Review Article

Advances in novel molecular typing and precise treatment strategies for small cell lung cancer

Rilan Bai, Lingyu Li, Xiao Chen, Yuguang Zhao, Wei Song, Huimin Tian, Jiuwei Cui

Cancer Center, the First Hospital of Jilin University, Changchun 130021, China

Correspondence to: Jiuwei Cui. Cancer Center, the First Hospital of Jilin University, Changchun 130021, China. Email: cuijw@jlu.edu.cn.

Abstract

Small cell lung cancer (SCLC) is a high-grade neuroendocrine (NE) cancer characterized by high circulating tumor-cell burden and early extensive metastasis. Considering the complexity of SCLC genes and the immune microenvironment, their unique molecular heterogeneity profiles have been continuously explored. The understanding of SCLC subtypes has recently changed from traditional "classical" and "variant" types to "NE" and "non-NE" phenotypes and to the subtypes defined by major transcriptional regulators, which indicates the gradual revelation of high intratumoral heterogeneity and plasticity characteristics of SCLCs. Advances in genomics as well as the development of single-cell sequencing analysis and new preclinical models have helped investigators gain many new insights into SCLCs and the development of targeted therapy and immunotherapy strategies. This article provides an overview of changes in molecular typing, tumor heterogeneity, and plasticity and that of advances in the precise treatment of different subtypes of SCLC.

Keywords: Small cell lung cancer; transcription factors; tumor heterogeneity; plasticity; immune

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Introduction

Small cell lung cancer (SCLC) is a high-grade neuroendocrine (NE) lung cancer, accounting for approximately 15% of all lung cancers, and is strongly associated with severe tobacco exposure (1). SCLCs are characterized by a high proliferation rate, high circulating tumor-cell (CTC) burden, early and extensive metastasis, high mortality, and poor prognosis (2-4), with a survival time of approximately 10 months and a 5-year overall survival (OS) rate of 6% (5). Although cytotoxic chemotherapy has been the standard treatment for decades, it is only temporarily effective in a vast majority of patients; no substantial progress has been made in systemic therapy. SCLC has been considered a homogeneous disease owing to the almost universal loss of tumor protein p53 (*TP53*), retinoblastoma 1 (*RB1*), and NE or epithelial differentiation features (6-8). Increasing evidence has shown that SCLC is a genetically complex disease with significant genomic instability, which manifests as aneuploidy, multiple intra- and inter-chromosomal rearrangements, and various genetic changes affecting cell fate, including tumor suppressor gene mutations, copy number variations, and somatic mutations in transcription factors (9), such as v-MYC avian myelocytoma viral oncogene homolog (*MYC*) family gene mutations, inactivating mutations in *NOTCH* family members, and phosphatase tension protein homolog (*PTEN*) deletion. However, most targeted therapies for these genetic changes have failed. The tumor immune microenvironment of SCLC is complex, and most reports reveal that it is of "immune desert" type, which resulted in mostly discouraging responses of SCLCs to immunotherapy. Considering the complexity of genes and the immune microenvironment of SCLCs, their unique molecular heterogeneity profiles have been continuously explored. The understanding of SCLC subtypes has recently changed from the traditional "classical/variant" type to the "NE/non-NE" phenotype and to the subtypes defined by

dominant transcriptional regulators (6,10), which led to the gradual revelation of its different gene expression profiles. Moreover, studies have shown that different subtypes are dynamically changing, emphasizing the intratumoral heterogeneity (ITH) and strong plasticity of SCLCs, which are associated with tumor evolution, metastasis, and acquired drug resistance. Recent advances in genomics and the development of new preclinical models have helped researchers gain new insights into ITH, specific genetic alterations, and molecular methods for the classification of this disease, and a better understanding of these biological features has facilitated the identification of new targets and the development of potentially suitable targeted therapies.

