Review Article

A review on type of cancer and role of histone deacetylase inhibitors in cancer

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Abstract Histone deacetylases (HDACs) are enzymes involved in the remodelling of chromatin, and have a key position in the epigenetic legislation of gene expression. In addition, the activity of non-histone proteins can be regulated via HDAC-mediated hypo-acetylation. In latest years, inhibition of HDACs has emerged as an attainable strategy to reverse aberrant epigenetic changes associated with cancer, and numerous instructions of HDAC inhibitors have been observed to have mighty and particular anticancer activities in preclinical studies. However, such research have additionally indicated that the results of HDAC inhibitors should be notably broader and greater intricate than originally understood. Here we summarize recent advances in the appreciation of the molecular occasions that underlie the anticancer outcomes of HDAC inhibitors, and talk about how such information may want to be used in optimizing the improvement and application of these retailers in the clinic, either as monotherapies or in combination with other anticancer drugs.

Keywords type of cancer, histone deacetylase inhibitors

Introduction

Human body consists of trillions of cells. Cell is the basic structural and functional unit of life. Cell undergoes cell divisions and forms new daughter cells. Human cells grow and multiply as the body needs them. When cells grow old or become damaged, they die, and new cells take their place. Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they shouldn't [1].

These cells aggregate and forms tumor. Tumors are the lumps of tissues. Tumors can be cancerous or not cancerous. Cancerous tumor spreads to the various parts of the body and starts growing there, while the non-cancerous tumors are site specific and grow at a specific site. Cancerous tumors may also be called malignant tumors. Many cancers form solid tumors, but cancers of the blood, such as leukemias, generally do not [2]. Non-cancerous tumors are known as benign tumor. When removed, benign tumors usually don't grow back, whereas cancerous tumors sometimes do.

Cancer is a genetic disease caused through changes to genes that control the way our cells function, specially how they grow and divide. Cancer is triggered by means of sure modifications to genes, the basic physical devices of inheritance. Genes are arranged in lengthy strands of tightly packed DNA called chromosomes. Body usually eliminates cells with damaged DNA earlier than they flip cancerous. But the body's potential to do so goes down as

we age [3]. Each person's most cancers has a unique mixture of genetic changes, within the equal tumor, one-of-a-kind cells might also have unique genetic changes. There are three essential types of genes: proto-oncogenes, tumor suppressor genes, and DNA repair genes in human body. Genetic adjustments to these genes contributes to the cancer. Proto-oncogenes are concerned in everyday cell boom and mobile division [4]. When these genes are altered in positive ways or are greater active than normal, might also come to be cancer-causing genes. Tumor suppressor genes are additionally concerned in controlling cellphone boom and division. Alteration in tumor suppressor genes may lead to the uncontrolled boom of cell. Cells can also divide in uncontrolled manner. DNA restore genes are worried in fixing damaged DNA. In metastasis, cancer cells spoil away from the place they first formed and structure new tumors in other parts of the body [5]. Metastatic most cancers cells generally appear the same as cells of the unique cancer.

Types of Cancers

There are more than 100 types of cancer. Types of cancer depends on the organs or tissues where the cancers form. For example cancer in lungs is called lung cancer, Cancer in brain is called brain cancer etc [6].
These are some categories of cancers that begin in specific types of cells.

Carcinoma

Epithelial cells provide upward thrust to carcinomas. The cells that cover the interior and exterior surfaces of the physique are recognised as epithelial cells. The most generic kind of most cancers is carcinoma. Epithelial cells come in a range of shapes and sizes. Carcinomas that start in special kinds of epithelial cells have distinctive names. Squamous phone carcinoma is a most cancers that develops in the cells of the squamous epidermis. Epidermoid carcinomas are some other name for squamous telephone carcinomas. Transitional cell carcinomas are malignancies of the bladder, ureters, and kidneys. Adenocarcinoma is a kind of cancer that develops in epithelial cells that create mucus or fluids. Basal phone carcinoma is a most cancers that starts in the epidermis, a person's outer layer of skin, in the decrease or basal (base) layer [7].

