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Metabolic Phenotypes, Dependencies, and Adaptation in Lung Cancer

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Lung cancer is a heterogeneous disease that is subdivided into histopathological subtypes with distinct behaviors. Each subtype is characterized by distinct features and molecular alterations that influence tumor metabolism. Alterations in tumor metabolism can be exploited by imaging modalities that use metabolite tracers for the detection and characterization of tumors. Microenvironmental factors, including nutrient and oxygen availability and the presence of stromal cells, are a critical influence on tumor metabolism. Recent technological advances facilitate the direct evaluation of metabolic alterations in patient tumors in this complex microenvironment. In addition, molecular alterations directly influence tumor cell metabolism and metabolic dependencies that influence response to therapy. Current therapeutic approaches to target tumor metabolism are currently being developed and translated into the clinic for patient therapy.

Lung cancer is a heterogeneous disease comprised of diverse tumor subtypes and molecular alterations that influence tumor metabolism. This article will cover the influence of molecular and microenvironmental factors on tumor metabolism and recent technological advances that facilitate the direct evaluation of metabolic alterations in patient tumors. Further, we will discuss metabolism-based imaging modalities that exploit the metabolic alterations of tumors for their detection and characterization. In addition, we will describe the current therapeutic approaches to target tumor metabolism and the clinical translation of these approaches for patient therapy.

METABOLOMIC CHANGES RELATED TO LUNG CANCER HISTOLOGY

Lung cancers are clinically subdivided into varying histopathological subtypes with distinct behaviors. It is therefore unsurprising that the different lung tumor subtypes have different metabolisms. Metabolomics analyses of lung tumors compared to normal tissues show that metabolomics can clearly distinguish tumor tissue

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from normal lung, but also distinct metabolic changes in lung adenocarcinoma (LUAD) compared to lung squamous cell carcinoma (LUSC) (Moreno et al. 2018). Indeed, recent studies have revealed differential expression of nutrient transporters between these non-small cell lung cancer (NSCLC) subtypes. Glucose transporter 1 (GLUT1), which mediates glucose uptake, is highly expressed in LUSC, which is sensitive to glycolytic inhibition (Goodwin et al. 2017). LUSC also demonstrates higher expression of monocarboxylate transporter 1 (MCT1) (Stewart et al. 2015), which may facilitate glycolytic flux. Similarly, the glutamine transporter SLC1A5 (ASCT2) is highly expressed in LUSC, and to a lesser extent in LUAD and neuroendocrine tumors (Hassanein et al. 2013). Indeed, mice that simultaneously develop both LUSC and LUAD demonstrate significantly higher glucose and glutamine uptake in LUSC tumors compared to LUAD. LUSC tumors demonstrated dual reliance on both glucose and glutamine, and up-regulate adaptive glutamine metabolism as a mechanism of resistance to mTOR inhibition (Momcilovic et al. 2018a). Much more work is needed to extend these observations about differential subtype metabolism to additional metabolic pathways.

Little work has been done directly comparing NSCLC with small-cell lung cancer (SCLC). However, we are beginning to understand the heterogeneity within the subtypes of SCLC. SCLC is thought to originate from pulmonary neuroendocrine cells (Sutherland et al. 2011), where the transcription factor ASCL1 normally directs the proper development of several neuronal and neuroendocrine populations. A subset of SCLC expresses low levels of ASCL1 and high levels of MYC, and is characterized by high expression of the guanosine biosynthetic enzymes inosine monophosphate dehydrogenases 1 and 2 (IMPDH1 and IMPDH2). Importantly, this subtype of SCLC is dependent on IMPDH activity for proliferation (Huang et al. 2018), which supports GTP production and ribosomal RNA transcription (Campbell and White, 2014; Huang et al. 2021). Other distinct metabolic alterations are characteristic of this subtype of SCLC, including the dependence on arginine-regulated pathways including polyamine biosynthesis and mTOR pathway activation (Chalishazar et al. 2019). Future studies will reveal the metabolic dependencies of the $ASCL1^{High}/MYC^{Low}$ subtype.

METABOLOMIC CHANGES IN PATIENTS

Recent technological advances have facilitated the analysis of patient tumor metabolism in vivo and ex vivo (Fig. 1). The utility of metabolomics analysis of freshly resected paired lung tissue slices has revealed the selective utilization of different nutrients to fuel the tricarboxylic acid (TCA) cycle in early-stage NSCLC. Tissue slices were cultured in stable isotope (SI)-labeled glucose (i.e., nonradioactive isotopes such as ^{13}C-glucose) or glutamine tracers, which revealed enhanced entry of glucose into the TCA cycle via pyruvate carboxylase rather than glutamine in tumors. Direct infusion of patients with SI glucose prior to tissue resection confirmed enhanced pyruvate carboxylase activity in tumors compared to normal lung (Sellers et al. 2015). Indeed, direct infusion of patients with SI tracers has significantly challenged our understanding of nutrient metabolism in lung cancer. While cell culture studies had long suggested that glucose is the primary fuel for cancer cells, and is converted mainly to lactate, in vivo studies revealed that, in tumors in patients, significant mitochondrial oxidation of glucose accompanies lactate production. Further, tumors are metabolically heterogeneous when different parts of the tumor are tested, and nonglucose fuel sources contribute to metabolism in well-perfused tumor areas (Hensley et al. 2016). Lactate was identified as the major TCA cycle carbon source in NSCLC tumors, and MCT1-mediated lactate uptake (Faubert et al. 2017). These SI tracing approaches, together with the use of hyperpolarized substrates including glucose, pyruvate, fumarate, and others that provide real-time information about substrate metabolism in vivo (Brindle 2015), will greatly increase our understanding of tumor metabolism and response to therapy under physiological conditions.

Imaging Tumor Metabolism

Noninvasive imaging modalities such as computed tomography (CT) and positron emission

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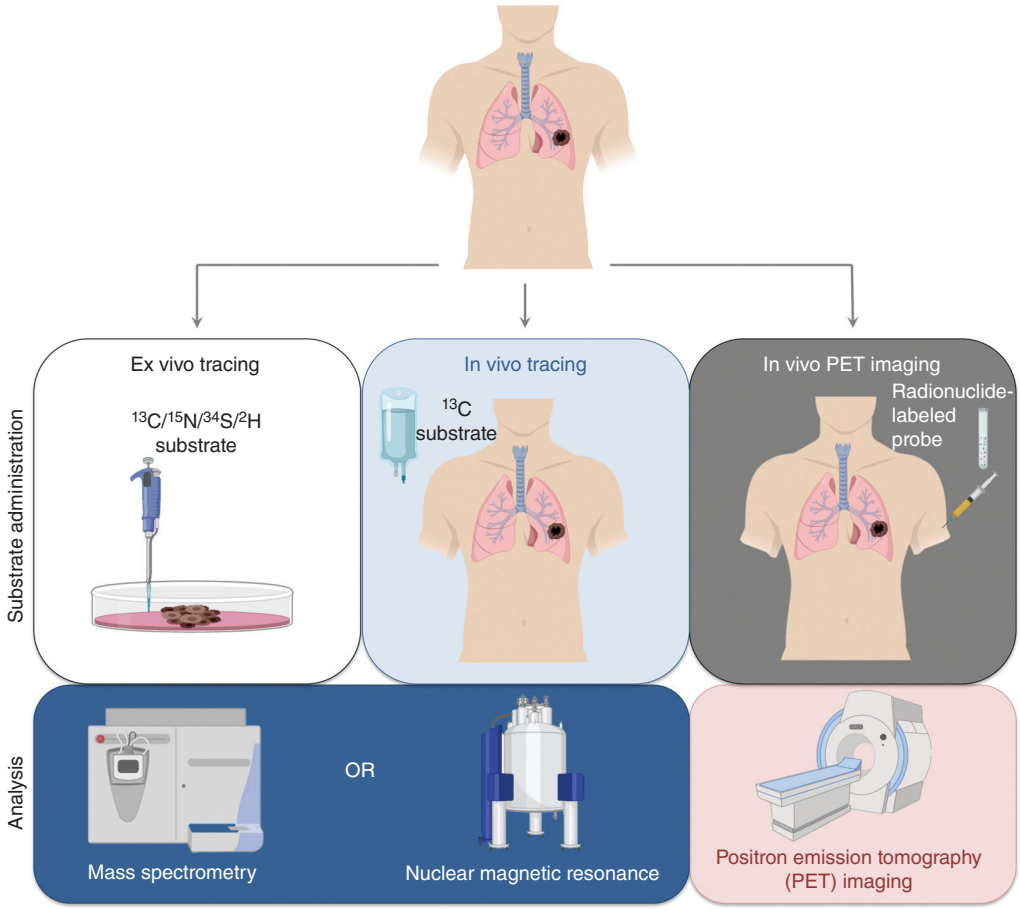