Transformation in molecular typing of SCLCs

Traditional classification of SCLCs

Thirty years ago, SCLC cell lines were implanted as xenografts, and their subtypes were first distinguished based on morphological differences: "classical" phenotype, high expression of NE markers and anchorage-independent growth patterns; "variant" phenotype, low expression of NE features and adherent or loosely adherent growth patterns (3). However, the 2015 World Health Organization classification of lung tumors considers SCLCs to be histologically homogenous, with generalized loss of *TP53*, *RB1*, and NE/epithelial differentiation features (6-8). They are characterized by small cells with scanty cytoplasm and a nucleus showing fine granular chromatin and a lack of prominent nucleoli, which are similar to the features of "classical" SCLC subtype. They initially described that the "variant" subtype may represent a mixed type of SCLC with large cell NE carcinoma (LCNEC) in the current classification (11). At present, SCLCs are primarily classified into "NE" subtype and "non-NE" subtype based on different NE markers (3,12). Zhang *et al*. (12) developed a large scoring system for lung cancer based on 50 genes [25 genes positively correlated with NE differentiation, such as achaete-scute homolog 1 (*ASCL1*), neurogenic differentiation factor 1 (*NEUROD1*), insulinoma-associated protein 1 (*INSM1*), syntaxin protein (*SYP*), brain expressed X-linked 1 (*BEX1*), and Nkx homeobox-1 gene (*NKX2-1*); 25 genes negatively correlated with NE differentiation, such as RE1 silencing transcription (*REST*), *ASCL2*, and B-cell lymphoma/leukemia -2 (*BCL2*)], confirming that the NE scores can be used to separate NE-high and NE-low subtypes of human SCLC and SCLC cell lines, with more than 90% concordance with related genes and pathways (12). Different subtypes exhibit significant heterogeneity in morphology, growth characteristics, genetic alterations, and immune infiltration (12) and exhibit different sensitivities to platinum-based chemotherapy, targeted therapy, and immunotherapy. The subtypes with high NE scores were associated with classical morphology, high expression levels of NE markers, epithelial cell phenotype, and expression of NKX2-1, delta-like protein 3 (DLL3), and delta-like 1 homolog (DLK1), whereas phenotypes with low NE scores were associated with variant morphology, low or no expression of NE markers, the activation of *MYC*, *REST*, NOTCH, HIPPO and transforming growth factor-β (*TGF-β*) pathway, and epithelial-mesenchymal transition (EMT). In terms of chemosensitivity, NE-high SCLCs were reported to be more sensitive to cisplatin, whereas "non-NE" SCLCs were mostly resistant to cisplatin. With regard to immune infiltration, NE-high SCLCs have an "immune desert" phenotype, whereas NE-low SCLCs exhibit an "immune oasis" phenotype (13,14). Nevertheless, the classification of SCLCs remains insufficient to guide precise treatment.

Novel SCLC subtypes defined by transcriptional regulators

Recently, based on the findings of large-scale gene expression profiling conducted using samples collected from patient with SCLC (15), patient-derived xenografts (PDXs) (16), cell lines (17,18), and genetically engineered mouse models (GEMMs) (19,20), researchers have proposed that different SCLCs can be defined based on unique transcription-factor expression profiles overlapping with RNA sequencing (RNA-seq) profiles. Moreover, they have identified several target genes that are differentially regulated by these transcription factors and are related to SCLC biology (6). SCLC-A is defined based on the expression of transcription factor *ASCL1*. High *ASCL1* expression is considered to be associated with high NE marker expression and to have the potential to regulate stemness, cell-cycle progression, and mitosis (19,21). The target genes of *ASCL1* include *MYCL* of the MYC family, *BCL2*, *SOX2*, rearranged during transfection (*RET*), oncogene nuclear factor IB (*NFIB*), and NOTCH ligands/inhibitors DLL3 and DLK1. The expression of the *NKX2-1* gene (encoding TTF-1) is also positively regulated by *ASCL1* (19). Subsequent analysis revealed that SCLC-A is divided into two clusters (SCLC-A and SCLC-A2), which differ in the expression of hairy and enhancer of split 1 (*HES1*) (17). SCLC-N is defined based on the expression

of *NEUROD1*, with an overall low expression level of NE markers (19,20). *NEUROD1* promotes neurogenic differentiation of cells during their development and malignant behavior of SCLC cell lines, and its target genes *MYC* (19) and oncogenic MycT58A can promote tumor development (20). The common target genes of *ASCL1* and *NEUROD1* are *INSM1*, a zinc finger transcription factor that acts as a driver of NE differentiation by inhibiting the NOTCH signaling pathway (22) and *HES6*, an inhibitor of the *HES1* transcription factor. SCLC-P is dependent on POU class 2 homeobox 3 (*POU2F3*), a transcription factor required for the generation, chemosensation, and immune function of specialized clusters of cells in the skin, oropharynx, gastrointestinal, and respiratory tracts (15). SCLC-P is *ASCL1/NEUROD1* double-negative "non-NE" SCLC, which involves the receptor tyrosine kinase insulin growth factor receptor 1 (*IFGR1*) pathway and is associated with the expression of TF *SOX9*, *ASCL2*, and *MYC*. Finally, the key transcriptional regulator yes-associated protein 1 (*YAP1*) in the HIPPO growth signaling pathway was found to drive the fourth subtype, SCLC-Y (6). YAP1 nuclear activity is associated with cancer stem cell renewal, metastasis, and chemo-resistance (18,23,24) and is considered one of the subtype-defining markers of "non-NE" SCLCs. SCLC-Y is associated with reduced expression of *INSM1*, enrichment of intact *RB1*, and possible overexpression of *MYC* (18); however, the expression of replication and proliferation genes is lower than that of other subtypes. Thus, some studies classify SCLC into the four subtypes "A, N, P, and Y" that is, SCLC-A (*ASCL1*), SCLC-N (*NEUROD1*), SCLC-P (*POU2F3*), and SCLC-Y (*YAP1*) (6). Studies have confirmed that there are significant differences in NE differentiation programs among these subtypes of transcriptional programs, with both *ASCL1*$^{+}$ and *NEUROD1*$^{+}$ subtypes being associated with a high NE program (NE marker^{high}/TTF-1^{high}/DLL3^{high}) and *POU2F3* and other *ASCL1/NEUROD1* double-negative subtypes being associated with a low NE program (NE marker^{low}/TTF-1^{low}/DLL3^{low}) (25).

