Oncogene-Driven Metabolic Alterations in Cancer

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Abstract
Cancer is the leading cause of human deaths worldwide. Understanding the biology underlying the evolution of cancer is important for reducing the economic and social burden of cancer. In addition to genetic aberrations, recent studies demonstrate metabolic rewiring, such as aerobic glycolysis, glutamine dependency, accumulation of intermediates of glycolysis, and upregulation of lipid and amino acid synthesis, in several types of cancer to support their high demands on nutrients for building blocks and energy production. Moreover, oncogenic mutations are known to be associated with metabolic reprogramming in cancer, and these overall changes collectively influence tumor-microenvironment interactions and cancer progression. Accordingly, several agents targeting metabolic alterations in cancer have been extensively evaluated in preclinical and clinical settings. Additionally, metabolic reprogramming is considered a novel target to control cancers harboring un-targetable oncogenic alterations such as KRAS. Focusing on lung cancer, here, we highlight recent findings regarding metabolic rewiring in cancer, its association with oncogenic alterations, and therapeutic strategies to control deregulated metabolism in cancer.

Key Words: Cancer, Non-small cell lung cancer, Cancer metabolism, Metabolic reprogramming, Aerobic glycolysis, Oncogenic alteration

INTRODUCTION

Despite numerous efforts for cancer treatment, cancer is the leading cause of human deaths worldwide (Mathers and Loncar, 2006; Torre et al., 2015). Thus, understanding the biology underlying the evolution of cancer is important for reducing the economic and social burden of cancer. Recent investigations have demonstrated the impact of metabolic reprogramming on the development and progression of several types of human cancer, and deregulated metabolism is now regarded as one of the hallmarks of cancer (Hanahan and Weinberg, 2011; Pavlova and Thompson, 2016). Moreover, several findings demonstrate that mutations in oncogenes and/or tumor suppressor genes can mediate metabolic rewiring in cancer cells to support the high demands for building blocks and energy production in these cells (Iurlaro et al., 2014; Nagarajan et al., 2016; Kerr and Martins, 2017). Because cancer cells are prone to several oncogenic mutations such as RAS, EGFR, MYC, and BRAF mutations, these genes could also influence the metabolic changes in cancer. Based on several studies on the association of oncogenic alterations with the metabolic reprogramming (Kroemer and Pouyssegur, 2008; Hanahan and Weinberg, 2011; Iurlaro et al., 2014; Nagarajan et al., 2016; Kerr and Martins, 2017), here, we summarize recent findings on the association of oncogenic alterations with metabolic reprogramming in cancer, focusing on lung cancer due to its great contribution to cancer incidence and mortality rates. Further, we discuss the impact of metabolic alterations on the tumor-microenvironment interaction and possible therapeutic options targeting metabolic reprogramming.

GENERAL FEATURES OF METABOLIC REPROGRAMMING IN CANCER

Cancer cells have been known to possess markedly different metabolic features compared with those of corresponding normal tissues (Tennant et al., 2010). Unlike normal cells, cancer cells rearrange their cellular metabolic networks to fulfill their high demands for building blocks and energy production.
Recent findings demonstrate the additional metabolic reprogramming in cancer cells compared with normal cells. This is illustrated in Fig. 1.

Fig. 1. Metabolic reprogramming in cancer cells compared with normal cells.

To support extensive proliferation and growth (Tennant et al., 2010; Kerr and Martins, 2017), the Warburg effect, an aerobic glycolytic process discovered by Otto Warburg in 1926 (Warburg, 1956), is a crucial metabolic alteration in cancer cells. In this process, cancer cells are dependent on glycolysis for glucose metabolism even in the presence of oxygen, thereby producing high levels of lactate and reducing the use of the tricarboxylic acid (TCA) cycle (Levine and Puzio-Kuter, 2010). Because the TCA cycle and subsequent oxidative phosphorylation produce cellular energy more efficiently than glycolysis, this metabolic rewiring has been suggested as an alternative to compensate for mitochondrial dysfunction in cancer cells (Warburg, 1956; Kerr and Martins, 2017). Indeed, mutations in the TCA cycle-associated enzymes, such as succinate dehydrogenase (SDH), fumarate hydratase (FH), and isocitrate dehydrogenase (IDH), have been found in several types of cancer including paraganglioma (mutations in SDH), phaeochromocytoma (mutations in SDH), renal carcinoma (mutations in FH), leiomyomatosis (mutations in FH), acute myeloid leukemia (mutations in IDH), and glioblastoma (mutations in IDH), and these alterations have been suggested to contribute to mitochondrial dysfunction in cancer and tumorigenesis (King et al., 2006; Dang et al., 2010; Galluzzi et al., 2013; Parker and Metallo, 2015). However, several recent findings have suggested the essential role of functional mitochondrial dysfunction in cancer cells (Magda et al., 2008; Whitaker-Menezes et al., 2011; Wallace, 2012). The upregulation of oxidative phosphorylation has been noted in cancer cells (Whitaker-Menezes et al., 2011), and the tumorigenic potential of cancer cells has also been shown to be significantly reduced by depletion of mitochondrial DNA (Magda et al., 2008). Therefore, in addition to ATP synthesis, metabolic switching to aerobic glycolysis appears to be a means of supplying cancer cells with the precursors of proteins, lipids, amino acids, and nucleic acids for building their cellular structure and maintaining their upregulated proliferation. Thus, mitochondria still play important roles in bioenergetics and biosynthesis in cancer cells (Wallace, 2012).

