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DENDRITIC CELLS AS POTENTIAL TARGETS FOR IMMUNOTHERAPY IN SJÖGRENS SYNDROME AND RELATED RHEUMATIC DISEASES.

Dendritic cells (DC) are the most potent antigen-presenting cells (APC) playing a crucial role in initiating and maintaining primary immune responses to pathogens as well as mediating tolerance to self-antigens. The proposed role of DC in breaking down tolerance could be a critical issue in the development of autoimmune diseases as dysfunctional DC might instead of inducing anergy promote immune responses towards autoreactivity.

Apart from initiating T cell activation via TCR-MHC class II interaction, DC are crucial for orchestrating a proper immune response via production of cytokines. Serological characteristics of systemic autoimmune diseases such as Sjögren's syndrome (SS), Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA) are the production of autoantibodies and a skewed profile of several cytokines. Notably, the type-I interferon-α (IFN-α) as well as B-cell activating factor (BAFF) have been shown to be associated with SS and SLE, whereas increased IL-6 levels are frequently found in plasma from patients with RA. Little is known on how dysfunctional DC might contribute to the disease development of these rheumatic diseases, and DC might serve as a potential source for the imbalanced cytokine network. Moreover, DC functions might be altered under influence of cytokines that have been implicated in these autoimmune diseases, such as IL-1alpha, IL-10, IL-12, IL-17 and TNF-alpha.

As many autoantibodies associated with autoimmune diseases are directed towards nuclear components, defective binding of self-molecules to TLR and inadequate activation of APC such as DC might be the trigger to the aberrant

immune activation seen in autoimmune patients. In particular TLR7, which detects nucleic-acid-containing immune complexes, seems to play a critical role since the stimulation of TLR7 leads to production of type-I IFN and an increased IFN signature can be found in salivary glands and blood cells of a subset of patients with SS.

DC comprise a heterogeneous population of cells, which in humans is divided into two main subsets, myeloid DC (mDC) and the type-I interferon producing plasmacytoid DC (pDC). DC populations are relatively rare in blood and thus difficult to analyze, but *in-vitro* generated monocyte-derived DC (moDC) are characterized as functional APC that also develop from monocytes under inflammatory conditions in the body and thus are a useful tool to study DC functions *ex-vivo*.

The goal of this study is to analyze the maturation state and cytokine secretion correlated to plasma cytokine levels of moDC after *in-vitro* stimulation in patients with SS, SLE and RA compared to healthy controls. MoDC from SS, SLE, RA patients and controls will be generated from fresh blood samples and stimulated with TLR ligands (TLR4: LPS, TLR7/8: CL097, TLR3: polyI:C) and several autoimmunity-related cytokines alone or in combinations. Cells will be analyzed by flow cytometry and cytokine levels will be measured by ELISA.

The overall aim of the study is to gain insights in the role of moDC and moDC-secreted cytokines in rheumatic autoimmune diseases in order to develop new diagnostic tools and improve current therapies.