JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 6, NO. 8, 2021

STATE-OF-THE-ART REVIEW

Cardio-Oncology

Understanding the Intersections Between Cardiac Metabolism and Cancer Biology

Anja Karlstaedt, MD, PhD,[a,b] Matthew Barrett, BS,[c] Ray Hu, MD, MTR,[d] Seth Thomas Gammons, PhD,[e] Bonnie Ky, MD, MSCE[c,d]

HIGHLIGHTS

- **Cancer cells can promote metabolic remodeling in the heart.**
- **Metabolic changes provide opportunities for novel treatment strategies to prevent heart failure and monitor disease progression through new imaging techniques.**
- **Translational biomarker and imaging studies are needed to further understand the impact of cancer cell biology on the heart.**

SUMMARY

An important priority in the cardiovascular care of oncology patients is to reduce morbidity and mortality, and improve the quality of life in cancer survivors through cross-disciplinary efforts. The rate of survival in cancer patients has improved dramatically over the past decades. Nonetheless, survivors may be more likely to die from cardiovascular disease in the long term, secondary, not only to the potential toxicity of cancer therapeutics, but also to the biology of cancer. In this context, efforts from basic and translational studies are crucial to understanding the molecular mechanisms causal to cardiovascular disease in cancer patients and survivors, and identifying new therapeutic targets that may prevent and treat both diseases. This review aims to highlight our current understanding of the metabolic interaction between cancer and the heart, including potential therapeutic targets. An overview of imaging techniques that can support both research studies and clinical management is also provided. Finally, this review highlights opportunities and challenges that are necessary to advance our understanding of metabolism in the context of cardio-oncology.
(J Am Coll Cardiol Basic Trans Science 2021;6:705–718) © 2021 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Metabolic reprogramming is a hallmark of both cancer and cardiac adaptation. In the heart, cardiac cells adapt to different types of stress (eg, hydrodynamic, oxygen, nutrient) by optimizing the utilization of nutrients and consequently acquiring metabolic adaptation (1,2). Some of these metabolic alterations precede structural remodeling by initiating the expression of specific

From the [a]Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA; [b]Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, California, USA; [c]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [d]Departments of Medicine and Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; and the [e]Department of Cancer Systems Imaging, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received March 15, 2021; revised manuscript received May 21, 2021, accepted May 23, 2021.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2021.05.008

ABBREVIATIONS AND ACRONYMS

[^{18}F]FDG = 2-deoxy-2-[fluorine-18]fluoro-D-glucose

^{99m}Tc-MIBI = ^{99m}technetium-sestamibi

α-KG = α-ketoglutarate

CVD = cardiovascular disease

D2-HG = D-2-hydroxyglutarate

FAO = fatty acid oxidation

FASN = fatty acid synthase

GLS = glutaminase

HF = heart failure

IDH = isocitrate dehydrogenase

IGF = insulin-like growth factor

MCT1 = monocarboxylate transporter 1

MRS = magnetic resonance spectroscopy

PTM = post-translational modification

PI3K = insulin-activated phosphoinositide-3-kinase

PDH = pyruvate dehydrogenase

PET = positron emission tomography

SGLT2 = sodium glucose co-transporter 2

TRF = time-restricted feeding

gene programs and promoting protein synthesis and growth (3-6), which allow for maintenance of cardiac contraction and cell survival. In the context of cancer, the heart is further challenged by a unique combination of extrinsic factors that is defined by the biology of the tumor and potentially cardiotoxic treatment exposures.

Recent insights arising from advanced analytic techniques in the pathogenesis of cardiovascular diseases (CVD) in cancer patients and survivors have improved our understanding of how tumors and cancer treatments may adversely affect the heart (7-10). These data contribute multiple lines of evidence that suggest that metabolic reprogramming plays an important role in cardiac adaptation during cancer. First, cardiac cells share many of the same stress response pathways and metabolic strategies with cancer cells, suggesting that metabolic alterations during tumor progression impact nonmalignant tissue. Second, chemotherapeutics targeting metabolic vulnerabilities in tumors often adversely affect the heart. In fact, metabolic phenotypes and liabilities in cancers evolve as the disease progresses, resulting in variable efficacy of therapies and severity of cardiovascular side effects. For example, inhibition of insulin-activated phosphoinositide-3-kinase (PI3K) has been associated with adverse systemic effects in patients, depending on the degree of insulin resistance in pancreatic tumor patients (11). Third, cardiovascular events accelerate cancer disease and progression, supporting a cross-communication between nonmalignant and malignant tissue (10). Understanding the complex interactions between cardiac cells and cancer cells can enable the development of new therapeutic strategies and yield improvements in mortality from both CVD and cancer. This review focuses on recent conceptual and technological advances in understanding the impact of cancer biology on cardiac metabolism and how these findings can inform the management and treatment of cancer patients and survivors from a cardio-oncology perspective.

