# HISTONE DEACETYLASES (HDACs) CLASS II GENES AS POTENTIAL DRUG TARGETS IN CANCER

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***Abstract:*** This review has been undertaken to investigate the role of histone deacetylases (HDACs) class II genes in various cancers. Efforts in cancer research mainly aims to identify the major drug targets, develop and improve treatment regimens which eventually helps into better prognosis. One of the major challenges is the determination and mapping of involvement of molecular pathways. So, there has been large interest in developing pathways and also determining driver genes and regulators. Bioinformatics helps to evaluate huge data from wetlab researches to explore biologically relevant interactions and pathways. Emerging evidence shows that many HDACs exists as biomarkers in cancers. The objective of this study is to present a review on the major and latest findings on class II HDACs and its association in cancers. Here, we summarize the current knowledge of class II HDACs, including their features and classification, biological mechanism as well as their function and reported clinical studies in cancers. In addition, we discuss various trials and clinically available inhibitors targeting them. These results provide valuable insights which helps to identify and develop cancer specific therapeutic options.

***Keywords:*** HDACs, epigenetics, cancer pathways, bioinformatics, drug target identification.

## I. INTRODUCTION

Cancer is a is a slow progressing disease eventually involving the uncontrolled division of cells. In normal cells, many genes control the cell growth and division process. During cancer development, cells attains the mode of rapid division, invasion and metastasis. Generally, a tumor forms with the influence of mutation of driver gene's and acts as passengers. These driver genes controls pathways and regulatory mechanisms in the cells. The basis of cancer research is the understanding of the pathways and its underlying mechanism. Several studies shows that, most cancer cells show multiple mutations in its genetic level (1–3). Therefore, studying mutations at domain level studies helps researchers to pin point the exact mechanisms relates to cancer. These Protein domain boundaries and architecture knowledge is important aspect for mainly understanding the protein function. In the present study, we provide a comprehensive review on the role of class II HDACs in cancer. The review summarizes the recent studies of the roles of class II HDACs and we mainly focus on recent discoveries related to molecular mechanisms of HDACs. Overall, the current available information will open new perspectives for a better understanding of HDACs in cancers.

## II. EPIGENETICS AND ROLE OF HDACs IN CANCER

Epigenetics is the field which studies the nature of heritable alterations in gene expression (4). These genetic abnormalities are one of the major causes in cancer. In eukaryotic DNA, chromatin is tightly bound with histone protein octamers, which restricts its accessibility to factors involved in DNA replication and transcription. Histone protein octamers or nucleosome contains or 146 bp DNA wrapping around protein complex with eight subunits of individual proteins namely H2A, H2B, H3 and H4 are situated at its center (5), Fig.1.

In 1964, it is found that, post-translational modifications (PTMs) of histones are one of the main cause of gene regulation process in RNA (6) and later it has been shown that the acetylation of lysine residue is regulated by two enzymes namely Histone acyltransferases (HATs) and histone deacetylases (HDACs) (7). These two enzymes function simultaneously and removes acetyl groups from chromatin which is known as chromatin remodeling, which regulates the gene expression (8–10). Histone acetylation and deacetylation, as one of the epigenetic mechanisms, occurs during the development of human cancer.

There are a large number of different histone PTMs such as phosphorylation, acetylation, ubiquitination and methylation in euchromatin. The dynamics of chromatin are regulated by the above processes. Euchromatin is a loosely compact structure (DNA, RNA and protein) which helps transcription factors to bind to regulatory sites on DNA, resulting transcriptional activation (11). In 1997, the crystal structure of the nucleosome was elucidated and proved PTMs causes the inter-nucleosomal interactions which influences transcription and DNA processes such as repair, replication and recombination (12). Further investigations revealed that, epigenetic modifications as well as alterations results in the regulation of gene expression by chromatin remodeling associated with reversible histone acetylation (13–15). HDACs reverse acetylation of chromatin and

altering transcription of oncogenes and tumor suppressor genes (16). Abnormal histone acetylation leads to cancer development which proves histone modifications plays a crucial role in influencing many fundamental biological processes (13). Histone acetylation modulates transcription in many ways. Acetylation of ε-amino groups of lysine residues in histone tails neutralizes their positive charge, thereby relaxing chromatin structure. This helps the transcription occur in a normal manner. The action between these enzymes serves as a key regulatory mechanism for gene expression (17). By removal of acetyl groups from histones, HDACs makes a non-permissive chromatin conformation which prevents the transcription of genes to proteins in cancer development (18). Chromatin assembly plays a major role in transcription (19,20). PTMs of histone proteins have crucial role in cancer development and progression by modulating gene transcription and chromatin remodeling. A lysine residue becomes acetylated by the action of these two enzymes namely, histone acetyltransferase enzymes and is removed by HDACs. Thus, histone lysine acetylation is highly reversible.