Sarcoma

Sarcoma is a type of cancer that develops in the bones. The most prevalent type of cancer is osteosarcoma. Leiomyosarcoma, Kaposi sarcoma, and malignant fibrous histiocytoma are the most frequent soft tissue sarcomas [8].

Leukemia

Leukemias are cancers that start in the bone marrow's blood-forming tissue. In leukaemia, abnormal white blood cells proliferate and crowd out normal blood cells in the blood and bone marrow. Solid tumours do not form in this type of cancer [9].

Lymphoma

Lymphocytic cancer is a malignancy that starts in lymphocytes (T cells or B cells). Abnormal cells accumulate in lymph nodes and lymph arteries, as nicely as other organs, in lymphoma. Lymphoma is divided into two types: non-Hodgkin lymphoma and Hodgkin lymphoma Non-Hodgkin lymphoma and Hodgkin lymphoma are two types of lymphoma [10].

Multiple Myeloma

This is a cancer that starts in a plasma cell, which is a type of immune cell. Abnormal plasma cells, known as myeloma cells, grow up in the bone marrow and cause tumours in bones throughout the body [11].

Melanoma
Melanoma is a cancer that starts in cells that develop into melanocytes, specialised cells that produce melanin (the pigment that gives skin its color) [12].

Brain and Spinal Cord Tumors
Tumors of many sorts can develop in the brain and spinal cord. These tumours are named by the sort of cell that gave rise to them [13].

Other Types of Tumors
Germ Cell Tumors: These are cancerous tumours that start in the cells that produce sperm or eggs.
Neuroendocrine Tumors: Neuroendocrine tumours arise when cells in the nervous system release hormones into the bloodstream in response to a signal. These tumours, which may produce more hormones than normal.
Carcinoid tumor: They are slow-growing tumours that most commonly occur in the gastrointestinal tract. Carcinoid syndrome is caused by the secretion of chemicals like serotonin and prostaglandins [13].
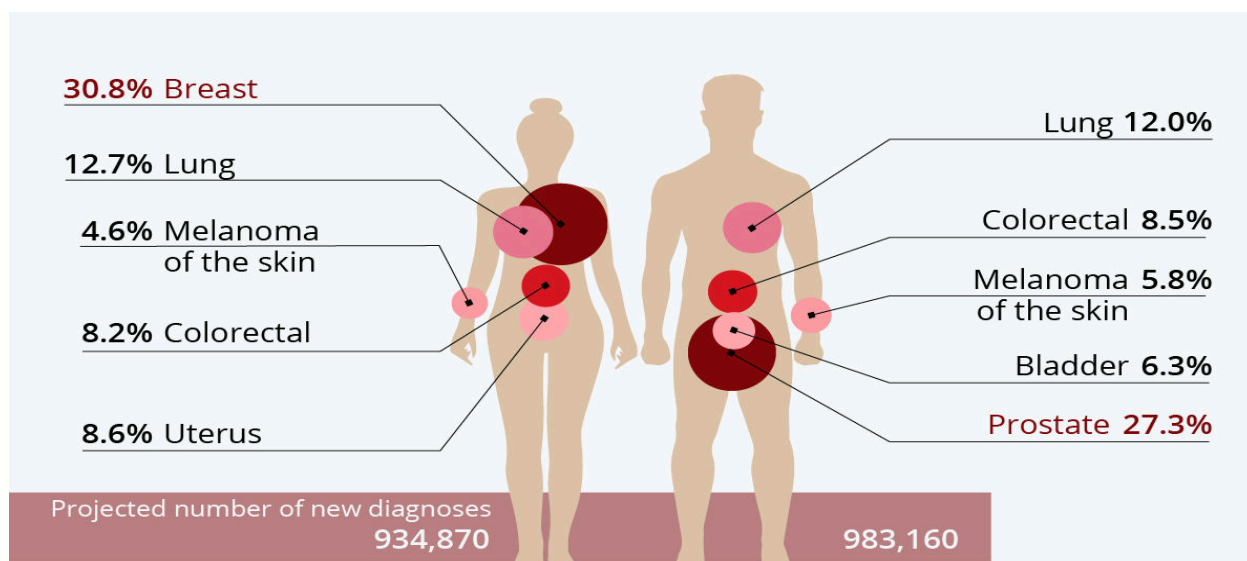

