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REVIEW

Natural Agents-Mediated Targeting of Histone Deacetylases

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Abstract In the past few years, basic and clinical scientists have witnessed landmark achievements in many research projects, such as those conducted by the US National Institutes of Health Roadmap Epigenomics Mapping Consortium, the International Human Epigenome Consortium, The Cancer Genome Atlas Network and the International Cancer Genome Consortium, which have provided near-complete resolution of epigenetic landscape in different diseases. Furthermore, genome sequencing of tumors has provided compelling evidence related to frequent existence of mutations in readers, erasers and writers of epigenome in different cancers. Histone acetylation is an intricate mechanism modulated by two opposing sets of enzymes and deeply studied as a key biological phenomenon in 1964 by Vincent Allfrey and colleagues. The research group suggested that this protein modification contributed substantially in transcriptional regulation. Subsequently, histone deacetylases (HDACs), histone acetyltransferases and acetyl-Lys-binding proteins were identified as transcriptional mediators, which further deepened our comprehension regarding biochemical modifications. Overwhelmingly increasing high-impact research is improving our understanding of this molecularly controlled mechanism; moreover, quantification and identification of lysine acetylation by mass spectrometry has added new layers of information. We partition this multi-component review into how both activity and expression of HDAC are targeted using natural agents. We also set spotlight on how oncogenic fusion proteins tactfully utilize HDAC-associated nano-machinery to modulate expression of different genes and how HDAC inhibitors regulate TRAIL-induced apoptosis in cancer cells. HDAC inhibitors have been reported to upregulate expression of TRAIL receptors and protect TRAIL from proteasomal degradation. Deeper understanding of HDAC biology will be useful for stratification and selection of patients who are responders, non-responders and poor-responders for HDACi therapy, and for the rational design of combination studies using HDACi.

Keywords Histone deacetylase (HDAC) · Transcription regulation · TRAIL · Natural agents · Cancer

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Introduction

With the arrival of high-throughput technology and advanced proteomics, we have witnessed unprecedented expansion of our knowledge in molecular oncology over

the last two decades. As tumors evolve, daughter cells originating from initiating cell become heterogeneous and develop functionally different characteristics to resist therapeutic targeting of protein network (Brown et al. 2014; Buchheit et al. 2014; Byrne et al. 2017; Jones and Baker 2014). Research over the years has gradually provided many links between genomic, genetic variations and cancer (Knowles and Hurst 2015). Data obtained through high-throughput technologies have considerably improved our understanding of how histone proteins tactfully package DNA into nucleosomes, which are chromatin repeating units. It is now well known that acetylation state of histones plays a dominant role in the modulation of chromatin structure, which, consequently is involved in gene expression (Buschbeck and Hake 2017). It is interesting to note that a push and pull exists between two classes of enzymes, histone acetyltransferases (HATs) and histone deacetylases (HDACs) to control acetylated states of histones (Johnstone 2002; Li and Seto 2016; Zagni et al. 2017). HDACs act as transcriptional repressors by interacting with corepressor complexes, resulting in the compaction of chromatin structure (Fig. 1). It is a multistep mechanism that involves removal of neutralizing acetyl groups from histone lysine tails. Nucleosome is a deeply and thoroughly studied structure consisting of 146 bp of DNA, which enwraps core histone octamer, comprising H2A, H2B, H3 and H4. These proteins are highly conserved and basic in nature and have an NH_2-terminal tail rich in lysine and contains most of post-translationally modifiable regions of the core histones and about half of the positively charged residues (Johnstone 2002).

There are some good reviews related to use of natural products as HDAC inhibitors (Damaskos et al. 2017; Hanikoglu et al. 2017; Losson et al. 2016; Ma et al. 2016); however, we put extra emphasis on the role of HDACs in modulation of apoptosis and how HDACs work synchronously with fused oncoproteins to hijack transcriptional machinery and trigger the expression of target genes.

We briefly review different categories of HDACs before summarizing most recent updates about natural agents which target these HDACs.

Class I HDACs

HDAC1 and HDAC2 exist as members of repressor complexes such as SIN3, nucleosome-remodeling deacetylase, PRC2 and CoResT complexes. HDAC3 distinctly complexed with nuclear-receptor co-repressor—silencing mediator for retinoid and thyroid hormone receptors complex (Gallinari et al. 2007; Khan and La Thangue 2012; Marks et al. 2001).

Class IIa HDACs

HDAC4, 9, 7 and 5 belong to the class IIa HDAC family. These HDACs have an extended amino terminal which contained docking regions for different proteins including chaperone protein 14-3-3 and myocyte enhancer factor 2 (MEF2). Kinase-mediated phosphorylation promoted structural association of HDACs with 14-3-3 and consequent nuclear exit. Dissociation of class II

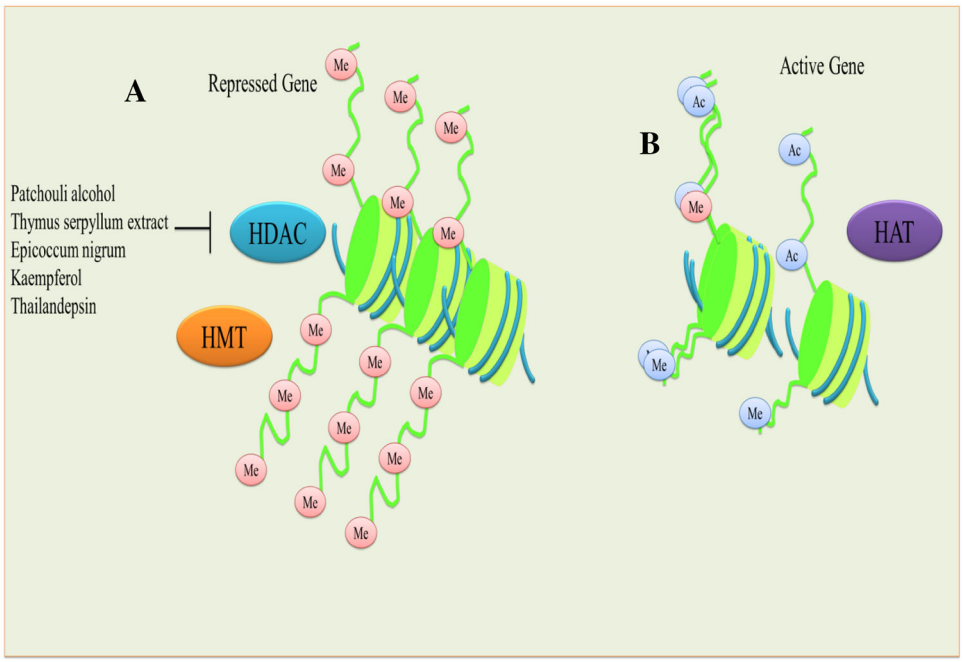

Fig. 1 **a** Transcriptionally repressive state of the gene. HDAC de-acetylates histone proteins and histone methyl transferase (HMT) methylates it. Various natural agents inhibit HDAC activity. **b** Transcriptionally active state of the gene is shown in which histone acetyltransferase (HAT) adds acetyl groups to histones

HDACs from MEF2 creates a binding site for HAT p300, and resultantly association of HAT with MEF2 converts it into a transcriptional activator from a transcriptional repressor. These HDACs are structurally associated via their regulatory domains with other transcriptional repressors including C-terminal-binding protein and heterochromatin protein 1 (Gallinari et al. 2007; Khan and La Thangue 2012; Marks et al. 2001).

