Description for the general public.

Human body functions based on many complex biological processes, in which various chemical compounds are converted into other ones with energy emission or consumption. One of those processes is proteolysis reaction which leads to the reversible cut of the peptide bond. Peptide bond is the basic way of bonding between aminoacids which make up proteins. Proteolysis reaction occurs in the presence of enzymes called proteases. Cathepsins, predominantly cysteine proteases (they initiate proteolysis reaction with cysteine residue present in the active site of a protein, a patch on the protein surface performing the enzymatic reaction) are present in intercellular space between cells called extracellular matrix as well as in lysosomes. Cathepsins play a key role in many biological processes including bone resorption, intracellular proteolysis, regulation of programmed cell death or degradation of antimicrobial peptides/proteins depending on the type of the cathepsin. Detailed description of those processes at the molecular level is needed in order to moderate the activity of those enzymes which in turn could be used in development of novel therapies for numerous diseases involving pycnodysostosis, osteoporosis, rheumatoid arthritis, osteoarthitis, asthma, psoriasis, atherosclerosis, cancer, obesity autoimmune disorders and viral infection. Even though the exact mechanisms are still unknown, it was proposed that enzymatic activity of cathepsins can be moderated by glycosaminoglycans (GAGs). GAGs are long unbranched periodic and negatively charged derivatives of saccharides. Similarly to cathepsins, GAGs are located in extracellular matrix in which they play a key role in various processes. Those include cell proliferation, angiogenesis, anticoagulation, adhesion and signaling cascades. Regulation of cathepsin activity by GAGs is fulfilled by formation of a complex between those molecules and depends on their types. A cathepsins can bind a GAG in an active site which makes it inaccessible for a substrate. Moreover, GAG can bind on the already formed complex between a protein and a substrate, which makes the unbinding of a substrate unfeasible. Additionally, a GAG can bind to a cathepsin surface somewhere else than in the active site, that causes allosteric change in that active site, which alters its accessibility for a substrate. GAGs can form complexes not only with cathepsins that are in the active form of enzymes but also with procathepsins, their inactive variants. In procathepsin, a propeptide part covers a cathepsin active site rendering its inactivity and making proteolysis reaction unfeasible. However, polypeptide chain covering active site can be cut off by another procathepsin in a process called protein maturation. This reaction can be mediated by GAGs through the formation of a complex between those polysaccharides with procathepsins. As a result, GAG binding leads to a conformational change of the propeptide part of the procathepsin which exposures the active site, which therefore is free to cut the propeptide part from an another procathepsin. This phenomenon was observed only for one procathepsin and moreover, it was not explained yet at the molecular level. Nevertheless, with the aid of the computational methodologies we will be able to explain and verify this mechanism at the atomic level for several procathepsins planned to be analyzed in this study. Using the available experimental structures and molecular modeling (a set of computational methodologies used for building structures and predicting physico-chemical properties of the molecule), we will be able to calculate representative complex structures, observe their behaviour in the course of the simulation and estimate stability of those systems. The data obtained in this study will allow us to determine the importance of GAGs in a process of procathepsin maturation, which will contribute to the general understanding of protein/GAG systems. Additionally, detailed description of this reaction might be used as a guide for further experimental studies and, moreover, as a theoretical basis which can be used in regenerative medicine therapies for numerous diseases involving glycosaminoglycan mediated processes and cathepsins.