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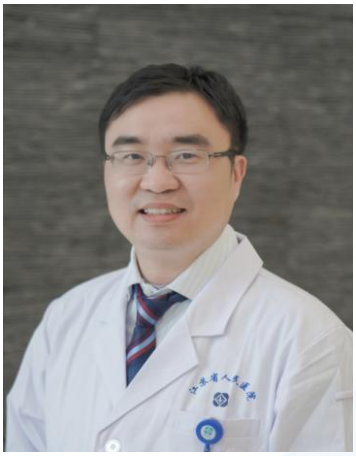

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Progress on the impact of lipid metabolism reprogramming on resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer

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Abstract: Non-small cell lung cancer (NSCLC) is the main type of lung cancer, accounting for 85% to 90%. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have improved the prognosis of NSCLC patients greatly. However, with prolonged drug use, the inevitable occurrence of acquired resistance leads to disease recurrence, progression, and even patient's death. Metabolic reprogramming is one of the hallmarks of malignant tumors and refers to metabolic changes in tumor cells to meet energy needs. In various cancers, lipid synthesis, distribution, and catabolism of tumor cells are altered to adapt to the lack of nutrients and oxygen in the tumor microenvironment. This paper focuses on how lipid metabolism reprogramming in NSCLC leads to resistance to EGFR-TKIs and how modulation of lipid metabolism increases the sensitivity of NSCLC to EGFR-TKIs. It summarizes and consolidates existing research progress to provide a reference for basic research and clinical treatment of EGFR-TKIs resistance in NSCLC.

Keywords: Non-small cell lung cancer; Lipid metabolism reprograming; Epidermal growth factor receptor tyrosine kinase inhibitors; Resistance; Statins

Lung cancer is the leading cause of cancer death, accounting for one-third of all cancer deaths worldwide, of which 85%-90% are non-small cell lung cancer (NSCLC), with 5-year survival rates as low as 18% [1]. In Asian population, the proportion of EGFR activation mutations occur in more than 50% of NSCLC patients [2]. The emergence of EGFR tyrosine kinase inhibitors (EGFR-TKIs), which target EGFR-activated mutations, improves the treatment pattern of EGFR-mutation-positive lung cancer and extends the progression-free survival of patients. It has important significance in the treatment development of NSCLC.

Exon 19 deletion and exon 21 L858R point mutation are the common EGFR mutations. While rare mutations, such as exon 20 insertion and secondary drug resistance mutations in T790M, confer resistance to EGFR-TKIs [3]. Activating mutations strengthen the affinity of EGFR-TKIs to the mutated receptor, which leads to the tumor cells sensitivity of EGFR-TKIs therapy. For example, gefitinib, the first-generation EGFR-TKI, is a reversible ATP-competitive EGFR inhibitor. Gefitinib can prevent the autophosphorylation of TK domain and block the activation of downstream EGFR signaling after binding to the receptor [4]. The emergence of the first-generation EGFR-TKI provides a new option for targeted therapy for most NSCLC patients with

EGFR-activating mutations, and has achieved remarkable clinical results. However, with the extension of treatment time, the emergence of acquired resistance limits the therapeutic effect of EGFR-TKI, leading to disease progression. Researchers continue to develop new generations of EGFR-TKIs to respond to newly identified mutation types. Unfortunately, apart from some mechanisms related to C797S mutations and MET amplification, the mechanism of drug resistance in third-generation EGFR-TKIs are largely unknown. New and alternative approaches are needed to overcome resistance. More and more evidence show that metabolic reprogramming is an important reason why EGFR mutant NSCLC cells tolerate EGFR-TKIs and maintain their carcinogenic phenotype [5].

Metabolic reprogramming, one of the hallmarks of malignant tumors, refers to metabolic changes in tumor cells to meet energy requirements. In the past two decades, the metabolic reprogramming of tumors to promote tumor development has attracted the interest of researchers, especially glucose metabolism and glutamine metabolism. Mayne studies have elaborated the relevant mechanisms of EGFR-TKIs resistance in NSCLC, and gradually improved the metabolic regulatory network. In recent years, lipid metabolism has been gradually recognized as an important pathway of cancer cells, and researchers are increasingly interested in the related mechanisms of lipid metabolic reprogramming in cancer. The increase in lipid uptake, synthesis, oxidation or storage has been proven to contribute to the growth of various cancers, especially lung cancer [6]. When the energy supply is sufficient, lipids are stored by cells in lipid droplets (LDs). When energy supply is insufficient, lipids can not only provide energy for cells, but also serve as signaling molecules that transmit information within and between cells, promoting tumor metastasis and drug resistance [7]. For now, a large amount of evidence has revealed the correlation between lipid metabolism and EGFR-TKIs resistance in NSCLC. However, few article has described the latest progress of abnormal lipid metabolism and EGFR-TKIs resistance in NSCLC completely. Therefore, based on the importance of lipid metabolism in malignant tumors, a comprehensive understanding of lipid metabolic reprogramming is critical to finding metabolic networks that target EGFR-TKIs resistant NSCLC cells. This review summarizes the effects of lipid metabolic reprogramming on EGFR-TKIs resistance in NSCLC and potential therapeutic strategies.

