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Targeting Epigenetics in Lung Cancer

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The epigenetic landscape, which in part includes DNA methylation, chromatin organization, histone modifications, and noncoding RNA regulation, greatly contributes to the heterogeneity that makes developing effective therapies for lung cancer challenging. This review will provide an overview of the epigenetic alterations that have been implicated in all aspects of cancer pathogenesis and progression as well as summarize clinical applications for targeting epigenetics in the treatment of lung cancer.

Cancers are marked by genetic, transcriptional, and phenotypic heterogeneity that affect cancer progression, metastasis, and drug resistance (Lawson et al. 2018; Hinohara and Polyak 2019). Epigenetic changes are responsible for the bulk of transcriptional heterogeneity that is not due to underlying mutations. Epigenetic alterations are more frequent than somatic mutations, but there is significant interplay between the two, as epigenetic silencing can lead to genetic mutations and conversely genetic mutations can alter epigenetic processes (Brzeziańska et al. 2013; Chatterjee et al. 2018). Lung cancer, in particular, is characterized by both well-defined genetic driver mutations as well as global and locus-specific epigenetic modifications. Dysregulation of the epigenome has been implicated in both smoking-related and smoking-unrelated malignant transformation and plays key roles in the acquisition of the hallmarks of cancer such as increased cell proliferation, resistance to apoptosis, angiogenesis, and metastasis (Lin et al. 2007; Sundar and Rahman 2016; Chatterjee et al. 2018; Duruisseaux and Esteller 2018). The Cancer Genome Atlas (TCGA), Human Epigenome Project, and the Human Epigenome Atlas are a few of the large-scale efforts that have annotated the epigenome and greatly contributed to our understanding of the epigenetic landscape in lung cancer.

Finding effective therapies in lung cancer has been difficult due to considerable intra- and intertumoral heterogeneity (Kris et al. 2014). The most common histologic subtypes of lung cancer, adenocarcinoma (ADC), lung squamous cell carcinoma (LUSC), and small-cell lung cancer (SCLC) are marked by distinct genotypes and phenotypes (Zito Marino et al. 2019). One explanation for this is that the subtypes arise from different lung stem or progenitor cells. The histologic subtypes demonstrate distinct somatic mutations; both classic oncogenic mutations and genes involved in epigenetic regulation have been shown to act as "drivers"

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(Campbell et al. 2016; Dong et al. 2017). One study of massively parallel sequencing identified 25 significantly mutated genes in lung ADC. Some of these genes could not be mapped against Hanahan and Weinberg's "hallmarks of cancer," so a new hallmark of "epigenetic or RNA deregulation" was proposed (Hanahan and Weinberg 2011; Imielinski et al. 2012). Compared with non-small-cell lung cancer (NSCLC), SCLC in particular harbors a unique pattern of DNA methylation compared to other lung cancers, which is enriched for genes involved in the differentiation of neuroendocrine cells (Kalari et al. 2013). Mutations in chromatin modifiers *CREBBP* and *EP300* as well as histone methyltransferases *MLL* and *MLL2* are frequent driver mutations present in SCLC patients (Peifer et al. 2012). One study demonstrated that there were epigenetically distinct subgroups within genetically homogeneous SCLC patients, providing further evidence for how epigenetic changes might contribute to intertumoral heterogeneity (Poirier et al. 2015).

Intratumoral heterogeneity attributed to genetic mutations can often be mapped along an evolutionary tree, but less is known about what specific epigenetic changes contribute to heterogeneity. One way in which epigenetic regulation can impact cellular heterogeneity within tumors is through lineage plasticity, or the reprogramming of cancer stem cells. During normal development, the epigenome is responsible for appropriate activation of genes that promote cellular differentiation while simultaneously repressing genes that induce "stemness," or the capacity for self-renewal, multipotency, and proliferation. One hypothesis is that epigenetic dysregulation alters this balance to favor stemness or tumor-initiating capacity in cancer (Easwaran et al. 2014; Zito Marino et al. 2019). Lineage plasticity is also especially relevant in the case of transformation of EGFR-driven ADC to SCLC, in which an epigenetic event may be the mechanism for the change in phenotype (Sequist et al. 2011). Similarly, in response to EGFR-TKI, a switch in phenotype known as epithelial-to-mesenchymal transition (EMT) has been observed, with preservation of the original driver mutation. The epigenome has been extensively studied as a key regulator of EMT in both normal development and in cancer (Easwaran et al. 2014).

Whereas the development of molecularly targeted therapy has transformed treatment for oncogene-driven lung ADC, even within oncogene-driven lung cancers there are genetically distinct subclones that exhibit phenotypic variation (Payne and Wagner 2019). Although targeting genetic drivers can engender brisk responses, alterations in the epigenome can account for heterogeneity in initial response to targeted therapy as well as secondary resistance. The Tracking Non-Small-Cell Lung Cancer Evolution through Therapy (TRACERx) study demonstrated that many of the classical targetable mutations (EGFR, MET, BRAF) were clonal, or early events in NSCLC, while mutations in genes involved in chromatin remodeling or histone methylation were subclonal, or occurred later during tumor progression (Jamal-Hanjani et al. 2017).

