

Mechanism and Application Strategy of Histone Modification in Targeted Therapy for Lung Cancer

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Abstract. Lung cancer is a global disease burden and severe malignant disease, which has been a major morbidity and mortality double burden. Current lung cancer treatment still suffers from severe problems, including drug resistance, high metastasis frequency, and tumor heterogeneity, and allows new therapeutic manner to be developed. Histone modification, which is the major epigenetic modification mechanism, has demonstrated great application potential of targeted therapy against lung cancer. This review systematically summarizes the central role of histone acetylation modification and methylation modification in the pathogenesis of lung cancer. Plus, it focuses on the mechanism of key enzymes such as HDAC and EZH2 to promote the malignant progression of tumors by gene expression as well as regulating chromatin structure. Research has established that inhibitors targeting these targets have yielded encouraging results in clinical studies, especially with the combination strategy of chemotherapy, targeted therapy and immunotherapy. However, challenges such as poor drug selectivity, epigenetic heterogeneity, and complex modification networks still need to be overcome. In the future, it is necessary to promote the clinical application of histone modification targeted interventions in the realm of precision treatment against lung cancer through interdisciplinary cooperation, combined with multi-omics analysis and new technical means.

Keywords: Histone Modification; Lung cancer; Targeted Therapy.

1. Introduction

As reported by the World Health Data Platform, lung cancer is the principal contributor to cancer death, causing an estimated 1.8 million lung cancer deaths in 2022, accounting for 18.7% of all global cancer deaths [1]. Pathologically, lung cancer is broadly classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC comprising approximately 85% of all cases. Surgery, radiation therapy and chemotherapy are still important cornerstones of lung cancer treatment, but the treatment landscape is gradually moving closer to the era of precision medicine. Currently, although small molecule inhibitors such as EGFR, ALK, and ROS1 have made significant progress in NSCLC treatment targeting specific driver genes, studies as of 2024 show that their clinical application still faces severe challenges of drug resistance, and even resistant EGFR mutations further drive lung cancer progression by stabilizing their self-activating conformation and promoting the formation of oncogenic oligomers [2]. Due to this therapeutic bottleneck, many scientists have drawn their attention to the research field of epigenetic regulation.

Epigenetic regulations reveal a new paradigm in elucidation of process of oncogenesis. It mainly consists of histone modification, DNA methylation, and silencing of non-coding RNA (ncRNA)-related genes, which together participate in the physiological process of fine regulation of gene expression to maintain normal cell function [3]. In normal cells, these mechanisms maintain homeostasis of gene expression. In cancer cells, they are often in an imbalance, driving the development of tumors. In other words, aberrant DNA methylation and histone modifications are hallmark features of epigenetic dysregulation in lung cancer [4]. At present, the function of DNA methylation in lung cancer has been substantially elucidated, as well as its inhibitors have also entered clinical practice [5]. In contrast, although a variety of histone modification inhibitors have entered the R&D and clinical stages, there is still a lot of content to be elucidated in the field of histone modification, and their specific mechanisms and combination treatment strategies still need to be systematically sorted out. This paper aims to discuss and analyze this, centering on histone

modifications in lung cancer, with a focus on the roles of methylation and acetylation. The application status, clinical challenges and future development directions of related inhibitors were discussed. It also provides a rationale for novel targeted therapy strategies against lung cancer.

2. The Main Types of Histone Modifications and Pathogenic Mechanisms in Lung Cancer

Histone modifications constitute the core epigenetic aspect of precise regulation of gene expression. Histones are a class of basic proteins in eukaryotic chromosomes that bind to DNA. Its primary function is to provide structural scaffolds for DNA, and positively charged histones are tightly bound to long negatively charged DNA strands, allowing the DNA strands to be highly compressed and contained within the nucleus [3]. This tight coiling state prevents the transcription machine from accessing the DNA, inhibiting gene transcription. The nucleosome, as the fundamental unit of chromatin, consists of a histone octamer core with approximately 146 base pairs of DNA wound around it. The N-terminal tail of histones rich in arginine and lysine protruding from the nucleosome core is the main source of alkaline histone and the key site for chemical modification, as well as the core of gene expression.