Since, the acetylation process is a key mechanism in cancer, studying the role of HDACs is a subject of interest and attracting a great attention from cancer researchers across the globe. Many research groups are working on the drug binding mechanisms and inhibitors search for HDACs. The integral approach of finding inhibitors lies in determining PTMs, identifying protein- protein interactions therefore, of considerable interest.

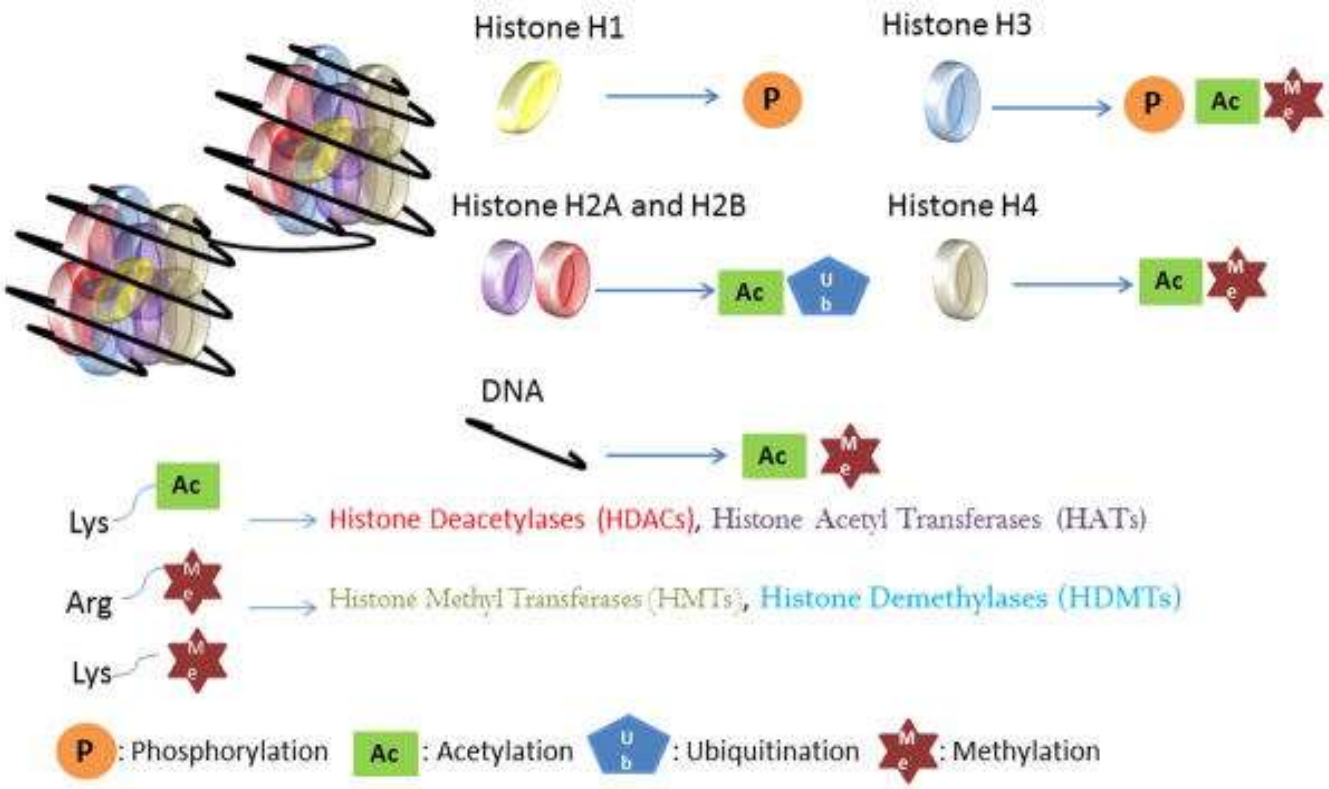


**Fig (1):** The nucleosome or histone core shows octamers (H2A, H2B, H3, and H4) with the linker histone (H1). Histone tails are modified through phosphorylation, acetylation, ubiquitination and methylation (13).

