

Glycobiology is a specific field of biochemistry. It deals with the structure and biological function of molecules called sugars. In common understanding, sugar is associated either with what we sweeten our morning coffee with, or possibly with "sugar in the blood", i.e. glucose. However, in fact, most of the proteins produced by all cells in our body are called glycoproteins, i.e. proteins with oligosaccharide chains attached to each other. These oligosaccharides are nothing more than a dozen of linked monosaccharide molecules, similar to glucose. The sugar portions of glycoproteins are called "glycans" by researchers. The biological functions of glycans have long been debated. After all, they cannot only be "ornaments" of proteins, since cells use a lot of their own energy to produce them. Moreover, the formation of glycans inside cells is a very complex process. Dozens of different enzymes take part in it, which systematically trim and extend the resulting glycan until it reaches its final shape. This cellular process called glycosylation is relatively well understood, although as usual in science, the more we know, the more questions we can ask. The basic functions of glycans are well understood. We know for sure that they increase the solubility of proteins, protect them against proteolysis, help them take their proper, strictly defined spatial shape. In addition, they participate in immune mechanisms, migration (movement) of cells or their adherence to each other within the tissue. These are, of course, only selected examples of the biological functions of glycans, many of which have already been described. It has been noticed that since sugars are involved in so many important biological processes, most likely disturbances in their structure or disturbances in the protein glycosylation pathway may accompany human diseases. It turns out that this assumption also turned out to be correct. Today, we learn more and more about the fact that altered glycosylation of proteins accompanies cancer, inflammatory, autoimmune and neurological diseases. It turns out that glycans have the potential to be universal markers of many diseases. Moreover, in recent years there have been reports of the predictive importance of altered glycosylation - on its basis, we will probably be able to predict whether someone is at risk of developing a given disease in the future. It sounds wonderful, but the reality is not so kind. It turns out that the analysis of glycans in cells, their structure and quantity is an extremely difficult task. It requires not only knowledge of their structure, but also the use of very modern and expensive measuring equipment. Nevertheless, many glycobiological centers are trying to do this. It turns out that the very beginning of the cell glycan synthesis pathway is an area where many questions remain unanswered. There are specific enzymes, the so-called alpha-mannosidases, whose task is to prepare the resulting glycan for further processing. There are 4 such enzymes, their role is similar - they are to cut off mannose residues from the sugar structure formed on the protein. The function of these enzymes is similar, virtually identical. So why are there so many of them? Do they all have similar importance in the glycosylation pathway? If one or more is missing, will the glycan repertoire in the cell change a lot? What might this mean for the cell or tissue in which that cell functions? I will try to answer these questions during the implementation of my research project. As a research model, I chose cells from which enterocytes are formed in laboratory conditions - that is, epithelial cells of our small intestine. The intestinal mucosa, which includes enterocytes, is a very important element of our digestive tract. On the one hand, it is responsible for the final digestion and absorption of nutrients. On the other hand, it protects us from invasion of pathogens. Its integrity, i.e. maintaining continuity and barrier functions, is at the heart of our health. In the laboratory, I will try to recreate the structure of the intestinal epithelium using its essential cellular elements - enterocytes, goblet cells that produce mucus and macrophages - that is, immune cells. Additionally, I will introduce genetic manipulations in enterocytes, which involve knock-out of the genes for individual alpha-mannosidases. Thanks to this, I will be able to check how such a defect in the glycosylation pathway affects the final repertoire of cell glycans. Additionally, I will try to answer the question whether alpha-mannosidases contribute to maintaining the integrity of the intestinal barrier? Finally, I will investigate how inflammation affects this integrity in the face of disabling the function of individual alpha-mannosidases? I will conduct my research using the most modern methods of glycan analysis (including mass spectrometry), fluorescence or electron microscopy and basic biochemical techniques. I hope that the implementation of the project will significantly contribute to an even deeper understanding of the role of glycosylation in the functioning of the human body in health and disease.