CVD IN CANCER PATIENTS AND SURVIVORS

Over the past few decades, advances in cancer treatment have allowed for considerable improvements in survival for patients with cancer. Reflective of this progress, the 5-year survival for all pediatric cancer types is now >80% compared with 20% just 3 decades ago (12). Despite these advancements, survivors are at a higher risk of premature mortality and chronic diseases as a direct consequence of their cancer and their cancer therapy (13). Compared with their siblings, survivors are 10 times more likely to die from CVD and 15 times more likely to develop heart failure (HF) (12,14-16). In fact, 73% of survivors will develop at least 1 chronic physical health condition, and 42% will develop a severe, life-threatening, or disabling condition or die from a chronic condition (12,17,18). Enmeshed within the advances in cancer treatment are the unintended consequences of cancer treatment-related cardiotoxicity, with notable implicated therapies including anthracyclines, radiation therapy, tyrosine kinase inhibitors, and immune therapy (13). Patients who have been treated for cancer are at increased risk of the development of CVD, including HF, coronary disease, and arrhythmias. Consequentially, CVD has emerged as a leading cause of morbidity and mortality in survivors of cancer. The development of CVD is driven by risk factors (eg, diabetes, hypertension), genetic predisposition, and direct and indirect toxicities of therapeutics, as well as the biology of the cancer itself (13).

Potential factors that contribute to the development of overt cardiotoxicity include cancer therapy exposure, as well as host and environmental factors, including prevalent and incident risk factors. However, a comprehensive understanding of the mechanisms and the management of established CVD secondary to cancer therapies remains unclear (19,20). This in turn underscores the need for a more robust intersection between cardiology and oncology to elucidate the mechanisms involved in the development of cardiotoxicity and subsequently establish more effective and stringent surveillance and treatment models.

CARDIOMETABOLIC ADAPTATION IN CANCER

There is increasing evidence that the crosstalk between cancer cells and the heart at a molecular level contributes to incident CVD risk in cancer patients (7,21-23). Metabolic reprogramming in tumors is driven through multiple mechanisms; moreover, mitochondrial metabolism plays a critical role in the regulation of tumorigenesis (24). Mutations in mitochondrial enzymes (eg, succinate dehydrogenase, fumarate hydratase, isocitrate dehydrogenase) result in the production of oncometabolites. Transcriptional regulators of mitochondrial function are often mutated in tumors including c-MYC (25), K-RAS (26), PI3K, and p53 signaling pathways (27,28). Together

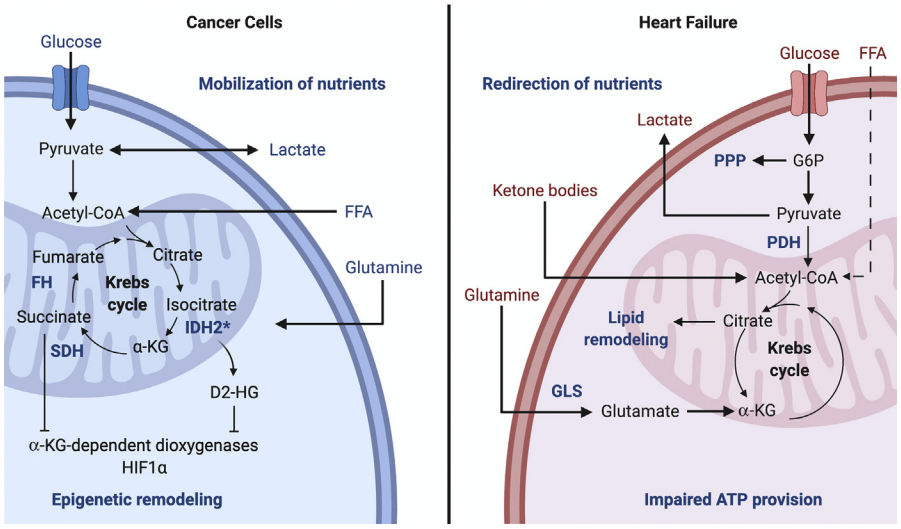
these factors contribute to tumor cell transformation and progression. The metabolic properties of tumors change as the disease progresses, and most malignancies demonstrate a vast metabolic heterogeneity even within the same tumor (29,30). Moreover, the metabolic phenotype of a tumor impacts both the local and systemic environment. Recent findings indicate that tumors can impair glucose homeostasis (31,32), sleep quality (33), and T-cell function (34). Similarly, the heart activates mechanisms to resist stress imposed by the tumors that lead to selective metabolic vulnerabilities depending on the genetic properties of the tumor.

In particular, the link between the epigenome and intermediary metabolism may provide mechanistic insights into both cancer and CVD progression. Epigenetic modifications are covalent post-translational modifications (PTMs) of DNA and histones that affect DNA accessibility and chromatin structure (35,36), thus directly affecting gene expression (37). PTMs range from small chemical groups, such as methyl groups, acetyl groups, or phosphate groups, to more complex oligosaccharide structures that require metabolic precursors derived from intermediary metabolism. Glycosylation represents one of the most widely studied and complex PTMs, which affects protein function, folding, localization, and stability. The oligosaccharide structures are derived from monosaccharides, including galactose, fucose, mannose, *N*-acetylglucosamine, and sialic acid, resulting in seemingly infinite combinations that regulate fundamental biological processes, including cell trafficking, signal transduction, cell differentiation, and immunity (38-42). Our understanding of metabolic competition and cooperation within the tumor microenvironment is limited. Recent observations that mutations in hematopoietic stem cells are associated with CVD and epidemiologic evidence suggest that cardiac pathologies are not exclusively a side effect of cancer therapy (16,22). How cancer cell metabolism affects tumor progression and cardiac remodeling at the molecular level is a focus of ongoing basic and translational research efforts.