1 Cholesterol metabolic reprogramming and EGFR-TKIs resistance

Cholesterol is essential for the integrity of cell membranes and is synthesized mainly through the mevalonate (MVA) pathway. Cholesterol reprogramming refers to the adjustment of the normal cholesterol metabolic pathway by tumor cells in the tumor microenvironment with insufficient energy supply to obtain more cholesterol. By regulating cholesterol synthesis and cholesterol content in the lipid raft, the proliferation, metastasis and drug resistance of tumor cells are affected.

1.1 Regulating cholesterol synthesis through the MVA pathway

The MVA metabolic pathway is a widespread, highly conserved and dynamically regulated metabolic pathway. In the 1950s, Bloch revealed the biochemical mechanism of dimethylallyl diphosphate (DMAPP), isopentenyl pyrophosphate (IPP) and their downstream cholesterol produced by the MVA metabolic pathway [8]. Statins exert biological effects by blocking the MVA pathway by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A(HMG-CoA) reductase. Studies have proved that statins can cooperate with EGFR-TKIs to promote the apoptosis of tumor cells and enhance the sensitivity of EGFR-TKIs resistant tumor cells to drugs [9-10]. Transmission of EGFR signaling pathway depends on lipid rafts on the cell membrane, and statins interfere with EGFR signaling by inhibiting the production of cholesterol and the formation of lipid rafts [11]. Both processes are essential for EGFR function and for the activity of proteins important for EGFR signaling.

In erlotinib-resistant NSCLC cancer cells, pitavastatin combined with erlotinib can increase the sensitivity of resistant cells to erlotinib, and at the same time, the levels of phosphorylated protein kinase B(p-AKT) and phosphorylated extracellular signal-regulated kinase (p-ERK) downstream of EGFR are significantly reduced, which leads to the apoptosis of cancer cells [10]. By inhibiting HMG-CoA reductase, pitavastatin blocks the MVA pathway and increases the sensitivity of drug-resistant cells to erlotinib, thereby reversing drug resistance [10]. In KRAS mutant NSCLC, atorvastatin can overcome gefitinib resistance. Atorvastatin (1 μmol/L) combined with gefitinib can inhibit the proliferation of KRAS mutant NSCLC cells, promote apoptosis, and inhibit p-AKT. Increasing the concentration of atorvastatin (5 μmol/L) can further inhibit p-ERK. Thus, atorvastatin and gefitinib inhibit the PI3K/AKT and MEK/ERK pathways synergistically. Atorvastatin also can inhibit the destruction of HMG-CoA reductase dependent KRAS/Raf and KRAS/PI3K complexes, overcoming gefitinib resistance in KRAS mutant NSCLC cells. Simvastatin can overcome EGFR-TKI resistance in T790M-mutated NSCLC by AKT/β-catenin signal-dependent down-regulation of survivin and induction of apoptosis. It was found that simvastatin combined with gefitinib can promote apoptosis of T790M-mutated NSCLC cells, increase the expression of caspase-3, caspase-8 and caspase-9, and inhibit the phosphorylation of AKT and β-catenin. Meanwhile, survivin is a key molecule in the resistance of T790M mutated NSCLC cells to apoptosis induced by gefitinib and simvastatin [12].

1.2 Regulating the content of cholesterol in lipid rafts

There is a small mobile, cholesterol-rich and sphingomyelin microdomain on the cell membrane called lipid raft, which functions as a platform for cell signal transduction [13]. More and more evidences prove that signals for cell proliferation and survival are transmitted through lipid rafts, which are special membrane microstructures rich in cholesterol [14]. EGFR is mainly localized in cell membranes and plays a role in the activation of MAPK and AKT signaling pathways [15]. It is found that EGFR localization to lipid rafts is correlated with EGFR-TKIs resistance [16]. Reduced cholesterol content in lipid rafts can re-sensitize resistant tumor cells to gefitinib. In EGFR-TKIs resistant cell lines, lipid rafts provide a platform for the activation of AKT, which lacks EGFR kinase activity, leading to EGFR-TKIs resistance. In NSCLC, statins can reduce the cholesterol content in lipid raft by inhibiting the synthesis of cholesterol in cells, thus increase the sensitivity of tumor cells to EGFR-TKIs, suggesting that the combination of EGFR-TKIs and statins in the treatment of EGFR-mutant NSCLC may be a new therapeutic approach.

