Modulation of Tumor Suppressor Genes by Histone Deacetylase Inhibitors in Cancer Therapy

Abstract

Histone deacetylase (HDAC) inhibitors have emerged as promising therapeutics for various cancers due to their ability to modulate gene expression profiles and restore normal cellular functions. Among the key targets of HDAC inhibitors are tumor suppressor genes, which play crucial roles in regulating cell cycle progression, apoptosis, and DNA repair. This review provides a comprehensive overview of the impact of HDAC inhibitors on tumor suppressor genes in cancer therapy. We discussed the mechanisms by which HDAC inhibitors regulate the expression of tumor suppressor genes, including p53, p21, BRCA1, PTEN, and others, through histone hyperacetylation and chromatin remodeling. Furthermore, we described the therapeutic implications of HDAC inhibitor-induced modulation of tumor suppressor genes in various cancer types, highlighting the potential for combination therapies and personalized treatment approaches. Understanding the interplay between HDAC inhibitors and tumor suppressor genes is critical for optimizing the efficacy of HDAC inhibitor-based therapies and advancing precision medicine in oncology.

Keywords: HDAC inhibitors, tumor suppressor genes, cancer therapy, epigenetics, chromatin remodeling

1. Introduction

Histone deacetylase (HDAC) inhibitors have garnered significant attention in cancer therapy owing to their capacity to modulate gene expression through histone acetylation targeting [1,2]. HDACs play a pivotal role in maintaining chromatin structure and gene transcription by catalyzing the removal of acetyl groups from histone proteins [3,4]. This process contributes to chromatin condensation and transcriptional repression, thereby influencing various cellular processes, including cell cycle progression and apoptosis [5]. HDAC inhibitors exert their effects by inhibiting HDAC activity, resulting in hyperacetylation of histones and subsequent relaxation of chromatin structure [5]. This epigenetic modulation impacts the expression of genes involved in cell proliferation, differentiation, and apoptosis, thereby influencing cancer cell behavior [6]. Notably, HDAC inhibitors can target different classes of HDAC enzymes, including Class I, II, and IV, exhibiting varying degrees of selectivity and potency [6]. Such diversity in target specificity enables HDAC inhibitors to modulate gene expression in a context-dependent manner, making them promising candidates for cancer therapy. Moreover, HDAC inhibitors extend their influence beyond histones to target non-histone proteins, such as transcription factors, chaperone proteins, and signaling molecules [7]. By modulating the acetylation status of these proteins, HDAC inhibitors disrupt oncogenic signaling pathways and promote tumor cell death [7]. This pleiotropic effect on gene expression and cellular functions broadens the therapeutic potential of HDAC inhibitors, positioning them as valuable tools in the treatment of various diseases, including cancer.

Tumor suppressor genes play a pivotal role in regulating cell growth, proliferation, and survival, acting as guardians of genomic integrity [8]. Dysregulation or inactivation of tumor suppressor

genes is a hallmark of cancer, contributing to tumorigenesis and disease progression [8]. Among the well-known tumor suppressor genes, p53 emerges as a central player in orchestrating cellular responses to DNA damage and stress [9–11]. By inducing cell cycle arrest, DNA repair, or apoptosis, p53 helps maintain genomic stability and prevent the accumulation of mutations [9–11]. Additionally, other tumor suppressor genes, including BRCA1, PTEN, and p21, play critical roles in cancer biology by regulating DNA repair, cell cycle progression, and apoptosis [8]. Dysregulation of these genes disrupts cellular homeostasis and contributes to tumor development and progression [8]. Therefore, restoring the normal function of tumor suppressor genes represents a promising therapeutic strategy in cancer therapy.

HDAC inhibitors have demonstrated efficacy in modulating the expression and activity of tumor suppressor genes in both preclinical and clinical studies [12]. By inducing hyperacetylation of histones associated with tumor suppressor gene promoters, HDAC inhibitors activate the expression of these genes, leading to inhibition of tumor growth and promotion of apoptosis in cancer cells [12]. Furthermore, HDAC inhibitors synergize with other anticancer therapies, such as chemotherapy and radiation therapy, to enhance the therapeutic response [13]. This combination approach sensitizes cancer cells to cytotoxic agents, overcomes drug resistance, and improves overall treatment outcomes [13].

In this review, we delve into the mechanisms underlying HDAC inhibitor-induced histone hyperacetylation, explore their therapeutic implications and clinical applications, and discuss the challenges and future directions in utilizing HDAC inhibitors in cancer therapy. Through a

comprehensive examination of these aspects, we aim to elucidate the precise mechanisms underlying the therapeutic effects of HDAC inhibitors and optimize their use in clinical practice.

2. Mechanisms of HDAC Inhibitor-Induced Histone Hyperacetylation

HDAC inhibitors exert their effects through multiple mechanisms. Firstly, they inhibit the activity of histone deacetylases (HDACs), enzymes responsible for removing acetyl groups from histone proteins, thereby preventing the removal of these acetyl groups and leading to an accumulation of acetylated histones and histone hyperacetylation [5] (Figure 1). This alteration in chromatin structure induced by HDAC inhibitors renders the chromatin more accessible and permissive for transcriptional activation [1]. Acetylated histones have a looser association with DNA compared to deacetylated histones, facilitating easier access for transcription factors and regulatory proteins to gene promoters and enhancers [14]. Furthermore, histone hyperacetylation induced by HDAC inhibitors promotes the activation of gene transcription [15]. The open chromatin environment created by acetylated histones facilitates the binding of transcriptional activators and recruitment of RNA polymerase II, resulting in increased transcription of target genes [1]. Additionally, HDAC inhibitors have been shown to induce apoptosis and cell cycle arrest in cancer cells [5]. These effects are mediated, at least in part, by the upregulation of pro-apoptotic and cell cycle regulatory genes through histone hyperacetylation [16]. Overall, the mechanisms underlying HDAC inhibitor-induced histone hyperacetylation contribute to their therapeutic effects in various diseases, including cancer, by promoting changes in gene expression that lead to cell cycle arrest, apoptosis, and inhibition of tumor growth.