Types of Cancers
HDAC (HISTONE DEACETYLASES) Role in Cancer Targeting
In order to preserve the compact nature of DNA, chromatin is tightly wrapped round nuclear histones in distinct devices known as nucleosomes. The enzyme household called histone deacetylases (HDAC) continues the histone proteins in a country of deacetylation so that DNA can bind tightly. HDACIs can promote tumor boom arrest, differentiation and apoptosis [14]. HDACIs have been proven to synergize with antitumor/chemotherapy drugs, such as paclitaxel, cisplatin, etoposide, doxorubicin A herbal balance exists between histone acetylases (HAC) and HDAC. There are massive evidences that indicates that inhibitors of HDAC reduce the proliferation of changed cells in vitro as nicely as the growth of experimental tumors *in vivo*. HDAC inhibitors have been used in the treatment of solid tumours in medical trials. Leukemias and multiple myeloma are often cancers that are first studied for remedy with HDAC inhibitors [15]. In transcription rules of eukaryotic cells acetylation and deacetylation performs a distinguished role. HDACs might also be higher referred to as 'N-epsilon-lysine deacetylase. HDAC stands for histone deacetylase and two HAT stands for histone acetyl-transferase. HDAC and HAT are necessary in the dedication of acetylation reputation of two histones and non -histones protiens [16]. Acetyl to the lysine residues is brought by means of the HAT This neutralizes the fine cost on histone tails, weakening the interplay between histones and negatively DNA, yielding an extra open, transcriptionally permissive chromatin conformation HDAC

eliminates the acetyl team resulting in an extra condensed, transcriptionally repressive chromatin conformation [17]. As such, the anti-tumor consequences of HDAC inhibitors amplify the expression of genes driving cellphone cycle, tumor suppression, differentiation and apoptosis. miR-129-5p, for example, is vital in order for HDACI-induced and drug cell loss of life to be achieved [18].
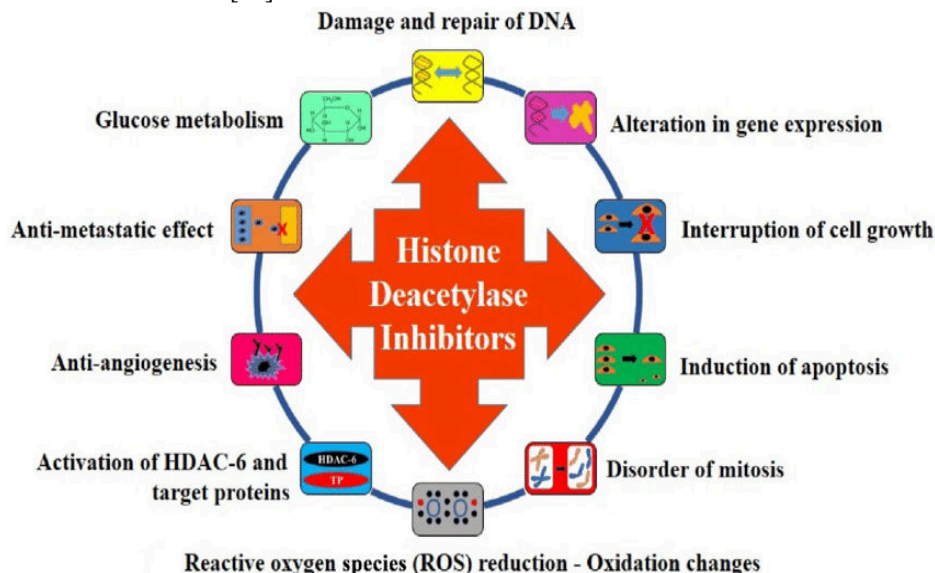
Mechanism Of Action of HDAC

