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Structural insights of HDAC6 deacetylase catalytic domains

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Histone Deacetylase 6, belong to class II HDAC family with unique structural characteristics since it possesses two deacetylase catalytic domains (DD1 and DD2), which are interconnected by linker region. HDAC6 deacetylate non-histone substrate such as cortactin, α-tubulin, P53, tau protein, among others. The malfunction or deregulation of this protein has been involved in several diseases including cancer, Alzheimer´s diseases and Parkinson´s diseases. Thus, it has emerged as a pharmacological target for the treatment of these diseases. In order to design new drugs to target HDAC6 selectively, it is important to have structural knowledge of this enzyme. Thus, in the present study we built a three-dimensional (3D) model of DD1 and DD2 bound by the linker region, in order to identify the interactions established selectively by HDAC6 inhibitors and elucidate the participation of both catalytic domains in the recognition we used molecular docking and molecular dynamic simulation tools. As results we found that the catalytic tunnel of DD1 is wider and shallower than DD2 with different residue composition that could be exploited to achieve ligand selectivity design. By MD simulation and docking it was possible to determine the residues that contribute favorably to the ligand-HDAC6 recognition, in in DD1 the residues were F105, S173, H215,G224, Y225, H255, W284, K353 and R383 and in DD2 were: H500, P501, S568, P608, H610, H611, H619, F620, H651, F680, P748, L749, E779, E780 and Y782. Finally, MD simulation reveals some structural difference in the terminal loops, linker region, and loops adjacent to the catalytic site between the apo-HDAC6 model and the ligand-HDAC6.

Biography

Yudibeth Sixto-Lopez is PhD student from Escuela Superior de Medicina of the Instituto Politecnico Nacional, Mexico were she also did her Master. She performed an academic stay in University of Granada, Spain. She has published 6 papers in reputed journals.

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