3. Effects of HDAC Inhibitors on Specific Tumor Suppressor Genes

Histone deacetylase (HDAC) inhibitors have been extensively studied for their ability to modulate gene expression and epigenetic regulation, including the regulation of tumor suppressor genes. Tumor suppressor genes play critical roles in inhibiting cell proliferation, promoting apoptosis, and maintaining genomic stability. Dysregulation or silencing of tumor suppressor genes is a hallmark of cancer, contributing to tumorigenesis and disease progression. HDAC inhibitors have been shown to re-express or upregulate specific tumor suppressor genes through epigenetic mechanisms, leading to anticancer effects in various malignancies. Overall, HDAC inhibitors exert their anticancer effects, in part, by reactivating or upregulating specific tumor suppressor genes through epigenetic modifications. Understanding the effects of HDAC inhibitors on tumor suppressor genes provides insights into their mechanisms of action and potential therapeutic applications in cancer treatment. Here, we will look into ten well-known tumor suppressor genes and their effects when influenced by HDAC inhibitors (Table 1). Please note that the list of tumor suppressor genes in Table 1 is not an exhaustive list, and there are many more tumor suppressor genes that may be impacted by HDAC inhibitors.

3.1. p53

The tumor suppressor protein p53 stands as a sentinel guardian of genomic integrity, orchestrating cellular responses to stress signals to maintain cellular homeostasis. Dysregulation or mutation of the p53 gene is a hallmark of cancer, contributing to tumor initiation, progression, and therapeutic resistance. Histone deacetylase (HDAC) inhibitors, a class of compounds that modulate gene expression by altering histone acetylation levels, have emerged as promising therapeutic agents in cancer treatment. Through their ability to inhibit HDAC enzymes, HDAC inhibitors induce hyperacetylation of histones, resulting in chromatin relaxation and increased

accessibility of DNA to transcription factors and other regulatory proteins. Among their diverse effects, HDAC inhibitors have been shown to influence the expression and activity of p53, offering a potential avenue for cancer therapy.

Mechanisms of Action: HDAC inhibitors exert their effects on p53 expression and activity through several mechanisms. One key mechanism involves the acetylation of histones associated with the p53 gene promoter region. Histone acetylation promotes an open chromatin structure, facilitating the binding of transcription factors and RNA polymerase II to the p53 gene promoter, thereby enhancing p53 transcriptional activity [17]. Additionally, HDAC inhibitors can directly acetylate p53 protein itself, leading to its stabilization and activation. Acetylation of p53 prevents its degradation by ubiquitin-mediated proteolysis, resulting in increased levels of active p53 protein in the cell [18]. In addition, HDAC inhibitors may indirectly influence p53 activity by modulating the expression of upstream regulators or downstream targets of p53. For instance, as shown in Figure 2, HDAC inhibitors can upregulate the expression of p53-target genes involved in cell cycle arrest (e.g., p21) and apoptosis (e.g., Bax), leading to cell cycle arrest and induction of apoptosis in cancer cells [19].

Therapeutic Implications: The restoration of p53 function by HDAC inhibitors holds significant therapeutic implications in cancer treatment. By reactivating or upregulating p53 expression and activity, HDAC inhibitors can induce cell cycle arrest, promote apoptosis, and sensitize cancer cells to chemotherapy and radiation therapy. Preclinical studies and clinical trials have demonstrated the efficacy of HDAC inhibitors, such as vorinostat, romidepsin, and panobinostat, in restoring p53 function and inhibiting tumor growth in various cancer types, including

colorectal cancer, breast cancer, and leukemia [6]. Moreover, the combination of HDAC inhibitors with other anticancer agents that activate p53-dependent pathways has shown synergistic effects in suppressing tumor growth and overcoming drug resistance. For example, the combination of HDAC inhibitors with DNA-damaging agents, such as cisplatin or doxorubicin, enhances DNA damage-induced apoptosis in cancer cells by promoting p53-mediated cell death [5].

In recap, HDAC inhibitors exert their anticancer effects, in part, by reactivating or upregulating p53 expression and activity through epigenetic modifications. The restoration of p53 function by HDAC inhibitors represents a promising therapeutic strategy for cancer treatment, offering opportunities to enhance the efficacy of conventional therapies and overcome drug resistance in various malignancies. Further elucidation of the molecular mechanisms underlying the interplay between HDAC inhibitors and p53 may pave the way for the development of more effective and personalized cancer therapies.

3.2. p21

The p21 protein, encoded by the CDKN1A gene, serves as a crucial regulator of cell cycle progression and apoptosis. It functions as a cyclin-dependent kinase inhibitor, inhibiting the activity of cyclin-dependent kinases (CDKs) and blocking the transition from G1 to S phase of the cell cycle. Additionally, p21 plays a role in mediating cellular responses to various stress signals, including DNA damage, oxidative stress, and oncogenic signals. Dysregulation of p21 expression is frequently observed in cancer, contributing to aberrant cell proliferation and tumor progression. Histone deacetylase (HDAC) inhibitors have become a popular possible therapeutic

agent for the treatment of cancer. This is due to HDAC inhibitor's ability to modulate gene expression and epigenetic regulation. HDAC inhibitors block the activity of the HDAC enzymes, creating hyperacetylation of histones and altering chromatin structure. The hyperacetylation of HDAC inhibitors will allow the chromatin structure to open and relax. This allows DNA and transcription factors to be modified easily. Through these histone acetylation, HDAC inhibitors can change p21 gene expression and activity. This change in gene expression may allow an increase in the binding of transcription factors as well as RNA polymerase II. All these factors make HDAC a viable avenue for future cancer therapies and treatments.

Mechanisms of Action: HDAC inhibitors modulate the expression of p21 through several mechanisms. One key mechanism involves the acetylation of histones associated with the CDKN1A gene promoter region. Histone acetylation promotes an open chromatin structure, facilitating the binding of transcription factors and RNA polymerase II to the CDKN1A gene promoter, thereby enhancing p21 transcriptional activity [5]. Additionally, HDAC inhibitors can directly acetylate p21 protein itself, leading to its stabilization and activation. Acetylation of p21 prevents its degradation by ubiquitin-mediated proteolysis, resulting in increased levels of active p21 protein in the cell [20]. Furthermore, HDAC inhibitors may indirectly influence p21 expression by modulating the activity of transcriptional regulators or signaling pathways involved in p21 regulation. For example, HDAC inhibitors can enhance the expression of p53, a transcription factor that directly regulates p21 transcription, thereby indirectly promoting p21 expression [17]. Additionally, HDAC inhibitors can activate signaling pathways, such as the MAPK/ERK pathway, which converge on the CDKN1A gene promoter and stimulate p21 expression [21].

