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Review article

HDACis (class I), cancer stem cell, and phytochemicals: Cancer therapy and prevention implications

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ABSTRACT

Epigenetics is independent of the sequence events that physically affect the condensing of chromatin and genes expression. The unique epigenetic memories of various cells trigger exclusive gene expression profiling. According to different studies, the aberrant epigenetic signatures and impaired gene expression profiles are master occurrences in cancer cells in which oncogene and tumor suppressor genes are affected. Owing to the facts that epigenetic modifications are performed earlier than expression and are reversible, the epigenetic reprogramming of cancer cells could be applied potentially for their prevention, control, and therapy. The disruption of the acetylation signature, as a master epigenetic change in cancers, is related to the expression and the activity of HDACs. In this context, class I HDACs play a significant role in the regulation of cell proliferation and cancer. More recently, cancer stem cell (CSC) has been introduced as a minority population of tumor that is responsible for invasiveness, drug resistance, and relapse of cancers. It is now believed that controlling CSC via epigenetic reprogramming such as targeting HDACs could be helpful in regulating the acetylation pattern of chromatin. Recently, a number of reports have introduced some phytochemicals as HDAC inhibitors. The use of phytochemicals with the HDAC inhibition property could be potentially efficient in overcoming the mentioned problems of CSCs. This review presents a perspective concerning HDAC-targeted phytochemicals to control CSC in tumors. Hopefully, this new route would have more advantages in therapeutic applications and prevention against cancer.

1. Introduction

The epigenetic aberration of genes through histone modifications in cell cycle, differentiation, cell growth and survival is a crucial occurrence in cancer development [1]. Acetylation is one of the significant epigenetic markers related to histones in enhancers and promoters of genes that trigger chromatin remodeling and positive regulation of gene expression [2].

The acetylation level of genome is regulated through engagement expression and activity of HDAC as well as histone acetyltransferase (HAT) [3]. Various studies have demonstrated that epigenetic gene silencing and high density of the chromatin state refer to the removal of acetylation of lysine residing in the tails of histone 3 and histone 4 by HDACs that occur in most cancers [4]. Therefore, HDACs play a significant role in the development of cancers pertaining to the stomach, prostate, colorectal, esophagus, lung, and breast [5]. In addition to their role in histone modification, they can also target non-histone proteins in cancer cells [6]. There are approximately 1700 non-histone proteins that can be deacetylated by HDACs. These include cytoplasmic and nuclear proteins with various functions [7].

Based on various studies, the overexpression of class I HDAC isotypes, including HDAC1, 2, 3 and 8, occurs in different cancer types [8]. On the other hand, recent studies have reported hopeful treatment outcomes in controlling cancer via HDACi [9]. Therefore, HDACi could be potentially applied for the prevention and therapy of various cancers [10]. Additionally, recent advances in herbal medicine have defined some advantages such as safer and biodegradable properties over the current drugs used in chemotherapy [11]. Phytochemicals include carotenoids and polyphenols (divided into three groups of phenolic acids, flavonoids, and stilbenes/lignans) [12]. More recently, some polyphenols were introduced with HDACi capacity, and there are ongoing clinical trials with some that are yet to be approved by the FDA (Fig. 1) [13]. Owing to these facts, herbal HDACi could be applicable for cancer therapeutic aims [14].

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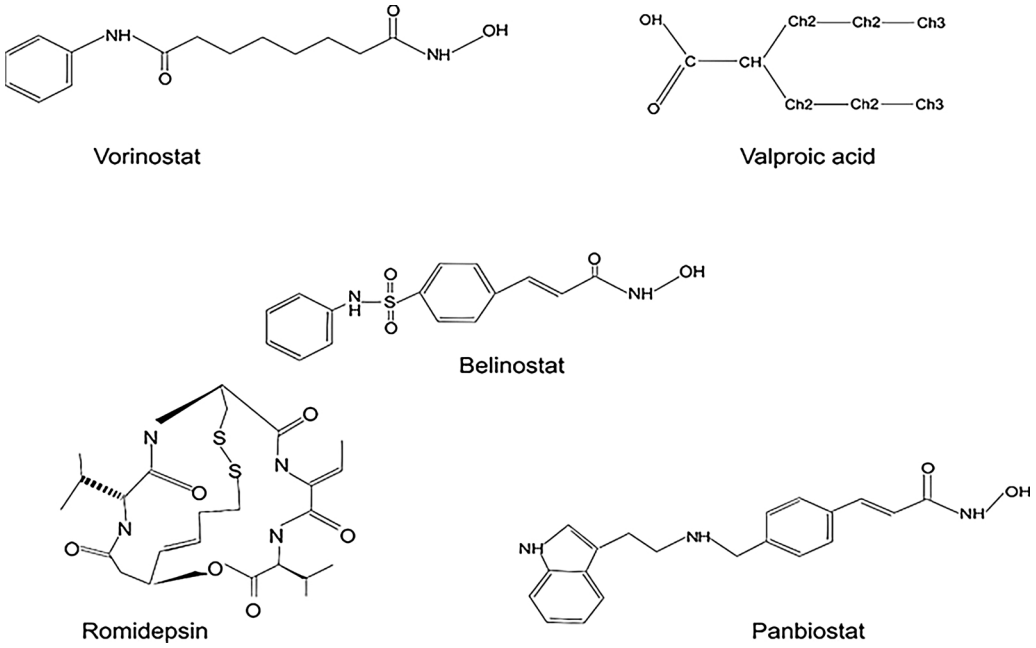

Fig. 1. Molecular structure of some FDA approved histone deacetylase inhibitors.

