Human Cathepsin B Interaction with Heparin: Influence of Acid pH Studied by Molecular Dynamics Simulation

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Cathepsin B is a cysteine-protease found in the acidic interior of animal cell lysosomes. In some physiopathologies, it is observed that the tumoral cells release cathepsin B to the extracellular matrix, an environment with physiological pH, more alkaline than lysosome, where the protease is related to the extracellular matrix degradation and tumoral metastasis. At physiological or higher pH, cathepsin B shows low activity and it is inactivated, but when interacting with sulfated glucosaminoglycans, found in the extracellular matrix, it is able to modulate the enzyme activity and protect against alkaline inactivation. In this work, it was characterized the interaction between cathepsin B and the tetrasaccharide heparin, a glucosaminoglycan model, using Generalized Simulated Annealing Docking and Molecular Dynamic computational methods. Complexes of cathepsin B and heparin were obtained only for both acid and alkaline pH. The identified complexes at physiological pH showed no stability under molecular dynamics simulation, because heparin is released from protein some ns after complex simulation started. Otherwise, complex obtained at acid pH showed stable after long 70 ns molecular dynamics simulation. The results suggest that the complex formation should be at acidic pH conditions. These results are in agreement with experimental data, since when pH of the solution of the complex is raised from acidic to basic condition, heparin is able to protect Cathepsin B from alkaline inactivation. Analysis of the stable complex can give information about Cathepsin B structural conformation with favorable superficial electrostatic distribution of interaction between these two molecules.