Chemical modifications of the histone N-terminal tail encompass a repertoire of chemical groups, comprising acetylation, methylation, phosphorylation, lactylation, ubiquitination, and other post-translational modifications (PTMs). Histone modification, is a reversible dynamic chemical modification pathway that can profoundly change the chromatin landscape and its dynamic accessibility, thereby finely regulating gene expression, being an epigenetic core mechanism [3]. Abnormal epigenetic histone modifications are strongly associated with the pathogenesis of cancer.

2.1. Acetylation modification

2.1.1. Mechanism of occurrence and key enzymes

Histone acetylation is currently the core and most studied epigenetic modification, which plays the role of "switch" in gene transcriptional regulation. The mechanism of histone acetyltransferases (HATs) is that acetyl-CoA is used as an acetyl-donor and mediates site-specific acetylation at a specific lysine site within the histone N-terminal tail [6]. Thereby, the positive charge of histones is neutralized, thereby weakening their interaction with negatively charged DNA, resulting in the relaxation of the tight chromatin structure, which transforms from heterochromatin a state of transcriptional repression to euchromatin with active transcription, allowing the transcription machinery to bind and activate gene expression [7,8].

The balance of histone acetylation is dynamically controlled by the antagonistic actions of HATs and histone deacetylases (HDACs). They orchestrate synergistically acetylation levels within the cell, which controls the correct expression of genes. HATs are responsible for catalyzing acetylation reactions, which activate gene transcription by catalyzing the transfer of acetyl groups from acetyl-CoA to histone tail lysines, neutralizing its positive charge and relaxing the chromatin structure [6,9]. Gcn5-related N-acetyltransferase (GNAT), MYST (MOZ, YBF2/SAS3, SAS2, TIP60), and E1A-binding protein p300 /CREB-binding protein (p300/CBP) are the three main families. By contrast, HDACs suppress gene transcription by removing acetyl groups and returning chromatin regularization [7,8].

2.1.2. Pathogenesis in lung cancer

Activation of proto-oncogenes and key signaling pathways: One important epigenetic process underlying oncogene expression during lung cancer was pointed to be Histone acetyltransferase p300/CBP. Recent researches revealed that this mechanism was fine regulated by long non-coding RNAs (lncRNAs) that is, specific lncRNAs like lncSmad7, which functions in a manner "molecular guidelines", It acted very specifically to direct p300/CBP to the regulatory site of target gene by forming the specific RNA-DNA triple structure [10]. This targeted recruitment leads to

hyperacetylation of local histone H3K27. This leads to a substantial increase in chromatin opening, which in turn, continuously activation of the transcript of important oncogenic an, particularly, Bcell Lymphoma 2 (BCL-2)1 and cellular Myelocytomatosis (c-Myc)2 and aids the cell proliferation and prolonged survival of lung cancer cells.

Inhibition of tumor suppressor genes: Blocked tumor suppressor gene transcription as the foundation of lung cancer development. Its mechanism involves various distinctive molecular pathways. The first is dual-control of H1.4K75 Acetylation. The Lysine acetylation at position 75 of ligation histone H1.4 plays an important role in the development of NSCLC. This epigenetic process drives tumor development by expressing Extracellular Signal-Regulated Kinase 1/2 (ERK1/2) pathway activation and inhibites p53 pathway process [11]. Secondly, class I histone deacetylases, especially HDAC1, drive tumorigenesis by removing histone acetylation markers and silencing key tumor suppressor genes such as p21 [8]. Finally, signal transduction and acetylation of transcriptional activator 3 (STAT3) are involved. Acetylation of STAT3 transcription factor at the K685 site is associated with the progression of various cancers. Acetylated STAT3 forms a complex with DNA methyltransferase 1 (DNMT1) to catalyze methylation of promoters such as p53, thereby achieving epigenetic silencing [6].

Promote epithelial-mesenchymal transition (EMT): By modulating the core process of EMT, the invasive metastasis of lung cancer is significantly enhanced. It involves multiple types of molecular pathways, such as p300/CBP-mediated histone acetylation, which activate key EMT-transcriptional regulators like Slug and ZEB1 [9]. At the same time, the acetylation of K631 site of STAT3 and its phosphorylation synergistically upregulated MMP9, ZEB1, and other invasion-related genes [6]. In contrast, HDACs are recruited to the promoter region of epithelial markers, including E-cadherin, and their induction is silenced by deacetylation [9]. This dynamic imbalance of acetylation and deacetylation jointly promotes the EMT process and promotes the invasive and metastatic capabilities of lung cancer cells.

