Research Progress of Abnormal Expression of LKB1/STK111 in Non-Small Cell Lung Cancer

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Abstract: Non small cell lung cancer (NSCLC) is a kind of malignant tumor originated from bronchial mucosa, bronchial glands and alveolar epithelium. It has become the main cause of death of malignant tumors in our population. *STK11* is a common tumor suppressor gene, its encoded protein liver kinase B1 (LKB1) is an essential serine / threonine protein kinase. LKB1/*STK111* inhibits the occurrence and development of tumors through a variety of mechanisms and plays a key regulatory role in malignant tumors. The increased risk of cancer development is also associated with the absence of *STK11*. More and more studies have found that the abnormal expression of LKB1/*STK111* will affect the occurrence and development of lung cancer, especially in NSCLC. This paper reviews the tumor suppressive mechanism of LKB1/*STK111* in the occurrence and development of NSCLC, its relationship with NSCLC, and the prognosis and treatment.

Keywords: LKB1/*STK111*; Non Small Cell Lung Cancer; Tumor Suppressive Mechanism; Prognosis; Treatment

Introduction

Global epidemiological studies reveal that lung cancer is still the leading cause of cancer-related death worldwide. Lung cancer is divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), while NSCLC can be further divided into three categories: lung adenocarcinoma, lung squamous cell carcinoma and large cell carcinoma, and lung adenocarcinoma accounts for about 50% of all lung cancer cases [1]. Lung cancer has become the primary factor threatening human life among malignant tumors. Faced with such a severe situation, Modern medicine should urgently improve the level of early diagnosis and treatment of lung cancer.

Liver kinase B1 (LKB1), also known as STK11(serine threonine protein kinase11), was sequenced from patients with Peutz-Jeghers syndrome. STK11 gene is considered to be an important tumor suppressor gene, and its mutation and deletion are involved in the occurrence and development of various malignant tumors. Some scholars have found that the top three mutation rates in non-small cell lung cancer are p53 mutation, K-ras mutation and STK11 somatic mutation. The mutation rate of STK11 has reached 15%-35% in non-small cell lung cancer. STK11 gene mutation or deletion promotes carcinogenesis mainly through the LKB1/AMPK/mTOR signaling pathway. With the deepening of research, people have a more thorough understanding of the relationship between LKB1/STK11 and tumors, but the relationship between LKB1/STK11 and the occurrence and development of non-small cell lung cancer needs to be further explored. This paper reviews the research progress of abnormal expression of LKB1/STK11 in non-small cell lung cancer in recent years.

1. LKB1/STK11 Summary

The protein LKB1 encoded by STK11 is an essential serine/threonine protein kinase and is considered as a tumor

suppressor. STK11 is inactivated in about 30% of lung cancer, and abnormal expression of STK11 is also found in other malignant tumors, such as gastric cancer, liver cancer, pancreatic cancer.In cancer cells with cancer-driving mutations (such as KRAS, EGFR or ALK), deletion or mutation of STK11 gene has been observed to accelerate the occurrence and progression of malignant tumors by inducing the metabolism of glucose, lipids, glutamine and serine [2]. In addition to regulating angiogenesis, lipogenesis and cardiac function, STK11 gene and liver kinase B1 are also involved in a variety of processes including cell polarity, cell cycle arrest,and metabolism. The inhibitory effect of LKB1/STK11 is mainly reflected in its ability to promote cancer cell apoptosis, inhibit cancer cell migration and tumor angiogenesis.

2. Relationship between abnormal expression of LKB1/STK11 and occurrence and development of non-small cell lung cancer

2.1 Abnormal expression of LKB1/STK11 is common in non-small cell lung cancer

STK11 is a major regulator of various processes, including metabolism, proliferation and immunity. About one-third of non-small cell lung cancers have STK11 mutations[3]. STK11 can be inactivated by somatic mutations, leading to susceptibility to sporadic cancers such as pancreatic and gastrointestinal cancers, especially lung cancer. Most non-small cell lung cancers are driven by gene defects such as EGFR, BRAF, ALK, and the abnormality of STK11 gene has also been shown to induce lung adenocarcinoma, which is the third most commonly mutated gene in NSCLC adenocarcinoma, accounting for about 30%[4]. In addition, the most common KRAS co-mutation partners found in non-small cell lung cancer are TP53 (40%), STK11 (32%), and CDKN2A (19.8%) [5]. In sporadic lung cancer, up to 80% of NSCLC cell lines have LOH loss at chromosome 19p, indicating a higher correlation between STK11 mutations and NSCLC. In recent years, some studies on LKB1/STK11 and non-small cell lung cancer confirmed that the expression of LKB1 protein decreased in the development process of lung adenocarcinoma. Results show that loss of LKB1 protein expression has been observed in severe dysplasia, suggesting that LKB1 inactivation occurs early in the development of this type of lung cancer. Obviously, these reports have revealed a fact that abnormal expression of LKB1/STK11 is closely related to the occurrence and development of non-small cell lung cancer.

