

# Metabolic Phenotypes, Dependencies, and Adaptation in Lung Cancer

Gina M. DeNicola<sup>1</sup> and David B. Shackelford<sup>2,3</sup>

<sup>1</sup>Department of Cancer Physiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida 33612, USA

<sup>2</sup>Division of Pulmonary and Critical Care Medicine; <sup>3</sup>Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at the University of California, Los Angeles, California 90095, USA

Correspondence: [gina.denicola@moffitt.org](mailto:gina.denicola@moffitt.org); [dshackelford@mednet.ucla.edu](mailto:dshackelford@mednet.ucla.edu)



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

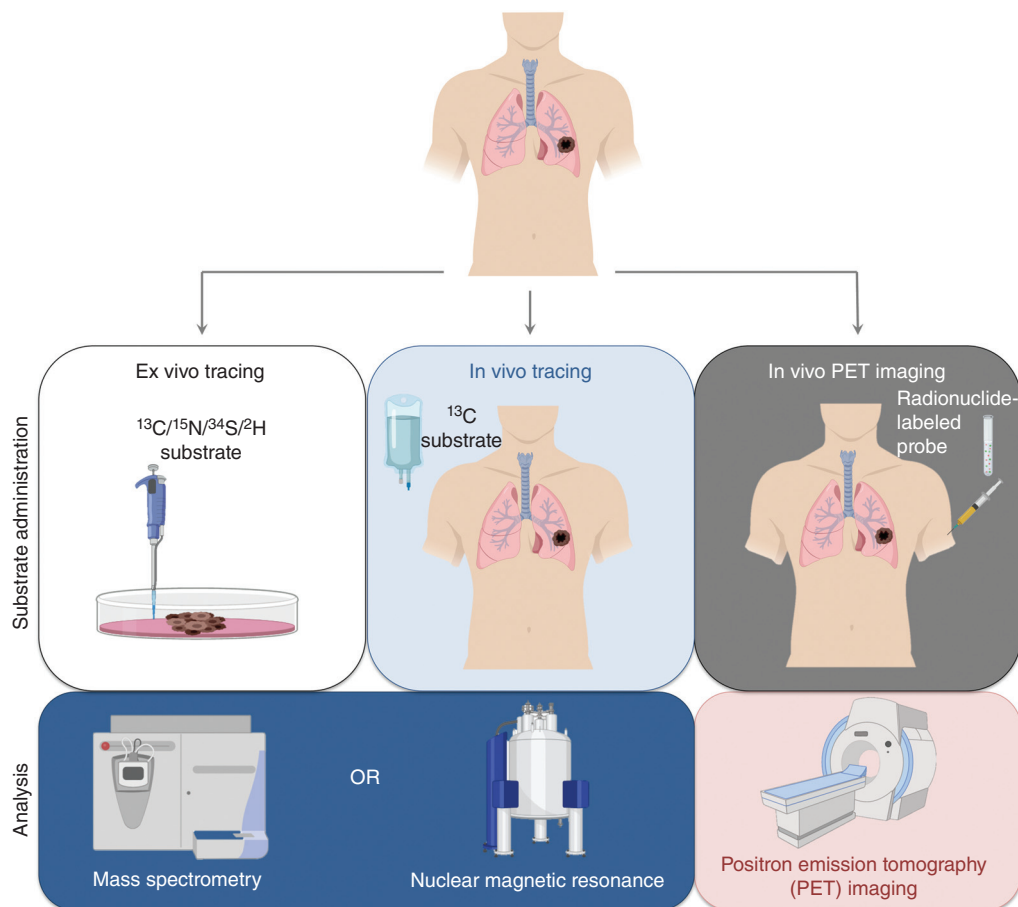
pathway activation (Chalishazar et al. 2019). Future studies will reveal the metabolic dependencies of the ASCL1<sup>High</sup>/MYC<sup>Low</sup> subtype.

## 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 <sup>13</sup>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



**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

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

### Positron Emission Tomography

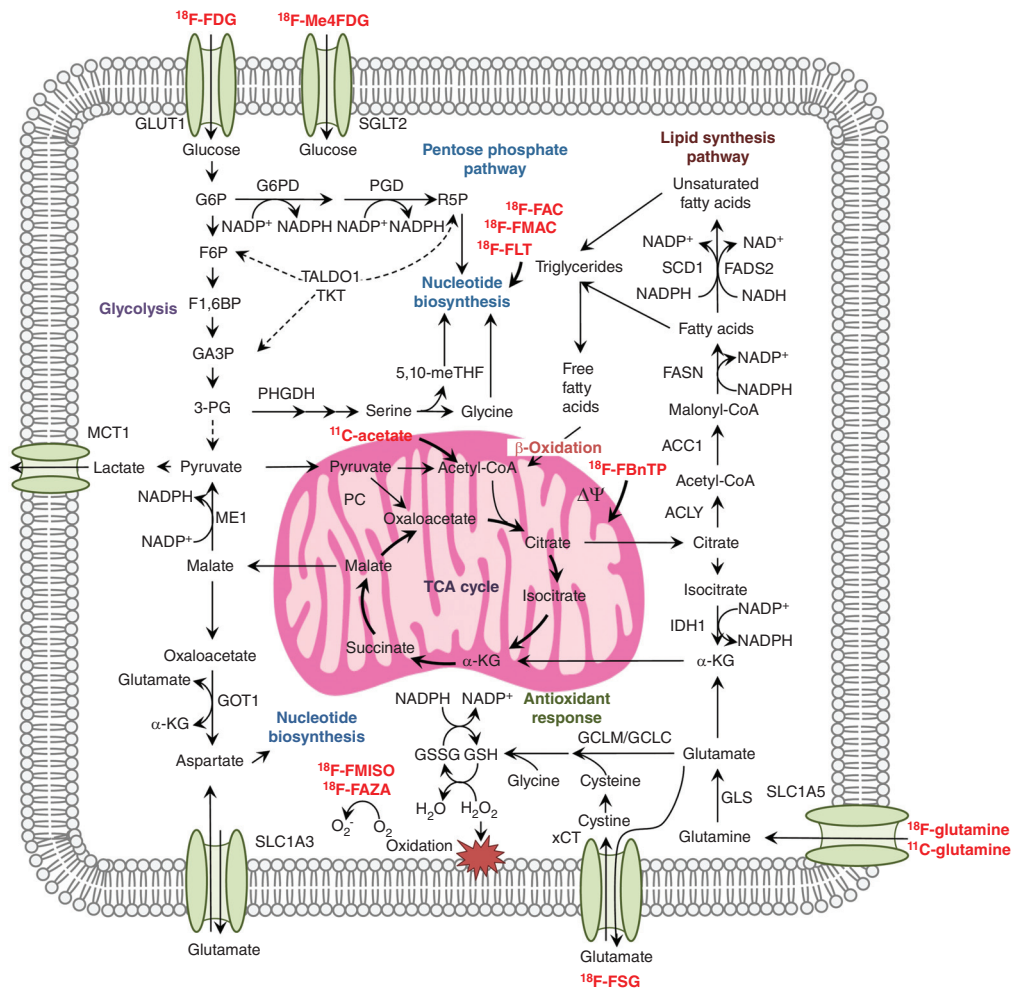
PET imaging is a widely used imaging modality employed in both clinical and basic research settings. PET imaging works by detection of gamma rays from positron emitting radionuclides that have been injected into a patient or animal. Detection of emitted gamma rays from a single source allows the three-dimensional image reconstruction and spatial resolution of tissue, in particular tumors. The most commonly used radionuclide is  $^{18}\text{F}$  but there is a wide range of radionuclides available—the more commonly used isotopes include  $^{18}\text{F}$ ,  $^{11}\text{C}$ , and  $^{15}\text{O}$ . 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  $^{18}\text{F}$ -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

*$^{18}\text{F}$ -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 [ $^{18}\text{F}$ ]-fluoro-2-deoxyglucose ( $^{18}\text{F}$ -FDG) PET. The high consumption of glucose by advanced lung tumors makes PET imaging with  $^{18}\text{F}$ -FDG an ideal probe for detecting and staging glycolytic tumors.  $^{18}\text{F}$ -FDG is transported into cells through the GLUTs, followed by rapid phosphorylation by hexokinase into  $^{18}\text{F}$ -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.  $^{18}\text{F}$ -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,  $^{18}\text{F}$ -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  $^{18}\text{F}$ -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  $^{18}\text{F}$ -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).

*$^{18}\text{F}$ -Me4FDG—monitoring sodium-dependent glucose transporters (SGLTs) for detection of very early lung cancers and preneoplastic lesions.* While  $^{18}\text{F}$ -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  $^{18}\text{F}$ -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; Scalfoglio et al. 2015). Importantly, SGLT-mediated glucose transport is not detected by  $^{18}\text{F}$ -FDG PET because the  $^{18}\text{F}$ -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



**Figure 2.** Metabolic processes support lung cancer proliferation and viability. Both anabolic (lipid biosynthesis, nucleotide biosynthesis) and catabolic processes (glycolysis, tricarboxylic acid [TCA] cycle,  $\beta$ -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, ( $\text{H}_2\text{O}_2$ ) 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<sup>-</sup>, ( $\alpha$ -KG)  $\alpha$ -ketoglutarate, (3-PG) 3-phosphoglycerate, (5,10-meTHF) 5,10-methylene tetrahydrofolate, ( $^{18}\text{F}$ -FDG) [ $^{18}\text{F}$ ]-fluoro-2-deoxyglucose, ( $^{18}\text{F}$ -Me4FDG) methyl-4-[ $^{18}\text{F}$ ] fluorodeoxyglucose, ( $^{18}\text{F}$ -Gln)  $^{18}\text{F}$ -glutamine, ( $^{11}\text{C}$ -Gln)  $^{11}\text{C}$ -glutamine, ( $^{18}\text{F}$ -Gln) [ $^{18}\text{F}$ ]-glutamine, ( $^{18}\text{F}$ -FSG) (S)-4-(3-[ $^{18}\text{F}$ ]fluoropropyl)-l-glutamic acid, ( $^{18}\text{F}$ BnTP) [ $^{18}\text{F}$ ]fluorobenzyl triphenylphosphonium, ( $^{18}\text{F}$ -FMISO)  $^{18}\text{F}$ -fluoromisonidazole, ( $^{18}\text{F}$ -FAZA)  $^{18}\text{F}$ -fluoroazomycin-araboside.

