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LKB1/AMPK/mTOR Signaling Pathway in Non-small-cell Lung Cancer

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Abstract: **Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer death in males globally. Even in the females, it is the second leading cause of cancer death. The discovery of somatic mutation in the LKB1 gene in certain type of cancers, especially in non-small-cell lung cancer (NSCLC), a critical emerging point was that the LKB1/AMPK/mTOR signaling pathway remains generally functional and could be stimulated by pharmacological molecules such as pemetrexed and metformin in cancer cells. Besides, AMP-activated protein kinase (AMPK) plays a critical role in the regulation of cell growth, proliferation and autophagy by the control of mammalian target of rapamycin (mTOR) activity, which is consistently deregulated in cancer cells. Currently, chemotherapy and radiotherapy have been widely used in clinical, but the treatment efficiency is poorly because drug resistance and adverse reactions, while targeted at AMPK/mTOR can avoid these defects, so it is an attractive strategy for the development of the rapeutic agents against NSCLC. Therefore, this article reviewed the composition of LKB1/AMPK/mTOR signaling pathway, highlighting its protective role, and opportunities for therapeutic intervention, and clinical trials in NSCLC.**

Keywords: LKB1/AMPK/mTOR; Non-small-cell lung cancer; NSCLC; Targeted therapy

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1. Introduction

Lung cancer is a type of malignant tumor with the highest incidence globally, more than one million patients died from it every year. It is the leading cause of cancer death in males and the second leading cause that followed breast cancer in females [1]. Moreover, it can be substituted into small-cell lung cancer (SCLC) and NSCLC from the histological cell types. NSCLC accounting for 80-87％of lung cancer [2]. Now, the treatment of NSCLC includes surgery, platinum-based combination chemotherapy, radiotherapy and targeted therapy [3], but only targeted therapy is the best and the most effective strategy which have less adverse reactions. Because surgery requires patients who have good body and an ability to withstand, and those are not sensitive to chemotherapy and radiotherapy. Molecular targeted therapy has currently been the most promising research area for the treatment of NSCLC with further researches in pathogenesis and biological behavior of lung cancer. In this view, to find a new and effective therapeutic target is imminent. Therefore, the LKB1/AMPK/ mTOR pathway is outlined in this paper.

2. Composition of LKB1/AMPK/mTOR Signaling Pathway

2.1. Molecular Structure and Distribution of LKB1

Peutz-Jeghers syndrome (PJS) is an autosomal dominant genetic disease, and its pathogenesis is germ line mutation of a gene. It is named LKB1/STK11 (liver kinase B1, Serine-threonine protein kinase 11, STK11) that can directly activate downstream 14 members of AMPK family. Human LKB1 is located on human chromosome 19p13.3 contains 10 exons. It is conding a 50kD protein that the existence of a nuclear localization signal sequence (NLS) that plays a central role in the function of LKB1. Since LKB1 protein is mainly distributed in the nucleus, while functional protein of LKB1 located in the cytoplasm [4], so only when it transferred to the cytoplasm from the nucleus to exert tumor suppression. Besides, NLS sequences mutation is beneficial to this process which can't inhibit tumor suppression function of LKB1, but significantly improving it in cancer. Furthermore, LKB1-STRADα (STE20-related adaptor) -MO25α (Mouse protein 25) trimeric is mainly formed of LKB1 in mammalian cells [5], which is an important

structure. Because the combination of fake kinase STRADα in favor of LKB1 transported out of the nucleus [6], MO25α has stable the combination of STRADα with LKB1 to encourage LKB1 kinase activity [5]. In this study, we identify MO25α as a novel component of the LKB1-STRADα complex.

2.2. Molecular Structure and Tissue Distribution of AMPK

AMPK is also a heterothermic serine/threonine protein kinases constituted of a catalytic α subunit and two regulatory subunits (β and γ). All of which can be formed 12 different compounds [7] that have different properties and relatives tissue specificity. α subunit has a typical serine/threonine kinase domain and the allosteric sites of binding to AMPK. The innermost region of β subunit has a glycogen-binding domain (GBD) which binds glycogen synthase thereby regulating glycogen metabolism. Targeted cytoplasmic, protein-protein interactions and the regulated of protein activity are relatives to four highly conserved cystathionine β-synthase (CBS) of C-terminal of γ subunit. From the above that AMPK not only function is unique but also tissue distribution is unlike. However, α1 widely distributed in all tissues, but mainly located in the cytoplasm. α2 mainly distributed in skeletal muscle, heart and liver which most located in the nucleus [8]. β1 has broad tissue distribution properties, but β2 mainly located in skeletal muscle, heart and pancreas [9]. Furthermore, γ1 and γ2 are wider distribution, but γ3 only unambiguous expression in skeletal [10].