2.2 LKB1/STK11 mutations promote the development of non-small cell lung cancer

In non-small cell lung cancer, lung cancer cells with STK11 mutation will show various abnormal forms, such as Golgi localization error and lamellar foot formation, and the ability to cooperate with MAP/MARK to maintain cell polarity after STK11 mutation is reduced [6]. It is speculated that STK11 deletion can promote the epithelial-mesenchymal transition (EMT), which is a complex phenomenon that forces differentiated cells to regain their stem-like properties. The generation of this phenomenon is closely related to the occurrence, development, migration and metastasis of malignant tumors. One study related to LKB1/STK11 used gene knockout technology to breed mice with STK11 gene deletion. It was found that the mice with LKB1 deletion had abnormal vascular development and significantly increased VEGF expression. This result indicated that LKB1 could down-regulate the expression level of VEGF, thus achieving the effect of inhibiting tumor occurrence and development. STK11 gene mutation has a negative impact on the tumor immune microenvironment. In particular, the accompanying activation of KRAS mutations may explain the reduced response to immunotherapy in STK11

mutant NSCLC. More and more studies have shown that downregulation of STK11 can affect the occurrence and development of non-small cell lung cancer, and is closely related to tumor size, lymph node metastasis and tumor differentiation, and lung cancer patients with low STK11 expression have worse prognosis and shorter overall survival compared with those with normal STK11 expression.

3. Progress and prospect of treatment of non-small cell lung cancer with abnormal expression of LKB1/STK11

In recent years, many studies have found that STK11 mutations have certain resistance to PD-L1 treatment [7]. So far, the methods available in non-small cell lung cancer, which are mainly represented by anti-PD-1 /PD-L1 inhibitors, have no prospect in the case of STK11 inactivation. In addition, STK11-negative tumors are highly aggressive and resistant to chemotherapy, targeted therapy and immune checkpoint inhibitors (ICIs) [8]. Studies have shown that the presence of STK11 mutation is significantly correlated with the shortening of OS, and the presence of STK11 mutation is significantly correlated with the increase of treatment failure. These latest data may explain the decreased response of STK11 mutant non-small cell lung cancer to immunotherapy [9]. In order to study the metabolism and immune microenvironment of lung adenoma, Best SA established a mouse model with LKB1/STK11 mutation and found that the increased glutamate abundance in the tumor microenvironment of STK11 mutant mice was correlated with the activation of CD8 T cells in response to anti-PD-1 [10]. Most clinical trials are currently looking at the safety and efficacy of glutaminase inhibitors (BeGIN trial, KEAPSAKE, NCT04471415), There are also several related clinical trials that are combining PD-L1 inhibitors with glutaminase inhibitors or mammalian target rapamycin inhibitors (BUNCH) [11], among which Devarakonda et al recently reported their Phase II study results, This study suggested that everolimus (a dual inhibitor of mTOR) could be a therapeutic agent for patients with solid malignancies carrying multiple mutations, including STK11 mutations [11]. In addition, the downstream signal transduction inhibitor benzoguanidine in combination with soapicotib, a potent mTOR inhibitor, also exhibited tumor inhibitory activity in human cell lines carrying KRAS/STK11 mutations and in mouse models of NSCLC [26]. Drugs targeting protein glycosylation, such as Tunimycin and the protein transport inhibitor Brefeldin A, as well as drugs targeting glycolytic and inducing metabolic stress, such as 2-deoxyglucose (2-DG), may induce synthetic lethality in cancers where LKB1 / AMPK activity is deficient. It is believed that the further exploration of LKB1/STK11 in the future will lead to a clearer relationship between LKB1/STK11 and non-small cell lung cancer, which will also provide new ideas and directions for the search for new therapeutic targets and cancer targeted therapeutic drugs.

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