Class IIb HDACs

HDAC10 and HDAC6 are members of class IIb family. HDAC6 is cytosolically located and reportedly involved in deacetylation of different cytoskeletal proteins including cortactin and α-tubulin, chaperones and cell surface proteins such as the interferon receptor.

DNA is noted to be methylated at cytosine of fifth position, predominantly within the CpG dinucleotide, by the DNA methyltransferases (DNMTs). Mechanistically, it has been shown that DNMTs directly recruited HDACs to deacetylate histone and transcriptionally repressed different genes. Additionally, methylated CpG islands were noted to be occupied by methyl-CpG-binding proteins (MBD1, MBD3, MBD2 and MECP2) which recruited chromatin remodeling proteins and HDACs to form tightly compact chromatin (Gallinari et al. 2007; Khan and La Thangue 2012; Marks et al. 2001; Minucci and Pelicci 2006).

Class III HDACs

Sirtuin (SIRT) is another term given to these HDACs. SIRT1–SIRT7 are homologs of yeast SIRT2 and due to structural variability differ from the other classes, requiring NAD^+ as a cofactor.

Class IV HDACs

HDAC11 belongs to this class having a catalytic domain shared with classes I/II HDACs. It is involved in deacetylation of DNA damage regulator (Cdc25A) (Lozada et al. 2016). HDAC6 has previously been reported to be associated with HDAC11 and modulated interleukin 10 expression (Cheng et al. 2014).

In the upcoming section, we set spotlight on most recent advances related to how fusion oncoproteins utilize HDAC and its associated machinery for epigenetic modifications. We also summarize how different natural agents inhibit activity, mRNA and protein expression of HDACs in cancer cells.

Fused Oncoproteins

Structural chromosome rearrangements have been extensively studied to play a contributory role in cancer development and progression (Mertens et al. 2015).

Mechanistically, HDACs have also been noted to be positioned at specific promoter regions by oncogenic fusion proteins thus contributing substantially in leukaemogenesis. AML1-ETO fusion protein recruited HDAC2, HDAC1 and/or HDAC3 to transcriptionally inhibit AML1 target genes, to inhibit myeloid differentiation. Valproic acid considerably reduced AML1-ETO protein levels in Kasumi-1 cells (Falkenberg and Johnstone 2014). Oroxylin A, derived from the root of *Scutcllana Baicalensis Georgi* markedly reduced expression level of AML1-ETO in AML cells. AML1-ETO transcriptionally repressed C/EBPα and P21. However, enhanced level of C/EBPα was noted in Oroxylin A-treated acute myeloid leukemia (AML) cells (Hui et al. 2016) (Fig. 2). Oroxylin A downregulated HDAC-1 and increased acetylation level of histone H3 in fusion-positive AML cells. 200 mg/kg of Oroxylin A for 60 days induced tumor regression in NOD/SCID mice. There was a marked increase in the number of CD45-positive cells in AML-bearing NOD/SCID mice; however, Oroxylin A exerted suppressive effects on CD45-positive cells (Hui et al. 2016).

Circumstantial evidence also provided information of similar mechanism triggered by fusion proteins PLZF-RARα and PML-RARα in directing loading of DNMTs and HDACs to silence RARα target genes (Falkenberg and Johnstone 2014).

Interplay of Fused Oncoproteins with HDACs: Therapeutic Targets

Combining HDAC inhibitor with Polo-like kinase 1 inhibitors, considerably enhanced apoptotic cell death in primary BCR/ABL^+ $CD34^+$ cells. Moreover, this combination also efficiently inhibited tumor growth in early- and late-stage BCR/ABL^+ xenografted mice (Dasmahapatra et al. 2013).

PML-RARα induced epigenetic inactivation of genes is reversible by HDAC inhibitor treatment. MC2392, a novel hybrid retinoid-HDAC inhibitor considerably inhibited HDACs present in PML-RARα-associated repressive complex (De Bellis et al. 2014).

LSD1 (KDM1A), a histone demethylase has been noted to demethylate mono- and di-methylated 4th lysine on histone 3. Higher LSD1 expression blocked differentiation and induced a prognostically challenging phenotype. SP2509 (LSD1 antagonist) significantly reduced LSD1 binding with corepressor CoREST and simultaneously

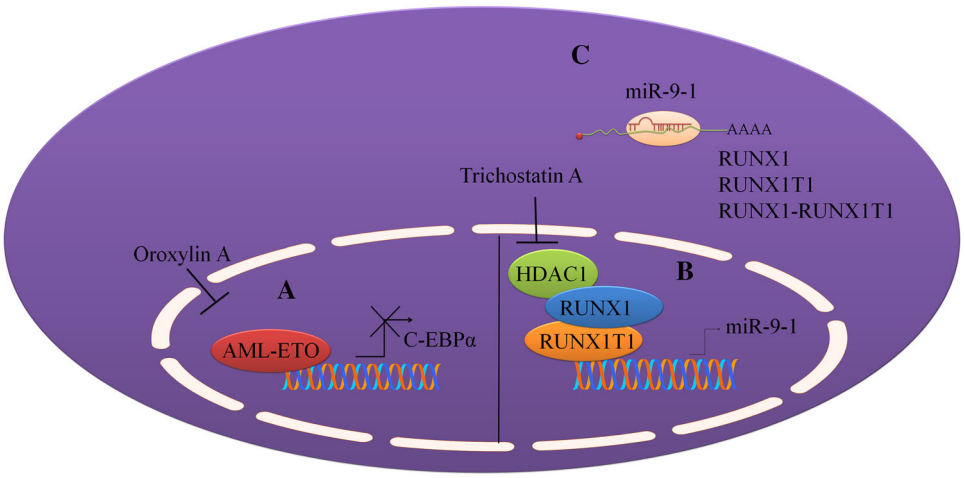

Fig. 2 **a** Oroxylin A mediated targeting of AML-ETO. AML-ETO transcriptionally repressed C-EBPα; however, Oroxylin A inhibited AML-ETO and enhanced expression of C-EBPα. **b** RUNX1, RUNX1T1 and HDAC1 worked synchronously to transcriptionally downregulate miR-9-1. Trichostatin upregulated the expression of miR-9-1 by inhibiting HDAC activity. **c** Furthermore, miR-9-1 negatively regulated RUNX1, RUNX1T1 in cancer cells

enhanced permissive H3K4Me3 marks on promoter regions of p21 and p27 in AML cells. However, SP2509 was not found to be effective against AML cells expressing mixed-lineage leukemia fusion oncoproteins (Fiskus et al. 2014b). Combining SP2509 with phytochemicals may prove to be useful and effective.

