Computational insights into procathepsin maturation mediated by glycosaminoglycans

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Cathepsins, lysosomal proteases are present in many living organisms [1]. The majority of cathepsins are cysteine proteases with a few exceptions: cathepsin A and G are serine proteases and cathepsin D and E are aspartyl proteases [2]. Cathepsins function in extracellular matrix and play a crucial role in various 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. Their malfunction in organism may lead to many serious diseases, such as pycnodysostosis, osteoporosis, rheumatoid arthritis, osteoarthitis, asthma, psoriasis, atherosclerosis, cancer, obesity autoimmune disorders and viral infection depending on the type of cathepsin. Therefore, it is important to understand the molecular basis of those processes.

It is known that cathepsin activity can be mediated by glycosaminoglycans (GAGs), a class of linear anionic and periodic polysaccharides [3]. Each GAG (excluding keratan sulfate) consists of a recurring disaccharide unit in which one aminosugar and one uronic acid are present. Like cathepsins, GAGs are also present in extracellular matrix, in which they are involved in diverse processes such as angiogenesis, anticoagulation, adhesion and signaling cascades [4]. The interactions between GAGs and their protein targets that are responsible for aforementioned processes and are electrostatic driven.

In addition to cathepsins, active enzymes, GAGs can also form complexes with procathepsins, inactive proenzymes [5]. In procathepsin, a propeptide part covers a cathepsin active site rendering its inactivity. In order to enable the process of maturation, an another procathepsin molecule, either of the same or other type has to be present in order to activate a procathepsin. In addition, it is known that GAGs can mediate this process. GAG binding on procathepsin surface can induce conformational change of a zymogen that leads to the exposure of active site. However, the detailed description of the maturation process mediated by GAGs at atomic level which could explain the obtained experimental data is still unavailable. Moreover, it is still unknown whether the maturation mechanism is conserved among different procathepsins.

In our approach we used several computational methodologies in order to get deeper understanding of procathepsin maturation process mediated by GAGs. Modeled GAG structures were docked to conformational ensemble of procathepsin models calculated with coarse-grained UNRES force field [6]. Afterwards, complex structures were simulated by the molecular dynamics approach. Post-processing free energy analysis of the produced molecular dynamics trajectories by various approaches such as Molecular Mechanics-Poisson Boltzmann with the entropy calculations by normal mode, quasi harmonic analysis or potential of mean force approach provided us valuable data on the stability of the complex. Moreover, with additional per-residue analysis of free energy we identified aminoacid residues that contribute mostly to the interactions between receptor and ligand and in turn – to overall stability of a complex.

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