1.3 Cholesterol regulatory element binding proteins (SREBPs) regulating fatty acid and cholesterol synthesis

SREBPs is an important nuclear transcription factor, among which SREBP1 regulates fatty acid synthesis and SREBP2 regulates cholesterol synthesis, and they have been shown to play an important role in maintaining cancer lipid synthesis [17-18]. In addition, the reduction of cholesterol in the plasma membrane will activate SREBPs, promote the expression of downstream genes, and thus increase cholesterol uptake. In NSCLC cells, inhibition of SREBP can down-regulate the expression of fatty acid synthase (FASN), stearoyl-CoA desaturase (SCD) and hydroxy-3-methylglutaryl-CoA reductase (HMGCR), and reduce the ratio of cholesterol and unsaturated fatty acids on the cell membrane, resulting in reduced cell membrane fluidity. EGFR is mainly distributed in cell membranes, and the decreased fluidity of cell membranes inhibits the activation of EGFR signals, thus increasing the sensitivity of cells to gefitinib [6]. At the same time, SREBPs promote the transcription of HMGCR, thereby enhancing the MVA pathway of cholesterol synthesis and promoting the uptake of cholesterol into cells via low density lipoprotein receptor (LDLR). Therefore, by regulating the expression of SREBPs and the content of lipid components in the cell membrane, the sensitivity of cells to EGFR-TKIs can be increased, indicating that targeting SREBP may be a new method to treat EGFR-TKIs resistance.

2 Fatty acid metabolic reprogramming and EGFR-TKIs resistance

Fatty acids are a class of molecules composed of hydrocarbon chains of different lengths and degrees of unsaturated, and their metabolism changes at the levels of uptake, synthesis and degradation during tumor growth. As a transmembrane glycoprotein, CD36 is highly expressed in ovarian cancer, gastric cancer, glioblastoma and oral squamous cell carcinoma, and can mediate the uptake of long-chain fatty acids [19]. The promoter of CD36 contains peroxisomal proliferator-activated receptor (PPAR) response elements (PPREs). In gastric cancer, phosphatidylinositol transporter 1 (PITPNC1) up-regulates the RNA level of PPARG, and then combines with PPARγ to enhance the expression of CD36, thereby increasing the intake of fatty acids [22].

2.1 Regulating fatty acid synthesis

In normal tissues, de novo synthesis of fatty acids is limited to fat and liver cells. But in order to meet their own high metabolic requirements, tumor cells up-regulate the expression of fatty acid synthetase (FASN) to enhance fatty acid synthesis. Citric acid is transported out of mitochondria by SLC25A1, and in the cytosol, under the action of ATP citrate lyase (ACLY), acetyl-CoA hydroxylase (ACC), FASN, stearoyl-CoA desaturase 1 (SCD1), fatty acids can be further synthesized into triglycerides (TG) and stored in LDs. Up-regulation of ACLY, ACC and FASN has been found in colorectal cancer, gastric cancer, breast cancer, liver cancer and lung cancer, and their overexpression is significantly correlated with the low survival rate of lung cancer patients [20-22]. SCD1 has also been proved that plays a key role in the onset and progression of cancer. Moreover, the researchers found that changes in fatty acid anabolism were associated with EGFR-TKI resistance, and blocking fatty acid synthesis in tumor cells could reverse EGFR-TKIs resistance. A study found that NSCLC had intracellular LDs accumulation under long-term treatment with EGFR-TKIs, while short-term treatment would reduce the LDs content in cells, suggesting that the abnormal accumulation of LDs may be the cause of EGFR-TKIs resistance [23]. The expression of key enzyme genes in fatty acid synthesis is increased in EGFR-TKIs resistant NSCLC cells, and the expression of bone morphogenetic proteins (BMPs) is increased in EGFR-TKIs resistant strains. BMPs promote the expression of acyl-CoA synthetase (ACSL). Thus, citric acid is converted into acetyl CoA in the cytoplasm to participate in lipid synthesis [24]. It has been reported that the expression of FASN, ACC and SCD1 is up-regulated in TKI-resistant NSCLC [22,25], and the sensitivity of cells to EGFR-TKI is reduced by promoting fatty acid synthesis, thus leading to drug resistance [26]. EGFR-TKI combined with SCD1 inhibitor (20S)-protopanaxatriol (g-PPT) can reverse the resistance of NSCLC cells to EGFR-TKIs, reduce the accumulation of LDs, inhibit EGFR phosphorylation and the activation of p-EGFR/p-AKT/p-ERK signaling pathway. Thus, the

cells are re-sensitized to drug-resistant EGFR-TKIs [23]. This suggests that increased fatty acid synthesis in drug-resistant cells may be responsible for the abnormal accumulation of LDs and is a potential target for treating EGFR-TKIs resistant NSCLC.