Recent findings demonstrate the additional metabolic reprogramming in cancer cells and consequent alterations in cellular signaling pathways and the tumor microenvironment, including changes in the metabolism of glucose, lipids, and amino acids; regulation of the cellular redox state to tolerate reactive oxygen species (ROS)-mediated damage in cellular compartments; and remodeling of the extracellular matrix surrounding cancer cells. For instance, cancer cells display elevated expression of the alternatively spliced form of pyruvate kinase (PK), PK muscle isozyme M2 (PKM2) (Kroemer and Pouyssegur, 2008; Dong et al., 2016). PK mediates the conversion of phosphoenolpyruvate (PEP) to pyruvate, the rate-limiting step of glycolysis (Dong et al., 2016). Owing to the reduced enzymatic activity of PKM2, the phosphorylated metabolites upstream of pyruvate in the glycolytic pathway accumulate and are finally diverted into several anabolic pathways to synthesize glycogen, triglycerides, phospholipids, nucleotides, and amino acids (Gatenby and Gillies, 2004; Kroemer and Pouyssegur, 2008; Dong et al., 2016). In addition, cancer cells introduce acetyl-CoA into a truncated TCA cycle, resulting in the export of acetyl-CoA into the cytosol, where it serves as a precursor of fatty acids, cholesterol, and isoprenoids, which are utilized for cell proliferation and growth (Kroemer and Pouyssegur, 2008). Fatty acid synthase and choline kinase, which mediate biosynthesis of long-chain fatty acids and phosphatidylcholines, respectively, are also known to be upregulated and activated in many types of cancer cells (Ramirez de Molina et al., 2002; Menendez and Lupu, 2007; Kroemer and Pouyssegur, 2008). In the case of amino acid metabolism, cancer cells express sensors of amino acid deficiency, such as GATOR1, foliculin, and the Ras-like small GTPase Rag complex, to ensure a sufficient supply of amino acids to activate rapamycin complex I (mTORC1) (Bar-Peled and Sabatini, 2014; Tsun and Possemato, 2015). The upregulated uptake of glutamine, a nonessential amino acid, through elevated expression of glutamine transporters such as SLC1A5 and SLC38A2 has been thought to play important roles in the supply of nitrogen, the uptake of essential amino acids, and the maintenance of mTORC1 activation in cancer cells (Wise and Thompson, 2010). Consistent with these hypotheses, elevated expression of these glu-
tamine transporters is correlated with poor clinical outcomes in breast and lung cancers (Hassanein et al., 2015; Jeon et al., 2015). Cancer cells also display extensive conversion of glutamine to glutamate and upregulation of several metabolic enzymes responsible for amino acid biosynthesis, including glutaminase (GLS), phosphoglycerate dehydrogenase (PHGDH), and asparagine synthetase (ASNS) (Gao et al., 2009; Locasale et al., 2011; Possemato et al., 2011; Zhang et al., 2014a; Tsun and Possemato, 2015). Moreover, the generation of nicotinamide adenine dinucleotide phosphate (NADPH) by metabolizing glucose through the pentose phosphate pathway (PPP) supports the defense of cancer cells against oxidative or cellular stresses and the synthesis of fatty acids in cancer cells (Gatenby and Gillies, 2004; Kroemer and Pouyssegur, 2008; Levine and Puzio-Kuter, 2010). Further, the acidic tumor microenvironment is constructed through the overproduction of lactate through aerobic glycolysis, facilitating the invasion of tumor cells and blood vessels via matrix remodeling and suppressing anticancer immunity (Fischer et al., 2007; Hunt et al., 2007; Swietach et al., 2007; Kroemer and Pouyssegur, 2008; Levine and Puzio-Kuter, 2010). Collectively, these complex processes allow cancer cells to survive and proliferate, but the details are known to be context dependent and differentially regulated by various factors such as oncogenes/tumor suppressor genes, microenvironments, and tissue of origin (Levine and Puzio-Kuter, 2010; Yuneva et al., 2012; Hensley et al., 2016; Mayers et al., 2016; Kerr and Martins, 2017). Thus, understanding the influence of cellular or environmental factors, such as oncogene-induced metabolic switches, on cancer cell metabolism is important for the development of better anticancer therapeutics targeting altered metabolism in cancer cells.

**METABOLIC ALTERATIONS IN NON-SMALL CELL LUNG CANCER**

Lung cancer is one of the main types of cancer due to its high prevalence and poor survival rates (Mathers and Loncar, 2006; Torre et al., 2015). Approximately 85% of all cases of lung cancer are non-small cell lung cancer (NSCLC) (Molina et al., 2008). The three major types of NSCLC (adenocarcinoma (ADC), squamous cell carcinoma (SQCQ), and large cell carcinoma) are classified based on histological and molecular/genetic features (Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM), 2013; Pikor et al., 2013). Mutations in KRAS and EGFR as well as ALK rearrangements, among others, are mainly found in lung ADC, which accounts for 30-40% of NSCLCs (Pikor et al., 2013). Lung ADCs carrying these genetic alterations are addicted to the associated signaling pathways for cell proliferation, growth, and survival and thus can be vulnerable to the disruption of these signaling pathways (Hrustanovic et al., 2015; Lin and Shaw, 2016). Indeed, several anticancer drugs specifically targeting EGFR or ALK have been clinically used as a first-line therapy for patients with lung ADC harboring these mutations (Saintigny and Burger, 2012). However, none of these drugs have shown remarkable clinical benefits, and drug resistance is still a large obstacle for efficient anticancer treatment using these regimens (Lin and Shaw, 2016). Moreover, there is no therapeutic option to control lung ADC carrying mutant KRAS. Although several alternative approaches have been suggested, including targeting the functional outputs of mutant KRAS or cellular addiction caused by mutant KRAS (Kerr and Martins, 2017), it is important to develop novel therapeutic strategies to meet clinical needs for the treatment of lung cancer, especially lung ADC carrying mutations in oncogenes such as KRAS.

