Review Article on Small Cell Lung Cancer: New Models, Markers and Beyond

Transcriptional deregulation underlying the pathogenesis of small cell lung cancer

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Abstract: The discovery of recurrent alterations in genes encoding transcription regulators and chromatin modifiers is one of the most important recent developments in the study of the small cell lung cancer (SCLC) genome. With advances in models and analytical methods, the field of SCLC biology has seen remarkable progress in understanding the deregulated transcription networks linked to the tumor development and malignant progression. This review will discuss recent discoveries on the roles of RB and P53 family of tumor suppressors and MYC family of oncogenes in tumor initiation and development. It will also describe the roles of lineage-specific factors in neuroendocrine (NE) cell differentiation and homeostasis and the roles of epigenetic alterations driven by changes in NFIB and chromatin modifiers in malignant progression and chemoresistance. These recent findings have led to a model of transcriptional network in which multiple pathways converge on regulatory regions of crucial genes linked to tumor development. Validation of this model and characterization of target genes will provide critical insights into the biology of SCLC and novel strategies for tumor intervention.

Keywords: small cell lung cancer (SCLC); transcription factor; chromatin modifier; genetically engineered mouse model (GEMM)

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Introduction

Small cell lung cancer (SCLC) is one of the few cancers for which mutations in transcription regulators, namely RB and P53, are a primary genetic cause. Genomic analyses of patient SCLC tumors revealed that a majority of recurrent somatic alterations affect transcription factors and chromatin modifiers including members of *MYC* family, *SOX2*, *MLL1/2*, *CREBBP-EP300*, *RBL2*, and *P73*. Frequent alterations in these proteins indicate that transcriptional deregulation beyond the loss of RB and P53 underlies cellular transformation and malignant progression of SCLC, causing aberrant expression of a broad range of genes related to cell proliferation and growth signaling pathways. As the concept of targeting chromatic modifiers including BRD4 using small molecule inhibitors have recently emerged for SCLC, characterization of the deregulated transcription programs is critical for discovery of potential targets and defining mechanism of targeted therapy. Recent integrated approaches using functional genomics and genetics and advanced mouse models have enabled interrogation of aberrant transcription program during SCLC development, identifying key oncogenic drivers and their mechanisms of action and conducting preclinical

studies involving targeting transcriptional alterations. This review summarizes recent progresses in our understanding of transcriptional deregulation in SCLC development and tumor heterogeneity.

Transcription deregulation for tumor initiation and early-stage progression

The most common alterations in the SCLC are chromosomal deletions, truncations and missense mutations in the genes encoding TP53 and RB, which are observed in up to 90% of tumors (1-4). This high prevalence of loss-of-function alterations supported the hypothesis that these genes were important tumor suppressors in SCLC development. This hypothesis was formally tested in the studies of genetically engineered mouse models (GEMMs) of SCLC in which deleting the two tumor suppressors resulted in lung tumors resembling SCLC with 100% penetrance. Below is a summary of what we have learned about the roles of these tumor suppressors in SCLC and what remains to be discovered.

Loss of RB and TP53 functions—the rate-limiting step for SCLC development

RB and TP53 are bona fide tumor suppressors whose inactivation is directly linked to tumorigenesis (5-10). RB is best known for its role in controlling cell cycle progression (5,11,12). RB directly binds to E2F family of transcription factors and recruits HDACs and other transcriptional repressor complex proteins such that it inhibits expression of a number of cell cycle-related proteins, including cyclins (5). Inactivation of RB is also associated with an increase in cell plasticity through failed regulation of cell proliferation and apoptotic signaling (5,13,14). TP53 plays an important role in maintaining genomic stability against genotoxic stresses, including DNA damage (15,16). P53 as a transcription factor positively regulates expression of a number of genes involved in cell cycle arrest, senescence, apoptosis, and DNA repair, that collectively promote genomic integrity and tumor suppression (17). As a result of the loss-of-function mutations in *P53* affected cells accumulate potentially oncogenic mutations evade oncogene-induced senescence and cell death, and propagate aberrantly due to cell cycle deregulation (16,17). The near-universal alteration of *RB* and *TP53* genes indicates that removal of their broad spectrum of tumor suppressor activity is essential for the genesis of SCLC. This idea was firmly validated by the study of an SCLC GEMM—*Rb/p53*-conditional mutant mice (18). Complete loss of *Rb* and *p53* via Cre-mediated recombination of floxed alleles in the lung epithelium results in development of mouse SCLC, whereas incomplete deletion of either *Rb* or *p53* allele produces only lung adenocarcinoma (18,19). The requirement of RB loss is seen in several neuroendocrine (NE) tumors, including retinoblastoma and pituitary tumor, suggesting that the tumor suppressive function of RB is in part related to regulating NE differentiation. In support of this idea, lung epithelium-specific *Rb*-knockout alone resulted in hyperplasia of NE cells (20).

