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Review

Relationship of immune response with intestinal flora and metabolic reprogramming in patients with non-small cell lung cancer

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Abstract: Numerous research conducted in recent years has revealed that gut microbial dysbiosis, such as modifications in composition and activity, might influence lung tissue homeostasis through specific pathways, thereby promoting susceptibility to lung diseases. The development and progression of lung cancer, as well as the effectiveness of immunotherapy are closely associated with gut flora and metabolites, which influence immunological and inflammatory responses. During abnormal proliferation, non-small cell lung cancer cells acquire more substances and energy by altering their own metabolic pathways. Glucose and amino acid metabolism reprogramming provide tumor cells with abundant ATP, carbon, and nitrogen sources, respectively, providing optimal conditions for tumor cell proliferation, invasion, and immune escape. This article reviews the relationship of immune response with gut flora and metabolic reprogramming in non-small cell lung cancer, and discusses the potential mechanisms by which gut flora and metabolic reprogramming affect the occurrence, development, and immunotherapy of non-small cell lung cancer, in order to provide new ideas for precision treatment of lung cancer patients.

Key words: non-small cell lung cancer; metabolic reprogramming; intestinal flora; immunity

非小细胞肺癌患者免疫反应与肠道菌群、代谢重编程之间的关系

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摘 要：近年来许多研究表明肠道微生物失调(包括构成和功能的改变)可通过特定的途径影响肺组织的稳态，进而促进肺部疾病的易感性。肠道菌群及代谢物可调节免疫、炎症反应等作用，与肺癌的发生、发展以及免疫治疗效果联系紧密。非小细胞肺癌细胞在异常增殖过程中通过改变癌细胞自身的代谢方式获取更多的物质和能量，其中葡萄糖和氨基酸代谢重编程分别为肿瘤细胞提供大量ATP和碳源、氮源，为肿瘤细胞的增殖、侵袭和免疫逃逸提供最佳条件。本文综述了非小细胞肺癌患者免疫反应与肠道菌群、代谢重编程的相关性，同时讨论肠道菌群、代谢重编程影响非小细胞肺癌发生、发展及免疫治疗的潜在机制，以期为肺癌患者的精准治疗提供新思路。

关键词：非小细胞肺癌；代谢重编程；肠道菌群；免疫

Lung cancer is the most prevalent cancer type, with around 2 million diagnoses and 1.8 million deaths worldwide each year. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the

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two primary pathological subtypes of lung cancer. Large-cell carcinoma, squamous carcinoma, and adenocarcinoma are among the more than 80% of lung malignancies that are classified by NSCLC [1]. NSCLC is a subtype of malignant lung tumors that originate from the bronchial mucosa, bronchial glands, and alveolar epithelium. These tumors may be identified under a microscope by their larger cells, copious amounts of cytoplasm, and heterogeneous nuclei [2]. Screening and diagnosing NSCLC are extremely difficult as its pathophysiology in early stages has never been well established. The emergence of genome sequencing technologies has facilitated the screening of cancerous cells in oncology. The presence of several molecules, such as epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene (KRAS), tumor suppressor protein p53 (TP53), anaplastic lymphoma kinase (ALK), mesenchymal-epithelial transition factor (MET), phosphatidylinositol 3-kinase (PI3K) catalytic factor, and others, has been revealed by sequencing results for NSCLC. A number of genes known as driver genes, including *ALK*, *MET*, phosphatidylinositol 3-kinase catalytic alpha (*PIK3CA*), proto-oncogene tyrosine-protein kinase receptor Ret (*RET*), and ROS proto-oncogene 1 (*ROS1*), are important in the pathophysiology of NSCLC [3].