In line with the general metabolic reprogramming in cancer cells that has been described previously, recent studies have demonstrated metabolic alterations in NSCLC. Studies using NSCLC tumors surgically resected from patients after radioisotope-labeled glucose (18F-glucose) infusion, NSCLC cells displayed enhancements in glycolysis and the TCA cycle and subsequent enrichment of TCA cycle intermediates compared with adjacent normal or benign lung tissues (Fan et al., 2009; Hensley et al., 2016). In addition, the activity of pyruvate carboxylase (PC), an enzyme mediating the irreversible carboxylation of pyruvate to generate oxaloacetate (Gray et al., 2011), was elevated in NSCLC tumors (Sellers et al., 2015; Hensley et al., 2016). Because upregulated PC activity plays a role in the replenishment of TCA intermediates that have been utilized in biosynthetic reactions (Kerr and Martins, 2017), this enhancement indicates the rewiring of glucose metabolism to meet the high metabolic demands of cancer cells. Moreover, silencing PC expression significantly reduced the proliferative, colony-forming, and tumorigenic abilities of NSCLC cells, suggesting that NSCLC cells are addicted to PC-mediated anaplerosis (the reduction of TCA intermediates due to biosynthetic reactions). Thus, PC has the potential to be a novel cellular target for anticancer drug development (Sellers et al., 2015). A recent study shows that a subset of NSCLC cells utilizes glycolysis for energy production and that these high glycolytic cells possess elevated hexokinase 2 expression (Wu et al., 2015). Another recent study also demonstrates the utilization of lactate as the main carbon source for the TCA cycle in tumors from NSCLC patients and NSCLC tumor xenografts (Faubert et al., 2017).

In addition to these changes in glucose metabolism, NSCLC cells exhibit alterations in the metabolism of lipids, amino acids, and nucleic acids. For example, the expression of acetyl-CoA carboxylase 1 (ACCC1), one of the key regulators of fatty acid synthesis, was elevated in NSCLC cells. Further, pharmacological inhibition of ACC1 displayed significant antitumor effects in a preclinical model of NSCLC (Svensson et al., 2016; Svensson and Shaw, 2016). The expression and activity of ATP citrate lyase (ACLY), another key fatty acid synthesis enzyme involved in the generation of cytosolic acetyl-CoA and oxaloacetate, were also upregulated in NSCLC (Migita et al., 2008) and are associated with poor clinical outcomes in NSCLC patients (Migita et al., 2008). Consistent with the results of experiments targeting ACC1, siRNA-based ablation of ACLY expression exhibited significant inhibitory effects on proliferation and lipogenesis (Migita et al., 2008). Glycine decarboxylase (GLDC), a component of a multienzyme complex responsible for glycine decarboxylation and serine biosynthesis (Go et al., 2014) and involved in pyrimidine metabolism (Newman and Maddocks, 2017), was also upregulated in lung tumor-initiating cells and promoted cell transformation and tumorigenesis (Zhang et al., 2012). Elevated GLDC expression was associated with poor survival in patients with NSCLC (Zhang et al., 2012).

However, compared to altered glucose metabolism in NSCLC, the rewiring of other metabolic pathways in NSCLC...
is still unclear and needs to be further elucidated. Additionally, despite commonalities in metabolic reprogramming, the metabolic alterations in individual NSCLC cells or tumors are highly heterogeneous (Brunelli et al., 2014; Chen et al., 2014; Wu et al., 2015; Hensley et al., 2016). Considering a high mutation burden in lung cancer, especially lung ADC (Cancer Genome Atlas Research Network, 2014; Swanton and Govindan, 2016; Kerr and Martins, 2017), and the association of alterations in oncogenes or tumor suppressor genes with metabolic reprogramming (Levine and Puzio-Kuter, 2010; Iurlaro et al., 2014; Chen et al., 2014; Wu et al., 2014; Kerr and Martins, 2017), the genetic heterogeneity of NSCLC appears to influence these metabolic diversities.