Multiple studies of leukemia survivors have suggested a markedly increased risk for HF (43-44). Metabolism is at the center in the pathogenesis of cancer and HF, making it an attractive focal point for further our understanding of the intersection between cancer and CVD, and to inform the development of new therapeutic strategies that target the tumor while protecting the heart. About 20% of acute myeloid leukemia patients harbor isocitrate dehydrogenase 2 (IDH2) mutations, which are associated with metabolic reprogramming and reduced overall patient survival (45,46). IDH1 and IDH2 catalyze the reversible NADPH-dependent oxidative decarboxylation of isocitrate to α-ketoglutarate (KG). In acute myeloid leukemia, a missense mutation of *IDH1* or *-2* at codon R140Q or R172K leads to the neomorphic activity of reducing α-KG to its structural homolog, the oncometabolite D-2-hydroxyglutarate (D2-HG), a metabolite that is normally found at very low concentrations in the blood (**Figure 1**) (47,48). Similarly, deficiency of D2-HG dehydrogenase (D2HGDH), which converts D2-HG to α-KG, causes a severe metabolic disorder, D2-hydroxyglutaric aciduria, with excessive production of D2-HG. In both IDH and D2HGDH mutations, the resultant high levels of D2-HG are associated with a wide spectrum of clinical disorders including dilated cardiomyopathy and cardiac hypertrophy (23,49-51). Recent preclinical studies indicate that D2-HG suppresses cardiac energy provision through inhibition of α-KG dehydrogenase activity (7). The oncometabolic stress causes both heart and skeletal muscle atrophy in mice and promotes cardiac contractile dysfunction ex vivo (7). Further, intracellular accumulation of succinate and acetyl-CoA cause epigenetic changes indicating that oncometabolic dysregulation may contribute to structural remodeling in the heart during cancer.

Succinate and fumarate have also been recognized as oncometabolites that are primarily produced in cancer types with mutations of succinate dehydrogenase (eg, paraglanglioma, renal cell carcinoma) and fumarate hydratase (eg, leiomyomatosis, renal cell carcinoma) (52-54). Similar to D2-HG, succinate inhibits several α-ketoglutarate dioxygenases and induces pseudohypoxia pathways and genomic hypermethylation (**Figure 1**) (7,22,55,56). Similarly, mutations of the fumarate hydratase cause increased flux through the argininosuccinate lyase and increased production of argininosuccinate from fumarate and arginine (52). Both metabolites are metabolic signals for stress, hypoxia, and inflammation. Succinate serves as a metabolite in innate immune signaling and activation of macrophages through HIF1-α signaling pathways (**Figure 1**) (57). Elevated levels of succinate in the blood can be observed with CV risk factors and disease states including hypertension (58), ischemic heart disease (54,59), and type 2 diabetes (58,60). Recent studies also suggest that the immune response during cancer facilitates adverse remodeling, not only in the tumor microenvironment, but also in other organ systems (61,62). How immune cells contribute to cardiac remodeling in the context of cancer is still unknown and the focus of current studies.

FIGURE 1 Metabolic Targets in HF and Cancer



Key nutrients and their pathways affect how cardiomyocytes and cancer cells use metabolism to maximize ATP provision, macromolecule synthesis, redox regulation. Key reactions in central carbon metabolism shown, including the Krebs cycle, are involved in metabolic adaptation. Enzymatic targets for pharmacologic modulation are shown for reference. Created with BioRender.com. ATP = adenosine triphosphate; FFA = free fatty acids; FH = fumarate hydratase; GLS = glutaminase; HF = heart failure; IDH2 = isocitrate dehydrogenase 2; KG = ketoglutarate; PDH = pyruvate dehydrogenase; SDH = succinate dehydrogenase.

Cardiometabolic derangements or systemic inflammation can occur due to the presence of cancer itself and may lead to increased risk factors in patients even before treatment (63,64). In this context, muscle wasting, and cachexia have been recognized as a direct consequence of the tumor burden with a strong metabolic component due to decreased nutrient intake, systemic metabolic dysfunction, inflammation, and increased energy expenditure (65,66). The genetic and metabolic basis for the development of cancer cachexia remains elusive. Recent studies suggest that the crosstalk between cancer cells and other organ systems (eg, muscle and adipose tissue) drive the pathogenesis of cachexia. The release of proinflammatory cytokines from cancer cells and activation of the immune system through tumor necrosis factor, interferon-gamma, and several interleukins (eg, IL-6, IL-1β) have been described as mediators of metabolic remodeling in muscle, including cardiac muscle (64,67). In addition, the metabolic derangement in cancer cells may play a pivotal role in promoting remodeling in both heart and skeletal muscle. Severe forms of cachexia are often associated with specific tumor types, including hematological malignancies (eg, leukemia, lymphoma), pancreatic tumors, and non-small cell lung tumors (68). The phenotype of these tumor types is characterized by metabolic heterogeneity that evolves as the cancer progress from premalignant lesions to primary tumors and then metastasis (29,69). Mobilization of energy providing substrates such as glucose and amino acids (eg, glutamine, leucine) from muscle tissue due to the tumor burden may cause a negative energy balance and loss of body weight (**Figure 1**). Correspondingly, insulin resistance and decreased glucose tolerance correlate with the degree of cachexia in pancreatic tumors and breast cancer.

