Local gene therapy and the identification of therapeutic targets in Sjögren’s syndrome
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Citation for published version (APA):

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GENERAL INTRODUCTION
SJÖGNEN’S SYNDROME, TARGETS AND THERAPY

Sjögren’s Syndrome (SS) is a chronic inflammatory exocrinopathy that affects an estimated 0.1-1.0% of the general population, most commonly women in their 4th or 5th decade. Patients diagnosed with SS complain of dry eyes and dry mouth, leading to pain, dyscomfort, frequent infections and poor dental health. This dryness is the result of a poorly understood autoimmune process that mainly affects the secretory glands, such as the lachrymal and salivary glands (SG). In addition, patients can suffer from extra-glandular manifestations including peripheral neuropathy and vasculitis and often experience disabling fatigue. A potential life threatening complication of SS is the development of lymphomas, mostly of the mucosa-associated-lymphoid type (MALT); SS patients have an estimated 16 times higher risk compared to the general population. Despite the prevalence of the disease, limited knowledge exists on its aetiology. Genetic (reviewed in 4), infectious, hormonal, neurological and immunopathological factors may all play a role in the development of the disease.

There is a large unmet need for effective therapy in SS; curative treatment for SS is not available. Immune based therapies such as tumor necrosis factor (TNF) antagonists, which are successful in the treatment of other autoimmune diseases such as rheumatoid arthritis, have failed in SS. Most SS patients today are using artificial tears and sympathomimetics to stimulate salivary flow with unsatisfactory results.

One of the major problems in finding a therapy for Sjögren’s syndrome is that the right therapeutic target has not been identified, mostly due to the poor understanding of the disease pathogenesis. This thesis addresses a few questions in this regard:

1. Based on current knowledge, which novel immunological targets can be identified for the treatment of SS?
2. Can additional targets be identified studying a spontaneous mouse model for SS; the NOD mouse?
3. Is it possible to alter auto-immune SG disease in this mouse model by inhibiting or altering the previously identified targets with local gene therapy?
4. Are there additional targets to be identified in patients with SS?

Chapter 2 and chapter 3 introduce the experimental studies. In chapter 2 the immunological disbalance in cytokines observed in human SS patients is summarized. In addition, experiences with cytokine directed therapies in SS are discussed. In chapter 3, the possibilities to address this disbalance with (local) gene therapy are discussed and potential immunological targets for the treatment of SS are proposed.

A reason for the poor understanding of SS is that most patients are diagnosed when inflammation is clearly present and therefore little is known about the early onset and progression of the disease. Mouse strains that spontaneously develop a SS-like disease offer an insight into early disease processes that may be extrapolated to SS in humans. In addition, studying a mouse model makes it possible to closely follow pathogenesis over time. Currently there are multiple of such animal models available for human SS. We have chosen to study the (most commonly used) non-obese diabetic (NOD) mouse. These mice spontaneously develop autoimmunity resulting in...
diabetes and thyroiditis. They also show progressive inflammation of the salivary and lachrymal glands, closely resembling the human inflammatory characteristics in SS disease. Over time these mice may develop salivary flow impairment. In chapter 4, the development of this SS-like disease in NOD mouse is followed and described in detail. The inflammatory and physiological changes in the salivary gland are specifically addressed.

Besides a model to study the pathogenesis of a SS-like disease, the NOD mouse also offers a model to test a variety of therapeutics. Based on the observations that were made in the NOD mouse and the current knowledge on pathological pathways in SS, we choose to target intercellular adhesion molecule type 1 (ICAM-1) (chapter 5), CD40 (chapter 6) and the B-cell activating factor (BAFF)/a proliferation inducing ligand (APRIL)-transmembrane activator and CAML interactor (TACI)-axis (chapter 7). These molecules and related pathways were found to be upregulated in the NOD mouse and are known to be aberrantly expressed in humans with SS. Immunomodulatory molecules interfering with the proposed targets were expressed in the salivary glands by local gene therapy in which the gene of interest is transferred into the SG with the aid of an adeno-associated viral vector (AAV). This ensures delivery of the gene into the epithelial cells (forming the ducts in the SG) and leads to a stable expression and secretion of the immunomodulating proteins. In chapter 8, two of these immunological targets identified in mice, the B cell related cytokines APRIL and BAFF and their receptors, are analyzed for their presence in human salivary gland biopsies and blood. In the last chapter, the findings described in this thesis are summarized, discussed and recommendations for the future are made.

REFERENCES