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# Small Cell Lung Cancer is Being Unveiled: Recent Advances are changing the Clinical Practices

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## Abstract

SCLC remains one of the most lethal lung cancers with limited therapeutic options. In recent years, we have made many advances on pathogenesis, heterogeneity and mechanism of resistance in SCLC. Increasing studies demonstrate that SCLC is a highly heterogeneous tumor. According to differentially expressed Neuroendocrine (NE) neuroendocrine, it can be divided into at least two categories, including NE and non-NE (or NE-low) subtypes. Charles M. Rudin and colleagues propose a novel method for SCLC subtypes defined by differential expression of key transcription regulators through integrating transcriptomic sequencing data. Each subtype has different clinicopathological characteristics. Cell line models *in vitro* demonstrate SCLC-A subtype is sensitive to BCL2 inhibitors, and SCLC-N subtype is highly sensitive to multiple Aurora Kinase (AURK) inhibitors. Besides, SCLC molecular subtypes exhibit distinct immunogenic feature, which could evoke varied responses to Immune Checkpoint Inhibitors (ICIs). Especially, *POU2F3*-expressing SCLC might origin from pulmonary tuft cells rather than neuroendocrine cells. And SCLC cells has enhanced plasticity and play an vital role in the cancer chemotherapy resistance and recurrence, and the mechanism underlying the cells plasticity has not yet been elucidated. It is vital to investigate the genetic characteristics of SCLC and their clinical significance. And our results provide some practical information. These advances are changing the clinical practices of SCLC.

**Keywords:** Small cell lung cancer; Neuroendocrine; Transcriptional subtyping; Cell plasticity; Genetic alteration

## Introduction

Small Cell Lung Cancer (SCLC) is a type of neuroendocrine carcinoma characterized by aggressive phenotypes with high frequency of *p53* and *Rb* mutation [1]. It accounts for 10%-15%of all lung cancer cases, and more than 80% SCLC cases are diagnosed as extensive-stage SCLC (ES-SCLC) and lose operation opportunity. Unlike Non-Small Cell Lung Cancer (NSCLC), almost no driver genes are targeted for SCLC in the past few decades [2]. Chemotherapy containing platinum has remained the most commonly used regimen for the first-line SCLC at extensive stage for decades. In recent years combination of atezolizumab and chemotherapy in the first-line treatment of ES-SCLC resulted in significantly longer overall survival and progression-free survival than chemotherapy alone (the median overall survival was 12.3 months in the atezolizumab group and 10.3 months in the placebo group (hazard ratio for death, 0.70, P=0.007) [3]. Most SCLC patients are sensitive to initial first-line treatment. However, almost all patients would relapse, the relapsed tumors are resistant to radiotherapy and chemotherapy, and the prognosis is poor. Topotecan is FDA-approved second-line drug for SCLC. The median Progress-Free Survival (PFS) is 3 to 3.5 months [4]. Thus, SCLC remains one of the most lethal cancers with limited therapeutic options.

## Review of Literature

### Neuroendocrine phenotype subtyping and the significance in SCLC

Increasing studies demonstrate that SCLC is a highly heterogeneous tumour [5]. According to differentially expressed Neuroendocrine (NE) markers, it can be divided into at least two categories, including NE and non-NE (or NE-low) subtypes [6]. The biological implications of NE subtypes in metastatic SCLC are being gradually clarified. The Non-NE SCLC usually chemotherapy-resistant and worse prognosis than NE SCLC. YAP/TAZ and Notch are required for generating non-NE SCLC tumor cells, but not for initiating SCLC [7]. NE SCLC are more likely to have mutations including *RB1*, NOTCH, and chromatin modifier genes, up regulation of DNA damage response genes, and are more prone to response to replication stress targeted therapies, SCLC

patients might benefit more from immunotherapy if their tumors were non-NE [8]. Christina and colleague found non-NE SCLC is more prone to Ferroptosis through subtype-specific lipidome remodeling. NE SCLC acquires addiction to the thioredoxin pathway and is resistant to Ferroptosis [9,10]. NE-low SCLC has more immune cells and checkpoint molecule distribution in the microenvironment than NE-high SCLC [11]. SCLC also has different epigenetic characteristics, which might cause different neuroendocrine phenotypes [12]. In summary these characteristics determine the need for personalized medical practice in the face of SCLC patients.