The GEMM study supports the concept that the inactivation of RB and TP53 is the rate-limiting step in SCLC development. However, the long tumor latency (9–12 months after Cre-mediated deletion of *Rb* and *p53*) seen in the GEMM also implies a dependency on additional oncogenic events driving *Rb/p53*-mutant cells toward malignancy (*Figure 1A*) (18,19). Indeed, the *Rb/p53*-mutant cells isolated from the lung epithelium of GEMM one month after Cre infection did not transform spontaneously, although they did continue to proliferate in culture (21). These benign characteristics of early-stage mutant cells, termed precancerous cells of SCLC (preSC for short), are largely attributed to the lack of oncogenic events typically seen in SCLC such as L-MYC overexpression (*Figure 1B*). These findings suggest that the loss of RB and P53 functions primarily confers upon cells unlimited replicative potential and the capacity to evade cell senescence and death and that later other oncogenic alterations drive malignant progression. This idea has been central to recent efforts aiming to determine these oncogenic alterations, some of which are discussed below with emphasis on transcription regulators. Defining transcription networks that drive the tumorigenic progression of cells lacking RB and p53 will provide critical insight to strategies for tumor intervention, as the concept of restoring RB and P53 function in lung cancer has yet to be translated into clinical strategy (22-24).

RBL2 and TP73—the secondary line of RB1/TP53 family-mediated tumor suppression

The presence of functional homologs may underlie the long tumor latency following loss of RB and P53. RBL1 and RBL2 (also known as p107 and p130, respectively) are structurally and functionally related to RB, and although they have distinct functions in some contexts, they also regulate the cell cycle (25-30). Mutations in RBL1 and

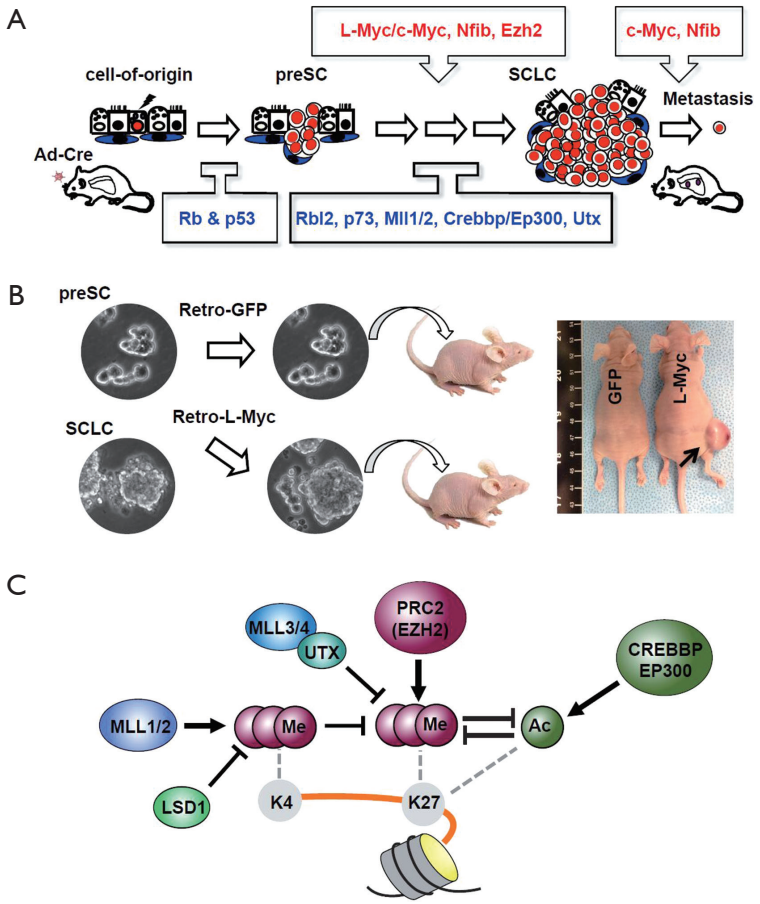

Figure 1 Proposed models of major genetic events and their roles in SCLC development and progression. (A) A model of SCLC development in the Rb/p53 conditional-mutant mice. Pulmonary neuroendocrine cells are likely cells-of-origin. Validated or potential tumor suppressors and oncogenic drivers are indicated in blue and red, respectively; (B) preSC-based model. Images of preSCs, L-Myc-transformed preSCs, and SCLC cells. The L-Myc-preSCs behave similar to SCLC, forming tumor in nude mice (arrow); (C) a model of interactions among chromatin modifiers on histone H3 lysine 4 and 27. preSC, precancerous neuroendocrine cells; Me, methylation; Ac, acetylation.

RBL2 have been identified in 13% of human SCLC (4,31). Impaired expression of RBL2 detected in patient-derived SCLC cell lines resulted from a single point mutation in the splice acceptor sequence of the first intron (31). Aberrant methylation at the promoter/regulatory region of *RBL2* resulted in the gene silencing in SCLC tumors (32). These observations led to the hypothesis that RBL2 serves as a secondary tumor suppressor during SCLC development. This was validated in a recent study in which *Rb/p53*-mutant GEMM with homozygous or heterozygous deletion of *Rbl2* showed significantly higher tumor incidence and shorter tumor latency than those with wild type (19). Notably, the dose-dependent phenotype of *Rbl2*-mutant mice is supported by the reduced *Rbl2* transcript level in *Rb/p53* tumors (19).

