Local immunomodulatory gene therapy for Sjögren’s syndrome
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Citation for published version (APA):
GENERAL SUMMARY

Sjögren’s syndrome (SS) is a systemic autoimmune disease. It is mainly characterized by symptoms of dry mouth and dry eyes caused by a decrease and/or changed composition of saliva and tears. In the salivary and lacrimal gland a focal inflammatory infiltrate of predominantly CD4\(^+\) T lymphocytes can frequently be found. SS patients commonly also have more generalized problems, such as fatigue, arthritis or vasculitis. Furthermore, there is an increased risk of the development of lymphoma. SS predominantly affects peri- and postmenopausal women. There is a distinction between primary and secondary SS; the latter develops in the presence of other autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis.

The etiology and pathogenesis of SS are largely unknown, which makes treatment more challenging. Unfortunately, only palliative therapies available are currently available, albeit steps have been taken in using immunomodulatory medication. This is further described in the introductory Chapter 1.

Part I. Gene Therapy Vectors

In the early nineties the first, promising steps in the field of gene therapy were made. Despite some mishaps and disappointments much progress has been made over the years and several clinical trials have been realized. Chapter 2 describes the latest advances in vector-mediated gene transfer with special focus on salivary glands and SS. A vector is necessary for a cell to uptake foreign DNA. Several viral vectors can be employed for gene transfer, such as the adenovirus (Ad), adeno-associated virus (AAV) or retrovirus. The non-enveloped Ad conveys robust transgene expression, but it is short-lived due to a potent immune response. Alternatively, AAV elicits only a minimal immune response and, consequently, the transgene expression, while often more modest than that seen with Ad vectors, is very stable, lasting for years.

Ad is commonly employed for ‘proof-of-concept’ studies in animal models. Chapter 3 describes the construction of an Ad encoding the vasoactive intestinal peptide (VIP) gene. It is the first report about a recombinant viral vector expressing biologically active VIP.

Part II. Gene Therapy in an Animal Model of Sjögren’s Syndrome

Currently, there is no treatment for SS and the palliative therapies offered are usually unsatisfactory. SS patients could potentially benefit from immunomodulatory gene therapy. Furthermore, additional insight into the pathogenesis of SS could be gained from this type of therapy. To study SS the non-obese diabetic (NOD) mouse model is often used. Besides diabetes mellitus type I the female
mouse also develops focal inflammatory infiltrates in the salivary glands and decreased salivary flow. A recombinant serotype 2 AAV (rAAV2) encoding human interleukin 10 (hIL-10), was tested in the NOD mouse, as described in Chapter 4. rAAV2hIL-10 or a control virus (rAAV2LacZ) was delivered by retrograde instillation directly to the submandibular salivary gland before or after disease onset. SS and diabetes parameters were measured and compared. rAAV2hIL-10 resulted in an increased salivary flow rate, lower focus score (less focal infiltrates), changes in submandibular gland cytokines, lower blood glucose levels, and higher insulin levels compared with control. The latter two parameters indicated a systemic effect of hIL-10 after local delivery. Administration of rAAV2hIL-10 after onset of SS-like disease was less effective than before.

The next two chapters illustrate testing rAAV2hVIP (Chapter 5) and an NF-κB inhibitor, rAAV2IkBα(sr) (Chapter 6), in a comparable setting as above, but only with administration before disease onset. Both immunomodulatory proteins resulted in a higher salivary flow rate and changes in submandibular gland cytokines. Although VIP is secreted into saliva with a small amount being directed to the bloodstream, no systemic side effects after rAAV2hVIP administration were observed.

The most commonly used animal model for SS uses the NOD mouse. Several reports describe variability in diabetogenesis in NOD mice and in Chapter 7 five different experimental studies are evaluated to determine if the same might apply for the SS phenotype. Unquestionably, there was instability in the SS phenotype in the NOD mice studied over a two-year time period, possibly due to changes in the environment.

The final Chapter 8 comprises a summary of several of the preceding chapters. Moreover, the lessons learned through experience with gene therapy and biological agents about the exocrine pathogenesis of SS are presented. Based on this information a most optimal treatment for SS is offered: a combination of local gene therapeutics.