**ROLE OF ONCOGENIC MUTATIONS IN METABOLIC REPROGRAMMING IN LUNG CANCER**

Alterations in several oncogenes, such as MYC, RAS, and BRAF, have been known to play a role in metabolic reprogramming (Iurlaro et al., 2014; Nagarajan et al., 2016; Kerr and Martins, 2017). Briefly, MYC transcriptionally regulates some metabolic enzymes involved in DNA synthesis and glycolysis, including thymidylate kinase and lactate dehydrogenase A, respectively (Pusch et al., 1997; Shim et al., 1997). MYC is also involved in the metabolic reprogramming of fatty acids, glutamine, proline, and nucleic acids by direct transcriptional regulation or indirect regulation utilizing microRNAs (Mannava et al., 2008; Gao et al., 2009; Liu et al., 2012; Edmunds et al., 2014). In addition, increases in the uptake and interconversion of a polyamine spermine, the metabolism of inositol phospholipids, and aerobic glycolysis were observed in RAS-transformed cells (Huang et al., 1988; Pakala et al., 1988; Chiaradonna et al., 2006). Further, mutated RAS was found to mediate metabolic reprogramming in pancreatic cancer by stimulating glucose uptake, channeling glycolytic intermediates into the hexosamine biosynthesis pathway or pentose phosphate pathway, and directly regulating aspartate transaminases (Ying et al., 2012; Son et al., 2013; Nagarajan et al., 2016). BRAF is also known to regulate glucose and glutamine metabolism in melanoma (Scott et al., 2011; Haq et al., 2013).

In the case of lung cancer, previous reports have suggested a link between genetic mutations and metabolic rewiring in NSCLC, especially lung ADC. The association of alterations in KRAS, EGFR, ALK, and STK11 genetic abnormalities in lung ADC (Ji et al., 2007; Pikor et al., 2013) with metabolic changes is described as follows (Fig. 2).

**Role of KRAS mutation in metabolic reprogramming in NSCLC**

Mutations in the RAS oncogene are known to be a major driver of tumorigenesis (Cox and Der, 2010; Pylayeva-Gupta et al., 2011; Hobbs et al., 2016). Three isoforms of the RAS gene (Kirsten rat sarcoma viral oncogene homolog (KRAS), neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS) and Harvey rat sarcoma viral oncogene homolog (HRAS) encode four RAS proteins (KRAS4A, KRAS4B, NRAS, and HRAS) (Pylayeva-Gupta et al., 2011; Hobbs et al., 2016). The two KRAS isoforms arise from alternative RNA splicing of the KRAS gene (Pylayeva-Gupta et al., 2011; Hobbs et al., 2016). Activating mutations have been identified at three hotspots within the RAS protein (G12, G13, and G61), but the mutation frequency at each of the hotspots in the RAS isoform is known to be quite different in each isoform (Pylayeva-Gupta et al., 2011; Hobbs et al., 2016). The RAS protein is a small G protein whose activity is regulated by the GDP/GTP cycle (Cox and Der, 2010; Pylayeva-Gupta et al., 2011; Hobbs et al., 2016). The RAS protein binds to downstream effectors and triggers activation of signal transduction pathways, such as the Raf-ERK pathway and the PI3K/Akt pathway, responsible for cell proliferation, survival, and growth (Cox and Der, 2010; Pylayeva-Gupta et al., 2011).

Mutations in the KRAS gene, including G12C, G12V, G12D, and G12A, are found in approximately 30% of NSCLC patients with ADC histology (Kempf et al., 2016). These mutations are found more frequently in smokers than in nonsmokers (25-35% in smokers and 5% in nonsmokers) (Mao et al., 2010; Dearden et al., 2013; Kempf et al., 2016). The KRAS mutation (G12D) is common in never-smokers, whereas the KRAS

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**Fig. 2. Contribution of genetic alterations to metabolic reprogramming in cancer.**

https://doi.org/10.4062/biomolther.2017.211
mutation (G12C) is the most common mutation in NSCLC patients with a history of smoking (Kempf et al., 2016). Mutations in KRAS and EGFR are mutually exclusive (Kempf et al., 2016), but mutations in STK11 or TP53 are positively correlated with KRAS mutations (Kempf et al., 2016). Although a recent report describes the weak prognostic impact of the KRAS mutations in NSCLC (Roberts and Stinchcombe, 2013), recent findings suggest a close association of the mutations in NSCLC (Meng et al., 2015; Kempf et al., 2016). Accordingly, several anticancer approaches targeting the RAS protein, including farnesyltransferase inhibitors, competitors disrupting the RAS-chaperone interaction, and inhibitors of the RAS effector or downstream signaling such as the MAPK pathway, mTOR, and Hsp90, have been evaluated in preclinical and clinical settings. None, however, has shown clinical benefits for anticancer treatment (Cox and Der, 2010; Kempf et al., 2016), emphasizing the necessity of procuring alternative approaches to treat cancer carrying RAS mutations.