Similar to how RBL2 provides redundancy in RB-deficient cells, the P53 homologs TP73 and TP63 cause cell cycle arrest and apoptosis through their ability to activate expression of P53-target genes (33-37). These members of the P53 family frequently exist in multiple isoforms, including those with truncated N-terminal domains. These N-terminal truncated forms, namely ΔNP73 and ΔNP63, are products of transcripts expressed from alternative promoters (38-41). Lacking the transactivation domain but retaining the domains for DNA binding and oligomerization, these truncated forms have dominant-negative activity that inhibits wild-type members of the P53 family (41-43). While ΔNP63 has not been detected

in SCLC, a recent study uncovered genomic breakpoints or mutations in the *P73* locus in 13% of patient samples (n=110). Some genomic rearrangements are expected to result in the N-terminal truncated variants of P73 (designated as P73Δex2, P73Δex2/3) (4). These variants may have dominant negative activity on wild-type P73 and P53 as previously shown (41,44). Their roles in SCLC progression remain unknown and are being determined using the preSC-based tumor model in which similar variants are generated using CRISPR-mediated deletion of target exons. This model, once developed, will also provide a robust system to test therapeutics targeting P73-dependent tumor growth (44).

MYC family—driving early transformation and defining molecular subsets of SCLC

The MYC family of transcription factors, including MYC (c-MYC), MYCL (L-MYC), and MYCN (N-MYC), are frequently amplified and overexpressed in both SCLC cell lines and patient tumors (4,45-49). While genomic amplification of the MYC genes is detected in a significant portion (6–24%) of the patient tumors (4,46,50), it is more prevalent (32–44%) in SCLC cell lines (46,49,51). The amplification of each MYC family member occurs in a mutually exclusive manner, indicating functional redundancy among the family members in their contribution to SCLC tumorigenesis (48,49). A large body of evidence demonstrates that the MYC proteins promote tumor progression by deregulating oncogenic transcription, cell cycle control, and metabolism (21,52). However, exact roles for MYC proteins and their temporal specificity remain far from being well understood (21,53-55). For instance, almost 30 years after its discovery in SCLC, the role of L-MYC was formally tested in recent studies in which retroviral L-MYC amplification in the *Rb/p53*-mutant mice and *Rb/p53*-mutant preSC enhanced tumor development and caused transformation, respectively (21,53,56). Conversely, deletion of L-Myc in two variants of the SCLC GEMM ($p53^{lox/lox}$; $Rb^{lox/lox}$; $Rbl2^{lox/lox}$ and $p53^{lox/lox}$; $Rb^{lox/lox}$; $Pten^{lox/lox}$) suppressed tumor incidence and burden in the affected lungs (21). Furthermore, enhanced ribosome biogenesis and protein synthesis were the most significant molecular alterations during L-Myc-driven transformation of the preSCs. Inhibition of the ribosome biogenesis using a specific inhibitor, CX-5461, was shown to suppress tumor growth in the *Rb/p53*-mutant GEMM (21).

Similar to the L-MYC studies above, an *in vivo* model of c-MYC-driven SCLC has also been developed using another variant of SCLC GEMM ($Rb^{lox/lox}$; $p53^{lox/lox}$; $Myc^{LSL/+}$) in which conditional expression of c-Myc drives development of tumors with a higher capacity for proliferation and metastasis than any other GEMMs, including the *Rb/p53*-mutant GEMM ($Rb^{lox/lox}$; $p53^{lox/lox}$) (54). Notably, these MYC-driven tumors showed increased expression of a neurogenic transcription factor, NeuroD1, but diminished expression of another neurogenic transcription factor, Ascl1. This expression pattern coincided with reduced expression of other NE markers including SYP and CGRP; this genetic association with MYC status is also observed in both SCLC tumors and cell lines (54). Furthermore, the MYC-driven tumors in the GEMM and human SCLC with high MYC expression both displayed specific (selective) sensitivity to Aurora kinase inhibition; treatment with alisertib (a small molecule inhibitor of Aurora A kinase) drastically suppressed the growth of mouse and human MYC-driven SCLC that otherwise rapidly relapsed following standard chemotherapy, e.g., single dose of cisplatin or etoposide, or combination of both treatment (54). Taken together, these findings from the study of the GEMMs and the novel preSC-based model have helped define molecular subtypes of MYC family-driven SCLC, uncovering the oncogenic mechanisms and vulnerabilities unique to each member of the family.

Transcription factors for neural differentiation and tumor heterogeneity

The NE features of SCLC formed the basis of the idea that pulmonary neuroendocrine cells (PNECs) are the cell-of-origin, which was proven in the studies of the *Rb/p53*-mutant GEMM (57-59). The NE characteristics of SCLC also led numerous efforts to determine roles for NE-lineage transcription regulators in the pathogenesis of SCLC. These lineage regulators include ASCL1, NEUROD1, SOX2, TTF-1, BRN2, INSM1, and GFI1/1B to name a few. Recent studies suggest that, in addition to functioning as lineage-survival oncogenes, these factors define molecular subsets of SCLC cells and contribute to intra-tumoral heterogeneity.