2.2 Regulating fatty acid β oxidation (FAO)

Activation of fatty acids under the action of ACS is a key step in FAO, in which fatty acids are broken down into acetyl-CoA to participate in the tricarboxylic acid (TCA) cycle, thus producing ATP to provide energy for cells. There is substantial evidence that many cancer cells reprogram FAO and rely on this process to proliferate, survive, metastases and even become resistant to drugs. ACS exists only in mitochondria, and fatty acids need to be transported to mitochondria to perform FAO. Carnitine palmitoyl transferase 1 (CPT1) can transport fatty acids from cytoplasm to mitochondria, thus enabling fatty acids to perform FAO under the action of ACS. Overexpression of CPT1A is also associated with poor prognosis of tumors [27]. In the course of osimertinib treatment, FAO increased with the extension of treatment time, and in osimertinib-resistant NSCLC cells, FAO level was significantly higher than that of sensitive cells. CPT1 is a key enzyme in the FAO process, and the use of the CPT1 inhibitor etomoxir can block FAO to reverse osimertinib resistance. This indicates that FAO plays an important role in the process of osimertinib resistance [28] and provides a new therapeutic target for the treatment of EGFR-TKIs resistance. Tumor cells regulate the uptake, synthesis, accumulation and degradation of fatty acids by regulating the expression of key enzyme genes related to fatty acid metabolism, thus creating conditions for the growth, proliferation, metastasis and even drug resistance of tumor cells. Targeting fatty acid metabolizing enzymes can increase the sensitivity of NSCLC cells to EGFR-TKIs, which provides a new therapeutic direction to overcome EGFR-TKIs resistance.

3 Other lipid metabolites reprogramming and EGFR-TKIs resistance

Sphingomyelin is a major component of cell membranes, where it can be converted into sphingosine-1-phosphate (S1P) catalyzed by two different sphingosine kinases (SPHK). Studies have found that the expression of SPHK2 is correlated with poor prognosis of NSCLC, as well as gefitinib resistance [29]. LDLR is a key mediator of cholesterol uptake, and p-EGFR can promote LDLR expression, thereby promoting the uptake of cholesterol by tumor cells to maintain their growth needs. Down-regulation of LDLR can reduce the uptake of cholesterol by tumor cells. Therefore, the combination of EGFR-TKI and statins can synergically reduce cholesterol uptake to inhibit the proliferation and growth of EGFR-mutated cells [30], but whether inhibition of LDLR expression can reverse EGFR-TKIs resistance still needs further research.

4 Conclusion

One of the major changes that occur in tumor cells is metabolic reprogramming, in which cancer cells alter their carbohydrate, amino acid, and lipid metabolic pathways to maintain their growth and proliferation needs, as well as block signals that may cause their growth to stall [31]. In recent years, glucose metabolic reprogramming has attracted the most attention from researchers, and it has been found that it is closely related to tumor progression and EGFR-TKIs resistance. With the gradual improvement of the mechanism of glucose metabolism reprogramming, researchers have turned their attention to the reprogramming of lipid metabolism, and found that during the occurrence and development of tumors, lipid metabolism is changed to meet the needs of proliferation and progression in the microenvironment of nutrition and oxygen deficiency. In recent years, more and more studies have found that in EGFR-TKIs resistant cells, lipid metabolism also changes, resulting in changes in tumor cells' sensitivity to EGFR-TKIs through changes in lipid synthesis, distribution, metabolism and other pathways, resulting in acquired drug resistance. These studies also provide potential therapeutic strategies for treating EGFR-TKIs resistant patients.

The intake, synthesis and degradation of fatty acids and cholesterol, as well as the expression of related key proteins and transcriptional regulators, constitute the core of lipid metabolic reprogramming. Therefore, most preclinical trials have also been conducted to study drugs and inhibitors of these pathways, and EGFR-TKIs drugs have been used in combination with these drugs with some positive results. Statins, as commonly used regulators of cholesterol synthesis in clinical practice, can improve the sensitivity of tumor cells to EGFR-TKIs when combined with EGFR-TKIs, thereby delaying or even reversing the occurrence of EGFR-TKIs resistance. In addition, the combination of drugs targeting key enzymes and transcription factors in lipid metabolism with EGFR-TKIs can also reduce the sensitivity of drug-resistant cells to EGFR-TKIs.

Lipid metabolic reprogramming is a complex regulatory network. However, lipid metabolic reprogramming in EGFR-TKIs resistant cells has not been adequately studied. Moreover, a large number of studies have demonstrated that lipid metabolic reprogramming plays an important role in EGFR-TKIs resistance, and targeted therapy of lipid metabolism may be a novel and potentially effective strategy to treat EGFR-TKIs resistance. Therefore, it is necessary to further study and understand the lipid metabolic network to perfect the mechanism of lipid metabolic reprogramming and EGFR-TKIs resistance.