Therapeutic Implications: The modulation of p21 expression and activity by HDAC inhibitors holds significant promise for success in cancer treatment. By upregulating p21 expression, HDAC inhibitors can induce cell cycle arrest, inhibit cell proliferation, and promote apoptosis in cancer cells. Preclinical studies and clinical trials have demonstrated the efficacy of HDAC inhibitors, such as vorinostat, romidepsin, and panobinostat, in inducing p21 expression and inhibiting tumor growth in various cancer types, including colorectal cancer, breast cancer, and leukemia [5]. Moreover, the combination of HDAC inhibitors with other anticancer agents that synergize with p21-mediated pathways has shown promise in suppressing tumor growth and overcoming drug resistance. For example, the combination of HDAC inhibitors with DNA-damaging agents, such as cisplatin or doxorubicin, enhances DNA damage-induced apoptosis in cancer cells by promoting p21-mediated cell cycle arrest and apoptosis [19].

In conclusion, HDAC inhibitors exert their anticancer effects, in part, by modulating the expression and activity of p21 through epigenetic modifications. The upregulation of p21 expression by HDAC inhibitors represents a promising therapeutic strategy for cancer treatment, offering opportunities to inhibit tumor growth and overcome drug resistance in various malignancies. Further elucidation of the molecular mechanisms underlying the interplay between HDAC inhibitors and p21 may pave the way for the development of more effective and personalized cancer therapies.

3.3. PTEN

The phosphatase and tensin homolog (PTEN) gene encodes a crucial tumor suppressor protein that acts as a lipid phosphatase, regulating the PI3K/AKT signaling pathway. PTEN plays a pivotal role in controlling cell survival, proliferation, and metabolism by antagonizing the PI3K/AKT pathway, thereby inhibiting downstream signaling cascades involved in cell growth and survival. Dysregulation or loss of PTEN expression is commonly observed in human cancers, leading to aberrant activation of the PI3K/AKT pathway and tumor progression.

Histone deacetylase (HDAC) inhibitors show promise in their therapeutic properties in treating cancer. HDAC inhibitors can hyperacetylate histones and alter chromatin structure. These effects occur once the inhibitor is bound to the HDAC enzyme, blocking enzyme activity. Through this hyperacetylation, HDAC inhibitors impact expression and activity of PTEN. Similarly to p21, the acetylation of histones will open the chromatin structure, allowing RNA polymerase II and transcription factors to bind to the PTEN gene promoter. This enhances gene activity of PTEN, which is a tumor suppressor. Using HDAC inhibitors to activate PTEN could be a useful method for cancer treatment.

Mechanisms of Action: HDAC inhibitors modulate the expression of PTEN through several mechanisms. One key mechanism involves the acetylation of histones associated with the PTEN gene promoter region. Histone acetylation promotes an open chromatin structure, which allows the binding of transcription factors and RNA polymerase II to the PTEN gene promoter, thereby enhancing PTEN transcriptional activity [22–24]. Additionally, HDAC inhibitors can directly acetylate PTEN protein itself, leading to its stabilization and activation. Acetylation of PTEN

enhances its phosphatase activity, resulting in increased inhibition of the PI3K/AKT pathway and suppression of downstream signaling cascades [25].

Besides, HDAC inhibitors may indirectly influence PTEN expression by modulating the activity of transcriptional regulators or signaling pathways involved in PTEN regulation. For example, HDAC inhibitors can upregulate the expression of transcription factors, such as p53, which directly regulate PTEN transcription [22,23]. Additionally, HDAC inhibitors can inhibit signaling pathways, such as the MAPK/ERK pathway, which negatively regulate PTEN expression through transcriptional or post-translational mechanisms [26].

Therapeutic Implications: The modulation of PTEN expression and activity by HDAC inhibitors holds significant therapeutic implications in cancer treatment. By upregulating PTEN expression, HDAC inhibitors can inhibit the PI3K/AKT pathway, induce cell cycle arrest, promote apoptosis, and inhibit tumor growth in cancer cells. Preclinical studies and clinical trials have demonstrated the efficacy of HDAC inhibitors, such as vorinostat, romidepsin, and panobinostat, in inducing PTEN expression and inhibiting tumor growth in various cancer types, including breast cancer, prostate cancer, and glioblastoma [22,27]. Moreover, the combination of HDAC inhibitors with other anticancer agents that synergize with PTEN-mediated pathways has shown promise in suppressing tumor growth and overcoming drug resistance. For example, the combination of HDAC inhibitors with PI3K inhibitors or AKT inhibitors enhances the inhibition of the PI3K/AKT pathway, leading to increased apoptosis and tumor regression in cancer cells [28].

In summary, HDAC inhibitors exert their anticancer effects, in part, by modulating the expression and activity of PTEN through epigenetic modifications. The upregulation of PTEN expression by HDAC inhibitors represents a promising therapeutic strategy for cancer treatment, offering opportunities to inhibit tumor growth and overcome drug resistance in various malignancies. Further elucidation of the molecular mechanisms underlying the interplay between HDAC inhibitors and PTEN may pave the way for the development of more effective and personalized cancer therapies.

3.4. BRCA1

BRCA1 (breast cancer 1, early onset) is a tumor suppressor gene that plays a critical role in maintaining genomic stability and DNA repair. Mutations in the BRCA1 gene are associated with an increased risk of breast, ovarian, and other cancers. The BRCA1 protein is involved in various cellular processes, including DNA damage repair, cell cycle regulation, and transcriptional regulation. Dysregulation of BRCA1 expression or function contributes to tumor initiation and progression in individuals with BRCA1 mutations or alterations.

HDAC inhibitors have shown the ability to not only inhibit the HDAC enzyme but activate many cancer fighting genes as well. One of these genes, BRCA1, can be expressed by the opening of the chromatin structure. This structure opening allows the binding of transcription factors as well as RNA polymerase II to the BRCA1 gene. This binding will enhance transcription of BRCA1 and allow BRCA1 to repair DNA.