Maintaining cancer stem cell properties: It is a key contributor to maintain self-renewal and differentiation of lung cancer stem cells arrest by regulating key signaling pathways and epigenetic status. Studies have shown that aldehyde dehydrogenase 1 family member A1 (ALDH1A1) high activity can screen lung cancer stem cell subsets with strong tumorigenicity and self-renewal ability, and their stem maintenance depends on the activity of the Notch signaling pathway [12]. From a mechanistic perspective, Oxidative stress-activated ataxia-telangiectasia mutated (ATM) kinase phosphorylates the E3 ubiquitin ligase TRIM21, thereby triggers the deacetylase SIRT1 degradation via the ubiquitin pathway. This degradation give rise to elevated histone H4 acetylation, ultimately activating the transcription of stemness-associated genes [13]. Although how acetylation and cancer stem cells function in lung cancer remains to be studied, this mechanism of dynamic balance regulation of chromatin state through acetylation/deacetyling provides a new perspective for understanding the stem maintenance of lung cancer stem cells.

Other: It can also facilitate the progression of lung cancer by regulating cellular stress response and immune microenvironment. H3K27 acetylation activates the expression of the copper chaperone for superoxide dismutase (CCS) gene, inhibits apoptosis and promotes protective autophagy by alleviating oxidative stress [14]. At the same time, CCS overexpression affects the tumor immune microenvironment (TIME), which is associated with regulatory T cell infiltration and helps tumor cells achieve immune escape. STAT3 acetylation was found to affect the tumor microenvironment (TME) through similar mechanisms in other cancers, implying a synergistic effect in lung cancer [6].

2.2. Methylation Modification

2.2.1. Mechanism of occurrence and key enzymes

Histone methylation is another core epigenetic mechanism that regulates gene expression, which occurs mainly on specific lysine (Lys, K) and arginine (Arg, R) residues at the histone terminus [15]. Unlike altered charge properties of acetylation, methylation is recognized by specific effector proteins by adding or removing methyl groups, which determine the configuration of chromatin (open or

closed) and ultimately affect the transcriptional activity of genes to modulate multiple biological processes, encompassing cell fate determination and genomic stability [3,15]. This process is highly dynamic and reversible, which is dictated by two antagonistic enzyme families—the "writers" histone methyltransferase (HMTs) and "erasers" histone demethylases (HDMs) [15].

Depending on the substrate residues in which they act, the enzymatic machinery regulating histone methylation comprises two antagonistic categories. The "write" enzymes that mediate histone lysine methylation and their corresponding "erasing" enzymes responsible for demethylation are histone lysine methyltransferases (KMTs) and histone lysine demethylases (KDMs), respectively. For histone arginine residues, the dynamic balance of their modifications is jointly regulated by protein arginine methyltransferase and histone arginine demethylase [4]. The current research focus is mainly on the methylation of lysine residues, which have become the main target of drug development because of its more diverse modifications, more defined functions, and more sufficient evidence of association with human diseases, especially cancer.

2.2.2. Pathogenic mechanism in lung cancer

Inhibition of tumor suppressor genes: In the enzyme family of histone methylation, the core protein EZH2 of the polycomb repressive complex 2 (PRC2) complex, as a representative of KMTs, catalyzes the production of H3K27me3 inhibitory markers to silence tumor suppressor genes, promoting lung cancer proliferation and metastasis [2]. The expression and function of EZH2 were differentially regulated by two key signaling pathways, the mitogen-activated protein kinase/ extracellular signal-regulated kinase signaling pathway (MEK/ERK) as well as the phosphatidylinositol 3-kinase/protein kinase B signaling pathway (PI3K/Akt). Phosphorylation of the downstream transcription factor Elk-1 in the MEK/ERK pathway activates EZH2 transcription [16]. Akt can indirectly promote its expression through direct phosphorylation of EZH2 or through E2F transcription factor 1 (E2F1) release [16]. This bidirectional regulation forms a positive feedback loop, which enhances EZH2-mediated epigenetic silencing, which in turn suppresses critical tumor suppressors including PTEN, thereby propelling lung tumorigenesis.