Notably, it has been reported that *YAP1* expression is completely absent or only present at low levels in patients with SCLC (26), and recent studies on SCLC CTC-derived xenografts (CDXs) have not found significant YAP1 subtypes (27). Subsequent immunohistochemical analysis results have also failed to confirm the unique YAP1 subtypes (25). In addition, although YAP1 is primarily expressed in "non-NE" cells, it can also be present at a low level in NE-low cells. Therefore, YAP1 may not define a unique SCLC subtype, and its role as a marker for typing transcription factors needs to be further clarified in future studies. Some investigators have further explored the association between *YAP1* and immunity. Owonikoko *et al.* (28) found that SCLCs with *YAP1* positive was enriched in long-term survivors, and associated with high expression levels of interferon-γ (*INF-γ*) gene, human leukocyte antigen (*HLA*) gene, and T-cell receptor gene, and high scores of T-cell inflammatory gene expression profile (GEP). They subsequently replicated this inflammatory phenotype using SCLC cell lines and tumor samples in two independent validation datasets (28). Similarly, another study revealed that although SCLC is a cancer with the lowest expression of immune-related genes, SCLC-Y cell lines evidently show a tendency for better antigenic presentation and innate immune response. The expression of innate immune effector genes *cGAS*, stimulator of interferon genes (*STING*), *HLA-E*, and INF-induced genes is positively correlated with *YAP1* expression, whereas NE subtypes represented by SCLC-N and SCLC-A are negatively correlated with those genes (29). Therefore, although YAP1 may not be a key transcription factor that can facilitate the precise definition of SCLC subtypes, these key findings suggest that, in patients with triple-negative SCLC, there may be a population of immunomarker-rich phenotype cells that are characterized by the loss of *ASCL1/NEUROD1/POU2F3* and may be responsive to immunotherapy.

Recently, Gay *et al.* (30) identified four transcriptionally distinct SCLC subtypes by using non-negative matrix factorization (NMF) analysis of RNAseq from 81 resected SCLC samples and 62 SCLC cell lines, three of which were confirmed to present the characteristics defined by Rudin *et al.* (6) (including SCLC-A/*ASCL1*, SCLC-N/*NEUROD1* and SCLC-P/*POU2F3*). The fourth is a previously undescribed subtype with NE marker negativity, generally low or no transcription factor levels, and moderately elevated RB1 protein expression. Interestingly, the expression of immune checkpoints [including programmed death-ligand 1 (PD-L1), cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), cluster of differentiation (CD) 38, indoleamine 2,3-dioxygenase 1 (IDO1), T-cell immunoreceptor with Ig and ITIM domain protein (TIGIT), VISTA, inducible T-cell co-stimulator (ICOS), and lymphocyte activation gene 3 (LAG3)], *HLAs* genes, *STING*, *INF-γ* signaling pathway, T-cell inflammatory GEPs, and a variety of other inflammatory

markers on this novel subtype are up-regulated (30); therefore, it was named SCLC-inflamed or SCLC-I subtype. This is consistent with the findings of George *et al.* (21), who showed significantly high expression levels of genes encoding *HLAs* and other antigen presentation mechanisms in SCLC-I tumors. Another study, using CIBERSORTx deconvolution (31), quantified various immune populations according to gene expression and found that SCLC-I tumors had the highest total immune cell infiltration, including cytotoxic T cells, NK cells, and macrophages, as well as cytolytic activity scores. In addition, Gay *et al*. (30) showed that SCLC-I cell lines comprised "mesenchymal" tumors that lost cytokeratin and expressed vimentin (VIM), with the highest mean score of EMT, while SCLC-A was the most epithelial subtype, with the lowest score of EMT. The results of reverse-phase protein array (RPPA) of 62 SCLC cell lines support the conclusion that SCLC-I tumors express very low levels of the epithelial marker, E-cadherin (CDH1), and high levels of the mesenchymal markers, VIM and AXL (a member of the TAM family of receptor tyrosine kinases), which suggests the possibility of using EMT markers for discriminating SCLC subtypes (30). Notably, Gay *et al.* (30) observed higher expression of *YAP1* and its transcriptional targets in both SCLC-P and SCLC-I subtypes than in the other two subtypes; therefore, SCLC-I was not specifically defined by *YAP1* expression, which is consistent with recent analyses of two clinical samples (25) and CDXs (27). The proposal of novel SCLC-I may become the key to a more precise definition of SCLC subtypes, which may facilitate the effective prediction of the benefit of immunotherapy in specific patients with SCLC; however, this hypothesis needs further validation. This evidence reveals advances in novel SCLC molecular subtyping and heterogeneous biology, driving the designing of biomarker-driven clinical trials. In the future, development of new models must be continued to provide strong evidence for further identification of SCLC subtypes and to dispense precise and effective subtype-based treatment for patients with SCLC.