Conflict of Interest None

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·学术前沿·

脂质代谢重编程对非小细胞肺癌表皮生长因子受体-酪氨酸激酶抑制剂耐药影响的研究进展

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摘要：非小细胞肺癌(NSCLC)是肺癌中的主要类型,占比 85%～90%。表皮生长因子受体-酪氨酸激酶抑制剂(EGFR-TKIs)的使用极大改善了 NSCLC 患者的预后。然而,随着药物使用时间的延长会不可避免地出现获得性耐药,从而导致疾病的复发、进展、甚至患者的死亡。代谢重编程是恶性肿瘤的标志之一,是指肿瘤细胞为满足能量需求而发生代谢改变。在多种癌症中,肿瘤细胞的脂质合成、分布以及分解代谢发生了改变,以适应肿瘤微环境中营养、氧气匮乏的特点。本文主要关注 NSCLC 中,脂质代谢重编程如何导致 EGFR-TKIs 的耐药以及如何通过调节脂质代谢增加 NSCLC 对于 EGFR-TKIs 的敏感性,归纳并总结现有的研究进展,以期为 EGFR-TKIs 耐药相关基础研究及临床治疗提供参考。

关键词：非小细胞肺癌；脂质代谢重编程；表皮生长因子受体—酪氨酸激酶抑制剂；耐药；他汀类药物
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Progress on the impact of lipid metabolism reprogramming on resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer

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Abstract: Non-small cell lung cancer (NSCLC) is the main type of lung cancer, accounting for 85% to 90% of cases. The use of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) has greatly improved the prognosis of NSCLC patients. However, with prolonged drug use, the inevitable occurrence of acquired resistance leads to disease recurrence, progression, and even patient's death. Metabolic reprogramming is one of the hallmarks of malignant tumors and refers to metabolic changes in tumor cells to meet energy needs. In various cancers, lipid synthesis, distribution, and catabolism of tumor cells are altered to adapt to the lack of nutrients and oxygen in the tumor microenvironment. This paper

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focuses on how lipid metabolism reprogramming in NSCLC leads to resistance to EGFR-TKIs and how modulation of lipid metabolism increases the sensitivity of NSCLC to EGFR-TKIs. It summarizes and consolidates existing research progress to provide a reference for basic research and clinical treatment of EGFR-TKIs resistance in NSCLC.

Keywords: Non-small cell lung cancer; Lipid metabolism reprogramming; Epidermal growth factor receptor tyrosine kinase inhibitors; Resistance; Statins

肺癌是癌症死亡的主要原因,占全球癌症死亡总数的三分之一,其中 85%～90% 是非小细胞肺癌(non-small cell lung cancer, NSCLC),5 年生存率低至 18%[1]。亚洲人群中,NSCLC 患者发生中表皮生长因子受体(epidermal growth factor receptor, EGFR)激活突变占比超过 50%[2],针对 EGFR 激活突变的靶向药——EGFR 酪氨酸激酶抑制剂(EGFR-tyrosine kinase inhibitors, EGFR-TKIs)的出现提升了 EGFR 突变阳性肺癌的治疗格局,延长了患者的无进展生存期,在 NSCLC 治疗发展上具有重要意义。

常见 EGFR 激活突变主要表现为 19 号外显子缺失突变和 21 号外显子 L858R 突变,而罕见突变如 20 外显子插入突变和 T790M 继发耐药突变,则会赋予细胞 EGFR-TKIs 耐药性[3]。激活突变增加了 EGFR-TKIs 对突变受体的亲和力,从而使肿瘤细胞对 EGFR-TKIs 治疗敏感。如第一代 EGFR-TKI 吉非替尼,是一种可逆 ATP 竞争性 EGFR 抑制剂,与受体结合后,可阻止 TK 结构域的自磷酸化并阻断 EGFR 下游信号传导的激活[4]。第一代 EGFR-TKI 的出现为大部分 EGFR 激活突变的 NSCLC 患者提供了靶向治疗的新选择,并获得了显著的临床效果。然而,随着治疗时间的延长,获得性耐药的出现限制了 EGFR-TKI 的治疗效果,导致疾病进展。为了对抗耐药的出现,研究者们不断研发出新一代的 EGFR-TKIs 以应对新发现的突变类型,不幸的是,对于第三代 EGFR-TKIs 的耐药,除了一些与 C797S 突变和 MET 扩增相关的机制外,其他发生机制很大程度是未知的,需要新的替代方法来克服耐药。越来越多的证据表明,代谢重编程是 EGFR 突变 NSCLC 细胞耐受 EGFR-TKIs,并维持其致癌表型的重要原因[5]。