Activation of proto-oncogenes and key signaling pathways: Key oncogenic signaling pathways are activated in lung cancer through EZH2-mediated mechanisms. It not only inhibits gene expression by depositing H3K27me3, but also directly forms complexes with β -catenin to synergistically activate downstream oncogenes. This interaction can upregulate Fat Mass and Obesity-Associated (FTO) gene expression, which transcribes the proto-oncogene c-Myc and drives the abnormal proliferation of tumor cells. Meanwhile, EZH2 postally regulates Wntless-related integration site/ β -catenin signaling pathway (Wnt/ β -catenin) associated with Long Coding non-protein RNAs (NEAT1) binding, on which have been put as an important epigenetic pathway involved lung carcinogenesis [16].

Drive epithelial-mesenchymal transition and metastasis: Dynamically regulates EMT, thereby harnessing this process to promote lung cancer metastasis. The study found that EZH2 has dual functions in lung cancer. That is, in addition to promoting proliferation, EZH2 also maintains epithelial status by inhibiting the transcription of hundreds of mesenchymal genes. When EZH2 activity is inhibited, cancer cells tend to stay in the mesenchymal state, enhancing their ability to metastasize. In addition, histone methylation modifiers such as SETD8 and KDM2A have also been shown to affect lung cancer progression by regulating EMT-related pathways, which together constitute an important epigenetic regulatory network for lung cancer metastasis [4].

2.3. Other Modifications

In addition to acetylation and methylation modifications, there are many types of histone modifications. In this chapter, only two types of research have been introduced in recent years, namely lactylation and phosphorylation modifications. In the future, specific interventions targeting lactylation and phosphorylation modifications may become a new direction in lung cancer treatment.

Histone lactylate is a novel modification mechanism that directly links cellular metabolism to epigenetic regulation. This modification uses the glycolysis product lactate as a precursor and is

catalyzed by acetyltransferases such as p300 to introduce lactylation groups on histone lysine residues, which can be reversed by snortylases such as HDAC1-3 to form a dynamic and reversible regulatory system [17]. In lung cancer, histone lactylation drives tumor progression through multiple mechanisms. It has been found that lactylate modifications such as H3K18la activate gene expression programs related to cell migration and invasion by altering the spatial conformation of chromatin. Meanwhile, lactylation may also modulate the characteristics of the immune microenvironment and promote immune escape in tumors by regulating tumor immune cell function. Additionally, lactylation can preserve tumor cell proliferation dominance by regulating various crucial factors including Methyltransferase-like 3 (METTL3) [17].

Histone phosphorylation is an epigenetic modulation mechanism gradually researched in recent years, which phosphorylates histone residues (serine, threonine, tyrosine) as basic mechanism to regulate dynamically chromatin framework and transcription gene. The catalyst for this process is kinases and dephosphorylation mediated by phosphatases, forming a reversible regulatory cycle [18]. In lung cancer, histone phosphorylation drives tumor progression through a variety of mechanisms. It was found that the Serine 90 (Ser90) site phosphorylation of Serine Hydroxymethyltransferase 2 (SHMT2), a key enzyme for serine metabolism, enhanced its stability, promoted the synthesis of S-adenosylmethionine, and then increased the level of RNA N⁶-methyladenosine (m6A) modification, ultimately promoting the development of lung adenocarcinoma by stabilizing the oncoprotrogenic mRNA [19]. In addition, histone phosphorylation also fine-tunes key cellular activities, notably the DNA damage response and cell cycle progression, and its abnormal activation correlates with increased tumor proliferation and metastasis in lung cancer [3].

3. Application and Clinical Progress of Histone Modification Targeted Therapy Strategy for Lung Cancer

3.1. Histone Deacetylase Inhibitors (HDACi)

HDACi, defined as antitumor drugs targeting histone modifications, has shown significant potential in therapeutic strategies for lung cancer. Its mechanism of action is mainly by inhibiting HDAC enzyme activity, inducing histone hyperacetylation, which in turn activates tumor suppressor gene expression and promotes tumor cell cycle arrest and apoptosis [8,20].