Mechanisms of Action: HDAC inhibitors modulate the expression of BRCA1 through several mechanisms. One key mechanism involves the acetylation of histones associated with the BRCA1 gene promoter region. Histone acetylation promotes an open chromatin structure, facilitating the binding of transcription factors and RNA polymerase II to the BRCA1 gene promoter, thereby enhancing BRCA1 transcriptional activity [29]. Additionally, HDAC inhibitors can directly acetylate BRCA1 protein itself, leading to its stabilization and activation. Acetylation of BRCA1 enhances its DNA repair activity and promotes homologous recombination-mediated DNA repair, thereby reducing genomic instability and inhibiting tumor growth [30].

Furthermore, HDAC inhibitors may indirectly influence BRCA1 expression by modulating the activity of transcriptional regulators or signaling pathways involved in BRCA1 regulation. For example, HDAC inhibitors can upregulate the expression of transcription factors, such as p53, which directly regulate BRCA1 transcription [31,32]. Additionally, HDAC inhibitors can inhibit signaling pathways, such as the PI3K/AKT pathway, which negatively regulate BRCA1 expression through transcriptional or post-translational mechanisms [33].

Therapeutic Implications: The modulation of BRCA1 expression and activity by HDAC inhibitors could be very helpful in cancer treatments. By upregulating BRCA1 expression, HDAC inhibitors can enhance DNA repair capacity, reduce genomic instability, and inhibit tumor growth in cancer cells (Figure 3). Preclinical studies and clinical trials have demonstrated the efficacy of HDAC inhibitors, such as vorinostat, romidepsin, and panobinostat, in inducing

BRCA1 expression and inhibiting tumor growth in various cancer types, including breast cancer, ovarian cancer, and pancreatic cancer [34].

Moreover, the combination of HDAC inhibitors with other DNA-damaging agents or targeted therapies that synergize with BRCA1-mediated pathways has shown promise in suppressing tumor growth and overcoming drug resistance. For example, the combination of HDAC inhibitors with PARP inhibitors, which target DNA repair pathways in BRCA-deficient cells, has demonstrated synergistic effects in inhibiting tumor growth and improving clinical outcomes in BRCA-mutant cancers [35].

To conclude, HDAC inhibitors exert their anticancer effects, in part, by modulating the expression and activity of BRCA1 through epigenetic modifications. The upregulation of BRCA1 expression by HDAC inhibitors represents a promising therapeutic strategy for cancer treatment, offering opportunities to enhance DNA repair capacity, reduce genomic instability, and inhibit tumor growth in various malignancies. Further elucidation of the molecular mechanisms underlying the interplay between HDAC inhibitors and BRCA1 may pave the way for the development of more effective and personalized cancer therapies.

3.5. RB1

The retinoblastoma tumor suppressor gene (RB1) encodes the pRB protein, which plays a critical role in regulating the cell cycle and inhibiting tumorigenesis. The pRB protein functions as a negative regulator of the cell cycle by binding to and inhibiting the activity of the transcription factor E2F, thereby suppressing the expression of genes required for cell cycle progression.

Dysregulation of RB1 expression or function is commonly observed in human cancers, leading to uncontrolled cell proliferation and tumor development.

Much like other tumor suppressor gene, RB1 can be activated using HDAC inhibition. This inhibition causes the hyperacetylation of histones, which then open the chromatin structure. This opening will allow transcription factors to bind to the gene promoter, therefore allowing RB1 production to continue.

Mechanisms of Action: HDAC inhibitors modulate the expression of RB1 through several mechanisms. One key mechanism involves the acetylation of histones associated with the RB1 gene promoter region. Histone acetylation promotes an open chromatin structure, facilitating the binding of transcription factors and RNA polymerase II to the RB1 gene promoter, thereby enhancing RB1 transcriptional activity [36]. Additionally, HDAC inhibitors can directly acetylate the pRB protein itself, leading to its stabilization and activation. Acetylation of pRB enhances its ability to bind to E2F transcription factors, resulting in increased inhibition of E2F-mediated transcription and cell cycle arrest [37,38] (Figure 4).

In addition, HDAC inhibitors may indirectly influence RB1 expression by modulating the activity of transcriptional regulators or signaling pathways involved in RB1 regulation. For example, HDAC inhibitors can upregulate the expression of transcription factors, such as p53, which directly regulate RB1 transcription [39]. Additionally, HDAC inhibitors can inhibit signaling pathways, such as the PI3K/AKT pathway, which negatively regulate RB1 expression through transcriptional or post-translational mechanisms [40].

Therapeutic Implications: The modulation of RB1 expression and activity by HDAC inhibitors holds significant therapeutic implications in cancer treatment. By upregulating RB1 expression, HDAC inhibitors can induce cell cycle arrest, inhibit cell proliferation, and promote apoptosis in cancer cells. Preclinical studies and clinical trials have demonstrated the efficacy of HDAC inhibitors, such as vorinostat, romidepsin, and panobinostat, in inducing RB1 expression and inhibiting tumor growth in various cancer types, including retinoblastoma, osteosarcoma, and lung cancer [41].

Moreover, the combination of HDAC inhibitors with other anticancer agents that synergize with RB1-mediated pathways has shown promise in suppressing tumor growth and overcoming drug resistance. For example, the combination of HDAC inhibitors with CDK4/6 inhibitors, which target the RB1 pathway, has demonstrated synergistic effects in inducing cell cycle arrest and inhibiting tumor growth in RB1-proficient cancers [42].

In a wrap-up, HDAC inhibitors exert their anticancer effects, in part, by modulating the expression and activity of RB1 through epigenetic modifications. The upregulation of RB1 expression by HDAC inhibitors represents a promising therapeutic strategy for cancer treatment, offering opportunities to induce cell cycle arrest, inhibit cell proliferation, and promote apoptosis in various malignancies. Further elucidation of the molecular mechanisms underlying the interplay between HDAC inhibitors and RB1 may pave the way for the development of more effective and personalized cancer therapies.

3.6. Other tumor suppressor genes

Tumor suppressor genes play pivotal roles in maintaining genomic stability and regulating cell growth, proliferation, and survival. Among these genes, CDKN2A, APC, NF1, VHL, and ATM have been extensively studied for their involvement in various cancers. Understanding the mechanisms underlying their regulation and the implications for cancer therapy is crucial for developing effective treatment strategies. Here, we explore the impact of histone deacetylase (HDAC) inhibitors on the expression and activity of these tumor suppressor genes and their therapeutic implications in cancer treatment.

