Description for the general public

In the project “Mechanistic insights into the specificity of glycosaminoglycan interactions with regulatory proteins”, we plan to answer one of the most fundamental questions that arises in the studies of complex biologically relevant processes going on in the space between cells – an extracellular matrix (ECM). In ECM, there is a huge variety of molecules belonging to different molecular classes (proteins, saccharides, small molecules, ions), which communicate with each other and so affect practically all the physiological events taking place in our organism. Among these molecules, in our research we are particularly interested in glycosaminoglycans (GAGs), a special class of saccharides, which participate in various biochemical processes underlying the phenomena of tissue regeneration and are involved in severe diseases as cancer or Alzheimer’s and Parkinson diseases. These molecules represent long negatively charged chains that are made up of repetitive blocks of di-sugar units. Depending on their particular content, they are split into several classes, some of which (as heparin or hyaluronic acid) are known for non-specialists due to their popular therapeutic properties. Why these molecules possess such features that are exploited by our organism to assist in resisting diseases or to speed up wound healing? In order to function they need to “talk” with other molecules in the ECM, and such communication occurs through physical contacts between them and other types of molecules, predominantly proteins, which are regulators of most of the biochemical processes. Due to their negative charges, GAGs prefer to interact with positively charged surfaces of the proteins what is revealed in many experimental and modeling studies. This means that the higher the charge of a GAG is, the stronger it should be involved in communication with proteins and the more effective is the “message” of a GAG telling the cell what should be done next. Such effect of a GAG charge on a process seems, however, to be independent of other GAG structural properties: which building blocks are there, how they are connected. Is it only charge that counts? Is everything just as simple as this, and why then the nature created GAGs of different types and compositions but with the same charge? Is there any natural redundancy? For several well described protein-GAG systems, it was shown that not only the charge but the position of the charged chemical groups on GAG molecule are important for the interactions, complex formation and, therefore, the biological effect of the GAG molecule. Such phenomena is called specificity of interactions. However, it is not clear if this specificity is something representative for GAGs. Therefore, our objective in the proposed project is to find out systematically if the interactions of GAGs with their protein partners are specific or not. This represents a fundamental question for GAG research and general understanding of molecular communication in the ECM.

We are going to tackle the above-mentioned problem from two perspectives: from a protein and a GAG “point of view”. The first case will be approached in two steps. In the first step, we would like to answer the question if there is a possibility that GAGs having the same charge could significantly different interact with the same protein. In the second step, we go even further and check if linear molecules of other origin (peptides, DNA, small molecules) possessing the same charge as GAGs, could therefore establish the interactions with the protein similarly to GAGs. Then, we will analyze the specificity from the “point of view of a GAG”: how different could be interactions of the same GAGs with the protein from the same family and therefore similar structure but with different charge distribution on their molecular surface.

In our work, we will combine both molecular modeling (University of Gdańsk) and experimental approaches (Leipzig University), which in our previous joint studies on other protein-GAG systems demonstrated to be very beneficial when applied together complementing each other than when they are applied alone. In modeling we will predominantly apply two computation methodologies: molecular docking and molecular dynamics. Molecular docking predicts how the structure of interacting molecules looks like if it is not known experimentally. However, this is usually not enough to understand what exactly happens in a system in terms of dynamics and energetics, which is required to describe the specificity of interactions. In contrast, molecular dynamics allows to track atomic movements of the system in time based on the knowledge of their initial coordinates obtained from the experiment or from the molecular docking and knowing which forces are applied between the atoms in the system. The experimental approach we will apply is nuclear magnetic resonance (NMR): the phenomena of NMR allows to characterize structures and dynamics of the molecules by observing the changes in the magnetic properties of atomic nuclei under the external magnetic field applied in the experiment. Combining these theoretical and experimental approaches we will characterize the specificity of the interactions for several protein-GAG systems. In particular, we will study interleukin-8 (a molecule important in immunological processes) and cathepsin B (an enzyme which is involved in cancerogenic processes). The data obtained in our project will contribute to the better understanding about processes in the ECM, which can have a striking potential significance for the development of various therapeutic applications in the future.