ASCL1 and NEUROD1—regulators of NE differentiation and subtypes of SCLC

ASCL1 (achaete-scute-like 1; also known as HASH1) is a member of the basic helix-loop-helix (bHLH)

transcription factor that has roles in neuronal commitment and differentiation of cells including PNECs during development. It also regulates stemness, cell cycle progression, and mitosis (60-62). Unlike its widespread expression among PNECs in the fetal lung, ASCL1 expression is limited to a subpopulation of PNECs—potentially dormant progenitor cells—in mature lung and is increased in subsets of high-grade NE tumors, including SCLC (63,64). ASCL1 was shown to be essential for maintaining the survival of SCLC cell lines and also required for the tumor development in GEMMs (65-67). Likewise, NEUROD1, another bHLH transcription factor, has critical roles in promoting neurogenic differentiation of cells during development and malignant behavior in SCLC cell lines (68). NEUROD1 expression is limited to a subset of SCLC cell lines distinct from those expressing ASCL1 (67,69). Intriguingly, however, NEUROD1 is not essential for the development of mouse SCLC that absolutely depends on ASCL1 expression (67). Stratification of SCLC based on differential expression patterns of ASCL1 and NEUROD1 reveals subtypes of $ASCL1^{High}$ (70%), $NEUROD1^{High}$ (15%), and $ASCL1^{Low}$/$NEUROD1^{Low}$ (15%) and indicates that the SCLC developed in *Rb/p53*-mutant GEMM may resemble more the $ASCL1^{High}$ subtype (67). These subtypes also express distinct sets of SCLC-related oncogenes, among which L-MYC, RET, SOX2, and NFIB are targets of ASCL1 while c-MYC is a target of NEUROD1. Notably, the $ASCL1^{High}$ subtype tends to express L-MYC and $NEUROD1^{High}$ subtype express c-MYC, indicating genetic relationship between ASCL1/NEUROD1 and L-MYC/MYC (21,54). Therefore, it will be interesting to test whether these ASCL1/NEUROD1 subtypes display similar vulnerabilities to ribosome biogenesis inhibition/Aurora kinase inhibition as seen in L-MYC/c-MYC subtypes do (21,49,54).

SOX2, TTF-1, BRN2, INSM1, GFI1—potential lineage factors for cellular homeostasis

SOX family of transcription factors are involved in various aspects of morphological determination during embryonic development and also in the specification and self-renewal of tissue stem/progenitor cells (70). Several members of the B and C groups of the SOX family, including SOX2 and SOX4/11, have been detected in SCLC. SOX2 is frequently amplified and over-expressed in SCLC tumors (~27%) and cell lines (71). A high titer of SOX2 is also detected in circulation, indicating that antibodies against these factors could serve as specific serological markers for detection of SCLC (72-74). The role of SOX2 is not known, although it has been proposed as a lineage-survival oncogene (75). Expression of SOX4 target genes is increased in lung tumors with SOX4 gene overexpression (76). Therefore, SOX family transcription factors may have important roles in the expression of various genes through communication with cells present in the surrounding microenvironment.

TTF-1 (thyroid transcription factor 1; also known as NKX2-1) is one of the master regulators of epithelial differentiation and branching morphogenesis during lung development (77,78). The observation of widespread TTF-1 expression in SCLC (almost 90% of patient tumors) led to the hypothesis that it functions as a lineage survival oncogene in SCLC as it does for lung adenocarcinoma (79). Additionally, TTF-1 expression was associated with improved response to chemotherapy treatment (80). The majority of TTF-1-positive SCLCs were found at the lung periphery, and this peripheral-type SCLC had a worse prognosis than centrally located tumors (80). Our current understanding of the role of TTF-1 in SCLC is not sufficient to determine whether its expression and activity are reliable biomarkers for prognosis and therapy, necessitating more functional and mechanistic studies.

BRN2 (brain-2; also known as POU3F2) is a neural cell-specific POU domain transcription factor for neural lineage determination (81). An ectopic expression and knockdown experiment suggested that BRN2 functions upstream of ASCL1 and NEUROD1 to promote expression of NE genes and promote cell proliferation (82). RB may be an upstream regulator of BRN2 as RB-mutant retinoblastoma expresses high levels of BRN2 which are reduced with restoration of RB expression (83). Additionally, the BRAF-mediated activation of BRN2 in melanoma could provide insight into this interaction in SCLC because *BRAF* mutation, although rare, has been discovered in SCLC patient tumor (4,84).

INSM1 (insulinoma-associated 1) is a transcription factor with zinc-finger DNA binding domain and a SNAG (SNAIL/GFI1)-domain that was originally isolated from a human insulinoma. It plays an important role in the development of NE cells in the pancreas and intestines, and adrenal medulla and basal neuronal progenitor cells in the neocortex (85-88). Insm1 binds directly to regulatory sequences in the *Hes1* gene to repress its expression, Mutation of *Insm1* leads to upregulated Hes1 expression and interferes with maintenance of *Ascl1* expression (89). Conversely,

NOTCH/HES1 signaling suppresses INSM1 (90). The observation of its expression in nearly all SCLC cells prompted the hypothesis that it is a crucial regulator of NE differentiation in this cancer (91-93). Knockdown of INSM1 reduced proliferation rates of SCLC cell lines and expression of neuroendocrine-specific genes, including *ASCL1*, *BRN2*, *CHGA*, *SYP*, and *NCAM* (90).

