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Histone deacetylase (HDAC) inhibitors used for the treatment of cancer

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Abstract

Histone deacetylases (HDACs) are enzymes that mediate reversible acetylation. They have an extensive effect on numerous physiological methods, many of which are dysregulated in tumour cells. A novel family of mechanism-based anti-cancer agents known as small-molecule HDAC inhibitors has been created, several of which have entered clinical trials, since HDAC inhibition induces tumour cells to undergo apoptosis. HDAC inhibitors have been demonstrated to have a variety of biological effects, however the causes are yet unknown. In addition, a detailed study of their use in combination with other drugs and when to take these combinations is needed. Clinical trials for a number of additional HDAC inhibitors are being conducted to treat solid and haematological malignancies. The study of HDAC biology has numerous early breakthroughs, including the discovering and cloning of human histone deacetylases (HDACs) and the swift approval of vorinostat for the treatment of cutaneous T-cell lymphoma.

Keywords: Histone deacetylase inhibitors, Apoptosis, cancer, vorinostat (SAHA).

1. Introduction

Many strategies have been used over the past few decades to try and find new, more potent anticancer medications. Numerous intriguing chemicals have so been researched. However, one of the primary reasons for treatment failure is chemoresistance, which can develop throughout chemotherapy. It is becoming clear that epigenetic modifications contribute to chemoresistence. These are the variations in cellular phenotype or gene expression brought about by causes other than mutations in DNA sequence. These consist of posttranslational modifications to chromatin and mRNA regulation, RNA transcripts and the proteins they encode, production of non-coding RNAs, and changes in DNA methylation and chromatin remodeling. One significant factor influencing how genes are expressed is histone acetylation. While deacetylated histones are frequently linked to gene repression, acetylation is typically associated with increased transcription. Histone deacetylase inhibitors (HDAC inhibitors) are a novel class of anticancer medications that function by promoting histone acetylation, which uncoils chromatin and activates a substantial number of genes that control the survival, division, proliferation, and death of

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cells. The four primary categories of HDIs are cyclic tetrapeptides, hydroxamic acid derivatives, short-chain fatty acids, and derivatives of synthetic benzamide. Individuals from every one of these classes are now enrolled in human clinical trials. Individual HDIs affect cell cycle regulation, signal transduction, and survival-related proteins in different ways even though they can all cause histone deacetylation [1]. Clarifying the processes by which HDIs cause neoplastic cells to undergo apoptosis and identifying the variables influencing these cells' decisions to undergo maturation or cell death in response to these agents are two of the main research topics surrounding HDIs.

Histone deacetylases (HDACs) are essential controllers of the expression of genes that catalyze the acetyl group removal from histones through enzymatic means [2]. Another important part of HDAC function is the activity of HDACs on nonhistone proteins [3]. In spite of the fact that a great number of nonhistone HDAC substrates have been found, most of these targets' molecular and biological effects of nonhistone protein deacetylation remain unknown. So far, 11 HDACs have been found in three classical HDAC classes (I, II, and IV), which are categorized based on their enzymatic activity, subcellular localization, and homology to yeast proteins. The cellular signaling pathways' inherent functionality and the compound's HDAC specificity determine the biological result of HDAC inhibition. HDACis are best described as anticancer drugs, and research into their modes of action and therapeutic effectiveness is still ongoing and vigorous [2]. The acetylation state of histones and other proteins is regulated by the enzymes histone acetyltransferase (HAT) and histone deacetylase (HDAC). An acetyl group is transferred from acetyl-CoA to lysine residues in proteins by HATs, and it is then removed by HDAC [4]. HDACs belong to two different groups, based on how the acetyl group is removed from them. The HDACs of the "classical family" are dependent on zinc (Zn^{2+}), while the second family of HDACs is dependent on NAD^+ for catalysis. Acetyl transfer results in the formation of nicotinamide and O-acetyl-ADP-ribose [5].