## III. HDACs Classification

In humans, HDACs enzymes are classified into four classes of 18 individual members based on sequence homology to yeast (21,22). Class I comprises of 1, 2, 3, and 8. Class II divided into two subcategories such as class IIa (4, 5, 7, and 9) and class IIb (6 and 10) as shown in Table 1. Class III known as sirtuins comprises of seven members (1-7) and class IV consists of 11. These have the cofactor $Zn^{2+}$ at the catalytic site and thus regarded as classical zinc-dependent HDACs. These HDACs present in the nucleus and cytoplasm and located in specific tissues such as the brain, heart, and muscle. Expression of class II HDACs has been found in many human cancers, including gastric cancer, lung cancer, liver cancer, prostate cancer and leukemia. In this review we will discuss about class II HDACs and evaluate the important finding and scientific interest in recent years. We searched recent research articles using keywords such as 'hdacs cancer and process', 'cancer and therapeutic options of hdacs' in pubmed and other literatures. Subsequently, the articles that matched such word criteria were completely reviewed and their findings noted.

**Table 1: Overview of Class II HDACs**

| Class II member | No. of Residues | UniprotKb Id | PDB Id | Cancer type |
|---|---|---|---|---|
| HDAC4 | 1084 | P56524 | 2VQJ | Gastric cancer, Lung cancer, Liver cancer, Prostate cancer |
| HDAC5 | 1122 | Q9UQL6 | 5UWI | Breast cancer<br>Hepatocellular carcinoma<br>Ovarian cancer |
| HDAC7 | 952 | Q8WUI4 | 3C10 | Lung cancer<br>Colorectal cancer<br>Leukemia |
| HDAC9 | 1011 | Q9UKV0 | No crystal structure available yet | Breast cancer, Oral cancer<br>Leukemia |
| HDAC6 | 1215 | Q9UBN7 | 3PHD | Gastric cancer<br>Breast cancer, Cervical cancer |
| HDAC10 | 669 | Q969S8 | 5TD7 | Lung cancer<br>Leukemia, Gastric cancer |

### 3.1 Class II a member, histone deacetylase 4 (HDAC4)

It is found that, HDAC4 promotes gastric cancer cell progression via p21 repression (23) and involvement of the MIAT/miR-29a-3p/HDAC4axis (24). Cancer upregulated gene 2 (CUG2) via HDAC4 signalling has been reported in lung cancer (25) and HDAC4 regulates HIF1α protein acetylation is shown in liver cancer (26) (27). Both HDAC4 and HDAC6 together with the TGF-β/Smad pathway involved in progression of glioblastoma, a type of tumor in nervous system (28). Class IIa HDACs are overexpressed in 22% of in leiomyosarcomas (LMS), where high levels of the myocyte enhancer factor 2 (MEF2), HDAC4 and HDAC9 expression is shown (29). MEF2 is a signalling pathway which control cell differentiation and organogenesis. Strong correlation has been proved in the expression levels of HDAC4 in acute myeloid leukemia (AML) (30).

### 3.2 Class II a member, histone deacetylase 5 (HDAC5)

HDAC6 has been identified as a promising biomarker for early detection of breast cancer by evaluating its higher expression levels in inferior prognosis (31) and in lung cancer cells (32). Several studies implicates its role in colorectal cancer cell lines (33), in hepatocellular carcinoma (34) and in breast cancer (35). In a study by yano et al, immunohistochemical analyses of major HDACs were performed to determine the expression using tissue microarrays data in prognosis of ovarian cancer (36).

### 3.3 Class II a member, histone deacetylase 7 (HDAC7)

HDAC7 has been experimentally studied using tube formation assay, immunofluorescence, microarray and western blot analysis to demonstrate angiogenesis process of endothelial progenitor cells (EPCs) in lung cancer (37). It is found that, HDAC7 promotes lung cancer by deacetylating stat3 leads to its inhibition (38). Studies confirms that, HDAC7 is overexpressed cancer stem cells (CSCs) (39). Studies confirms that, HDAC7 is overexpressed cancer stem cells (CSCs) (39). MiR-489 play a key role as suppressor of tumor growth and invasion in colorectal cancer by targeting HDAC7 (40). Isobaric labeling and mass spectrometry proteomics on chronic lymphocytic leukemia (CLL) samples have provided evidence linking the overexpression of HDAC7 (41) (42) and its deregulation contribute to the pathogenesis of the diseases leukemia and lymphoma (43).

### 3.4 Class II a member, histone deacetylase 9 (HDAC9)

HDAC9 is identified as an oncogene and its elevated expression level was evaluated in breast cancer patients (44) and in triple negative breast cancer (TNBC) HDAC9 acts as a mediator of cell invasion and angiogenesis (45). HDAC9 is found to be as a target of miR-377 and its target, NR4A1/Nur77 in Oral Squamous Cell Carcinoma (OSCS) (46). HDAC9 is found as overexpressed in acute lymphoblastic leukaemia (ALL) (47), acute myeloid leukaemia (AML) (48) and in chronic lymphocytic leukemia (CLL) (49).