GFI1 (growth factor independent-1) and its homolog GFI1B, proteins with zinc-finger DNA binding domains and SNAG domains, are transcriptional repressors critical for development of the hematopoietic system (94,95). GFI1/1B, acting downstream of proneural bHLH factors such as ASCL1 and MATH1, also plays a role in NE differentiation and SCLC development (96-98). GFI1 knockout drastically reduces NE differentiation and impairs PNEC proliferation (97,99). Mechanistically, GFI1 binds to regulatory regions of target genes and recruit's chromatin modifiers, including LSD1, that in turn demethylase H3K4 to repress gene expression (100). This interaction likely explains the effect of LSD1 inhibitors on SCLC growth, together with the finding that one of the inhibitors interfered with the interaction of LSD1 with GFI1B and INSM1, another SNAG-containing protein (101,102).

Signaling pathways to transcription effectors for intratumoral heterogeneity

Recently, studies have determined the cellular and molecular origin of the intratumoral heterogeneity seen in SCLC. NOTCH singling plays an important role in cell-fate decisions in a variety of tissues (103). During lung development, a subset of epithelial progenitor cells expressing Delta-like ligands (DLLs) inhibits NE differentiation of adjacent progenitor cells expressing NOTCH via DLL-NOTCH interaction-mediated signaling that suppresses ASCL1 expression in the NOTCH-expressing cells (104). However, much less is known about the role of the NOTCH signaling in the differentiation of SCLC that consists mainly of DLLs-expressing NE cells but only few other type of epithelial cells expressing NOTCH receptors. Somatic mutations affecting genes encoding NOTCH 1, 2, 3 and 4 are detected in 25% of patient tumors, and the majority of cases also had high levels of DLK1 (delta-like 1 homolog), an inhibitor of Notch signaling (4,105). Activation of NOTCH signaling through expression of N1ICD/N2ICD, the transcriptional effectors, inhibits cell cycle progression in SCLC cells and reduces tumor development in the lungs of *Rb/p53*-mutant GEMM (4,106). These data, while suggesting a tumor suppressive role for the NOTCH pathway, do not readily support activation of the pathway as a viable therapeutic strategy, in part because this pathway acts tumor suppressive and oncogenic in different populations of SCLC (107).

Using NE cell-specific adeno-CGRP-Cre and a *Hes1*$^{GFP/+}$ allele (a knock-in reporter of NOTCH activity) with SCLC GEMM, a study found that NOTCH/HES1-active GFP^{positive} cells coexisted with NOTCH/HES1-inactive GFP^{negative} cells originating from the NE cells (107). The HES1-active cells express known target genes of the pathway, including *Notch* genes themselves and *Nrarp*, while suppressing NE genes. This NOTCH/HES1-driven switch to non-NE phenotype occurred in 10–50% of NE cells and coincided with induction of REST, a transcriptional repressor and a direct target of NOTCH pathway that represses expression of NE genes. On the other hand, the HES1-negative NE cells expressed ligands, *DLL1*, *3*, and *4* and NE genes typical of SCLC. Additionally, the HES1-active non-NE cells were relatively resistant to carboplatin and irinotecan at doses that effectively killed the HES1-inactive NE cells. These findings led to a model in which the non-NE SCLC cells promote malignant progression and facilitate regeneration of NE cells following chemotherapies, suggesting that Notch inhibition in combination with chemotherapy may be more efficacious in preventing early-stage SCLC progression or relapse following existing chemotherapies. Furthermore, given the NOTCH/HES1-driven regulation of ASCL1 and L-MYC/c-MYC, it is possible that the pathway may play a role in defining ASCL1^{High}/NEUROD1^{High}/double-negative subtypes and/or L-MYC/c-MYC subtypes of SCLC cells described above (66,106,108) and that these molecular subtypes would have differential sensitivities to a combination of NOTCH inhibition and conventional chemotherapy (54). These findings have advanced our understanding of intratumoral heterogeneity in SCLC since the initial model that proposed a role of non-NE cells in metastasis of NE cells (109).

Signaling pathways that contribute to SCLC heterogeneity via transcriptional change are likely complex, including more pathways implicated in normal lung development and homeostasis and cross talks among them. For instance, PEA3, a member of the ETS transcription factor family, has been implicated in maintaining the intratumoral heterogeneity (110). High

expression of PEA3 was detected in NE cells in tumor that were treated with conditioned medium from non-NE cells. The increased PEA3 was sufficient to induce the invasive migration property in NE cells. Fibroblast growth factor (FGF)/RAS/MAPK pathway regulated the PEA3 expression and invasiveness in NE cells, suggesting that the FGF pathway is responsible for paracrine signaling between NE and non-NE cells in SCLC. These findings are in line with previous studies that showed that PEA3 was expressed in metastatic tumors, and that its expression correlated with metastasis of various human cancers, including breast cancer and NSCLC (111-113), implying a role of PEA in paracrine signaling in the lung tumor microenvironment. In light of these roles of signaling pathways initiated by membrane-bound receptors, it is also worth revisiting the Hedgehog (HH) signaling in the context of SCLC intratumoral heterogeneity. Similar to NOTCH and FGFR pathways, HH signaling is transmitted to activate the GLI family of zinc-finger transcription factors that induce numerous oncogenes including *c-MYC*, *CCND1*, and the *GLIs* themselves (114). Preclinical studies have shown that an autocrine, ligand-dependent signaling promotes SCLC development, while other studies showed a significance of a paracrine signaling to tumor-associated stroma cells (115-118). While it remains debatable, to what extent these modes of signaling contribute to the pathogenesis of SCLC, the activated GLI promotes proliferation and cell-cell interactions. It is tempting to speculate whether non-NE cells described above are HH-responsive stroma cells and the transcriptional activity of GLI contributes the development and maintenance of tumor heterogeneity. Better understanding of HH signaling in this emerging context of SCLC would provide novel insight into targeted therapy against the signaling (119).