JQ1, BET protein antagonist, was notably effective against AML cells expressing mutant NPM1c^{+} and FLT3-ITD^{+} or FLT3-ITD^{-}. JQ1 also exerted inhibitory effects on AML cells expressing mixed-lineage leukemia fusion oncoprotein. Synergistic administration of an HDACi (panobinostat) and JQ1 considerably enhanced apoptotic cell death in AML cells (Fiskus et al. 2014a). Panobinostat had been tested for efficiency in mice xenografted with AML1/ETO9a expressing AML cells and results revealed panobinostat-mediated proteasome-directed degradation of A/E9a (Bots et al. 2014).

5-Lipoxygenase (5-LO), encoded by ALOX5 gene, is involved in regulation of pro-inflammatory leukotrienes. MLL-AF4 activated 5-LO promoter, whereas AF4-MLL modulated calcitriol/TGF-β-induced 5-LO elongation of transcript. HDAC class I inhibitors significantly inhibited AF4-MLL-triggered 5-LO transcript elongation by TGF and calcitriol (Ahmad et al. 2015).

EWS-ERG/EWS-Fli-1 inhibited RXRα-mediated transcriptional activation of tumor suppressor genes by complexing with HDACs. Valproic acid considerably inhibited fusion protein EWS-Fli-1 in TC-135 cells and EWS-ERG in 5838 cells (Kayarthodi et al. 2014).

SB939, an inhibitor of class 1 and 2 was tested for clinical efficacy in patients with metastatic or recurrent translocation-associated sarcoma (Chu et al. 2015). Patients were given 60 mg/day every other day for 3 of 4 weeks. Patients having higher expression of HDAC2 showed response to SB939; however, because of smaller sample size, study did not provide definitive conclusion (Xia et al. 2014).

Trichostatin-A

Histone deacetylation and DNA methylation contributed to the transcriptional downregulation of miR-9-1 in RUNX1–RUNX1T1 positive AML cells. 5 putative RUNX1-binding sites surrounded by CpG islands were identified in upstream region of miR-9-1 (Fu et al. 2017). RUNX1–RUNX1T1, HDAC1, DNMTs were detected at the miR-9-1 chromatin regulatory regions which surrounded proximal RUNX1-binding site (Fig. 2). Interestingly, miR-9-1 inhibits RUNX1–RUNX1T1, RUNX1 and RUNX1T1. Trichostatin-A and trichostatin-C (glucopyranosyl derivative) were isolated from *Streptomyces hygroscopicus*. Trichostatin-A markedly enhanced miR-9-1 via targeting of HDAC in AML cells (Fu et al. 2017).

RARα-PLZF recruited HDAC1 to de-acetylate histone H3 at C/EBPα target loci, to downregulate expression of C/EBPα target genes. HDAC1 co-existed with C/EBPα in RARα-PLZF transfected cells and treating cells with trichostatin-A considerably enhanced expression of target genes (Girard et al. 2013).

Trichostatin-A and valproic acid significantly reduced TMPRSS2-ERG expression in prostate cancer cells (Fortson et al. 2011). 500 nM of class I selective MS-275 limited AR protein cytosolically, thus inhibiting AR-mediated upregulation of TMPRSS2-ERG-fusion transcript. Similarly, 2.5 μM of pan-HDAC inhibitor SAHA reduced both cytosolic and nuclear AR, in treated cancer cells (Björkman et al. 2008).

Naturopathy

Wealth of information suggested a paradigm shift in translational oncology and continuously expanding list of natural agents with notable tumor growth inhibitory activity has opened new horizons to overcome resistance

against wide-ranging molecular therapeutics and restoration of apoptosis. In the following section, we briefly discuss how different natural agents inhibit activity, mRNA and protein expression of HDACs in cancer cells and some of the chemical structures of these compounds are displayed in Fig. 3.

Neo-Tanshinlactone Analogs

Neo-tanshinlactone, an isolate from the roots of *Salvia miltiorrhiza* is a planar molecule having four rings. Through the modification of D-ring, different analogs were synthesized and tested for efficacy against HDACs in breast cancer cells (Banerji et al. 2017). p53 and retinoblastoma protein (Rb) are tumor-suppressors which modulate cellular responses to DNA damage. In hypo-phosphorylated form, Rb stably associated with E2F1. Rb can bind to HDAC1 and HDAC2. HDAC1 preferentially associated with an active, hypo-phosphorylated form of Rb. Consequently, trimerically associated proteins (E2F1, Rb and HDAC1) are essential prior to G1-S transition. However, 1J analog dose-dependently down regulated/depleted HDAC1 and HDAC2 and induced accumulation of HDAC-3 from nucleus to cytoplasm (Banerji et al. 2017).

Phenethyl Isothiocyanate

Phenethyl isothiocyanate (PEITC) is a bioactive molecule noted to effectively inhibit binding of HDAC1 and HDAC3 to open regions of active euchromatin. Significantly reduced tumor growth was noted in nude mice subcutaneously injected with SW620-PEITC cancer cells (Park et al. 2017). Expression levels of HDAC1, 2, 4 and 6 were also inhibited by 5 μM PEITC in prostate cancer cells (Boyanapalli et al. 2016).

Pterostilbene and Resveratrol

Five μM pterostilbene and 15 μM resveratrol significantly inhibited SIRT1 both at mRNA and protein level (Kala et al. 2015). Highly enriched acetyl-H3, acetyl-H3K9 and acetyl-H4 active chromatin markers were noted between 48 and 72 h in breast cancer cells after treatment with pterostilbene and resveratrol. Both chemicals significantly decreased HDAC activity ($p < 0.01$) in treated breast cancer cells (Kala and Tollefsbol 2016).