Figure 1. Techniques for the study of metabolism in situ. Incubation of fresh tissue biopsies with stable isotope-labeled substrates ex vivo facilitates the analysis of metabolic pathway by mass spectrometry or nuclear magnetic resonance (NMR). Alternatively, radionuclide-labeled probes can be delivered directly to patients prior to tumor resection via venous infusion. Positron emission tomography (PET) imaging is an alternative, noninvasive method for very targeted analysis of specific metabolic activities and is established in the clinic. (C) Carbon, (N) nitrogen, (S) sulfur, (H) hydrogen.

tomography (PET) are routinely used clinically to diagnose and stage NSCLC. In addition to anatomical registration, imaging probes may be used as surrogate biomarkers to functionally profile the metabolic activity within the tumor(s) and may be used to complement SI tracing studies in animal studies and in patients (Sellers et al. 2015; Davidson et al. 2016; Hensley et al. 2016; Momcilovic et al. 2018a,b). Here we summarize the use of PET and CT imaging in lung cancer and its applications for noninvasive detection and diagnosis of metabolism in both early- and late-stage tumors.

Computed Tomography

CT imaging uses multipositional X-ray imaging to generate a three-dimensional view of the imaged area. Tomographic reconstruction of the X-ray images provides detailed anatomical information of the imaged patient or animal. CT imaging can be performed with contrast agents that register vasculature within the tumor and perfusion within the tumor(s). CT imaging with iodine-based contrast agents such as iohexol, iodixanol, and ioversol are advantageous because it renders a quantitative measure of blood

vessels supplying the tumors (Kao et al. 2003; Mukundan et al. 2006; Karathanasis et al. 2009; de Vries et al. 2010).

Positron Emission Tomography

PET imaging is a widely used imaging modality employed in both clinical and basic research settings. PET imaging works by detection of gamma rays from positron emitting radionuclides that have been injected into a patient or animal. Detection of emitted gamma rays from a single source allows the three-dimensional image reconstruction and spatial resolution of tissue, in particular tumors. The most commonly used radionuclide is ^{18}F but there is a wide range of radionuclides available—the more commonly used isotopes include ^{18}F, ^{11}C, and ^{15}O. While it also serves to detect a tumor mass, importantly it provides valuable functional information about the metabolic needs of the tumor (Fig. 2). The noninvasive nature of PET imaging allows for repeat scans to be performed on patients during the course of treatment. The PET response criteria in solid tumors (PERCIST) are a set of criteria that uses PET imaging with ^{18}F-FDG to determine therapeutic response in patients. Thus, it is important to emphasize that nearly every lung cancer patient has PET imaging before and after therapy that currently provides a ready, clinically available source of metabolism data. It will be important for further clinical and laboratory metabolism studies to relate new findings to these current large PET data sets.

Glucose Tracers

^{18}F-FDG—monitoring glucose transporters (GLUTs) for detection and monitoring of otherwise clinically evident lung cancers. Increased glucose utilization is a hallmark of cancer that can be imaged with [^{18}F]-fluoro-2-deoxyglucose (^{18}F-FDG) PET. The high consumption of glucose by advanced lung tumors makes PET imaging with ^{18}F-FDG an ideal probe for detecting and staging glycolytic tumors. ^{18}F-FDG is transported into cells through the GLUTs, followed by rapid phosphorylation by hexokinase into ^{18}F-FDG-6-phosphate, which can no longer be metabolized. The radiotracer remains trapped in the first steps of glycolysis allowing the detection of emitted gamma rays as the probe decays. ^{18}F-FDG is used to successfully diagnose glucose metabolism in a broad range of tumors that include cancers of the lung, liver, bone, and soft tissue (Minn et al. 1997; Oshida et al. 1998; Shiomi et al. 2001; Shi et al. 2015; Hwang et al. 2016). In NSCLC, ^{18}F-FDG PET has been used successfully to assess tumor responses to targeted therapies, including gefitinib (Takahashi et al. 2012) and erlotinib (Benz et al. 2011). The prompt reduction of ^{18}F-FDG uptake in tumors in response to epidermal growth factor receptor (EGFR) inhibitors appears to be explained by a translocation of membrane-bound GLUTs into the cytoplasm and thus their inactivation (Su et al. 2006) and additional effects on hexokinase 2 (HKII). Reduced tumor ^{18}F-FDG uptake measured by PET in NSCLC patients treated with erlotinib but not previously molecularly characterized for EGFR mutations predicts response to erlotinib and progression-free survival (Benz et al. 2011).

^{18}F-Me4FDG—monitoring sodium-dependent glucose transporters (SGLTs) for detection of very early lung cancers and preneoplastic lesions. While ^{18}F-FDG is a standard tracer for staging clinically evident lung cancer and detecting glucose uptake into tumor cells through the GLUTs, it has low sensitivity for identifying premalignant, so-called "ground glass nodules (GGNs)," and early invasive disease (Ambrosini et al. 2012; Wu et al. 2015). The absence of ^{18}F-FDG uptake in premalignant and early-stage LUAD has been interpreted as a consequence of a slow growth rate and low requirement of glucose (Higashi et al. 1998; Yap et al. 2002; Ambrosini et al. 2012; Wu et al. 2015). However, cancers can take up glucose by using an alternative glucose transport system, mediated by the SGLTs, which are normally required for glucose reabsorption in the kidneys (Yu et al. 2010; Scafoglio et al. 2015). Importantly, SGLT-mediated glucose transport is not detected by ^{18}F-FDG PET because the ^{18}F-FDG tracer is a selective substrate for only GLUT transporters and not the SGLTs (Yu et al. 2010, 2013). SGLT-dependent glucose uptake can be selectively measured

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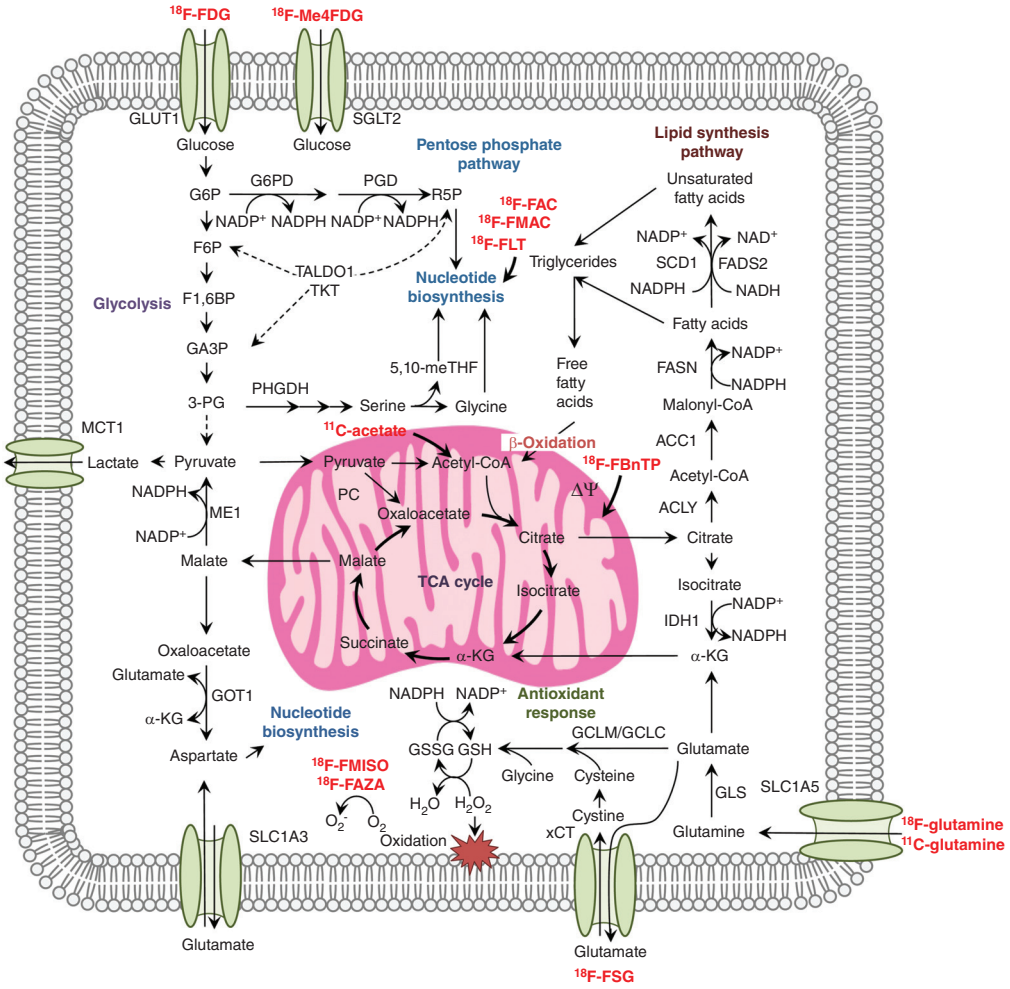

