act1-deficient mice develop B cell hyperplasia, lymphocytic infiltration of the salivary and lachrymal glands, anti-SSa/Ro and anti-SSB/La antibodies and symptoms of xerostomia and xerophthalmia. We propose to use Act1-deficient mice to study the origin of autoreactive B cells present in gland infiltrates in order to further understand how B cell dysregulation contributes to the development of SjS. In addition, as Act1-deficiency clearly has such an impact

in mouse models, we will test if polymorphisms in the human homolog, ACT1, are associated with the diagnosis of SjS in a controlled population. We hope that our studies will open for new and more specific therapeutics for the treatment of SjS.