Abstract of the PhD thesis

„Computational approaches to study protein-glycosaminoglycan systems”

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Glycosaminoglycans (GAGs), a class of long anionic unbranched polysaccharides made up of recurring disaccharide units, are located in the extracellular matrix as well as in lysosomes. They mediate activity of various enzymes and non-enzymatic proteins including growth factors, chemokines or cathepsins via predominantly electrostatic interactions. Although many studies recently focused on explaining the biological role of protein-GAG interactions, there is still a number of questions regarding how these interactions might impact the mechanisms underlying activity of the GAG binding proteins. While experimental studies deliver certain data about the structure and binding characteristics of these complexes, due to the nature of protein-GAG systems studying them at atomic level represents a substantial challenge. Therefore, in many cases, the experimental data are complemented by computational results. However, theoretical studies of protein-GAG interactions might also be difficult because of GAG specific properties. The length of polysaccharide chain and its high conformational freedom add significantly to the computational cost of simulations. GAGs might interact with solvent which is important for their structure and biological function. Moreover, GAGs bind to positively charged long and flexible side chains of lysine and arginine. Despite all these challenges, the application of computational methods allowed to explain molecular mechanisms underlying the biological function of various proteins.

The aim of this PhD thesis was to analyse interactions in protein-GAG systems from two different perspectives. First, interactions in particular cathepsin-GAG complexes were studied, which allowed to explain biological system-specific role of these interactions. I proposed the role of chondroitin 4-sulphate in collagen degradation of rat and human cathepsin K, the potential role of heparan sulphate interactions with cathepsin V in the development of mucopolysaccharidosis as well as the role of GAGs in procathepsin B maturation. Then, I rigorously characterised a new class of phosphorylated GAGs and their potential interactions with proteins. Secondly, I analysed Fibroblast Growth Factors 1 and 2 complexes with GAGs in order to improve and develop new computational protocols calibrated for GAG containing systems suggesting that the length of molecular dynamics simulation as well as the GAG orientations might be crucial factors for the accurate description of these systems. The results of my PhD study contributed to the basic understanding of the biological role of protein-GAG interactions, the limitations of computational methods and allowed to propose ways to overcome them when applied to these systems, which might have potential application in the rational development of novel biomaterials for regenerative medicine.