There's growing evidences that the 18 histone deacetylases (HDAC) found in humans aren't redundant. Based on their similarity to yeast proteins, the 18 HDACs are divided into three groups. HDAC1, HDAC2, HDAC3, and HDAC8 belong to Class I and are homologous to yeast RPD3. HDAC4, HDAC5, HDAC7, and HDAC9 are all members of class II and are related to yeast HDA1. [19, 58] HDAC6 and HDAC10 are classed as class IIa because they have two catalytic sites, but HDAC11 is designated as class IV because it includes conserved residues in its catalytic centre that are shared by both class I and class II deacetylases. The majority of Class I HDACs are found in the nucleus. HDACs of class II travel between the nucleus and the cytoplasm. HDACs in class I serve a function in cell survival and proliferation [20, 59].

ROLE OF HDAC
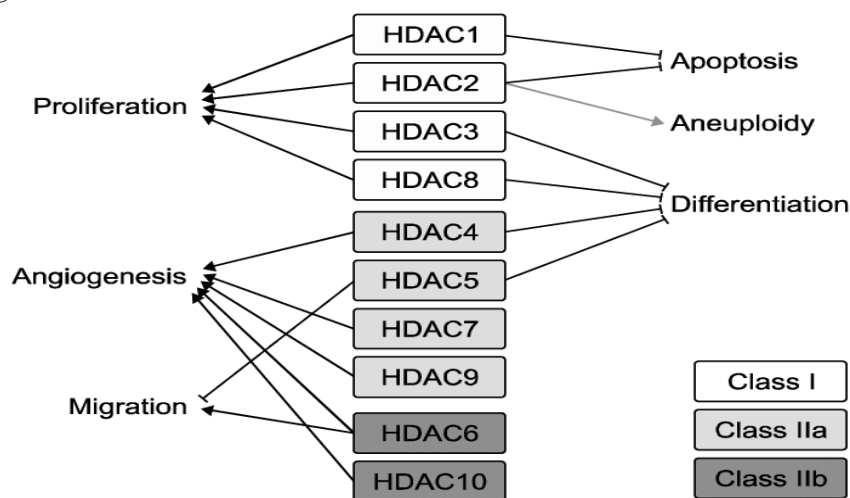
HDAC Group	HDAC Enzyme	Cellular Locality	Interacting Protein
Class I (Homologue to yeast Rpd3)	HDAC1	Nucleus	p53, RB, MYOD, NF-κB, DNMT1, DNMT3a, MBD2, Sp1, BRCA1, MeCP2, ATM, Smad7
	HDAC2	Nucleus	RB, NF-κB, BRCA1, DNMT1
	HDAC3	Nucleus/Cytoplasm	RB, NF-κB, Smad7, Stat3, SRY
	HDAC8	Nucleus	
Class IIa (Homologue to yeast Hda 1)	HDAC4	Nucleus/Cytoplasm	MEF2
	HDAC5	Nucleus/Cytoplasm	MEF2
	HDAC7	Nucleus/Cytoplasm	MEF2
	HDAC9	Nucleus/Cytoplasm	
Class IIb	HDAC6	Nucleus/Cytoplasm	Smad7, α-Tubulin, Hsp90
	HDAC10	Nucleus/Cytoplasm	
Class III (Homologue to yeast Sir2)	SIRT1	Nucleus	p53, FOXO1, p300, NF-κB
	SIRT2	Cytoplasm	α-Tubulin
	SIRT3	Mitochondria	
	SIRT4	Mitochondria	
	SIRT5	Mitochondria	
	SIRT6	Nucleus	Relate to heterochromatin
	SIRT7	Nucleus	Relate to nucleolus
Class IV (Similar to Both Class I and II)	HDAC11	Nucleus	

