

# Research and Analysis of Drug Resistance Mechanism of HDACi in the Treatment of Skin Melanoma

Ming Yin, Hua Tang, Hao Feng

The First Affiliated Hospital of Hunan Normal University (Hunan Provincial People's Hospital), Changsha, Hunan, 410000, China

**Abstract:** Histone deacetylase inhibitors (HDACi) have shown potential as an epigenetic therapy in various cancer treatments. However, its application in the treatment of skin melanoma faces the challenge of drug resistance. This article reviews the drug resistance mechanism of HDACi in the treatment of skin melanoma, analyzes the mechanism of action of HDACi, the drug resistance characteristics of melanoma, the drug resistance mechanism of HDACi in the treatment of melanoma, and potential solutions to drug resistance, aiming to provide reference for the further application of HDACi in the treatment of skin melanoma.

**Keywords:** Treatment; Melanoma; Drug Resistance Mechanisms.

## 1. Introduction

As shown in Figure 1, skin melanoma, as a highly malignant tumor, has a worrisome increasing trend in its incidence rate and mortality worldwide. With the advancement of medical technology, in-depth exploration of the molecular mechanisms of melanoma has brought new breakthroughs in treatment.



Figure 1. Skin Melanoma Image

New treatment methods such as targeted therapy and immunotherapy have emerged, significantly improving the survival rate of patients and bringing new hope to melanoma

patients. However, the issue of tumor drug resistance during the treatment process remains an urgent problem that needs to be addressed. As shown in Figure 2, although significant progress has been made in targeted therapy and immunotherapy, low response rates and the development of drug resistance remain the main clinical obstacles affecting patient prognosis. The complex interactions between multiple signaling molecules and pathways have limited understanding of the pathogenesis and drug resistance of melanoma.

HDACi (histone deacetylase inhibitor), as a class of drugs that can regulate histone acetylation levels and affect gene expression, has shown good anti-tumor activity in the treatment of various cancers, providing a new option for cancer treatment. However, when HDACi is applied for the treatment of skin melanoma, it also faces the challenge of drug resistance. Melanoma cells may develop resistance to HDACi through various mechanisms, leading to poor therapeutic outcomes. Therefore, in-depth research on the drug resistance mechanism of HDACi in the treatment of skin melanoma, exploring its molecular basis and cellular biology mechanism of drug resistance, is of great clinical significance for overcoming drug resistance and improving treatment efficacy. This not only helps us better understand the biological characteristics of melanoma, but also provides a theoretical basis for developing new treatment strategies and drugs, which is expected to bring more effective treatment methods for patients with skin melanoma.

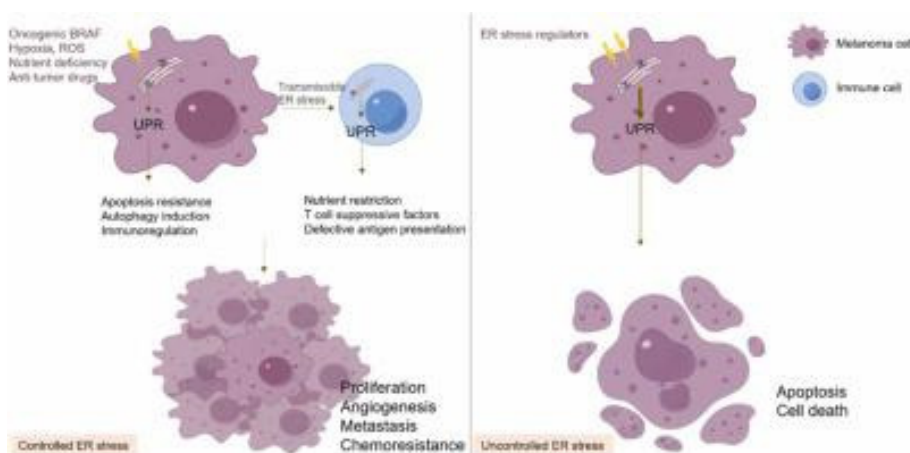


Figure 2. Schematic diagram of melanoma drug resistance mechanism

## 2. The Mechanism of Action of HDACi

HDACi (histone deacetylase inhibitor), as an epigenetic regulatory drug, has shown great potential in anti-tumor therapy. The core mechanism of its action is to effectively increase the acetylation level of histones by inhibiting the activity of histone deacetylase. This change in turn triggers an adjustment in chromatin structure, affecting the transcription and expression processes of genes. Due to the crucial role of epigenetic regulation in cellular life activities, the mechanism of action of HDACi has laid a solid foundation for its application in the field of anti-tumor.