Numerous findings demonstrate the involvement of mutant KRAS in the metabolic rewiring of several types of human cancer (Pylayeva-Gupta et al., 2011; Kimmelman, 2015; Lv et al., 2016; Kawada et al., 2017; Kerr and Martins, 2017), including upregulation of glucose uptake, glutamine utilization, and aerobic glycolysis (Onetti et al., 1997; Ying et al., 2012; Son et al., 2013). Using patient-derived NSCLC tumors, cell lines, and animal models, several studies have consistently identified the influence of mutant KRAS on metabolic reprogramming in NSCLC. A recent study demonstrated the metabolism-related proteomic profiles of NSCLC cell lines carrying intrinsic mutant KRAS (A549 and H460) in comparison with those of normal bronchial epithelial cells (Martin-Bernabe et al., 2014). These NSCLC cell lines expressed elevated levels of enzymes involved in glycolysis (GAPDH, PKM2, LDHA, and LDHB) and PPP (G6PD, TKT, and 6PGD) compared with normal cells, suggesting alterations in glucose metabolism in NSCLC cells carrying mutant KRAS. It is known that these two cell lines carry different KRAS mutations (G12S for A549; Q61H for H460) (Mahoney et al., 2009; Acquaviva et al., 2012) and that the different amino acid substitutions display distinct biological properties in terms of signaling activation and sensitivity to anticancer agents (Garassino et al., 2011; Stolze et al., 2015). Thus, cellular metabolism could be influenced by different KRAS mutations. In line with this notion, a recent study demonstrated the impact of different KRAS mutations on changes in metabolomic profiles (Brunelli et al., 2014). In this study, different KRAS mutations at codon 12 (G12C, G12D, and G12V) were evaluated. NSCLC cells carrying each of these mutations displayed differential metabolic remodeling, including differences in redox buffering systems and glutamine dependency (Brunelli et al., 2014). Among these mutations, mutant KRAS (G12C) showed the most prominent metabolic changes in vitro. Of note, these metabolic changes were maintained in a tumor xenograft model bearing the same NSCLC cell line (Brunelli et al., 2014, 2016), suggesting that the in vitro cell line model can be utilized to investigate metabolic alterations in NSCLC patients. However, another independent study demonstrated discrepancies in glucose metabolism using in vitro versus in vivo models (Davidson et al., 2016). In this study, several mouse models, including two autochthonous mouse models that develop spontaneous lung tumors (the Kras<sup>G12D+</sup> mouse model and the Kras<sup>G12D+;Trp53<sup>fl/fl</sup></sup> (KP) mouse model with intratracheal delivery of adenoviral Cre), a syngeneic xenograft model involving intratracheal inoculation with lung tumor cells derived from the KP mouse model, and a tumor xenograft model involving subcutaneous inoculation with human lung cancer cell lines, were used for determining metabolic changes in vivo. Tumor cells arising in the KP mouse model were used for in vitro determination of metabolic alterations (Davidson et al., 2016). Both in vitro and in vivo models exhibited upregulated lactate production. However, in contrast to a dependence on glutamine for TCA cycle entry in vitro, lung tumors from these in vivo mouse models minimally utilized glutamine as a carbon source for TCA cycle entry. Additionally, some oxidative glucose metabolic enzymes, including pyruvate carboxylase and pyruvate dehydrogenase (which generate oxaloacetate and acetyl-CoA, respectively), were necessary for tumor formation and growth in these mouse models (Davidson et al., 2016). Therefore, the environmental context needs to be taken into consideration in the investigation of physiologically relevant metabolic alterations, especially in the case of glucose metabolism.

Additional studies also suggest that mutant KRAS mediates the changes in the metabolism of amino acids, lipids, and folates. In a recent study using a mutant Kras-driven model of spontaneous lung tumorigenesis (the KP mouse model), the uptake and utilization of branched-chain amino acids (BCAAs), such as leucine and valine, were elevated in KP mice possessing lung tumors (Mayers et al., 2016). The expression of enzymes responsible for the catabolism of BCAAs, including SLC7A5, BCAT, and BCKDH, was also upregulated in human NSCLC tumors, and ablation of Bcat expression resulted in decreases in in vitro NSCLC cell proliferation and in vivo NSCLC tumor growth (Mayers et al., 2016), indicating the requirement of BCAA metabolism in NSCLC. In the same study, pancreatic ductal adenocarcinoma (PDAC) carrying the same genetic alterations did not utilize BCAA as a nitrogen source (Mayers et al., 2016), suggesting the influence of tissue microenvironment-specific differences on metabolic reprogramming over genetic mutations. In addition to amino acid metabolism, mutant KRAS activated lipogenesis in lung ADC via induction of fatty acid synthase through the ERK2-mediated pathway (Gouw et al., 2017). NSCLC cells carrying mutant KRAS also showed a tendency to be dependent on the folate metabolism pathway compared with those carrying wild-type KRAS (Moran et al., 2014). Consistent with these findings, KRAS mutant NSCLC cells were sensitive to antifolates such as methotrexate and pemetrexed, and the expression level of enzymes related to folate metabolism, such as methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) was positively (Moran et al., 2014).

Moreover, despite the metabolic switch to aerobic glycolysis in cancer cells, mitochondria are known to have a functional role in cell proliferation and tumorigenesis (Magda et al., 2008; Whitaker-Menezes et al., 2011; Wallace, 2012). Likewise, deregulation of mitochondrial function through the ablation of the expression of mitochondrial transcription factor A (TFAM) significantly suppressed mutant Kras-driven lung tumor formation (Weinberg et al., 2010). In this study, mitochondrial ROS generated through Complex III was essential for mutant KRAS-induced anchorage-independent growth of cancer cells (Weinberg et al., 2010). A previous report demonstrated the reduced expression of components of Complex I in KRAS-transformed cells (Baracca et al., 2010). Consid-
ering that both Complex I and Complex II mediate electron transfer to Complex III (Mailloux, 2015), presumably, NSCLC cells expressing mutant KRAS might acquire an alternative method (e.g., upregulation of Complex II) of compensating for the KRAS-induced decrease in Complex I activity in order to maintain mitochondrial function.