Types of HDAC

Description of HDAC Types

HDAC1 :- HDAC 1 belongs to the class 1 and have homology to yeast RPD3. HDAC1 (formerly termed HD1) contains histone deacetylase activity, according to immunoprecipitation of this 55-kDa protein. HDAC1-1 is expressed only in planarian ASCs, and RNAi of this gene causes a neoblast deficient phenotype, which includes cephalic structural regression, ventral curling, and a failure to initiate a regenerative response after amputation. Atrichia With Papular Lesions and Retinoblastoma are two diseases linked to HDAC1 [21, 22].

HDAC2 :- HDAC2 (formerly known as mRPD3), a second human histone deacetylase protein with significant similarity to yeast Rpd3, has been identified as a transcription factor . HDAC2 is a transcription inhibitor that is bound to DNA as a corepressor. HDAC2 modulates transcriptional activity through regulation of p53 binding activity. Protein kinase 2 (CK2) and protein phosphatase 1 (PP1) regulate HDAC2, although biochemical study reveals that its regulation is more complicated. HDAC2 has been linked to heart hypertrophy, Alzheimer's disease, Parkinson's disease, acute myeloid leukaemia (AML), osteosarcoma, and stomach cancer, among other things [23, 24].

HDAC3 :- HDAC3, the third human Rpd3-related protein, was found by a search of the GenBank database for DNA and protein sequences that were similar to HDAC1 and HDAC2. HDAC 3 plays a positive regulatory role by attaching to the NF-B p65 subunit and deacetylating different lysines at the same time. Deacetylation of NF-kB by HDAC 3 enhances interaction with the inhibitor protein IkB, which leads to nuclear export of NF-kB and, as a result, inhibition of inflammatory gene expression [25, 26].

HDAC4 :- Ca MKIV is important for HDAC4 phosphorylation and its nucleocytoplasmic shuttling. HDAC4 was discovered after GenBank databases search for human HDACs with sequence similarity to yeast Had1. HDAC4 is involved in the regulation of gene expression, which is vital for a variety of biological processes. HDAC4 regulates bone and muscle development, according to research. Chromosome 2Q37 Deletion Syndrome and Brachydactyly are two diseases linked to HDAC4. NOTCH1 Signaling and Mitotic G1-G1/S Phases are two linked mechanisms [27, 28, 43].

HDAC5 :- HDAC 5 belongs to the class 2 and have homlogy to HDA1 . HDAC5 was discovered after GenBank databases search for human HDACs with sequence similarity to yeast Had1. In urothelial cancer cell lines, overexpression of HDAC5 suppresses long-term proliferation but promotes epithelial-to-mesenchymal transition. Alzheimer Disease 19 and Anhidrosis, Isolated, With Normal Sweat Glands are two diseases linked to HDAC5.

Phospholipase-C Pathway and fMLP Pathway are two related pathways. The human HDAC5 gene is found on chromosome 17q21, a region of the genome where chromosomal material is lost in many malignancies. Furthermore, HDAC5 expression is typically reduced in cancers such as colon cancer and acute myeloid leukaemia, and is linked to a poor prognosis in lung cancer patients [29, 30, 43].