Given the diverse and far-reaching role of epigenetic regulation in lung cancer, targeting the epigenome is an attractive therapeutic strategy to overcome the inter- and intratumoral heterogeneity that has been challenging. Most epigenetic alterations are heritable but also reversible, so targeting the epigenome is theoretically less toxic than cytotoxic chemotherapy. Furthermore, reversing key epigenetic alterations within cancer stem cells can affect lineage plasticity by "reprogramming" cancer stem or progenitor cells to a more differentiated/normal phenotype (Ahuja et al. 2016). Various epigenetic alterations have been implicated as resistance mechanisms to targeted therapies as well as to chemotherapy and radiation. Ultimately, targeting the complex and highly orchestrated epigenetic network that provides transcriptional and posttranscriptional regulation of gene expression in cancer cells and the tumor microenvironment has great potential to produce antitumor effects via multiple pathways. In this review, we will discuss key epigenetic mechanisms including DNA methylation, histone modifications, chromatin remodeling, and posttranscriptional modification of RNA by noncoding RNAs that have been implicated in lung cancer and discuss any therapeutic applications (Table 1).

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Table 1. Summary of mechanisms of epigenetic regulation and examples of key targets within each class

Class of epigenetic regulators	Example of key targets
DNA methyltransferases	DNMT1, DNMT3, DNMT3a, DNMT3b
Histone lysine methyltransferases (KMTs)	EZH1/2, SETD2, SMYD3
Histone lysine demethylases (KDMs)	LSD1, KDM2, KDM3A
Histone arginine methyltransferases	PRMT1, PRMT4, PRMT6
Histone arginine demethylases	JMJD6
Histone acetyltransferases (HATs)	CREBBP/EP300, CBP, CAT6B
Histone deacetylases (HDACs)	HDAC1, HDAC3, HDAC6, HDAC7
Histone readers	BRD2/3/4, YEATS2
MicroRNA (miRNA)	Let-7, miR-200
Long noncoding RNA (lncRNA)	MALAT1, HOTAIR
Circular RNA (circRNA)	CDR1as, circ-FOXO3
Small nucleolar RNA (snoRNA)	SNORA42. SNORA78

DNA METHYLATION

DNA methylation occurs at the cytosine of CpG sequences, which are often unevenly distributed within the genome and concentrated in promoter regions called "CpG islands" (Ahuja et al. 2016). There are three DNA methyltransferases (DNMTs) that are responsible for DNA methylation. DNMT1 is the most abundant DNMT and maintains existing methylation, while DNMT3A and -3B establish de novo methylation. DNMT1 expression is high in smoking-related lung cancer and is directly involved in the silencing of tumor suppressors during lung cancer pathogenesis (Belinsky et al. 1996; Belinsky 2004). Knockdown of DNMT1 decreases growth of lung cancer cells in vitro and in vivo (Lai et al. 2017). DNMT3b overexpression accelerates carcinogen-induced transformation and is associated with poor prognosis (Rhee et al. 2002; Teneng et al. 2015). Conversely, DNMT3a overexpression correlates with a more favorable prognosis, and deletion in a Kras-mutant mouse model promotes tumor growth and progression (Gao et al. 2011; Husni et al. 2016).

Genomic DNA is normally heavily methylated, but in lung cancer there is widespread aberrant DNA methylation, both hypo- and hypermethylation. Dysregulated expression of various master epigenetic regulators leads to alterations in global DNA methylation patterns (Yang et al. 2015). Global DNA hypomethylation leads to activation of oncogenes, microsatellite instability, or loss of imprinting (Brzeziańska et al. 2013). Conversely, hypermethylation of normally unmethylated CpG islands results in silencing of tumor suppressor genes and is an early event of lung carcinogenesis (Belinsky et al. 1998; Belinsky 2004). In LUSC, high-resolution mapping showed aberrant DNA methylation patterns in lung tumors when compared to matched normal lung tissue. Lung tumors demonstrated extensive DNA hypomethylation but also gene-specific hypermethylation in most of the LUSC tumors evaluated (Rauch et al. 2008; Pfeifer and Rauch 2009). Furthermore, several reports have found that malignant transformation and cancer progression occur when genes involved in cell differentiation, EMT, and cell-cycle regulation (e.g., *CDKN2A/p16*, *APC*, *MGMT*, *RASSF1A*, *FHIT*, and *TSCL1*) are aberrantly methylated (Belinsky et al. 1998; Langevin et al. 2015).

Hypothetical advantages to epigenetic therapies that target DNMTs include less cytotoxicity from more selective targeting of cancer cells that exhibit aberrant epigenetic alterations compared to normal cells. The most well-studied DNMT inhibitors (DNMTi) are azacitidine and decitabine, but both have been ineffective as monotherapy in NSCLC (Liu et al. 2013; Duruisseaux and Esteller 2018). One explanation for earlier clinical trial disappointment is that doses were too high; use of DNMTi may require titration to a dose that is able to induce DNA demethylation but is not cytotoxic to healthy