Specifically, HDACi can act in a multi pronged manner, inhibiting tumor cell proliferation, inducing cell apoptosis, and effectively inhibiting angiogenesis. These effects together constitute its powerful anti-tumor activity. HDACi has demonstrated good efficacy and broad application prospects in the treatment of various cancers. With the continuous deepening of research and the accumulation of clinical experience, it is believed that HDACi will play an important role in the treatment of more types of cancer in the future, bringing more treatment options and survival hope to cancer patients. Therefore, as a representative drug regulated by epigenetics, HDACi's anti-tumor mechanism and application prospects deserve continuous attention and in-depth exploration by researchers and clinical doctors.

## 3. Drug Resistance Characteristics of Skin Melanoma

The issue of drug resistance in melanoma is a major challenge in the treatment process and one of the main reasons for treatment failure. The special structure of melanoma cells shown in Figure 3 exhibits complex drug resistance characteristics, which involve multiple mechanisms, mainly including genetic mechanisms, epigenetic mechanisms, and changes in cell plasticity.

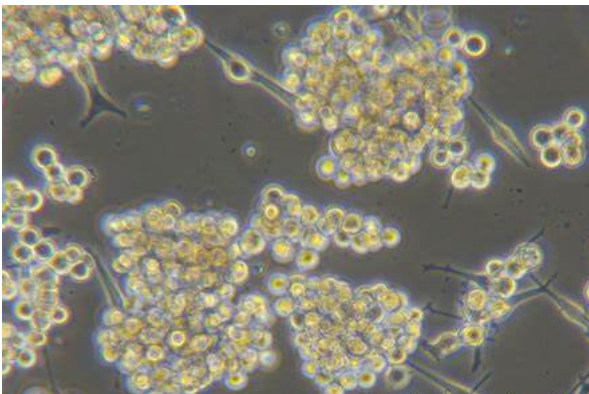


Figure 3. Image of Black Skin Cells

In terms of genetic mechanisms, melanoma cells may undergo genetic mutations under the pressure of treatment, which make the cells resistant to previously sensitive therapeutic drugs and reduce the efficacy of the drugs. In terms of epigenetic mechanisms, melanoma cells can alter gene expression patterns through epigenetic modifications such as DNA methylation, histone modifications, etc., allowing some genes that should have been suppressed by drugs to be expressed or downregulating the expression of drug target genes, thereby avoiding the attack of therapeutic

drugs.

In addition, changes in cellular plasticity are also an important reason for melanoma cell drug resistance. Melanoma cells have a high degree of plasticity, and they can adapt to the therapeutic environment by changing cell morphology, adjusting metabolic pathways, and reducing sensitivity to drugs, thus exhibiting drug resistance characteristics. The existence of these drug resistance mechanisms makes the treatment of melanoma more complex and difficult, requiring researchers to constantly explore new treatment strategies to overcome melanoma's drug resistance and improve treatment effectiveness.

## 4. The Resistance Mechanism of HDACi in the Treatment of Melanoma

### 4.1. Resistance Caused by Genetic Mechanisms

The resistance of melanoma cells to HDACi (histone deacetylase inhibitor) may originate from genetic changes. During the treatment process, melanoma cells may undergo genetic mutations that alter the target of HDACi, thereby reducing the sensitivity of the drug to the cells. Especially those genes related to cell cycle regulation and apoptosis, once mutated, may make melanoma cells resistant to HDACi induced cell cycle arrest and apoptosis, thereby evading the therapeutic effect of drugs. In addition, melanoma cells also have a cunning adaptive mechanism, which is to counteract HDACi therapy by activating specific signaling pathways. For example, the MAPK pathway and PI3K/AKT pathway may be activated, and the activation of these pathways can interfere with the normal function of HDACi, allowing melanoma cells to continue to survive and proliferate in the presence of drugs. Therefore, the resistance of melanoma cells to HDACi is a complex issue involving multiple levels such as genetic mutations and signaling pathway activation, which also poses greater challenges for the treatment of melanoma. In the future, it is necessary to conduct in-depth research on these resistance mechanisms in order to develop more effective treatment strategies to overcome melanoma's resistance to HDACi.