HDAC6 :- HDAC6 is a major cytoplasmic protein with key substrates such as α-tubulin. HDAC6 is unique in that it has an internal duplication of two deacetylase catalytic domains that appear to work independently of one another. HDAC 6 belongs to the class 2 and have homlogy to HDA1. The HDAC6 gene is found on chromosome Xp11.23 and codes for a 1215-amino-acid protein, the largest in the HDAC family.[31, 32] HDAC6 is unique in that it has two functioning catalytic domains, both of which are homologous and functionally independent of HDAC6's total activity. HDAC6 has a ubiquitin-binding zinc finger domain (ZnF-UBP domain, also known as the PAZ, BUZ, or DAUP domain) at its C-terminus that is involved in ubiquitination-mediated degradation control. Due to the inclusion of a nuclear export sequence (NES) and the SE14 motif, which is necessary for cytoplasmic retention, HDAC6 is mostly found in the cytoplasm [33, 34].

HDAC7 :- HDAC7 was first discovered as a protein that interacts with the retinoid or thyroid hormone receptor transcription corepressor silencing mediator (SMRT). HDAC7 has three repression domains, two of which are independent of the third deacetylase repressor activity and include autonomous repressor functions. HDAC7 has an important role in cancer progression [35]. HDAC7 is a member of the class IIa HDACs that mediate the repression activity of MEF2s, a family of master transcription factors involved in heart, blood vessel, neuron, and muscle differentiation. In chondrocytes, HDAC7 inhibits proliferation and -catenin activity. HDAC7 knockdown resulted in considerable cell arrest between the G(1) and S stages of the cell cycle, according to the study. In breast cancer stem cells, HDAC7 regulates histone 3 lysine 27 acetylation and transcriptional activity at super-enhancer-associated genes [36, 37, 38].

HDAC8 :- Early in evolution, HDAC8 separated from other class I enzymes, indicating a distinct functional specialisation. In humans, it is X-linked, and its action is unaffected by extra co-factors 6, 7, and 8. HDAC8 is either unregulated or overexpressed in cancer, and it has been shown to interact with transcription factors 17, 18, 19, 20. HDAC8 has a multifaceted role in human pathophysiology [39]. Human HDAC8 differs from the other HDAC isoforms in the class due to its X-linked structure and co-factor independent action. In addition, HDAC8 lacks the C-terminal protein binding domain observed in other HDACs. Furthermore, non-histone proteins like as cohesin, cortactin, and the Estrogen Related Receptor (ERR) have been found to bind to HDAC8 [40, 41].

HDAC9 :- HDAC9 possesses a conserved deacetylase domain, which represses gene activity when recruited to a promoter through deacetylation of histones. HDAC9 (Histone Deacetylase 9) is a gene that codes for a protein. [42] Cutaneous T Cell Lymphoma and Maxillary Cancer are two diseases linked to HDAC9. Phospholipase-C Pathway and fMLP Pathway are two related pathways [43]. Transcription factor binding and histone deacetylase binding are two Gene Ontology (GO) annotations for this gene. HDAC5 is an important paralog of this gene. HDAC9 (histone deacetylase 9) is a member of the class IIa histone deacetylase family. Inhibition or activation of HDAC9 is thus a prospective treatment option for a variety of illnesses [44]. HDAC9 overexpression is also prevalent in cancer cells, where it affects the expression and function of a number of key proteins involved in cancer development. Human HDAC9 is encoded by several protein isoforms and is found on chromosome 7p21.1. A region within exons 2–26 encodes the full-length HDAC9 protein, which contains 1,069 amino acids [45, 46].

HDAC10 :- Histone deacetylase 10 (HDAC10) is an enzyme that is encoded by the HDAC10 gene in humans [47, 10]. Determination of acetylation state of histone is assissted by HDAC10. Histone deacetylase (HDAC) 10 inhibits matrix metalloproteinase (MMP) 2 and 9 expression, which inhibits cervical cancer spread. Neuroblastoma is one of the diseases linked to HDAC10 [48]. In patients with NSCLC, HDAC10 is linked to PD-L1 expression and a poor prognosis. HDAC10 immunostaining was seen primarily in the nucleus and cytoplasm of cancer cells [49]. HDAC10 expression is substantially higher in lung cancer tissue than in comparable para-cancer tissue. HDAC10 is abundant in the liver, spleen, and kidney18,19, is concentrated in the cytoplasm19, and is resistant to sodium butyrate inhibition. Studies suggests that a polyamine transition state analogue inhibitor complexed with HDAC10 [50, 51].

