

Nowadays cancer is ranked as a leading cause of death. According to estimates from International Agency for Research on Cancer in 2020 there was 19.3 million new cancer cases and almost 10.0 million cancer deaths worldwide. Furthermore, an estimated cancer burden will continue to increase and in 2040 will reach 28.4 million cases that is 47% increase comparing to 2020. In the case of stomach cancer, only early diagnosis can significantly improve chances of patients' survival. Diagnosis in the early stage of the disease is unfortunately difficult due to the lack of characteristic symptoms of the disease at this stage. Therefore, it is justified to develop new methods that can be used to effectively detect tumor markers, since the biomarkers currently used, i.e. carcinoembryonic antigen (CEA) or carbohydrate antigens (CA19-9 or CA72-4) are characterized by low specificity. It is worth searching for new biomarkers among metabolites. The specific level of some metabolites may reflect disorders that occur in the body at the cellular level. Identification of metabolic pathways in the cancer cell and its environment may help to better understand the metabolism of the cancer cell.

The kynurenine pathway is involved in the modulation of the body's immune response during cancer and is a promising target for immunotherapy. Many recent studies have confirmed that tumor size, advanced disease stage, and poor prognosis of patients with cancer correlate with the overexpression of IDO1 (indoleamine 2,3-dioxygenase), which is the first enzyme to break down tryptophan (Trp) in this pathway. Overexpression of this enzyme results in a deficiency of tryptophan and an increase in the level of kynurenine and other metabolites of the pathway. These metabolites (in particular KYN, 3HKYN, XA) can inhibit the activity of T lymphocytes and NK cells. As a result, this leads to a weakening of the body's defense mechanism, which in turn affects a worse prognosis for patients. The overexpression of IDO1, and the presence of metabolites in the serum and peritoneal fluid or lavage fluid have already been confirmed in gastric cancer patients. In our preliminary studies, we found that metabolites of the kynurenine pathway represent promising diagnostic and therapeutic targets in gastric cancer. However, the pathogenic mechanisms of IDO1 activation and the role of Trp metabolites (kynurenines) require further research in this type of cancer. Although the diagnostic potential of kynurenines has already been confirmed in many studies, there is still no clear information on the correlation between the level of local kynurenines - in the peritoneal fluid and in the circulatory system. The relationship between the level of secretion of individual kynurenines and the severity of the disease also remains to be investigated.

The objective of this project is to develop novel methods for quantification of tryptophan metabolites to understand the diagnostic potential of kynurenines in the pathogenesis of gastric cancer by searching for the correlation between the levels of kynurenines in the body fluids and the disease stage, prognosis, and survival. Studying a correlation between the local and systemic kynurenine level will reveal the possible applicability of the more available human samples for diagnostic purpose and will answer the question on the local contribution of KP to the immune response within tumor microenvironment.

In my project, I plan to use samples of serum and peritoneal fluid or washings obtained in collaboration with the Medical University of Lublin. I intend to develop new and improve the available methods of measuring tryptophan and its metabolites in serum and peritoneal fluid. I will expand on the already developed by our team approach employing liquid chromatography electrospray ionization tandem mass spectrometric (LC-ESI-MS/MS) to assess tryptophan and kynurenine concentrations in patients' samples. It is a well-known and widely used analytical technique in metabolomics. LC-ESI-MS/MS has already found wide applications for the quantification of Trp metabolites from various metabolic pathways and other bioactive compounds in samples of biological origin.

The obtained results will enable a better understanding of the diagnostic potential of kynurenines in the pathogenesis of gastric cancer and in the future may be used to develop new, less invasive, and more effective diagnostic methods for gastric cancer. The results of the studies may be of clinical importance with a potential to be used for better assessment of the gastric cancer patients' prognosis.