Fungal Products

Bio-guided identification of inhibitors against HDACs is gaining attraction currently. Fungal products are potential HDAC inhibitors and different isolated products are currently being used. Romidepsin isolated from

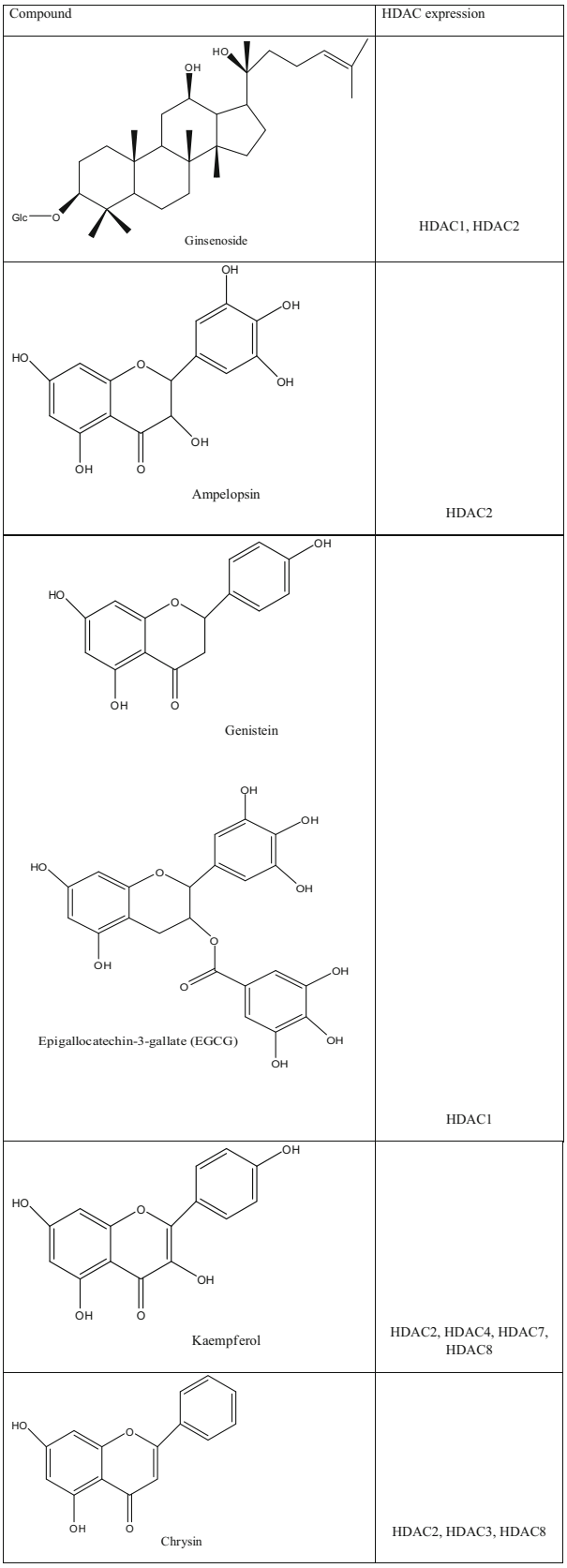

Fig. 3 Structures of different natural agents with notable activity against HDACs

Chromobacterium violaceum and trapoxin B, a selective HDAC1 inhibitor obtained from *Helicoma ambiens* have shown efficacy.

Recently, gliocladride C and salirepol have been obtained from *Penicillium griseofulvum*. Gliocladride C selectively targeted HDAC1 and salirepol exerted inhibitory effects on HDAC6 (Zwick et al. 2017).

Ginsenoside

Ginsenoside Rh2 (G-Rh2) isolated from root of *Panax ginseng* has recently been reported to time-dependently and dose-dependently inhibit proliferation of K562 cells at a dosage ranging 20–80 μmol/L. HDAC1 and HDAC2 expressions were notably reduced in cell treated with G-Rh2 as evidenced by western blot analysis (Xia et al. 2014).

Runt-related transcription factor 3 (RUNX3) belonged to family of RUNX genes and frequently downregulated in cancer cells. Mechanistically, hypoxic cells demonstrated upregulated HDAC1 and G9a, a histone methyltransferase which worked synchronously to epigenetically inhibit RUNX3. Levels of H3K9 methylation and histone H3 acetylation were reduced at the RUNX3 promoter in cancer cells. Compound K, a metabolite of ginseng saponin time-dependently inhibited HDAC that resulted in RUNX3 re-expression in colorectal cancer cells. Significantly enhanced apoptotic rate was noted in Compound K-treated colorectal cancer cells (Kang et al. 2013).

Hydnophytum formicarum Jack

It was noted that treating cancer cells with ethanolic and phenolic-rich extracts prepared from rhizome of *Hydnophytum formicarum* Jack induced an increase in hyperacetylated histone H4 molecules. Ethanolic and phenolic-rich extracts treated cancer cells demonstrated considerably enhanced levels of H4 with three acetylated lysine residues. Sinapinic acid, an active constituent isolated from extracts also induced an increase in di and triacetylated H4 molecules with 2 and 3 acetylated lysine residues, respectively. Ethanolic crude extract was noted to significantly inhibit activity of HDAC up to 55.2 ± 3.2% (Senawong et al. 2013).

Ampelopsin

Ampelopsin, a flavonoid isolated from *Ampelopsis grossedentata* has been shown to dose-dependently reduce HDAC2 mRNA and protein levels in treated lung adenocarcinoma cells (Chen et al. 2015).

Epigallocatechin-3-Gallate and Genistein

Epigallocatechin-3-gallate and genistein concentration-dependently inhibited HDAC activity and protein levels of HDAC1 in treated colon carcinoma cells (Groh et al. 2013).

Green tea polyphenols and sulforaphane combinatorially inhibited HDAC activity in MDA-MB-231 cells. It has previously been convincingly revealed that HDAC repressor complex, DNMT1 and HDAC1 synchronously modulated epigenetic inactivation by increasing loading of co-repressor complexes at methylated ERα promoter. In accordance with this approach, it has also been experimentally verified that interfering with positioning of transcriptional repressor complex, HDAC1/DNMT1/SUV39H1, resulted in transcriptional activation of ERα in ERα-breast cancer cells. Synergistically, both chemicals remarkably downregulated HDAC4, HDAC1 and HDAC6 (Meeran et al. 2012). Polyphenols from green tea reportedly inhibited HDAC activity and HDAC protein levels via proteasomal degradation. However, HAT activity was markedly enhanced in treated melanoma cells (Prasad and Katiyar 2015).

Soy phytoestrogens and the natural hormone 17b-estradiol considerably reduced H3K27me3 marks in MCF7 and MDA-MB 231 cells. Genistein and daidzein also significantly inhibited methylation at K4 of H3 in MDA-MB 231 and MCF7 cancer cells (Dagdemir et al. 2013).