THE ROLE OF METABOLIC MODULATION TO TREAT HF

Therapeutic interventions targeting tumor cells have increasingly focused on liabilities that arise from reprogrammed metabolism in cancer cells or proliferating tumors (70,71). Metabolic vulnerabilities in cancer cells are often part of the metabolic adaptation in CVD. Therefore, focusing therapeutic interventions and risk reduction strategies on shared metabolic pathways may have positive outcomes for both CVD and certain cancers (72).

Current efforts in targeting cancer cells and treating CVD focus on the metabolism of 4 substrate classes: 1) glucose; 2) fatty acids; 3) ketone bodies;

and 4) amino acids (eg, glutamine) (**Figure 1**). The nutrient selection by tissues and nutrient flux between them depend on various factors, including hormonal regulation, nutrient availability, and the activity of metabolic enzymes. Together, these systemic factors can result in a competition between nutrients most notably between the oxidation of glucose and fatty acids in muscle and adipose tissue (73). The "glucose-fatty-acid cycle" (or Randle cycle) conceptualizes the dynamic interactions of nutrients in a complex environment that contains different specialized tissues and cells with specific metabolic requirements. Ketone bodies as "precursors" for fatty acids show a similar interaction with glucose, and likewise amino acids (eg, glutamate, glutamine) are increasingly recognized as energy-providing substrates under hemodynamic stress (74,75).

In the failing heart, early metabolic adaptation is characterized by a "fetal pattern" of substrate use including enhanced glucose uptake and utilization, whereas fatty acid oxidation (FAO) is decreased (76,77). In later stages of HF, glucose metabolism may decrease due to the development of insulin resistance (78,79). In the failing heart, glycolysis is increased without a corresponding increase in glucose oxidation, pointing toward mitochondrial dysfunction (76). Reminiscent of the Warburg effect in cancer cells, studies of left ventricular assist device patients who experience recovery of systolic function suggest that cardiac recovery may be in part mediated by the shunting of glycolytic metabolites into nonoxidative pathways of the pentose phosphate pathway to increase biosynthesis of NADPH and decrease oxidative stress (80). However, pharmacologic inhibition of glycolytic enzymes has not shown to be effective in HF during clinical trials due to severe side effects (81,82).

The biological consequences of the Warburg effect are still not fully understood. In the 1920s, Otto Warburg showed that cultured ascites tumor cells have high rates of glucose uptake and lactate secretion, even in the presence of oxygen (83-85). The Warburg effect describes a metabolic observation, but does not imply a loss of oxidative metabolism in the presence of increased glycolysis. In fact, recent advancements in studying cancer metabolism have shown that certain tumors can simultaneously upregulate glycolysis while redirecting intermediates into the Krebs cycle and maintaining mitochondrial metabolism. The increased conversion of glucose to lactate that is observed in cancer or the failing heart has no obvious biosynthetic purpose, because shifting glucose metabolism entirely towards lactate production means that cells are losing carbons. In fact, neither cancer cells nor failing hearts are fully losing oxidative metabolism, which is further supported by an up-regulation of ketone body metabolism. An increased demand for glucose with heart failure may overwhelm endogenous enzyme systems (eg, pyruvate dehydrogenase activity), thus preventing the incorporation of carbons into the Krebs cycle and causing increased lactate secretion.

Pharmacologic strategies that enhance overall glucose oxidation through increased availability (eg, GLUT1 and GLUT4 transporters), incorporation into the Krebs cycle (eg, pyruvate dehydrogenase activation, pyruvate dehydrogenase kinase inhibition), or targeting signaling pathways (eg, hexokinase-II activation, insulin-dependent phosphoinositide 3-kinase) have shown promising results in both preclinical and clinical trials (86-89). Targeting kinase activity through pharmacologic modulation has enormous therapeutic potential. Pyruvate dehydrogenase (PDH) hydrolyzes pyruvate to acetyl-CoA in the mitochondria, which is critical for the entry of glucose-derived carbons into the Krebs cycle and linking glucose to fatty acid metabolism for the provision of ATP. The activity of PDH is regulated by various PDH kinases (PDK1, -2, and -4), which phosphorylate and inhibit PDH (90). Similar, PI3K signaling can contribute to tumorigenesis and a broad range of diseases, including immunological disorders, diabetes, and CVD. Insulin-dependent growth is mediated by PI3K in heart and skeletal muscle (91). Downstream phosphorylation of proteins within the Akt-mTOR signaling pathways can lead to complex feedback loops allowing cells to efficiently integrate growth signals and use nutrients (91).