3.3. Structual Characteristics of the Molecule mTOR

The earliest mTOR molecules have highly conserved homologous genes that were separated from yeast cells. The homology of mTOR amino acid levels up to 95％in humans, rats and mice [11]. It is a conserved serine/threonine protein kinase that located in the short arm of human chromosome 1p36.2 which condone a proteinaceous is 289kD [12]. mTOR successively includes HEAT, FAT, FRB, KIN and FATC domains from N to C-terminus. It is insensitive to rapamycin after FRB mutation, in that FRB has an essential role in rapamycin binding to mTOR. In vivo, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) are functions performed of mTOR. The regulatory mechanism of mTORC1 is that rapamycin binding to immunodefficiency protein FKBP12, so that could adhesion to the C-terminal of mTOR to block the activation of it and thus to inhibit the activity of mTORC1, while mTORC2 tolerance to rapamycin that mainly correlation with cell polarity and growth spatial [13].

3. LKB1/AMPK/mTOR Signaling Pathway in NSCLC

Currently, the LKB1 has been recognized as a tumor suppressor gene and it was a key regulator of cell proliferation. Its mutation of loss function and abnormal expression of certain tumor genes is working together to promote tumor development. Function inactivating mutations in LKB1 plays a crucial role in the differentiation and metastasis of lung cancer, even in NSCLC. Sanchez-Cespddes reported [14] that a substantial proportion of LKB1 functions mutations in NSCLC in 2002. Moreover, Matsumoto obtained [15] the same conclusion by means of large-scale sequence analysing of NSCLC in 2007. Meera and her colleagues found that the AMPK signal pathway significantly dropped, overall AMPK and phosphorylation TSC2 declined in patients with NSCLC relapse, but acetyl coenzyme A rose [16], all of which contributed to the development and progress of the tumor. On smokers and poorly differentiated NSCLC, LKB1 mutations occur frequently passivation [17] that is closely related to short-latency, frequent transfer and promote the development of lung cancer. Above studies suggested that LKB1 plays an extremely important role in the development of lung cancer.

AMPK, an energy sensor, is mainly maintaining the energy balance of the cell, and upstream kinases LKB1 is a need for activate AMPK in response to metabolic stress [18]. In various kinds of stress, consume large amounts of ATP and produce large amounts of AMP to activate AMPK. Besides, AMPK should generate a

large number of ATP through promotion catabolism, while lower biosynthesis to reduce the consumption of ATP to relieve the stress in order to maintainly the body's normal metabolic [19]. AMPK not only impacts the metabolic, but also adjusts the mitochondrial biogenesis and autophagy, cell polarity, cell growth and proliferation [18]. In recent years, studies have shown that AMPK has positively correlated with tumorigenesis [20-21]. Metformin is AMPK agonist that may improve tumor progression and prolong survival. Patients who were treated with metformin cancer recurrence rate are significantly lower than others [22]. Furthermore, three different AMPK activators, such as metformin, phenformin or A-76922, treated tumor-prone mice all of which can significantly inhibit tumor development. Studies data recently denominated that patients whoses non-smoking pAMPK expression levels were significantly higher than those whoses smoking with NSCLC, which is associated with overall survival (OS) and disease-free survival [24] (RFS). In adenocarcinoma and squamous cell carcinoma, total number of survival and disease-free survival rate of pAMPK positives is more highly than pAMPK negatives. All above results shown that pAMPK expression is closely correlated with patient survival, especially in NSCLC adenocarcinoma. Nevertheless, what important mechanisms are regulatory by active AMPK? Let us look down. The active AMPK increased when intracellular AMP/ATP ratio increased, and then regulated direct targets that involved in many metabolic pathways, such as glycolysis (PFK2), fatty acid and cholesterol synthesis [25]. In all, activation of AMPK can accumulate energy for cell survival inhibited cell growth and proliferation [26]. In tumor cells, AMPK plays an important role in cell growth, proliferation and autophagy generally through regulation of mTOR activity [27]. mTOR is a center integrator of trophic and growth factors inputs that control cell growth in all eukaryotes, and it always down regulated in most human cancers [28]. It is constituted of mTORC1 and mTORC2 that are separation in the biochemically and functionally [29]. The mTORC1 is acutely inhibited by rapamycin, but rapamycin does not fully suppress mTORC1 activity in many cell types [30]. Additionally, mTORC1 can control the phosphocreatine of related protein kinase at S473 and control serum glucocorticoid to regulate protein kinase activity through mTOR partner that tolerated rapamycin interaction with mTOR, but it appeared lately in cancer biology research [31].