cells. When used in combination with chemotherapy, demethylating agents are thought to prime cancer cells by reactivating tumor suppressor genes or DNA repair pathways. Azacitidine plus cisplatin or gemcitabine resulted in synergistic anticancer activity on colony formation and on-target effect of DNA hypomethylation of tumor suppressor genes (Füller et al. 2015). Treatment with azacitidine and trichostatin A reversed cisplatin resistance and restored candidate gene expression (Chang et al. 2010; Ibanez de Caceres et al. 2010; Zhang et al. 2014b). NCT01209520 was a pilot study that enrolled patients with hypermethylation in a selected set of genes (DAPK, RASSF1A, p16INKa, GATA-4, APC) to see whether combination cytotoxic chemotherapy combined with azacitidine improved response to adjuvant therapy; however, this study was closed due to poor accrual. In addition to chemoresistance, use of DNMTi resensitizes cancer cells after development of resistance to EGFR-TKIs. EGFR promoter methylation is one potential acquired resistance mechanism to gefitinib, and combination treatment with azacitidine and gefitinib resulted in growth inhibition and apoptosis of cancer cells (Li et al. 2013). DNMTi in combination with immune checkpoint inhibition (ICI) is also being explored since low dose of azacitidine results in up-regulation of immunomodulatory pathway genes including PD-L1, and the degree of induction correlated with loss of methylation (Wrangle et al. 2013; Li et al. 2014). Clinical trials investigating DNMTi and ICI are underway, which include combinations of azacitidine with durvalumab (NCT02250326) and decitabine with nivolumab (NCT02664181) (Table 2).

CHROMATIN REMODELING

There are multiple layers of epigenetic regulation, with methylation at the DNA level subsequently affecting histone modifications, nucleosome organization, and chromatin conformation (Gilbert et al. 2007). Methylated DNA leads to the tight winding of genomic DNA around histone proteins H2A, H2B, H3, and H4, forming a nucleosome, while unmethylated DNA has a more open conformation. Chromatin remodeling or conformational changes dictate either transcriptional activation or repression. Chromatin remodeling complexes are responsible for the packing and unpacking of DNA into chromatin. Components of the SWI/SNF chromatin remodeling complex are often mutated in both NSCLC and SCLC (Wilson and Roberts 2011; Biegel et al. 2014; The Cancer Genome Atlas Research Network 2014). Chromatin regulators SMARCA4/BRG1 and ARID1A are among the most commonly mutated genes in lung ADC and play a role in lung carcinogenesis (Orvis et al. 2014; Walter

Table 2. Ongoing clinical trials targeting epigenetic regulators in non-small-cell lung cancer (NSCLC) (as of March 11, 2020)

NCT number	Drug(s)	Epigenetic target
NCT01928576	azacitidine + entinostat + nivolumab	DNMT, HDAC
NCT03233724	decitabine + tetrahydrouridine + pembrolizumab	DNMT, HDAC
NCT03220477	guadecitabine + mocetinostat + pembro	DNMT, HDAC
NCT02664181	nivolumab + decitabine + tetrahydrouridine	DNMT
NCT02250326	nab-paclitaxel + azacitidine	DNMT
NCT02546986	azacitidine + pembrolizumab	DNMT
NCT02959437	azacitidine + pembrolizumab + epacadostat	DNMT
NCT02635061	ACY-241 + nivolumab	HDAC6
NCT02805660	mocetinostat + durvalumab	HDAC
NCT02437136	entinostat + pembro	HDAC
NCT02638090	pembrolizumab + vorinostat	HDAC
NCT02954991	mocetinostat + nivolumab	HDAC
NCT03590054	abexinostat + pembrolizumab	HDAC
NCT02718066	HBI-8000 + nivolumab	HDAC

et al. 2017). Loss of BRG1/SMARCA4 results in widespread changes in nucleosome positioning and chromatin reorganization leading to decreased expression of downstream tumor-suppressor genes (Orvis et al. 2014). SMARCA4 is generally a tumor suppressor, but in certain contexts acts as an oncogene. Patients with NSCLC who have concurrent mutations in SMARCA4 and SMARCA2, another chromatin remodeler, have worse prognosis because of a disease that is generally resistant to chemotherapy (Reisman et al. 2003; Romero et al. 2014). Recent preclinical studies have demonstrated that SMARCA4-deficient cancers may have unique sensitivities to the targeting of other pathways. Targeting of BRD4 and HER3 with bromodomain and extra-terminal motif protein (BET) inhibitors decreased proliferation of SMARCA4-deficient NSCLC cells. Similarly, SMARCA4 loss in NSCLC cells also leads to cyclin D1 deficiency and subsequent sensitivity to CDK4/6 inhibitors (Shorstova et al. 2019; Xue et al. 2019).

