

Molecular dynamics simulations and docking studies on histone deacetylases

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Histone deacetylases (HDACs) mediate changes in nucleosomal conformations and are important in the regulation of gene expression. They are involved in cell-cycle progression and differentiation, their deregulation is associated with several cancers. HDACs catalyse the removal of acetylgroups from the ϵ -amino group of lysine residues at the N-terminal tails of core histones and therefore lead to a deactivation of chromatin. The inhibition of HDACs could cause a hyperacetylation of chromatin which results in cell-cycle arrest, differentiation or even apoptosis.

HDAC inhibitors, such as trichostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA), inhibit cell growth, induce terminal differentiation, prevent the formation of tumors in mice models and are effective in promyelocytic leukemia. Therefore, HDACs have emerged as an attractive target for new anticancer drugs and there is a great demand for novel inhibitors. Unfortunately the three dimensional structure of HDAC1 is still unknown. However, the crystal structure of the histone deacetylase-like protein (HDLP), a bacterial enzyme which shares 35% identity and the structure of the isoenzyme HDAC8 which shares 40% with the human HDAC1, were solved recently. They both reveal the constitution of the binding pocket which is conserved across the whole HDAC-family.

Based on the known X-ray structures of HDLP and HDAC8 a homology model of HDAC1 was generated and validated. To analyze the stereochemical quality of model and template structures PROCHECK and PROSA studies, as well as molecular dynamics simulations (GROMACS) were carried out. In order to find an appropriate method to reproduce the solved HDAC8-inhibitor complexes, several docking and scoring methods were tested. The procedure which showed the highest accuracy and predictivity is now applied to virtually screen for HDAC1 inhibitors.