ABSTRACT

IgA nephropathy and nephritis in Systemic Lupus Erythematosus (SLE) are two common forms of glomerulonephritis with unknown etiology. As for many other complex diseases, both genetic and environmental factors could be of importance for disease development. However, immunological and biochemical similarities between SLE and IgA nephropathy demonstrate a direct link to impaired immune function in both diseases. In our study we tested the hypothesis that there is an overlap in genetic susceptibility between Lupus nephritis and IgA nephropathy and we aimed to identify specific biomarkers associated with the severity of nephritis. We addressed this question in cohorts of 212 individuals with IgA nephropathy, 272 individuals with SLE, including 106 with nephritis and up to 1569 individuals from a healthy control population, by analysis of genetic variants in genomic DNA and by investigation of plasma from patients and controls.

Our analysis of distribution of HLA-DRB1 variants showed a significant association with IgA nephropathy, with the HLA-DRB1 *03, and *15 revealing a strong protective effect for IgA nephropathy. In contrast, the HLA-DRB1 *03, and *15 indicated a risk effect to SLE. We found a similar contrast in respect to non-HLA risk factors for these two types of nephritis. While TGFBI gene variants are associated with IgA nephropathy, this was not demonstrated for Lupus nephritis. On the other hand, several genetic polymorphisms previously found in association with SLE, like IRF5, STAT4 and TRAF1-C5, were not demonstrated to associate with Lupus nephritis or with IgA nephropathy in our cohort. Additionally, we found no evidence for an association of FCAR (CD89) gene polymorphisms in the investigated nephritis groups. No genetic factors associated with the progress of IgA nephropathy were detected in these genetic association studies.

Two biomarkers were tested in nephritis patients: mannose-binding lectin (MBL) and soluble CD89 receptor (sCD89, Fc alpha receptor). A new method for detection of sCD89-IgA complex in human serum/plasma was developed and applied in the IgA nephropathy cohort. Our study does not suggest that it is possible to predict development of nephritis based on these biomarkers. However, a significant association between low levels (less than 10 relative units) of sCD89-IgA complex in sera of IgA nephropathy patients and disease progression was detected. In a disease control group of patients with other forms of glomerulonephritis, including Lupus nephritis, who had similar renal function and proteinuria as the IgA nephropathy group, no correlation to disease progression was observed. When sCD89 analysis was performed on individuals, with repetitive samples during 5-15 years of follow-up, we found that serum levels of sCD89 remained stable and low in IgA nephropathy patients with disease progression and were continuously high (more than 40 relative units) in IgA nephropathy patients without disease progression. Thus, the sCD89 level could be a valuable prognostic marker of progressive renal failure in IgA nephropathy patients.

In our study we identified several genetic factors and a specific biomarker, which are different for IgA nephropathy and Lupus nephritis risk or progression. These findings point to a difference in the possible mechanisms of renal failure and suggest detection of HLA-DRB1 alleles for differential diagnostics of IgA nephropathy and Lupus nephritis at early stages of the disease. The discovery of a prognostic factor for disease progression in IgA nephropathy suggests that earlier and more aggressive therapy should be instituted, as well as opening the possibility of developing new methods of treatment for severe IgA nephropathy cases.