Micromanagement of lupus autoimmunity by microRNAs
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Chapter 1

General Introduction
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Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by chronic immune activation and multiple immunologic phenotypes (1). The pathogenesis of SLE is poorly understood, and current therapies are based on nonspecific immunosuppression. However, genetic evidence supports a central role for IFN signaling in lupus pathogenesis. And among numerous immunologic alterations present in lupus patients, the type I interferon (IFN) system is thought to play a pivotal role in pathogenesis (2-4). These interferons have important biological functions, including the regulation of the function of CD4+CD25+Foxp3+ cells by IFN-alpha (5). Many patients with SLE have elevated serum levels of IFN, and these increased levels correlate with disease activity and severity (6). More recently, we have shown that type I IFNs are linked to vascular damage (7).

Using peripheral blood samples from SLE patients, we and other groups of investigators have independently identified expression patterns of IFN-inducible genes, collectively referred to as the IFN signature (8-11). Many of these IFN-inducible genes have an important role in the regulation of innate and adaptive immune system. And extensive analysis shows that this signature is also associated with severe manifestations of the disease, such as nephritis (12).

MicroRNAs (miRNAs) are a novel class of endogenous, non-coding small RNAs of 19 to 25 nucleotides in length. They ubiquitously exist in a wide range of species such as virus, worms, flies, plants and animals, and function to negatively regulate gene expression at the posttranscriptional level. It has gradually become accepted that miRNAs can modulate gene expression as effectively as transcription factors (TFs) in higher eukaryotes, representing a new layer of gene regulation. In parallel, mixed regulatory circuits are emerging in which close interplay between miRNAs and TFs cooperatively contributes to the formation of a complex post-transcriptional network. It has been well established that miRNAs are involved in multiple physiological and pathological processes including stem cell development, cell differentiation and organogenesis, proliferation and apoptosis, immune regulation and disease development. A growing body of evidence indicates that miRNA have the ability to alter cellular pathways and events, such as development and differentiation(13,14).

The role of miRNA in immunity is also beginning to be explored. A recent study that identified miR-146 as a key player in innate immunity was among the first to demonstrate the importance of miRNA in immune regulation (15). The role of miRNA in adaptive immunity has also been described, since miR-181a was found to modulate T cell sensitivity and selection (16). Investigations on the role of miRNA in immune-related diseases conducted by several groups of scientists have found altered expression of miRNA in rheumatoid arthritis (17-19). We hypothesized that miRNAs expression is altered in SLE, influencing key lupus disease pathways. Consequently, in this thesis we focus on key scientific questions: What is the miRNA expression signature in lupus? What are the targets for the disease related miRNA’s, which signaling pathway(s) are modulated, and finally, what causes the abnormal expression of these disease related miRNAs? More insight into the role of micro-RNA in the pathogenesis of SLE may help us develop novel microRNA-based biomarkers, which help us to steer treatment
decisions in the individual SLE patient. Furthermore, identification of key pathways may help us to develop novel targeted interventions for lupus patients.

Outline of this thesis

Chapter 2 reviews the available literature regarding microRNAs in SLE.

Chapter 3 demonstrates that MicroRNA-146a contributes to abnormal activation of the type I interferon pathway in lupus patients by regulating the key signaling molecules including IRF5 and STAT1.

Chapter 4 describes a novel functional variant in the microRNA-146a promoter which modulates its expression and confers disease risk for SLE.

Chapter 5 describes that microRNA-21 and microRNA-148a contribute to DNA hypomethylation in lupus CD4+ T cells by directly and indirectly targeting DNA Methyltransferase 1.

Chapter 6 describes how microRNA-125a induces the inflammatory chemokine RANTES by targeting KLF13 in systemic lupus erythematosus.

Chapter 7 describes microRNA-31 as a novel regulator contributing to impaired IL-2 production in T cells from patients with systemic lupus erythematosus.

Chapter 8 describes how miR-155 and its star-form partner miR-155* cooperatively regulate type I interferon production by human plasmacytoid dendritic cells.

Chapter 9 summarizes the main findings of the studies presented in this thesis and provides perspectives for future research in this area.
References