Figure 2. Metabolic processes support lung cancer proliferation and viability. Both anabolic (lipid biosynthesis, nucleotide biosynthesis) and catabolic processes (glycolysis, tricarboxylic acid [TCA] cycle, β-oxidation) support macromolecular synthesis, cellular bioenergetics, and detoxification of reactive oxygen species. (ACC) Acetyl-CoA carboxylase, (ACLY) ATP citrate lyase, (CoA) coenzyme A, (FADS2) fatty acid desaturase 2, (FASN) fatty acid synthase, (F1,6BP) fructose-1,6-bisphosphate, (F6P) fructose-6 phosphate, (GA3P) glyceraldehyde-3 phosphate, (GCLC) glutamate-cysteine ligase catalytic subunit, (GCLM) glutamate-cysteine ligase modifier subunit, (GLS) glutaminase, (GLUT1) glucose transporter 1, (GSH) glutathione, (GSSG) glutathione disulfide, (G6P) glucose-6 phosphate, (G6PD) glucose-6 phosphate dehydrogenase, (GOT1) glutamate-oxaloacetate aminotransferase 1, (H_2O_2) hydrogen peroxide, (HK) hexokinase, (IDH1) isocitrate dehydrogenase 1, (LDH) lactate dehydrogenase, (ME1) malic enzyme 1, (NAD) nicotinamide adenine dinucleotide, (NADP) nicotinamide adenine dinucleotide phosphate, (PC) pyruvate carboxylase, (PGD) phosphogluconate dehydrogenase, (PFK) phosphofructokinase, (PHGDH) phosphoglycerate dehydrogenase, (R5P) ribose 5-phosphate, (SCD1) steroyl coA desaturase 1, (SGLT2) sodium/glucose cotransporter 2, (SLC1A3) sodium-dependent glutamate/aspartate transporter 1, (SLC1A5) sodium-dependent neutral amino acid transporter type 2 (ASCT2), (TALDO1) transaldolase 1, (TCA) tricarboxylic acid, (TKT) transketolase, (xCT) cystine/glutamate transporter system Xc^-, (α-KG) α-ketoglutarate, (3-PG) 3-phosphoglycerate, (5,10-meTHF) 5,10-methylene tetrahydrofolate, (^{18}F-FDG) [^{18}F]-fluoro-2-deoxyglucose, (^{18}F-Me4FDG) methyl-4-[^{18}F] fluorodeoxyglucose, (^{18}F-Gln) ^{18}F-glutamine, (^{11}C-Gln) ^{11}C-glutamine, (^{18}F-Gln) [^{18}F]-glutamine, (^{18}F-FSG) (*S*)-4-(3-[^{18}F]fluoropropyl)-l-glutamic acid, (^{18}FBnTP) [^{18}F]fluorobenzyl triphenylphosphonium, (^{18}F-FMISO) ^{18}F-fluoromisonidazole, (^{18}F-FAZA) ^{18}F-fluoroazomycinarabinoside.

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in vivo by PET imaging using the radiotracer methyl-4-[^{18}F] fluorodeoxyglucose (^{18}F-Me4FDG). ^{18}F-Me4FDG is a novel PET tracer transported specifically by SGLTs, and not by GLUTs (Scafoglio et al. 2015). The SGLT2 transporter is expressed early in lung tumorigenesis and found specifically in premalignant lesions and well-differentiated adenocarcinomas, compared with low SGLT2 expression in poorly differentiated LUAD and LUSC (Scafoglio et al. 2018). Thus, imaging SGLT2 activity with ^{18}F-Me4FDG represents a new biomarker that may be used to identify metabolically active lung tumors at early stages of development.

Amino Acid Tracers

Tumors do not solely rely on glucose. Therefore, radiolabeling of additional metabolites such as acetate, choline, methionine, and glutamine with either ^{18}F or ^{11}C provide opportunities to perform broad profiling of cancer metabolism with PET imaging. ^{11}C and ^{18}F-glutamine have been used in both clinical and basic research to evaluate reliance of tumor cells on glutamine uptake and glutaminolysis (Lieberman et al. 2011; Ploessl et al. 2012; Wu et al. 2014; Venneti et al. 2015; Hassanein et al. 2016; Momcilovic et al. 2017; Schulte et al. 2017; Zhou et al. 2017). Preclinical studies have shown that EGFR-mutant adenocarcinomas and LUSC show dependency on glutamine and elevated uptake of ^{11}C-Gln and ^{18}F-Gln (Hassanein et al. 2016; Momcilovic et al. 2018a, 2017). Glutamate analogs (*S*)-4-(3-[^{18}F]fluoropropyl)-L-glutamic acid (^{18}F-FSG) and ^{18}F-hGTS13 have been used to measure activity of the xCT transporter, a sodium-independent antiporter that regulates the exchange of cysteine and glutamate important for glutathione synthesis and redox buffering in cancer (Baek et al. 2012; McCormick et al. 2019). Increased xCT transporter expression correlates with glutamine dependency in triple-negative breast cancer cells and supported cisplatin resistance and antioxidant metabolism lung cancer cells (Timmerman et al. 2013; Wangpaichitr et al. 2017). Additionally, ^{11}C-methionine is used as a marker of amino acid uptake and protein synthesis where uptake of the radiotracer correlates with tumor grade and has been examined in lung cancer (Kubota et al. 1993; Pirotte et al. 2004; Kim et al. 2005; Van Laere et al. 2005; Hsieh et al. 2008).

Oxygen and Nucleotide Metabolism

Tumor oxygenation is an important measure of both metabolism and hypoxia may be prognostic value as predictors of response or resistance to therapy. Nitroimidazole-based radiotracers ^{18}F-FMISO and ^{18}F-FAZA have demonstrated strong correlations with the measurement of oxygen concentration and response to mitochondrial complex I inhibition in NSCLC (Chang et al. 2015b; Yip et al. 2015). Tumor cell proliferation is readily measured by uptake of ^{18}F-FAC, a deoxycytidine kinase (dCK) analog that is phosphorylated by dCK and incorporated in DNA synthesis pathways (Radu et al. 2008; Laing et al. 2009). ^{18}F-FAC had a better selectivity for lymphoid organs compared to ^{18}F-FDG and allowed for stratification and precise targeting of acute lymphoblastic leukemia (ALL) using targeted therapies against the ataxia telangiectasia and Rad3-related (ATR) protein and the dCK enzyme (Le et al. 2017). Two additional probes can be used to determine activity of enzymes involved in the DNA salvage pathway. Tumor uptake of ^{18}F-FMAC relies on activity of cytidine deaminase (CDA) and uptake of ^{18}F-FLT is dependent on activity of thymidine kinase (TK) (Shields et al. 1998; Grierson and Shields 2000; Rasey et al. 2002; Lee et al. 2012). The importance of the ^{18}F-FAC probe was further demonstrated in a metabolomics based study on which LC-MS and ^{18}F-FAC uptake in liposarcomas identified dependency on nucleoside metabolism and successfully predicted sensitivity to gemcitabine treatment (Braas et al. 2012).

Additional PET Tracers

Mitochondria biogenesis and function are critical to support lung tumor initiation and progression in autochthonous, genetically engineered mouse models of oncogenic Kras-driven NSCLC (Weinberg et al. 2010; Martínez-Reyes et al. 2020; Ward et al. 2020). Lipophilic tetraphenylphosphonium

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cations such as 4-[^{18}F]fluorobenzyl-triphenylphosphonium (^{18}F-BnTP) have been used as radiotracers to measure mitochondrial membrane potential in these models (Madar et al. 2009; Momcilovic et al. 2019). Importantly, ^{18}F-BnTP uptake was demonstrated to be elevated in lung tumors with increased activity in complex I of the mitochondrial electron transport chain. ^{18}F-BnTP-positive tumors were also shown to be responsive to complex I inhibitors (Momcilovic et al. 2019). Lactate metabolism identified in NSCLC suggests that ^{11}C-lactate tracers may find utility in lung cancer diagnosis and treatment (Herrero et al. 2007; Faubert et al. 2017). ^{11}C-acetate is converted to acetyl-CoA and used in mitochondria in TCA cycle or incorporated into cell membranes (Yoshimoto et al. 2001; Vavere et al. 2008) and along with ^{11}C- and ^{18}F-choline both are used in management of prostate cancer (Testa et al. 2016; Wibmer et al. 2016).