Tumor heterogeneity and plasticity of SCLCs

Tumor heterogeneity of SCLCs

SCLCs that look similar at the histopathological level may represent different tumor subtypes. SCLC tumors and cell lines exhibit significant differences in tumor morphology, growth characteristics, and molecular properties owing to the expression or absence of NE, presenting significant intertumoral heterogeneity. The NE-high subtype lineage is primarily driven by the transcription factors *ASCL1* and *NEUROD1*, which express *NKX2-1* but lack the expression of *REST* (12). The NE-low subtype lacks most NE markers but can express *REST*; it shows activation of the NOTCH, HIPPO, *TGF-β* pathways and *MYC* oncogenes (12). Recently, emerging evidence supports a model in which biologically relevant ITH can occur within SCLC tumors and during SCLC progression, including distinct subpopulations of interacting cells. Several findings suggest that multiple transcriptional subtypes may exist in a single tumor (32-34). A study with comprehensive immunohistochemical and histopathological characterization of SCLC subtypes showed that 69% and 17% of tumors were *ASCL1*-dominant and *NEUROD1*-dominant, respectively, and 22% expressed both the factors at high levels (IHC H-score >50 for both markers) (25), which is in good agreement with the findings of Zhang *et al.* (12), who showed a 19.8% double high expression of *ASCL1* and *NEUROD1*. In a study by Gay *et al*. (30), while <1% of cells expressed *POU2F3* in any model, these rare *POU2F3*$^+$ cells all showed co-expression of *ASCL1*; in addition, in MDA-SC39, approximately 10% of cells expressed both *ASCL1* and *NEUROD1*, although this proportion was lower than that in other tumors. The expression profiles of these markers showed more heterogeneity in native samples than in experimental models, particularly in terms of the high incidence of *ASCL1*/*NEUROD1* co-expression. Together, these data suggest that while most tumors or cells express only one of these transcription factors, their expression is not mutually exclusive, and this co-expression can occur on the same tumor or on the same cell.

Plasticity transformation and associated mechanisms of SCLCs

Single-cell and bioinformatic analyses revealed that SCLC subtype-specific ITH may be a dynamic transition process. Single-cell RNA sequencing (scRNA-seq) analysis of SCLC GEMM revealed that single tumor cells can gradually undergo evolution from one transcription factor-defined subtype/phenotype to another (32,35). For example, mesenchymal, inflamed descendants can appear spontaneously in cultures of SCLC-A cell lines (36,37). Data from SCLC cell lines of mice suggest that there may be a developmental hierarchy among subtypes that evolve

from SCLC-A to SCLC-N and subsequently to SCLC-Y (32). This indicates the possibility that these subtypes may represent the development of lineages or the existence of a continuum. ITH subtypes may underlie the natural history of SCLC. Notably, this subtype plasticity shift in SCLC is accompanied by the emergence of resistance to treatment. ScRNA-seq analysis of SCLC CTC-derived CDX models exhibited higher transcriptional ITH after platinum resistance (38). The emergence of SCLC-Y may be associated with chemo-resistance (18,23), and it has been shown that *YAP1*-positive "non-NE" cells cultured with CDX30P and CDX31P exhibit 5- to 7.5-fold higher resistance to cisplatin than *YAP1*-negative NE cells (27). A study by Song *et al.* (23) found that patients exhibiting high *YAP1* expression had shorter survival and more advanced disease stages than those exhibiting low *YAP1* expression. *YAP1* may induce multidrug resistance by inhibiting apoptosis of SCLCs, and this process may be involved in the expression of CD74. Gay *et al.* (30) performed scRNA-seq on two SCLC-A CDX models before and after platinum treatment and observed a decrease in the proportion of *ASCL1*$^+$ cells and the appearance of triple-negative (*ASCL1*$^-$/*NEUROD1*$^-$/*POU2F3*$^-$) SCLC-I cells with EMT scores in the post-treatment relapse model; although *HLA* expression was almost universally absent in naïve model cells, the expression of *HLA class II* genes, including *HLA-DRB1* and *HLA-DQA1*, was observed in the relapse model, and this was accompanied by platinum resistance, suggesting that the continuous evolution of decreased *ASCL1* expression and increased SCLC-I characteristics (e.g., EMT) of tumors may underlie platinum resistance. Researchers have found that the expression of *MYC* genes increased and that of *MYCL* and *ASCL1* decreased in chemo-resistant mice and humans with SCLC (38,39). A higher expression of *MYC* is associated with a shorter patient survival and a more aggressive resistance phenotype (10,40), suggesting that this phenotypic transformation and the development of resistance may be driven by the genes of the *MYC family*.