The immunosuppressive tumor microenvironment (TME) and the aberrant biological features of tumor cells are key factors in the growth and metastasis of NSCLC [4]. These factors are closely related to the metabolic adaptation of tumor cells, which occurs in tumors to meet the needs of malignant cells for bioenergy and biosynthesis. When a tumor progresses, its metabolic preferences and characteristics change. This process is known as metabolic reprogramming, and it may be the cause of treatment resistance or tumor cell escape [5, 6]. Aerobic glycolysis, amino acid metabolism, oxidative phosphorylation, fatty acid metabolism, and nucleotide metabolism are the primary modalities of tumor cell metabolic reprogramming, which is one of the key elements in the processes of cancer formation, progression, and immune evasion [7]. Tumor cells' energy metabolism is different from normal cells' in aerobic conditions. Specifically, they switch from oxidative phosphorylation to aerobic glycolysis for the metabolism of glucose, which supplies the energetic foundation for tumor cell proliferation [8]. Actually, many cancer cells rely on the amino acid glutamine to fulfill their increased energy requirements, which has an impact on tumor invasion, metastasis, and the effectiveness of therapeutic interventions. Glutamate is a crucial metabolic fuel for rapidly reproducing tumor cells [9].

The vast and intricate microbial community known as the intestinal flora, which colonizes the intestine, is essential for human metabolism and health. Together with the host, it forms a complex superorganism whose homeostasis is crucially important in regulating the onset and progression of human diseases [10]. Through a complex network of interactions including energy metabolism, immunology, and neuroendocrine function, the intestinal flora and the host develop a symbiotic connection [11]. Using a range of biological correlates, including immunological channels, neurological channels, and embryonic developmental homology, Budden *et al*.[12] hypothesized a pathogenic relationship between bacteria and the gut-lung axis, which regulates the gut and lungs in concert. This finding implies that specific communication mechanisms exist between gut flora and lung cancer. Nonetheless, a thorough comprehension of the interplay of metabolic reprogramming, immunological evasion, and gut flora in NSCLC is deficient, and so more clarification of these correlations is necessary for more efficacious cancer management.

1 Influence of intestinal flora on the pathogenesis and immunotherapy of NSCLC

1.1 Influence of intestinal flora on the development of NSCLC

In recent years, a great deal of research has revealed a strong link between gut flora and lung problems. Mutations in lung microbiology and even lung cancer might result from gut microecological dysbiosis, which increases the number of microbiota generating toxic compounds and antigens [13]. Gastrointestinal bacteria alter the NSCLC response to inflammation and immunity, mostly through the lung-gut axis, by interfering with the metabolic processes of lungs, where inflammatory response and immunological dysregulation are two essential hallmarks of NSCLC [14]. Compared to healthy individuals, lung cancer patients have reduced metabolic biological activity and a less diverse gut flora [15]. Researchers have observed that NSCLC patients had a higher density of dangerous bacteria, such as intestinal actinomyces, streptococcus, fusobacterium, and bacte-

rium fusiformis, while a lower density of beneficial probiotics, such as bifidobacterium and lactobacillus, was present [16, 17]. The intestinal microbiome of lung cancer patients was predominantly characterized by decreased diversity and biological activity associated with metabolism, as opposed to healthy individuals [18]. Studies have indicated that respiratory bacteria disorders are most commonly associated with *Veillonella parvula*, whose characteristics are linked to interleukin-17 (IL-17), PI3K, mitogen-activated protein kinase (MAPK), and extracellular regulated protein kinases (ERK) pathway reconfiguration [19]. Inflammation-promoting factors alter the composition of pulmonary bacteria through the gut-lung axis; When the gut flora is disrupted, harmful bacteria cluster and break the intestine barrier and immune function, causing intestinal immune cells to produce large amounts of inflammatory factors such as interferon-γ (IFN-γ), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and IL-18 [18]. An inflammatory microenvironment can lead to cellular damage, disrupt immunological homeostasis in the lungs, and accelerate the onset and spread of lung cancer [15]. Low levels of short-chain fatty acids (SCFA) in the bloodstream can result from gut microecological dysregulation [20, 21]. Propionate of SCFA can cause lung cancer cells to undergo apoptosis and cell cycle arrest [22]. Additionally, SCFA are important for both host systemic immunity and systemic inflammation [21, 23]. *In vivo*, they can directly modulate Toll-like receptor 4 (TLR-4) signaling, inhibit the production of pro-inflammatory factors like TNF-α, IL-6, and IL-12, and increase the production of the anti-inflammatory cytokine IL-10, which directly suppresses immune responses [24]. It is evident that the development of NSCLC is associated with changes in the gut flora, which can also have an impact on the lower respiratory flora through the intestinal-pulmonary axis in reverse. Additionally, an imbalance in the gut flora and lower respiratory flora exacerbates the production of pro-inflammatory factors, indicating that the occurrence and development of lung cancer are closely related processes involving the bacterial microbiota (Fig. 1).