METABOLIC CHANGES RELATED TO MOLECULAR ALTERATIONS

Lung cancer demonstrates significant genetic diversity (mutations in oncogenes and tumor suppressor genes as well as "passenger" mutations), both within histologic subtypes and between subtypes. For example, LUAD can have KRAS or EGFR mutations not found in LUSC or SCLC, and SCLCs have nearly universal mutations in RB1 found infrequently in the other histologic types, while all types of lung cancer can have TP53 mutations. Consequently, the influence of individual mutations is complicated by tissue-specific metabolic programs (e.g., differences between LUAD, LUSC, and SCLC) and co-occurring mutations (such as the combination of KRAS and STK11/LKB1 mutations), which both direct metabolic programs that may promote or antagonize the metabolic programs driven by the mutation of interest (Fig. 3). Recent efforts to profile lung cancer cells for metabolic pathway activity, oncogenotype, gene expression, protein expression, and therapeutic sensitivity has significantly increased our understanding of the relationship between lung cancer metabolism, tumor mutations (Huang et al. 2018; Chen et al. 2019), and metabolic vulnerabilities. These connections are important to establish because nearly every new lung cancer patient has a tumor sent for CLIA-certified oncogenotype analyses to direct targeted therapy selection (e.g., EGFR tyrosine kinase inhibitors for EGFR-mutant tumors) and also provide information on tumor mutation burden to evaluate response to immune checkpoint blockade (ICB). Thus, understanding the connections between metabolic alterations and oncogenotype could immediately translate to therapeutic options for patients. Here, we summarize what is known about the influence of the most common molecular alterations on cellular metabolism.

p53

p53 is the most commonly altered tumor suppressor across the different lung cancer subtypes (46% LUAD, 81% LUSC, 100% SCLC) (The Cancer Genome Atlas Research Network 2012, 2014; George et al. 2015). The effect of p53 on cellular metabolism has been studied extensively. p53 opposes Warburg metabolism by repressing the expression of glucose and lactate transporters (GLUT1, MCT1), and transactivating the expression of glycolytic inhibitors. Further, p53 promotes the entry of pyruvate and glutamate into mitochondria (PDK2, GLS2). Many p53-regulated metabolic pathways promote or antagonize the metabolism of ROS (Berkers et al. 2013). Because p53 loss-of-function (LOF) is so frequent and the effects of p53 LOF on tumor initiation and progression are complex, it is difficult to ascertain the direct metabolic effects of p53 in lung cancer. However, specific p53 mutations may have unique metabolic effects on lung tumor cells. The p53^{R172H} (human R175H) and p53^{R270H} (human R273H) mutants were found to have unique transcriptional signatures in murine lung tumor cells and patient tumor samples, with the mevalonate pathway up-regulated by the p53^{R270H} mutation. Consequently, p53^{R270H} tumors were uniquely sensitive to mevalonate pathway inhibition by statin treatment (Turrell et al. 2017). Interestingly, the p53^{P72R} polymorphism is also associated with a unique metabolic program mediated by

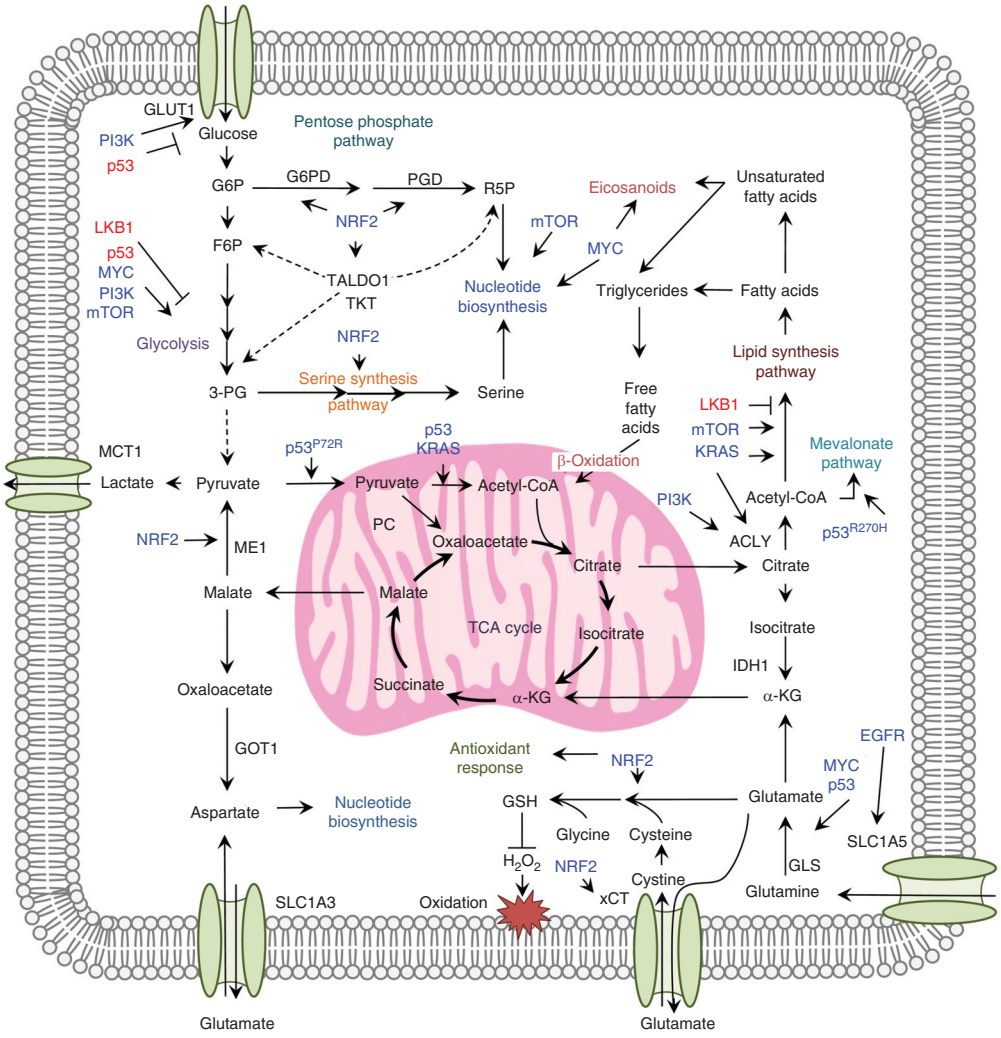

Figure 3. Molecular alterations deregulate lung cancer metabolism. Loss of tumor suppressors like p53 and LKB1, or activation of oncogenes like KRAS, mTOR, phosphoinositide-3-kinase (PI3K), NRF2, epidermal growth factor receptor (EGFR), and MYC increases the activity of catabolic and anabolic metabolic pathways. Further, specific p53 mutations ($p53^{P72R}$, $p53^{R270H}$) have unique gain-of-function effects on pyruvate and mevalonate metabolism. (ACLY) ATP citrate lyase, (CoA) coenzyme A, (F6P) fructose-6 phosphate, (GLS) glutaminase, (GLUT1) glucose transporter 1, (GSH) glutathione, (G6P) glucose-6 phosphate, (G6PD) glucose-6 phosphate dehydrogenase, (GOT1) glutamate-oxaloacetate aminotransferase 1, (H_2O_2) hydrogen peroxide, (IDH1) isocitrate dehydrogenase 1, (ME1) malic enzyme 1, (PC) pyruvate carboxylase, (PGD) phosphogluconate dehydrogenase, (R5P) ribose 5-phosphate.

PGC1α, which promotes mitochondrial metabolism and metastasis (Basu et al. 2018). Consequently, precision medicine approaches targeting tumor metabolism may need to consider not just the presence of tumor mutations, but also the specific residue.