Several HDACi have shown therapeutic potential throughout the lung cancer drug development pipeline, from preclinical models to clinical trials. Tragustatin activates both mitochondrial and death receptor pathways to induce apoptosis in lung cancer cells [20]. According to clinical trial (NCT01027676) data, vorinostat in combination with chemotherapy in advanced NSCLC can increase the objective response rate from 12% to 34% [20]. Belinostat was used in phase I clinical trials to treat treatment-naïve advanced NSCLC patients, with a confirmed objective response in 35%, coupled with a median duration of 5.7 months until disease progression [20]. Based on the well-documented tumor-promoting functions of HDACs in pulmonary oncology and accumulating clinical evidence, HDAC inhibitors have shown clear biological activity and certain clinical application potential in the field of lung oncologic care. Multiple clinical trials are actively evaluating this approach (NCT02638090, etc.), which are expected to broaden the spectrum of available treatments for individuals with lung cancer.

3.2. Histone Methylation Modification Inhibitors

EZH2, defined by its role as the catalytic core of the PRC2 complex, represents a prominent target in contemporary epigenetic drug discovery focusing on methylation modulation. In lung cancer, EZH2 drives tumorigenesis and development by catalyzing the abnormal silencing of various tumor suppressor genes by the H3K27me3 inhibitory marker [16,21].

The therapeutic targeting of EZH2 has witnessed remarkable progress in recent inhibitor development. Tazemetostat, as the first approved EZH2 inhibitor, achieved an overall response rate

of 69% in clinical trials (NCT01897571) in the clinical management of follicular lymphoma, particularly in its relapsed or refractory forms. However mono therapy has poor erosion in many solid tumors, but combination therapy incorporating targeted drugs reveal synergistic Antitumor effects in solid tumor [16]. Among them, Osimertib is a third-generation EGFR tyrosine kinase inhibitor which has similarly found affinity with EZH2 and interfering PRC2 complex instability provides novel paradigms about additional therapeutically mechanisms for patients with EGFR-mutated lung cancer [16]. While EZH2 inhibitors possess high efficacy in hematological tumor, their clinical development concerning solid malignancies-especially lung cancer-remains steadfast face obstacles.

Beyond EZH2 inhibitors, other histone demethylase inhibitors have also shown promising applications. LSD1 inhibitors have shown therapeutic potential in small cell lung cancer by modulating tumor stempage and immunogenicity. At present, drugs such as ORY-1001 have entered the clinical trial stage [22].

3.3. Combination Treatment Strategies

Although histone target inhibitors such as EZH2 and LSD1 have shown great potential in lung cancer treatment, the limitations of single-targeting strategies are increasingly apparent. The complexity and compensatory mechanisms of epigenetic networks often lead to limited or resistance to monotherapy, prompting researchers to turn their attention to combination treatment strategies. The combination therapy strategy provides a new direction for breaking through the current bottleneck of lung cancer treatment, marking a new stage in epigenetic targeted therapy from single-target intervention to systematic regulation.

3.3.1. Combination Chemotherapy

Accumulating evidence from the literature supports the combined use of HDAC inhibitors and chemotherapy drugs can produce significant synergistic effects. Preclinical studies have confirmed that HDACi can reverse paclitaxel resistance, and its mechanism is mechanistically linked to p53 upregulation and concurrent tubulin hyperacetylation [20]. Clinical studies further validate the potential of this strategy. A phase II trial showed that the regimen of vorinostat plus carboplatin and paclitaxel in advanced NSCLC significantly improved evidence-based response rates (34% vs 12%) compared with chemotherapy alone [20]. In addition to EZH2 inhibitors, other histone demethylase inhibitors also have found encouraging application in another phase I trial, bellistat in combination with chemotherapy obtained objective response rate of 35% in previously treated patients [20]. Throughout such related trials, epigenetic drugs combined with chemotherapy has created a viable option to overcome the current drug resistance crisis among Lung Cancer.