Role of EGFR mutations in metabolic reprogramming in NSCLC

Approximately 15-30% of NSCLC patients carry abnormalities in EGFR (Gridelli et al., 2015). EGFR mutations are frequently observed in lung ADCs derived from Asian patients with no smoking history (Gridelli et al., 2015). The most common mutations in EGFR are a deletion at exon 19 (E746–A750) and substitutions at exon 19 (G719C, G719S, G719A) and exon 21 (L858R), all of which are sensitive to EGFR-targeted therapy (Pao and Miller, 2005; Gridelli et al., 2015). aberrantly activated EGFR activates signaling pathways driving the mitogenic, prosurvival, and proinvasive phenotypes of the cancer cells (Zhang et al., 2010). In addition to the direct modulation of signal transduction, aberrant EGFR mediates metabolic reprogramming in NSCLC. For instance, global metabolic reprogramming, such as enhanced aerobic glycolysis and upregulation of PPP, alters pyrimidine biosynthesis and redox metabolism in EGFR mutant lung ADC cell lines (Makinoshima et al., 2014). Combination treatment with erlotinib and a glutaminase inhibitor (CB-839) drives EGFR mutant NSCLC cells to undergo metabolic crisis, thereby leading to enhanced cell death, decreased cell viability in vitro, and a rapid tumor regression in vivo (Momcilovic et al., 2017), indicating the necessity of glutamine as a source for bioenergetics and biosynthesis in NSCLC harboring EGF

Role of ALK rearrangement in metabolic reprogramming in NSCLC

ALK rearrangement accounts for approximately 3-7% of NSCLC cases (Katayama et al., 2015). The most frequently observed ALK rearrangement is the EML4-ALK fusion (Katayama et al., 2015). Several ALK inhibitors, including crizotinib and ceritinib, have been clinically used for the treatment of patients with lung ADC harboring alterations in ALK (Katayama et al., 2015). The impact of ALK aberrations on metabolism in lung ADC has not been well characterized, but a recent report indicates presence of upregulated glucose metabolism and highly metastatic phenotypes in lung ADCs carrying ALK rearrangements (Choi et al., 2013).

Role of LKB1 loss in metabolic reprogramming in NSCLC

LKB1, encoded by the STK11 gene, is a tumor suppressor gene which plays an important role in the regulation of cellular growth and metabolism by phosphorylation and activation of AMP-activated kinase (AMPK), an upstream kinase controlling the mammalian target of rapamycin (mTOR) pathway, MARK/par-1, and other AMPK-related kinases (Shackelford and Shaw, 2009). Approximately 15-35% of NSCLC patients harbor mutations in STK11 (Ji et al., 2007; Shackelford and Shaw, 2009), which is more frequently observed in lung ADC than in lung SQCC (Sanchez-Cespedes et al., 2002; Ji et al., 2007). According to its primary role in the regulation of cellular metabolism, loss of LKB1 leads to deregulation of cellular metabolism under conditions of energy stress (Carretero et al., 2007), causing enhanced sensitivity to therapies targeting metabolism such as phenformin (Shackelford et al., 2013) or therapies that induce energetic stress such as erlotinib (Whang et al., 2016). In addition, metabolic reprogramming in NSCLC harboring altered LKB1 has been demonstrated in a recently published study. Using NSCLC cell lines carrying either KRAS mutations alone or both KRAS mutations and loss of LKB1, this study identified that the additional loss of LKB1 resulted in the accumulation of metabolites associated with the urea cycle through upregulation of carbamoyl phosphate synthetase-1 (CPS1) (Kim et al., 2017). Silencing of CPS1 expression suppressed the growth of tumor xenografts derived from KRAS/STK11-mutant NSCLC cells through reduction of the pyrimidine to purine ratio, thereby disrupting DNA replication (Kim et al., 2017). These results indicate the existence of alterations in pyrimidine metabolism in LKB1-deficient NSCLC cells and provides a novel therapeutic target for the treatment of NSCLCs harboring loss of LKB1 expression.

TUMOR MICROENVIRONMENT-MEDIATED METABOLIC REPROGRAMMING IN CANCER

The interaction between tumors and the surrounding stromal cells that make up the tumor microenvironment has been known to be implicated in cancer development and progression (Quail and Joyce, 2013). Given the role of metabolic alterations in cancer, the tumor-microenvironment interaction could be affected by metabolic alterations in cancer cells and vice versa. For example, the differences in BCAA metabolism between lung cancer and PDAC (Mayers et al., 2016) and in glutamine dependent metabolism between in vitro and in vivo models (Davidson et al., 2016) appear to be influenced by the environmental context. Nutrient sharing, nutrient competition, and metabolite exchange between tumor and stromal cells are known to influence and shape the tumor-microenvironment interaction (Lyssiotis and Kimmelman, 2017). Indeed, lactate, amino acids, and fatty acids act as signaling molecules that can be exchanged between tumor and stromal cells, resulting in the regulation of signal transduction, gene expression, and characteristics of neighboring cells (Lyssiotis and Kimmelman, 2017). Macromolecules or organelles released from stromal cells can also support the biosynthetic and bioenergetic needs of cancer cells (Spees et al., 2006; Chaudhri et al., 2013; Lyssiotis and Kimmelman, 2017). Specifically, compared with normal fibroblasts, basal autophagy was elevated in lung cancer-associated fibroblasts (CAFs) through the influence of high glycolytic lung cancer cells, leading to the release of dipeptides that could support surrounding cancer cells (Chaudhri et al., 2013). Additionally, interactions with bone marrow-derived nonhematopoietic stem/progenitor cells or skin fibroblasts rescued lung cancer cells with mitochondrial defects and led to reactivation of their mitochondrial function including electron
transport chain activity (Spees et al., 2006). These phenomena occurred through the transfer of mitochondria or mitochondrial DNA from stem/progenitor cells or fibroblasts to lung cancer cells (Spees et al., 2006). Collectively, these findings suggest a crucial association between metabolic reprogramming and the tumor-microenvironment interaction. However, details regarding mechanisms of action, the lung microenvironment-specific consequences of these interactions, and their clinical impacts need to be explored in further studies.

