Abstract

Primary immunodeficiencies (PIDs) are a rare group of congenital disorders including more than 485 diseases, which are classified into ten groups based on the predominant disorder of the immune mechanism. PIDs are manifested not only by susceptibility to infections, but also by a whole range of non-infectious complications. Understanding the basic pathophysiological mechanisms can thus significantly contribute to early diagnosis and initiation of adequate therapy not only of the underlying disease but also of complications associated with the given disease.

This thesis is mainly devoted to explaining the mechanisms of dysregulation of the immune system, which contribute to the development of non-infectious complications. The thesis is divided into a theoretical and a practical part. The theoretical introduction summarizes basic knowledge about the epidemiology, etiology, pathogenesis, clinical manifestations, diagnostic and therapeutic possibilities of particular PID groups. PID groups including primary antibody immunodeficiencies (common variable immunodeficiency, CVID), diseases associated with dysregulation of the immune system (X-linked lymphoproliferative syndrome type 2, XLP-2) and combined immunodeficiencies with syndromic features (DiGeorge's syndrome, DGS) covered by my experimental work are discussed in more detail.

The second part describes the main results achieved during work on the postgraduate project, which are published in the 6 most important scientific publications. They include results regarding the role of homeostatic lymphoproliferation and senescence in patients with DGS, the role of apoptosis in the dysregulation of the immune system in the development of non-infectious complications in patients with XLP-2 caused by a newly described mutation in the X-linked inhibitor of apoptosis gene, and the impact of congenital disorders of antibody production on specific antibody and cellular post-vaccination response in patients with CVID. It also summarizes the results of research aimed at evaluating risk factors for the severe course of the disease COVID-19 in patients with congenital immune disorders and the influence of immunoglobulin replacement therapy in the diagnosis of autoimmune diseases associated with the formation of autoantibodies. The methodology was also used in solving parallel projects involving patients with immune-mediated inflammatory diseases, sarcomas, head and neck tumors.

This work significantly contributed to the clarification of the basic pathophysiological mechanisms and their contribution to the dysregulation of the immune system. In addition, our results contributed not only to improved diagnostics, but also to new therapeutic options.

Keywords: primary immunodeficiency, common variable immunodeficiency, DiGeorge syndrome, XIAP, immunoglobulin replacement therapy, COVID-19