HISTONE MODIFICATIONS—METHYLATION

Posttranslational modifications of histones add additional levels of gene expression regulation beyond chromatin conformation. Whether a particular histone modification is repressive or activating depends on the chemical group and its position within the histone (Schiffmann et al. 2016). Histone modifications are modulated by "writer" and "eraser" enzymes, which add or remove modifications, respectively. Methylation of histones is an important modification that is mediated by methyltransferases and demethylases. In lung cancer, globally elevated H3 and H4 methylation and increased expression of histone methyltransferases are associated with poor prognosis (Song et al. 2012). Histone lysine methyltransferases (KMTs) play key roles in many cellular processes such as DNA replication, DNA damage response, cell-cycle progression, and transcriptional regulation, and are commonly dysregulated in cancer. The outcomes of aberrant histone modifications are context-dependent, cell-type dependent, affected by coexisting mutations, and lead to both gene activation and repression. One of the most well-studied KMTs is EZH2, which is overexpressed in NSCLC and even more so in SCLC (Coe et al. 2013). Histone methylation by EZH2, the enzymatic component of the polycomb repressive complex 2 (PRC2), is the mechanism by which PRC2 represses transcription. Increased EZH2 expression correlates with resistance to chemotherapy and poor survival and is sufficient for malignant transformation to lung ADC (Xu et al. 2014; Zhang et al. 2016). Overexpression of EZH2 promotes lung cancer progression through a myriad of signaling pathways, including VEGF-A, AKT, E2F/Rb, and TGF-β (Coe et al. 2013; Riquelme et al. 2014; Xu et al. 2014; Geng et al. 2015; Murai et al. 2015; Serresi et al. 2016). Conversely, loss of the KMT, SETD2, results in accelerated progression of early- and late-stage tumors in a Kras G12D mouse model of lung ADC (Walter et al. 2017). KMTs also regulate tumorigenesis via lysine methylation of non-histone proteins. One example is SMYD3, which is up-regulated in Ras-driven cancers and potentiates activation of Ras/Raf/MEK/ERK signaling by methylation of MAP3K2 (Mazur et al. 2014).

Histone lysine demethylases (KDMs) have been implicated in lung cancer pathogenesis and frequently participate in cross-epigenetic regulation. LSD1 is the most well-studied KDM and often overexpressed in NSCLC. Overexpression of LSD1 promotes proliferation and invasion of lung cancer cells (Lv et al. 2012). Expression of KDM2, another demethylase, is increased in NSCLC cell lines and patient tumor samples compared to normal adjacent lung. Moreover, histone demethylation by KDM2 specifically occurs at the promoter region of genes that promote lung tumorigenesis and are involved in the epigenetic regulation of other histone modifiers (Wagner et al. 2013; Dhar et al. 2014). KDM3A demethylates the HOXA1 promoter, which leads to downstream activation of cell-cycle regulator CCND1. KDM3A acts in a feedback loop with other epigenetic regulators like EZH2 and miRNA let-7c (Cho et al. 2012; Zhan et al. 2016). Histone methylation also occurs at arginine residues. PRMT1, PRMT4, and PRMT6 are all arginine methyltransferases that

are increased in lung cancer tissues. Inhibition of these proteins suppresses tumor growth (Yoshimatsu et al. 2011; Elakoum et al. 2014). Similarly, histone arginine demethylase JMJD6 is increased in lung ADC and correlates with tumor size, pleural invasion, and poor survival. In lung cancer xenograft models, targeting JMJD6 upstream leads to decreased tumor growth and migration (Zhang et al. 2013, 2017).

Drugs targeting histone methyltransferase EZH2 and histone demethylase LSD1 have shown promise in preclinical models (Jambhekar et al. 2017; Chen et al. 2018). Deazaneplanocin A (DZNep) was the first EZH2 inhibitor identified and inhibited growth of NSCLC cell lines in vitro, but the clinical potential was limited due to short half-life and poor specificity (Kikuchi et al. 2012). GSK126 is another EZH2 inhibitor that blocks migration and angiogenesis in vitro and in vivo (Chen et al. 2016b). In mouse models, the EZH2 inhibitor JQEZ5 induced tumor regression (Zhang et al. 2016). Moreover, cancer cells become selectively more sensitive to TopoII inhibitors like doxorubicin following EZH2 pharmacologic inhibition (Fillmore et al. 2015). LSD1 blockade by GSK2879552 leads to both growth inhibition and an increase in global gene expression in SCLC cells (Mohammad et al. 2015). This compound was tested in a phase 1 clinical trial (NCT02034123) for relapsed/refractory SCLC but terminated early due to lack of efficacy. RG6016 is another histone demethylase inhibitor that suppresses xenograft growth of SCLC, and a phase I clinical trial for SCLC patients has been completed and results are pending (NCT02913443). The combination of EZH1/2 inhibitor DS-3201b (valemetostat) and irinotecan is currently under study for recurrent SCLC (NCT03879798) (Table 3).

Table 3. Ongoing clinical trials targeting epigenetic regulators in small-cell lung cancer (SCLC) (as of March 11, 2020)

NCT number	Drug(s)	Epigenetic target
NCT03879798	DS-3201b (valemetostat) + irinotecan	EZH1/2 inhibitor
NCT03913455	guadecitabine + carboplatin	DNMT
NCT03460977	PF-06821497	EZH2
NCT03297424	PLX2853	BRD4

HISTONE MODIFICATIONS—ACETYLATION

In general, histone acetyltransferases (HATs) are "writers" that add acetyl groups to lysines of histone tails. This leads to open conformation of chromatin and therefore active transcription by making DNA accessible to transcription factors. In SCLC, mutations in the CREBBP/EP300 family of HATs are commonly observed, although exactly how they contribute to tumorigenesis is poorly understood (Kim et al. 2018). Regulation of EMT is one possible mechanism, as silencing P300 leads to repression of Snail and induction of E-cadherin expression in lung ADC cells (Chang et al. 2017). Mutations in CBP, which is structurally and functionally similar to EP300, were detected in 10% of lung cancer cell lines and five of 95 surgical specimens of lung cancer patients (Kishimoto et al. 2005). KAT6B is another HAT that is mutated in a subset of SCLC cell lines and patients. Knockdown of KAT6B in nonmutated SCLC cells enhances tumorigenesis in vitro and in vivo (Simó-Riudalbas et al. 2015).

