The project aims to determine the molecular implications of gut microbiota disorders in the context of the functioning of the immune system in patients with primary glomerulonephritides (GN).

Research description

In the presented project, research will be carried out to determine the involvement of Toll-like receptors (TLRs), expressed extracellularly and intracellularly, in the development and progression of primary GN and the potential use of TLRs as biomarkers. The composition of the gut microbiota in patients with primary GN in relation to healthy individuals and the relationship between the disturbances of the gut microbiota with the functioning of the immune system and the clinical course of primary GN, as well as the response to standard treatment will be all determined. In addition, we will analyze whether changes in the expression of genes in the transcriptomic profiles of patients with primary GN, caused by dysbiosis of the gut microbiota and abnormal expression of TLRs, may weaken the functioning of the immune system and lead to the progression of primary GN towards renal failure. The study group will consist of 120 untreated patients with newly diagnosed primary GN - per 30 patients for membranous nephropathy, minimal change disease, IgA nephropathy, and membranoproliferative GN. The control group will consist of 30 healthy individuals. The research tasks planned for implementation are innovative due to a comprehensive approach to the above issue in *ex vivo* (analysis of samples from patients and healthy people), *in vivo* (studies of a model organism - zebrafish), and *in silico* (studies of changes in the expression of genes of the immune system cells in the transcriptomic profiles of patients with particular types of primary GN, taking into account the comparative assessment between the data obtained from the analyzes of patient samples and zebrafish after implantation of the gut microbiota to this model organisms from patients with primary GN and healthy donors). Many methods will be used to carry out the studies mentioned above, including flow cytometry, enzyme immunoassays, molecular techniques, and the single-cell sequencing method for human samples and the zebrafish model.

Reasons why the research topic was undertaken

The interrelationship between the functioning of the immune system, the microbiota, and the development and course of diseases resembles a multi-threaded plot of a theater play, in which tension is graded, and the end of each act is intertwined with the beginning of the next one. Newer and newer research techniques contribute to introducing new "actors" to this stage, i.e., molecules in which scientists place their hope on optimizing the diagnostic and therapeutic process. Primary GN are common causes of end-stage renal failure and the reason for undertaking renal replacement therapy. The etiopathogenesis of primary GN and the reason for their heterogeneous course are the subject of intensive research but remain evidently unknown. In the light of the available knowledge on the role of microbiota disorders in the development and progression of diseases, including allergic and autoimmune diseases, it seems extremely important to assess the role that this "actress" plays in the immunopathogenesis of primary GN. Due to the enormous diversity of primary GN and the complicated diagnostic and therapeutic process, it is essential to conduct research on the causes of the development of this group of diseases and to search for new biomarkers that will allow for easy determination of an accurate diagnosis and prediction of the course of primary GN. As was shown by research performed, among others, by our team, one of the possible causes of the development of this group of diseases may be TLRs dysfunction, which constitutes the "bridge" between the innate and acquired immune response. Activation of TLRs triggers a cascade of reactions in the course of which a variety of mediators are produced, including those stimulating the development of inflammation, which may eventually damage the glomeruli. An abnormal TLRs response may occur as a result of disturbed gut microbiota.

The most important expected effects

The problems that are to be the subject of this project have not been discussed in such an interdisciplinary context so far, so the novelty of the research will result in a significant expansion of the current state of knowledge, numerous publications in prestigious international scientific journals and presentations at scientific conferences. In the light of the results obtained in our preliminary research, the project's results may be of interest to a wide group of scientists dealing with animal models of human diseases, nephrology, immunology, and microbiology and become an inspiration for further research. The innovative research methodology will allow us to assess whether the gut microbiota implanted from patients with primary GN may lead to the development of renal failure in the zebrafish model. The discovery of the link between the microbiota and immunological disorders in primary GN may completely change the view of etiopathogenesis, causes of course heterogeneity, and then also the therapeutic approach to primary GN, with implications for personalized immunomodulation methods, immunotherapy, and possibly even for preventive management in individuals genetically predisposed to develop primary GN.