KRAS

KRAS is the most commonly altered oncogene in LUAD, but is rarely altered in LUSC or SCLC (The Cancer Genome Atlas Research Network 2012, 2014; George et al. 2015). The effect of

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oncogenic KRAS on metabolism has been extensively studied in animal models of lung cancer. Surprisingly, the tissue of origin is as important as the genetic driver when considering metabolic alterations in tumors. Expression of the $Kras^{G12D}$ mutation with concomitant deletion of Tp53 induces NSCLC and pancreatic ductal adenocarcinoma (PDAC) formation in mice, but only NSCLC can use branch chain amino acids (BCAAs) (Mayers et al. 2016). Importantly, these metabolic differences translate to metabolic dependencies. Deletion of the aminotransferases that mediate BCAA metabolism, Bcat1 and Bcat2, impairs NSCLC tumor growth but not PDAC growth (Mayers et al. 2016). $Kras^{G12D}$ also induces other metabolic vulnerabilities in NSCLC associated with increased pathway activity including sensitivity to inhibition of acetyl-coA carboxylases and fatty acid synthase associated with increased de novo lipogenesis (Svensson et al. 2016; Singh et al. 2018), and a requirement for pyruvate dehydrogenase a1 due to increased glucose, but not glutamine, contribution to the TCA cycle (Davidson et al. 2016). Further, KRAS activation is associated with a dependence on the cystine/glutamate antiporter xCT (Hu et al. 2020). While targeting any one of these metabolic vulnerabilities may prove efficacious for the treatment of KRAS-mutant lung tumors in the clinic, recently, small-molecule inhibitors have been developed specifically for the $KRAS^{G12C}$ mutation, which is found in ~10%–15% of LUADs, and is demonstrating clinical benefit (Hallin et al. 2020; Hong et al. 2020). In addition, $KRAS^{G12C}$ targeting leads to significant antitumor immune responses in preclinical models (Canon et al. 2019). Thus, it will be important to consider the influence of this inhibitor on both tumor and tumor microenvironment (TME) metabolism.

PI3K

The phosphoinositide-3-kinase ([PI3K], encoded by the *PIK3CA* gene) is mutated and/or demonstrates copy number gains in LUSC, and is activated following loss of the tumor suppressor PTEN and downstream of growth factor signaling in LUAD (The Cancer Genome Atlas Research Network 2012, 2014). PI3K is a major regulator of glucose metabolism. Lung tumors from mice with an engineered $PI3K^{H1047R}$ mutation avidly take up glucose (Engelman et al. 2008). PI3K promotes glucose via increased transcription, membrane trafficking, and activity of GLUTs, and entry of glucose into glycolysis via the regulation of HK2 and PFK2 (Engelman et al. 2006; Beg et al. 2017; Waldhart et al. 2017). Indeed, overexpression of GLUT1 in LUSC, but not LUAD, was positively correlated with activation of the PI3K pathway (Goodwin et al. 2017), further highlighting the complex interaction of both mutation and histology in the regulation of metabolism. While these effects are mediated by AKT, PI3K also activates glycolysis directly via aldolase release from the actin cytoskeleton (Hu et al. 2016). The PI3K/AKT pathway also promotes de novo lipogenesis via AKT-mediated phosphorylation and activation of ATP citrate lyase (ACLY), and lung cancer cells were found to be dependent on ACLY for proliferation (Migita et al. 2008).

KEAP1/NRF2

KEAP1/NRF2 mutations are common across NSCLC subtypes but absent in SCLC (The Cancer Genome Atlas Research Network 2012, 2014; George et al. 2015). These mutations activate the NRF2 transcription factor, which is emerging as a major regulator of cellular metabolism (Hayes and Dinkova-Kostova 2014). NRF2-regulated metabolism is at the interface between the antioxidant program and proliferation. In addition, KEAP1/NRF2 alterations are associated with metastatic disease, poor survival, drug and radiation resistance, but also provide opportunities for targetable vulnerabilities (Bar-Peled et al. 2017; Jeong et al. 2017, 2020; Lignitto et al. 2019; Wang et al. 2020). For example, NRF2 promotes the transcription of enzymes that generate NADPH, including the pentose phosphate pathway enzymes and malic enzyme (Wu et al. 2011; Mitsuishi et al. 2012; Singh et al. 2013). NADPH supports both detoxification of reactive oxygen species (ROS) and reductive biosynthesis of lipids and other macromolecules for proliferation. Importantly, inhibition of the pentose phos-

phate pathway abrogated tumor growth in a mouse model of LUAD driven by mutant Kras and Keap1 deletion (Best et al. 2019). The pentose phosphate pathway also generates ribose-5-phosphate for nucleotide synthesis. Similarly, NRF2 supports both antioxidant function and glutathione synthesis by promoting serine biosynthesis (DeNicola et al. 2015). NRF2 supports the production of the antioxidant glutathione both by the transcriptional regulation of glutathione synthesis and the uptake of the amino acid cysteine, the rate-limiting substrate for glutathione synthesis, via the cystine/glutamate antiporter xCT (Sasaki et al. 2002). However, cystine uptake is associated with several metabolic liabilities. First, because the NRF2 metabolic program consumes significant glutamate for both the uptake of cystine and the synthesis of glutathione, NRF2 active lung tumors are highly dependent on glutamine (Romero et al. 2017; Sayin et al. 2017; Galan-Cobo et al. 2019) and other nonessential amino acids (LeBoeuf et al. 2020) for growth. Second, high intracellular cysteine stabilizes cysteine dioxygenase 1, which metabolizes cysteine to wasteful and toxic products (Kang et al. 2019). However, these metabolic liabilities may depend on the nutritional state of the cell. Under cystine starvation, consumption of glutamate by the NRF2-regulated glutathione synthesis enzyme glutamate-cysteine ligase catalytic subunit (GCLC) protects against the iron-mediated form of cell death known as ferroptosis (Kang et al. 2021). Keap1-mutant murine lung tumors were also found to be dependent on the endoplasmid reticulum coenzyme A transporter Slc33a1, and loss of this transporter resulted in widespread metabolic changes and endoplasmic reticulum (ER) stress (Romero et al. 2020). Because of the frequency of KEAP1/NRF2 alterations, new approaches targeting this pathway and its metabolic consequences should be a high basic and clinical translational research priority.

LKB1 (STK11)

The tumor suppressor gene liver kinase B1 (LKB1) (also known as STK11) encodes for a serine threonine kinase that directly phosphorylates and regulates the adenosine monophosphate-activated protein kinase (AMPK) and 12 other AMPK-like kinases to regulate a broad spectrum of cellular functions including growth, metabolism, autophagy, and polarity (Shackelford and Shaw 2009). LKB1 was first identified as the causal mutation in Peutz–Jeghers syndrome (PJS), which is a rare inherited autosomal dominant disorder characterized by the development of benign gastrointestinal hamartomas and the early onset of cancer (Hemminki et al. 1998). LKB1 mutations were detected in ~20%–30% of LUADs, 70% of mucinous bronchiolar adenocarcinomas (mBACs), and to a lesser extent in squamous and large-cell carcinomas (Sanchez-Cespedes et al. 2002; Ji et al. 2007; Ding et al. 2008; Osoegawa et al. 2011; Hammerman et al. 2012; Wilkerson et al. 2012). LKB1 inactivation leads to deregulation of metabolism and energy homeostasis following misregulation of AMPK and mechanistic target of rapamycin complex I (mTORC1) signaling pathways (Shaw et al. 2004a,b). Deletion of LKB1 in human cancer cell lines and murine embryonic fibroblasts (MEFs) resulted in hyperactivation of mTORC1 (Bardeesy et al. 2002; Shaw et al. 2004a) that promotes metabolic reprogramming of cancer cells to a glycolytic metabolic phenotype that is dependent upon mTORC1 and HIF1α (Shackelford et al. 2009; Faubert et al. 2014). mTORC1 controls the translation of proteins that regulate cell growth and metabolism including HIF1α, MYC, and cyclin D1 (Guertin and Sabatini 2007). In addition to glucose metabolism, mTORC1 is a central regulator of nucleic acid and lipid metabolism (Duvel et al. 2010; Ben-Sahra et al. 2013, 2016; Robitaille et al. 2013) as well as a sensor of amino acids (Sancak et al. 2008, 2010; Bar-Peled et al. 2012, 2013; Wang et al. 2015). mTORC1 regulates lysosomal biogenesis and autophagy during periods of cellular starvation and oncogenic stress (Kim et al. 2011; Martina et al. 2012; Roczniak-Ferguson et al. 2012; Settembre et al. 2012). A dependency on autophagy was identified in KRAS-driven LKB1/STK11-mutant LUADs, and this cellular pathway was required to support tumor metabolism through recycling of amino acids. Growth was inhibited in KRAS/STK11 (LKB1)-mutant lung tumors following

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deletion of the essential autophagy gene ATG7 forcing tumors to up-regulated fatty acid oxidation to support energy production (Bhatt et al. 2019).