**Targeting deregulated signaling pathways**

Recent studies demonstrate the effectiveness of targeting the signaling pathways downstream of oncogenes such as AMPK and mTOR, alone or in combination, in several types of cancer. For example, metformin, an AMPK activator, inhibited the biosynthesis of fatty acids and nucleic acids (Li et al., 2015), suppressed the proliferation of lung cancer and the self-renewal capacity of hepatocellular carcinoma stem cells by inducing apoptosis (Saito et al., 2013; Storozhuk et al., 2013), and increased the radiosensitivity of lung and breast cancer cells (Storozhuk et al., 2013; Zhang et al., 2014b). The mTOR inhibitor rapamycin also inhibited the cell proliferation in several types of cancer including colorectal cancer, glioma, pancreatic cancer, and recurrent glioblastoma (Houchens et al., 1983; Eng et al., 1984; Grewe et al., 1999; Cloughesy et al., 2008). In a phase I clinical trial, rapamycin showed anticancer activity in PTEN-deficient glioblastoma (Cloughesy et al., 2008). Rapamycin analogs with improved water solubility, such as everolimus and temsirolimus, also exhibited potent anticancer effects on several types of cancer alone or in combination with other anticancer agents (Vignot et al., 2005).

### Targeting Metabolic Reprogramming for the Treatment of Cancer

According to the importance of metabolic alterations in the development and progression of cancer, several agents targeting cancer metabolism have been developed and evaluated under preclinical and clinical studies (Kroemer and Pouyssegur, 2008; Tennant et al., 2010; Nagarajan et al., 2016). Some metabolism-targeting agents, such as mTOR inhibitors [rapamycin (sirolimus), everolimus, and temsirolimus] and metformin (AMPK activator and mitochondrial Complex I inhibitor) are now approved for clinical use (Carracedo et al., 2013; Nagarajan et al., 2016) (Table 1). Strategies targeting metabolic alterations for anticancer therapy are detailed in the following sections (Nagarajan et al., 2016).

**Table 1. Compounds targeting cancer metabolism in clinical studies**

| Name                          | Target          | Clinical development stage | Cancer types targeted                                      |
|-------------------------------|-----------------|-----------------------------|------------------------------------------------------------|
| Agents targeting deregulated signaling pathways |                 |                             |                                                            |
| Rapamycin (Sirolimus)         | mTOR            | Phase I/II                  | Glioblastoma, Advanced cancer                              |
| Everolimus (RAD001)           | mTOR            | FDA approved                | Advanced renal cell carcinoma, Pancreatic neuroendocrine tumors, Subependymal giant cell astrocytoma |
| Temsirolimus (CCI-779)        | mTOR            | FDA approved                | Advanced renal cell carcinoma                              |
| Ridaforolimus                 | mTOR            | Phase I/II/III              | Advanced solid tumors                                      |
| AZD8055 (MK-8669)            | mTOR            | Phase I                     | Advanced solid tumors                                      |
| Metformin                     | AMPK            | Phase I/II/III              | Various advanced solid tumors                              |
| Agents targeting metabolic enzymes |                |                             |                                                            |
| 2-Deoxygluose (2-DG)          | HK              | Phase I                     | Various advanced solid tumors                              |
| TCD-717                       | CK              | Phase I                     | Advanced solid tumors                                      |
| Dichloroacetate               | PDK1            | Phase I                     | Advanced solid tumors, Head and neck carcinoma, Brain tumor |
| Indoximod                     | IDO             | Phase I/II                  | Adult solid tumors, Advanced solid tumors, Acute myeloid leukemia, Glioma, Advanced cholangiocarcinoma, Advanced solid tumors |
| Ivosidenib (AG-120)           | IDH1            | Phase I/II                  | Acute myeloid leukemia, Glioma, Advanced myeloid leukemia, Glioma, Advanced solid tumors |
| Enasidenib mesylate (AG-221)  | IDH2            | Phase I/II                  | Acute myeloid leukemia, Glioma, Advanced solid tumors      |
| AG-881                        | IDH1 or IDH2    | Phase I                     | Acute myeloid leukemia, Glioma, Glioma                     |
| IDH1 peptide vaccine         | IDH1            | Phase I                     | Glioma                                                    |
| PEPIDH1M                      | IDH1            | Phase I                     | Glioma                                                    |
| Agents depleting metabolites using recombinant enzymes (PEG-conjugated) | |                             |                                                            |
| Arginase 1                    | Arginine        | Phase I/II/III              | Acute myeloid leukemia, Hepatocellular carcinoma, Other solid tumors |
| Arginine deiminase            | Arginine        | Phase I/II/III              | Advanced solid tumors, mesothelioma, small cell lung cancer, skin cancer |
| Asparaginase                  | Asparagine      | Phase I/II/III              | Various types of leukemia and lymphoma                      |

mTOR: mammalian target of rapamycin, AMPK: AMP activated protein kinase, HK: hexokinase, CK: choline kinase, PDK1: pyruvate dehydrogenase kinase 1, IDO: indoleamine 2,3-dioxygenase.
and have been clinically used for the treatment of advanced renal cell carcinoma, pancreatic neuroendocrine tumors, and subependymal giant cell astrocytoma (Benjamin et al., 2011).