1.2 Effects of intestinal flora on immunotherapy for NSCLC

Drug therapies, which includes immunotherapy, chemotherapy, and other treatments, are frequently the cornerstone for the treatment of NSCLC patients; nevertheless, immunotherapy is progressively emerging as a novel anti-NSCLC strategy [25]. In recent years, human clinical studies and preclinical trials have shown that the efficacy of immunotherapeutic agents is influenced by the patient's intestinal flora, and that certain intestinal bacteria promote the action of a programmed death 1 (PD-1) inhibitor, which, together with its ligand PD-L1, is a potent therapeutic agent for the treatment of metastatic NSCLC that lacks sensitizing EGFR or ALK mutations [26] (Fig. 2). Fecal specimens from cancer patients who reacted to anti-PD-L1 immunotherapy

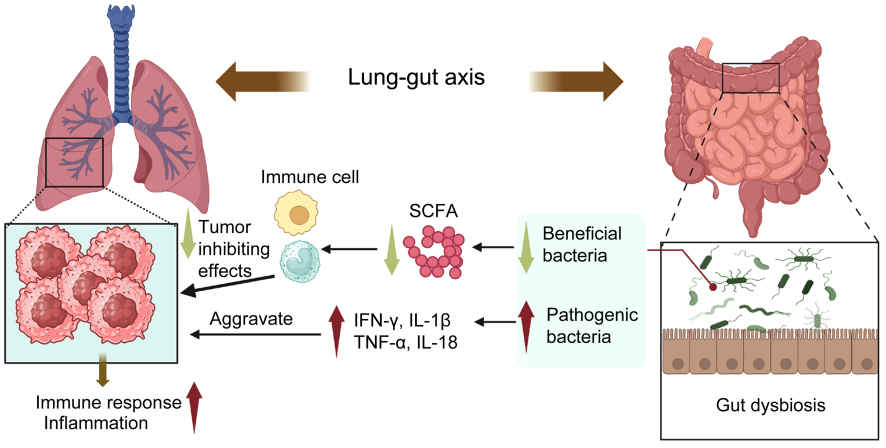

Fig. 1. Immune relationship between intestinal flora and non-small cell lung cancer (NSCLC). A microecological imbalance within the gut causes the number of beneficial bacteria to decline, which in turn causes a decrease in the synthesis of short-chain fatty acids (SCFA). This decline directly impacts immune cell function, and pro-inflammatory factors secreted by pathogenic bacteria intensify lung inflammation via the lung-gut axis. IFN-γ, interferon-γ; IL-1β/18, interleukin-1β/18; TNF-α, tumor necrosis factor-α. Figure created using FigDraw.

