Abstract for general public

Every living organism functions based on biochemical processes in which chemical compounds are processed with energy consumption or emission. An example of such a reaction might be an enzymatic reaction, in which a protein called an enzyme breaks chemical bonds in a substrate with which it interacts. Enzymes are classified into classes, subclasses, and groups depending on the mechanism of the reaction in which they participate and the substrates they target. One of the subclasses of enzymes is proteases, which cause hydrolysis (degradation) of the peptide bond, which is the basic way of bonding between amino acids that make up proteins. Among proteases, there are cathepsins, which in most cases are cysteine proteases (they initiate enzymatic reaction with cysteine), but some may initiate a reaction with serine (serine proteases) and aspartate (aspartic proteases). Cathepsins are located in the extracellular matrix as well as in lysosomes, and they are involved in many biologically-relevant processes, including bone resorption, collagen degradation, or programmed cell death. A better understanding of the molecular processes responsible for cathepsin activity might help us to control them, which, in turn, could be reflected in novel therapies targeted at diseases caused by cathepsin malfunction. These diseases include pycnodysostosis, osteoporosis, rheumatoid arthritis and osteoarthritis, asthma, obesity, various autoimmune diseases, and cancer. Cathepsin activity might be regulated by glycosaminoglycans. They belong to a group of long, unbranched, and negatively charged carbohydrates that contain sulfate groups in their chain. Similarly to cathepsins, glycosaminoglycans can be found in the extracellular matrix, and in most cases, they are a part of different molecules called proteoglycans (molecules that are made up of proteins that are covalently bound with aminosugars, especially glycosaminoglycans). The biological role of glycosaminoglycans involves participation in cell proliferation, angiogenesis, anticoagulation, cell adhesion, and signaling cascades. Glycosaminoglycans may also regulate the enzymatic activity of cathepsins, and the binding region of the carbohydrate might have a different effect on the activity of the enzyme. Glycosaminoglycan can bind in the cathepsin's active site (residues directly involved in proteolysis), block it for a substrate, and, as a result, inhibit enzymatic activity. Glycosaminoglycan can also bind to a cathepsin-substrate complex in a way that substrate dissociation is blocked by the carbohydrate. Glycosaminoglycan can also bind to residues other than the active site and, as a result, promote conformational changes in the cathepsin's active site region, which make it inaccessible for a substrate. Similarly, glycosaminoglycans may mediate the activity of immature and inactive cathepsin precursors – procathepsins. To date, it has been shown that, depending on the type of procathepsin, glycosaminoglycan binding might have a different effect: it can either stabilize the conformation (spatial distribution of amino acid residues) of the active site or induce conformational changes of the propeptide, which is responsible for proenzyme inactivity. The aim of this project is to thoroughly understand the mechanism of regulation of the enzymatic activity of cathepsins and procathepsins. The focus will be on the aspect of conformational changes (allostery) caused by glycosaminoglycan binding. A thorough understanding of this mechanism using experimental and computational methods will allow us to select the characteristics of glycosaminoglycans and the parameters of their interactions with (pro)cathepsins, which may be important for allosteric enzymatic regulation. As a result, new glycosaminoglycan mimetics that can more effectively control enzyme activity will be proposed in this project. These may help treat diseases caused by malfunctioning of these enzymes.