LKB1 regulates energy stress, mitochondrial homeostasis, and lung tumorigenesis in part through activation of 14 AMPK family kinases (AMPKRs) that include AMPK and the AMPK-related salt-inducible kinases 1 and 3 (SIK1, SIK3) (Mihaylova and Shaw 2011; Eichner et al. 2019). AMPK was shown to support growth of KRAS-driven lung tumors, whereas the SIK1 and SIK3 kinases were identified as having a tumor suppressor function whose loss of function phenocopied LKB1 inactivation in these tumors (Eichner et al. 2019; Hollstein et al. 2019; Murray et al. 2019). Deletion of *lkb1* in murine hematopoieitic stem cells (HSCs) revealed mitochondrial defects including increased mitochondrial content and reduced mitochondrial membrane function (Gan et al. 2010; Gurumurthy et al. 2010; Nakada et al. 2010). AMPK regulates selective degradation of damaged mitochondrial in an autophagy-related process known as mitophagy as well as mitochondrial fission through direct phosphorylation of Unc51-like kinases 1 and 2 (ULK1/2) and mitochondrial fission factor (MFF) (Egan et al. 2011; Toyama et al. 2016). These studies suggest that inactivation of LKB1 may result in defects in both mitophagy and mitochondrial networks that alter cellular metabolism in lung cancer cells. Recent work has demonstrated that LKB1-deficient lung tumor cells have leaky mitochondria leading to increased cytosolic double-stranded mitochondrial DNA (mtDNA) that functions as a potential mediator of aberrant STING (stimulator of interferon), thus connecting the regulation of mitochondria to innate immune responses in lung tumors (Kitajima et al. 2019). Additionally, LKB1 inactivation in KRAS-mutant lung tumors leads to impaired oxidative mitochondrial metabolism, defects in purine and pyrimidine metabolism with dependencies on fatty acid synthesis and glutamine that support anabolic metabolism and tumor growth (Liu et al. 2013; Svensson et al. 2016; Kim et al. 2017; Parker et al. 2017). Of importance, for reasons that are not yet clear, LUADs with STK11/LKB1 mutations are resistant to front-line ICB therapies (Skoulidis et al. 2018). Thus, targeting metabolic abnormalities associated with LKB1 alterations could potentially have a major therapeutic impact on tumors resistant to ICB therapy. LUADs bearing comutations in KRAS and STK11/LKB1 were shown to be highly responsive to combined treatment with small-molecule inhibitors targeting OXPHOS and glycolysis (Momcilovic et al. 2015). Clinically, intermittent fasting in combination with the OXPHOS inhibitor metformin is being tested in the FAME (FAsting—mimicking diet and MEtformin) trial for patients with LUAD with KRAS and STK11/LKB1-mutant LUAD (Vernieri et al. 2019). Importantly, these issues need to be addressed in further preclinical models and in patients.

EGFR

The EGFR gene (also known as ERBB1 or HER1) belongs to the receptor tyrosine kinase (RTK) superfamily of cell-surface receptors that regulate cellular growth by extracellular growth factors. Mutations in the EGFR are found in ~20% of LUADs with higher rates observed in patients of East Asian descent, females, and never-smokers (Pao et al. 2004; Sun et al. 2007; Ding et al. 2008; Shi et al. 2014; The Cancer Genome Atlas Research Network 2014; Midha et al. 2015). EGFR-mutant LUADs are uniquely sensitive to suppression of oncogenic signaling by selective tyrosine kinase inhibitors (TKIs) (Lynch et al. 2004; Politi et al. 2006). Activating mutations center around the kinase domain that result in constitutive EGFR kinase activity and oncogenic dependency on EGFR signaling (Zhang et al. 2006), which drives cellular growth through activation of the PI3K-AKT-mTOR and JAK-STAT pathways (Sordella et al. 2004). Metabolic studies in EGFR-mutant LUADs identified that aerobic glycolysis was regulated by the PI3K-AKT-mTOR pathway (Makinoshima et al. 2014). Overexpression of the glutamine transporter SLC1A5 (also known as ASCT2) was detected in EGFR-mutant lung cancer cell lines and in vivo tumor models (Hassanein et al. 2016; Momcilovic et al. 2017). Analysis of EGFR-mutant LUADs in cell lines and tumors identified

metabolic dependencies on both glycolysis and glutaminolysis (Momcilovic et al. 2017). Much less is known about EGFR's role in nucleic acid and lipid metabolism. Routinely, nearly all new NSCLC patient tumors are tested for EGFR mutations, and most also receive a PET scan, so this information is at hand to correlate with tumor metabolism studies. Importantly, although we now have third-generation EGFR-targeting TKIs that provide substantial clinical and survival benefit to patients with EGFR-mutant tumors, nearly all of these patients will relapse (O'Leary et al. 2020). In addition, the response rates to ICB are low in EGFR-mutant tumors, and combining EGFR TKIs with ICB has been met with significant toxicities (Lisberg and Garon 2017; Hastings et al. 2019). Thus, in attempts to develop targeted therapy with curative or long-term survival potential it may prove useful to explore metabolic-based strategies targeting TKI-resistant EGFR-mutant lung tumors.

MYC

The transcription factor MYC is activated downstream of growth factor signaling pathways (Hsieh et al. 2015). Indeed, MYC activity is critical for tumor maintenance in a mouse model of LUAD driven by mutant Kras (Soucek et al. 2013). Further, MYC is frequently amplified in LUSC (Malchers et al. 2014). In addition, genetic alterations in all three MYC family members, MYC, MYCL, and MYCN, are common in SCLC (George et al. 2015). MYC alterations drive SCLC from the classic form to the variant form, and promote metabolic alterations and vulnerabilities. Some of these have already been discussed as they relate to the MYC^{High} subtype of SCLC. In addition, MYC is a potent transcriptional regulator of glycolysis (Kim et al. 2004) and promotes the alternative splicing of pyruvate kinase to the M2 isoform (David et al. 2010), which promotes channeling of glycolytic intermediates into biosynthetic pathways (Chaneton et al. 2012). Further, MYC promotes glutamine metabolism and increased reliance on glutamine for mitochondrial metabolism (Wise et al. 2008; Gao et al. 2009). MYC also up-regulates glutamine synthase in murine lung tumor cells to promote survival under glutamine-limiting conditions (Bott et al. 2015), suggesting that MYC can promote metabolic flexibility. Murine LUADs with high levels of MYC are characterized by increased arachidonic acid metabolism to produce eicosanoids for proliferation and survival, which is associated with sensitivity to cyclooxygenase/lipoxygenase inhibitors (Hall et al. 2016). Importantly, both small molecules and new biologics targeting myc and its interacting proteins with therapeutic potential have been developed (Castell et al. 2018; Han et al. 2019; Massó-Vallés et al. 2020). Additional work in preclinical models is needed to determine whether they alter the effect of myc on tumor metabolism.

METABOLIC CROSS TALK IN THE TUMOR MICROENVIRONMENT

It is becoming clear that it is critical to study the metabolism of tumors in their relevant TME, where the availability of oxygen and nutrients can impact cellular metabolism. In contrast, standard cell culture conditions have superphysiolgical levels of oxygen and most nutrients and do not recapitulate the metabolic complexity of the TME. In addition, tumor cell adaptation to cell culture conditions can permanently alter cellular metabolism and induce artifacts that confound our interpretation of cancer metabolism and metabolic dependencies (Davidson et al. 2016). For example, the superphysiolgical levels of cystine found in cell culture media increases the reliance of cultured cells on glutamine and glutaminolysis to supply glutamate for cytine/glutamate exchange (Muir et al. 2017). Recent analyses of metabolite levels in serum and interstitial tumor fluid have revealed that many metabolites are missing from culture media that can influence tumor cell metabolism and response to chemotherapeutics (Cantor et al. 2017; Sullivan et al. 2019; Vande Voorde et al. 2019).