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in vivo by PET imaging using the radiotracer methyl-4- $^{18}\text{F}$  fluorodeoxyglucose ( $^{18}\text{F}$ -Me4FDG).  $^{18}\text{F}$ -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  $^{18}\text{F}$ -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  $^{18}\text{F}$  or  $^{11}\text{C}$  provide opportunities to perform broad profiling of cancer metabolism with PET imaging.  $^{11}\text{C}$  and  $^{18}\text{F}$ -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  $^{11}\text{C}$ -Gln and  $^{18}\text{F}$ -Gln (Hassanein et al. 2016; Momcilovic et al. 2018a, 2017). Glutamate analogs (S)-4-(3- $^{18}\text{F}$ fluoropropyl)-L-glutamic acid ( $^{18}\text{F}$ -FSG) and  $^{18}\text{F}$ -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,  $^{11}\text{C}$ -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  $^{18}\text{F}$ -FMISO and  $^{18}\text{F}$ -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  $^{18}\text{F}$ -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).  $^{18}\text{F}$ -FAC had a better selectivity for lymphoid organs compared to  $^{18}\text{F}$ -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  $^{18}\text{F}$ -FMAC relies on activity of cytidine deaminase (CDA) and uptake of  $^{18}\text{F}$ -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  $^{18}\text{F}$ -FAC probe was further demonstrated in a metabolomics based study on which LC-MS and  $^{18}\text{F}$ -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



cations such as 4- $^{18}\text{F}$ fluorobenzyl-triphenylphosphonium ( $^{18}\text{F}$ -BnTP) have been used as radiotracers to measure mitochondrial membrane potential in these models (Madar et al. 2009; Momcilovic et al. 2019). Importantly,  $^{18}\text{F}$ -BnTP uptake was demonstrated to be elevated in lung tumors with increased activity in complex I of the mitochondrial electron transport chain.  $^{18}\text{F}$ -BnTP-positive tumors were also shown to be responsive to complex I inhibitors (Momcilovic et al. 2019). Lactate metabolism identified in NSCLC suggests that  $^{11}\text{C}$ -lactate tracers may find utility in lung cancer diagnosis and treatment (Herrero et al. 2007; Faubert et al. 2017).  $^{11}\text{C}$ -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  $^{11}\text{C}$ - and  $^{18}\text{F}$ -choline both are used in management of prostate cancer (Testa et al. 2016; Wibmer et al. 2016).

### METABOLIC CHANGES RELATED TO MOLECULAR ALTERATIONS

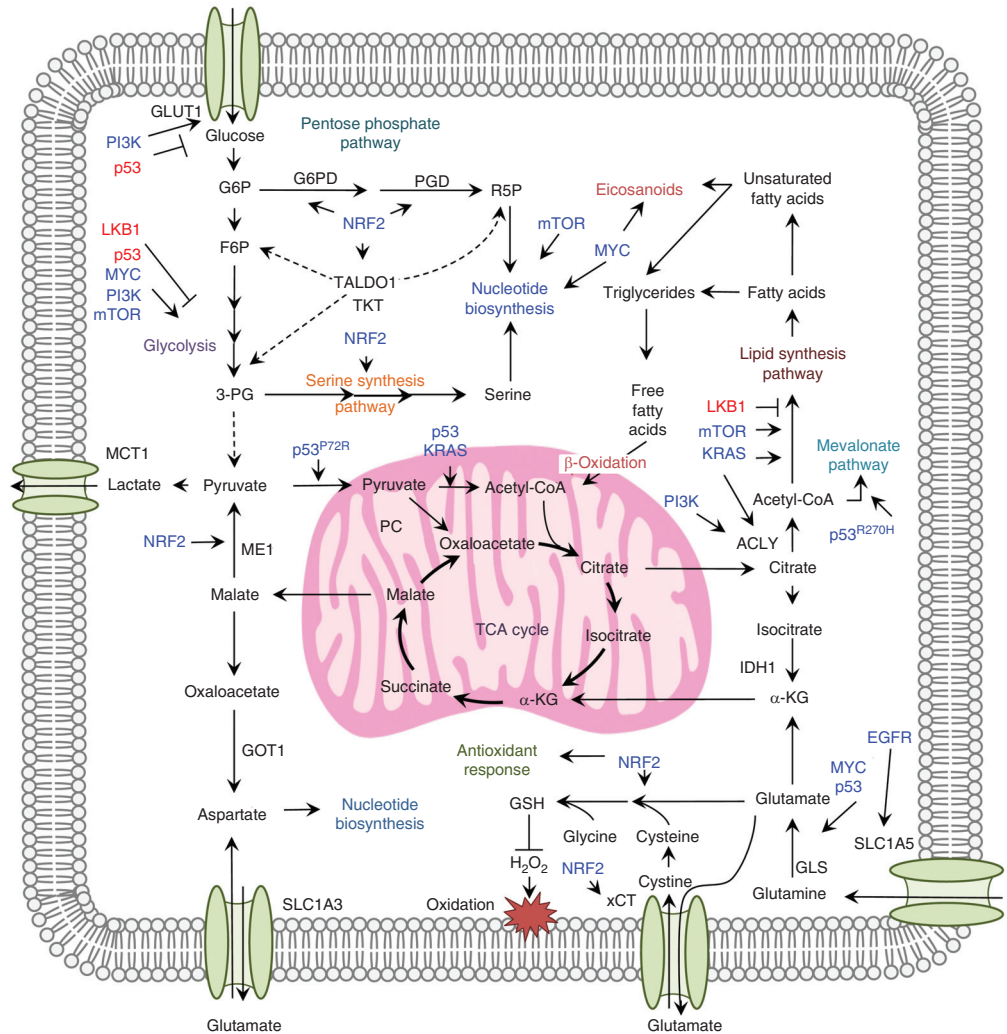
Lung cancer demonstrates significant genetic diversity (mutations in oncogenes and tumor suppressor genes as well as “passenger” mutations), both within histologic subtypes and between subtypes. For example, LUAD can have KRAS or EGFR mutations not found in LUSC or SCLC, and SCLCs have nearly universal 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 vulnera-

bilities. 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<sup>R172H</sup> (human R175H) and p53<sup>R270H</sup> (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<sup>R270H</sup> mutation. Consequently, p53<sup>R270H</sup> tumors were uniquely sensitive to mevalonate pathway inhibition by statin treatment (Turrell et al. 2017). Interestingly, the p53<sup>P72R</sup> polymorphism is also associated with a unique metabolic program mediated by

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**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<sup>P72R</sup>, p53<sup>R270H</sup>) 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<sub>2</sub>O<sub>2</sub>) hydrogen peroxide, (IDH1) isocitrate dehydrogenase 1, (ME1) malic enzyme 1, (PC) pyruvate carboxylase, (PGD) phosphogluconate dehydrogenase, (R5P) ribose 5-phosphate.

PGC1 $\alpha$ , 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



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 Re-

search 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-

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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 endoplasmic 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 phosphory-

lates 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 HIF1 $\alpha$  (Shackelford et al. 2009; Faubert et al. 2014). mTORC1 controls the translation of proteins that regulate cell growth and metabolism including HIF1 $\alpha$ , 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



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 hematopoietic 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 resis-

tant 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 mutations 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

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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<sup>High</sup> 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 (Chanon 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 superphysiological 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 superphysiological levels of cystine found in cell culture media increases the reliance of cultured cells on glutamine and glutaminolysis to supply glutamate for cystine/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



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

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**Table 1.** Therapies for the targeting of lung cancer metabolism

Target(s)	Agent(s)	Preclinical findings	Clinical indications
<b>Nucleic acids</b>			
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
<b>Glucose metabolism</b>			
KRAS	KRAS <sup>G12C</sup> inhibitors (sotorasib, JNJ-74699157, MRTX849, JQ443)	KRAS alters glucose metabolism in preclinical studies in cell lines and mouse models of NSCLC	Early-phase clinical trials in KRAS <sup>G12C</sup> -positive lung adenocarcinomas
EGFR	Tyrosine kinase inhibitors (TKIs) (erlotinib, gefitinib, 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; alectinib (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	Gliiflozins	SGLT2 inhibition with gliiflozins 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, temisorlinimus	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, trametinib; 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
<b>Amino acids</b>			
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 $\gamma$ -L-glutamyl-p-nitroamillide (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	
<b>Mitochondrial metabolism</b>			
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
<b>Lipid metabolism</b>			
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	





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<sup>G12D</sup>-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 (Scarfoglio 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). Likewise, 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  $\gamma$ -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

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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 mutations 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.

## REFERENCES

- Adjei AA. 2000. Pemetrexed: a multitargeted antifolate agent with promising activity in solid tumors. *Ann Oncol* **11**: 1335–1342. doi:10.1023/A:1008379101017
- Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, Børresen-Dale AL, et al. 2013. Signatures of mutational processes in human cancer. *Nature* **500**: 415–421. doi:10.1038/nature12477
- Ambrosini V, Nicolini S, Caroli P, Nanni C, Massaro A, Marzola MC, Rubello D, Fanti S. 2012. PET/CT imaging in different types of lung cancer: an overview. *Eur J Radiol* **81**: 988–1001. doi:10.1016/j.ejrad.2011.03.020
- Baek S, Choi CM, Ahn SH, Lee JW, Gong G, Ryu JS, Oh SJ, Bacher-Stier C, Fels L, Koglin N, et al. 2012. Exploratory clinical trial of (4S)-4-(3-[<sup>18</sup>F]fluoropropyl)-L-glutamate for imaging x<sub>c</sub><sup>-</sup> transporter using positron emission tomography in patients with non-small cell lung or breast cancer. *Clin Cancer Res* **18**: 5427–5437. doi:10.1158/1078-0432.CCR-12-0214
- Bardeesy N, Sinha M, Hezel AF, Signoretti S, Hathaway NA, Sharpless NE, Loda M, Carrasco DR, DePinho RA. 2002. Loss of the Lkb1 tumour suppressor provokes intestinal polyposis but resistance to transformation. *Nature* **419**: 162–167. doi:10.1038/nature01045
- Bar-Peled L, Schweitzer LD, Zoncu R, Sabatini DM. 2012. Regulator is a GEF for the rag GTPases that signal amino acid levels to mTORC1. *Cell* **150**: 1196–1208. doi:10.1016/j.cell.2012.07.032
- Bar-Peled L, Chantranupong L, Cherniack AD, Chen WW, Ottina KA, Grabiner BC, Spear ED, Carter SL, Meyerson