### 4.2. Drug Resistance Caused by Epigenetic Mechanisms

In addition to genetic mechanisms, epigenetic mechanisms also play a crucial role in the resistance process of HDACi (histone deacetylase inhibitor) treatment for melanoma. As a therapeutic drug targeting epigenetics, the efficacy of HDACi is greatly influenced by the epigenetic status of melanoma cells. During the treatment process, melanoma cells may directly resist the inhibitory effect of HDACi by upregulating the expression or activity of HDACs (histone deacetylases), making it difficult for drugs to effectively reduce histone acetylation levels, alter chromatin structure, and regulate gene expression. In addition, melanoma cells may also utilize other epigenetic modifications such as DNA methylation, histone methylation, etc. to alter gene expression patterns. These epigenetic modifications can act independently or synergistically, allowing melanoma cells to evade the therapeutic effects of HDACi and continue to maintain their malignant phenotype. Therefore, a deeper understanding of the epigenetic resistance mechanisms of melanoma cells is of great significance for developing new therapeutic strategies

and improving the therapeutic efficacy of HDACi.

### 4.3. Drug Resistance Caused by Changes in Cellular Plasticity

Melanoma cells exhibit a high degree of plasticity, which allows them to flexibly adapt to therapeutic environments, including treatment against HDACi (histone deacetylase inhibitors). This plasticity change is one of the important mechanisms for HDACi treatment of melanoma drug resistance. Specifically, melanoma cells may enhance their resistance to oxidative stress by upregulating the expression of antioxidant enzymes. HDACi often induces oxidative stress damage during treatment, and melanoma cells can effectively reduce drug induced oxidative damage to cells through this adaptive change, thereby avoiding the therapeutic effect of drugs.

In addition, melanoma cells may also counteract HDACi induced cell cycle arrest and apoptosis by altering the cell cycle regulation mechanism. The cell cycle is an important process for cell proliferation and division, and HDACi often inhibits tumor cell proliferation by interfering with the cell cycle. However, melanoma cells can evade this inhibitory effect and continue to maintain their proliferation and survival ability by adjusting the expression or activity of cell cycle related genes. Therefore, this plasticity change in melanoma cells poses a challenge for HDACi therapy, and further in-depth research is needed to develop more effective treatment strategies to overcome melanoma's resistance to HDACi.

### 4.4. The Impact of Tumor Microenvironment

The tumor microenvironment plays a crucial role in the resistance of melanoma to HDACi (histone deacetylase inhibitor). The tumor microenvironment is a complex ecosystem that includes various cellular components such as immune cells, fibroblasts, and endothelial cells. They have a profound impact on the biological behavior of melanoma cells by secreting soluble factors and altering the extracellular matrix. Especially tumor associated macrophages (TAMs), they may provide melanoma cells with a favorable environment for immune escape and drug resistance by secreting immunosuppressive factors such as cytokines and growth factors.

These immunosuppressive factors not only weaken the anti-tumor effect of the immune system, but may also directly promote the enhancement of drug resistance in melanoma cells. In addition, the hypoxic state in the tumor microenvironment is also an undeniable factor. Hypoxia may activate a series of genes and signaling pathways adapted to the hypoxic environment by upregulating the expression of hypoxia inducible factor (HIF), thereby enabling melanoma cells to acquire resistance to therapeutic drugs such as HDACi. Therefore, a deeper understanding of the role of the tumor microenvironment in melanoma drug resistance is of great significance for developing novel therapeutic strategies targeting the tumor microenvironment and improving the therapeutic efficacy of HDACi.

### 4.5. Limitations of HDACi Drugs Themselves

In addition to known genetic, epigenetic, and tumor microenvironment factors, the limitations of HDACi (histone deacetylase inhibitor) drugs themselves are also an important reason for their resistance in the treatment of melanoma. In the design of the first generation HDACi drugs, hydroxamic acid salts were often used as  $Zn^{2+}$  binding groups (ZBG).

Although this design has certain inhibitory activity, its specificity is relatively poor and its toxicity is high. Due to the presence of various metal ions in the body, these ions may compete with HDACi for binding sites, thereby interfering with the normal action of drugs and reducing their efficacy. In addition, the metabolism and distribution of HDACi in the body may also have a significant impact on its efficacy and drug resistance.