Epigenetic alterations driving malignant progression

Discovery of aberrant epigenetic drivers of SCLC progression has been an important step toward understanding the SCLC biology. Recent studies have uncovered a novel function of NFIB in regulating chromatin states for metastasis and have begun to unravel the complex network of chromatin modifiers, including histone methyltransferases, demethylases, and acetyltransferases, and other components of multi-protein histone modifying complexes.

NFIB altering chromatin states for SCLC metastasis

NFIB, a member of the nuclear factor I (NFI) family of transcription factors, binds to promoter, enhancer, and silencer regions in the genome and regulates a plethora of genes in almost all tissues during development (120,121). A study of Nfib knockout mice showing developmental defects in lung and brain supports a fundamental role for the gene in a wide range of biological processes (122,123). NFIB alterations have been implicated in malignancies; particularly, it is amplified in human SCLC tumors (15%), cell lines (34%) and mouse SCLC developed in the *Rb/p53*-mutant GEMM (124,125). Nfib knockdown reduced cell proliferation while increasing cell death, suggesting a role for the gene in maintaining tumor cell homeostasis (124). Recently, a novel role of NFIB and its *in vivo* relevance have been determined in three independent studies using variants of the SCLC GEMM (125-127). These studies found that (I) Nfib amplification and overexpression are more prevalent in metastases than primary tumors; (II) ectopic Nfib expression accelerated mouse SCLC progression with increased tumor burden and metastasis; and (III) increased Nfib was both sufficient and required for multiple steps of metastasis to lymph nodes and liver from primary tumors. Furthermore, ATAC-seq (assay of transposase-accessible chromatin with sequencing) and lung tumors and liver metastasis from the same GEMM showed that Nfib, once bound to target DNA elements, initiates and stabilizes accessible chromatin configuration that promotes expression of genes required for metastatic progression of mouse SCLC cells (124,126). These Nfib-induced changes in chromatin accessibilities genome-wide coincide with altered expression of a large number of genes functionally related to neural development/differentiation, cell adhesion, and motility (124,126). Transcriptional analyses in the other studies revealed that Nfib regulates the expression of genes related to axon guidance, focal adhesion and extracellular matrix-receptor interactions, and cellular movement (125,127). High levels of Nfib are associated with expansive growth of a poorly differentiated and E-cadherin (CDH1)-negative invasive population of tumor cells, which corresponds to features of stage III/IV high-grade NE carcinomas in patients (125). These findings strongly suggest that concerted actions of Nifb target genes drive metastasis of SCLC mainly by altering cell-adhesion and movement. NFIB and its mechanism of action in tumor development and metastasis may present viable targets for intervening in tumor development and metastasis.

EZH2 (Enhancer of zeste homolog 2)—epigenetic regulator for malignant progression

EZH2 is a histone methyltransferase that, together with EED and SUZ12, forms the polycomb repressive complex 2 (PRC2) (128). It mediates tri-methylation of histone H3 at lysine 27 (H3K27me3) in discrete promoter CpG islands, leading to transcriptional repression (128,129). In addition to its role in promoting heterochromatin formation and gene silencing during development and differentiation, increased EZH2 expression has been linked to numerous cancer types including lung cancers (130-132). In cancer cells, high EZH2 activity results in the long-term repression of tumor suppressor genes (133). Remarkably, ectopic expression of EZH2 alone was sufficient to cause NSCLC in mice (134). EZH2 overexpression also promotes development of K-Ras-driven NSCLC (135). In SCLC cell lines, EZH2 levels are expressed three times greater than those in NSCLC lines and twelve times greater than in normal lungs (132). Since EZH2 is a known target of E2F transcription factor, complete loss of RB in SCLC likely results in deregulated EZH2 expression (129,132). Overexpression of EED and SUZ12 coincided with high EZH2 overexpressed in SCLC tumor samples, further indicating the presence of the PRC2 complex (136). Functionally, EZH2 plays a role in homeostasis of SCLC cells as its knockdown increased apoptotic activity by up-regulating the pro-apoptotic factors such as PUMA and BAD and by elevating P21 protein levels (137). ChIP-seq analysis indicated that JUB (AJUBA) is the most repressed gene of hyper-methylated H3K27me3 in SCLC cell lines (136). Notably, the extents of JUB gene repression correlated with reduced patient survival, suggesting role of the PRC2 activity is linked with poor SCLC prognosis (136,138).

