

Despite numerous studies the pathogenesis of chronic lymphocytic leukemia (CLL) still remains unknown. In recent years, it was speculated that inflammatory and immune factors, including antigen stimulation, might play a role in the CLL development. Independent, unrelated and geographically distinct CLL patients have almost identical B cell receptors (BCR) on malignant B cells, indicating evolutionary adaptation to stimulation with particular, same antigen. Thus, some common antigens, being a fragments of certain bacteria or fungi, might be involved in the CLL development by stimulation of leukemic B cells growth. There is an evidence of the role of certain antigens derived from pathogens occurring in particular geographical areas in the pathogenesis of CLL. One of them might be diversity of CLL geographic occurrence, another recurrent infections, which are often observed in the disease course. In addition, it was reported that some strains of bacteria secrete factors maintaining proinflammatory environment in the organism, what indirectly contributes to the carcinogenesis process. Therefore, in this project we plan to investigate inverse hypothesis, according to which the infection can be not only a consequence but also a cause of the CLL development and progression. In previous study we showed accumulation of B1 cells in tonsil tissue during chronic antigenic stimulation accompanying chronic or recurrent tonsillitis inflammation in children. Based on these results, we plan to evaluate the origin of B cells derived from hypertrophied tonsillar tissue with respect to the BCR repertoire, characteristic of adult CLL patients, to determine the cell type from which the leukemic cells originates. Results of the molecular analysis will allow for determination of relation between obtained bacterial profile and the presence of known prognostic factors. We also plan to evaluate the effect of the oral cavity and gut bacterial profile on the development of malignant B cells derived from one cell line, as we hypothesize that stimulation by microbial antigens might be involved in the pathogenesis of CLL as well as responsible for disease progression.

The project will be carried out with utilization of genetic tests allowing for the assessment of the oral cavity and gut bacterial profile diversity. We also plan to evaluate the origin of CD5+CD19+ B cell obtained from tonsillar tissue with respect to the BCR repertoire, characteristic of CLL patients, using genetic engineering, molecular biology, and functional studies. This will clarify whether and which pathogen species can cause leukemia. Analysing both oral and gut microflora of CLL patients, we would not only define characteristic of CLL bacterial profile, but also define which species are present in patients not requiring treatment. In addition, we plan to evaluate the potential prognostic value of microorganism diversity and refer it to a number of known diagnostic factors.

This project will address several crucial issues concerning the role of CLL microflora: (1) whether CLL might result from chronic inflammation, such as tonsillitis, (2) whether the bacterial flora can affect the course of the disease, (3) which bacterial strains can cause CLL development and to what extent? The latter question will be answered with utilization of a database of >25 000 sequences of genes responsible for the antibodies diversity collected by the European Research Initiative for CLL (ERIC), with whom the Experimental Hematooncology Department is in cooperation.