The absorption, distribution, metabolism, and excretion of drugs in the body are complex and varied, and any abnormality in any link may lead to insufficient or excessive drug concentration, thereby affecting its therapeutic effect. Especially if the distribution of drugs in tumor tissue is uneven, or if metabolism is too fast and the effective concentration is maintained for a short period of time, it may give melanoma cells the opportunity to escape the inhibitory effect of drugs and develop drug resistance. Therefore, optimizing the drug design of HDACi, improving its specificity and reducing toxicity, as well as conducting in-depth research on its metabolism and distribution patterns in vivo, are of great significance for overcoming the resistance of melanoma to HDACi.

## 5. Potential Solutions for Drug Resistance

### 5.1. Development of New HDACi Drugs

Researchers are working on developing new HDACi drugs to address the limitations of poor specificity and high toxicity of the first generation HDACi (histone deacetylase inhibitor) drugs. These new drugs, by optimizing their chemical structures such as designing complex cap groups, not only enhance the specificity of inhibiting HDACs (histone deacetylases), but also significantly reduce toxicity, thus better exerting the inhibitory effect on HDACs activity and improving therapeutic efficacy. Endostat is one of the representative new HDACi drugs, which has good metabolic stability and can maintain effective drug concentrations in the body. The results of preclinical studies and large phase III clinical trials both show that entepista performs well in the treatment of HR+/HER2 advanced breast cancer, can significantly extend the progression free survival (PFS) and total survival (OS) of patients, and shows good safety. This research achievement not only provides new treatment options for patients with HR+/HER2 advanced breast cancer, but also provides a strong basis for the development and application of new HDACi drugs, which indicates that new HDACi drugs are expected to play a greater role in the treatment of more tumor types in the future.

### 5.2. Combination Therapy Strategy

Combination therapy is one of the key strategies to enhance the efficacy of HDACi (histone deacetylase inhibitor) and overcome drug resistance. In clinical treatment, by combining HDACi with other anti-tumor drugs such as chemotherapy drugs, targeted drugs, and immune checkpoint inhibitors, the synergistic effect of drugs can be fully utilized, significantly improving treatment efficacy. Taking HR+breast cancer as an example, the combination of HDACi and CDK4/6 inhibitors can significantly enhance the inhibitory effect on the proliferation of breast cancer cells, effectively reverse the drug resistance of endocrine therapy, and bring new therapeutic hope to patients. In addition, the combination of HDACi and immune checkpoint inhibitors has also shown

broad prospects. In various tumor models, this combination therapy strategy not only enhances anti-tumor activity, but may also enhance the immune system's anti-tumor response by regulating the tumor microenvironment, thereby achieving better therapeutic effects. Therefore, the combination therapy strategy provides new ideas and methods to overcome the resistance of HDACi and improve its efficacy in different types of tumors, which is worthy of further in-depth research and clinical application promotion.

### 5.3. Targeting the Tumor Microenvironment

Researchers are actively exploring novel therapeutic strategies targeting the tumor microenvironment to address its significant impact on melanoma drug resistance. They focus on key components in the tumor microenvironment, such as tumor associated macrophages (TAMs), and aim to reduce their immunosuppressive effect on melanoma cells by inhibiting their activity or function, thereby enhancing the body's ability to attack tumor cells. At the same time, researchers are also paying attention to the hypoxic state in the tumor microenvironment, by altering this state to reduce the expression of hypoxia inducible factor (HIF), thereby inhibiting the drug resistance characteristics of melanoma cells in hypoxic environments. In addition, components such as fibroblasts and endothelial cells in the tumor microenvironment also play an important role in the growth and drug resistance of melanoma. Therefore, targeted therapy targeting these components, such as inhibiting the activation of fibroblasts and disrupting tumor angiogenesis, is also expected to improve the efficacy of HDACi (histone deacetylase inhibitor) and overcome the resistance of melanoma to treatment. These strategies provide new ideas for the treatment of melanoma and are expected to bring good news to more patients in the future.

### 5.4. Personalized Treatment Plan

Due to significant individual differences among melanoma patients, developing personalized treatment plans is particularly important for improving the efficacy of HDACi (histone deacetylase inhibitor) and overcoming drug resistance. To achieve this goal, researchers are actively using modern molecular biology techniques such as gene sequencing and proteomic analysis to conduct in-depth molecular typing of tumor tissues from patients. These technologies can reveal the genetic characteristics and protein expression patterns of tumor cells, providing important basis for accurately judging the patient's condition and predicting treatment response. Based on the results of molecular typing, doctors can tailor personalized treatment plans for patients, selecting the most suitable HDACi drugs and their combination therapy regimens to meet their treatment needs to the greatest extent possible. This personalized treatment strategy is not only expected to improve the efficacy of HDACi, but also to reduce unnecessary drug side effects, improve patients' quality of life, and bring more precise and effective treatment hope to melanoma patients.