Given its widespread involvement in malignancy, there has been considerable interest in reversing EZH2-mediated repression of tumor suppressor genes. Recent efforts to test small molecule inhibitors of EZH2 in lung cancer have met with some success. EZH2 inhibition using GSK126 and DNZep sensitized BRG1 and EGFR-mutant lung adenocarcinoma to existing chemotherapy (139). Another inhibitor, JQEZ5, also suppressed growth of EZH2-driven/addicted lung tumors in GEMMs and xenografts of human NSCLC cell lines (134). Likewise, inhibition of EZH2 using EPZ-6438, suppressed growth of patient-derived xenograft as well as SCLC cells in culture (140). These results strongly support EZH2 inhibition as strategy for intervening in SCLC progression. However, it may be challenging to stratify SCLC tumors for this EZH2-targted therapy, as EZH2 expression alone may not be sufficient for SCLC development. Identification of EZH2-targets would help identify reliable biomarker to predict the efficacy of EZH2 inhibitors. One potential biomarker for EZH2 activity is SLFN11 (Schlafen family member 11), a putative DNA/RNA helicase whose expression could sensitize cells to DNA-damaging agents (141-144). SLFN11 expression was diminished by EZH2-driven methylation in SCLC cells treated with talazoparib, a PARP inhibitor, and inactivation of SLFN11 using shRNA or CRISPR/Cas9 conferred resistance to the drug (145). These findings indicated SLFN11 as a predictive biomarker of sensitivity to PARP-targeted therapy in SCLC and led to a preclinical study in which EZH2 inhibition in combination with PARP inhibition restored SLFN11, thereby restoring chemo-sensitivity.

MLL family of histone methyltransferases

The MLL (mixed lineage leukemia; also known as KMT2) proteins as part of multi-protein complexes, regulate methylation of lysine 4 and 27 residues on histone H3 tails (H3K4 and H3K27) in regulatory elements of genes (146). MLL1/4 (KMT2A/B) complex methylates H3K4 and MLL2/3 (KMT2D/C)-UTX (KDM6A) complex demethylases H3K27 (146,147). Initially discovered in hematopoietic malignancies with SET domain deletion leading to hypomethylation of H3K4 and transcriptional inactivation, MLL family mutations are among the most frequent alterations in cancer (148-150). In SCLC, multiple types of mutations, including missense mutations and truncations, were discovered in the genes encoding the MLLs; a majority of the mutations were truncating mutations, and MLL1 (KMT2A) and MLL2 (KMT2D) were the most frequently mutated in both SCLC cell lines and the patient tumors (48,71,151-153). These mutations were associated with low protein levels and global reductions in mono-methylation of histone H3 lysine 4 (H3K4me1), a chromatin marker of transcriptional enhancers (152). A few SCLC cells with normal MLL2 mutation instead had truncating mutations in UTX with similar defects in H3K4 methylation (152). This reduced H3K4me1, given its antagonistic relationship with H3K27 methylation, may have increased H3K27 methylation driven by PRC2/EZH2 that results in gene silencing. It remains unknown how these epigenetic alterations caused by loss-

of-function mutations influence tumorigenesis.

LSD1—H3K4 demethylase

LSD1 (lysine-specific demethylase 1; also known as KDM1A) demethylases mono- and di-methylated lysine 4 of histone H3 (H3K4me1/2), thereby epigenetically regulating the activation or repression of gene expression in different contexts (154-156). LSD1 is overexpressed in hematologic malignancies and solid tumors including SCLC (157-161). Two independent drug screening studies recently found that two small molecule inhibitors of LSD1, designated GSK2879552 and T-3775440, had antitumor effects on SCLC cells *in vitro* and *in vivo* (101,102). Mechanistically, GSK2879552 caused widespread hypomethylation that altered expression of a number of genes including *ZEB1* and *IGFBP2* (101) and T-3775440 disrupted the interaction between LSD1 and the SNAG (SNAIL/GFI1) domain transcription factors INSM1 and GFI1B, thereby inhibiting expression of NE-associated genes, such as *ASCL1* (102,162). The mechanism of LSD1 action in SCLC remains to be determined; demethylation of H3K4 on enhancer regions of tumor suppressor genes may cause transcription inhibition and modify the histones near MYC binding sites to promote its transcription activity (163). Elucidation of LSD1-mediated transcriptional regulation will provide important insight into a novel therapeutic strategy involving inhibition of LSD1, which is being tested in a clinical trial.

CREBBP/EP300 family of acetyltransferases

CREBBP [cAMP response element-binding (CREB)-binding protein] and EP300 (E1A associated p300) have intrinsic histone acetyl transferase (HAT) activity and play critical roles in embryonic development, growth control, and homeostasis by coupling chromatin remodeling to transcription factor recognition (164-166). Somatic mutations in these homologous factors were found in multiple cancer types, including lung cancers (48,167,168). In SCLC, a significant fraction of patient tumors carries mutations in the genes encoding these factors (4,48,71,152). The clustering pattern of missense mutations in the exons encoding the HAT domain indicates significance of the catalytic function for tumor suppression and, together with mutual exclusiveness between CREBBP and EP300 mutations, also suggests that those affecting the HAT domain may have dominant-negative functions on wild-type proteins and functional paralog (4). The functional significance of these mutant forms of CREBBP/EP300 in SCLC is currently being determined using the *Rb/p53*-mutant GEMMs as well as the preSCs. It is expected that removing Crebbp or Ep300 from mouse lung epithelium already lacking Rb and p53 will accelerate SCLC development. CRISPR-mediated mutation of the HAT domain, resulting in its truncation, is expected to cause transformation of the preSCs. These studies will support a tumor-suppressive role for these HAT-containing transcription co-factors.