Osthole

Osthole, a bioactive ingredient, has been used as an effective hydrophobic capping agent by fusing it with aliphatic-hydroxamate core of suberoylanilide hydroxamic acid (SAHA). Results revealed that HDAC inhibiting efficacy of osthole-fused SAHA was dramatically enhanced as evidenced by inhibition of HDAC1, HDAC4, HDAC6 and HDAC8 in different cancer cell lines (Huang et al. 2011).

Different novel osthole-based *N*-hydroxycinnamides have been tested for efficacy against wide-ranging HDACs and results revealed that compounds 9d, 9e, 9g were effective against HDACs located in nucleus in HeLa cells. 9d and 9e revealed SAHA-like activity against HDAC6 and HDAC1; however, compound 9g selectively targeted HDAC1 (Huang et al. 2010).

Patchouli Alcohol

Patchouli alcohol, an essential oil of *Pogostemon cablin* induced apoptosis by effectively inhibiting HDAC2 activity and expression in colorectal HCT116 and SW480 cancer cells (Jeong et al. 2013).

Thymus serpyllum Extract

Thymus serpyllum extract induced apoptosis in MDA-MB-231 cells by efficiently inhibiting DNA methyltransferase and HDAC activities (Bozkurt et al. 2012).

Epicoccum nigrum

Chemicals isolated from endophytic fungus *Epicoccum nigrum* have also been reported to inhibit HDAC activity (El Amrani et al. 2014).

Kaempferol

Kaempferol, a natural polyphenol has recently been reported to fit within the binding pocket of HDAC2, HDAC4, HDAC7 or HDAC8. It binds to the zinc ion in catalytic center. Kaempferol induced hyperacetylation of histone complex H3 in hepatoma cell lines Hep3B and HepG2 (Berger et al. 2013).

Acridocarpus orientalis

Acridocarpus orientalis, a traditional medicinal plant and its aqueous ethanol crude extract markedly inhibited HDAC activity (Ksiksi and Hamza 2012).

Apigenin

Treating prostate cancer 22Rv1 and PC-3 cells with apigenin, 4′,5,7,-trihydroxyflavone resulted in the inhibition of HDAC1 and HDAC3 both at mRNA and protein levels (Pandey et al. 2012). Apigenin-treated prostate cancer cells had globally increased acetylated histone H3 and H4 levels as well as localized hyper-acetylated H3 on the p21 promoter. Protein levels of HDAC1 and HDAC3 were also reduced in athymic nude mice xenografted with prostate cancer cells (Pandey et al. 2012).

Chrysin

Chrysin, 5,7-dihydroxy flavone at a concentration of 40 μM significantly reduced HDAC2, HDAC3 and HDAC8 protein levels in melanoma A375 cells (Pal-Bhadra et al. 2012). Notably reduced number of histone H3me2K9 foci were detected and expectedly H3me2K9 foci distribution on the metaphase chromosomes isolated from A375 cells treated with chrysin was comparably lesser in intensity than DMSO-treated cells. Acetylation levels of H3 and H4 increased steadily in nuclei at interphase stage in chrysin-treated A375 cells (Pal-Bhadra et al. 2012).

Diarylheptanoids

Diarylheptanoids isolated from *Betula platyphylla* selectively targeted HDAC6 in treated colon cancer cells. Different phytochemicals (−)-centrolobol or aceroside VIII with A452 (selective HDAC6 inhibitor) synergistically targeted HDAC (Ryu et al. 2015). Moreover, A452-mediated inhibitory effects were notably enhanced when administered combinatorially with paltyphyllone, aceroside VIII and (−)-centrolobol to induce apoptosis and growth inhibition (Ryu et al. 2015).

Tropolone

Structurally, HDACs contained hydrophobic pockets located closely to bound $Zn2^{+}$ ion thus providing accessibility to lipophilic substituents placed proximally to metal-binding headgroup. Thujaplicins, are members of the tropolone family obtained from the heartwood of trees of Cupressaceae family. Metal-binding moiety of the tropolone shows an extended vinylogous carboxylic acid (Ononye et al. 2013). α- and β-substituted tropolones potently inhibited HDAC2 because of larger groups than isopropyl group present at β-position in β thujaplicin. Inhibitory effects exerted by β-substituted derivatives were significant against HDAC2. More importantly, increase in group size correlated with efficacy as compared to naturally occurring isopropyl substituent (Ononye et al. 2013).

Propolis

Brazilian propolis extract inhibited HDAC activity in Neuro2a cells (Ishiai et al. 2014). Caffeic acid phenethyl ester, a major active component in propolis induced an increase in acetylated histones in breast cancer MDA-MB-231 and MCF-7 cells (Omene et al. 2013).

Thailandepsin

Thailandepsin A and thailandepsin B isolated from *Burkholderia thailandensis* E264, potently inhibited HDAC2, HDAC1, HDAC6, HDAC3, HDAC9 and HDAC7. Moreover, GI50 was noted against 90% of different cancer cells tested (Wang et al. 2011b).

Largazole

Largazole, isolated from a cyanobacterium has been studied spectroscopically and skeleton of 1 embodied two distinct domains. Functionally, tetrapeptide-derived units and 3-hydroxy-7-octanoylmercaptohept-4-enoic acid of which the thiol residues in cysteine components were condensed with the adjacent amides to generate vicinal

azole rings. Largazole and 2-epi-largazole dose-dependently increased acetylated histone H3 levels (Wang et al. 2011a).

Cyclic Tetrapeptide 1-Alaninechlamydocin

Cyclic tetrapeptide 1-alaninechlamydocin, purified from *Tolypocladium* sp notably inhibited HDAC activity at low nanomolar concentrations in pancreatic MIA PaCa-2 cancer cells (Du et al. 2014).

Plant Isoquinoline Alkaloid Berberine

Plant isoquinoline alkaloid berberine (BBR) was found to be efficient against all classes of zinc-dependent HDACs (class I, II-a, II-b, and IV). HDACs of class I and II were observed to be significantly reduced by BBR as compared to the class IV HDAC subtypes (Kalaiarasi et al. 2016) (Table 1).