## Transcriptional subtyping and the significance in SCLC

Charles Rudin and colleagues apply a novel method for SCLC subtypes defined by differential expression of four key transcription regulators: *ASCL1* (called SCLC-A subtype), *NEUROD1* (called SCLC-N subtype), *YAP1* (called SCLC-Y subtype) and *POU2F3* (called SCLC-P subtype) through integrating transcriptomic sequencing data [13,14]. Subsequent results suggest that *YAP1* subtype is inappropriate, and an inflamed subtype of SCLC (SCLC-I subtype) is recently proposed to replace *YAP1* subtype [15]. In addition, cell line models *in vitro* demonstrate SCLC-A subtype is sensitive to BCL2 inhibitors, and SCLC-N subtype is highly sensitive to multiple Aurora Kinase (AURK) inhibitors. For Cisplatin, SCLC-P subtype has the highest sensitivity, while SCLC-N and SCLC-I subtypes are resistant to Cisplatin, and SCLC-A subtype was found differentiated sensitivities [16]. SYP is mainly expressed in SCLC-A and N subtypes and the microenvironment lacks CD8+ T cells comparing to SCLC-I subtype [17]. Comparing SCLC-A subtype SCLC-N exhibits less infiltrating lymphocytes and more obvious cytotoxic T cell dysfunction [18]. Lurbinectedin might be a novel therapeutic option for SCLC because it binds to transcriptionally active regions (promoters of *ASCL1*- and *NEUROD1*-dependent genes) in SCLC [13]. *POU2F3*-expressing SCLC might origin from pulmonary tuft cells rather than neuroendocrine cells. It is an effective strategy to targeting receptor tyrosine kinase IGF1R (insulin-like growth factor 1 receptor) for the tuft cell-like variant of SCLC [19]. Lurbinectedin might also be a great choice for *POU2F3*-expressing SCLC [20]. SCLC molecular subtypes exhibit distinct immunogenic feature, which could evoke varied responses to Immune Checkpoint Inhibitors (ICIs) [21]. Although SCLC-I subtype benefit most from ICIs, clinical significance of this molecular subtyping in predicting effectiveness and estimating prognosis remains limited in other therapeutic options for SCLC [22].

## Cell plasticity and the significance in SCLC

Nevertheless, we have to also recognize that SCLC cell plasticity would be a new challenge. Single cell sequencing indicate that Myc could drives a dynamic shift in SCLC from *ASCL1*+ to *NEUROD1*+ to *YAP1*+ states through Notch pathway [23,24]. After standard chemotherapy, patients with high *FOXM1* expression had shorter progression-free survival compared to those with low *FOXM1* expression (3.90 *vs*. 8.69 months) [25]. Soluble guanylate cyclase (sGC) is upregulated in post-chemotherapy progression and associates with acquired chemoresistance [26]. Dihydroorotate dehydrogenase (DHODH) is a key enzyme in pyrimidine biosynthesis pathway, and PDX models indicated that DHODH has been a promising target in SCLC [27]. Myc-driven SCLC has specific metabolic features and is vulnerable to arginine depletion [28]. High SLFN11 expression is a predictor for benefiting from temozolomide plus PARP inhibitor, SLFN11 expression was absent in 40% of tumors, especially those negative for the four subtype markers. However, the researchers do not observe greater sensitivity for temozolomide plus PARP inhibitor in a specific SCLC subtype (SCLC-A, SCLC-N, SCLC-I or SCLC-P) [29]. Further study indicate that SCLC exhibits SCLC-I subtype phenotype after EP treatment, including loss expression of subtype specific TF, up regulated MHC levels, and an enhanced epithelial mesenchymal transition. NOTCH pathway is re-activated after chemotherapy and it is an indicator of NE to non-NE transition [30], which suggests that SCLC-I cells might be highly plastic and have capacity to relapse. SCLC plasticity is linked to therapeutic resistance, and the mechanism underlying the cells plasticity has not yet been elucidated. Increased evidences have led to the hypothesis that there might be a stem cell-like subset called Cancer Stem Cells (CSCs) or Tumor Initiating Cells (TICs) in solid tumors. And these cells have enhanced plasticity and play a vital role in the cancer chemotherapy resistance and recurrence [31]. SCLC cell lines have a higher proportion of stem cells comparing to lung adenocarcinoma [32]. Joseph and colleagues [18] found that there is a *PLCG2*-high subset with pro-metastatic and stem-like phenotype across different SCLC subtypes *via* single cell RNA-sequencing. Further observation indicates that the recurrent *PLCG2*-high SCLC is associated with the profibrotic and immunosuppressive microenvironment, which is related to poor prognosis.