### 3.5 Class II b member, histone deacetylase 6 (HDAC6)

The aberrant regulation of HDAC6 results the progression of malignancy in various cancers. HDAC6 has been identified as a promising biomarker for early detection of gastric cancer (50). The expression levels of HDAC6 and androgen receptor have strong correlation in breast cancer however its role is not clearly identified (51). G-protein-coupled receptor kinase 2 (GRK2), a key player in breast cancer acts as a regulator in HDAC6 mediated breast cancer. Its increased functionality and phosphorylation activates HDAC6 which leads to tumor progression (52). HDAC6 possess redundant effect on HDAC8 in cervical cancer cells (53).

### 3.6 Class II b member, histone deacetylase 10 (HDAC10)

HDAC10 was identified from a human cDNA library (20,54). In recent years, a number of studies have shown the mechanisms and functions of HDAC10 protein in cancer cells, such as autophagy (55), cell cycle (56) immunoregulation and specially, HDAC10 serve as oncogenic stimuli or tumor suppressors in cancer. Recent study by Shinksy et al shows that, HDAC10 is an emerging biomarker in cancers and considered as a target for the isozyme-selective inhibitors for design of autophagy mediated responses to cancer treatment (57). Studies shows that increased HDAC10 expression leads to increased phosphorylation of AKT in lung cancer (56), leukemia and lymphoma (58). HDAC10 regulates cyclin A2 expression and represses transcription which reveals its potential as targets in diseases associated with cell cycle dysregulation (59).

## IV. TRIALS AND COMPOUNDS SCREENING STUDIES TOWARDS CLASS II HDACs

Li et al investigated the effects of two synthetic curcumin derivatives to restore Nrf2 activity in TRAMP C1 cells, which are hypermethylated in prostrate cancer (60). Enzyme inhibitory activity against HDAC isoforms revealed nonhydroxamate compounds shown strong inhibitory activity against class IIa HDACs especially HDAC4 (61) and strong inhibitory activity against HDAC6 (62). Two ebselen analogs namely, ebselen oxide and ebsulfur inhibited HDAC4, HDAC5, HDAC6, HDAC7 and HDAC9 (63). A flavone component namely, 3,4'-dimethoxy-3',5,7-trihydroxyflavone induces cell cycle arrest of MCF-7 in HDAC4 mediated breast cancer Cells (64). (-)-Epigallocatechin gallate (EGCG) is a component from a green tea catechin which changes the levels of acetylation of histones in and suppresses the activity of HDAC4, 5 and 6 in lung cancer (65). Screening of epigenetic modifying drugs showed, sulforaphane, downregulated HDAC5 transcription by blocking USF1 activity in breast cancer (66). Apicidin selectively reduced HDAC7 siRNAs expression in salivary mucoepidermoid carcinoma (MEC) cells (67). Antiproliferative effect of A452 was found effective for colorectal cancer treatment (68). ACY-1215 (ricolinostat) which is a known HDAC6 inhibitor, which is undergoing clinical trials for hematological malignancies (69). A series of synthetic compounds were tested and TC24 which showed strong anti-proliferative ability towards HDAC6 mediated gastric cancer cells (70). Similarly, a compound named B-R2B was identified through in silico method and its possible HDAC6 inhibitory action specifically anti proliferative activity on cervical cancer and leukemia cells were evaluated based on a reference compound namely tubacin. According to molecular dynamics (MD) simulations, the compound showed a non-competitive effect in a similar manner that tubacin does (71).

## V. DISCUSSION

In this paper, we describe HDACs, which plays an important role in cancer by deacetylation process of lysine residue. Extensive research over the past years indicates their role in cell cycle progression, apoptosis, and autophagy. From our review results, it is clear that cancer development is a complex and heterogenous process which involves different steps. Researchers have identified several signalling pathways has been reported to promote the cancer. These signalling mechanisms are predominantly activated by modulation through various pathways. This creates a complexity within cancer cells. Tissue type and specificity in signalling mechanism increases the level of complexity in cancers, thus there is high demand for identification of targets and its inhibition mechanism.

## VI. CONCLUSION

In the recent years, there has been an increased interest in the field of HDACs research in cancer treatments. This review article focuses relatively on the latest findings towards class II HDACs in cancer research and majority of studies shows that pathway analysis contributed significantly. There are more publications related to class II mediated HDACs and their role in cancers. The latest evidences of clinical information that have discussed in this study may provide ample observations for further studies on its molecular mechanisms. Like nearly all enzymes that are involved in critical cellular functions, the activities of HDACs are highly regulated.

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## VIII. CONFLICT OF INTEREST

None

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