Role of HDAC Inhibition in TRAIL-Induced Apoptosis

High-throughput technologies have helped us to develop a better understanding of interactions that interweave different programmed cell death-associated transduction cascades, which form intricate signaling networks that cross-guard each other in the evolutionary "arms race" against cancer cells (Lemke et al. 2014). Intrinsic and acquired resistance against different drugs had added more layers of complexity to standardization of therapy and various synthetic and natural agents are currently being investigated for efficacy against different cancers (Lemke et al. 2014). Interest in drug development has been fuelled by the concept that drugs should be effective with minimum off-target effects and maximum clinical outcome. There has always been a quest to search for molecules having minimum off-target effects and remarkable clinical efficacy. Because of differential killing activity, TNF-related apoptosis-inducing ligand (TRAIL)-mediated signaling is an extensively studied dimension of molecular oncology (Dimberg et al. 2013; Naoum et al. 2016). The discovery of a unique property of TRAIL to selectively induce apoptosis in cancer cells laid the foundation for evaluation of potential of TRAIL-based therapeutics in different preclinical models. Genetic and proteomic analysis suggest that TRAIL-induced apoptosis is deregulated in many cancers (de Miguel et al. 2016; Fox and MacFarlane 2016). TRAIL binds to its native receptors DR4 and/or DR5 present on the surface of cancer cells. Binding of TRAIL induces receptor clustering and recruitment of Fas-associated death domain and an initiator caspase 8, forming a death-inducing signaling complex. Functionally active caspase-8 proteolytically processed caspase-3 to transduce the signals to induce apoptosis. Intrinsically controlled pathway is triggered by entry of truncated Bid into mitochondria. Different stimuli trigger

Table 1 List of natural agents with notable activity against different HDACs

Chemical/source	Target	References
Compound K, a metabolite of ginseng saponin	HDAC1 and G9a (histone methyltransferase)	Kang et al. (2013)
	RUNX3	
Sinapinic acid (*Hydnophytum formicarum Jack*)	HDAC	Senawong et al. (2013)
Ampelopsin (*Ampelopsis grossedentata*)	HDAC2	Chen et al. (2015)
Saikosaponin	HDAC6	Li et al. (2016)
Patchouli alcohol (*Pogostemon cablin*)	HDAC2	Jeong et al. (2013)
Thymus serpyllum extract	HDAC	Bozkurt et al. (2012)
	DNMT	
Epicoccum nigrum	HDAC	El Amrani et al. (2014)
Kaempferol	HDAC2, HDAC4, HDAC7 or HDAC8	Berger et al. (2013)
Acridocarpus orientalis	HDAC	Ksiksi and Hamza (2012)
Apigenin	HDAC1 and HDAC3	Pandey et al. (2012)
Chrysin	HDAC2, HDAC3 and HDAC8	Pal-Bhadra et al. (2012)
Diarylheptanoids (*Betula platyphylla*)	HDAC6	Ryu et al. (2015)
Thujaplicins	HDAC2	Ononye et al. (2013)
Brazilian propolis extract	HDAC	Ishiai et al. (2014)
Thailandepsin (*Burkholderia thailandensis*)	HDAC2, HDAC1, HDAC6, HDAC3, HDAC9, HDAC7	Wang et al. (2011b)
Formononetin (*Astragalus membranaceus*)	HDAC5	Liu et al. (2015)

activation of BH3-only family members, which exert inhibitory effects on pro-survival BCL-2-like proteins, to activate pro-apoptotic effectors BAX and BAK (Arafat et al. 2015; de Miguel et al. 2016; Fox and MacFarlane 2016). Release of Cytochrome *c* from the mitochondrion promoted activation of caspase-9 on the scaffold protein apoptotic protease-activating factor 1. X-linked inhibitor of apoptosis protein (XIAP) is a caspase inhibitor and second mitochondria-derived activator of caspases (SMAC) efficiently blocked XIAP in cancer cells. There is evidence of use of SMAC mimics to improve TRAIL-induced apoptosis in cancer cells (Petrucci et al. 2012). Functionally active caspase-9 triggered activation of caspase-3.

OBP-801, an HDAC inhibitor has recently been documented to show impressive results when used in combination with celecoxib. OBP-801 and celecoxib markedly reduced mRNA levels of survivin and FLIP in UM-UC-11 and T24 cells. There was a considerable upregulation of DR5 in combinatorially treated cancer cells. OBP-801 and celecoxib significantly inhibited tumor growth in xenografted mice (Toriyama et al. 2016).

c-Myc has also recently been reported to occupy promoter region of TRAIL. c-Myc dimerically associated with Max to enhance its affinity for DNA and transcriptionally modulated an array of target genes (Nebbioso et al. 2017). HDAC inhibitors were noted to increase H3K9 acetylation level in presence of higher levels of H3K4me3 to maintain an active epigenetic state of TRAIL. H3K9me3 was a repressive transcriptional mark and reduced dramatically after 24 h of exposure to HDAC inhibitors. c-Myc is reportedly involved in repression of TRAIL with multiple Sp1-binding sites through Sp1/Sp3 (Fig. 4). Transcriptional repression of TRAIL is triggered through association of Myc-Max dimers to Sp1 or Miz1 at GC boxes (Nebbioso et al. 2017). HDAC inhibitors enhanced transcriptional activation of TRAIL by interfering with structural association of transcriptional factors. HDAC inhibitor induced acetylation of c-Myc at 323rd Lysine and there was a transient increase in c-MycK323ac at promoter region of TRAIL. c-MycK323ac was found to be inversely correlated with c-Myc accumulation at promoter region and correlated with HDAC inhibitor mediated displacement of HDAC1 or masking of its activity (Nebbioso et al. 2017) (Fig. 4).

TRAIL and SAHA combinatorially induced Bax and inhibited Bcl-2 mRNA expression in MDA-MB-231 cells. 50 ng/ml TRAIL and 5 μM SAHA exerted most significant inhibitory effects on cell growth (Zhou et al. 2016).

Magnolol and polyphenol mixture (PM) derived from *Magnolia officinalis* showed strong activity against lung cancer cells (Liu et al. 2016). PM and Magnolol reduced nuclear protein expression levels of HDAC1, HDAC2, HDAC3 and HDAC8 in H1299 and A549 cells in a dose dependent manner. Magnolol at 60 μM considerably reduced protein expression levels of HDAC3 (53.62%) and HDAC8 (22.77%) in H1299 cells (Liu et al. 2016). PM significantly decreased protein expression levels of HDAC3 in both H1299 and A549 cells. PM treatment at 16 μg/mL markedly reduced HDAC3 (protein levels) by 53.63% in A549 and 51.09% in H1299 cells (Liu et al. 2016). H3K27 site was hyper-acetylated within DR5 gene after treatment with magnolol and PM (Fig. 4). Data obtained from ChIP assays revealed that PM and magnolol treatments enhanced histone acetylation within DR5 promoter region because of significantly inhibited HDACs catalytic activities. PM and magnolol markedly enhanced caspase 3 and cleaved caspase 3 in H1299 and A549 cells. Bax was upregulated but Bcl-2 reduced significantly in PM and magnolol treated cancer cells.