代谢重编程是恶性肿瘤的标志之一,是指肿瘤细胞为满足能量需求而发生代谢改变。在过去的二十年中,肿瘤的代谢重编程促进肿瘤发生发展引起了研究人员的兴趣,尤其是糖代谢与谷氨酰胺代谢。大量研究阐述了 NSCLC 的 EGFR-TKIs 耐药的相关机制,并逐渐完善代谢调控网络。近几年,脂质代谢逐渐被认为是癌细胞的重要途径,研究者们对于癌症中脂质代谢重编程的相关机制也越来越感兴趣,脂质的摄取、合成、氧化或储存的增加已被证实有助于多种癌症的生长,尤其是肺癌[6]。当能量供应充足时,脂质被细胞储存在脂滴中;能量供应不足时,脂质不仅可为细胞提供能量,也可作为细胞内和细胞间传递信息的信号分子,促进肿瘤的转移与耐药[7]。目前,大量证据揭示了脂质代谢与 NSCLC 的 EGFR-TKIs 耐药相关,但是仍未有文章完整阐述 NSCLC 脂质代谢异常与 EGFR-TKIs 耐药的最新进展,因此,基于脂质代谢在恶性肿瘤中的重要性,全面了解脂质代谢重编程对于寻找靶向 EGFR-TKIs 耐药的 NSCLC 细胞代谢网络具有关键作用。本文总结脂质代谢重编程对 NSCLC 的 EGFR-TKIs 耐药的影响及潜在的治疗策略。

1　胆固醇代谢重编程与 EGFR-TKIs 耐药

胆固醇对细胞膜的完整性至关重要,它主要通过甲羟戊酸途径(mevalonate pathway, MVA pathway)合成。胆固醇代谢重编程是指肿瘤细胞在能量供应不足的肿瘤微环境中,为了获取更多的胆固醇而对正常的胆固醇代谢途径做出的调整,通过调节胆固醇的合成、脂筏(lipid raft)中胆固醇的含量等途径,从而影响肿瘤细胞的增殖、转移与耐药。

1.1　通过 MVA 途径调节胆固醇合成

MVA 代谢途径是一条广泛存在、高度保守且动态调控的代谢通路,Bloch 于二十世纪 50 年代揭示 MVA 代谢通路产生二甲烯丙基二磷酸(DMAPP)、异戊二烯焦磷酸(IPP)及其下游胆固醇的生物化学机制[8]。他汀类药物通过抑制 3-羟基-3-甲基戊二酰辅酶 A(HMG-CoA)还原酶阻断 MVA 途径从而发挥生物学效应。研究证明,他汀类药物可以与 EGFR-TKIs 协同促进肿瘤细胞的凋亡以及促进 EGFR-TKIs 耐药的肿瘤细胞对药物的敏感性[9-10]。同时,EGFR 信号通路的传导依赖于胞膜上的脂筏,他汀类药物可通过抑制胆固醇的生成而抑制脂筏的形成,从而干扰 EGFR 信号的传导[11]。这两个过程对于 EGFR 的功能和 EGFR 信号传导重要蛋白的活性都至关重要。

在厄洛替尼耐药的 NSCLC 癌细胞中,匹伐他汀联合厄洛替尼可以增加耐药细胞对于厄洛替尼的敏感性,同时,EGFR 下游磷酸化蛋白激酶 B(p-AKT)和

磷酸化细胞外信号调节激酶(p-ERK)水平显著降低,导致细胞凋亡[10]。匹伐他汀通过抑制 HMG-CoA 还原酶阻断 MVA 途径,增加耐药细胞对于厄洛替尼的敏感性,从而逆转耐药[10]。在 KRAS 突变型 NSCLC 中阿托伐他汀可以克服吉非替尼耐药。阿托伐他汀(1 μM)联合吉非替尼可抑制 KRAS 突变型 NSCLC 细胞的增殖,促进细胞凋亡,同时抑制 p-AKT,增加阿托伐他汀的药物浓度(5 μM)可以进一步抑制 p-ERK。因此,阿托伐他汀和吉非替尼协同抑制 PI3K/AKT 和 MAPK/ERK 通路。另外,阿托伐他汀可以抑制 HMG-CoA 还原酶依赖性的 KRAS/Raf 和 KRAS/PI3K 复合物的破坏,克服 KRAS 突变型 NSCLC 细胞中的吉非替尼耐药。辛伐他汀可以通过 AKT/β-catenin 信号依赖的下调生存素和诱导细胞凋亡来克服 T790M 突变 NSCLC 中的 EGFR-TKI 耐药。研究发现,辛伐他汀联合吉非替尼可促进 T790M 突变的 NSCLC 细胞凋亡,显著增加 caspase-3、caspase-8 和 caspase-9 的表达,显著抑制 AKT 和 β-catenin 的磷酸化。同时,发现生存素是使 T790M 突变的 NSCLC 细胞抵抗吉非替尼和辛伐他汀诱导的细胞凋亡的关键分子[12]。

1.2　调节脂筏中胆固醇的含量　在细胞膜上有一个流动性小、富含胆固醇和鞘磷脂微结构域称为脂筏,作为细胞信号传导的平台发挥作用[13]。越来越多的证据表明,细胞增殖和存活的信号是通过脂筏传递的,脂筏是富含胆固醇的特殊膜微结构[14]。EGFR 主要定位在细胞膜上,作用于 MAPK 和 AKT 信号通路的激活[15]。研究发现,EGFR 定位到脂筏与 EGFR-TKIs 抗性相关[16]。脂筏中胆固醇含量减少可以使耐药的肿瘤细胞重新对吉非替尼敏感。在 EGFR-TKIs 耐药的细胞系中,脂筏为缺乏 EGFR 激酶活性的 AKT 的激活提供了一个平台,从而导致 EGFR-TKIs 的耐药。在 NSCLC 中,他汀类药物通过抑制细胞中胆固醇的合成,从而减少脂筏中胆固醇含量,增加肿瘤细胞对于 EGFR-TKIs 敏感性,这表明 EGFR-TKIs 和他汀类药物联合治疗 EGFR 突变型 NSCLC 可能是一种新型治疗方法。

