Small-Cell Lung Cancer

Subjects: Oncology

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Small-cell lung cancer (SCLC) is an aggressive type of cancer with an incidence of about 15% among lung cancers and has a very poor prognosis due to its rapid development of resistance to chemo- and radiotherapies. Unlike the increase in personalized approaches to the clinical care of patients with non-small-cell lung cancer (NSCLC), clinical protocols for SCLC still mainly depend on the stage of the disease, prior therapies, and lack of specific molecular support. This approach was mainly due to the idea of SCLC as a monolithic entity with common genetic features, which was strictly linked to the lack of an adequate quantity of tissue samples in this inoperable class of patients, for the lack of a clear and comprehensive biological profile presented an obstacle.

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1. Introduction

Many large studies were published due to technological advances, supporting a new and more complex definition of SCLC. The studies suggested the existence of four biologically distinct subtypes of SCLC associated with specific therapeutic vulnerabilities and outcomes. Each of these subtypes is defined by its inter tumor expression levels of the four key transcription regulators: Achaete–Scute Family BHLH Transcription Factor 1 (ASCL1), Neuronal Differentiation 1 (NEUROD1), POU Class 2 Homeobox 3 (POU2F3), and yes–associated protein 1 (YAP1). The results from studies on genetically engineered mouse models of SCLC suggested that different neuroendocrine and non-neuroendocrine tumor cells could coexist in the same tumor mass, guiding its ability to evolve under selective pressure induced by a specific treatment [1] rapidly. Given the availability of highly sensitive and high-throughput molecular technologies, the peculiar blood and lymphatic spreading of SCLC and some of their neuroendocrine features became critical features that offered the opportunity to access SCLC molecular markers noninvasively.

2. Neuroendocrine-Related Circulating Transcripts in Small-Cell Lung Cancers

Tumor cells circulating in the blood (circulating tumor cells (CTCs) have a widely reported prognostic value in many tumors. They offer the advantage of extracting nucleic acids from the nucleated cell fraction of peripheral blood to obtain information, such as the expression levels of specific molecular SCLC markers. This could help obtain both a more molecular background, which could differentiate early or metastatic SCLC from NSCLC, and easily define the specific subtypes of SCLC, thus improving disease management. The noninvasive strategy to monitor disease was purposed for SCLC patients and was successfully assessed in some papers and was confirmed on a few patient cohorts.

This entry summarizes the scientific knowledge about a group of ectopic neuroendocrine tumor-associated transcripts of SCLC. These transcripts were detected in the whole peripheral blood (PB) of SCLC patients by highly sensitive techniques and were suggested as surrogates and noninvasive biomarkers of CTCs. Specifically, this review covers all published data in the field about somatostatin receptors (SSTRs), neuronal embryonic lethal, abnormal vision, Drosophila-like proteins (nELAVs), synaptophysin (SYP), chromogranin A (CHGA), delta-like ligand 3 (DLL3), pro-bombesin-like peptide (ProGRP), and secretogranin III (SGC3). Some of these transcripts are reported to be strictly related to one of the four proposed SCLC subtypes. By consequence, their detection in blood could represent an option to profile SCLC patients rapidly. To confirm the published data about SCG3, we described the optimization of a simple and real-time quantitative PCR approach as a noninvasive methodology to detect this transcript in the PB of SCLC patients. One key insight emerging from the complementary human and mouse models studies is the classification of SCLC subtypes defined by a distinct gene expression profile that could impact treatment definition and planned clinical trials. The observed dynamic change in these new markers and the lack of available tissue during disease progression represent one of the main points for the SCLC patient care implementation. A large and compelling body of evidence has accumulated in the past decade and highlights the potential role of CTCs and circulating tumor nucleic acids (ctNAs) in the liquid biopsy to help in neoplastic patients' clinical care. In SCLC patients, the ability to detect SCLC biomarkers in

blood, such as specific neuroendocrine-related transcripts, is poorly investigated but could have multiple potential applications in early detection, patient stratification, prognosis, or predicting the response to specific therapies. Currently, the best application of CTC will be in preclinical studies to understand SCLC biology, chemoresistance, and, most importantly, the existing phenotypic subtypes in a noninvasive way.

In this context, the features of SCLC rapidly disseminating in blood will be useful to set high-throughput methodologies to quickly profile SCLC patients by measuring some mRNAs levels instead of measuring their protein levels, which could have a different turnover time. Few papers were published in this field, where data need to be confirmed and expanded. The detection of specific transcripts in blood-related to distinct SCLC subtypes may help define the vulnerabilities of patients, and therapeutic targets focused on recent, active, and planned clinical trials. All possible approaches that could help to clarify the differences in SCLC subtypes, including noninvasive detection of specific transcripts of tumor cells, may represent an important path forward in defining better treatments for SCLC.