Metabolic disorders, such as diabetes, are prevalent both in HF and cancer. Patients with diabetes have a higher risk for cancer, and elevated blood glucose levels are associated with tumorigenesis, invasion and migration, and resistance to chemotherapy (62,92-94). Metastatic tumors with known mutations of mitochondrial enzymes are often susceptible to strategies that reduce glucose availability or prevent glycolysis (95-97). Among several inhibitors of glycolytic enzymes (eg, 3-bromopyruvate, 2-deoxyglucose, GEN-27, benserazide, and lonidamine) that have shown efficacy in preclinical studies, only 2-deoxyglucose is currently in phase I/II clinical trials for solid tumors and prostate cancer. Despite these promising results, the potential for severe side effects may limit the application of pharmacologic modulation for glycolytic enzymes in both cancer and HF.

Fatty acid and mitochondrial metabolism are impaired in HF and serve as attractive therapeutic

targets for the treatment of HF (**Figure 1**) (98). Of note, pharmacologic strategies targeting fatty acid metabolism in both CVD and cancer aim to inhibit de novo lipogenesis or stimulate FAO (99,100). Approaches to limit de novo lipogenesis have mainly focused on inhibiting fatty acid synthase (101) or ATP citrate lyase (102), which catalyzes the conversion of glucose-derived citrate to acetyl-CoA. Clinical trials aimed at inhibiting fatty acid synthase have been shown to be effective for the treatment of metastatic KRAS mutant non-small cell lung cancers and metastatic HER2 breast cancer (now in phase II clinical trials) (103); however, this relationship has yet to be recapitulated in similar trials for HF. Other promising approaches have focused on modulating key regulators of FAO such as selective inhibition of carnitine palmitoyl-transferase 1 (104) and 3-ketoacyl coenzyme-A thiolase (99,100) or activation of peroxisome proliferator-activated receptor α (105). However, the application of CPT-1 inhibitors has been limited due to severe side effects including hepatotoxicity. In relation to mitochondrial metabolic targets, there has been a recent push to leverage the use of metformin, a pleiotropic antidiabetic agent that inhibits electron transport chain I, in the treatment of cancer and heart disease. Metformin decreases mitochondrial ATP provision and reduces plasma levels of insulin and insulin-like growth factor (IGF) 1. These effects increase reliance on glycolysis for ATP provision and make cancer cells more vulnerable to limited glucose availability, thus highlighting the anticancer properties of metformin, particularly in tumors with high levels of organic cation transporters (106,107). However, there have been mixed results and uncertainty on the role that metformin may play in reducing risk for CVD (107). In a recent post hoc analysis, metformin use was not associated with lower rates of cardiovascular death among patients with type 2 diabetes mellitus and high cardiovascular risk (108). Furthermore, metformin use was not associated with cardiovascular events in patients with prior HF or moderate-to-severe chronic kidney disease. Metformin has the potential to complement existing chemotherapeutic regimens without increasing the risk for cardiovascular events.

As the failing heart becomes inefficient in fatty acid and glucose oxidization, ketone bodies provide an alternative energy source because ketone oxidation bypasses the dysregulation of the β-oxidation pathway and pyruvate dehydrogenase complex in HF (**Figure 1**). End-stage HF patients have been shown to have increased expression of ketolytic enzymes and ketogenic derivatives (75), suggesting that, in contrast with FAO, ketone bodies can be completely oxidized in the failing heart despite metabolic dysregulation. Limited data in humans suggest that ketone supplementation has therapeutic potential in HF. In a randomized crossover study in patients with compensated HF with reduced ejection fraction, an infusion of 3-hydroxybutyrate increased cardiac output and improved hemodynamics compared with saline in a dose-dependent manner (109). It is unclear whether these short-term beneficial hemodynamic effects translate into long-term clinical benefit.

Recently, targeting sodium-glucose transport in the kidney through sodium glucose co-transporter 2 (SGLT2) inhibitors has emerged as a primary therapy for HF, which resulted in a significant reduction in HF hospitalization and mortality (110,111). Although the exact mechanisms are unknown, SGLT2 inhibitors induce systemic ketosis by decreasing the insulin-to-glucagon ratio and increasing lipolysis. SGLT2 inhibitors have been shown to increase ketone levels in diabetic patients and animal models of HF, which may in turn increase myocardial use of ketones as an energy source (112,113). The systemic ketosis achieved with SGLT2 inhibitors that improve HF clinical outcomes is comparable to levels shown to be beneficial in HF via ketone infusions. Emerging evidence suggest that therapeutic ketosis may be a viable way to treat HF. In the context of cancer, ketone bodies have been described as oncometabolites, and studies using preclinical cell culture models suggested that increased ketone body availability may promote tumor growth and progression (114). However, more recent studies have shown that cancer cells are more metabolically heterogeneous than previously thought, and even within the same solid tumor, different metabolic profiles can be observed (30).