Overall, the copy number amplification of *MYC family* genes accounts for approximately 20% of SCLCs [*MYCL* (*MYCL1* or *L-MYC*), 9%; *MYCN*, 4%; and *MYC* (*c-MYC*), 6%] (41,42), suggesting that this gene family is involved in tumor carcinogenesis (21). Among them, *MYCL* overexpression is associated with the classical NE status of SCLC (primarily ASCL1 subtype) (19), while the amplification or overexpression of *c-MYC* is required to maintain the NEUROD1 subtype lineage status and can also appear in SCLC-P and SCLC-Y subtypes (6,21). In this study, replacement of *c-MYC* with *MYCL* gene in c-MYC SCLC cells induced cell transition to NE lineage state, which is highly similar to ASCL1-SCLC but could not lead to a complete transition to ASCL1-SCLC, suggesting that it could not completely control the trans-differentiation from NE-low or variant state to NE-high or classical state (43). However, in human SCLC cell lines and PDX models, *c-MYC* induced the trans-differentiation from ASCL1-SCLC to variant morphology with *NEUROD1* expression (33,40), accompanied by LCNEC-like/variant SCLC histological transition. Furthermore, findings of scRNA-seq analysis indicate that the *MYC* gene in GEMM could drive *ASCL1*$^+$ NE cells to *YAP1*$^+$ "non-NE" phenotype through *NEUROD1*$^+$ intermediates (32), while *ASCL1/NEUROD1* double-positive cells identified by Gay *et al.* (30) may support the hypothesis of this transition state and reveal the dynamic, potential transcriptional pattern transition of SCLC subtypes defined by different transcription-factor expressions. Drivers that regulate this unique transcriptional program and achieve lineage plasticity of molecular and histological subtypes may be the oncogenes *c-MYC* and *MYCL*, in which *MYCL* regulates the NE developmental pathway and *c-MYC* regulates EMT and NOTCH signaling.

NOTCH is considered to be a tumor suppressor associated with SCLCs, and approximately 25% of SCLCs (primarily NE-high type) have functionally inactivating mutations in the NOTCH pathway (21). In the absence of *RB1* and *TP53*, the loss of NOTCH function is postulated to lock cells in a self-renewing NE stem-like state (44), which leads to the development of SCLC. Activation of NOTCH can induce the transition from *MYCL*-associated NE SCLC model to "non-NE" SCLC fate in mouse and human SCLC cells by inhibiting the expression of *ASCL1* (35), which can slow down tumor-cell growth but typically leads to chemo-resistance (21,35); in mouse and human models, studies using time-series single-cell RNA-seq analysis showed that the activation of NOTCH signaling by *MYC* dedifferentiated NE tumor cells and promoted a continuous transition of SCLC from *ASCL1*$^+$ to *NEUROD1*$^+$ and to *YAP1*$^+$ state (32), revealing the dynamic evolutionary mechanism of SCLC subtypes. Regulation of SCLC by the NOTCH signaling pathway may be achieved by the transcriptional repression of the differentiation effector gene *hASH1* by the downstream target molecule of NOTCH signaling, *HES1* (45), which has also been shown to be particularly enriched in *MYC*-driven tumor-cell

transition to a "non-NE" fate (32). Another study found that the loss of NE differentiation and concomitant activation of NOTCH signaling is promoted by the activation of the *REST* factor, a transcriptional repressor of NE and neuronal differentiation (46), which could further lead to the specific expression of *HES1* in "non-NE" phenotype cells. Consistently, *REST* is absent in most NE SCLCs, which also leads to the inhibition of NOTCH signaling (3,12,35,47). The above studies propose a transcriptional network linking SCLC subtypes to *MYC* and its paralogs as well as the NOTCH and HIPPO pathways. Thus, it has been proposed that one of the mechanisms by which the NE differentiation program is absent in SCLC, may be mediated by *c-MYC* in a NOTCH signaling pathway-dependent manner, and the activation of NOTCH signaling is promoted by the activation of its target gene *REST*, which further promotes *HES1* transcription, ultimately leading to "non-NE" phenotype SCLC. However, it has also been proposed that this trans-differentiation can be mediated independent of NOTCH signaling or can be directly activated by *REST* (43).

In addition, researchers have proposed that epigenetic regulation might control a continuum of expression ranging from *ASCL1*-only to *NEUROD1*-only, with co-expression representing a transition state and driving NE differentiation. Gay *et al.* (30) revealed that different subtypes can be distinguished by methylation β values in the region upstream of the *NEUROD1* transcription start site (TSS). Specifically, the *ASCL1*-only cell line exhibited a relatively high methylation of sites both proximal and distal to the *NEUROD1* TSS, and the *NEUROD1*-only cell line exhibited almost no methylation of proximal sites and little methylation of highly distal sites; furthermore, the double-positive cell line exhibited low methylation of proximal sites and high methylation of highly distal sites. As predicted, the manipulation of epigenetic mechanisms modulates *NEUROD1* expression, and, to some extent, *ASCL1* expression. Treatment with lysine-specific histone demethylase 1 (LSD1) inhibitors revealed little change in *NEUROD1* expression, whereas treatment with decitabine, an inhibitor targeting DNA methyltransferase 1 (DNMT1), resulted in a significant and consistent upregulation of *NEUROD1*, including cell lines with no detectable *NEUROD1* expression at baseline (30); furthermore, both LSD1 inhibitors and decitabine can lead to a modest downregulation of *ASCL1* (30), indicating that epigenetic mechanisms may regulate transformation between SCLC-A and SCLC-N models.

