Study on structure and binding sites of the human thrombin by computational methods

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Human thrombin is a protein of 295 amino acids that has an important role in the mechanism of blood coagulation. In fact, it is able to transform the fibrinogen in fibrin and therefore to favour the coagulation. This protein is inhibited by antithombin 3(AT3), a protein of 450 amino acids, on the other side experimental evidences have shown that a small protein of rat, said SV4 (Seminal Vesicle 4), it is able to favour the pro-coagulative action of the thrombin, preventing the action of the AT3. The aim of this project is to design a mimetic-drug acting similarly to SV4.
As a preliminar study, we analyzed the 3D thrombin structure. There are 159 entries of human thrombin in PDB (Protein Data Bank), where this protein always bound different ligands. We selected 60 entries on the basis of the best resolution among complexes with similar ligands. Thrombin structures have been analyzed in order to identify amino acids interacting with the ligands. The structural regions of thrombin involved in such interactions are: 30-40, 70-80, 130-140, 170-190, 215-225 (Swissprot numeration). This structural regions resulted always similar. The interaction between thrombin and AT3 has been simulated by using the GRAMM program. We selected 10 thrombin entries from PDB and simulated the interaction with monomeric AT3, dimeric AT3, with as well as without thrombin ligands. In any simulation, thrombin regions involved in AT3 interaction were similar to that previously indicated.
These preliminary studies will help us to investigate the interaction between thrombin and SV4. For this scope, we have modelled a new structure of thrombin, without ligands, by using the FAMS server (Full Automatic Modeling System),as well as by optimizing the PDB entry structure at higher resolution with energy minimization, having removed the ligand. The superimpose of these two modelled structures showed a very high similarity.