CDKN2A: The CDKN2A gene, encoding the p16INK4a protein, acts as a critical tumor suppressor by inhibiting cyclin-dependent kinases (CDKs) and regulating cell cycle progression. Dysregulation or loss of CDKN2A expression is commonly observed in human cancers, leading to uncontrolled cell proliferation and tumor development. HDAC inhibitors modulate CDKN2A expression and activity through various mechanisms, including histone acetylation-mediated transcriptional activation and direct acetylation of the p16INK4a protein itself. Therapeutically, HDAC inhibitors induce cell cycle arrest, inhibit cell proliferation, and promote cellular senescence in cancer cells, offering promising avenues for cancer treatment.

APC: The adenomatous polyposis coli (APC) gene serves as a tumor suppressor by negatively regulating the Wnt signaling pathway through the degradation of β-catenin, thereby inhibiting aberrant cell proliferation and tumorigenesis. Mutations in APC are associated with familial adenomatous polyposis (FAP) and sporadic colorectal cancer. HDAC inhibitors modulate APC

expression and activity by promoting histone acetylation-mediated transcriptional activation and direct acetylation of the APC protein. Therapeutically, HDAC inhibitors suppress tumor growth in colorectal cancer and other malignancies by inhibiting Wnt signaling and promoting β-catenin degradation.

NF1: The neurofibromatosis type 1 (NF1) gene encodes neurofibromin, a negative regulator of the Ras signaling pathway. Mutations in NF1 lead to dysregulated cell growth and proliferation, predisposing individuals to neurofibromatosis type 1 and various cancers. HDAC inhibitors impact NF1 expression and activity through histone acetylation-mediated transcriptional activation and direct acetylation of neurofibromin. Therapeutically, HDAC inhibitors inhibit Ras signaling, suppress cell proliferation, and induce apoptosis in NF1-mutant cancers, offering potential avenues for targeted therapy.

VHL: The Von Hippel-Lindau (VHL) gene functions as a tumor suppressor by regulating cellular responses to oxygen availability through the degradation of hypoxia-inducible factors (HIFs). Mutations in VHL are associated with Von Hippel-Lindau disease and various cancers. HDAC inhibitors modulate VHL expression and activity by promoting histone acetylation-mediated transcriptional activation and direct acetylation of the VHL protein. Therapeutically, HDAC inhibitors inhibit angiogenesis, suppress tumor growth, and sensitize cancer cells to anti-angiogenic therapy in VHL-associated tumors.

ATM: The ataxia telangiectasia mutated (ATM) gene plays a crucial role in maintaining genomic stability and orchestrating the cellular response to DNA double-strand breaks. Mutations in ATM

are associated with ataxia telangiectasia and increased cancer risk. HDAC inhibitors impact ATM expression and activity through histone acetylation-mediated transcriptional activation and direct acetylation of the ATM protein. Therapeutically, HDAC inhibitors enhance the DNA damage response, promote DNA repair, and sensitize cancer cells to DNA-damaging agents in ATM-deficient cancers.

In summary, HDAC inhibitors exert their anticancer effects by modulating the expression and activity of CDKN2A, APC, NF1, VHL, and ATM through epigenetic modifications. The upregulation of these tumor suppressor genes represents promising therapeutic strategies for cancer treatment, offering opportunities to inhibit cell proliferation, suppress tumorigenesis, and enhance the cellular response to DNA damage. Further elucidation of the molecular mechanisms underlying the interplay between HDAC inhibitors and these tumor suppressor genes may lead to the development of more effective and personalized cancer therapies.

4. Clinical Applications

4.1. Preclinical and clinical studies evaluating HDAC inhibitors in cancer therapy

Histone deacetylase (HDAC) inhibitors have emerged as promising therapeutic agents for cancer treatment due to their ability to modulate gene expression and epigenetic regulation. Preclinical studies have demonstrated the efficacy of HDAC inhibitors in various cancer types, including hematological malignancies and solid tumors. For example, studies have shown that vorinostat, a potent HDAC inhibitor, induces apoptosis and cell cycle arrest in leukemia cells through the upregulation of pro-apoptotic genes and downregulation of anti-apoptotic genes [5]. Similarly,

romidepsin has shown activity against cutaneous T-cell lymphoma by inhibiting cell proliferation and inducing apoptosis through the modulation of various signaling pathways [43].

In clinical trials, HDAC inhibitors have shown promising results either as monotherapy or in combination with other anticancer agents. Drugs such as vorinostat, romidepsin, and belinostat have been approved by regulatory agencies for the treatment of cutaneous T-cell lymphoma, highlighting the clinical significance of HDAC inhibitors in cancer therapy [6]. Furthermore, combination therapies involving HDAC inhibitors and standard chemotherapeutic agents have demonstrated improved clinical outcomes in patients with various solid tumors, including breast, lung, and colorectal cancers [44].

However, challenges remain, including drug resistance and adverse effects, which necessitate further optimization and development of HDAC inhibitors for better clinical outcomes. Ongoing research efforts focus on identifying novel HDAC inhibitors with improved selectivity and efficacy, as well as exploring combination strategies to enhance therapeutic responses and overcome resistance mechanisms.

4.2. Synergistic effects of HDAC inhibitors with other therapies targeting tumor suppressor genes

Combination therapies involving HDAC inhibitors and agents targeting tumor suppressor genes have shown synergistic effects in preclinical studies and clinical trials. For instance, the combination of HDAC inhibitors with DNA-damaging agents such as cisplatin or topoisomerase inhibitors enhances DNA damage response and apoptosis in cancer cells [45]. Additionally,

HDAC inhibitors have been found to sensitize cancer cells to immunotherapy by upregulating the expression of tumor antigens and major histocompatibility complex (MHC) molecules, thereby promoting antitumor immune responses [46].

Moreover, combination strategies targeting both histone acetylation and DNA methylation have shown promise in overcoming drug resistance and improving therapeutic efficacy in cancer treatment [47]. For example, the combination of HDAC inhibitors with DNA methyltransferase inhibitors synergistically reactivates silenced tumor suppressor genes and inhibits tumor growth in preclinical models of cancer [48,49]. These findings underscore the potential of combination therapies targeting multiple epigenetic pathways for the treatment of cancer.

4.3. Biomarkers for predicting response to HDAC inhibitor-based therapies

Identifying biomarkers predictive of response to HDAC inhibitor-based therapies is crucial for patient stratification and personalized cancer treatment. Various biomarkers, including histone acetylation levels, gene expression profiles, and genetic mutations, have been investigated to predict the clinical outcomes of HDAC inhibitor therapy [50].