**Targeting metabolic enzymes**

2-Deoxyglucose (2-DG) has a similar structure to glucose and is unable to be metabolized in mammals (Nagarajan et al., 2016). Thus, 2-DG can inhibit multiple glycolytic steps by competitively acting with glucose (Nagarajan et al., 2016). 2-DG is phosphorylated by HK2 and phosphorylated 2-DG acts an inhibitor of HK2 (Wick et al., 1957). In addition, various inhibitors targeting metabolic enzymes, including l-lysine, fumaric acid, and 3-bromopyruvate (hexokinase inhibitors), TLN-232 (a pyruvate kinase inhibitor), orlistat and cerulenin (fatty acid synthase inhibitors), dichloroacetate (a PDK1 inhibitor), MNS5b and TCD-717 (choline kinase inhibitors), soraphen A (an acetyl-CoA carboxylase inhibitor), indoximod [an indoleamine 2,3-dioxygenase (IDO) inhibitor], ivosidenib (AG-120), enasidenib mesylate (AG-221 mesylate), AG-881, IDH305, PEPIDH1M (IDH1R132H-specific peptide vaccine) (inhibitors targeting mutated IDH1 or IDH2), and SB-2049990 (an ATP citrate lyase inhibitor), have been evaluated in preclinical and clinical studies (Table 1) (Hatzivassiliou et al., 2005; Wang et al., 2005; Al-Saffar et al., 2006; Beckers et al., 2007; Kroemer and Pouyssegur, 2008; Tennant et al., 2010; Mondesir et al., 2016; Nagarajan et al., 2016).

**Depleting metabolites using recombinant enzymes**

Strategies to inhibit a specific metabolic pathway using recombinant enzymes to reduce a specific oncogenic metabolic have been developed recently (Nagarajan et al., 2016). For instance, recombinant arginine deiminase and arginase I (which degrade and deplete arginine) conjugated with polyethylene glycol (PEG) (pegylated arginine deiminase and pegylated arginase 1, respectively) have been evaluated in phase I/II clinical trials for the treatment of advanced melanoma and advanced hepatocellular carcinoma (Izzo et al., 2004; Glazer et al., 2010; Yang et al., 2010; Ott et al., 2013; Yau et al., 2013; Nagarajan et al., 2016). Recombinant l-asparaginase (which degrades and depletes asparagine) conjugated with PEG (PEG-asparaginase) is also in clinical trials for the treatment of pediatric and adult acute lymphoblastic leukemia, multiple myeloma, and advanced solid tumors (Taylor et al., 2001; Agrawal et al., 2003; Fu and Sakamoto, 2007; Kurtzberg et al., 2011).

Specifically, in lung cancer, despite the various anticancer approaches targeting cancer metabolism described above, no metabolism-targeted drugs have been approved for lung cancer treatment. Currently, most metabolism-targeting agents for lung cancer are still under preclinical evaluation (Nagarajan et al., 2016). Of note, agents targeting unique oncogene-driven metabolic rewiring have been relatively poorly developed and should be investigated in further studies. For lung cancer treatment, cellular markers specifically elevated in NSCLC cells harboring oncogenic alterations, including BCAT (Mayers et al., 2016), SCD1 (Zhang et al., 2017), and CPS1 (Kim et al., 2017), could be potential candidates for developing novel anticancer agents specifically disrupting oncogene-driven metabolic reprogramming in NSCLC. In addition, metabolic synthetic lethality can be a valuable therapeutic approach considering the metabolic vulnerabilities of NSCLC carrying oncogenic mutations (Bensaad and Harris, 2013; Megchelen-brink et al., 2015; Kerr and Martins, 2017).

**CONCLUSION**

Cancer cells demand large nutrient supplies and thus reprogram their metabolic pathways to ensure metabolic flexibility, cellular homeostasis, energy production, cell proliferation, and survival. In addition to direct modulation of signal transduction pathways causing oncogenic addiction, alterations in oncogenes also contribute to metabolic rewiring in cancer cells, resulting in the promotion of cancer cell proliferation, survival, and metastatic dissemination. Accordingly, metabolic reprogramming is now considered an important characteristic of several types of cancer, including NSCLC. Despite several ongoing approaches to target cancer metabolism, metabolic reprogramming should be therapeutically explored in additional studies. In addition, the influence of metabolic rewiring on the interaction between cancer cells and the tumor microenvironment needs to be extensively investigated to comprehensively understand the course of cancer development and progression, providing mechanistic insights on several anticancer therapies targeting metabolism, microenvironmental interactions, and evasion of anticancer immunity. However, metabolic heterogeneity may reduce the responsiveness of metabolism-targeting anticancer drugs; thus, an in-depth exploration of metabolic status in cancer cells will be necessary to determine detailed metabolic changes at the cellular and molecular levels. Further, the clinical impact of metabolic alterations on cancer and the relevant biomarkers to predict or diagnose metabolic reprogramming should also be identified to develop tailored precision medicine targeting metabolic rewiring for the treatment of cancer.

**ACKNOWLEDGMENTS**

This work was supported by a grant from the National Research Foundation of Korea (NRF), the Ministry of Science and ICT (MSIT), Republic of Korea (No. NRF-2016R1A3B1908631).

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