The immune microenvironment is a major component of tumors that is missing from tumor cell cultures and influenced by metabolite concentrations. Tumor cells and immune cells share many metabolic pathways related to the

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proliferative nature of both cell types. Metabolic pathways and metabolites provide energy and substrates for immune cell proliferation, survival, and cellular function, but also influence cellular differentiation status and gene expression (Buck et al. 2017). Consequently, competition between tumor and immune cells within the microenvironment has consequences for immune cell function and tumor progression. For example, T cells are critically dependent on glucose for proliferation and cytokine production, and glucose consumption by tumors impairs T-cell function and their ability to control tumor growth (Chang et al. 2015a). Glycolytic waste in the form of lactate accumulation inhibits tumor cell clearance by T and natural killer (NK) cells (Brand et al. 2016). Arginine depletion suppresses T-cell function directly, but also promotes the accumulation of myeloid-derived suppressor cells (MDSCs), thereby indirectly suppressing their function as well (Fletcher et al. 2015). These metabolic dependencies need to be considered when targeting metabolism for cancer therapy, especially in combination with immunotherapy, and more work is needed to functionally link the specific metabolic microenvironment within lung tumors to immune function.

Therapeutic Targeting of Metabolism in Lung Cancer

As discussed above, in considering individual oncogenic driver mutations found in lung cancer, there are many driver mutation–tumor metabolism interactions that need to be studied in preclinical models and in patient tumors. Current clinical strategies for treating surgically unresectable both NSCLC and SCLC include the use of chemotherapy in combination with immune checkpoint inhibitors. These same strategies are being tested or brought into treatment of nonmetastatic lung cancer including as neoadjuvant therapies. In fact, several "frontline" chemotherapy agents—pemetrexed and gemcitabine—disrupt nucleotide metabolism in tumor cells representing some of the first approved metabolic-based therapies in cancer (Table 1; Plunkett et al. 1995; Adjei 2000). Approximately 20%–25% of NSCLC patients experience a durable response to immunotherapy. Importantly, subsets of LUADs bearing comutations in *KRAS* and *LKB1* or *EGFR* have proven to be immune-cold and highly resistant to immune-based therapy but metabolically active (Momcilovic et al. 2015, 2017; Gainor et al. 2016; Skoulidis et al. 2018). Lung tumors frequently possess a high mutational burden often rendering single-agent therapies targeting oncogenic driver mutations unsuccessful (Alexandrov et al. 2013). The exceptions in lung cancer are mutations in the EGFR, ALK, ROS1, BRAF, and NTRK genes for which single-agent targeted therapies exist (Table 1). However, we re-emphasize that the majority of lung cancer patients who receive the best available combinations of surgery, radiation therapy, chemotherapy, targeted therapy, or immunotherapy will eventually relapse and experience disease progression. Thus, it will be important to classify tumors by their metabolic signatures, to allow one to group tumors by their metabolic dependencies in addition to (or in lieu of) their driver oncogene mutations. This would allow clinical translation for the alternative strategy of precision-medicine-based delivery of metabolic targeted therapies.

Targeting Glucose Metabolism

TKIs represent clinically approved small-molecule targeted therapies. TKIs targeting EGFR and ALK have been shown to suppress glucose metabolism in cell culture and mouse models (Makinoshima et al. 2014; Ma et al. 2016). Additional TKIs that target the ROS1 and NTRK kinases are approved for lung ADC; however, metabolic studies in these lung tumor subtypes are lacking. Inhibition of glucose metabolism in LUSC was suppressed by targeted inhibition of the fibroblast growth factor receptor (FGFR) (Fumarola et al. 2017). Preclinical studies have demonstrated that targeted inhibition of the PI3K-AKT-mTORC1 and RAS-MEK-ERK pathways suppress glucose metabolism in NSCLC (Table 1; Chen et al. 2012; De Rosa et al. 2015; Momcilovic et al. 2015). Numerous clinical trials have been testing kinase inhibitors as single agents or in combination that include

Table 1. Therapies for the targeting of lung cancer metabolism

Target(s)	Agent(s)	Preclinical findings	Clinical indications
Nucleic acids			
TH, DHFR, GARFT	Pemetrexed	Inhibits purine and pyrimidine synthesis	FDA approved for the treatment of lung adenocarcinoma; >500 clinical trials in non-small-cell lung cancer (NSCLC)
DNA synthesis	Gemcitabine	Inhibits DNA synthesis	FDA approved for the treatment of NSCLC; >500 clinical trials in NSCLC
Glucose metabolism			
KRAS	$KRAS^{G12C}$ inhibitors (sotorasib, JNJ-74699157, MRTX849, JDQ443)	KRAS alters glucose metabolism in preclinical studies in cell lines and mouse models of NSCLC	Early-phase clinical trials in $KRAS^{G12C}$-positive lung adenocarcinomas
EGFR	Tyrosine kinase inhibitors (TKIs) (erlotinib, gefetinib, afatinib, osimertinib)	Preclinical studies in cell lines and mouse models show suppression of glucose uptake and metabolism in NSCLC	Approved for the treatment of epidermal growth factor receptor (EGFR)-mutant lung adenocarcinoma; >500 clinical trials in NSCLC
ALK; ROS1	Crizotinib; LDK378 (ceritinib); cabozantinib; PF-06463922; lorlatinib; alkotinib (ZG 0418); X-396 capsule (ensartinib); WX-0593; entrectinib	Identification of distinct metabolic dependencies in RTK-driven cancers	Approved for treatment of ALK and ROS1-mutant lung adenocarcinoma; >80 clinical trials in NSCLC
Fibroblast growth factor receptor (FGFR)	AZD4547; BGJ398; LY2874455; JNJ-42756493; FP-1039	Distinct metabolic signatures identified in FGFR-positive NSCLC	Early-phase clinical trials in FGFR-positive lung adenocarcinomas and in squamous cell carcinomas
GLUTs	STF31, WZB117, BAY-876	Tool compounds inhibited glucose uptake and tumor growth in preclinical studies	
SGLT2	Gliflozins	SGLT2 inhibition with gliflozins inhibited glucose uptake in early-stage lung adenocarcinomas via the SGLT2 transporter and significantly extended survival in mouse models of NSCLC	FDA approved for the treatment of type II diabetes
MCT1/4	AZD3964	Preclinical studies identified overexpression of MCT1/4 NSCLC	
PI3K	BKM120; GDC-0941; gedatolisib (PF-05212384); GSK2636771	Preclinical studies in cell lines and mouse models show suppression of glucose uptake and metabolism in NSCLC	Ongoing clinical trials

Continued

Table 1. *Continued*

Target(s)	Agent(s)	Preclinical findings	Clinical indications
AKT	MK2206; AZD5363	Preclinical studies in cell lines and mouse models show suppression of glucose uptake and metabolism in NSCLC	BATTLE, BATTLE-2 clinical trials
mTOR	TAK-228, AZD2014, everolimus, temisorlimus	Preclinical studies in cell lines and mouse models show suppression of glucose uptake and metabolism in NSCLC	Multiple ongoing clinical trials; early-phase clinical trial(s) evaluating TAK-228 in KRAS and NRF2/KEAP1-mutant NSCLC
MEK	Selumetinib, tremetinib; MEK162; AZD6244; PD-325901; ASN007	Preclinical studies in cell lines and mouse models show suppression of glucose uptake and metabolism in NSCLC	BATTLE, BATTLE-2 clinical trials; ≥30 clinical trials testing MEK inhibitors for the treatment of NSCLC
HKII	2DG, 3-bromopyruvate	Tool compounds inhibited glucose uptake and tumor growth in preclinical studies	
Energetics	Intermittent fasting + metformin	Preclinical studies in cell lines and mouse models show LKB1 loss sensitizes to bioenergetic stress	FAME clinical trial; phase 2 clinical trial evaluating this combination in LKB1 inactive, advanced lung adenocarcinomas
Amino acids			
Glutamine metabolism, glutaminase (GLS)	GLS inhibitors CB-839, BPTES	Preclinical studies in cell lines and mouse models identified glutamine dependencies in NSCLC; EGFR and KRAS/KEAP1-mutant lung adenocarcinoma (LUAD) were sensitive to GLS inhibition; LUSC responded to inhibition of GLS in combination with TAK-228	Early-phase clinical trials evaluating CB-839 in combination with nivolumab or osimertinib in NSCLC
Asparagine metabolism	L-asparaginase	Preclinical studies demonstrated in vivo response in KRAS- mutant LUAD mouse models L-asparaginase in combination with targeted AKT inhibition, and in KRAS/LKB1-mutant LUAD mouse model asparagine deprivation in combination with metformin	Approved for treatment of acute lymphoblastic leukemia (ALL)
Amino acid transporter ASCT2 (SLC1A5)	GPNA, V-9302	Selective targeting of the glutamine transporter ASCT2 (SLC1A5) using the small-molecule inhibitors γ-L-glutamyl-p-nitroanilide (GPNA) and V-9302 have demonstrated efficacy in restricting glutamine uptake and tumor growth	