A comprehensive analysis of the identification of molecular subtypes of SCLCs in a previous study revealed the association between different molecular subtypes and cellular programs (e.g., "stemness," "interstitial," or "NE" programs), and their evolution over time and treatment may explain the prominent plasticity and strong metastatic potential of SCLCs (48,49). These studies provide evidence of SCLC tumor heterogeneity and transcriptional plasticity as well as clues to investigate tumor evolution, responsiveness to specific therapeutic agents, and the development of acquired resistance; additionally, they help investigators focus on the development of therapies for patients who may benefit from a particular therapeutic approach.

Precision treatment strategies for different SCLC subtypes

Currently, no significant benefits of targeted therapy and immunotherapy for patients with SCLC have been observed. The association of SCLCs with the selective activation of major transcriptional regulators has recently attracted interest in transcriptional regulatory strategies. Identifying subtype-specific molecular signatures and clinically meaningful biomarkers and improving the understanding of the key signaling pathways that play a role in specific SCLC subtypes may help explore new targets and corresponding targeted therapeutic strategies for SCLCs.

Treatments for SCLC-A

Inactivating mutations in NOTCH family members and abnormally high expression of DLL3, a key negative regulator of NOTCH signaling, are commonly observed in SCLC-A subtype (50). DLL3 is a direct transcriptional target of *ASCL1*. DLL3 inhibitors selectively target SCLC-A tumors (50,51). The antibody-drug conjugate, rovalpituzumab teserine (Rova-T), was the first targeted therapy that used DLL3 as a novel biomarker for the treatment of SCLC (52,53). First-in-human clinical trials of Rova-T on patients with recurrent SCLC have shown encouraging activities despite causing serious adverse events. Subsequent studies including the phase II TRINITY study and the phase III TAHOE trial of second-line therapy revealed discouraging efficacy data, leading to the discontinuation of the development of Rova-T (53,54). Nevertheless, DLL3 remains an important target for the

development of SCLC drugs, and other active strategies include bispecific antibody T-cell technology (BiTE), AMG 757 (NCT03319940), chimeric antigen receptor (CAR)-T, and AMG119 (NCT03392064). *BCL-2* is another direct transcriptional target of *ASCL1*. *BCL2* inhibitors (venetoclax) have been the focus of research and development of multiple targeted inhibitors in SCLC clinical trials; however, these may exhibit high activity only against SCLC-A (16,51). In addition, recent data suggest that the inhibition of another epigenetic modifier, LSD1, drives NOTCH1 activation and leads to ASCL1 inhibition in patients with SCLC (55), indicating the selective activity of LSD1 inhibitors in patients with SCLC-A, which is being explored in patients with SCLC (NCT02034123).

Treatments for SCLC-N

SCLC-N is typically associated with *c-MYC* amplification, which can serve as a potential target for therapeutic agents. Tumors characterized by high *c-MYC* expression are preferentially sensitive to aurora kinase (AURK) A/B, checkpoint kinase (CHK) 1, and IMPDH (inosine-5'-monophosphate dehydrogenase) 1/2 inhibition (39,51, 56,57). *MYC*-driven SCLC cells are highly dependent on arginine-regulated pathways, including polyamine biosynthesis and mammalian target of rapamycin (mTOR) pathway activation. Selective arginine depletion appears to be significantly effective in *MYC*-driven preclinical models of SCLC-N (39). Oncolytic Seneca Valley virus (SVV), which selectively targets SCLC-N tumor cells, could have selective efficacy either as a single agent or as a strategy to enhance immunotherapy by selectively introducing viral antigens in tumor cells (58). Alternatively, the SCLC-N model is highly sensitive to multiple AURK inhibitors (AURKi), and c-MYC protein expression is a predictive biomarker of AURKi sensitivity (34,59). The phase II clinical trial (NCT01045421) tested the activity and safety of AURKi and alisertib in patients with relapsed or refractory SCLCs or other cancers (60,61). Aurora amplification is associated with taxane resistance. A recent clinical trial showed that, compared with paclitaxel alone, alisertib combined with paclitaxel was associated with a significantly higher progression-free survival (PFS) in patients with *c-MYC*-positive SCLCs (59), while patients with low c-MYC expression showed a better response to paclitaxel alone. Phase II clinical trials of alisertib, alone or in combination with other drugs, for the treatment of multiple tumor types, have shown its antitumor activity and provided therapeutic strategies for recurrent SCLCs (61). Other strategies for SCLC-N may involve inhibition of the phosphatidylinositide 3-kinase (PI3K)/mTOR pathway and heat shock protein 90 (HSP90) (51).

