The objective of the project

Primary glomerulonephritides (GN) are a common cause of end-stage renal failure and the second, after diabetic nephropathy, the reason for dialysis therapy in Poland. Etiopathogenesis of glomerulonephritides and the reason for their heterogeneous course is the subject of intensive research, but remains unknown. In recent years, thanks to the advances in molecular biology and genetics, opportunities for analysing new particles that could enter into the diagnostic panel of the GN type and GN activity have expanded. The aim of the project is to evaluate selected co-stimulatory and immunomodulatory molecules, and Toll-like receptors (TLR) in the immune response against the Epstein-Barr virus (EBV) in patients with primary GN. The discovery of the link between infection by one of the most common virus, i.e. EBV and immune disorders observed in the primary GN can completely change the view on the etiopathogenesis, causes of heterogeneic course, and also in the further therapeutic approach of primary GN.

Description of the research to be carried out

In this project, for the first time worldwide, we will evaluate the effect of stimulation of dendritic cells (DC) generated from peripheral blood monocytes derived from 180 untreated patients with newly diagnosed primary GN (submicroscopic GN, focal segmental glomerulosclerosis, membranous GN, IgA nephropathy, membranoproliferative GN and rapidly progressive GN) with EBV antigens on the expression of co-stimulatory molecules, TLR, and PD-1, PD-L1, PD-L2, CTLA-4, CD200 as well as CD200R in comparison with the control group (60 healthy, age- and sex- similar individuals). In addition, we will evaluate the expression of abovementioned molecules on T and B cells in patients with primary GN and healthy donors, depending on the presence of EBV genetic material in the blood in both groups, and describe the profile of virus latency. We will assess the expression of CD80, CD86, B7-H1, B7-H3, B7-H4, PD-1, PD-L1, PD-L2, CTLA-4, CD200, CD200R, and TLR antigens on the lymphocytes infiltrating glomeruli. Evaluation of T and B cell proliferation in response to stimulation with DC and EBV antigens will determine whether the virus affects indirectly the proliferation of cells within glomeruli. We will examine the effectiveness of a cytotoxic response against the B cells in the presence or absence of EBV antigens; this part of the research will answer the question concerning the mechanism of the cell-mediated immunity weakening in the course of the primary GN. There is a huge demand for conducting this kind of research, because the literature shows little items describing similar themes. Results of the proposed project will not have direct applications, but in light of the results obtained by our preliminary and initial research, that might be interesting for a wide group of scientists. We believe that the innovative nature of the proposed project will result in numerous publications in journals with significant Impact Factor (IF). The results will be presented at national and international scientific conferences in the field of clinical immunology, nephrology, and virology.

Reasons for choosing the research topic

In the world of literature, little attention has been paid so far to research examining immune mechanisms of the development of primary GN. It seems to be obvious that there should be the reason for common occurrence of reports describing clinical cases of patients who after reactivation of EBV infection develop GN and EBV DNA is present in their kidney biopsies. Although anecdotal observations were confirmed in animal models, the subject seems to remain suspended. Markers of EBV infection are not routinely assessed in patients with primary GN in most diagnostic and treatment centres. The clinical practice shows however that patients with primary GN suffer from recurrent infections of unknown etiology, so their immune system is not functioning properly, which is not only caused by immune globulin deficiency, which develop because of proteinuria. In the course of cooperation with clinical immunology, our team revealed the existence of disturbances in the cellular immune system in patients with primary GN, which incidence is higher than the number of identified secondary humoral immune deficiencies in these patients. Is it possible that the immune system of patients with primary GN did not „work” properly even before GN development and this is the reason of GN onset? In addition, although variety of recent treatment regimens is used, still a large number of patients are not able to achieve remission during therapy of primary GN. Some patients also develop serious infections, often leading to death. The cause of heterogeneous course of primary GN remains unknown. Results of the pilot study made by our team indicate the importance of the molecules responsible for the "anergy" of lymphocytes and dendritic cells in the role of fatal outcome of GN. In 1/3 of the examined patients we found the presence of EBV reactivation markers. Perhaps improper recognition of viral antigens leads to the "attack" of components of the immune system on units building glomeruli up and to the development of the clinical symptoms. There is a high probability, that the implementation of such a large project will shed new light on the pathogenesis of the group of diseases, currently known as primary GN.