Conversely, histone deacetylases (HDACs) are "erasers" that remove acetyl marks from histones. Acetylation/deacetylation by these enzymes also occurs on nonhistone proteins, in which case the acetyl groups function as docking sites for the assembly of protein complexes at promoters. HDACs are commonly overexpressed in NSCLC and various members of the HDAC family have been implicated in malignant transformation, metastasis, and all hallmarks of cancer (Osada et al. 2004; Adeegbe et al. 2017). Whereas there is little evidence regarding specific roles for individual HDACs, HDAC7 knockdown results in increased acetylation of Stat3 and inhibits tumorigenesis in Kras mutant lung cancer (Lei et al. 2017). In general, HDACs facilitate transcriptional repression of cell-cycle-related genes, but are also involved in the gene regulation of apoptosis,

DNA-damage response, EMT, and angiogenesis (Li and Seto 2016).

HDAC inhibitors (HDACi) potentially exert direct gene effects by preventing gene repression that consequently induces apoptosis and autophagy in cancer cells, up-regulates tumor suppressor genes, and inhibits expression of prosurvival genes. HDACi can also have indirect effects on cancer cells by enhancing antitumor immune responses and preventing angiogenesis (Damaskos et al. 2018). HDACi vary in their specificity from pan-HDAC to more class-targeted. In general, there are few selective HDACi and few reported clinical responses to single-agent HDACi. Moreover, nonselective HDACi used in early clinical trials were poorly tolerated. A phase 1 clinical trial of entinostat, a HDAC-1 and -3 inhibitor, was completed in patients with NSCLC and other advanced solid tumors (NCT00020579) and found to have intolerable dose-limiting toxicity (Ruiz et al. 2015).

Given the limited success with HDACi monotherapy, various combinations are under exploration. Addition of HDACi may be one way to overcome resistance to EGFR-TKI. Using EGFR-mutated NSCLC cell lines, inhibition of HDAC3 by vorinostat increased sensitivity to osimertinib in vitro and in vivo (Tanimoto et al. 2017). However, a phase 2 trial that evaluated erlotinib and entinostat failed to show any difference in progression-free survival compared to erlotinib alone (Witta et al. 2012). Combination with chemotherapy has also been explored, with the goal of inducing DNA damage or apoptosis and using HDACi to overcome resistance. One study showed that resistance to cisplatin was diminished by adding panobinostat to destabilize HIF-1α (Fischer et al. 2015). Other studies have shown that HDACi may be synergistic when used with taxanes or pemetrexed to restore tumor suppressor gene expression and inhibit tumor growth (Zuco et al. 2011; Del Bufalo et al. 2014).

Dual epigenetic therapy with DNMTi and HDACi has potential to improve on the poor results of single-agent epigenetic therapy. DNMTi SGI-110 is converted to decitabine and when used in combination with HDACi entinostat induced widespread demethylation and decreased lung tumor growth in preclinical models (Tellez et al. 2014). The combination of entinostat and low-dose azacitidine has shown some efficacy demonstrated in a phase 1/2 clinical trial (NCT00387465) that resulted in objective and durable responses in refractory NSCLC patients, with on-target effects assessed by demethylation of four epigenetically silenced genes (*APC*, *CDH13*, *RASS1a*, and *CDKN2a*) (Cameron et al. 1999; Juergens et al. 2011). Notably, Juergens et al. observed that following double-combination epigenetic therapy, several patients had durable responses to their next immediate line of therapy. This evidence suggests that sequential therapy (priming with DNMTi followed by HDACi) instead of concurrent dual epigenetic therapy may be best to synergize and potentiate the antitumor response (Topper et al. 2017).

Not only is combination epigenetic therapy more effective than monotherapy, but also could have enhanced potential for modulating epigenetic regulation responsible for immune evasion. The combination of DNMTi azacitidine and HDACi givinostat induced expression of genes in the IFNa/b pathway (Topper et al. 2017). A similar combination induced expression of cancer antigens, facilitated recognition of tumors through increased immune surveillance, altered the tumor microenvironment by altering the transcriptome of tumor-associated macrophages, and increased the number of $CD8^+$ tumor-infiltrating lymphocytes. This work and others are the basis for the testing of dual epigenetic therapy in combination with ICI (Adeegbe et al. 2017). Combinations of HDACi, DNMTi, and ICI that are currently being tested include guadecitabine, mocetinostat, pembrolizumab (NCT03220477) and entinostat, azacitidine, nivolumab (NCT01928576) (Table 2).