Besides genetic mutations, abnormal epigenetic changes are the cause of many diseases, most notably cancer. Histone acetylation and/or deacetylation-induced chromatin remodelling is an illustration of epigenetic control [6]. Histones are less likely to interact with negatively charged DNA when they are acetylated by HAT, which turns their positive charge into a negative one. Transcriptional activation is the result of this increasing accessibility for the transcriptional machinery. HDACs have the ability to deacetylate, which will reverse this sequence of events. Variations in the balance between HATs and HDACs can lead to epigenetic modifications that impact global transcriptional patterns. In reality, abnormal epigenetic modifications suppressors like p53 and RUNX3 in a large number of malignancies [6]. In contrast to traditional tumour suppressors like p53 and Rb, mutations of the RUNX3 gene are extremely uncommon, and epigenetic modifications are primarily responsible for the gene's inactivation [6]. This shows that RUNX3 may be a good molecular target for anti-cancer medications that regulate epigenetic alterations due to its ability to inhibit tumors can be regained by RUNX3-targeted therapies. The reason HDACs got their name is because they were initially discovered to be enzymes that work to eliminate acetyl groups from lysine residues on histone N terminal tails [6].

The removal of acetyl groups from histones by HDAC enzymes results in a closed chromatin shape and the silence of genes. Tumor suppressor genes are silenced in many malignancies, enabling the growth and survival of cancer cells. This process is reversed by HDAC inhibitors, which reactivate genes that

have been silenced and encourage the death of cancer cells. HDAC inhibitors belong to a more recent class of focused medicines, as opposed to conventional chemotherapy, which destroys both healthy and malignant cells. They have the ability to specifically change the expression of certain genes in cancer cells, which could make treatments more accurate and less harmful. One important area of epigenetic drug development, which is a quickly developing topic in cancer research, is HDAC inhibitors. Researching them can result in fresh perspectives on the biology of cancer and innovative treatment approaches.

2. Therapeutic development of HDAC inhibitors:

Although it was the first in the cyclic peptide HDAC inhibitor class, depsipeptide was the second HDAC inhibitor to be licensed for the treatment of CTCL after vorinostat (in November 2009). Preclinical and clinical trials have evaluated over fifteen HDAC inhibitors. The data on drugs from the three main HDAC classes—vorinostat, depsipeptide, and MS-275—that are currently available are discussed in the sections that follow, and the evidence for anticancer action in these studies is assessed. The FDA approved vorinostat, the most sophisticated HDAC inhibitor, in October 2006 to treat advanced types of CTCL that were unresponsive to systemic or multiple medication therapy [6]. Additionally, vorinostat has been studied in additional phase I and II clinical studies for solid tumours and various haematological malignancies [6]. For haematological malignancies, vorinostat can be administered orally at a maximum tolerated dosage (MTD) of 400 mg once daily or 200 mg twice daily. For the treatment of solid tumours, it can also be administered at a dose of 300 mg twice daily for three days in a row throughout a 4-week cycle [6]. Oral vorinostat 400 mg/day was administered to 74 patients with progressive, persistent, or recurrent CTCL who had received at least two prior medications in a phase IIb trial [6]. The treatment was continued until the disease progressed or severe toxicity was noted. 29.7% was the objective response rate (ORR). The median time to progression was 4.9 months for all responders and ≥ 9.8 months for those in stage IIB or later. Of the patients, 32% said that their pruritus has been relieved.

3. Histone deacetylases and cancer:

The amounts of HDACs class I and II differ amongst cancer cells. Prostate, stomach, lung, esophageal, colon, and breast cancers are among the tumours where HDAC1 is overexpressed and indicates a poor prognosis [7]. There is evidence that colorectal, cervical, and stomach malignancies have elevated HDAC2 levels [7]. Furthermore, high expression of HDAC1 and 2 is associated with a lower patient survival rate in colorectal carcinomas, while HDAC3 is overexpressed in gastric, prostate, and colorectal cancers [7]. Breast cancer has high levels of HDAC6 expression, while neuroblastoma cells have high levels of HDAC8 expression, which is associated with metastases and an advanced phase of the ailment with a poor prognosis [7]. Class III HDACs are crucial to the development of cancer. While some function as anti-tumorogens, others affect tumours by regulating the metabolism of cells [7]. Reduced HDAC activity is linked to inhibited tumour cell proliferation and development [7]. Additionally, HDAC4 mutations have been discovered in breast cancer samples, and human epithelial cancer cell lines exhibit HDAC2 mutations that result in protein truncation [7].