Ketogenic diets have shown promising results as adjuvant therapies in randomized controlled clinical trials with glioblastoma, ovarian, endometrial, or breast cancer (115-117). Preclinical studies demonstrate that a ketogenic diet, together with caloric restriction, reduces circulating blood glucose levels, which may decrease adverse cardiac remodeling in HF and inhibition of growth of certain solid tumors. The reduction in blood glucose level is accompanied by a reduction of insulin and/or the IGF levels (11). Both insulin and IGF receptor signaling pathways contribute to tumorigenesis and cardiac remodeling in HF. Pharmacologic modulation of this signaling pathway through inhibition of the insulin-activated enzyme PI3K is an effective chemotherapeutic strategy (118-120). However, targeting PI3K leads to the activation of a feedback loop, and often results in hyperglycemia and subsequent treatment resistance. Clinical trials have shown that drug resistance against

PI3K inhibitors is attenuated by a ketogenic diet (11). These findings support the hypothesis that the reduction of blood glucose is a contributing factor in the effectiveness of ketogenic diets. To further elucidate the underlying mechanisms and therapeutic benefits of ketone bodies in the treatment of cancer and HF, further randomized controlled trials and molecular studies are needed.

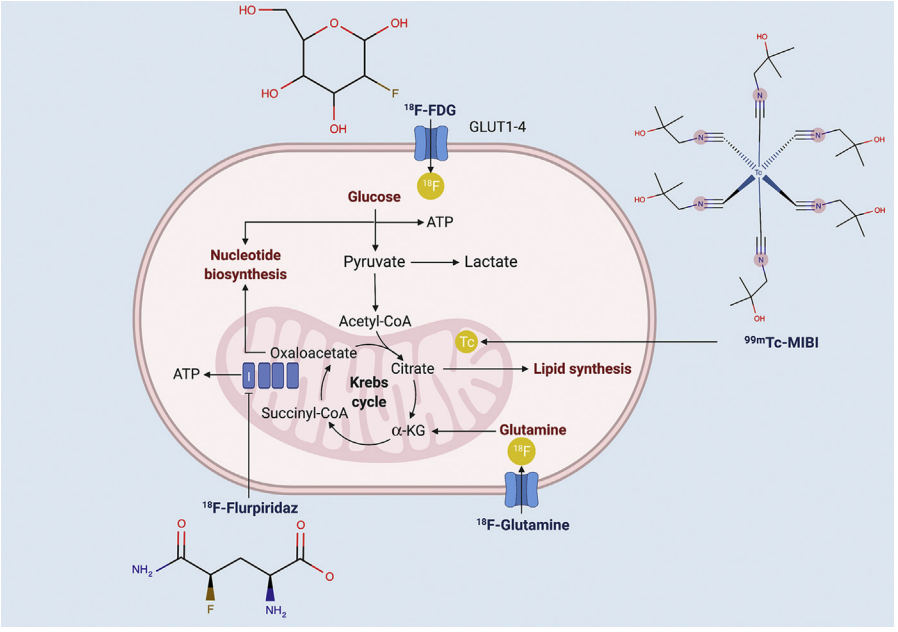
Similarly, intermittent fasting or time-restricted feeding (TRF) has shown cardiovascular benefits in both preclinical models and human trials, including reduced blood pressure, low-density lipoprotein cholesterol levels, triglycerides, fasting insulin, insulin resistance, inflammation, and oxidative stress (121,122). The time frames for caloric restrictions vary between short-term fasting or TRF (4 to 10 h), and alternate-day fasting, or 2-day fasting followed by "feast days" (5:2 diet). Recent preclinical studies have shown promising results for TRF regimes in both CVDs and certain types of breast cancer. The reduction of plasma lipid concentration and insulin level through short-term fasting slows tumor growth and potentially removes risk factors associated with both CVDs and cancer. However, future trials are needed to examine the long-term effects and benefits of TRF on the cardiovascular system, as well as different cancer types.

Glutamine metabolism plays a critical role in nitrogen balance and nitrogen exchange between organs, intermediary metabolism, immune modulation, and pH homeostasis. In the failing heart, glutamine complements glucose and fatty acids in core metabolic tasks: it participates in ATP provision, supports cell defenses against oxidative stress, and aids in the production of macromolecules (eg, proteins, lipids) (1,123). Increased plasma glutamine levels are inversely associated with obesity, hypertension, and insulin resistance. Although glutamine is a highly abundant metabolite in the blood, glutamate is not. The metabolic fate of glutamine is driven by reactions that use glutamine for its γ-nitrogen (nucleotide synthesis and hexosamine synthesis) and those that use either the α-nitrogen or the carbon skeleton, which require glutamate. Intracellular glutamate pools are dependent on the ability to convert glutamine to glutamate through the activity of the mitochondrial glutaminase (GLS) (**Figure 1**). Furthermore, glutamine exclusively contributes to the synthesis of asparagine by providing nitrogen. Expression of GLS1 is increased in proliferating tumors, in right ventricular hypertrophy during pulmonary hypertension, and in rodent models of ischemia-reperfusion injury. Recent studies indicate that modulation of GLS1 in endothelial cells may result in high rates of ammonia synthesis, endothelial cell senescence, proliferation, redox potential (eg, glutathione synthesis), and energy balance (124). Loss of GLS1 in endothelial cells results in impaired angiogenesis, suggesting a critical role in blood vessel formation and as a potential pharmacologic target in proliferating tumors (125,126). The GLS inhibitor CB-839 is currently being tested in phase I/II clinical trials for the treatment of metastatic KRAS mutant non-small cell lung cancers, colorectal cancer, and other solid tumors. In the treatment of CVD, GLS1 inhibition has shown efficacy in preclinical models of pulmonary arterial hypertension with reduced arterial remodeling, improved right ventricular function, and improved cardiac glucose oxidation (74). A new experimental glutaminase antagonist, JHU-083 (or DRP-083), has shown promising results in preclinical models by preventing cancer cells from utilizing glutamine for macromolecule synthesis (34,127,128). Collectively, evidence from preclinical and clinical studies supports targeting key metabolic pathways in ameliorating disease progression in both cancer and CVD. The challenge is to conceptualize therapies targeting tumor cells without harming the heart and other cells that constrain tumor growth.