- M, Sabatini DM. 2013. A tumor suppressor complex with GAP activity for the Rag GTPases that signal amino acid sufficiency to mTORC1. *Science* **340**: 1100–1106. doi:10.1126/science.1232044
- Bar-Peled L, Kemper EK, Suciú RM, Vinogradova EV, Backus KM, Horning BD, Paul TA, Ichu TA, Svensson RU, Olucha J, et al. 2017. Chemical proteomics identifies druggable vulnerabilities in a genetically defined cancer. *Cell* **171**: 696–709.e23. doi:10.1016/j.cell.2017.08.051
- Basu S, Gnanapradeepan K, Barnoud T, Kung CP, Tavecchio M, Scott J, Watters A, Chen Q, Kossenkov AV, Murphy ME. 2018. Mutant p53 controls tumor metabolism and metastasis by regulating PGC-1 $\alpha$ . *Genes Dev* **32**: 230–243. doi:10.1101/gad.309062.117
- Beg M, Abdullah N, Thowfeik FS, Altorki NK, McGraw TE. 2017. Distinct Akt phosphorylation states are required for insulin regulated Glut4 and Glut1-mediated glucose uptake. *eLife* **6**: e26896. doi:10.7554/eLife.26896
- Ben-Sahra I, Howell JJ, Asara JM, Manning BD. 2013. Stimulation of de novo pyrimidine synthesis by growth signaling through mTOR and S6K1. *Science* **339**: 1323–1328. doi:10.1126/science.1228792
- Ben-Sahra I, Hoxhaj G, Ricoult SJH, Asara JM, Manning BD. 2016. mTORC1 induces purine synthesis through control of the mitochondrial tetrahydrofolate cycle. *Science* **351**: 728–733. doi:10.1126/science.aad0489
- Benz MR, Herrmann K, Walter F, Garon EB, Reckamp KL, Figlin R, Phelps ME, Weber WA, Czernin J, Allen-Auerbach MS. 2011. <sup>18</sup>F-FDG PET/CT for monitoring treatment responses to the epidermal growth factor receptor inhibitor erlotinib. *J Nucl Med* **52**: 1684–1689. doi:10.2967/jnumed.111.095257
- Berkers CR, Maddocks OD, Cheung EC, Mor I, Vousden KH. 2013. Metabolic regulation by p53 family members. *Cell Metab* **18**: 617–633. doi:10.1016/j.cmet.2013.06.019
- Best SA, Ding S, Kersbergen A, Dong X, Song JY, Xie Y, Reljic B, Li K, Vince JE, Rathi V, et al. 2019. Distinct initiating events underpin the immune and metabolic heterogeneity of KRAS-mutant lung adenocarcinoma. *Nat Commun* **10**: 4190. doi:10.1038/s41467-019-12164-y
- Bhatt V, Khayati K, Hu ZS, Lee A, Kamran W, Su X, Guo JY. 2019. Autophagy modulates lipid metabolism to maintain metabolic flexibility for *Lkb1*-deficient *Kras*-driven lung tumorigenesis. *Genes Dev* **33**: 150–165. doi:10.1101/gad.320481.118
- Bott AJ, Peng IC, Fan Y, Faubert B, Zhao L, Li J, Neidler S, Sun Y, Jaber N, Krokowski D, et al. 2015. Oncogenic *Myc* induces expression of glutamine synthetase through promoter demethylation. *Cell Metab* **22**: 1068–1077. doi:10.1016/j.cmet.2015.09.025
- Boysen G, Jamshidi-Parsian A, Davis MA, Siegel ER, Simcecka CM, Kore RA, Dings RPM, Griffin RJ. 2019. Glutaminase inhibitor CB-839 increases radiation sensitivity of lung tumor cells and human lung tumor xenografts in mice. *Int J Radiat Biol* **95**: 436–442. doi:10.1080/09553002.2018.1558299
- Braas D, Ahler E, Tam B, Nathanson D, Riedinger M, Benz MR, Smith KB, Eilber FC, Witte ON, Tap WD, et al. 2012. Metabolomics strategy reveals subpopulation of liposarcomas sensitive to gemcitabine treatment. *Cancer Discov* **2**: 1109–1117. doi:10.1158/2159-8290.CD-12-0197
- Brand A, Singer K, Koehl GE, Kolitzus M, Schoenhammer G, Thiel A, Matos C, Bruss C, Klobuch S, Peter K, et al. 2016. LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. *Cell Metab* **24**: 657–671. doi:10.1016/j.cmet.2016.08.011
- Bridges HR, Jones AJ, Pollak MN, Hirst J. 2014. Effects of metformin and other biguanides on oxidative phosphorylation in mitochondria. *Biochem J* **462**: 475–487. doi:10.1042/BJ20140620
- Bridges HR, Sirviö VA, Agip AN, Hirst J. 2016. Molecular features of biguanides required for targeting of mitochondrial respiratory complex I and activation of AMP-kinase. *BMC Biol* **14**: 65. doi:10.1186/s12915-016-0287-9
- Brindle KM. 2015. Imaging metabolism with hyperpolarized <sup>13</sup>C-labeled cell substrates. *J Am Chem Soc* **137**: 6418–6427. doi:10.1021/jacs.5b03300
- Buck MD, Sowell RT, Kaech SM, Pearce EL. 2017. Metabolic instruction of immunity. *Cell* **169**: 570–586. doi:10.1016/j.cell.2017.04.004
- Campbell KJ, White RJ. 2014. MYC regulation of cell growth through control of transcription by RNA polymerases I and III. *Cold Spring Harb Perspect Med* **4**: a018408. doi:10.1101/cshperspect.a018408
- Canon J, Rex K, Saiki AY, Mohr C, Cooke K, Bagal D, Gaida K, Holt T, Knutson CG, Koppada N, et al. 2019. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature* **575**: 217–223. doi:10.1038/s41586-019-1694-1
- Cantor JR, Abu-Remaileh M, Kanarek N, Freinkman E, Gao X, Louissaint A Jr, Lewis CA, Sabatini DM. 2017. Physiologic medium rewires cellular metabolism and reveals uric acid as an endogenous inhibitor of UMP synthase. *Cell* **169**: 258–272.e17. doi:10.1016/j.cell.2017.03.023
- Castell A, Yan Q, Fawcner K, Hydbring P, Zhang F, Verschut V, Franco M, Zakaria SM, Bazzar W, Goodwin J, et al. 2018. A selective high affinity MYC-binding compound inhibits MYC:MAX interaction and MYC-dependent tumor cell proliferation. *Sci Rep* **8**: 10064. doi:10.1038/s41598-018-28107-4
- Chalishazar MD, Wait SJ, Huang F, Ireland AS, Mukhopadhyay A, Lee Y, Schuman S, Guthrie MR, Berrett K, Vahrenkamp J, et al. 2019. MYC-driven small cell lung cancer is metabolically distinct and vulnerable to arginine depletion. *Clin Cancer Res* **25**: 5107–5121. doi:10.1158/1078-0432.CCR-18-4140
- Chaneton B, Hillmann P, Zheng L, Martin ACL, Maddocks ODK, Chokkathukalam A, Coyle JE, Jankevics A, Holding FP, Vousden KH, et al. 2012. Serine is a natural ligand and allosteric activator of pyruvate kinase M2. *Nature* **491**: 458–462. doi:10.1038/nature11540
- Chang CH, Qiu J, O'Sullivan D, Buck MD, Noguchi T, Curtis JD, Chen Q, Gindin M, Gubin MM, van der Windt GJ, et al. 2015a. Metabolic competition in the tumor microenvironment is a driver of cancer progression. *Cell* **162**: 1229–1241. doi:10.1016/j.cell.2015.08.016
- Chang E, Liu H, Unterschemmann K, Ellinghaus P, Liu S, Gekeler V, Cheng Z, Berndorff D, Gambhir SS. 2015b. <sup>18</sup>F-FAZA PET imaging response tracks the reoxygenation of tumors in mice upon treatment with the mitochondrial complex I inhibitor BAY 87-2243. *Clin Cancer Res* **21**: 335–346. doi:10.1158/1078-0432.CCR-14-0217

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- Chen Z, Cheng K, Walton Z, Wang Y, Ebi H, Shimamura T, Liu Y, Tupper T, Ouyang J, Li J, et al. 2012. A murine lung cancer co-clinical trial identifies genetic modifiers of therapeutic response. *Nature* **483**: 613–617. doi:10.1038/nature10937
- Chen PH, Cai L, Huffman K, Yang C, Kim J, Faubert B, Borroughs L, Ko B, Sudderth J, McMillan EA, et al. 2019. Metabolic diversity in human non-small cell lung cancer cells. *Mol Cell* **76**: 838–851.e5. doi:10.1016/j.molcel.2019.08.028
- Crofford OB. 1995. Metformin. *N Engl J Med* **333**: 588–589. doi:10.1056/NEJM199508313330910
- David CJ, Chen M, Assanah M, Canoll P, Manley JL. 2010. HnRNP proteins controlled by c-Myc deregulate pyruvate kinase mRNA splicing in cancer. *Nature* **463**: 364–368. doi:10.1038/nature08697
- Davidson SM, Papagiannakopoulos T, Olenchock BA, Heyman JE, Keibler MA, Luengo A, Bauer MR, Jha AK, O'Brien JP, Pierce KA, et al. 2016. Environment impacts the metabolic dependencies of Ras-driven non-small cell lung cancer. *Cell Metab* **23**: 517–528. doi:10.1016/j.cmet.2016.01.007
- DeNicola GM, Chen PH, Mullarky E, Sudderth JA, Hu Z, Wu D, Tang H, Xie Y, Asara JM, Huffman KE, et al. 2015. NRF2 regulates serine biosynthesis in non-small cell lung cancer. *Nat Genet* **47**: 1475–1481. doi:10.1038/ng.3421
- De Rosa V, Iommelli F, Monti M, Fonti R, Votta G, Stoppelli MP, Del Vecchio S. 2015. Reversal of Warburg effect and reactivation of oxidative phosphorylation by differential inhibition of EGFR signaling pathways in non-small cell lung cancer. *Clin Cancer Res* **21**: 5110–5120. doi:10.1158/1078-0432.CCR-15-0375
- de Vries A, Custers E, Lub J, van den Bosch S, Nicolay K, Grüll H. 2010. Block-copolymer-stabilized iodinated emulsions for use as CT contrast agents. *Biomaterials* **31**: 6537–6544. doi:10.1016/j.biomaterials.2010.04.056
- Ding L, Getz G, Wheeler DA, Mardis ER, McLellan MD, Cibulskis K, Sougnez C, Greulich H, Muzny DM, Morgan MB, et al. 2008. Somatic mutations affect key pathways in lung adenocarcinoma. *Nature* **455**: 1069–1075. doi:10.1038/nature07423
- Dowling RJ, Niraula S, Stambolic V, Goodwin PJ. 2012. Metformin in cancer: translational challenges. *J Mol Endocrinol* **48**: R31–R43. doi:10.1530/JME-12-0007
- Duvel K, Yecies JL, Menon S, Raman P, Lipovsky AI, Souza AL, Triantafellow E, Ma Q, Gorski R, Cleaver S, et al. 2010. Activation of a metabolic gene regulatory network downstream of mTOR complex 1. *Mol Cell* **39**: 171–183. doi:10.1016/j.molcel.2010.06.022
- Dykens JA, Jamieson J, Marroquin L, Nadanaciva S, Billis PA, Will Y. 2008. Biguanide-induced mitochondrial dysfunction yields increased lactate production and cytotoxicity of aerobically-poised HepG2 cells and human hepatocytes in vitro. *Toxicol Appl Pharmacol* **233**: 203–210. doi:10.1016/j.taap.2008.08.013
- Egan DF, Shackelford DB, Mihaylova MM, Gelino S, Kohnz RA, Mair W, Vasquez DS, Joshi A, Gwinn DM, Taylor R, et al. 2011. Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy. *Science* **331**: 456–461. doi:10.1126/science.1196371
- Eichner LJ, Brun SN, Herzig S, Young NP, Curtis SD, Shackelford DB, Shokhirev MN, Leblanc M, Vera LI, Hutchins A, et al. 2019. Genetic analysis reveals AMPK is required to support tumor growth in murine Kras-dependent lung cancer models. *Cell Metab* **29**: 285–302.e7. doi:10.1016/j.cmet.2018.10.005
- Engelman JA, Luo J, Cantley LC. 2006. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat Rev Genet* **7**: 606–619. doi:10.1038/nrg1879
- Engelman JA, Chen L, Tan X, Crosby K, Guimaraes AR, Upadhyay R, Maira M, McNamara K, Perera SA, Song Y, et al. 2008. Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. *Nat Med* **14**: 1351–1356. doi:10.1038/nm.1890
- Faubert B, Vincent EE, Griss T, Samborska B, Izreig S, Svensson RU, Mamer OA, Avizonis D, Shackelford DB, Shaw RJ, et al. 2014. Loss of the tumor suppressor LKB1 promotes metabolic reprogramming of cancer cells via HIF-1 $\alpha$ . *Proc Natl Acad Sci* **111**: 2554–2559. doi:10.1073/pnas.1312570111
- Faubert B, Li KY, Cai L, Hensley CT, Kim J, Zacharias LG, Yang C, Do QN, Doucette S, Burguete D, et al. 2017. Lactate metabolism in human lung tumors. *Cell* **171**: 358–371.e9. doi:10.1016/j.cell.2017.09.019
- Fletcher M, Ramirez ME, Sierra RA, Raber P, Thevenot P, Al-Khami AA, Sanchez-Pino D, Hernandez C, Wyczzechowska DD, Ochoa AC, et al. 2015. L-arginine depletion blunts antitumor T-cell responses by inducing myeloid-derived suppressor cells. *Cancer Res* **75**: 275–283. doi:10.1158/0008-5472.CAN-14-1491
- Fumarola C, Cretella D, La Monica S, Bonelli MA, Alfieri R, Caffarra C, Quaini F, Madeddu D, Falco A, Cavazzoni A, et al. 2017. Enhancement of the anti-tumor activity of FGFR1 inhibition in squamous cell lung cancer by targeting downstream signaling involved in glucose metabolism. *Oncotarget* **8**: 91841–91859. doi:10.18632/oncotarget.19279
- Gainor JF, Shaw AT, Sequist LV, Fu X, Azzoli CG, Piotrowska Z, Huynh TG, Zhao L, Fulton L, Schultz KR, et al. 2016. EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer: a retrospective analysis. *Clin Cancer Res* **22**: 4585–4593. doi:10.1158/1078-0432.CCR-15-3101
- Galan-Cobo A, Sitthideatphaiboon P, Qu X, Poteete A, Pissegnat MA, Tong P, Chen PH, Borroughs LK, Rodriguez MLM, Zhang W, et al. 2019. LKB1 and KEAP1/NRF2 pathways cooperatively promote metabolic reprogramming with enhanced glutamine dependence in KRAS-mutant lung adenocarcinoma. *Cancer Res* **79**: 3251–3267. doi:10.1158/0008-5472.CAN-18-3527
- Gan B, Hu J, Jiang S, Liu Y, Sahin E, Zhuang L, Fletcher-Sananikone E, Colla S, Wang YA, Chin L, et al. 2010. Lkb1 regulates quiescence and metabolic homeostasis of haematopoietic stem cells. *Nature* **468**: 701–704. doi:10.1038/nature09595
- Gao P, Tchernyshyov I, Chang TC, Lee YS, Kita K, Ochi T, Zeller KI, De Marzo AM, Van Eyk JE, Mendell JT, et al. 2009. c-Myc suppression of miR-23a/b enhances mito-