3.3.2. Combination Targeted Drugs

Combining epigenetic drugs and targeting drugs is a promising strategy against the drug resistance against Lung Cancer the research found that by HDAC inhibitors which play an important role in reversing EGFR-TKI resistance in lung cancer patients, For example, The next generation inhibitor MPT0E028 could induce significant apoptosis increase the effect of erlotinib in colorectal cancer (CRC)-epidemiologically well-documented including interstitial fluid, Histopathological examination of the tumor specimens, the histopathology of the specimens from the tumor specimens, and immunohistopathological examination of the specimens from tumor specimens" [3].Preclinical experiments have demonstrated that the combination of vorinostat with EGFR-TKIs can successfully reverses drug resistance, induction of apoptosis on tumor cells [3].The combination of two inhibitors: DNMT and HDAC is rich in human tumor tissues using nano-delivery system, showing special synergistic antitumor activity for dual-inhibitors [8].This strategy offered new ideas for combination therapy of lung cancer.

3.3.3. Combination Immunotherapy

A combined combination of epigenetic modulators with immune checkpoint inhibitors (ICI) herald new ways to improve immunotherapeutic activity against lung cancer. Recent studies have shown

that, through increased Major Histocompatibility Complex (MHC) class I molecules and Programmed Death-Ligand 1 (PD-L1) expression, their hepatocellular Nuclear Antigens (HDAC) expression in tumor cells, the HDAC inhibitors lead to enormously tumor immunogenicity [3]. There is evidence from pre-clinical studies, which showed that, entilastat synergized with Programmed Cell Death Protein 1 (PD-1) inhibitors can promote Cluster of Differentiation 8 Positive T Cell (CD8⁺ T) cell infiltration and improve the immune microenvironment [23]. Combining Iago studies not alone with clinical studies, can validate the potential of this combination or combination strategy as illustrated in case study of phase I/II trial also (NCT02638090), which showed the satisfactory tolerance of vorinostat plus pembrolizumab in patients with advanced NSCLC, and revealed the activity of this regime with this combinatorial treatment of vorinostat in advanced NSCLC with 83% disease control rate in previously untreated patients [23]. Moreover, Indoleamine 2,3-Dioxygenase 1 (IDO1)/HDAC1 is a dual-target inhibitor documented to possess synergistic antitumor activity in lung cancer Models [8]. The data outlined highlight new directions in circumventing the immunity to immunotherapy and shows indeed the regimens of epigenetic drugs when combined with immunotherapy will be in the forefront as standard paradigm in lung cancer therapies.

4. Clinical Challenges and Future Research Directions

However, despite the offer of specificity, mechanism to compensate resistance with the single drug inhibitors can limit their performance. Combination regimen can enhance therapeutic efficiency but with a burden of accompanying toxicity. These observations underline that epigenetic targeted therapies are still facing a number of clinical issues and need an immediate urgency to fulfill an effective and Safety, with carefully chosen drugs and best treatment regimens.

4.1. Complex Drug Resistance Mechanisms

Histone modification Abnormality Factor It is an important mechanism for drug resistance to treatment. Research has demonstrated that various types of histone modifying enzymes including EZH1A gene encodes EZH2 kinase (viz EZH2), KDM5A zinc finger domain histone kinase (viz KDM5A), KDM3A histone kinases (viz KDM3A), are overexpressed in drug-resistant cancer within lung cancer cells and promote its development of drug tolerance involving epigenetic regulation [21]. For instance, EZ1 h epigenetic deregulation could induce silence tumor suppressor gene (via the histone methyltransferase EZH1A), which could promote tumor cell's resistance to chemotherapy agents. KDM5 Members induce stem cell properties by regulating important signaling pathways to cause treatment failures [24]. Illuminating the mechanisms of drug resistance will pioneer a new generation of epigenetic drugs, and a key objective for future work is to develop combination therapies against specific resistance pathways and precision medicine protocols based on epigenetic signatures.