Treatments for SCLC-P

SCLC-P may be the most sensitive subtype to antimetabolites and poly ADP-ribose polymerase (PARP) inhibitors that target DNA damage repair pathways. A phase II trial of veliparib in combination with temozolomide in patients with previously treated SCLC did not meet its primary endpoint of PFS improvement but showed an improvement in objective response rate of 39% (NCT0163854697). Previous studies have demonstrated that the expression of Schlafen11 (SLFN11) is the most sensitive predictive biomarker of efficacy in studies on DNA-damaging chemotherapy and PARP inhibitors (62-64). Approximately 40% of 116 SCLC cell lines from a global drug and genomic database (SCLC-Global) do not express SLFN11, which predicts resistance to DNA-damaging agents (29). Notably, it was also found that most of the models showing the highest expression of SLFN11 were SCLC-A and showed a bimodal expression pattern (29), and when the expression level of SLFN11 distinguished SCLC-A groups, there was a significant difference in sensitivity to cisplatin and olaparib. Therefore, additional biomarker analysis may be required to further identify sensitive drug-target candidates after the identification of SCLC subtypes using transcription-factor markers. In addition, on the basis of results of clustered regularly interspaced short palindromic repeats (CRISPR) screening, SCLC-P cells may be sensitive to insulin-like growth factor 1 receptor (IGF1R) inhibitors (15); however, no such inhibitors are currently used in clinical practice.

Treatment for SCLC-Y

The SCLC-Y cell line shows the highest resistance to standard chemotherapy, and an obvious resistance phenotype between YAP1 expression and the response of etoposide and camptothecin can be observed throughout the database of the Cancer Cell Line Encyclopedia (CCLE)/Cancer Therapeutics Response Portal (CTRP) (29). SCLC-Y cells express the "non-NE" markers CD151 and ephrin type-A receptor (EPHA2) and may respond to inhibitors targeting *YAP1* and NOTCH in clinical development (65,66). In addition, considering the

association of SCLC-Y with immunity, the likelihood of its response to immune checkpoint inhibitors (ICIs) is high (67). On the basis of the results of gene expression and recent in silico studies, SCLC-Y shows the highest sensitivity to mTOR, polo-like kinase 1 (PLK1), and potentially to cyclin-dependent kinase (CDK) 4/6 inhibitors (18,68).

Treatment for SCLC-I

Although the current scenario of immunotherapy for SCLC is not optimistic as a whole, with a response rate of only approximately 15% (69-71), evidence suggests that SCLCs have immunogenic potential, and an in-depth exploration of SCLC immunophenotypes and molecular subtypes may improve the understanding of the potential immunological characteristics of patients with SCLC to facilitate effective immunotherapy. Recently, the newly identified SCLC-I subtype was found to potentially have a high response to immunotherapy, and this finding will revolutionize SCLC immunotherapy. Gay *et al.* (30) divided patients in the IMpower133 study (72) into four groups and reanalyzed patient survival to explore whether patients with SCLC-I tumors may preferentially benefit from ICIs. Patients with SCLC-I were found to have a significantly higher OS benefit than those with other subtypes in the chemotherapy combined with atezolizumab group [hazard ratio (HR): 0.566; 95% confidence interval (95% CI): 0.321−0.998), but not in the control group (placebo combined with chemotherapy), indicating that SCLC-I could predict the benefit of ICIs (30). Although this trial was not designed for this analysis, a trend toward a preferential response to immune combination chemotherapy was observed in patients with SCLC-I, and these data deserve further validation in future SCLC-based umbrella trials. Interestingly, Bruton's tyrosine kinase (BTK), another target commonly associated with immune cells, is highly expressed in SCLC-I tumors (30). Therefore, this subtype may be sensitive to the BTK inhibitor, imbruvica. Furthermore, EMT is another potentially targetable feature of SCLC-I tumors. It was found that mocetinostat, a histone deacetylase inhibitor, reduced VIM expression and increased E-cadherin expression in the SCLC-I (H841) cell line, which is consistent with EMT reversal (30) and might be a future direction for therapeutic development. *Table 1* summarizes the different subtypes of SCLC, genes/pathways related to each subtype, and the corresponding treatment strategies.

Summary and prospects

Over the past three decades, no significant progress has been made in the systemic treatment of SCLCs, primarily because of tumor heterogeneity and high plasticity. Recently, substantial progress has been made in understanding the biology of SCLC, defining different SCLC subtypes using major transcriptional regulators, clarifying their different gene expression profiles, and indicating that different subtypes are dynamically changing, emphasizing the strong plasticity and ITH of SCLC. Recently, advances in genomics, the development of single-cell sequencing analysis, and the development of new preclinical models have helped researchers gain new insights into the disease-specific genetic alteration, molecular typing, and tumor heterogeneity of SCLCs and better explain the similarity, diversity, and biological behavior of different subtypes. These biologically distinct subtypes may define unique therapeutic vulnerabilities and resistance, facilitating the development of molecular targeted therapies and immunological strategies.