- chondrial glutaminase expression and glutamine metabolism. *Nature* **458**: 762–765. doi:10.1038/nature07823
- George J, Lim JS, Jang SJ, Cun Y, Ozretić L, Kong G, Leenders F, Lu X, Fernández-Cuesta L, Bosco G, et al. 2015. Comprehensive genomic profiles of small cell lung cancer. *Nature* **524**: 47–53. doi:10.1038/nature14664
- Goodwin J, Neugent ML, Lee SY, Choe JH, Choi H, Jenkins DMR, Ruthenborg RJ, Robinson MW, Jeong JY, Wake M, et al. 2017. The distinct metabolic phenotype of lung squamous cell carcinoma defines selective vulnerability to glycolytic inhibition. *Nat Commun* **8**: 15503. doi:10.1038/ncomms15503
- Grierson JR, Shields AF. 2000. Radiosynthesis of 3'-deoxy-3'-[<sup>18</sup>F]fluorothymidine: [<sup>18</sup>F]FLT for imaging of cellular proliferation in vivo. *Nucl Med Biol* **27**: 143–156. doi:10.1016/S0969-8051(99)00104-3
- Guertin DA, Sabatini DM. 2007. Defining the role of mTOR in cancer. *Cancer Cell* **12**: 9–22. doi:10.1016/j.ccr.2007.05.008
- Gurumurthy S, Xie SZ, Alagesan B, Kim J, Yusuf RZ, Saez B, Tzatsos A, Oszolac F, Milos P, Ferrari F, et al. 2010. The Lkb1 metabolic sensor maintains haematopoietic stem cell survival. *Nature* **468**: 659–663. doi:10.1038/nature09572.
- Gwinn DM, Lee AG, Briones-Martin-Del-Campo M, Conn CS, Simpson DR, Scott AI, Le A, Cowan TM, Ruggero D, Sweet-Cordero EA. 2018. Oncogenic KRAS regulates amino acid homeostasis and asparagine biosynthesis via ATF4 and alters sensitivity to L-asparaginase. *Cancer Cell* **33**: 91–107.e6. doi:10.1016/j.ccell.2017.12.003
- Hall Z, Ament Z, Wilson CH, Burkhardt DL, Ashmore T, Koulman A, Littlewood T, Evan GI, Griffin JL. 2016. Myc expression drives aberrant lipid metabolism in lung cancer. *Cancer Res* **76**: 4608–4618. doi:10.1158/0008-5472.CAN-15-3403
- Hallin J, Engstrom LD, Hargis L, Calinisan A, Aranda R, Briere DM, Sudhakar N, Bowcut V, Baer BR, Ballard JA, et al. 2020. The KRAS<sup>G12C</sup> inhibitor MRTX849 provides insight toward therapeutic susceptibility of KRAS-mutant cancers in mouse models and patients. *Cancer Discov* **10**: 54–71. doi:10.1158/2159-8290.CD-19-1167
- Hammerman PS, Lawrence MS, Voet D, Jing R, Cibulskis K, Sivachenko A, Stojanov P, McKenna A, Lander ES, Gabriel S, et al. 2012. Comprehensive genomic characterization of squamous cell lung cancers. *Nature* **489**: 519–525. doi:10.1038/nature11404
- Han H, Jain AD, Truica MI, Izquierdo-Ferrer J, Anker JF, Lysy B, Sagar V, Luan Y, Chalmers ZR, Unno K, et al. 2019. Small-molecule MYC inhibitors suppress tumor growth and enhance immunotherapy. *Cancer Cell* **36**: 483–497.e15. doi:10.1016/j.ccell.2019.10.001
- Hassanein M, Hoeksema MD, Shiota M, Qian J, Harris BK, Chen H, Clark JE, Alborn WE, Eisenberg R, Massion PP. 2013. SLC1A5 mediates glutamine transport required for lung cancer cell growth and survival. *Clin Cancer Res* **19**: 560–570. doi:10.1158/1078-0432.CCR-12-2334.
- Hassanein M, Qian J, Hoeksema MD, Wang J, Jacobovitz M, Ji X, Harris FT, Harris BK, Boyd KL, Chen H, et al. 2015. Targeting SLC1a5-mediated glutamine dependence in non-small cell lung cancer. *Int J Cancer* **137**: 1587–1597. doi:10.1002/ijc.29535
- Hassanein M, Hight MR, Buck JR, Tantawy MN, Nickels ML, Hoeksema MD, Harris BK, Boyd K, Massion PP, Manning HC. 2016. Preclinical evaluation of 4-[<sup>18</sup>F]Fluoroglutamine PET to assess ASCT2 expression in lung cancer. *Mol Imaging Biol* **18**: 18–23. doi:10.1007/s11307-015-0862-4
- Hastings K, Yu HA, Wei W, Sanchez-Vega F, DeVeaux M, Choi J, Rizvi H, Lisberg A, Truini A, Lydon CA, et al. 2019. EGFR mutation subtypes and response to immune checkpoint blockade treatment in non-small-cell lung cancer. *Ann Oncol* **30**: 1311–1320. doi:10.1093/annonc/mdz141
- Hayes JD, Dinkova-Kostova AT. 2014. The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. *Trends Biochem Sci* **39**: 199–218. doi:10.1016/j.tibs.2014.02.002
- Hemminki A, Markie D, Tomlinson I, Avizienyte E, Roth S, Loukola A, Bignell G, Warren W, Aminoff M, Höglund P, et al. 1998. A serine/threonine kinase gene defective in Peutz–Jeghers syndrome. *Nature* **391**: 184–187. doi:10.1038/34432
- Hensley CT, Faubert B, Yuan Q, Lev-Cohain N, Jin E, Kim J, Jiang L, Ko B, Skelton R, Loudat L, et al. 2016. Metabolic heterogeneity in human lung tumors. *Cell* **164**: 681–694. doi:10.1016/j.cell.2015.12.034
- Herrero P, Dence CS, Coggan AR, Kisrieva-Ware Z, Eisenbeis P, Gropler RJ. 2007. L-3-<sup>11</sup>C-lactate as a PET tracer of myocardial lactate metabolism: a feasibility study. *J Nucl Med* **48**: 2046–2055. doi:10.2967/jnumed.107.044503
- Higashi K, Ueda Y, Seki H, Yuasa K, Oguchi M, Noguchi T, Taniguchi M, Tonami H, Okimura T, Yamamoto I. 1998. Fluorine-18-FDG PET imaging is negative in bronchioalveolar lung carcinoma. *J Nucl Med* **39**: 1016–1020.
- Hollstein PE, Eichner LJ, Brun SN, Kamireddy A, Svensson RU, Vera LI, Ross DS, Rymoff TJ, Hutchins A, Galvez HM, et al. 2019. The AMPK-related kinases SIK1 and SIK3 mediate key tumor-suppressive effects of LKB1 in NSCLC. *Cancer Discov* **9**: 1606–1627. doi:10.1158/2159-8290.CD-18-1261
- Hong CS, Graham NA, Gu W, Espindola Camacho C, Mah V, Maresh EL, Alavi M, Bagryanova L, Krotee PAL, Gardner BK, et al. 2016. MCT1 modulates cancer cell pyruvate export and growth of tumors that co-express MCT1 and MCT4. *Cell Rep* **14**: 1590–1601. doi:10.1016/j.celrep.2016.01.057
- Hong DS, Fakhri MG, Strickler JH, Desai J, Durm GA, Shapiro GI, Falchook GS, Price TJ, Sacher A, Denlinger CS, et al. 2020. KRAS<sup>G12C</sup> inhibition with sotorasib in advanced solid tumors. *N Engl J Med* **383**: 1207–1217. doi:10.1056/NEJMoa1917239
- Hsieh HJ, Lin SH, Lin KH, Lee CY, Chang CP, Wang SJ. 2008. The feasibility of <sup>11</sup>C-methionine-PET in diagnosis of solitary lung nodules/masses when compared with <sup>18</sup>F-FDG-PET. *Ann Nucl Med* **22**: 533–538. doi:10.1007/s12149-007-0142-8
- Hsieh AL, Walton ZE, Altman BJ, Stine ZE, Dang CV. 2015. MYC and metabolism on the path to cancer. *Semin Cell Dev Biol* **43**: 11–21. doi:10.1016/j.semcdb.2015.08.003
- Hu H, Juvekar A, Lyssiotis CA, Lien EC, Albeck JG, Oh D, Varma G, Hung YP, Ullas S, Lauring J, et al. 2016. Phosphoinositide 3-kinase regulates glycolysis through mobi-