CARDIAC METABOLIC IMAGING AND APPLICATIONS IN CARDIO-ONCOLOGY

To understand the impact of cardiac metabolic processes during CVD progression on a translational level, scientists have turned to the use of existent radiopharmaceuticals and imaging techniques. Currently, there are a number of clinical radiopharmaceuticals such as ^{99m}technetium-sestamibi (^{99m}Tc-MIBI) (129), or CardioLite (Lantheus), and [^{18}F]FDG (130), and emerging techniques for interrogating metabolic parameters such as glutamine uptake and pyruvate transport potential (**Figure 2**). There has been a desire in the cardiology community for a pure, safe, noninvasive flow tracer, essentially equivalent to ^{3}H-microsphere retention in the heart. ^{99m}Tc-MIBI, or CardioLite, a lipophilic cation with high first-pass extraction and exceptionally high molar activities, was developed as a high first-past extraction flow tracer (**Figure 2**). In the context of metabolic reprograming of the heart, the correlation between the total cellular delta psi (131) might be as or more important than simple changes in perfusion. Adequate perfusion is critical for delivery to cardiac tissue. However, the driving force for retention of lipophilic cations is the Nernstian potential, or delta psi, at the cell membrane and more importantly at the mitochondrial membrane (132-134). Although ^{99m}Tc-MIBI was

FIGURE 2 Metabolic Vulnerabilities and Use of PET Imaging



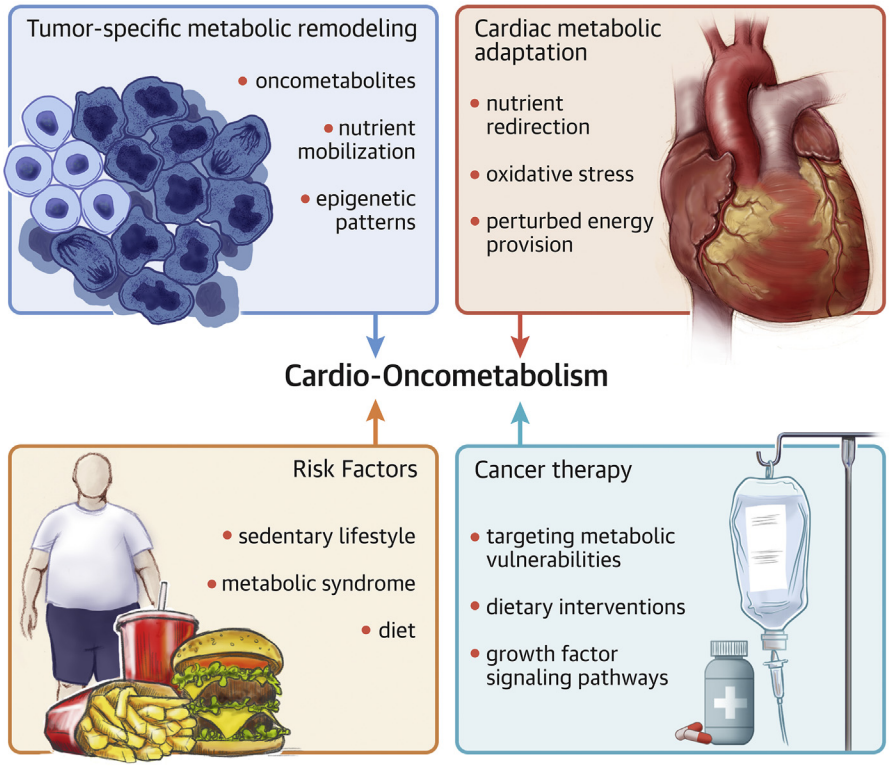
Radiopharmaceuticals to study cardiac metabolic processes during disease progression and their metabolic targets are shown. Several different types of tracers have emerged that allow interrogation of metabolic pathways in patients and in vivo for pre-clinical studies. ^{18}F-FDG = 2-deoxy-2-[fluorine-18]fluoro-D-glucose; ^{99m}Tc-MIBI = ^{99m}technetium-sestamibi; ATP = adenosine triphosphate; PET = positron emission tomography. Created with BioRender.com.

originally imaged with both 2-dimensional gamma cameras and single-photon emission computed tomography, new positron emission tomography (PET)-based lipophilic cations such as ^{68}Ga-ENBPI (135) and ^{18}F-TPP (131), have been introduced in preclinical research. PET tracers may enable the deconvolution of perfusion and net delta psi trapping. Through kinetic imaging protocols and kinetic modeling, one might capture both the pure flow component as well as the trapping and the net delta psi from a single imaging session (131).