HISTONE MODIFICATIONS—READERS

Histone modifications are subsequently interpreted by "readers." Bromodomains are the best-characterized acetyl-lysine readers, and many are aberrantly expressed in cancer (Jenuwein and Allis 2001; Jain and Barton 2017). For example, the BET protein family contains not

only a bromodomain but also an extraterminal domain that has effector functions in transcriptional activation and chromatin remodeling (Xu and Vakoc 2017). BRD4 is a member of the BET protein family that is up-regulated in patient samples and increases migration and invasion when knocked down in NSCLC cells (Liao et al. 2016). Inhibition of BRD4 results in selective blockade of MYC in multiple myeloma, and this strategy may have therapeutic potential to target MYC-driven lung cancer as well (Lovén et al. 2013). YEATS domain–containing proteins are histone readers that recognize acetylation. YEATS2 is commonly amplified in NSCLC and acts to stabilize the HAT complex. Repression of YEATS2 leads to decreased cancer growth and transformation and alters transcriptional regulation of a large number of genes important for cell growth and survival (Mi et al. 2017).

BET proteins frequently activate the expression of genes associated with enhancers, which are promising therapeutic targets as they can be pharmacologically inhibited, are context and tissue specific, and exhibit specific activation in cancer cells compared to normal tissues (Hamdan and Johnsen 2019). BET inhibitors therefore act through super-enhancer "reprogramming." JQ1 is a bromodomain inhibitor that has shown preclinical activity in both SCLC and NSCLC cell lines (Shimamura et al. 2013; Kato et al. 2016). Treatment with JQ1 enhances radiosensitivity through the up-regulation of p21 (Wang et al. 2017b). JQ1 in combination with other epigenetic or immune therapies have also been tested. JQ1 with the HDACi SAHA suppresses tumor growth through MYC repression and immune modulation in a mouse model of lung ADC (Mazur et al. 2015). Combined with PD-1 blockade, JQ1 leads to synergistic antitumor response through suppression of Tregs and activation of tumor-associated T cells (Adeegbe et al. 2018). Although sensitivity to BET inhibitors seems to correlate with MYC amplification, SCLC cells appear sensitive to BET inhibition with JQ1 via a MYC-independent mechanism (Kaur et al. 2016; Wang et al. 2017a). Expression of ASCL1, a transcription factor essential for the development of lung neuroendocrine cells, correlates with growth inhibition by JQ1 in SCLC, suggesting that reprogramming to a more differentiated state results from BET inhibition (Lenhart et al. 2015). HDAC6 was identified in a synthetic lethal screen of JQ1 and a short hairpin RNA (shRNA) library against 550 epigenetic genes in SCLC xenograft models. Use of an HDAC6 inhibitor in combination with JQ1 resulted in significant tumor growth inhibition (Liu et al. 2018). The selective HDAC6 inhibitor, ricolinostat, induces T-cell activation and improves function of antigen-presenting cells. When combined with JQ1, ricolinostat suppresses Tregs and leads to immune-mediated tumor growth arrest (Adeegbe et al. 2017). Birabresib (OTX015/MK-8628) selectively blocks BET proteins BRD2/3/4 and has antitumor activity against both NSCLC and SCLC cell lines independent of oncogenic driver mutation status (Riveiro et al. 2016). A recent phase 1b trial of this compound was completed with tolerable toxicity profile and some clinical activity, as seven of nine patients with NSCLC exhibited stable disease (Lewin et al. 2018).

MicroRNAs

Although they comprise the majority of transcripts, noncoding RNAs (ncRNAs) were long thought to be of little importance. There is now a wealth of evidence that ncRNAs have diverse roles and are intimately involved in complex signaling networks that regulate many cancer-relevant cellular processes. MicroRNAs (miRNAs) are a class of small ncRNAs for which both tumor suppressor and oncogenic roles have been identified in lung cancer. miRNAs participate in all steps of malignant transformation and the metastatic cascade, from cell survival, angiogenesis, migration, and invasion (Zhang et al. 2014a; Del Vescovo and Denti 2015). Let-7 is one of the earliest described miRNAs that correlates with poor prognosis in patients, and targets key oncogenic drivers like KRAS (Takamizawa et al. 2004; Johnson et al. 2005; Osada and Takahashi 2011). miR-16, frequently down-regulated in NSCLC patient samples and cell lines, inhibits tumorigenesis and prolifera-

tion through gene repression of hepatoma-derived growth factor (HDGF) when ectopically expressed (Ke et al. 2013). Similarly, miR-146a expression suppresses cell growth and migration and induces apoptosis in NSCLC cells (Chen et al. 2013). Examples of oncogenic miRNAs include miR-221/miR-222, miR-155, and miR-21, which promote tumorigenesis by multiple mechanisms, such as by targeting tumor suppressors PTEN and p53, repressing negative regulators of Ras, inducing resistance to apoptosis through TRAIL, activating migration through AKT, and preventing expression of tissue inhibitors of metalloproteinases (Garofalo et al. 2009; Hatley et al. 2010; Van Roosbroeck et al. 2017). TP53, one of the most commonly mutated genes in lung cancer, directly regulates the expression of many miRNAs (He et al. 2007). In a lung ADC model driven by mutant Kras and p53, suppression of miR-200 was found to be necessary for invasion, migration, and metastasis (Gibbons et al. 2009; Kundu et al. 2016). In this model, ZEB1-mediated repression of miR-200 leads to derepression of PD-L1, increased immunosuppression, and metastasis (Chen et al. 2014). Low expression of miR-200 family members was subsequently found to correlate with worse survival and increased tumor angiogenesis in lung ADCs (Pecot et al. 2013; Chen et al. 2014; Kundu et al. 2016). Notably, miRNAs both repress epigenetic regulators and are epigenetically regulated. For example, expression of miRNAs is controlled by CpG methylation, leading to repression of tumor-suppressive miRNAs (Lopez-Serra and Esteller 2012). Histone modifications also affect miRNA expression, as treatment with HDACi leads to restored miR-373 expression and reversed an EMT phenotype (Seol et al. 2014). Another example includes the miR-29 family, which is down-regulated in lung cancer and results in increased expression of target genes DNMT3A and DNMT3B, both of which silence a host of tumor suppressors (Fabbri et al. 2007).