## Genetic alteration and the significance in SCLC

Nowadays, NGS is widely used in routine clinical practice of non-SCLC to assist in therapeutic options and prognosis evaluation. Therefore, it is vital to investigate the genetic characteristics of SCLC and their clinical significance. Our results provide some practical information. In our cohort the co-mutation of *TP53* and *RB1* have a mutation rate of 72%. Previous reports reveal that *RB1* status plays a vital effect on the treatment outcome in pulmonary large-cell neuroendocrine carcinoma [33]. Gene mutation rate is significantly higher in SCLC with *RB1* gene mutated when compared to samples with wild type *RB1* [34]. Notably, SCLC treatment with wild-type *RB1* must be further explored.

## Discussion

Our previous works found LRP1B or MAP3K13 mutation could significantly shortened PFS in SCLC patients [35]. Moreover, SCLC patients with MSH6 or SPEN mutation status could guide the overall prognosis of the patient. Mutant-PIK3CA and mutant-FAT1 might play a role in regulating organ-specific metastasis. Furthermore, the signaling pathways analysis linked to PFS and OS were identified, and these findings may provide genetic explanations for clinicopathological features, which could contribute to the personalized clinical practices in SCLC. We have to point out that due to the limited sample size the conclusion of this further investigation.

## Prospects

New advances of tumor pathogenesis, heterogeneity and mechanism of resistance are expected to change the clinical practices. Overall, it is indispensable to integrate molecular subtyping (neuroendocrine phenotype and transcriptional subtyping) and genetic alteration in the therapeutic options and prognosis evaluation for SCLC patients. We believe that the future clinical practice of SCLC will greatly benefit from this therapeutic modality in Figure 1.

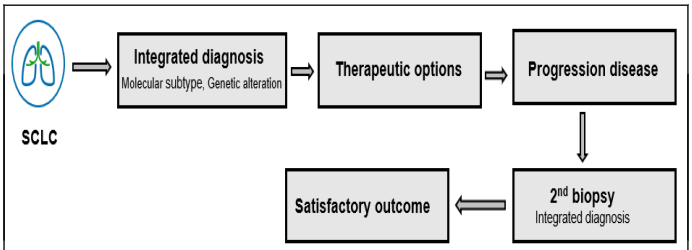


**Figure 1:** The Future clinical therapeutic modality of SCLC.

## Conclusion

According to differentially expressed Neuroendocrine (NE) neuroendocrine, SCLC can be divided into at least two categories, including NE and non-NE (or NE-low) subtypes. Charles M. Rudin and colleagues propose a novel method for SCLC subtypes defined by differential expression of key transcription regulators through integrating transcriptomic sequencing data. Each subtype has different clinicopathological characteristics. Besides, SCLC molecular subtypes exhibit distinct immunogenic feature, which could evoke varied responses to Immune Checkpoint Inhibitors (ICIs). Especially, *POU2F3*-expressing SCLC might origin from pulmonary tuft cells rather than neuroendocrine cells. And SCLC cells has enhanced plasticity and play an vital role in the cancer chemotherapy resistance and recurrence, and the mechanism underlying the cells plasticity has not yet been elucidated. It is vital to investigate the genetic characteristics of SCLC and their clinical significance. And our results provide some practical information. These advances are changing the clinical practices of SCLC.

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## Disclosure

The authors declare that they have no conflicts of interest in this work.

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