4.2. Poor Drug Selectivity and Off-target Toxicity

Currently, histone-modified targeted drugs usually have the problem of insufficient selectivity, resulting in serious non-targeted toxicity. HDAC inhibitors often cause hematologic toxicity such as thrombocytopenia and neutropenia in the treatment of lung cancer, which directly affects patient tolerability. Similarly, LSD1 inhibitors have shown unexpected systemic toxicity in preclinical studies [7]. This suggests that even epigenetic drugs with clear therapeutic potential can cause unforeseen toxic side effects due to side effects, posing serious challenges to their clinical translation. This suggests that efforts should be made in the future to develop highly selective inhibitors, such as allosteric inhibitors of epigenetic drugs or chimera technology aimed at protein degradation, to reduce exposure to normal tissues while maintaining efficacy. Meanwhile, using artificial intelligence approach to assist-drug development opens up new prospects for the development of more fine accuracy of epigenetic therapies.

4.3. Crosstalk and Complexity of Histone Modifications

The complexity of histone modification networks presents as a crucial challenge for targeted therapy of lung cancer. There is a considerable crosstalk among different modification types ((methylation, phosphorylation, ubiquitination, etc.) which constitute a regulation complex. The complex network displays an influential propagation in the role of all cancer occurrence and development process, affecting the progression of all malignant tumor's treatment response by the global gene expression interface modification. The complexity crosstalk exists in multi-layers interaction. That is, there is mutual antagonism between different histone modifications, such as H3K9me3 inhibiting H3K4 monomethylation. Modifications form bidirectional regulation with ncRNAs networks, such as long intergenic non-protein coding RNA 511 (LINC00511) altering the modification pattern of target genes through recruitment of EZH2 [5,21]. The extreme complexity of this epigenetic regulatory network makes traditional single-targeted therapy strategies face great challenges in clinical application. Therefore, these findings provide a rationale for developing network pharmacological strategies that can intervene in multiple key nodes at the same time, and establish a multi-omics integrated analysis platform based on artificial intelligence to systematically analyze the epigenetic network characteristics specific to lung cancer, providing a new theoretical foundation and methodological support for the development of more accurate and effective combination treatment plans.

4.4. Epigenetic Heterogeneity

Epigenetic heterogeneity poses an important challenge for targeted therapy for lung cancer. Within tumors, different cell subsets exhibit significantly different histone modification profiles, and this heterogeneity directly leads to unpredictability of treatment response [3]. Epigenetic drugs may only work upon the specific subsets and other subpopulations avoid treatment via various epigenetic states along with overall effect. More remarkably, this heterogenic trait is highly linked with the response to immunotherapy. Research has demonstrated that intra-tumoral heterogeneity is a possible potential biomarker for the intratumoral response to Intervention (ICI) [25]. Differences in epigenetic status further increase the complexity of treatment strategy development by affecting immune signatures in the tumor microenvironment. The research on the development of single-cell epigenetic analysis technology and establishment of patient stratification system based on epigenetic heterogeneity within treatment strategies are the next level for assessing future strategy for individualized treatment.

5. Conclusion

In this review, the fundamental function and potential clinical application of histone modification in the targeted therapy of lung cancer are comprehensively expounding; indeed, researches have shown that histone modifications, mostly histone acetylation and methylation, are crucial for the occurrence, development, and treatment of lung cancer via the all-Most Exact Control of Gene Expression Programs. Inhibitors of key epigenetic regulators like EZH2 and HDAC not only show the potential of monotherapy therapy, but more importantly, their combined strategies with chemotherapy, targeted therapy and immunotherapy have shown synergistic anti-tumor effects, representing a novel therapeutic strategy for lung cancer.

However, there are still many challenges in this field. Problems such as drug resistance mechanism, off-target toxicity, cross-crosstalk of complex modification networks, and differences in treatment response caused by epigenetic heterogeneity caused by insufficient drug selectivity seriously restrict clinical efficacy. These challenges suggest the limitations of single-targeting strategies, and there is an urgent need to develop more precise treatment models.

Future research should focus on the following directions: interpreting lung cancer-specific epigenetic maps through multi-omics integrated analysis; development of highly selective inhibitors and dual-target drugs; establish an accurate typing system based on epigenetic characteristics; Explore innovative technologies such as epigenetic editing. Interdisciplinary cooperation will become

the key to promoting the development of the field, requiring deep integration of chemistry, biology, clinical medicine and other fields to jointly promote the transformation of basic research results into clinical treatment, and ultimately achieve new breakthroughs for precision oncology in lung cancer.

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