The development of cancer is known to be a result of accumulated abnormalities in multiple cellular and molecular events [15]. Recently, a new layer of complexity to cancer biology namely cancer stem cell (CSC) has been added that potentially leads to achieving proliferation, self-renewal, and quiescence properties [16]. In cancer therapy, considering the fact that CSCs are responsible for the development, invasiveness, resistance to chemotherapy and relapse of various tumors, the targeting of CSC for therapy can highlight the importance of these investigations in treating cancer [17]. On the other hand, recent studies have shown that HDACs play an important role in CSC properties [10]. Therefore, HDACi could add to the efficiency and the efficacy of CSC therapy.

The combination of recent advances such as CSC-targeted cancer therapy with phytochemical-based HDACi is a new approach to upgrading cancer therapy [18]. In the current review, we have discussed the role of HDACs, especially class I in cancer, the introduction of conventional HDACi, the advantages of phytochemical-based HDACi, and their relationships with the new model of cancer therapy targeting CSCs.

2. HDACs

The acetylation of the e-amino group of lysine residue in histones was first discovered in 1968, but the enzymes involved in this process—namely histone acetyltransferases (HATs) and deacetylases (HDACs)—were not identified until the mid-1990s [19].

Since their identification, the association of histone acetylation to gene regulation has been declared [19]. In addition to the effect of HDACs on histones, they also target and regulate non-histone proteins, including hormone receptors, signal transducers, transcription factors, chaperones, DNA repair enzymes, and proteins of the cytoskeleton in both normal and cancer cells [3]. Some examples of these non-histone proteins include DNA-binding transcriptional factors (p53, c-Myc, AML1, BCL-6, E2F, GATA, YY1, NF-kB, MEF2, CREB, HIF-1a, BETA2, POP-1, IRF, SRY, EKLF), steroid receptors (estrogen receptor, androgen receptor), DNA repair enzymes (Ku70, WRN, TDG, FEN1, NEIL2), and chaperone protein (HSP90).These substrates are involved in the regulation of gene expression, cell proliferation, and cell death [6].

HDACs are covered by 18 genes, and categorized into four classes (I–IV) according to their sequence homology to HDAC of yeast, their subcellular localization, and their enzymatic activities[4]. Classes I, II, and IV are classical HDACs, while the members of class III are called sirtuins [8,20]. The class I HDACs (1, 2, 3 and 8) are yeast RPD3 homologues, and will be discussed in detail in a subsequent section [8]. Class II HDACs (4, 5, 6, 7, 9, and 10) travel between the cytoplasm and the nucleus, and they are further subdivided on the basis of their structures into subgroups (class IIa, class IIb). The class IIb HDACs (6 and 10) are found in the cytoplasm and have two catalytic sites [19]. The class III HDACs (SIRT1-7) are homologues of the yeast Sirtuin 2, and all are NAD^+ -dependent. HDAC11, the only member of the class IV HDACs, is Zn^{2+}-dependent, and it has sequence similarity with both class I and II enzymes [21].

2.1. Class I HDACs

Class I HDACs (HDAC1, 2, 3, and 8) are conservative enzymes and localized in the nucleus, where they are present in multi-protein complexes with transcription factors and co-repressors. HDAC3 is an exception, and it is localized in the nucleus and cytoplasm [3]. These enzymes are ubiquitously expressed and homologous to the yeast transcriptional regulator Rpd3 [8]. Class I HDACs are involved in the regulation of cell proliferation during cancerous events [22], and they are exclusively expressed practically in many types of cell nucleus [23].

HDAC8 is a protein that carries out the deacetylation action on non-histone proteins related to different cancers such as p53, estrogen-related receptor alpha (ERRα), inversion (inv) fusion protein, structural maintenance of chromosomes 3 (SMC3), retinoic acid induced protein 1(RAI1), zinc finger RAN-binding domain containing 2 (ZRANB2), nuclear receptor co-activator 3 (NCOA3), thyroid hormone receptor-associated protein 3 (THRAP3), AT-rich interactive domain-containing protein 1A (ARID1A), and cortactin [24]. Class I HDACs (and also Class II HDACs), particularly HDAC1 and HDAC2, cannot directly bind to DNA, and are commonly found to be active only when incorporated into activating multi-protein co-repressor complexes known as Sin3, CoREST (co-repressor for element-1-silencing transcription factor), NuRD (nucleosome remodeling and deacetylation), and NCoR/SMRT (nuclear receptor co-repressor/silencing mediator of retinoic and thyroid receptors), depending on the type of HDAC [25–30]. These multi-protein complexes are then targeted to chromatin by transcription factors such as p53, GATA4, E2F, pRb, and/ or STAT3 [31–35], and/or chromatin-altering enzymes [25,27,29].

As mentioned earlier, class I HDACs are overexpressed in various