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- lization of aldolase from the actin cytoskeleton. *Cell* **164**: 433–446. doi:10.1016/j.cell.2015.12.042
- Hu K, Li K, Lv J, Feng J, Chen J, Wu H, Cheng F, Jiang W, Wang J, Pei H, et al. 2020. Suppression of the SLC7A11/glutathione axis causes synthetic lethality in KRAS-mutant lung adenocarcinoma. *J Clin Invest* **130**: 1752–1766. doi:10.1172/JCI124049
- Huang F, Ni M, Chalishazar MD, Huffman KE, Kim J, Cai L, Shi X, Cai F, Zacharias LG, Ireland AS, et al. 2018. Inosine monophosphate dehydrogenase dependence in a subset of small cell lung cancers. *Cell Metab* **28**: 369–382.e5. doi:10.1016/j.cmet.2018.06.005
- Huang F, Huffman KE, Wang Z, Wang X, Li K, Cai F, Yang C, Cai L, Shih TS, Zacharias LG, et al. 2021. Guanosine triphosphate links MYC-dependent metabolic and ribosome programs in small-cell lung cancer. *J Clin Invest* **131**: e139929. doi:10.1172/JCI139929
- Hwang JP, Lim I, Kong CB, Jeon DG, Byun BH, Kim BI, Choi CW, Lim SM. 2016. Prognostic value of SUVmax measured by pretreatment fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in patients with Ewing sarcoma. *PLoS ONE* **11**: e0153281. doi:10.1371/journal.pone.0153281
- Jeong Y, Hoang NT, Lovejoy A, Stehr H, Newman AM, Gentles AJ, Kong W, Truong D, Martin S, Chaudhuri A, et al. 2017. Role of *KEAP1/NRF2* and *TP53* mutations in lung squamous cell carcinoma development and radiation resistance. *Cancer Discov* **7**: 86–101. doi:10.1158/2159-8290.CD-16-0127
- Jeong Y, Hellyer JA, Stehr H, Hoang NT, Niu X, Das M, Padda SK, Ramchandran K, Neal JW, Wakelee H, et al. 2020. Role of *KEAP1/NFE2L2* mutations in the chemotherapeutic response of patients with non-small cell lung cancer. *Clin Cancer Res* **26**: 274–281. doi:10.1158/1078-0432.CCR-19-1237
- Ji H, Ramsey MR, Hayes DN, Fan C, McNamara K, Kozlowski P, Torrice C, Wu MC, Shimamura T, Perera SA, et al. 2007. LKB1 modulates lung cancer differentiation and metastasis. *Nature* **448**: 807–810. doi:10.1038/nature06030
- Ji X, Qian J, Rahman SMJ, Siska PJ, Zou Y, Harris BK, Hoeksema MD, Trenary IA, Heidi C, Eisenberg R, et al. 2018. xCT (SLC7A11)-mediated metabolic reprogramming promotes non-small cell lung cancer progression. *Oncogene* **37**: 5007–5019. doi:10.1038/s41388-018-0307-z
- Kang YP, Torrente L, Falzone A, Elkins CM, Liu M, Asara JM, Dibble CC, DeNicola GM. 2019. Cysteine dioxygenase 1 is a metabolic liability for non-small cell lung cancer. *eLife* **8**: e45572. doi:10.7554/eLife.45572
- Kang YP, Mockabee-Macias A, Jiang C, Falzone A, Prieto-Farigua N, Stone E, Harris IS, DeNicola GM. 2021. Non-canonical glutamate-cysteine ligase activity protects against ferroptosis. *Cell Metab* **33**: 174–189.e7. doi:10.1016/j.cmet.2020.12.007
- Kao CY, Hoffman EA, Beck KC, Bellamkonda RV, Annapragada AV. 2003. Long-residence-time nano-scale liposomal iohexol for X-ray-based blood pool imaging. *Acad Radiol* **10**: 475–483. doi:10.1016/S1076-6332(03)80055-7
- Karathanasis E, Chan L, Karumbaiah L, McNeeley K, D'Orsi CJ, Annapragada AV, Sechopoulos I, Bellamkonda RV. 2009. Tumor vascular permeability to a nanoprobe correlates to tumor-specific expression levels of angiogenic markers. *PLoS ONE* **4**: e5843. doi:10.1371/journal.pone.0005843
- Kim JW, Zeller KI, Wang Y, Jegga AG, Aronow BJ, O'Donnell KA, Dang CV. 2004. Evaluation of myc E-box phylogenetic footprints in glycolytic genes by chromatin immunoprecipitation assays. *Mol Cell Biol* **24**: 5923–5936. doi:10.1128/MCB.24.13.5923-5936.2004
- Kim S, Chung JK, Im SH, Jeong JM, Lee DS, Kim DG, Jung HW, Lee MC. 2005. <sup>11</sup>C-methionine PET as a prognostic marker in patients with glioma: comparison with <sup>18</sup>F-FDG PET. *Eur J Nucl Med Mol Imaging* **32**: 52–59. doi:10.1007/s00259-004-1598-6
- Kim J, Kundu M, Viollet B, Guan KL. 2011. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat Cell Biol* **13**: 132–141. doi:10.1038/ncb2152
- Kim J, Hu Z, Cai L, Li K, Choi E, Faubert B, Bezwada D, Rodriguez-Canales J, Villalobos P, Lin YF, et al. 2017. CPS1 maintains pyrimidine pools and DNA synthesis in KRAS/LKB1-mutant lung cancer cells. *Nature* **546**: 168–172. doi:10.1038/nature22359
- Kim J, Lee HM, Cai F, Ko B, Yang C, Lieu EL, Muhammad N, Rhyne S, Li K, Haloul M, et al. 2020. The hexosamine biosynthesis pathway is a targetable liability in KRAS/LKB1 mutant lung cancer. *Nat Metab* **2**: 1401–1412. doi:10.1038/s42255-020-00316-0
- Kitajima S, Ivanova E, Guo S, Yoshida R, Campisi M, Sundaraman SK, Tange S, Mitsuishi Y, Thai TC, Masuda S, et al. 2019. Suppression of STING associated with LKB1 loss in KRAS-driven lung cancer. *Cancer Discov* **9**: 34–45. doi:10.1158/2159-8290.CD-18-0689
- Krall AS, Mullen PJ, Surjono F, Momcilovic M, Schmid EW, Halbrook CJ, Thambundit A, Mittelman SD, Lyssiotis CA, Shackelford DB, et al. 2021. Asparagine couples mitochondrial respiration to ATF4 activity and tumor growth. *Cell Metab* doi:10.1016/j.cmet.2021.02.001
- Kubota K, Yamada S, Ishiwata K, Ito M, Fujiwara T, Fukuda H, Tada M, Ido T. 1993. Evaluation of the treatment response of lung cancer with positron emission tomography and L-[methyl-<sup>11</sup>C]methionine: a preliminary study. *Eur J Nucl Med* **20**: 495–501. doi:10.1007/BF00175162
- Laing RE, Walter MA, Campbell DO, Herschman HR, Satyamurthy N, Phelps ME, Czernin J, Witte ON, Radu CG. 2009. Noninvasive prediction of tumor responses to gemcitabine using positron emission tomography. *Proc Natl Acad Sci* **106**: 2847–2852. doi:10.1073/pnas.0812890106
- Le TM, Poddar S, Capri JR, Abt ER, Kim W, Wei L, Uong NT, Cheng CM, Braas D, Nikanjam M, et al. 2017. ATR inhibition facilitates targeting of leukemia dependence on convergent nucleotide biosynthetic pathways. *Nat Commun* **8**: 241. doi:10.1038/s41467-017-00221-3
- LeBoeuf SE, Wu WL, Karakousi TR, Karadal B, Jackson SR, Davidson SM, Wong KK, Korolov SB, Sayin VI, Papagianakopoulos T. 2020. Activation of oxidative stress response in cancer generates a druggable dependency on exogenous non-essential amino acids. *Cell Metab* **31**: 339–350.e4. doi:10.1016/j.cmet.2019.11.012
- Lee JT, Campbell DO, Satyamurthy N, Czernin J, Radu CG. 2012. Stratification of nucleoside analog chemotherapy using 1-(2'-deoxy-2'-<sup>18</sup>F-fluoro-β-D-arabinofuranosyl) cytosine and 1-(2'-deoxy-2'-<sup>18</sup>F-fluoro-β-L-arabinofura-