Delphinidin, an anthocyanidin synergistically with TRAIL induced downregulation of HDAC3 in prostate cancer cells. Enforced expression of HDAC3 increased the expression of antiapoptotic factors BCL-2, survivin, XIAP, cIAP-2 and BID dose-dependently. Moreover, pro-apoptotic factors were reduced thus overriding apoptosis-inducing effects of combinatorially used TRAIL and delphinidin. Interestingly, HDAC3 was proteolytically processed in TRAIL sensitive Du145 and TRAIL resistant LNCaP cells (Fig. 5).Chemical inhibition of caspase 3/7 using DQMD inhibited the delphinidin and TRAIL mediated activation of caspase 3/7 and formation of caspase mediated proteolytically processed HDAC3 (Ko et al. 2015). Chemical inhibition of Class III HDAC, SIRT1 considerably enhanced cell surface DR5 expression. Moreover, RNA interference strategy also indicated that cell surface expression of DR5 was remarkably enhanced in SIRT1 silenced cancer cells. Amurensin G isolated from *Vitis amurensis* also inhibited SIRT1 (Kim et al. 2012). Homoharringtonine, a natural alkaloid, isolated from Cephalotaxus, dose-dependently upregulated DR5 expression (Cao et al. 2013).

Long terminal repeat (LTR) of human endogenous retrovirus type 9 (ERV9) acted as a germline-specific promoter that transcriptionally upregulated isoform of a tumor suppressor homologue p63, GTAp63. HDAC inhibitors induced expression of ERV9-LTR associated target genes, particularly, a transcript encoding the DR5 originated from an ERV9-LTR inserted upstream of the protein coding regions of the TNFRSF10B gene. Testicular cancer cells combinatorially treated with HDAC inhibitors and TRAIL demonstrated considerably enhanced apoptotic cell death (Beyer et al. 2016).

Interfering with HDAC2, considerably improved TRAIL-induced apoptosis in pancreatic Panc1 and MiaPaCa2 cancer cells. Moreover there was a markedly

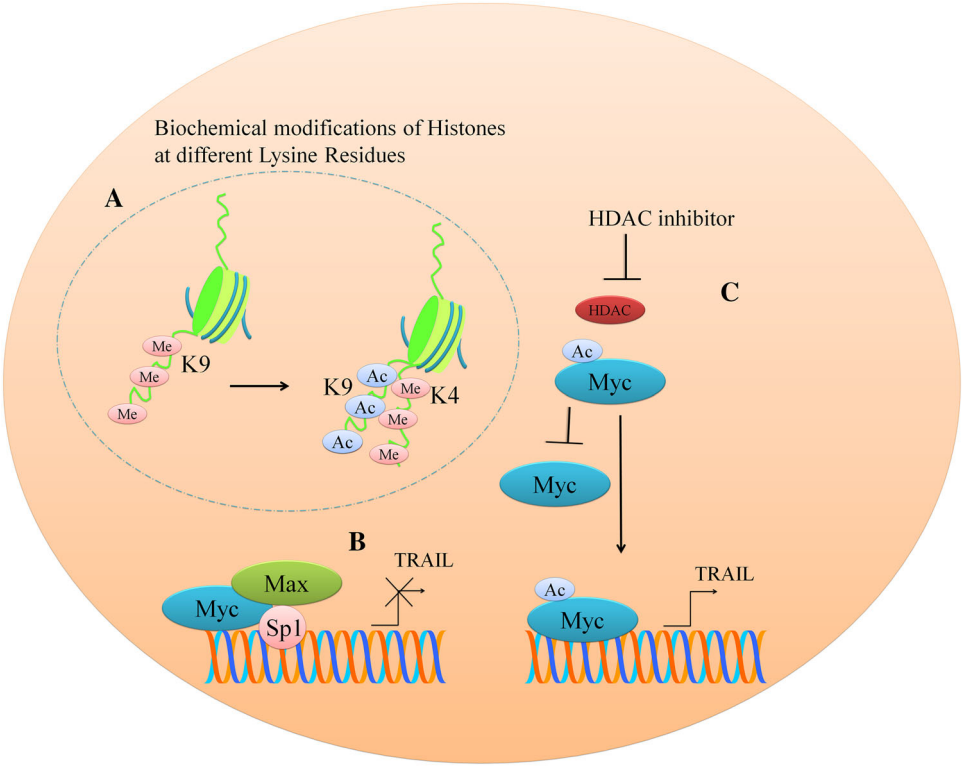

Fig. 4 **a** Biochemical modifications of histone at lysine 9 and 4. Lysine 9 undergoes de-methylation and subsequently acetylation. Lysine is methylated. **b** Myc, Max and Sp1 occupy promoter region of TRAIL and downregulate expression of TRAIL. **c** However, acetylation of Myc markedly reduced accumulation of non-acetylated Myc at promoter region

