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Review Article

Abnormally activated signaling pathways as potential therapeutic targets, and diagnostic biomarkers in the management of small-cell lung cancers – A review

Lihai Zhang, Longxia Dai, Jian Xiao, Bixiu He*
Department of Elderly Respiratory, Xiangya Hospital, Central South University, Changsha 410008, China

For correspondence:* ***Email:* *hebixiuhbx@163.com*

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Abstract

Small-cell lung cancer (SCLC) has relatively aggressive spread characteristics and a poor prognosis. Current treatment methods include surgery, chemotherapy, radiotherapy, and immunotherapy. However, the prognosis remains poor. This article summarizes the related signaling pathways and factors that may be used as therapeutic targets and early diagnostic biomarkers in the pathogenesis of SCLC. Furthermore, this study provides a theoretical reference for the clinical treatment of SCLC.

Keywords: *Small cell lung cancer (SCLC), Signaling pathway, Biomarker, Lung cancer, Chemotherapy, Radiotherapy, Immunotherapy*

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INTRODUCTION

Small-cell lung cancer (SCLC) is the most malignant type of lung cancer, accounting for approximately 20% of new lung cancers. SCLC includes three subtypes: oat cell type, spin type, and mixed type.–SCLC is divided into limited and extensive stages depending on the extent of the lesion. Due to the short doubling time, rapid progression, early metastasis, and easy recurrence of SCLC, the incidence of morbidity is increasing yearly and only one-third of the patients are properly diagnosed in the early stages of the cancer Presently, treatment methods include surgery, chemotherapy, and radiotherapy. However, its prognosis is extremely poor. Targeted therapies and immunotherapies that have emerged in recent years are also undergoing extensive clinical trials. Although highly sensitive to initial therapy and radiotherapy, most patients have poor long-term survival, with a five year survival rate of approximately 12 – 17 % [1]. A number of factors affect the prognosis of SCLC; this includes: age, smoking history, tumor stage, presence or absence of metastasis, sensitivity to chemotherapy, and radiotherapy [2]. Furthermore, the pathogenesis of SCLC remains unclear. In recent years, along with the development of molecular biology and cell biology techniques, the understanding of the pathogenesis of SCLC has gradually deepened.

This study reviews the signaling pathways involved in the progression of SCLC as well as possible therapeutic targets and prognostic tumor markers.

SCLC signaling pathways in SCLC progression

SCLC is a neuroendocrine tumor with a very poor prognosis. In the past eight years, advances in various aspects of SCLC have been reported. In the present study, we have summarized the cancer-related signaling pathways involved in the progression of SCLC (Figure 1).

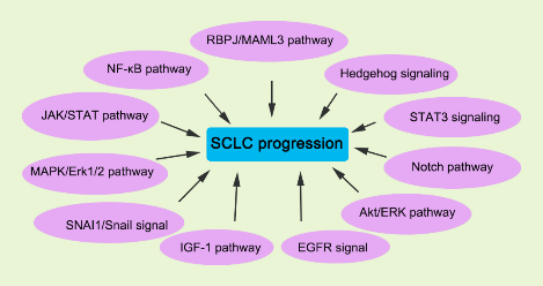

Figure 1: Abnormal activation of various signaling pathways in the progression of SCLC. The activated signaling pathways referred to in this study include the MAPK/Erk signaling pathway, Notch related pathway, EGFR related pathway, NF-κB signaling pathway, and Hedgehog/Gli signaling pathway. Among them, the Notch pathway regulates the differentiation of tracheal epithelium cells to the neuroendocrine cell and activation of the Hedgehog pathway in the tracheal epithelial cells directly accelerates the conversion of neuroendocrine cells

The Notch signaling pathway plays an oncogenic or anti-proliferative role in the development of various human cancers. It also mediates angiogenesis, facilitating tumor growth in SCLC patients. Arsenic trioxide exerts tumor suppressor effects by blocking angiogenesis and reducing microvessel density via Notch signaling in SCLC [3]. Notch1 is reported to be absent in SCLC *in vivo*, but appears after chemoresistance development. It has been reported that ASCL1 is negatively affected by the Notch pathway and that it promotes neuroendocrine differentiation as well as EMT. However, it has also been reported that Notch1 controls the epithelial mesenchymal transition (EMT) phenotype. Overexpression of Notch1 inhibits EMT, cell motility, and metastatic potential of SCLC cells [4].

Some small chemical molecules targeting the main kinases in the RAF/MEK/ERK pathway are good choices for the treatment of SCLCs. This includes combination with other therapeutic drugs. During hyperthermia treatment, hypoxia-triggered HIF-1a expression in SCLCs is regulated by the AKT pathway, but not by the ERK signaling pathway. This revealed the molecular mechanisms of SCLC following hyperthermia treatment[5]. Curcumin inhibits cell proliferation and angiogenesis by suppressing STAT3. Retinoic acid amide exerts antiproliferative effects against lung cancers *in vitro* and *in vivo* by inhibiting JAK/STAT activation and inducing cell apoptosis [6].