Mechanistically, CREBBP/EP300 acetylates H3K27 in the enhancer regions of target genes throughout the genome to promote transcription which, in concert with the MLL3/4-UTX demethylase complex, opposes the PRC2-mediated methylation of the histones that usually represses gene expression (169-171). In the context of tumor cells with altered CREBBP/EP300 activities, modification of H3K27 is perturbed and the affected genes, likely tumor suppressors, are highly methylated and suppressed. Identification of these suppressed genes will enhance our understanding of the tumorigenesis driven by these alterations. However, a different mechanism of CREBBP/EP300 actions explains their regulation of oncogenes including MYC. It has been reported that CREBBP-deficient cancer cell lines and CREBBP-knockout cells are uniquely susceptible to EP300 depletion. Inactivation of both CREBBP and EP300 enhances the H3K27 methylation but also cause decreased expression of MYC; the latter turns out to be detrimental to the NSCLC cells (172). Therefore, the mutually exclusive pattern of CREBBP and EP300 mutation may suggest not only functional redundancy of these paralogs but also a synthetic lethal relationship. Given the mutually exclusive pattern of these alterations also present in SCLC, it is critical to test the CREBBP-EP300 synthetic lethality relationship.

Other proteins in chromatin modifying complexes

Components of the BAF-SWI/SNF and PBAF-SWI/SNF complexes are implicated in SCLC (152). Mutations have been found in ARID1A/B (AT-rich interaction domain 1 A and B), PBRM1 (polybromo 1; also known as BAF180), and BRG1 (SMARCA4). CHD7 (chromodomain helicase DNA binding protein 7), known to interact with the PBRM1-containing PBAF complex, is also mutated in SCLC. Collectively, these mutations are found in significant portions of SCLC, suggesting a role for SWI/

SNF complexes-mediated epigenetic regulation in SCLC development. While the functional significance of these mutations remains to be determined, their known function and relationships with other oncogenic factors have been exploited to devise therapeutic strategies. For example, in line with the opposing functions of BAF complexes and the PRC2 complex, cancers with ARID1A loss are highly sensitive to inhibition of EZH2 in the PRC2 (173). Also, the additional function of ARID1A in response to DNA double-strand DNA breaks (DSBs) supports the concept that loss of ARID1A sensitizes tumor cells to DSB-inducing radiation or PARP inhibitors. Thus, ARID1A mutation may a reliable biomarker for treatment with a PARP inhibitor shown to reduce tumor growth in preclinical models (174). BRG1 regulates expression of MAX, the dimerization partner of MYC, and cooperates with MYC/MAX in expression of a common set of genes in SCLC. But depletion of BRG1 causes lethality specifically in MAX-deficient cell by significantly affecting MYC in gene expression (175). Additionally, BRD4 (Bromodomain-containing protein 4), a protein that binds to acetylated histones and recruit's chromatin modifiers and transcription factors, has been a molecular target of interest since a bromodomain inhibitor JQ1 inhibited the growth of cancer cells with a significantly higher efficacy in MYC-amplified SCLC lines (176,177). Although not altered in SCLC, BRD4 may be a rational target, given its role in expression of MYC and other oncogenes (178). Other reports, however, show that BRD4 occupies the enhancer region of ASCL1 and JQ1 inhibits expression of ASCL1, not MYC, in SCLC cells (179) and that the sensitivity to JQ1 does not correlate with the levels of L-MYC, N-MYC, and ASCL1 but rather with CDK6 (180). These different results reflect cell context-specific BRD4 occupation in the regulatory regions of target genes.

Conclusions

Propelled by the discovery of genomic alterations and advances in models and analytical methods, the field of SCLC research has seen remarkable progress in understanding tumor development and malignant progression and developing new strategies for treatment. However, only a few of the altered transcription regulators have been evaluated for their roles in the tumor development and *in vivo* relevance. In addition to determining the roles of individual factors altered in the cancer genome, understanding functional relationships among them will lead to a model of transcriptional pathways that converge on regulatory regions of crucial genes during tumor development. Upregulated transcription factors such as MYCs and NFIB occupy the regulatory regions of oncogenes and recruit histone modifiers such as LSD1 to enhance transcription. Repressor complexes such as EZH2-containing PRC2 methylate H3K27 at the regulatory regions of tumor suppressor genes. Resulting gene expression changes favor oncogenic progression that is further amplified by loss-of-function alterations in MLL1/2, MLL3/4-UTX complex, and CREBBP/EP300, which normally antagonizes the PRC2/EZH2-mediated silencing of target genes (*Figure 1C*). Validation of this model and characterization of target genes will move the field forward to define oncogenic mechanisms and vulnerabilities common in molecular subtypes and provide critical insights into novel strategies for tumor intervention.

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Footnote

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