Poster

Crystal structures of human histone deacetylase 8 in complex with novel hydroxamic acid inhibitors

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Histone deacetylases (HDACs), also known as lysine deacetylases, are enzymes involved in the control of gene expression. They catalyze the removal of acetyl moieties from acetyl-lysine residues in histones and non-histone proteins and the hydrolysis of amides of short and long fatty acids, playing a key role in the regulation of many biological processes, such as cell differentiation, proliferation, senescence, and apoptosis. HDACs are also involved in the occurrence and progression of several diseases, including cancer. HDACs are validated targets for drug design: treatment with HDAC inhibitors (HDIs) leads to restrict the DNA repairing, cell cycle arrest, alteration in genetic expression and induces cellular apoptosis. Some HDIs have been approved by the Food and Drug Administration for the treatment of cutaneous or peripheral T-cell lymphoma and multiple myeloma. Currently approved compounds lead to adverse effects and some of them are not selective. [1,2]

Among the 18 different isotypes of HDACs known, HDAC8, a Zn^{2+}-dependent class I HDAC, is an emerging anticancer target for structure-based drug design and exhibits unique structural features, including the high flexibility of the L1 loop (Ser30-Lys36) in the proximity of the active site: this loop can adopt two different conformations, open and closed, upon binding of specific inhibitors and substrates. Consequently, the size of the binding pocket can change, and this aspect can be exploited to develop selective inhibitors.

[2] Novel hydroxamic acid inhibitors, which are tetrahydroisoquinoline (TIQ)-based HDAC8 inhibitors, have shown an improvement in potency and selectivity for HDAC8 compared to other HDAC8 inhibitors studied.[3]

We solved several X-ray crystal structures of human HDAC8 in complex with TIQ-based HDAC8 inhibitors. The 3D structures, obtained by co-crystallization of hHDAC8 with these compounds, show that the inhibitors are bound at the catalytic site, occupying a hydrophobic and narrow tunnel with their hydroxamic acids group chelating the Zn^{2+} ion. Unlike HDAC8 bound to the HDAC8 isoform-selective aromatic acid-based inhibitors, TIQ compound(s) bind to the "closed" conformation with the L1 loop that moves toward the active site, making it deep and narrow. These findings provide insights for further rational design of novel HDAC8- selective TIQ-based inhibitors.

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