The Hedgehog signaling pathway is highly activated in SCLC cells. In particular, constitutive expression of Smoothened (Smo) increases the proliferation ability of human SCLC cells *in vitro* and mouse SCLC cells *in vivo* [7]. The tropomyosin-related kinase B (TRKB) pathway and Hedgehog signaling pathway exhibited negative crosstalk and inhibited the Hedgehog signaling pathway to upregulate TRKB levels. This could antagonize the suppression in SCLC cells. However, the combined interference of TRKB and GLI1 decreased the invasiveness of SCLC cells. Combinatorial therapy with TRKB inhibitor and Hh inhibitor would be helpful in treating refractory SCLC.

In SCLC cells, EGFR and mTOR pathways contribute to the progression of SCLC. Combination treatment with erlotinib and RAD001 had a synergistic effect on reducing cell viability and proliferation suggesting that combined inhibition of EGFR/mTOR pathways might be a useful approach in SCLC therapy [8]. Bone morphogenetic protein 7 (BMP7) belongs to the BMP family of signaling molecules. rhBMP7 inhibited the proliferation, motility, and invasion of SBC-3 and SBC-5 cells by increasing the proportion of cells in the G1 phase and decreasing the proportion of cells in the S phase suggesting that BMP7 plays a key role in regulating the progression of SCLC [9]. Multidrug resistance (MDR) is a major obstacle affecting the long-term survival rate of patients with SCLC. Research on miRNAs and their putative target genes is useful for providing clues for research on MDR of SCLC. Downregulation of the anti-apoptotic BAG3 protein promotes cell death and sensitizes SCLC cells to cisplatin treatment [10].

Therapeutic targets and potential biomarkers in the prognosis of SCLCs

As SCLC has the marked potential to invade and migrate to distant organs, such as the brain and bone, it is urgent to identify early detection biomarkers and new targets for the treatment of SCLC. Here, we summarized several factors that could be used as new targets in clinical therapy for SCLC (Table 1).

Table 1: Promising therapeutic targets in the context of SCLC

Target gene	Expression in SCLC samples	Function in SCLC progression
EZH2	Up	EZH2 is an oncogene that promotes the progression of SCLC.
Smoothened	Up	Smo promotes the proliferative ability of human SCLC *in vitro* and mouse SCLC *in viv.*
DLL3	Up	Overexpression of DLL3 increases tumor growth in mouse via modulation of SNAI1/Snail expression.
BAG3	Up	BAG3 inhibits apoptosis, resulting in resistance to chemotherapy.
Aurora B	Up	Barasertib (AZD1152), a small molecule aurora B inhibitor, inhibits the growth of SCLC cell lines *in vitro* and *in vivo.*
BMP7	Down	rhBMP7 inhibits the proliferation of SCLC cells by inducing the G1 phase arrest.

The expression of STAT3 and VEGF-C is markedly higher in SCLC tumors than in adjacent normal tissues. Therefore, they could be used as new targets in the clinical therapy of SCLC patients. The E2F/Rb pathway was found to be deregulated in 96 % of the SCLC samples and was associated with higher levels of EZH2. EZH2 is an oncogene that promotes SCLC growth [11]. Delta-like protein 3 (DLL3) is highly expressed in SCLC samples and promotes tumorigenesis and invasion of SCLC cells by positively regulating the SNAI1/Snail pathway [12]. Aurora kinase inhibitors are effective in 3 – 7 % of SCLC patients, and inhibition of Aurora B induces the G2/M-arrest and cell apoptosis in SCLC [13]. SCLC tumors with high copies of cMYC amplification respond to Aurora B inhibitors such as barasertib (AZD1152), which could suppress SCLC cell proliferation *in vitro* and *in vivo* [14].

The high metastatic potential of SCLCs, including brain metastasis (BM), is a major cause of mortality. PLGF may be a potential therapeutic target for inhibiting the BM of SCLCs. It has been reported that the transcription factor CREB is activated and its expression is elevated in SCLC tumors. CREB activity is blocked by a dominant-negative form of PKA and it inhibits the progression of SCLC [15]. Thus, CREB has been recognized as a promising therapeutic target for SCLC [16]. Fidgetin-like 1 (FIGNL1) functions in DNA double-strand repair. FIGNL1 is a promising potential therapeutic target and biomarker for SCLC[17]. TRPA1 is highly expressed in human SCLC cell lines. TRPA1 prevents apoptosis in SCLC cells, and thus, could be a promising target for SCLC therapy [18]. The cell-cell interaction between tumor-associated macrophages (TAMs) and SCLC cells could be a target for clinical therapy of SCLCs. For example, immunohistochemical analysis revealed that STAT3 is activated in SCLC cells near TAMs in the stroma, and macrophage-derived culture supernatant (CS) induces STAT3 activation in SCLC cells as shown in Figure 2 [19].