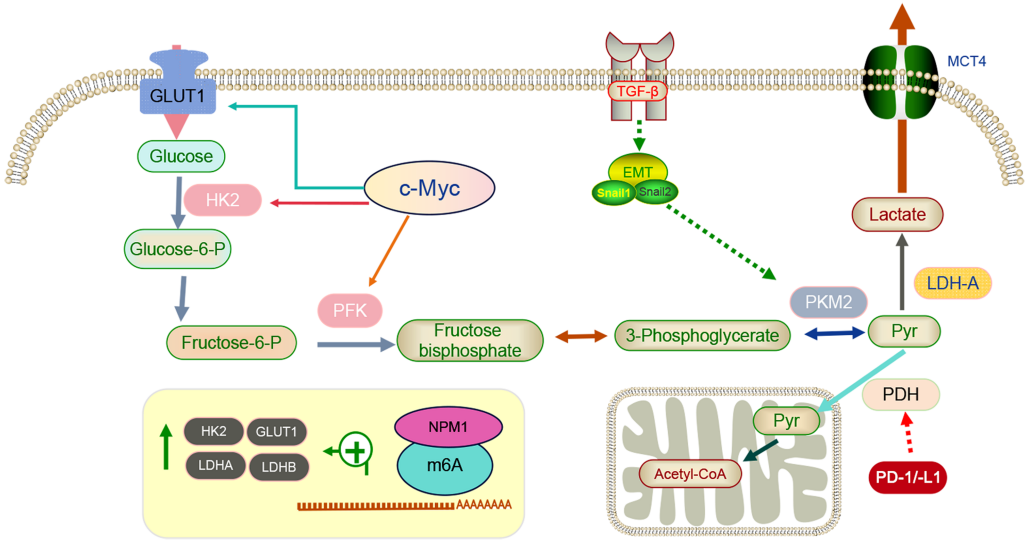

Fig. 2. Regulation of glycolysis in non-small cell lung cancer (NSCLC). Increased glycolysis in NSCLC produces a lot of lactic acid, which is released into the extracellular space via monocarboxylate transporter 4 (MCT4), creating an acidic extracellular environment; Transforming growth factor β (TGF-β) induces epithelial-mesenchymal transition (EMT), upregulating pyruvate kinase isoform M2 (PKM2), increasing the production of pyruvate (Pyr); The proto-oncogene c-Myc enhances the activities of glucose transporter 1 (GLUT1), hexokinase 2 (HK2), and phosphofructokinase (PFK); n6-methyladenosine (m6A) modification of RNA upregulates mRNA expression levels of GLUT1, HK2, lactate dehydrogenase A (LDHA), and B (LDHB). NPM1, nucleophosmin 1; PD-1, programmed death 1; PD-L1, programmed death-ligand 1.

were shown to include certain bacterial species, whereas non-responders showed a high abundance of other bacterial sources. For this reason, the gut microbiota may be a promising best response indicator for immunotherapy [27]. The antitumor effects of PD-1 blockade were enhanced when fecal microbiota transplantation (FMT) of cancer patients responding to immune checkpoint inhibitors (ICI) was administered into germ-free or antibiotic-treated mice [16, 28]. Similarly, macrogenomics of fecal samples from patients with NSCLC showed a correlation between the clinical response to ICI and the relative abundance of *Akkermansia* and *Prevotella* [29]. Furthermore, individuals exhibiting favorable gut flora, such as those with elevated diversity, demonstrated elevated expression of memory T cells and NK cells in peripheral blood [30]. This implies that gut microbes may regulate anti-PD-1 therapy. Moreover, antibiotics have been shown to modify the intestinal flora's variety and composition, resulting in dysbiosis, which may reduce the effectiveness of ICI [31]. Their effects may impact the likelihood of responding to ICI. The findings of these investigations indicate that, in order to maximize therapeutic success, immunotherapy for NSCLC should be combined with a balanced intestinal microecology, probiotic additions, adjustments to the dosage of antibiotics, and dietary modifications. Increasing the amount of gut flora is the most effective treatment method to improve immune surveillance against cancer and increase the efficacy of ICI.