Furthermore, miRNAs are involved in chemo- and radioresistance. Cancer cells that are resistant to cisplatin express a unique miRNA signature compared to sensitive cells (Galluzzi et al. 2010). In one study, treatment with anti-miR-155 in combination with chemotherapy reversed chemoresistance in an orthotopic lung cancer model (Van Roosbroeck et al. 2017). miRNAs mediate chemoresistance via various mechanisms, such as targeting drug transporters or apoptosis regulators like Bcl-2 or TRAIL (Garofalo et al. 2008; Qiu et al. 2013; Dong et al. 2014). Similarly, NSCLC cells that are radioresistant differentially express miRNAs compared to radiosensitive cells and this set of miRNAs is up-regulated under hypoxic conditions (Grosso et al. 2013).

LONG NONCODING RNAs

Long noncoding RNAs (lncRNAs) are ncRNAs of >200 bp in size and can be epigenetically regulated by DNA methylation and histone marks (Xie et al. 2016). Although many functions of lncRNAs have yet to be discovered, they participate in gene regulation by a variety of mechanisms, including serving as a molecular scaffold to recruit chromatin-remodeling complexes, controlling the cellular localization of transcription factors, acting as enhancers, affecting post-transcriptional processing of messenger RNAs (mRNAs), and modifying histone codes (Tsai et al. 2010; Huang et al. 2012; Forrest and Khalil 2017). Adding to the complexity of epigenetic regulation, lncRNAs act as miRNA sponges, thereby leading to derepression of miRNA target genes. LncRNAs control many important signaling pathways involved in DNA repair, cell cycle, and apoptosis (Herrera-Solorio et al. 2017). LncRNA expression is both cell-type specific and may be temporally expressed. Over 1000 lncRNAs were found to be differentially expressed in S-phase in various cancers, and a subset of these exhibited differential methylation. Silencing of eight of these "S-phase lncRNAs" that demonstrated the highest frequency of differential expression across TCGA data sets resulted in apoptosis and decreased tumor growth in a lung cancer xenograft model (Ali et al. 2018).

LncRNAs are also important for lung cancer pathogenesis. MALAT1, a predictive biomarker for metastasis associated with worse prognosis, induces expression of metastasis-

associated genes, and promotes migration and cell growth (Zhu et al. 2015). HOTAIR silences transcription of the HOXD locus by altering chromatin configuration to a repressed state by recruiting PRC2. Overexpression of HOTAIR alters histone methylation and increases invasion. Similarly, increased expression of lncRNA H19 correlates with poor lung cancer prognosis, higher metastasis index, and poor response to chemotherapy (Kondo et al. 1995; Wang et al. 2017c). LncRNAs have also been implicated in mechanisms of chemoresistance. HOTAIR is overexpressed in platinum-resistant NSCLC and SCLC cells and silencing of HOTAIR resensitizes cells to platinum treatment (Liu et al. 2016). CCAT1 is another oncogenic lncRNA that acts as a sponge to miRNAs let-7 and miR-130a-3p, increasing chemoresistance to docetaxel and cisplatin (Chen et al. 2016a; Hu et al. 2017). Genomic profiling demonstrated that differential expression of lncRNAs may be one mechanism of resistance to EGFR-TKIs (Cheng et al. 2015b). In one such study, patients with resistance to gefitinib overexpress lncRNA UCA1, which acts downstream of the mTOR pathway (Cheng et al. 2015a).