The mTORC1 is consisted of the tuberous sclerosis complex 2 (TSC2) and tuberous sclerosis complex 1 (TSC1) [32]. TSC2 indirectly regulated GTPase Ras homologue by inhibiting mTORC1 that could hyperventilation when loss of TSC1 or TSC2, which indicated that TSC1 and TSC2 complexs are negatively correlated with the activity of mTORC1 [33]. AMPK direct phosphorylation conserve serine sites of TSC1 can activate TSC1 to inhibit mTOR activity when ATP, and glucose or oxygen content declined [34]. TSC2 is a centralizer that accepts regulator mTORC1, but loss of TSC2 cells to inhibit mTORC1 partly action through activation of AMPK [35]. In vivo, AMPK direct action substrate raptor lead to binding to 14-3-3 so that can induce phosphorescence of its two conserved phosphorylation sites by AMPK, which ultimately inhibited the activity of the mTORC1 [35]. Phosphorylation of raptors to down regulation mTOR activity and cell cycle arrest in G2/M are necessary after activation of AMPK [35]. In human, PJS syndrome and NSCLC model, mTORC1 is only binding sites of down-regulated signaling pathway of downstream of LKB1 in tumor cells, which indicated that mTORC1 has vital significance in cancer research. In contrast, the role of the mTORC2 complex, which is based on the interaction between raptor and mTOR [36], has only recently emerged in cancer cell biology and is mainly related to the control of SGK activity and Akt S473 phosphorylation [37].

4. Treatment of NSCLC

Chemotherapy is one of the conventional therapy methods for advanced NSCLC, but its effect is poor. Gene polymorphisms of bone morphogenesis protein 4 (BMP-4) is related to platinum-based chemotherapy sensitivity so that NSCLC patients with higher expression of BMP-4 are easy to tolerance to

chemotherapy than lower. Furthermore, the expression of BMP-4 is also closely related to PFS and OS of NSCLC. Besides, radiotherapy is one of the main treatments for NSCLC, but it easy produces radiation resistance. Ionizing radiation (IR) can activate AMPK bypass LKB1 in NSCLC. Conversely, AMPK not only regulated IR to regulate p53 and p21 waf/cip, but also induced G2/M checkpoint and blocked p53 and p21 waf/cip as IR induced G2/M arrest. In addition, metformin greatly enhanced the activating of AMPK by RI and reduced the number of surviving cells [38]. Many studies have shown that lovastatin and trihydroxy three acetyl coenzyme A reductase inhibitors may inhibit the survival and enhance radiosensitivity of NSCLC cells through activation of AMPK signaling pathway to induce apoptosis of NSCLC [38].

New research showed that pemetrexed exerts inhibitory effects through the AMPK/mTOR pathway. It can activate AMPK, such as direct targets of AMPK activated calcium carbonate (ACC) hyperphosphorylation at S79, eukaryotic elongation factor (eEF2) hyperphosphorylation at Thr56 and mTOR downstream target S6K1 hyperphosphorylation at T389 [39]. Studies revealed that pemetrexed activate AMPK by inhibited mTORC1 dependent or independent pathways, and thus control protein translation and lipid metabolism. Han and colleagues reported that the resignation inhibits the growth of NSCLC cells by PFARγ independent signaling pathway [40]. They concluded that rosiglitazone induced AMPKα protein phosphorylation and inhibited phosphorylation of p70S6K protein in a dose and time dependent manner, but had no effect on LKB1. In addition, it can enhance the inhibitory effect of rapamycin on NSCLC cell proliferation. Above studies indicated that rosiglitazone to inhibit NSCLC cell proliferation by the AMPK/mTOR/p70S6K signaling pathway. Recently, Shao and colleagues reported that AMPK activation is beneficial to chrysin inhibit proliferation and induce apoptosis of NSCLC [41]. Similarly, Chrysin also inhibit mTOR activity, but it has been restored when knockdown AMPK.

5. Prospect

The LKB1/AMPK/mTOR signaling pathway, an impact on cancer biology, has been studied more in depth in metabolic abnormalities. The somatic mutation of the STK11 gene, encoding serine/threonine kinase of LKB1, has been detected in lung cancer and cervical cancer indicated that LKB1 is closely related to promote oncogenesis in cancer. In addition, many researchs have been shown that pharmacologically activation of LKB1/AMPK using metformin, AICAR or A-769662 compound could significantly inhibit the proliferation of cancer cells, so that it has a valuable therapeutic strategy for the treatment of cancers. LKB1 can inhibit the activity of mTOR by activates AMPK to play an important role in cell proliferation in cancer cell energy metabolism, indicated that AMPK and mTOR as a potential target of cancer targeted therapy. Furthermore, the LKB1 is related to cell cycle arrest, autophagy and induction apoptosis in various types of cancer, but the exact mechanism is unclear. These are worth to be explored further.

However, AMPK activators have different molecular targets and likely to occur off-target effects, so it is difficult to clearly elucidate its mechanism of action. Moreover, AMPK can also regulate glucose, fatty acids and protein metabolism, but its exact inhibitory mechanism should be further researched. Although there are still many questions about the targeted therapy of the LKB1/AMPK/mTOR pathway, this therapy is worth further studying in many tumors, especially in lung cancer.

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