HDAC11 :- HDAC11 is overexpressed in cancers such as breast cancer, hepatocellular carcinoma, and renal pelvis urothelial carcinoma, and has different expression levels and biological functions in different systems of the human body [52]. It is also among the top 1% to 4% of genes overexpressed in cancers such as breast cancer, hepatocellular carcinoma, and renal pelvis urothelial carcinoma [53, 54]. HDAC11 expression is generally seen in brain and testis tissue, but it has also been discovered to be upregulated in cancer cells. In antigen-presenting cells, HDAC11 has been found to be a negative regulator of IL-10 production [55]. Inhibition of HDAC11 has also been demonstrated to boost the expression of OX40L in Hodgkin lymphoma cells. HDAC11 is a histone deacetylase that regulates interleukin 10 production and immunological tolerance [56,57].

HDAC AND HAT
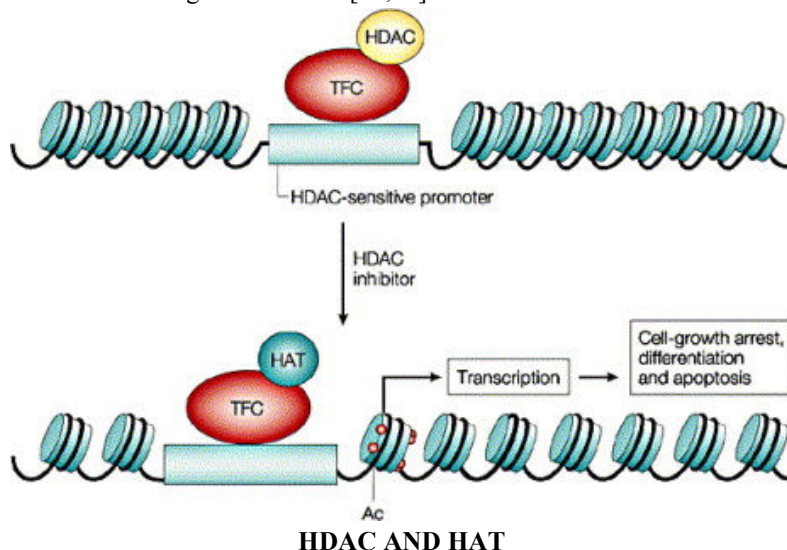
Conclusions

HDACi are exciting new anticancer sellers that induce tumour mobile phone death, differentiation and/or cell-cycle arrest. As nicely as their intrinsic effects on tumour cells, HDAC imight additionally affect neoplastic boom and survival via regulating host immune responses and tumour vasculature. The pleiotropic cellular results of HDACi can act cooperatively to mediate potent antitumour activities; however, the molecular techniques underlying the results of HDACi continue to be to be wholly elucidated. Ashistone acetylation has a crucial role in chromatin remodelling and transcription, it was once in the beginning proposed that HDACi mediate their organic results via the regulation of gene expression by means of direct histone hyperacetylation. More recently, it has been proven that in addition to transcription, histone acetylation can affect other molecular processes, which includes mitosis, DNA replication and DNA repair. Moreover, the endeavor of diverse non-histone proteins can additionally be regulated via acetylation, indicating that HDACi should have a a whole lot broader effect on cellular physiology than at first understood. Consequently, defining the molecular occasions underpinning a number antitumour activities of HDACi will require a larger perception of the effects of HDACi on diverse mobile proteins and pathways. Such records will be critical for the decision and stratification of sufferers who are plausible candidates for HDACi therapy, and for the rational format of combination studies using HDAC.

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