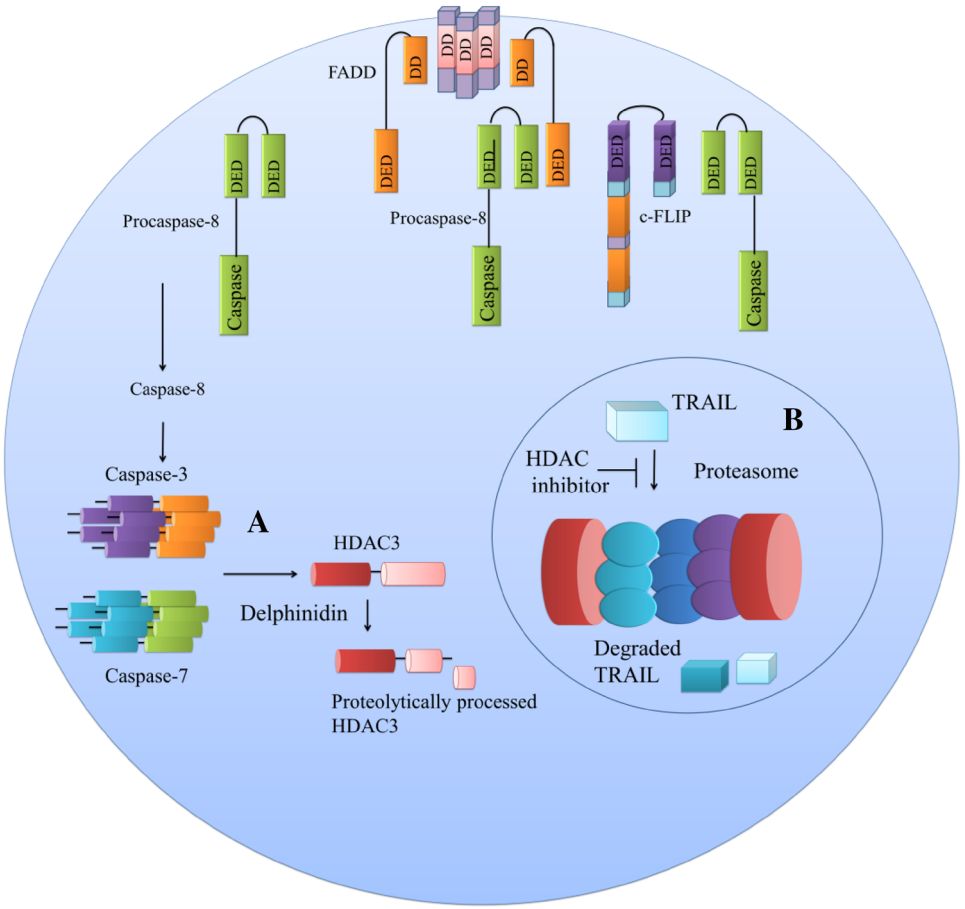

Fig. 5 Caspase-8-mediated activation of caspase-3. FADD, cFLIP and death receptors assemble to form a signalosome known as death-inducing signaling complex (DISC). **a** Delphinidin induced caspase-3- and caspase-7-mediated HDAC3 processing. **b** TRAIL is often proteasomally degraded and HDAC inhibitor notably reduced TRAIL degradation

enhanced DR5 expression in HDAC2 inhibited pancreatic cancer cells (Schüler et al. 2010).

HDAC inhibitor had previously been reported to stabilize TRAIL as evidenced by disappearance of TRAIL protein in cycloheximide-treated cells, however detectable levels were noted in cycloheximide-SAHA-treated cells. SAHA protected TRAIL from proteasomal degradation in thyroid-transformed cells by altering the ubiquitin dependent pathway. Using immunoprecipitation technique, SAHA treated cell lysates were immunoprecipitated with an anti ubiquitin antibody. Notably higher levels of ubiquitinated TRAIL protein were detected (Borbone et al. 2010) (Fig. 5). Flavone isolated from *Feijoa sellowiana* effectively induced TRAIL upregulation in NB4 cells (Bontempo et al. 2007).

Data clearly suggested that HDAC inhibitors effectively enhanced TRAIL-induced apoptosis in cancer cells (Fandy et al. 2005; Shankar et al. 2005; Singh et al. 2005).

Different other proteins of epigenetic machinery are also being tested to improve TRAIL-mediated apoptosis in cancer cells. Histone lysine demethylase 4A (KDM4A or JMJD2A), a histone demethylase belongs to Jumonji C domain-containing KDM4 subfamily and frequently over-expressed in different cancers. KDM4A was noted to occupy promoter region of TRAIL and inhibition of KDM4A triggered transcriptional upregulation of TRAIL. Moreover, KDM4A transcriptionally inhibited DR5 via downregulation of CHOP thus decreasing its accumulation at promoter region of DR5 (Wang et al. 2016). It will be interesting to see the synergistic effects of inhibitors of HDACs and Histone demethylases on different cancer cell lines.

It will also be exciting to test combinatorial treatments consisting of TRAIL-based therapeutics and natural HDAC inhibitors in preclinical studies.

Concluding Remarks

Epigenetic mechanisms, particularly those involving DNA methylation, are somatically heritable and contributory changes in gene expression. These changes in expression levels in the presence of gene mutations make tumor cells more capable of evolving much more rapidly than what they could have gained by relying on genetic alterations alone (Roberts and Gordenin 2014).

Keeping in view the encouraging advancements made in the epigenetic modifying drugs and a speedy approval given by FDA to Novartis' HDACi "panobinostat" for multiple myeloma patients priorly treated with two rounds of therapies, it will not be a fantasy if it is claimed that epigenetic drugs represent true "genomic medicines". This approval has re-invigorated interest in epigenetic modification based therapeutics and opened new horizons for researchers working on identification and evaluation of therapeutically effective HDAC inhibitors in a range of tumor types.

Overview of the timeline indicated that vorinostat was also approved for cutaneous T cell lymphoma in 2006. Different strategies are currently being tested to overcome resistance against wide-ranging molecular therapeutics and maximize therapeutic effects. In line with this approach, HDAC inhibitors are tested for efficacy by combining with other epigenetic-targeted agents to synergistically restore expression of tumor suppressor genes. Detailed analysis of the therapeutic and off-target effects obtained from Phase III trial of an HDAC inhibitor pracinostat combined with Celgene's DNMT inhibitor azacitidine in AML will further improve our understanding. Rapidly emerging experimentally verified data has provided near-complete resolution of the molecular roleplay of distinct HDACs and HDAC containing nano-complexes. Better and finer understanding of HDACs will be helpful in designing clinically effective novel therapeutic agents.

However, there is recent evidence of pan-HDACi SAHA mediated increase in the expression of tumor-supportive pro-inflammatory mediators in stromal fibroblasts. In a syngeneic, orthotopic pancreatic ductal adenocarcinoma mouse model, systemic treatment with the pan-HDACi SAHA suppressed tumor growth. Analysis of treated tumor explants on 37th day after implantation revealed presence of tumor cells which had homogeneous morphology. It is relevant to mention that PDAC cells are sensitive to HDAC inhibitors. MIA PaCa-2 cells were highly sensitive to SAHA at a concentration of 4 μM. However, certain hints have emerged suggesting that presence of fibroblasts reduced sensitivity of tumor cells to HDAC inhibitors. Using a 3D TC:CAF co-culture model it was shown that GFP-expressing PANC-1 TCs formed 3D tumor-like spheres in the presence of cancer-associated fibroblasts (CAFs). PANC-1 and MIA PaCa-2 cells had a higher proliferation rate when cultured in conditioned media from CAFs pre-treated with HDAC inhibitors. Similarly, PANC-1 TCs grew faster in the TC:CAF Matrigel model with SAHA treated CAFs. Tumor growth was significantly higher in mice implanted with MIA PaCa-2 cells in bilateral subcutaneous flanks and supplemented thrice weekly with conditioned media from cultured SAHA treated CAFs. Therefore these areas of research also need extensive and detailed analysis (Nguyen et al. 2016).

In this review we summarized most recent breakthroughs related to natural agents-mediated targeting of HDACs in different cancers. Many of these agents have shown encouraging results in clinical and preclinical studies. It will be even more effective if these natural agents are conjugated to different nanoparticles for an

effective delivery to the target site and internalization into the cell. Epigenetic modifications are frequently noted in different cancers and combination treatments consisting of clinically approved drugs with natural agents will maximize clinical outcomes. TRAIL-based therapeutics are currently being tested in clinical trials and combining these agents with HDAC inhibitors will improve clinical efficacy.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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