Continued

Table 1. *Continued*

Target(s)	Agent(s)	Preclinical findings	Clinical indications
Amino acid transporter xCT (SLC7A11)	Sulfasalazine	Targeted suppression of the amino acid transporter xCT with sulfasalazine-inhibited NSCLC tumors overexpressing xCT	
Mitochondrial metabolism			
Complex I	Biguanides, BAY-87, IACS-010759	Metformin approved for treatment of type II diabetes; preclinical studies demonstrate biguanides, BAY-87, and IACS-010759 reduce tumor growth in KRAS-mutant LUAD; ongoing prospective clinical trials testing metformin in combination with chemotherapy, immune checkpoint blockade, or targeted therapies	FDA approved for the treatment of type II diabetes; nearly 20 clinical trials are testing
Lipid metabolism			
FASN	TVB-2640; C75	Preclinical studies demonstrated that de novo lipid synthesis represents a therapeutic target in KRAS-mutant NSCLC; PMID: 29906244 (C75)	Phase 2 clinical trial targeting de novo lipid synthesis using FASN inhibitors in KRAS-mutant NSCLC
Acetyl-CoA carboxylase (ACC)	ND-646	Targeted inhibition of ACC with the drug ND-646 inhibited KRAS-mutant lung tumors in cell culture and mouse models of NSCLC	

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the BATTLE and BATTLE-2 biomarker integrated clinical trials targeting EGFR, AKT, and MEK in patients with KRAS-mutant lung cancer (Papadimitrakopoulou et al. 2016). In addition, targeted inhibition of mTOR with the kinase inhibitor TAK-228 is in early-phase clinical testing in lung cancer patients NRF2/KEAP1 or KRAS-mutant lung cancer (Table 1).

Inhibitors of the GLUTs have shown efficacy targeting glycolytic LUSC tumors (Goodwin et al. 2017) and are still in preclinical phase development. In preclinical studies, overexpression and activity of SGLT2 was detected in premalignant and early-stage LUAD. Inhibition of $Kras^{G12D}$-driven LUAD with targeted SGLT2 inhibitors known as gliflozins, suppressed glucose uptake in early-stage lung tumors and extended survival in vivo in animal models (Scafoglio et al. 2018). Gliflozins are FDA approved for the treatment of type II diabetes and while not currently approved for treatment of LUAD, this class of drug has the potential to be repurposed for treatment of early-stage lung cancer. The monocarboxylate transporters 1 and 4 (MCT1/4) regulate cellular transport of lactate and pyruvate and are expressed in NSCLC and inhibition of MCT1 through knockout studies in mice or using the MCT1 inhibitor AZD3965 result in suppressed glucose and increased oxygen consumption (Table 1; Hong et al. 2016; Faubert et al. 2017). Last, the hexosamine biosynthetic pathway (HBP) was recently identified to be up-regulated in KRAS and STK11/LKB1-mutant LUADs, which were sensitive to inhibitors of the HBP, suggesting that this may represent a targetable pathway for these metabolic active lung tumors (Kim et al. 2020).

Targeting Amino Acid Metabolism

Targeted inhibition of amino acid uptake and cellular metabolism in cancer cells represents another therapeutic strategy that has begun testing in clinical trials. Targeted inhibition of glutaminolysis using CB-839, an allosteric small-molecule inhibitor of glutaminase (GLS), has demonstrated efficacy in preclinical studies in LUSC or LUAD bearing KEAP1 or EGFR mutations (Momcilovic et al. 2017, 2018a; Romero et al. 2017). Likwise, inactivating mutations in the LKB1 and KEAP1 were shown to cooperatively promote metabolic reprogramming with enhanced glutamine dependence in oncogenic KRAS-driven LUAD (Galan-Cobo et al. 2019). In preclinical studies, CB-839 demonstrated improved efficacy targeting LUSC and EGFR-mutant LUAD when combined with either the TKI erlotinib or the mTOR inhibitor TAK-228 (Momcilovic et al. 2017, 2018a). Additionally, selective targeting of the glutamine transporter ASCT2 (SLC1A5) using the small-molecule inhibitors γ-L-glutamyl-p-nitroanilide (GPNA) and V-9302 has demonstrated efficacy in restricting glutamine uptake and tumor growth (Table 1; Hassanein et al. 2015; Schulte et al. 2018). Likewise, targeted suppression of the amino acid transporter xCT (SLC7A11) with sulfasalazine inhibited NSCLC tumors overexpressing xCT. Sulfasalazine is used to treat rheumatoid arthritis, ulcerative colitis, and Crohn's disease and represents a class of drug with potential for repurposing for cancer treatment (Table 1; Ji et al. 2018). CB-839 has also been shown to sensitize lung tumor cells to radiation, which may be due to suppression glutathione synthesis and increase ROS in lung tumor cells (Momcilovic et al. 2017; Romero et al. 2017; Boysen et al. 2019). KRAS was shown to regulate asparagine biosynthesis through the AKT and NRF2 pathways in NSCLC tumors. Inhibition of AKT reduced expression of asparagine synthase (ASNS) and sensitized tumors to L-asparaginase (Gwinn et al. 2018). Likewise, autochthonous mouse models and human xenografts bearing LUADs with co-mutations in KRAS and STK11/LKB1 were identified as sensitive to combined restriction of asparagine and the complex I inhibitor metformin (Krall et al. 2021). L-asparaginase depletes the body of circulating asparagine and is currently approved for the treatment of ALL.

Targeting Mitochondrial Metabolism

The mitochondria functions as a central hub of cellular biosynthesis and bioenergetics and mitochondrial metabolism represents a target for cancer therapies. The GLS enzyme resides in the

mitochondria and has been successfully targeted in lung cancer. Targeting of the mitochondrial bioenergetics through inhibition of respiratory chain complexes has emerged as a tractable target in cancer therapy. The biguanides metformin and phenformin, which are complex I inhibitors, have been extensively studied in a broad range of cancers including NSCLC (Dowling et al. 2012; Bridges et al. 2014, 2016). Metformin is approved for the treatment of type II diabetes. As a single agent, metformin has shown limited efficacy in reducing tumor growth in animal models. However, its more potent chemical analog phenformin has demonstrated efficacy in mouse models of LUAD with Kras and Stk11 comutations resulting in reduced tumor growth and improved overall survival (Shackelford et al. 2013). In combination, biguanides cooperate with mTOR inhibition to suppress glycolysis and reduce lung tumor growth (Momcilovic et al. 2015). Clinically, metformin is currently being tested in over 300 cancer-related clinical trials. There are multiple ongoing or completed clinical trials testing metformin in NSCLC in combination with chemotherapy or targeted therapies (refer to Table 1 for a complete list). Because of the associated toxicity of lactic acidosis, phenformin was removed from the market and is not currently being tested in clinical trials (Crofford 1995; Dykens et al. 2008). Recently, a potent complex I inhibitor, IACS-101759, was shown to demonstrate in vivo efficacy targeting KRAS-mutant LUAD (Lissanu Deribe et al. 2018; Molina et al. 2018).

Targeting Lipid Metabolism

Metabolic plasticity found in tumors can mediate resistance to inhibition of lipid metabolism. Only a subset of cancers are sensitive to inhibitors of fatty acid desaturation. KRAS-mutant lung tumor cells and GEMMs showed selective sensitivity to targeted ACC inhibition (Svensson et al. 2016). Recently, an alternative fatty acid desaturation pathway, mediated by fatty acid desaturase 2 (FADS2) rather than steroyl-CoA desaturase (SCD), was identified in human lung carcinomas, which mediates the desaturation of palmitate to sapienate to support membrane biosynthesis (Vriens et al. 2019). Dual inhibition of both FADS2 and SCD was required to block the proliferation of cells with this activity.

CONCLUSIONS AND FUTURE PERSPECTIVES

Our increasing understanding of lung cancer heterogeneity, its molecular alterations, and how they influence tumor metabolism has revealed many unique metabolic vulnerabilities that have therapeutic potential. This knowledge, coupled with improved imaging technology and an ever-expanding list of metabolic inhibitors entering the clinic, will pave the way for a personalized medicine-based approach for targeting metabolism for patient treatment. Future challenges include tumor metabolic plasticity as a mechanism of resistance to therapy and therapeutic strategies that target tumor cells while sparing immune cells and other cells within the microenvironment.

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