CIRCULAR RNAs

First discovered in RNA viruses, circular RNAs (circRNAs) are ncRNAs with closed loop structures and no 5′ caps or 3′ poly(A) tails (Sanger et al. 1976). In lung cancer, circRNAs are dysregulated in tumors compared to normal lung tissue (Zhao et al. 2017; Ding et al. 2018; Jiang et al. 2018; Xu et al. 2018). CircRNAs have wide-ranging roles in epigenetic gene regulation (Hansen et al. 2013a; Zheng et al. 2016; Hu et al. 2018). Some circRNAs promote tumor progression by serving as miRNA sponges, allowing for the downstream expression of target genes involved in promoting proliferation, migration, and invasion that would otherwise be repressed by the miRNA (Wan et al. 2016; Luo et al. 2017; Li et al. 2018; Chen et al. 2019). The most well-characterized example of a circRNA–miRNA axis is CDR1as-miR-7. CDR1as, also known as ciRS-7, acts as a sponge to miR-7 to up-regulate key downstream target genes like EGFR, mTOR, CCNE1, and PIK3CD (Hansen et al. 2013b; Su et al. 2018; Zhang et al. 2018a). CircRNAs also increase transcription of host genes by forming RNA–protein complexes with U1 snRNP proteins to recruit RNA pol II (Li et al. 2015). Circ-FOXO3 is another circRNA that exerts effects via several avenues. Circ-FOXO3 acts as a sponge for miR-155 and as a positive regulator for FOXO3, a known tumor suppressor. In NSCLC tumors and cell lines, circ-FOXO3 and its downstream target FOXO3 are down-regulated, leading to increased miR-155 expression (Zhang et al. 2018b). Besides sequestering miRNA, circ-FOXO3 also binds to cell-cycle proteins CDK2 and p21 to form a ternary complex that results in blockade of G1 to S-phase transition (Du et al. 2016).

SMALL NUCLEOLAR RNAs

Small nucleolar RNAs (snoRNAs) are a class of small ncRNAs that until recently were regarded as mainly housekeeping genes involved in ribogenesis. However, recent evidence suggests that snoRNAs have novel roles in tumorigenesis, capable of serving as both tumor suppressors and oncogenes (Mannoor et al. 2012; Williams and Farzaneh 2012). Gene profiling of snoRNAs in lung tumor–initiating cells (TICs) revealed that the majority of differentially expressed snoRNAs were overexpressed in TICs and inversely correlated with poor survival in NSCLC patients (Mannoor et al. 2014). SNORA42 and SNORA78 are two such snoRNAs that were overexpressed in a lung TIC signature and function as oncogenes (Mei et al. 2012; Zheng et al. 2015).

SnoRNAs are detectable in plasma and sputum. A panel of three miRNAs and two snoRNAs was able to discriminate early-stage NSCLC from cancer-free patients using sputum samples, with an ROC AUC of 0.94 with a sensitivity and specificity of 89% (Su et al. 2016). In other studies, expression profiles of snoRNAs and other ncRNAs was able to distinguish between smokers and nonsmokers, distinguish between early-stage cancers and cancer-free patients, and to prognosticate (Liao et al. 2010; Gao et al. 2015; Su et al. 2016; Nogueira Jorge et al. 2017).

THERAPEUTIC TARGETING OF ncRNAs

As ncRNAs have diverse roles in tumorigenesis, cancer progression, and drug resistance, targeting ncRNAs holds clinical promise (Pecot et al. 2011). Approaches to targeting ncRNAs include siRNAs or antisense oligonucleotides, which may be delivered systemically and locally. Barriers include degradation by nucleases, off-target effects, immunogenicity, and toxicity (Pecot et al. 2011). Various delivery modalities and nanoparticle formulations have been tested as ways to improve therapeutic RNA delivery to tumors, with some success in preclinical models, but few have been tested in patients (Pecot et al. 2013, 2014; Fujita et al. 2015; Kasinski et al. 2015; Tian et al. 2017). Although there are trials testing the clinical application of ncRNAs in use as biomarkers, few have tested targeting ncRNAs specifically in lung cancer. NCT02369198 was a phase 1 study of nanoparticles targeted to EGFR-containing miR-16 synthetic mimic for patients with mesothelioma and NSCLC, which showed some clinical benefit in the cohort of mesothelioma patients (van Zandwijk et al. 2017). New approaches for ligand-targeted miRNA delivery, such as with chemically stabilized FolamiRs, may eventually obviate the need for nanocarriers and improve the drug-like properties of ncRNA-based therapeutics (Orellana et al. 2017).

APPLICATIONS AS BIOMARKERS IN LUNG CANCER

Various components of the epigenome have been studied as potential diagnostic, prognostic, and therapeutic biomarkers. Aberrant DNA methylation is detectable in the sputum, bronchoalveolar lavage, and plasma of lung cancer patients, as are miRNA, circRNAs, and snoRNAs (Dong et al. 2017). Various signatures of miRNAs have been developed that distinguish lung cancer tissues from adjacent normal tissue suggesting value as a diagnostic biomarker (Lu et al. 2005). These signatures can be used to distinguish between lung ADC and squamous histologies (Lu et al. 2005; Lebanony et al. 2009; Landi et al. 2010). Differential miRNA expression can also differentiate between primary lung tumors and metastases, suggesting use as a biomarker for advanced disease or for progression (Barshack et al. 2010). Finally, the components of the epigenome have the potential ability to prognosticate and predict treatment response (Raponi et al. 2009; Tan et al. 2011; Balgkouranidou et al. 2013).

CONCLUSIONS

Many factors in the lung tumor and immune microenvironment affect epigenetic alterations within cancer cells and greatly contribute to the intratumoral heterogeneity. Therapeutic targeting of the epigenome yields promise as a way to affect both cancer and immune compartments. Further exploration of the exact epigenetic changes that are both preexisting and acquired during various treatments will be required to achieve clinical benefit. Although an exciting field, the epigenome is exceedingly complex and will likely require specific, multidimensional reprogramming to yield effective therapy against lung cancer.

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