2 Tumor cell metabolic reprogramming

2.1 Glucose metabolic reprogramming

Reprogramming of energy metabolism in tumor cells has been identified as a novel hallmark of cancer. It facilitates fast cell division and growth by controlling energy metabolism so that glycolysis takes over from oxidative phosphorylation as the primary pathway for supplying energy to tumor cells [8]. As primary source of energy for the human body, glucose is generated in the small intestine from the breakdown of fructose by intestinal bacteria. Once glucose reaches the circulation, it feeds tumor cells and promotes their development and multiplication [32]. Tumor cells produce adenosine triphosphate (ATP) primarily through the glycolytic pathway for their own fast development and biomolecules for cell reproduction through the amino acid metabolic pathway for cell replication, even in settings with enough oxygen [33]. It has been reported that

transforming growth factor (TGF)-β-induced epithelial-mesenchymal transition (EMT) in lung adenocarcinoma cells is accompanied by increased expression of pyruvate kinase isoform M2 (PKM2) [34]. This suggests that TGF-β regulates PKM2 expression to promote glycolysis in tumor cells. Glycolysis in tumor cells is down-regulated when PKM2 activity is inhibited. (Fig. 2). Studies show that TGF-β can dramatically boost glucose uptake and lactate production in hypoxic environments by upregulating PKM2 expression, which meets the metabolic requirements of tumor cell growth and proliferation [35, 36]. Additionally, lactate is expelled from the cell through the monocarboxylate transporter 4 (MCT4) and suppresses the ability of a range of immune cells [37], which aids the immune escape of tumor cells.

There is mounting evidence that the n6-methyladenosine (m6A) alteration of RNA regulates tumor glycolysis via a variety of pathways. By improving the stability of nucleophosmin 1 (NPM1), which boosts glycolytic capacity and development, m6A modification may up-regulate the expression of glycolytic enzymes in lung adenocarcinomas, including hexokinase 2 (HK2), lactate dehydrogenase A (LDHA), lactate dehydrogenase B (LDHB), and glucose transporter protein 1 (GLUT1) [38] (Fig. 2). In conclusion, in the process of glycolysis reprogramming in NSCLC, m6A modification enhances the expression of GLUT in tumor cells, accelerates glucose input, and promotes the high expression of key glycolytic enzymes in order to enable tumor cells to quickly obtain ATP to meet their energy needs. This provides a large amount of ATP for gene mutation, drug resistance acquisition, and immune escape of tumor cells.

2.2 Glutamine metabolism

Glutamine is the most prevalent free amino acid in plasma, and it is extensively used by rapidly reproducing cells, particularly cancer cells, for energy generation as well as as a source of carbon and nitrogen for the synthesis of several biological molecules [39]. Glutamine is second only to glucose in the energy supply substances of tumor cells. A portion of the glutamine is used in the cytoplasm for nucleotide and asparagine biosynthesis [40], and the remainder is transported through a variant of the mitochondrial glutamine transporter protein, SLC1A5, into the mitochondrial inner membrane to support mitochondrial oxidative phosphorylation [41]. The glutamine is transported into the cell cytosol by its transporters SLC1A5, SLC38A1, and SLC38A2. Following that, glutamine is converted to glutamate by GLS (glutamine deaminases, which can be identified on mitochondria and include GLS1, GLS2, and GAC) [42]. The SLC25A18 and SLC25A22 transporters on the mitochondria allow glutamate produced during catabolism to be exported to the cytoplasm. From there, it is used in the biosynthesis of glutathione (a tripeptide made up of glutamate, cysteine, and glycine) and nonessential amino acids (NEAAs, including aspartate, alanine, proline, arginine, and asparagine) [43]. Glutamate production is directly dependent on glutamine. The leftover glutamate in the mitochondria is then transformed into α-ketoglutarate (α-KG) by glutamate dehydrogenase 1 (GLUD1 or GDH1), and some of α-KG is exported to the cytoplasm, where it plays a role in the synthesis of fatty acids and nicotinamide adenine dinucleotide (NADH). Additionally, α-KG in the mitochondria participates in the tricarboxylic acid (TCA) cycle, which enables the oxidative phosphorylation pathway to produce ATP [40]. Research on increased glutamine metabolism in cancer cells has also demonstrated that metabolic reprogramming is improved by glutamine catabolism, suggesting a critical role for glutamine metabolism in the development and spread of tumors [41]. The aforementioned metabolic pathways convert glutamine into glutamine-derived metabolites, such as fumarate, succinate, and R-2-hydroxyglutarate (R-2-HG) [44, 45]. These metabolites are thought to be cancer-related and contribute to carcinogenesis.