For example, high levels of histone acetylation in tumor tissues or peripheral blood mononuclear cells have been associated with favorable responses to HDAC inhibitors [5]. Furthermore, specific genetic alterations, such as mutations in histone-modifying enzymes or oncogenic pathways, may influence the sensitivity of cancer cells to HDAC inhibitors [7]. Overall, the identification of reliable biomarkers holds promise for optimizing patient selection and improving the efficacy of HDAC inhibitor-based therapies in cancer treatment.

5. Challenges and Future Directions

5.1. Limitations and adverse effects of HDAC inhibitors

Despite their promising therapeutic potential, HDAC inhibitors have several limitations and adverse effects that impact their clinical utility. Common adverse effects associated with HDAC inhibitors include fatigue, nausea, diarrhea, thrombocytopenia, and cardiac toxicity [6]. Additionally, HDAC inhibitors can cause off-target effects due to their non-selective inhibition of HDAC isoforms, leading to altered gene expression and cellular functions [7]. For instance, pan-HDAC inhibitors like vorinostat and panobinostat can lead to the inhibition of HDAC6, resulting in undesirable side effects such as cardiac toxicity and peripheral neuropathy [51].

Furthermore, drug resistance poses a significant challenge to the efficacy of HDAC inhibitors in cancer therapy. Cancer cells can develop resistance to HDAC inhibitors through various mechanisms, including alterations in drug metabolism, epigenetic modifications, and activation of pro-survival signaling pathways [5]. Overcoming these limitations and adverse effects is essential for maximizing the clinical benefits of HDAC inhibitor-based therapies. Strategies such as the development of isoform-specific HDAC inhibitors and combination therapies with targeted agents aim to mitigate these challenges and improve treatment outcomes [48,52].

5.2. Strategies to overcome resistance and enhance therapeutic efficacy

To address the challenge of drug resistance, researchers are exploring various strategies to enhance the therapeutic efficacy of HDAC inhibitors in cancer therapy. One approach is the development of selective HDAC inhibitors that target specific HDAC isoforms implicated in

cancer progression while minimizing off-target effects [45]. Additionally, combination therapies involving HDAC inhibitors and other anticancer agents, such as immune checkpoint inhibitors or targeted therapies, have shown promise in overcoming resistance and improving treatment outcomes [47]. For example, preclinical studies have demonstrated synergistic effects between HDAC inhibitors and bromodomain and extraterminal (BET) protein inhibitors in suppressing tumor growth and enhancing apoptosis in cancer cells [53].

Moreover, efforts are underway to identify biomarkers predictive of response to HDAC inhibitor-based therapies, allowing for personalized treatment strategies and improved patient outcomes. Advances in genomic profiling and molecular imaging techniques offer new opportunities for identifying biomarkers associated with sensitivity or resistance to HDAC inhibitors, guiding treatment decisions and optimizing therapeutic responses [50]. Incorporating pharmacogenomic approaches into clinical trials may facilitate the identification of patient subpopulations most likely to benefit from HDAC inhibitor therapy, thereby optimizing treatment outcomes and minimizing adverse effects [54].

5.3. Emerging technologies and novel approaches for targeting tumor suppressor genes in cancer therapy

In addition to HDAC inhibitors, emerging technologies and novel approaches are being developed to target tumor suppressor genes and exploit epigenetic vulnerabilities in cancer cells. For example, small molecule inhibitors targeting other epigenetic regulators, such as histone methyltransferases and bromodomain-containing proteins, are being investigated as potential anticancer agents [55]. Furthermore, gene editing technologies, such as CRISPR/Cas9, offer new

opportunities for precise manipulation of tumor suppressor genes and therapeutic intervention in cancer [56,57]. Recent advances in CRISPR-based epigenome editing have enabled targeted modulation of gene expression and epigenetic modifications, providing a powerful tool for investigating the functional roles of tumor suppressor genes and identifying novel therapeutic targets [58].

Moreover, immunotherapies targeting tumor suppressor genes, such as p53, are being explored as novel treatment modalities for cancer. Strategies to restore p53 function or enhance its activity in cancer cells, either alone or in combination with other therapeutic agents, hold promise for overcoming drug resistance and improving treatment outcomes [59–61]. For instance, therapeutic vaccines targeting mutant p53 peptides have shown encouraging results in preclinical studies and early-phase clinical trials, demonstrating their potential as a personalized immunotherapy approach for p53-mutant cancers [62].

These innovative approaches represent exciting avenues for future research and clinical translation in cancer therapy. By addressing the challenges associated with HDAC inhibitors and exploring novel strategies for targeting tumor suppressor genes, we can advance cancer therapy and improve patient outcomes.

6. Conclusion

The elucidation of histone deacetylase (HDAC) inhibitor-mediated modulation of tumor suppressor genes has revealed promising avenues for cancer therapy. HDAC inhibitors, potent epigenetic modulators, reprogram gene expression patterns, particularly of tumor suppressor

genes, to exert anticancer effects. By inhibiting HDAC enzymes, these inhibitors induce histone hyperacetylation, leading to chromatin remodeling and alterations in gene transcription. Consequently, tumor suppressor genes involved in cell cycle regulation, apoptosis, DNA repair, and other critical processes are upregulated, ultimately inhibiting tumor growth and metastasis.

Understanding HDAC inhibitor-mediated modulation of tumor suppressor genes emphasizes the importance of personalized cancer treatment. Targeting specific tumor suppressor genes, such as p53, p21, PTEN, BRCA1, RB1, CDKN2A, APC, NF1, VHL, ATM, and SMAD4, offers potential to restore normal cellular functions and overcome dysregulated signaling pathways in cancer cells. Additionally, the synergistic effects of HDAC inhibitors with other modalities like chemotherapy, radiation therapy, and immunotherapy highlight their versatility in combination therapy approaches.

