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Editorial

Naturally Occurring Cyclic Peptides as HDAC Inhibitors

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The term cancer is used to describe a group of over 100 different diseases all of which have a similar characteristic about them: the out-of-control abnormal growing of cells. Every sixth death in the world is due to cancer, making it the second leading cause of death (second to cardiovascular diseases). Thus, the need for new cancer therapies is also on the rise. It has been shown that histone deacetylases (HDACs) are over expressed in cancer tissues and therefore, inhibiting them is considered to be a way to slow down the progression or stop the spread of cancer in the body.

Histone deacetylase enzymes (HDACs) are a class of enzymes that catalyze the deacetylation of lysine residues in the amino terminal tails of core histones. Histones are basic proteins, that in their protonated forms bind to the negatively charged phosphate backbone of the DNA double helix, forming a complex with DNA known as chromatin [1]. The DNA within this chromatin structure is highly compact, and it is not possible for the transcriptional machinery to access the genetic information when the chromatin is in this condensed form. On the other hand, HATs (histone acetyltransferases) acetylate histones, thereby gradually loosen the chromatin structure and aid transcription through increasing accessibility of gene promoter regions to transcription factors, regulatory complexes and the RNA polymerase. Histone acetylation by HAT plays a key role in transcriptional activation, whereas deacetylation of histones promotes transcriptional repression and silencing of genes. An excessive level of histone acetylation induces apoptotic cell death, whereas excessive level of histone deacetylation has been linked to cancer pathologies by promoting the repression of tumor regulatory genes. Disruption of HAT and HDAC activities has been associated with the development of a wide variety of human cancers. 18 HDAC family members have been identified in the human genome. HDACs are grouped into class I, class II, class III and class IV. Class I (HDACs 1, 2, 3, and 8) and class II (HDACs 4, 5, 6, 7, 9, and 10). HDACs are Zn^{2+}-dependent amidohydrolases with a conserved catalytic core but differing in size, domain structure, and tissue expression pattern. Class III HDACs are NAD+ dependent, unrelated in sequence and mechanism to classes I and II. Class IV consists of HDAC11. Zn^{2+} dependent enzymes harbor a catalytic pocket with a Zn^{2+} ion at its base that can be inhibited by Zn^{2+} chelating compounds.

The proposed mechanism says that the hydrolysis of N-acetylated lysine residue gets accelerated because of coordination in between carbonyl group of the N-acetyl amide bond of the acetylated lysine residue and the Zn^{2+} ion. HDACi (HDAC inhibitors) have been proposed to prevent histone deacetylation activity by binding in the active site pocket and chelating the Zn^{2+} ion of class I and class II Zn^{2+}-dependent HDACs [2].

In the past three decades, a number of HDACis have been reported naturally occurring such as trichostatin A (TSA), apicidin, trapoxin (TPX), FK-228 (romidepsin). Based on structure activity relationship (SAR) studies and crystallographic data [3], it was found that efficient HDACis should have three characteristic features: (i) a cap region (CAP) that binds with enzyme surface, (ii) a zinc-binding group (ZBG), and (iii) a spacer, linking the CAP

to ZBG (Figure 1). According to their structural characteristics, HDACis are categorized as hydroxamates, benzamides, short-chain fatty acids, and macrocyclic peptides.

Out of all naturally occurring HDACis, cyclic peptide-based HDACis possess the most complex CAP group responsible for interaction with the surface of the enzyme [4]. They are relatively less toxic with high pharmacokinetic properties and having an optimum structural balance between hydrophilicity and hydrophobicity due to which their structural features are advantageous for *in vivo* applications. Cyclic peptide based HDACis are mostly found to be cyclotetrapeptide and it is observed that they share some common structural features like having (1) a proline or pipecolic acid residue; (2) at least one amino acid with R configuration; and (3) a non-proteinogenic amino acid.

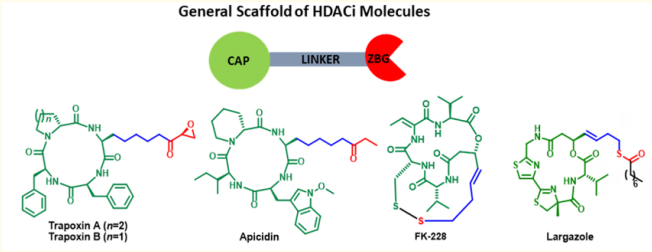

Figure 1: General scaffold of HDACi molecules and some examples of HDAC inhibitors.

Based on the structural advantages of cyclic peptide based HDACis, a class of molecules were named as Cyclic hydroxamic-acid-containing peptides (CHAPs) [5] were designed which are found to be very potent HDACis. The current naturally occurring HDACis that exhibit differential HDAC inhibitory activities provide not only lead structures on which to build, but also important tools for the elucidation of HDAC functions.

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