- nosyl)-5-methylcytosine PET. *J Nucl Med* **53**: 275–280. doi:10.2967/jnumed.111.090407
- Lieberman BP, Ploessl K, Wang L, Qu W, Zha Z, Wise DR, Chodosh LA, Belka G, Thompson CB, Kung HF. 2011. PET imaging of glutaminolysis in tumors by <sup>18</sup>F-(2S,4R) 4-fluoroglutamine. *J Nucl Med* **52**: 1947–1955. doi:10.2967/jnumed.111.093815
- Lignitto L, LeBoeuf SE, Homer H, Jiang S, Askenazi M, Karakousi TR, Pass HI, Bhutkar AJ, Tsigiros A, Ueberheide B, et al. 2019. Nrf2 activation promotes lung cancer metastasis by inhibiting the degradation of Bach1. *Cell* **178**: 316–329.e18. doi:10.1016/j.cell.2019.06.003
- Lisberg A, Garon EB. 2017. Epidermal growth factor tyrosine kinase inhibitor therapy inferior to second-line chemotherapy in EGFR wild-type non-small cell lung cancer patients: results of French nationwide observational study. *Transl Lung Cancer Res* **6**: S39–S40. doi:10.21037/tlcr.2017.10.16
- Lissanu Deribe Y, Sun Y, Terranova C, Khan F, Martinez-Ledesma J, Gay J, Gao G, Mullinax RA, Khor T, Feng N, et al. 2018. Mutations in the SWI/SNF complex induce a targetable dependence on oxidative phosphorylation in lung cancer. *Nat Med* **24**: 1047–1057. doi:10.1038/s41591-018-0019-5
- Liu Y, Marks K, Cowley GS, Carretero J, Liu Q, Nieland TJ, Xu C, Cohoon TJ, Gao P, Zhang Y, et al. 2013. Metabolic and functional genomic studies identify deoxythymidylate kinase as a target in *LKB1*-mutant lung cancer. *Cancer Discov* **3**: 870–879. doi:10.1158/2159-8290.CD-13-0015
- Lynch TJ, Bell DW, Sordella R, Gurubhagavata S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, et al. 2004. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* **350**: 2129–2139. doi:10.1056/NEJMoa040938
- Ma Y, Yu C, Mohamed EM, Shao H, Wang L, Sundaresan G, Zweit J, Idowu M, Fang X. 2016. A causal link from ALK to hexokinase II overexpression and hyperactive glycolysis in EML4-ALK-positive lung cancer. *Oncogene* **35**: 6132–6142. doi:10.1038/onc.2016.150
- Madar I, Huang Y, Ravert H, Dalrymple SL, Davidson NE, Isaacs JT, Dannals RF, Frost JJ. 2009. Detection and quantification of the evolution dynamics of apoptosis using the PET voltage sensor <sup>18</sup>F-fluorobenzyl triphenyl phosphonium. *J Nucl Med* **50**: 774–780. doi:10.2967/jnumed.108.061283
- Makinoshima H, Takita M, Matsumoto S, Yagishita A, Owada S, Esumi H, Tsuchihara K. 2014. Epidermal growth factor receptor (EGFR) signaling regulates global metabolic pathways in EGFR-mutated lung adenocarcinoma. *J Biol Chem* **289**: 20813–20823. doi:10.1074/jbc.M114.575464
- Malchers F, Dietlein F, Schöttle J, Lu X, Nogova L, Albus K, Fernandez-Cuesta L, Heuckmann JM, Gautschi O, Diebold J, et al. 2014. Cell-autonomous and non-cell-autonomous mechanisms of transformation by amplified *FGFR1* in lung cancer. *Cancer Discov* **4**: 246–257. doi:10.1158/2159-8290.CD-13-0323
- Martina JA, Chen Y, Gucek M, Puertollano R. 2012. MTORC1 functions as a transcriptional regulator of autophagy by preventing nuclear transport of TFEB. *Autophagy* **8**: 903–914. doi:10.4161/auto.19653
- Martínez-Reyes I, Cardona LR, Kong H, Vasan K, McElroy GS, Werner M, Kihshen H, Reczek CR, Weinberg SE, Gao P, et al. 2020. Mitochondrial ubiquinol oxidation is necessary for tumour growth. *Nature* **585**: 288–292. doi:10.1038/s41586-020-2475-6
- Massó-Vallés D, Beaulieu ME, Soucek L. 2020. MYC, MYCL, and MYCN as therapeutic targets in lung cancer. *Expert Opin Ther Targets* **24**: 101–114. doi:10.1080/14728222.2020.1723548
- Mayers JR, Torrence ME, Danai LV, Papagiannakopoulos T, Davidson SM, Bauer MR, Lau AN, Ji BW, Dixit PD, Hosios AM, et al. 2016. Tissue of origin dictates branched-chain amino acid metabolism in mutant Kras-driven cancers. *Science* **353**: 1161–1165. doi:10.1126/science.aaf5171
- McCormick PN, Greenwood HE, Glaser M, Maddocks ODK, Gendron T, Sander K, Gowrishankar G, Hoehne A, Zhang T, Shuhendler AJ, et al. 2019. Assessment of tumor redox status through (S)-4-(3-[<sup>18</sup>F]fluoropropyl)-L-glutamic acid PET imaging of system x<sub>c</sub><sup>-</sup> activity. *Cancer Res* **79**: 853–863. doi:10.1158/0008-5472.CAN-18-2634
- Midha A, Dearden S, McCormack R. 2015. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). *Am J Cancer Res* **5**: 2892–2911.
- Migita T, Narita T, Nomura K, Miyagi E, Inazuka F, Matsuuru M, Ushijima M, Mashima T, Seimiya H, Satoh Y, et al. 2008. ATP citrate lyase: activation and therapeutic implications in non-small cell lung cancer. *Cancer Res* **68**: 8547–8554. doi:10.1158/0008-5472.CAN-08-1235
- Mihaylova MM, Shaw RJ. 2011. The AMPK signalling pathway coordinates cell growth, autophagy and metabolism. *Nat Cell Biol* **13**: 1016–1023. doi:10.1038/ncb2329
- Minn H, Lapela M, Klemi PJ, Grenman R, Leskinen S, Lindholm P, Bergman J, Eronen E, Haaparanta M, Joensuu H. 1997. Prediction of survival with fluorine-18-fluoro-deoxyglucose and PET in head and neck cancer. *J Nucl Med* **38**: 1907–1911.
- Mitsuishi Y, Taguchi K, Kawatani Y, Shibata T, Nukiwa T, Aburatani H, Yamamoto M, Motohashi H. 2012. Nrf2 redirects glucose and glutamine into anabolic pathways in metabolic reprogramming. *Cancer Cell* **22**: 66–79. doi:10.1016/j.ccr.2012.05.016
- Molina JR, Sun Y, Protopopova M, Gera S, Bandi M, Bristow C, McAfoos T, Morlacchi P, Ackroyd J, Agip AA, et al. 2018. An inhibitor of oxidative phosphorylation exploits cancer vulnerability. *Nat Med* **24**: 1036–1046. doi:10.1038/s41591-018-0052-4
- Momcilovic M, McMickle R, Abt E, Seki A, Simko SA, Magyar C, Stout DB, Fishbein MC, Walser TC, Dubinett SM, et al. 2015. Heightening energetic stress selectively targets LKB1-deficient non-small cell lung cancers. *Cancer Res* **75**: 4910–4922. doi:10.1158/0008-5472.CAN-15-0797
- Momcilovic M, Bailey ST, Lee JT, Fishbein MC, Magyar C, Braas D, Graeber T, Jackson NJ, Czernin J, Emberley E, et al. 2017. Targeted inhibition of EGFR and glutaminase induces metabolic crisis in EGFR mutant lung cancer. *Cell Rep* **18**: 601–610. doi:10.1016/j.celrep.2016.12.061

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- Momcilovic M, Bailey ST, Lee JT, Fishbein MC, Braas D, Go J, Graeber TG, Parlati F, Demo S, Li R, et al. 2018a. The GSK3 signaling axis regulates adaptive glutamine metabolism in lung squamous cell carcinoma. *Cancer Cell* **33**: 905–921.e5. doi:10.1016/j.ccell.2018.04.002
- Momcilovic M, Bailey ST, Lee JT, Zamilpa C, Jones A, Abdelhady G, Mansfield J, Francis KP, Shackelford DB. 2018b. Utilizing <sup>18</sup>F-FDG PET/CT imaging and quantitative histology to measure dynamic changes in the glucose metabolism in mouse models of lung cancer. *J Vis Exp* **137**: 57167. doi:10.3791/57167
- Momcilovic M, Jones A, Bailey ST, Waldmann CM, Li R, Lee JT, Abdelhady G, Gomez A, Holloway T, Schmid E, et al. 2019. In vivo imaging of mitochondrial membrane potential in non-small-cell lung cancer. *Nature* **575**: 380–384. doi:10.1038/s41586-019-1715-0
- Moreno P, Jiménez-Jiménez C, Garrido-Rodríguez M, Calderón-Santiago M, Molina S, Lara-Chica M, Priego-Capote F, Salvatierra A, Muñoz E, Calzado MA. 2018. Metabolic profiling of human lung tumor tissues—nucleotide metabolism as a candidate for therapeutic interventions and biomarkers. *Mol Oncol* **12**: 1778–1796. doi:10.1002/1878-0261.12369
- Muir A, Danai LV, Gui DY, Waingarten CY, Lewis CA, Vander Heiden MG. 2017. Environmental cystine drives glutamine anaplerosis and sensitizes cancer cells to glutaminase inhibition. *eLife* **6**: e27713. doi:10.7554/eLife.27713
- Mukundan S Jr, Ghaghada KB, Badea CT, Kao CY, Hedlund LW, Provenzale JM, Johnson GA, Chen E, Bellamkonda RV, Annapragada A. 2006. A liposomal nanoscale contrast agent for preclinical CT in mice. *AJR Am J Roentgenol* **186**: 300–307. doi:10.2214/AJR.05.0523
- Murray CW, Brady JJ, Tsai MK, Li C, Winters IP, Tang R, Andrejka L, Ma RK, Kunder CA, Chu P, et al. 2019. An LKB1-SIK axis suppresses lung tumor growth and controls differentiation. *Cancer Discov* **9**: 1590–1605. doi:10.1158/2159-8290.CD-18-1237
- Nakada D, Saunders TL, Morrison SJ. 2010. Lkb1 regulates cell cycle and energy metabolism in haematopoietic stem cells. *Nature* **468**: 653–658. doi:10.1038/nature09571
- O’Leary C, Gasper H, Sahin KB, Tang M, Kulasinghe A, Adams MN, Richard DJ, O’Byrne KJ. 2020. Epidermal growth factor receptor (EGFR)-mutated non-small-cell lung cancer (NSCLC). *Pharmaceuticals (Basel)* **13**: 273. doi:10.3390/ph13100273
- Oshida M, Uno K, Suzuki M, Nagashima T, Hashimoto H, Yagata H, Shishikura T, Imazeki K, Nakajima N. 1998. Predicting the prognoses of breast carcinoma patients with positron emission tomography using 2-deoxy-2-fluoro[<sup>18</sup>F]-D-glucose. *Cancer* **82**: 2227–2234. doi:10.1002/(SICI)1097-0142(19980601)82:11<2227::AID-CNCR18>3.0.CO;2-W
- Osoegawa A, Kometani T, Nosaki K, Ondo K, Hamatake M, Hirai F, Seto T, Sugio K, Ichinose Y. 2011. LKB1 mutations frequently detected in mucinous bronchioloalveolar carcinoma. *Jpn J Clin Oncol* **41**: 1132–1137. doi:10.1093/jcco/hyr102
- Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, Singh B, Heelan R, Rusch V, Fulton L, et al. 2004. EGF receptor gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci* **101**: 13306–13311. doi:10.1073/pnas.0405220101
- Papadimitrakopoulou V, Lee JJ, Wistuba II, Tsao AS, Fossella FV, Kalhor N, Gupta S, Byers LA, Izzo JG, Gettinger SN, et al. 2016. The BATTLE-2 study: a biomarker-integrated targeted therapy study in previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* **34**: 3638–3647. doi:10.1200/JCO.2015.66.0084
- Parker SJ, Svensson RU, Divakaruni AS, Lefebvre AE, Murphy AN, Shaw RJ, Metallo CM. 2017. LKB1 promotes metabolic flexibility in response to energy stress. *Metab Eng* **43**: 208–217. doi:10.1016/j.ymben.2016.12.010
- Pirotte B, Goldman S, Massager N, David P, Wikler D, Vandesteene A, Salmon I, Brotchi J, Levivier M. 2004. Comparison of <sup>18</sup>F-FDG and <sup>11</sup>C-methionine for PET-guided stereotactic brain biopsy of gliomas. *J Nucl Med* **45**: 1293–1298.
- Ploessl K, Wang L, Lieberman BP, Qu W, Kung HF. 2012. Comparative evaluation of <sup>18</sup>F-labeled glutamic acid and glutamine as tumor metabolic imaging agents. *J Nucl Med* **53**: 1616–1624. doi:10.2967/jnumed.111.101279
- Plunkett W, Huang P, Xu YZ, Heinemann V, Grunewald R, Gandhi V. 1995. Gemcitabine: metabolism, mechanisms of action, and self-potential. *Semin Oncol* **22**: 3–10.
- Politi K, Zakowski MF, Fan PD, Schonfeld EA, Pao W, Varmus HE. 2006. Lung adenocarcinomas induced in mice by mutant EGF receptors found in human lung cancers respond to a tyrosine kinase inhibitor or to down-regulation of the receptors. *Genes Dev* **20**: 1496–1510. doi:10.1101/gad.1417406
- Radu CG, Shu CJ, Nair-Gill E, Shelly SM, Barrio JR, Satyamarthy N, Phelps ME, Witte ON. 2008. Molecular imaging of lymphoid organs and immune activation by positron emission tomography with a new [<sup>18</sup>F]-labeled 2'-deoxycytidine analog. *Nat Med* **14**: 783–788. doi:10.1038/nm1724
- Rasey JS, Grierson JR, Wiens LW, Kolb PD, Schwartz JL. 2002. Validation of FLT uptake as a measure of thymidine kinase-1 activity in A549 carcinoma cells. *J Nucl Med* **43**: 1210–1217.
- Robitaille AM, Christen S, Shimobayashi M, Cornu M, Fava LL, Moes S, Prescianotto-Baschong C, Sauer U, Jenoe P, Hall MN. 2013. Quantitative phosphoproteomics reveal mTORC1 activates de novo pyrimidine synthesis. *Science* **339**: 1320–1323. doi:10.1126/science.1228771
- Roczniak-Ferguson A, Petit CS, Froehlich F, Qian S, Ky J, Angarola B, Walther TC, Ferguson SM. 2012. The transcription factor TFEB links mTORC1 signaling to transcriptional control of lysosome homeostasis. *Sci Signal* **5**: ra42. doi:10.1126/scisignal.2002790
- Romero R, Sayin VI, Davidson SM, Bauer MR, Singh SX, LeBoeuf SE, Karakousi TR, Ellis DC, Bhutkar A, Sanchez-Rivera FJ, et al. 2017. Keap1 loss promotes Kras-driven lung cancer and results in dependence on glutaminolysis. *Nat Med* **23**: 1362–1368. doi:10.1038/nm.4407
- Romero R, Sánchez-Rivera FJ, Westcott PMK, Mercer KL, Bhutkar A, Muir A, González Robles TJ, Lamboy Rodríguez S, Liao LZ, Ng SR, et al. 2020. Keap1 mutation renders lung adenocarcinomas dependent on Slc33a1. *Nature Cancer* **1**: 589–602. doi:10.1038/s43018-020-0071-1
- Sancak Y, Peterson TR, Shaul YD, Lindquist RA, Thoreen CC, Bar-Peled L, Sabatini DM. 2008. The Rag GTPases