The current data demonstrate that glutamine metabolic reprogramming, which sustains mitochondrial oxidative phosphorylation and supplies metabolic intermediates for the TCA cycle, glutathione synthesis, NEAA synthesis, and NADPH production, is a critical component of metabolic adaptation in tumor cells. Carbon derived from glutamine is an essential substrate for the TCA cycle and the synthesis of glutathione. Furthermore, nucleotide, glucosamine, and NEAA production all depend on nitrogen, which is obtained from glutamine [46]. Targeted therapeutic strategies for glutamine metabolism are a promising anticancer approach to improve the efficacy of antitumor therapy.

3 Impact of NSCLC metabolic reprogramming on immune cells in the TME

Metabolic transformation is not limited to tumor cells; it also refers to the swift growth of other immune cells,

including regulatory T cells, activated T cells, and neutrophils [47]. These cells can detect different signals in the microenvironment and will quickly become activated in response to a nucleotide stimulating the body, which will initiate specific immune functions [48]. Activated M1 macrophages, neutrophils, and dendritic cells, for instance, primarily rely on glycolysis as a source of energy [49]. Ultimately, immune cells and tumor cells compete locally for nutrients, with glucose primarily being absorbed and consumed by tumor cells [50]. T cell function is also reduced in the NSCLC microenvironment due to the competitive absorption of glucose [49]. Large amounts of glucose are used in abnormal tumor glycolysis to produce large amounts of lactate, which builds up in tumor cells and is eventually exported to the extracellular environment by activating monocarboxylic acid transporter (MCT) proteins on cell membranes. As a result, an acidic tumor-immune milieu is created [51], and lactic acid may also suppress tumor immunity in this environment by encouraging IL-23- and IL-17-mediated inflammation and aiding in the proliferation [52].

In general, activated immune cells consume glutamine in amounts comparable to those of glucose. During immune cell proliferation, glutamine stimulates the proliferation of immune cells by activating proteins such as ERK and JNK kinases to induce the transcription of genes related to cell proliferation [53]. Glutamine is necessary for the growth of T and B cells, the synthesis of proteins and antibodies, and it also controls the activation of macrophages and the production and release of pro-inflammatory cytokines (including IL-1, TNF-α, and IL-6) [54]. Similar to this, reprogramming glutamine metabolism is essential for both tumor and immune cell survival. Additionally, there is competition between the two types of cells for glutamine uptake in the TME, with tumor cells actively seeking out glutamine. These results in a restricted glutamine supply for immune cells, which in turn affects the immune system's ability to fight cancer [55]. In summary, these data imply that tumor cells' use of glycolysis to produce higher concentrations of lactic acid and the resulting acidified TME will suppress immune cell activity and competitively deprive immune cells of glutamine needed for proliferation. The inhibition will impede the synthesis of essential cytokines by immune cells, leading to the termination of immune surveillance in NSCLC and ultimately resulting in evasion from the immune response.