1.3　胆固醇调节元件结合蛋白(SREBPs)对于脂肪酸和胆固醇合成的调节　SREBPs 是一种重要的核转录因子,其中 SREBP1 可以调控脂肪酸合成,SREBP2 调控胆固醇的合成,它们已被证明在维持癌症脂质合成中起重要作用[17-18]。并且质膜中胆固醇降低会激活 SREBPs,促进下游基因的表达,从而增加胆固醇的摄取。在 NSCLC 细胞中,抑制 SREBP 可下调脂肪酸合酶(FASN)、SCD 和 HMGCR 的表达,降低细胞膜上胆固醇和不饱和脂肪酸的比例,从而导致细胞膜流动性降低,其降低抑制了细胞膜上 EGFR 信号的激活,从而增加细胞对于吉非替尼的敏感性[6]。同时,SREBPs 促进 HMGCR 的转录,增强 MVA 途径合成胆固醇同时促进胆固醇经低密度脂蛋白受体(LDLR)摄入细胞。从而通过调节 SREBPs 的表达,调节细胞膜中脂质成分的含量,可以增加细胞对于 EGFR-TKIs 的敏感性,提示靶向 SREBP 可能成为治疗 EGFR-TKIs 耐药的新方法。

2　脂肪酸代谢重编程与 EGFR-TKIs 耐药

脂肪酸是一类由不同长度和不饱和程度的烃链组成的分子,在肿瘤生长过程中,其代谢在摄取、合成和降解水平上发生改变。CD36 作为一种跨膜糖蛋白,在卵巢癌、胃癌、胶质母细胞瘤和口腔鳞状细胞癌中高表达,可以介导长链脂肪酸的摄取[19]。CD36 的启动子含有过氧化物酶体增殖体激活受体(PPAR)反应元件(PPREs),在胃癌中,磷脂酰肌醇转运蛋白 1 上调 PPARG 的 RNA 水平,与 PPARγ 结合进而增强 CD36 的表达,从而提高脂肪酸的摄取。

2.1　调节脂肪酸合成　正常组织中,脂肪酸从头合成仅限于脂肪、肝细胞中,但为了满足自身高代谢需求,肿瘤细胞会上调脂肪酸合成相关酶的表达来增强脂肪酸合成。柠檬酸通过 SLC25A1 转运出线粒体,在细胞质中,在 ATP 柠檬酸裂解酶(ACLY)、乙酰辅酶 A 羟化酶(ACC)、FASN、硬脂酰辅酶 A 去饱和酶 1(SCD1)的作用下生成脂肪酸,脂肪酸可以进一步合成甘油三酯,并储存在脂滴中。ACLY、ACC 和 FASN 上调已在结直肠癌、胃癌、乳腺癌、肝癌和肺癌中被发现,其过表达与肺癌患者的低生存率显著相关[20-22]。SCD1 也已被证明在癌症的发生和进展中发挥关键作用。并且,研究者发现脂肪酸合成代谢的改变与 EGFR-TKI耐药相关,阻断肿瘤细胞的脂肪酸合成可以逆转 EGFR-TKIs 耐药。一项研究发现 NSCLC 在 EGFR-TKIs长期治疗状态下,细胞内脂滴积聚,而短期的治疗会降低细胞中的脂滴含量,表明脂滴的异常积聚可能是 EGFR-TKIs 耐药的原因[23]。在 EGFR-TKIs 耐药的 NSCLC 细胞中脂肪酸合成中的关键酶基因表达增加,EGFR-TKIs 耐药株中骨形态发生蛋白(BMPs)表达升高,BMPs 通过促进 ACSL 表达,从而使柠檬酸在细胞质中转化为乙酰 CoA 参与脂质合成[24]。有报道指出,FASN、ACC、SCD1 在 TKI 耐药的 NSCLC 中表达上调[22,25],通过促进脂肪酸合成降

低细胞对 EGFR-TKI 的敏感性,从而导致耐药[26]。当 EGFR-TKIs 联合 SCD1 抑制剂 g-PPT 时,可以逆转 NSCLC 细胞对 EGFR-TKIs 的抵抗,减少脂滴的积聚并且抑制 EGFR 的磷酸化以及 p-EGFR/p-AKT/p-ERK 信号通路的激活,从而使细胞对耐药的 EGFR-TKIs 再敏感[23]。这表明在耐药细胞中脂肪酸合成增加可能是导致脂滴异常积聚的原因,也是治疗 EGFR-TKIs 耐药的 NSCLC 的潜在靶点。