## 6. Conclusion

HDACi (histone deacetylase inhibitor) has shown encouraging anti-tumor activity in the treatment of skin melanoma, however, the emergence of drug resistance severely limits its clinical potential and effectiveness. In order to fully leverage the therapeutic advantages of HDACi, it is particularly important to conduct in-depth research on its

resistance mechanism in treating melanoma. This not only helps us understand how melanoma cells evade the inhibitory effects of HDACi, but also provides a theoretical basis for developing more effective treatment strategies. To overcome drug resistance, researchers are actively exploring various approaches, including developing novel HDACi drugs to enhance drug specificity and reduce toxicity; Adopting a combination therapy strategy to enhance efficacy through synergistic effects with other anti-tumor drugs; Targeting the tumor microenvironment, inhibiting the growth and drug resistance of melanoma by regulating key components in the microenvironment; And develop personalized treatment plans, selecting the most suitable treatment strategy based on the patient's molecular typing results. In the future, we need to further strengthen basic and clinical research, deeply explore the mechanism of action and resistance of HDACi, and verify the safety and effectiveness of new drugs and combination therapy regimens. I believe that in the near future, these efforts will provide strong support for the widespread application of HDACi in the treatment of skin melanoma, bringing hope for cure to more patients.

## References

- [1] Wu Dan Construction and experimental validation of a prognostic model for skin melanoma related to lipid metabolism genes based on bioinformatics analysis [D]. Mentor: Zhu Xiaohai PLA Naval Medical University, two thousand and twenty-four.
- [2] Yang Wenchao Identification of tumor microenvironment related prognostic markers for metastatic cutaneous melanoma based on bioinformatics [D]. Mentor: Zhang Baolin; Qiu Lixia Shanxi Medical University, two thousand and twenty-three.
- [3] Luo Yining Prediction of prognosis and therapeutic efficacy of skin melanoma based on necrotic apoptosis related lncRNA [D]. Mentor: Zhang Jianglin Central South University, two thousand and twenty-three.
- [4] Pan Yinghao Study on the role of GRP78-GPX4 pathway in enhancing iron death tolerance and promoting migration of melanoma cells in the skin [D]. Mentor: He Yuanmin Southwest Medical University, two thousand and twenty-three.
- [5] Dragon triumphs over courage Comprehensive analysis of oncogene AURKA and targeted drug screening in skin melanoma based on bioinformatics and molecular docking technology [D]. Mentor: Zhang Xuanfen Lanzhou University, two thousand and twenty-three.
- [6] Zhang Man, Liu Aichun New progress of HDAC inhibitors in the treatment of hematological malignancies [J]. *Modern oncology*, 2022, 30 (14): 2654-2658.
- [7] Ping Shuai Construction and Validation of a Prognostic Model for Iron Death Genes in Skin Melanoma [D]. Mentor: Weizhuo Huazhong University of Science and Technology, two thousand and twenty-two.
- [8] Wang Xuliang The therapeutic effect and mechanism of HDACi in heart failure with preserved ejection fraction [D]. Mentor: Tang Yida Peking Union Medical College, two thousand and twenty-two.
- [9] Li Guanhu The inhibitory effect of HDACi valproic acid combined with ionizing radiation on the proliferation of breast cancer cells and its mechanism [D]. Supervisor: Wang Zhenqi Jilin University, two thousand and twenty-one.
- [10] Chen Xinrui Clinical study on targeted therapy of elderly relapsed refractory B-cell lymphoma with HDACi combined with CD20 monoclonal antibody [D]. Mentor: Wang Huaqing Tianjin Medical University, two thousand and twenty-one.

[11] Premi Sanjay, Qin Yong, Ahmad Nihal. Editorial: Mechanisms of resistance to the targeted therapy and immunotherapy in cutaneous melanoma [J]. *Frontiers in Oncology*, 2022, 12.

[12] Zhulikov Ya. A., Samoylenko I. V., Demidov L. V. Mechanisms of resistance to anti-Pd-1 therapy in metastatic cutaneous melanoma [J]. *Russian Journal of Biotherapy*, 2018, 17 (1).