4. Mechanisms of cell death mediated by histone deacetylase inhibitors:

Histone and non-histone protein alterations as well as altered gene expression are some of the ways that different HDAC inhibitors kill cancer cells. A multitude of cancers exhibit increased histone acetylation, which modifies the expression of genes involved in cell signaling. Around 2-10% of the genes involved in a number of biological processes, including the triggering of apoptosis and cell cycle arrest, exhibit altered expression when HDACs are inhibited [8]. It was discovered that HDAC inhibition alters a large number of genes involved in the control of the cell cycle and apoptosis [7]. Additionally, certain HDAC inhibitors have antiangiogenic properties [7].

5. Histone deacetylase inhibitors and apoptosis:

HDAC inhibitors cause tumor cells to undergo apoptosis by controlling the expression of genes that promote and inhibit apoptosis [9]. Apoptotic mechanisms that are both intrinsically and externally activated is one of the mechanisms by which various HDAC inhibitors cause apoptosis. It has been shown that HDAC inhibitors affect death receptors and their ligands [10]. It has also been shown that the intrinsic route is activated in response to HDAC inhibitor-induced apoptosis [9]. We find that pro-apoptotic genes implicated in the intrinsic and extrinsic apoptotic pathways are up-regulated in tumor cells treated to HDAC inhibitors, whilst the expression of anti-apoptotic genes is decreased [7]. Furthermore, it was discovered that cancer cells treated with HDAC inhibitors had higher amounts of reactive oxygen species (ROS), which cause apoptosis, whereas nonmalignant cells treated with the same medications did not. The death of cells caused by HDAC inhibitors is not prevented by caspase inhibition. This indicates that HDAC inhibitors also cause cancer cell death in non-caspase forms [7]. There are two possible methods by which HDAC inhibitors induce oxidative stress: mitochondrial damage and altered cellular antioxidant defences [11]. In cells that are resistant to apoptosis, HDAC inhibitors can also cause cell death. Autophagy activation is one potential mechanism of HDAC inhibitor-induced non-apoptotic cell death. SAHA (suberoylanilide hydroxamic acid) stimulated autophagy and slowed the growth of tumours in glioblastoma xenografts in mice. This HDAC inhibitor decreased p62, attracted LC3-II to the autophagosomes, enhanced the production of intracellular acidic vesicle organelles, and potentiated the levels of Beclin1 protein. SAHA inhibited AKT-MTOR signalling, which in turn caused autophagy. Chloroquine's combined effects of inhibiting SAHA-induced autophagy increase apoptosis [7].

6. Histone deacetylase inhibitors and cell signaling pathways:

The control of cell variation by initiation of certain protein kinases, including as mitogen-activated protein kinases (MAPK), c-Jun Nterminal kinase (JNK), and p38, which affect cell proliferation, differentiation, and apoptosis, is a significant mechanism of the anticancer impact of HDAC inhibitors. In certain cancer cells, HDAC inhibitors boost c-Jun expression and phosphorylation [7]. GSK-3β is phosphorylated by VPA and natrium butyrate, which also affects Wnt signalling, which is significant in a number of cancers [12]. Additionally, some of the enzymes involved in the proteasomal degradation pathway are expressed in response to HDAC inhibitors [7].

7. Combining histone deacetylase inhibitors with additional treatment plans:

The grouping of HDAC inhibitors with other anticancer medications has been shown to have synergistic or additive effects based on the outcomes of in vitro and in vivo tests employing different cancer cells [7]. Clinical trials have also employed combinations of chemotherapy and HDAC inhibitors [13]. HDAC inhibitors have been researched in combination with a range of medical strategies.

HDAC inhibitors were used with additional epigenetic modifiers. When combined with HDAC inhibitors, the anticancer effects of 5-aza-2'-deoxycytidine (decitabine) and 5-aza-azacytidine (azacitidine) inhibitors were enhanced [14]. Combinations of ROS-generating drugs and HDAC inhibitors have shown encouraging outcomes [7]. Adaphostin is one such medication that causes leukaemia cells to undergo apoptosis in response to vorinostat and entinostat. Additionally, the properties of vorinostat on AML cells are amplified when GSH, a ROS scavenger, is depleted [7]. Microtubule stabilisers comprise additional medications that have been used with HDAC inhibitors. Because VPA interacts with the tubulin β subunit, it amplifies the toxic effects of paclitaxel in anaplastic thyroid cancer cells. The stabilising effect of tubulin hyperacetylation on microtubule structures is enhanced by VPA [7]. The stimulation of the intrinsic mitochondria-dependent pathway mediated by trichostatin A and paclitaxel treatment of endometrial cancer cells resulted in a similar increase of apoptosis. Through α-tubulin acetylation, trichostatin A also maintains microtubule stability in both vitro and in vivo settings [7].