2.2　调节脂肪酸 β 氧化　脂肪酸在脂酰辅酶 A 合成酶(ACS)作用下活化是脂肪酸 β 氧化(FAO)的关键步骤,脂肪酸被分解为乙酰辅酶 A 参与三羧酸循环,从而生成 ATP,为细胞提供能量。大量证据表明,许多癌细胞对 FAO 进行了重编程,并依靠这一过程进行增殖、存活、转移甚至耐药。ACS 仅存在于线粒体中,脂肪酸需转运至线粒体才可以进行 FAO,肉碱棕榈酰转移酶 1(CPT1)可以将脂肪酸从细胞质转运至线粒体中,从而使脂肪酸在 ACS 的作用下进行 FAO。CPT1A 的过表达也与肿瘤的不良预后相关[27]。在奥希替尼治疗过程中,FAO 随着治疗时间的延长而增加,在奥希替尼耐药 NSCLC 细胞中,FAO 水平明显高于敏感细胞,CPT1 是 FAO 过程中的关键酶,使用 CPT1 抑制剂依托莫西可以阻断 FAO 以逆转奥希替尼耐药,表明 FAO 在奥希替尼耐药过程中发挥了重要作用[28],可为 EGFR-TKIs 耐药的治疗提供新的治疗靶点。肿瘤细胞通过调节脂肪酸代谢相关的关键酶基因的表达,调控脂肪酸的摄取、合成、积累与降解,从而为肿瘤细胞的生长、增殖、转移甚至耐药创造条件。靶向脂肪酸代谢酶可以增加 NSCLC 细胞对于 EGFR-TKIs 的敏感性,有望为克服 EGFR-TKIs 耐药提供新的治疗方向。

3　其他脂质代谢重编程与 EGFR-TKIs 耐药

鞘磷脂是细胞膜的主要成分,在细胞膜上鞘磷脂可以转化为鞘氨醇,在两种不同的鞘氨醇激酶(SPHK)的催化下合成鞘氨醇-1-磷酸(S1P)。研究发现 SPHK2 的表达与 NSCLC 的不良预后相关,也与吉非替尼的耐药相关[29]。LDLR 是胆固醇摄取的关键介质,p-EGFR 可以促进 LDLR 表达,从而促进肿瘤细胞摄取胆固醇以维持其生长需要。LDLR 的下调可降低肿瘤细胞对胆固醇的摄取。因此,EGFR-TKI 和他汀类药物联用,可协同减少胆固醇摄取,以抑制 EGFR 突变细胞的增殖和生长[30],但抑制 LDLR 表达能否逆转 EGFR-TKIs 耐药仍需进一步研究。

4　结　语

肿瘤细胞中发生的主要变化之一是代谢重编程,癌细胞通过改变其碳水化合物、氨基酸和脂质代谢途径,以维持其生长和增殖的需要,以及阻断可能导致其生长停滞的信号[31]。近年来,糖代谢重编程最受研究者关注,已经发现糖代谢重编程与肿瘤进展、与 EGFR-TKIs 耐药密切相关。随着糖代谢重编程的机制研究逐渐完善,研究者们将目光转向了脂质代谢的重编程,发现在肿瘤的发生发展过程中,脂质代谢发生了改变,以满足其在营养和氧气匮乏的微环境下增殖和进展的需要。越来越多的研究发现通过改变脂质的合成、分布、代谢等途径导致肿瘤细胞对 EGFR-TKIs 的敏感性发生变化,从而产生获得性耐药。这些研究也为治疗 EGFR-TKIs 耐药的患者提供了潜在的治疗策略。脂肪酸、胆固醇的摄入、合成和降解,以及相关的关键蛋白和转录调节因子表达构成了脂质代谢重编程的核心。因此,大多数临床前实验中,也针对这些途径的药物和抑制剂进行研究,将 EGFR-TKIs 药物与这些药物联合使用并得出一些积极的结果。他汀类药物作为临床上常用的胆固醇合成调节剂,在与 EGFR-TKIs 药物联用时,可以改善肿瘤细胞对 EGFR-TKIs 的敏感性,从而延缓甚至逆转 EGFR-TKIs 耐药的发生。另外,还有各种脂质代谢中的关键酶、转录因子的靶向药物与 EGFR-TKIs 联用也可以降低耐药细胞对于 EGFR-TKIs 的敏感性。因而,脂质代谢靶向治疗可能是一种新颖且潜在有效的治疗 EGFR-TKIs 耐药的策略。脂质代谢重编程是一个复杂的调节网络,然而,对于 EGFR-TKIs 耐药的细胞,其脂质代谢重编程的研究还不够充分。因此,需要进一步研究并了解脂质代谢网络,以完善脂质代谢重编程与 EGFR-TKIs 的耐药机制。

利益冲突　无

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