4 Influence of intestinal flora on immune cells in the TME

The communication between the microbiota and immune cells is mediated by microbial metabolites, and in the colon, carbohydrates provide a rich substrate for bacterial fermentation. The primary metabolic byproduct of this process is SCFA, which play numerous regulatory roles in addition to serving as a localized substrate for energy production. Furthermore, the impact of SCFA on host immunity is continuously being studied [55]. Histone deacetylase (HDAC) has been reported to be a key regulator of nuclear factor-κB (NF-κB) activity and pro-inflammatory innate immune responses, and SCFAs can directly bind to HDAC and inhibit its activity in tumor cells, leading to differential recruitment of pro-inflammatory genes by NF-κB [56]. Tolerogenic, anti-inflammatory cellular phenotypes are tendered to be promoted by SCFA-driven HDAC inhibition, which is essential for the maintenance of immune homeostasis. Peripheral blood mononuclear cells and neutrophils are exposed to SCFA in a manner similar to their exposure to overall HDAC inhibitors, inactivation of NF-κB, and down-regulation of the production of the pro-inflammatory cytokine TNF [57]. Furthermore, it has been shown that SCFA controls the respiratory factors GATA3, oxidative phosphorylation, and glycolytic metabolic pathways in type 2 innate lymphocytes (ILC2s) of the lung. Dysbiosis of the intestinal flora has also been linked to increased neutrophil recruitment in the airways and the secretion of inflammatory factors IL-5, IL-13, and IL-17a in lung ILC2s [57, 58]. According to the current research [59], intestinal flora modulates immune cells in peripheral blood by secreting advantageous metabolites, which eventually reach the lungs via the lung-gut axis and continue to stimulate other immune cells in the active TME. The aforementioned studies show that intestinal flora plays a significant role in lung homeostasis, but the mechanism of action is rarely reported.

5 Immunization escape

The immune system's ability to identify and attack cancer cells is greatly aided by mechanisms of antigen presentation and processing. By downregulating or elimi-

nating the expression of proteins identified as antigens by immune cells, cancer cells create an immunosuppressive microenvironment in the context of cancer. They do this by employing a number of strategies to avoid immune cell recognition or to stifle anti-tumor immune responses [60, 61]. Tumor cells use the oncogene c-Myc to promote their own survival when they are deprived of nutrients like glucose and glutamine. This oncogene regulates the serine synthesis pathway by controlling the expression of metabolic enzymes like 3-phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase 1 (PSAT1), phosphoserine phosphatase (PSPH), and other metabolic enzymes. Tumor cells can survive because of this improved serine ab initio synthesis and preservation of redox equilibrium [62]. One of the oncoproteins that is most frequently activated in human malignancies is c-Myc. The majority of cancers have mutations in the *myc* gene or increased expression of the *myc*-related pathway, and these activated cancers are characterized by boundless replication and continuous proliferation [63]. Numerous studies have demonstrated that c-Myc controls the metabolism of glucose and glutamine, promoting the metabolic transition from oxidative phosphorylation to glycolysis, increasing glutamine catabolism, and promoting adipogenesis in cancer cells. These actions enhance cellular adaptation and provide cancer cells with a survival advantage [64] (Fig. 2). Excess lactic acid is produced by the glycolytic process in cancer cells. This excess lactic acid helps to create an immunosuppressive environment that supports the growth of cancer cells, resulting in an acidic tumor immune microenvironment and impeding immune cell function, which leads to immune evasion [65].

6 Conclusion

Clinical research indicates that the overuse of medications such as macrolides and cephalosporins increases the risk of lung cancer [66]. This is likely because antibiotics drastically reduce intestinal flora, which in turn alters the immune system and immune homeostasis of the lungs through the lung-intestinal axis and raises the risk of lung cancer [67]. Research has demonstrated that the intestinal flora of patients with lung cancer exhibits decreased bacterial diversity, a reduction in probiotics, and an increase in conditionally pathogenic bacteria. The latter type of bacteria compromises the integrity of the intestinal barrier, increasing the risk that the bacteria and their byproducts will spread to other areas of the body and aid in the formation of tumors [68]. A thorough investigation into the relationship between lung microorganisms and the development of lung cancer is of little significance, despite the fact that changes in gut flora affect the diversity of the lung microbiota and that changes in the latter can worsen inflammation. The composition of the lung microbiota in patients with lung cancer has been linked to lifestyle, pollution, and smoking [69]. These factors may result in different outcomes being reported. Both the quantity and percentage of thick-walled bacteria in the gut flora were considerably decreased, and the energy metabolism pathway of intestinal flora in lung cancer was found to be changed, being dominated by glutamate metabolism [70]. There was also a decrease in the functional groups involved in metabolism and sugar transport [71]. These findings suggest that variations in gut flora cause altered energy metabolism pathways in lung cancer. Additionally, variations in the gut flora's metabolic activity promote the course of lung cancer [72].