Future directions in HDAC inhibitor-based cancer therapy include further elucidating molecular mechanisms underlying inhibitor specificity and selectivity in modulating tumor suppressor gene expression. Exploration of interactions between HDAC inhibitors and other epigenetic regulators, such as DNA methyltransferases and histone methyltransferases, is necessary to uncover synergistic or antagonistic effects impacting therapeutic outcomes. Moreover, developing novel HDAC inhibitors with enhanced potency, selectivity, and pharmacokinetic properties is crucial to improve efficacy and minimize off-target effects. Advances in drug design, structure-activity relationship studies, and computational modeling hold promise for discovering next-generation HDAC inhibitors with improved therapeutic profiles. Clinical translation of HDAC inhibitor-based therapy requires identifying reliable biomarkers predictive

of treatment response and patient stratification. Biomarkers like histone acetylation levels, gene expression signatures, and genetic mutations can guide treatment decisions and optimize therapeutic outcomes in cancer patients.

In conclusion, understanding HDAC inhibitor-mediated modulation of tumor suppressor genes provides a foundation for future research and clinical translation in cancer therapy. Leveraging the therapeutic potential of HDAC inhibitors and elucidating their mechanisms of action can lead to more effective and personalized treatments targeting molecular alterations driving cancer progression. Through interdisciplinary collaboration and innovation, HDAC inhibitor-based therapy holds promise for improving patient outcomes and advancing the fight against cancer.

Author Contributions

All authors conceived the review. SKK prepared the initial draft. All authors revised the manuscript and approved the final draft. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable

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Conflict of Interest

The authors declare no conflict of interest

Table 1. Tumor suppressor genes and their effects influenced by HDAC inhibitors

Tumor Suppressor Gene	Effects of HDAC Inhibitors	References
p53 (TP53)	Induction of cell cycle arrest and apoptosis	[9]
p21 (CDKN1A)	Control of cell cycle progression and senescence	[63]
PTEN	Modulation of PI3K/Akt signaling pathway and tumor growth inhibition	[8]
BRCA1	Implications for DNA repair and genomic stability	[8]
RB1	Control of cell cycle progression and tumor suppression	[64,65]
CDKN2A	Regulation of cell cycle progression and senescence	[63]
APC	Inhibition of Wnt signaling pathway and cell cycle regulation	[66]
NF1	Regulation of Ras signaling pathway and cell proliferation	[67]
VHL	Inhibition of hypoxia-inducible factor (HIF) signaling pathway and angiogenesis	[68]
ATM	Maintenance of genomic stability and DNA damage response	[69,70]

Figure 1

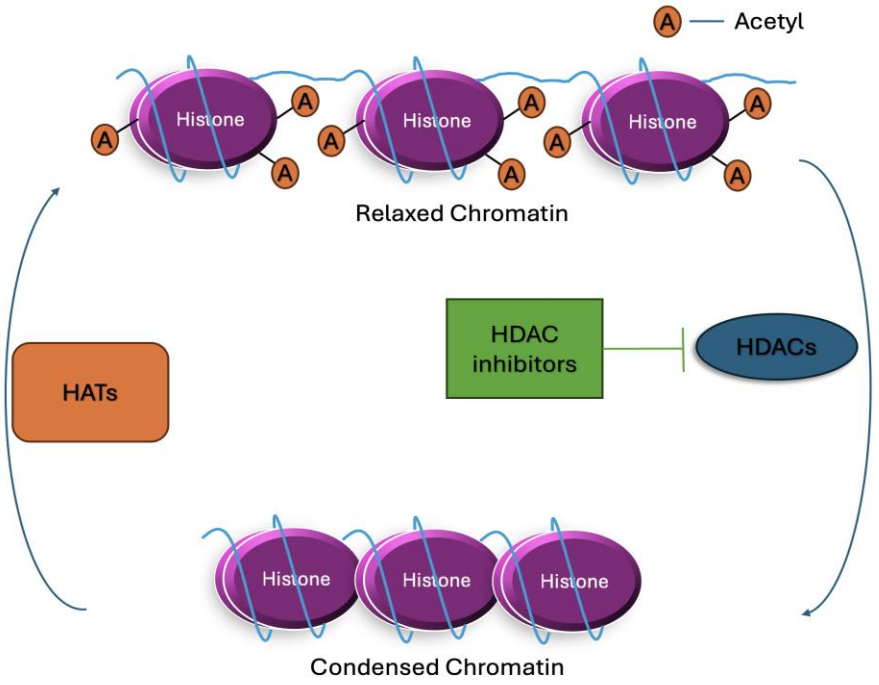

Figure 1. The impact of HDAC inhibitors (HDACi) on chromatin remodeling by altering the balance of histone acetylation. Histone deacetylases (HDACs) and histone acetyltransferases (HATs) play crucial roles in this balance, with HDACs removing acetyl groups from histones, leading to transcriptional repression, while HATs add acetyl groups, promoting transcriptional activation. By inhibiting HDACs, HDACi disrupts this balance, maintaining a chromatin conformation that favors transcriptional activation.

Figure 2.