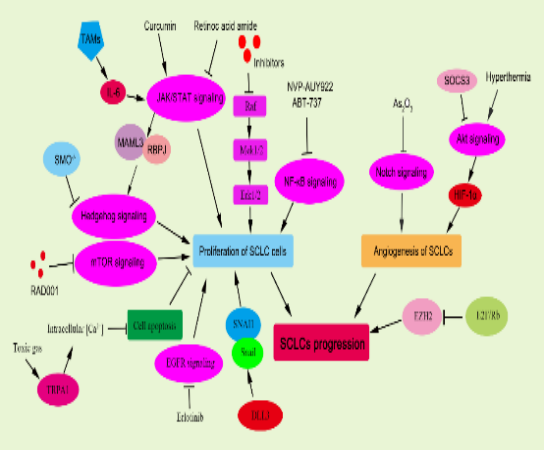

Figure 2: Possible therapeutic targets and regulatory agents in the progression of SCLC

MicroRNAs are a class of endogenous and conserved RNAs with lengths of 20 - 24 nucleotides. Several differentially expressed miRNAs (DEMs) have been identified in SCLC specimens (Table 2). For example, the expression of hsa-miR-96, hsa-miR-183, hsa-miR-182, hsa-miR-130b, hsa -miR-301b, hsa-miR-18a, and hsa-miR-7 is upregulated in SCLC specimens compared with that in normal lung tissues (Table 2). However, the expression of hsa-miR-126, hsa-miR-638, hsa-miR-1, hsa-miR-451, hsa-miR-144, hsa-miR-145, hsa-miR-26a hsa-miR-486-5p, hsa-miR-26a, hsa-miR-338-3p, hsa-miR-140-3p, hsa-miR-140-5p, and hsa-miR-498 is downregulated in SCLC specimens compared to that in normal control lung tissues (Table 3).

Table 2: miRNAs upregulated in SCLC tissues

DEM	Expression in SCLC tissues	Function in human tumors
Hsa-miR-96	Up	It has been found to be highly expressed in SCLC specimens. Moreover, miR-96 promotes invasion and metastasis and induces development of cisplatin chemoresistance in NSCLC.
Hsa-miR-183	Up	The hsa-miR-183 level could be used as a diagnostic biomarker for the early detection of lung cancer with high sensitivity and specificity. hsa-miR-183 promotes lung cancer progression through FoxO1 inhibition or PTEN repression.
Hsa-miR-182	Up	It has been reported that miR-182 increases radioresistance in NSCLC cells by regulating FOXO3 expression. The role of hsa-miR-182 is controversial. Several studies have reported that it suppresses tumor progression and metastasis; however, a study has reported that it promotes tumor cell proliferation.
Hsa-miR-130b	Up	miR-130b has been reported to regulate DNA methylation in human lung cancer and modulate epithelial-mesenchymal crosstalk by targeting IGF-1.

Table 3: miRNAs downregulated in SCLC tissues

DEM	Expression in SCLC tissues	Function in human tumors
Hsa-miR-126	Down	miR-126 suppresses EMT and metastasis by targeting PI3K/AKT signaling in lung cancer cells. Long noncoding RNA MINCR and PVT1-5 modulate cell proliferation by regulating the miR126/SLC7A5 axis in lung cancers.
Hsa-miR-638	Down	Hsa-miR-638 regulates gene expression networks and it has been used as a new biomarker to predict the treatment outcomes of NSCLC patients receiving chemotherapy
Hsa-miR-1	Down	MiR-1 is downregulated in lung cancer, a phenomenon that could inhibit lung adenocarcinoma tumorigenesis. MiR-1 is used as a novel biomarker for lung disease.
Hsa-miR-145	Down	The expression of miR-145 is downregulated in SCLC cells. Moreover, miR-145 is involved in EMT and invasion via targeting ZEB2 in NSCLC cells, a novel biomarker for screening early-stage NSCLC.

CONCLUSION AND PERSPECTIVES

SCLC is a neuroendocrine tumor with a very poor prognosis. In recent years, advances in many aspects of SCLC have helped researchers discover new treatments for SCLC. In addition, new technologies for the early diagnosis of lung cancer have been continuously explored and large-scale genomic, transcriptomic, and proteomic analyses have facilitated the identification of therapeutic targets for SCLC. This article reviewed the recent advances in the field of SCLC, including aberrant activation of key proteins involved in SCLC development and possible targets for treatment, molecular markers, and clinical treatment for SCLC.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Bixiu He sought references and wrote the draft of the manuscript. Lihai Zhang wrote a part of the SCLC signaling pathways in SCLC progression. Longxia Dai and Jian Xiao checked the paper and wrote the Introduction section on SCLC.

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