Development of New Histone Deacetylase Inhibitors using Chemical Genomics

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Chemical genomics is a multidisciplinary research engine at the interface between chemistry and genetics/genomics, which has been coined to signify the use of small molecules to perturb systematically, and determine the function of proteins in the same way that mutations are used in conventional genetics. One of major goals of chemical genomics is to develop biologically active small molecules which can interact with their cognate cellular target proteins to discover molecular mechanism in basic cell biology. The result, in turn, is applied to develop new drugs or biochemical reagents.

Histone deacetylase (HDAC) plays a key role in gene expression and is one of the best examples that has been developed using chemical genomics approach. Most of specific HDAC inhibitors have originally developed from cell based assay systems such as differentiation induction of murine erythroleukemia cells and detransformation of oncogene transformed fibroblasts with no information on the target. Forward chemical genomics was applied to clone the HDAC using trapoxin affinity matrix-based purification. It was turned out that the epoxy ketone moiety of trapoxin forms an irreversible complex with nucleophilic amino acid residue in the catalytic pocket of HDAC. Furthermore, development of more potent and clinically applicable HDAC inhibitors has been developed by reverse chemical genomics. The X-ray crystal structure of HDAC catalytic domain showed that the catalytic domain of HDAC is consisted of a tubular pocket, a zinc-binding site, and two asparagines-histidine charge-relay systems. It was speculated from this enzyme-inhibitor binding structure that trichostatin A (TSA)-like inhibitors block the activity of HDAC through the chelation of zinc ion using the polar group, such as hydroxamic acid or benzamide group in the end of hydrophobic spacer. Accordingly, several types of HDAC inhibitors with different chemical structure, as well as different inhibitory spectrum for HDAC isotypes, have been extensively developed on the basis of known HDAC inhibitors and protein structure. Some of agents including phenylbutyrate and valproic acid (short chain fatty acids), CI-994 and MS-27-275 (benzamides), SAHA (suberoylanilide hydroxamic acid) and FK228 (cyclic peptide) are undergoing Phase I or II evaluation both alone and in combination with cytotoxic or differentiation inducing agents. Taken together, chemical genomics based approaches on the development of HDAC inhibitors have successfully provided both a new promising target and drug candidate toward anti-cancer therapy.