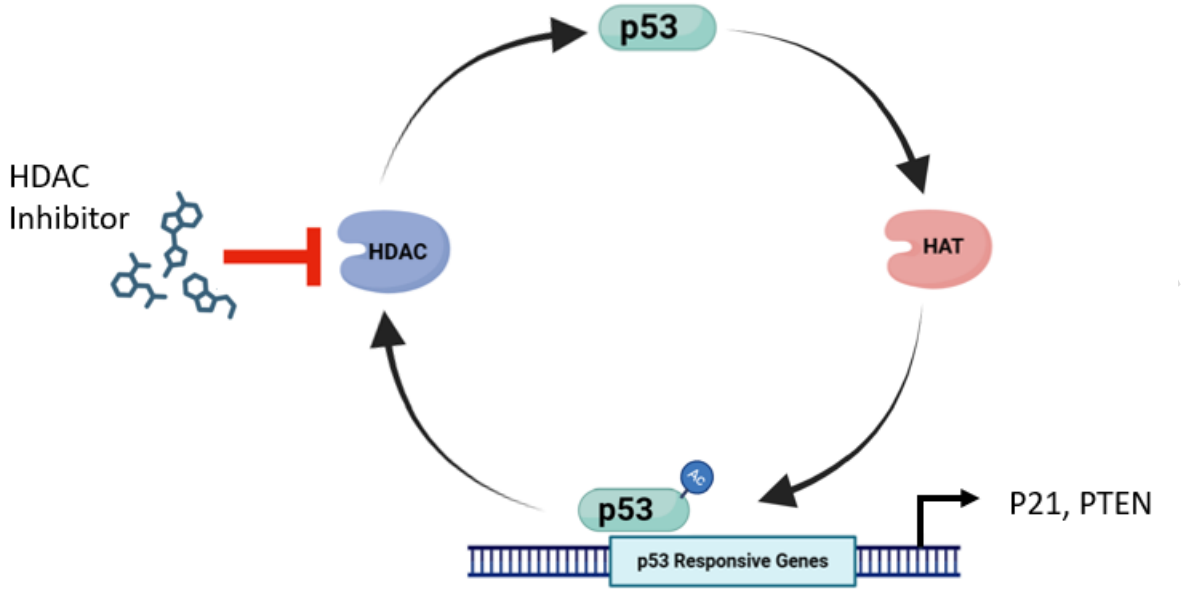

Figure 2. Schematic representation of the molecular mechanism of HDCAi-induced acetylation on p53. Inhibition of HDAC activates transcription of p21 and PTEN, where p21 stimulates cell cycle arrest and PTEN inhibits tumor growth. The figure was created with BioRender.

Figure 3.

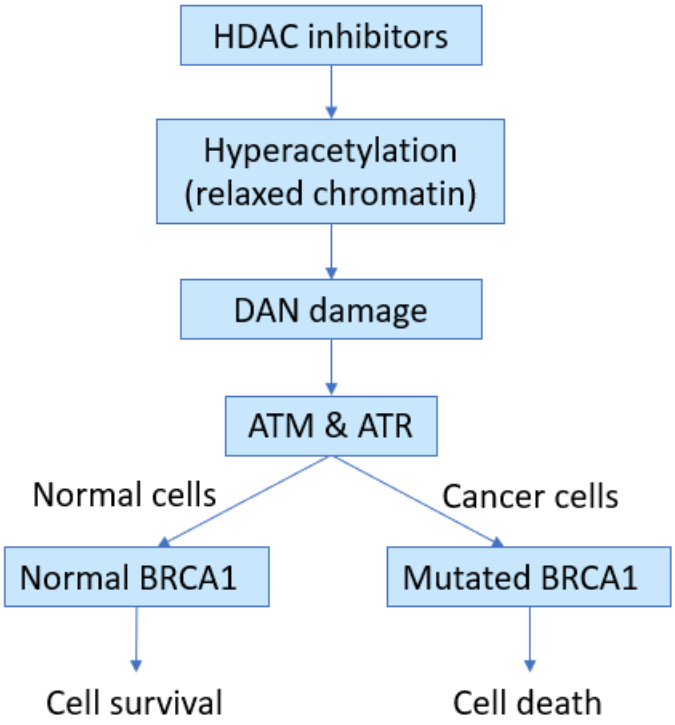

Figure 3. Schematic representation of the molecular mechanism between HDAC inhibitors and BRCA1. Blocking HDAC activity triggers DNA damage and interferes with DNA repair mechanisms. HDAC inhibition results in increased acetylation of both DNA and chromatin, promoting a more open and relaxed DNA structure. This alteration makes DNA more susceptible to damage from cytotoxic agents that target DNA. Consequently, there's an upregulation of ATM and ATR, which in healthy cells activate BRCA1 to initiate DNA repair. However, in cancer cells with mutated BRCA1, this repair mechanism is compromised, ultimately leading to cell death.

Figure 4.

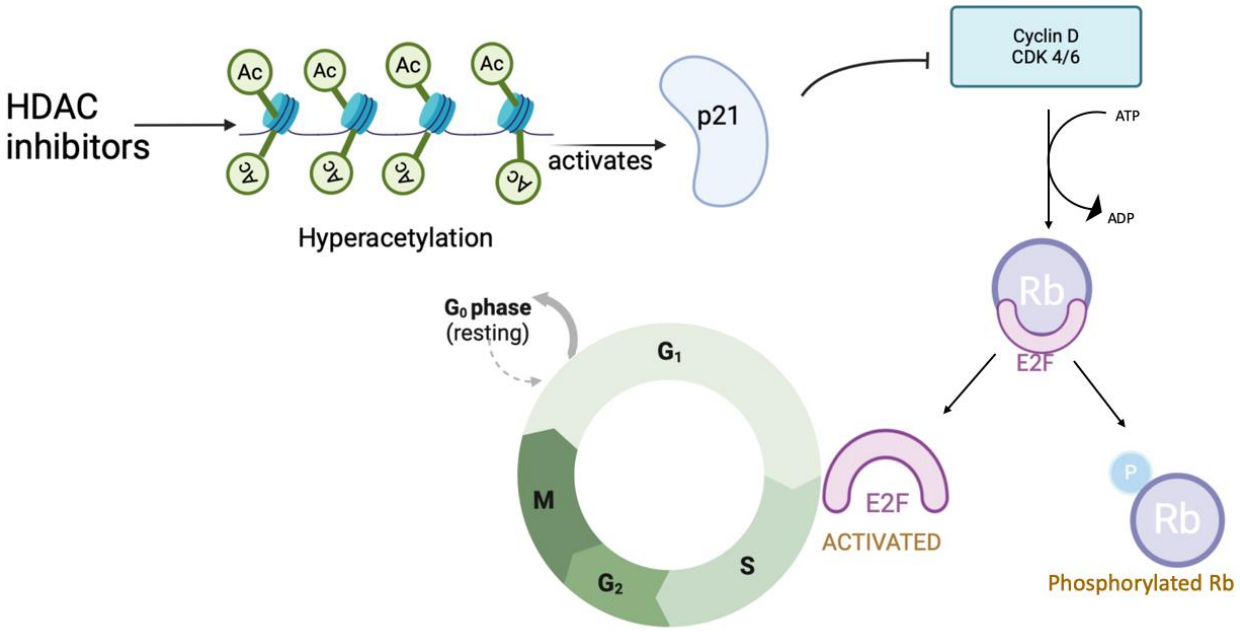

Figure 4. Schematic representation of the molecular mechanism between HDAC inhibitors and Rb. The p53 protein interacts with DDX3 and activates the p21 protein that inhibits the cyclin/cdk complex. As a result, Rb is not phosphorylated and remains linking with E2F transcription factor, and the cell cycle remains in the G1 phase. If p21 is not activated. the complex cyclin A/CDK2 is free to phosphorylate pRb, and the E2F transcription factor is released and determines the cell cycle and S-phase entry. The figure was created with BioRender.

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