A recent study published in *Nature Metabolism* demonstrated [73] that acetic acid is the most abundant SCFA in human NSCLC tissues, increased acetic acid uptake with tumor enrichment, and that NSCLC cells take up acetic acid in a monocarboxylate transporter 1 (MCT1)-dependent manner. Acetic acid-derived and acetyl-CoA synthetase (ACSS)-mediated acetyl coenzyme A production induces dihydrolipoamide S-acetyltransferase (DLAT)-mediated acetylation of c-Myc Lys148, which recruits ubiquitin-specific peptidase 10 (USP10) to deubiquitinate and stabilize c-Myc, leading to enhanced expression of PD-L1, promotion of immune escape of tumors, glycolysis, and cell cycle progression genes expression and acceleration of cell proliferation [74].

A significant number of immune and inflammatory cells are drawn to the lungs in the lung cancer microenvironment; nevertheless, tumor cells absorb a significant amount of energy and macromolecules, such as lipids and amino acids, that are necessary for the survival of the drawn-in cells and the upkeep of cellular processes. Cancer cells frequently undergo metabolic reprogramming in aerobic circumstances in order to effectively promote their continuation and development. To satisfy fast cellular proliferation, tumor cells use glycometabolic reprogramming to make huge amounts

of lactic acid and adequate ATP, which in turn creates an acidic local environment that inhibits immune cell proliferation and anticancer efficacy [75]. Numerous PD-1 inhibitors have been created, with Pembrolizumab/Keytruda being the most widely utilized. This medication inhibits the binding of PD-L1 to PD-1, hence inducing an immune response against tumor cells [76]. Gut flora transplantation is anticipated to change the gut microbiota of patients who have become resistant to anti-PD-1 monotherapy, improve their response to immunotherapy, and provide this group of drug-resistant patients fresh hope [77].

Tumor immunotherapy, exemplified by ICI, has revolutionized the way advanced NSCLC is treated in recent years. Of particular note are anti-PD-1 and PD-L1 therapeutic agents, which have the advantage of causing fewer autoimmune side effects due to the fact that PD-L1 is primarily expressed on the surface of tumor cells and that PD-L1 binding to PD-1 occurs primarily in the tumor immune microenvironment [68]. Even if a number of immunotherapeutic medications have shown promising clinical outcomes, there is a need to investigate more efficacious treatment options due to the broad concern raised by the related side effects. Studies have demonstrated [16] that gut flora plays a significant role in the response to immunotherapy with PD-1 inhibitors in NSCLC patients, with a significant increase in bacterial diversity in patients who responded to anti-PD-1 therapy. While gut microorganisms and metabolism indirectly influence cellular immune responses in the gut and lungs. As a result, we ought to be mindful of the application of microbiological agents in immunotherapy, since this might result in improved therapeutic outcomes [78].

All things considered, this work comes to the conclusion that NSCLC is associated with alterations in the intestinal flora, and that the loss of beneficial bacteria in the intestinal flora causes a great deal of pro-inflammatory factors to enter the lungs through the lung-intestinal axis, thereby intensifying inflammation in the TME. Focusing on the changes in glycolysis and reprogramming amino acid metabolism in tumor cells can provide a novel approch and strategy to prevent their development and immune escape. Consequently, a greater understanding of the host's features, the immune milieu around the tumor, and the tumor cells themselves is necessary for the development of the immunotherapy territory.

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