Future research should focus on the following: First, further insight into SCLC genetic characteristics, tumor heterogeneity, and molecular subtypes should be sought to analyze different SCLC subtype-specific treatment vulnerabilities and the correlation of each subtype classification with specific treatment outcomes and corresponding predictive biomarkers; new targets and innovative biomarkers should be used to guide the stratification of patients with SCLC to develop and integrate corresponding targeted or immuno-personalized treatment strategies, to provide clinical insights into the prognostic significance of subtype classification and the predictive significance of standard and investigational therapies, and ultimately to expand the therapeutic benefit to a larger proportion of patients. Second, the development of new drugs, such as blocking the transition of different SCLC-phenotypes by targeting epigenetic regulators and the combination of different subtype-specific therapies, may have a substantial effect on this fatal disease. Furthermore, considering the emerging preclinical data on functional plasticity and phenotypic diversity, it is recommended that in future studies, liquid biopsy techniques should be fully combined (e.g., CTCs, peripheral immune cell profiling, and circulating tumor DNA) to dynamically and continuously monitor the spatiotemporal heterogeneity of tumors before and during treatment, which may be suggestive of treatment benefits.

Table 1 Different subtypes of SCLC, related genes/pathways, and corresponding treatment strategies

Traditional classification of SCLCs	Characteristics	Related genes/pathways	Novel SCLC subtypes defined by transcriptional regulators	Major transcriptional factor	Related genes/pathways	Treatments
NE-high subtype	Classic SCLC morphology; Epithelial phenotype	*ASCL1*, *INSM1*, *SYP*, *BEX1*, *CHGA*, *NKX2-1*, *DLL3*, *DLK1*, *HES6*, *TTF-1*, *CDH1*	SCLC-A	*ASCL1*	*MYCL*, *BCL2*, *SOX2*, *RET*, *NFIB*, *DLL3*, *DLK1*, *NKX2-1*, *INSM1*, *HES6*, *TTF-1*	DLL3 inhibitors: Antibody-drug conjugate, rovalpituzumab teserine (Rova-T); Bispecific antibody T-cell technology (BiTE), AMG 757 (NCT03319940); Chimeric antigen receptor (CAR)-T, AMG119 (NCT03392064); BCL2 inhibitors: venetoclax; LSD1 inhibitors: (NCT02034123)
			SCLC-N	*NEUROD1*	*MYC*, *MycT58A*, *INSM1*, *HES6*	AURKA/B, CHK1, IMPDH1/2 inhibition; Arginine depletion; Oncolytic Seneca Valley virus (SVV); AURK inhibitors: Alisertib
NE-low subtype/non-NE SCLC	Variant form of SCLC; Mesenchymal phenotype	*NOTCH*, *HES1*, *MYC*, *REST*, *ASCL2*, *HIPPO/YAP1*, *TGF-β*, *EMT* (vimentin, SNAI2, CD44), *MYB*, *BCL2*	SCLC-P	*POU2F3*	IFGR1 pathway, *SOX9*, *ASCL2*, *MYC*	Antimetabolites: anti-folates and nucleoside analogues; PARP inhibitors (veliparib, olaparib)
			SCLC-Y	*YAP1*	HIPPO signaling, intact *RB1*, overexpress *MYC*	mTOR inhibitors, PLK inhibitors*; CDK4/6 inhibitors*; YAP1 and NOTCH inhibitors*; ICIs*
					INF-γ gene, T-cell inflammatory GEP score, human leukocyte antigens (*HLAs*) gene, T-cell receptor gene, *cGAS*, *STING*	
			SCLC-I/ inflamed	*ASCL1*$^{-}$/*NEUROD1*$^{-}$/*POU2F3*$^{-}$	Inflamed: immune checkpoints, *HLAs* genes, *STING*, *INF-γ* pathway, T-cell inflammatory GEPs, immune cell infiltration	ICIs (atezolizumab); BTK inhibitor (imbruvica)*
					EMT: vimentin, AXL	

*, Therapeutic agents have only preliminary exploration results in SCLC subtypes or may become one of the treatments in the future; SCLC, small cell lung cancer; NE, neuroendocrine.

Finally, the development of new experimental models combining various genetic alterations and different putative cell-of-origin types will be the key to modeling all subtypes. In the future, SCLC patient-relevant preclinical models spanning different subtypes should be developed and characterized, with an emphasis on expanding the number of models to evaluate the molecular characteristics and treatment sensitivity of different SCLC subtypes. The availability of large biobanks of relevant models for patients with SCLC, including longitudinal models, could allow the fields to explore inter- and intratumoral heterogeneity in further detail to find optimized and personalized therapies for this aggressive cancer.

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Footnote

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