- bind raptor and mediate amino acid signaling to mTORC1. *Science* **320**: 1496–1501. doi:10.1126/science.1157535
- Sancak Y, Bar-Peled L, Zoncu R, Markhard AL, Nada S, Sabatini DM. 2010. Ragulator-Rag complex targets mTORC1 to the lysosomal surface and is necessary for its activation by amino acids. *Cell* **141**: 290–303. doi:10.1016/j.cell.2010.02.024
- Sanchez-Cespedes M, Parrella P, Esteller M, Nomoto S, Trink B, Engles JM, Westra WH, Herman JG, Sidransky D. 2002. Inactivation of LKB1/STK11 is a common event in adenocarcinomas of the lung. *Cancer Res* **62**: 3659–3662.
- Sasaki H, Sato H, Kuriyama-Matsumura K, Sato K, Maebara K, Wang H, Tamba M, Itoh K, Yamamoto M, Bannai S. 2002. Electrophile response element-mediated induction of the cystine/glutamate exchange transporter gene expression. *J Biol Chem* **277**: 44765–44771. doi:10.1074/jbc.M208704200
- Sayin VI, LeBoeuf SE, Singh SX, Davidson SM, Biancur D, Guzelhan BS, Alvarez SW, Wu WL, Karakousi TR, Zavit-sanou AM, et al. 2017. Activation of the NRF2 antioxidant program generates an imbalance in central carbon metabolism in cancer. *eLife* **6**: e28083. doi:10.7554/eLife.28083
- Scafoglio C, Hirayama BA, Kepe V, Liu J, Ghezzi C, Saty-murthy N, Moatamed NA, Huang J, Koepsell H, Barrio JR, et al. 2015. Functional expression of sodium-glucose transporters in cancer. *Proc Natl Acad Sci* **112**: E4111–E4119. doi:10.1073/pnas.1511698112
- Scafoglio CR, Villegas B, Abdelhady G, Bailey ST, Liu J, Shirali AS, Wallace WD, Magyar CE, Grogan TR, Elashoff D, et al. 2018. Sodium-glucose transporter 2 is a diagnostic and therapeutic target for early-stage lung adenocarcinoma. *Sci Transl Med* **10**: eaat5933. doi:10.1126/scitranslmed.aat5933
- Schulte ML, Hight MR, Ayers GD, Liu Q, Shyr Y, Washington MK, Manning HC. 2017. Non-invasive glutamine PET reflects pharmacological inhibition of BRAFV600E in vivo. *Mol Imaging Biol* **19**: 421–428. doi:10.1007/s11307-016-1008-z
- Schulte ML, Fu A, Zhao P, Li J, Geng L, Smith ST, Kondo J, Coffey RJ, Johnson MO, Rathmell JC, et al. 2018. Pharmacological blockade of ASCT2-dependent glutamine transport leads to antitumor efficacy in preclinical models. *Nat Med* **24**: 194–202. doi:10.1038/nm.4464
- Sellers K, Fox MP, Bousamra M II, Slone SP, Higashi RM, Miller DM, Wang Y, Yan J, Yuneva MO, Deshpande R, et al. 2015. Pyruvate carboxylase is critical for non-small-cell lung cancer proliferation. *J Clin Invest* **125**: 687–698. doi:10.1172/JCI72873
- Settembre C, Zoncu R, Medina DL, Vetrini F, Erdin S, Erdin S, Huynh T, Ferron M, Karsenty G, Vellard MC, et al. 2012. A lysosome-to-nucleus signalling mechanism senses and regulates the lysosome via mTOR and TFEB. *EMBO J* **31**: 1095–1108. doi:10.1038/emboj.2012.32
- Shackelford DB, Shaw RJ. 2009. The LKB1-AMPK pathway: metabolism and growth control in tumour suppression. *Nat Rev Cancer* **9**: 563–575. doi:10.1038/nrc2676
- Shackelford DB, Vasquez DS, Corbeil J, Wu S, Leblanc M, Wu CL, Vera DR, Shaw RJ. 2009. mTOR and HIF-1 $\alpha$ -mediated tumor metabolism in an LKB1 mouse model of Peutz–Jeghers syndrome. *Proc Natl Acad Sci* **106**: 11137–11142. doi:10.1073/pnas.0900465106
- Shackelford DB, Abt E, Gerken L, Vasquez DS, Seki A, Leblanc M, Wei L, Fishbein MC, Czernin J, Mischel PS, et al. 2013. LKB1 inactivation dictates therapeutic response of non-small cell lung cancer to the metabolism drug phenformin. *Cancer Cell* **23**: 143–158. doi:10.1016/j.ccr.2012.12.008
- Shaw RJ, Bardeesy N, Manning BD, Lopez L, Kosmatka M, DePinho RA, Cantley LC. 2004a. The LKB1 tumor suppressor negatively regulates mTOR signaling. *Cancer Cell* **6**: 91–99. doi:10.1016/j.ccr.2004.06.007
- Shaw RJ, Kosmatka M, Bardeesy N, Hurley RL, Witters LA, DePinho RA, Cantley LC. 2004b. The tumor suppressor LKB1 kinase directly activates AMP-activated kinase and regulates apoptosis in response to energy stress. *Proc Natl Acad Sci* **101**: 3329–3335. doi:10.1073/pnas.0308061100
- Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, Heeroma K, Itoh Y, Cornelio G, Yang PC. 2014. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thoracic Oncol* **9**: 154–162. doi:10.1097/JTO.0000000000000033
- Shi D, Cai G, Peng J, Li D, Li X, Xu Y, Cai S. 2015. The preoperative SUVmax for <sup>18</sup>F-FDG uptake predicts survival in patients with colorectal cancer. *BMC Cancer* **15**: 991. doi:10.1186/s12885-015-1991-5
- Shields AF, Grierson JR, Dohmen BM, Machulla HJ, Stayanoff JC, Lawhorn-Crews JM, Obradovich JE, Muzik O, Mangner TJ. 1998. Imaging proliferation in vivo with [<sup>18</sup>F]FLT and positron emission tomography. *Nat Med* **4**: 1334–1336. doi:10.1038/3337
- Shiomi S, Nishiguchi S, Ishizu H, Iwata Y, Sasaki N, Tamori A, Habu D, Takeda T, Kubo S, Ochi H. 2001. Usefulness of positron emission tomography with fluorine-18-fluorodeoxyglucose for predicting outcome in patients with hepatocellular carcinoma. *Am J Gastroenterol* **96**: 1877–1880. doi:10.1111/j.1572-0241.2001.03888.x
- Singh A, Happel C, Manna SK, Acquaah-Mensah G, Carrero J, Kumar S, Nasipuri P, Krausz KW, Wakabayashi N, Dewi R, et al. 2013. Transcription factor NRF2 regulates miR-1 and miR-206 to drive tumorigenesis. *J Clin Invest* **123**: 2921–2934. doi:10.1172/JCI66353
- Singh A, Ruiz C, Bhalla K, Haley JA, Li QK, Acquaah-Mensah G, Montal E, Sudini KR, Skoulidis F, Wistuba II, et al. 2018. De novo lipogenesis represents a therapeutic target in mutant Kras non-small cell lung cancer. *FASEB J* **32**: fj201800204.
- Skoulidis F, Goldberg ME, Greenawalt DM, Hellmann MD, Awad MM, Gainor JF, Schrock AB, Hartmaier RJ, Trabucco SE, Gay L, et al. 2018. *STK11/LKB1* mutations and PD-1 inhibitor resistance in *KRAS*-mutant lung adenocarcinoma. *Cancer Discov* **8**: 822–835. doi:10.1158/2159-8290.CD-18-0099
- Sordella R, Bell DW, Haber DA, Settleman J. 2004. Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. *Science* **305**: 1163–1167. doi:10.1126/science.1101637
- Soucek L, Whitfield JR, Sodir NM, Masso-Valles D, Serrano E, Karnezis AN, Swigart LB, Evan GI. 2013. Inhibition of Myc family proteins eradicates KRas-driven lung cancer