Protease inhibitors and HDAC inhibitors together are another potent combo. Protease and HDAC inhibitor-induced cancer cell death is brought on by oxidative stress induction, endoplasmic reticulum (ER) stress, and JNK stimulation. Protease inhibitors such as carfilzomib, marizomib (NPI-0052), and boratezamib have been used with HDAC inhibitors. Bortezomib treatment increased the sensitivity of multiple myeloma cells to vorinostat and sodium butyrate-induced apoptosis [7]. Vorinostat's anticancer effects when combined with bortezomib were shown to increase in clinical trials involving patients with multiple myeloma [7]. Combining protease and HDAC inhibitors has been demonstrated to have anticancer effects via a number of pathways, including as mitochondrial damage, disruption of aggresome development, activation of caspases and JNK, and increased oxidative and ER stress [7]. The combination of vorinostat or entinostat and the proteasome inhibitor marizomib triggered apoptosis in certain leukaemia cells; these advantageous effects were caused by oxidative stress and caspase 8 activation [7].

Many studies have demonstrated additive effects or synergisms between HDAC inhibitors and agents that damage DNA, such as ionising radiation and doxorubicin, epirubicin, etoposid, cisplatin, 5-fluorouracil, melphalan, and temozolomide. These compounds include DNA intercalators, agents that covalently change DNA, inhibitors of DNA synthesis, and topoisomerase inhibitors [15].

8. Pharmacology and indications of HDACs:

The US FDA has approved four HDACs as of October 2018: belinostat, vorinostat, panobinostat, and romidepsin. Of these, only panobinostat has received EMA approval. Another medication that has received approval in China is chidamide, often referred to as tucidinostat [16].

A wide range of side effects, including nausea, vomiting, exhaustion, rash, coughing, fever, headaches, and anorexia, are linked to HDACs, they are typically readily controlled and rarely severe enough to cause therapy to be stopped. It is possible to distinguish between class-related and more drug-specific serious or life-threatening side effects caused by HDACs. These are covered in the sections that follow, as they relate to the HDACs that are currently authorized [16].

9. The Effects on Stem Cells:

Reprogramming somatic cells into pluripotent stem cells requires epigenetic modifications. Thus, by altering a chromatin structure and increasing its permissiveness to transcription factors, a number of inhibitors of epigenetic-modifying enzymes, such as HDAC, can transform somatic cells into pluripotent stem cells [17, 18]. HDAC inhibitors have been shown to enhance the epithelial–mesenchymal transition of colorectal and breast cancer cells, amplify and maintain normal human hematopoietic stem cells, and induce the expression of CD133, a marker of cancer stem cells in certain cancers, including brain tumors, in human gliomas [18-22]. The experimental in vitro investigation demonstrated that HDAC3 stimulated glioma stem cell self-renewal, and the studies employing tumor tissues further supported those experimental findings [23].

10. Conclusion

A relatively recent class of anti-cancer medications known as histone deacetylase (HDAC) inhibitors causes cancer cells to undergo cell cycle arrest, apoptosis, and death in addition to other crucial epigenetic and non-epigenetic regulatory mechanisms. Due to the FDA's recent clinical validation of their usage in cancer patients, two HDAC inhibitors vorinostat and depsipetide were approved. Additionally, Clinical trials are being conducted on several HDAC inhibitors to be used as anti-cancer medications, either by themselves or in conjunction with other anti-cancer therapies. Nevertheless, little is known about the molecular mechanisms behind cancer patients' responsiveness to HDAC inhibitors. Numerous other HDAC inhibitors are undergoing clinical trials to treat solid and haematological cancers. Despite the fact that HDAC inhibitors have been revealed to have a wide variety of biological effects, causes are yet unknown. Furthermore, a thorough investigation is required into their usage in conjunction with other medications and the timing of these combinations.

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