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- in mice. *Genes Dev* **27**: 504–513. doi:10.1101/gad.205542.112
- Stewart PA, Parapatics K, Welsh EA, Müller AC, Cao H, Fang B, Koomen JM, Eschrich SA, Bennett KL, Haura EB. 2015. A pilot proteogenomic study with data integration identifies MCT1 and GLUT1 as prognostic markers in lung adenocarcinoma. *PLoS ONE* **10**: e0142162. doi:10.1371/journal.pone.0142162
- Su H, Bodenstern C, Dumont RA, Seimille Y, Dubinett S, Phelps ME, Herschman H, Czernin J, Weber W. 2006. Monitoring tumor glucose utilization by positron emission tomography for the prediction of treatment response to epidermal growth factor receptor kinase inhibitors. *Clin Cancer Res* **12**: 5659–5667. doi:10.1158/1078-0432.CCR-06-0368
- Sullivan MR, Danai LV, Lewis CA, Chan SH, Gui DY, Kunchok T, Dennstedt EA, Vander Heiden MG, Muir A. 2019. Quantification of microenvironmental metabolites in murine cancers reveals determinants of tumor nutrient availability. *eLife* **8**: e44235. doi:10.7554/eLife.44235
- Sun S, Schiller JH, Gazdar AF. 2007. Lung cancer in never smokers—a different disease. *Nat Rev Cancer* **7**: 778–790. doi:10.1038/nrc2190
- Sutherland KD, Proost N, Brouns I, Adriaensen D, Song JY, Berns A. 2011. Cell of origin of small cell lung cancer: inactivation of Trp53 and Rb1 in distinct cell types of adult mouse lung. *Cancer Cell* **19**: 754–764. doi:10.1016/j.ccr.2011.04.019
- Svensson RU, Parker SJ, Eichner LJ, Kolar MJ, Wallace M, Brun SN, Lombardo PS, Van Nostrand JL, Hutchins A, Vera L, et al. 2016. Inhibition of acetyl-CoA carboxylase suppresses fatty acid synthesis and tumor growth of non-small-cell lung cancer in preclinical models. *Nat Med* **22**: 1108–1119. doi:10.1038/nm.4181
- Takahashi R, Hirata H, Tachibana I, Shimosegawa E, Inoue A, Nagatomo I, Takeda Y, Kida H, Goya S, Kijima T, et al. 2012. Early [<sup>18</sup>F]fluorodeoxyglucose positron emission tomography at two days of gefitinib treatment predicts clinical outcome in patients with adenocarcinoma of the lung. *Clin Cancer Res* **18**: 220–228. doi:10.1158/1078-0432.CCR-11-0868
- Testa C, Pultrone C, Manners DN, Schiavina R, Lodi R. 2016. Metabolic imaging in prostate cancer: where we are. *Front Oncol* **6**: 225. doi:10.3389/fonc.2016.00225
- The Cancer Genome Atlas Research Network. 2012. Comprehensive genomic characterization of squamous cell lung cancers. *Nature* **489**: 519–525. doi:10.1038/nature11404
- The Cancer Genome Atlas Research Network. 2014. Comprehensive molecular profiling of lung adenocarcinoma. *Nature* **511**: 543–550. doi:10.1038/nature13385
- Timmerman LA, Holton T, Yuneva M, Louie RJ, Padró M, Daemen A, Hu M, Chan DA, Ethier SP, van 't Veer LJ, et al. 2013. Glutamine sensitivity analysis identifies the xCT antiporter as a common triple-negative breast tumor therapeutic target. *Cancer Cell* **24**: 450–465. doi:10.1016/j.ccr.2013.08.020
- Toyama EQ, Herzig S, Courchet J, Lewis TL, Loson OC, Hellberg K, Young NP, Chen H, Polleux F, Chan DC, et al. 2016. Metabolism. AMP-activated protein kinase mediates mitochondrial fission in response to energy stress. *Science* **351**: 275–281. doi:10.1126/science.aab4138
- Turrell FK, Kerr EM, Gao M, Thorpe H, Doherty GJ, Cridge J, Shorthouse D, Speed A, Samarajiwa S, Hall BA, et al. 2017. Lung tumors with distinct p53 mutations respond similarly to p53 targeted therapy but exhibit genotype-specific statin sensitivity. *Genes Dev* **31**: 1339–1353. doi:10.1101/gad.298463.117
- Vande Voorde J, Ackermann T, Pfetzer N, Sumpton D, Mackay G, Kalna G, Nixon C, Blyth K, Gottlieb E, Tardito S. 2019. Improving the metabolic fidelity of cancer models with a physiological cell culture medium. *Sci Adv* **5**: eaau7314. doi:10.1126/sciadv.aau7314
- Van Laere K, Ceyssens S, Van Calenbergh F, de Groot T, Menten J, Flamen P, Bormans G, Mortelmans L. 2005. Direct comparison of <sup>18</sup>F-FDG and <sup>11</sup>C-methionine PET in suspected recurrence of glioma: sensitivity, inter-observer variability and prognostic value. *Eur J Nucl Med Mol Imaging* **32**: 39–51. doi:10.1007/s00259-004-1564-3
- Vavere AL, Kridel SJ, Wheeler FB, Lewis JS. 2008. 1-<sup>11</sup>C-acetate as a PET radiopharmaceutical for imaging fatty acid synthase expression in prostate cancer. *J Nucl Med* **49**: 327–334. doi:10.2967/jnumed.107.046672
- Venneti S, Dunphy MP, Zhang H, Pitter KL, Zanzonico P, Campos C, Carlin SD, La Rocca G, Lyashchenko S, Ploessl K, et al. 2015. Glutamine-based PET imaging facilitates enhanced metabolic evaluation of gliomas in vivo. *Sci Transl Med* **7**: 274ra17. doi:10.1126/scitranslmed.aaa1009
- Vernieri C, Signorelli D, Galli G, Ganzinelli M, Moro M, Fabbri A, Tamborini E, Marabese M, Caiola E, Brogginini M, et al. 2019. Exploiting fasting-mimicking diet and metformin to improve the efficacy of platinum-pemetrexed chemotherapy in advanced LKB1-inactivated lung adenocarcinoma: the FAME trial. *Clin Lung Cancer* **20**: e413–e417. doi:10.1016/j.clcc.2018.12.011
- Vriens K, Christen S, Parik S, Broekaert D, Yoshinaga K, Talebi A, Dehairs J, Escalona-Noguero C, Schmieder R, Cornfield T, et al. 2019. Evidence for an alternative fatty acid desaturation pathway increasing cancer plasticity. *Nature* **566**: 403–406. doi:10.1038/s41586-019-0904-1
- Waldhart AN, Dykstra H, Peck AS, Boguslawski EA, Madaj ZB, Wen J, Veldkamp K, Hollowell M, Zheng B, Cantley LC, et al. 2017. Phosphorylation of TXNIP by AKT mediates acute influx of glucose in response to insulin. *Cell Rep* **19**: 2005–2013. doi:10.1016/j.celrep.2017.05.041
- Wang S, Tsun ZY, Wolfson RL, Shen K, Wyant GA, Plovnick ME, Yuan ED, Jones TD, Chantranupong L, Comb W, et al. 2015. Metabolism. Lysosomal amino acid transporter SLC38A9 signals arginine sufficiency to mTORC1. *Science* **347**: 188–194. doi:10.1126/science.1257132
- Wang Q, Xu L, Wang G, Chen L, Li C, Jiang X, Gao H, Yang B, Tian W. 2020. Prognostic and clinicopathological significance of NRF2 expression in non-small cell lung cancer: a meta-analysis. *PLoS ONE* **15**: e0241241. doi:10.1371/journal.pone.0241241
- Wangpaichitr M, Wu C, Li YY, Nguyen DJM, Kandemir H, Shah S, Chen S, Feun LG, Prince JS, Kuo MT, et al. 2017. Exploiting ROS and metabolic differences to kill cisplatin resistant lung cancer. *Oncotarget* **8**: 49275–49292. doi:10.18632/oncotarget.17568
- Ward NP, Kang YP, Falzone A, Boyle TA, DeNicola GM. 2020. Nicotinamide nucleotide transhydrogenase regulates mitochondrial metabolism in NSCLC through



- maintenance of Fe-S protein function. *J Exp Med* **217**: e20191689. doi:10.1084/jem.20191689
- Weinberg F, Hamanaka R, Wheaton WW, Weinberg S, Joseph J, Lopez M, Kalyanaraman B, Mutlu GM, Budinger GR, Chandel NS. 2010. Mitochondrial metabolism and ROS generation are essential for Kras-mediated tumorigenicity. *Proc Natl Acad Sci* **107**: 8788–8793. doi:10.1073/pnas.1003428107
- Wibmer AG, Burger IA, Sala E, Hricak H, Weber WA, Vargas HA. 2016. Molecular imaging of prostate cancer. *Radiographics* **36**: 142–159. doi:10.1148/rg.2016150059
- Wilkerson MD, Yin X, Walter V, Zhao N, Cabanski CR, Hayward MC, Miller CR, Socinski MA, Parsons AM, Thorne LB, et al. 2012. Differential pathogenesis of lung adenocarcinoma subtypes involving sequence mutations, copy number, chromosomal instability, and methylation. *PLoS ONE* **7**: e36530. doi:10.1371/journal.pone.0036530
- Wise DR, DeBerardinis RJ, Mancuso A, Sayed N, Zhang XY, Pfeiffer HK, Nissim I, Daikhin E, Yudkoff M, McMahon SB, et al. 2008. Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. *Proc Natl Acad Sci* **105**: 18782–18787. doi:10.1073/pnas.0810199105
- Wu KC, Cui JY, Klaassen CD. 2011. Beneficial role of Nrf2 in regulating NADPH generation and consumption. *Toxicol Sci* **123**: 590–600. doi:10.1093/toxsci/kfr183
- Wu Z, Zha Z, Li G, Lieberman BP, Choi SR, Ploessl K, Kung HF. 2014. [<sup>18</sup>F](2S,4S)-4-(3-Fluoropropyl)glutamine as a tumor imaging agent. *Mol Pharm* **11**: 3852–3866. doi:10.1021/mp500236y
- Wu HB, Wang L, Wang QS, Han YJ, Li HS, Zhou WL, Tian Y. 2015. Adenocarcinoma with BAC features presented as the nonsolid nodule is prone to be false-negative on <sup>18</sup>F-FDG PET/CT. *Biomed Res Int* **2015**: 243681.
- Yap CS, Schiepers C, Fishbein MC, Phelps ME, Czernin J. 2002. FDG-PET imaging in lung cancer: how sensitive is it for bronchioloalveolar carcinoma? *Eur J Nucl Med Mol Imaging* **29**: 1166–1173. doi:10.1007/s00259-002-0853-y
- Yip C, Blower PJ, Goh V, Landau DB, Cook GJ. 2015. Molecular imaging of hypoxia in non-small-cell lung cancer. *Eur J Nucl Med Mol Imaging* **42**: 956–976. doi:10.1007/s00259-015-3009-6
- Yoshimoto M, Waki A, Yonekura Y, Sadato N, Murata T, Omata N, Takahashi N, Welch MJ, Fujibayashi Y. 2001. Characterization of acetate metabolism in tumor cells in relation to cell proliferation: acetate metabolism in tumor cells. *Nucl Med Biol* **28**: 117–122. doi:10.1016/S0969-8051(00)00195-5
- Yu AS, Hirayama BA, Timbol G, Liu J, Basarah E, Kepe V, Satyamurthy N, Huang SC, Wright EM, Barrio JR. 2010. Functional expression of SGLTs in rat brain. *Am J Physiol Cell Physiol* **299**: C1277–C1284. doi:10.1152/ajpcell.00296.2010
- Yu AS, Hirayama BA, Timbol G, Liu J, Diez-Sampedro A, Kepe V, Satyamurthy N, Huang SC, Wright EM, Barrio JR. 2013. Regional distribution of SGLT activity in rat brain in vivo. *Am J Physiol Cell Physiol* **304**: C240–C247. doi:10.1152/ajpcell.00317.2012
- Zhang X, Gureasko J, Shen K, Cole PA, Kuriyan J. 2006. An allosteric mechanism for activation of the kinase domain of epidermal growth factor receptor. *Cell* **125**: 1137–1149. doi:10.1016/j.cell.2006.05.013
- Zhou R, Pantel AR, Li S, Lieberman BP, Ploessl K, Choi H, Blankemeyer E, Lee H, Kung HF, Mach RH, et al. 2017. [<sup>18</sup>F](2S,4R)4-Fluoroglutamine PET detects glutamine pool size changes in triple-negative breast cancer in response to glutaminase inhibition. *Cancer Res* **77**: 1476–1484. doi:10.1158/0008-5472.CAN-16-1945



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