A more recent PET perfusion agent, ^{18}F-flurpiridaz (Lantheus) (**Figure 2**), demonstrates a variety of favorable flow tracer characteristics including low "roll off" of uptake with high flow velocities (136). Like lipophilic cations, ^{18}F-flurpiridaz is retained in mitochondria but is trapped through a different molecular mechanism. Complex I is a critical protein component of the electron transport chain found and localizes to the mitochondrial matrix. ^{18}F-flurpiridaz has a high affinity (half maximal inhibitory concentration = 16 nmol/L) to mitochondrial complex I, therefore trapping reflects the total mitochondrial concentration per voxel (137). Thus, analogous to lipophilic cations, kinetic modeling of ^{18}F-flurpiridaz will yield quantitative information about both flow and mitochondria mass. With the right combination of both classical and emerging "flow tracers," both the imaging and quantification of how metabolic reprogramming affects the mass and energetics of the cardiac mitochondria can be performed. Indeed, it is well known that the Nernst potential of cardiac cells can rapidly change during ischemia reperfusion injury through a variety of mechanisms including loss of ATP that can occur even when there is not complete loss of flow and perfusion (138). Furthermore, D/L-2-HG, a potent oncometabolite, dramatically changes the mitochondrial polarization of tumor cells (139,140) and could signal to the heart (7). Note that in vivo, these lipophilic cations are substrates for ABCB1 (MDR1pgp), which could complicate the interpretation of their retention in some classes of tumors unlike in the healthy heart (141). As a final example, heritable loss of complex I is a known risk factor for CVD, and ^{18}F-flupiridaz might be leveraged to study this risk factor (142).

PET radiopharmaceutical [^{18}F]FDG is the workhorse of molecular imaging in oncology and is also

CENTRAL ILLUSTRATION **Factors Contributing to Cardio-Oncometabolic Remodeling**



Karlstaedt, A. et al. J Am Coll Cardiol Basic Trans Science. 2021;6(8):705–18.

used in CVD as a diagnostic strategy (**Figure 2**). Emerging data in cardio-oncology suggest that this reporter can be used to gain insight into the cardiotoxic effects of cancer therapy (143). Moreover, small studies have suggested that aortic vascular uptake by [^{18}F]FDG may be a marker of cancer disease severity and its effects on the vasculature (144). Transport of extracellular [^{18}F]FDG into the cell depends upon the relative expression of up to 14 glucose transporters (145). Cardiomyocytes typically express only a subset of these glucose transporters; the primary glucose transporter in the heart and skeletal muscle is GLUT4 (146,147). Once inside the cell, FDG is then trapped by a combination of 1 of 4 hexokinases (148). Once phosphorylated, [^{18}F]FDG-phosphate (FDG-P) is no longer a substrate for glucose transporters and can no longer simply diffuse out of the cell due to the highly localized negative charge contained on phosphate. However, in cells expressing glucose-6-phosphatase complex, such as hepatocytes (149) or activated murine macrophages (150), FDG-P can be dephosphorylated and lost from the cell (150). Imaging of this pathway is generally correlated with either aerobic or anaerobic glycolysis. Although related to glycolysis, the net retention of [^{18}F]FDG is a robust, but complex, integration of the fluxes through multiple enzymes.

Similar to [^{18}F]FDG, ^{18}F-glutamine is emerging from preclinical research into active clinical research (**Figure 2**). Labeling of glutamine with ^{18}F creates a complex set of chemical isomers through the creation of a new chiral center. Unlike [^{18}F]FDG, which is a substrate for both glucose transport and hexokinase, with ^{18}F-glutamine, 1 isomer (2S,4R) is taken up by the glutamine transporters, including SLC1A5, and another is recognized by glutaminase (2S,4S) (151). To interrogate intracellular glutaminase, a cell-permeant prodrug of the (2S,4S) isomer has now been synthesized and tested in preclinical models (152). As cardiac cells adjust their homeostatic needs for glutamine during differentiation, changes in SLC1A5 activity might concomitantly (153) change the uptake of ^{18}F-glutamine (2S,4R). Although tumor cells up-regulate the expression of glutamine transporters such as SLC1A5 (154), analysis of human cardiac samples demonstrated that the failing heart down-regulates

SLC1A5 at both the messenger and protein level (155). Although cardiac biopsies are possible, longitudinal evaluation of these patients by PET over time with heart failure progression or recovery might be more informative.

The use of ^{13}C-hyperpolarzied magnetic resonance spectroscopy (MRS) is also emerging as a tool to study both tumor and cardiac metabolism (156-159). Although a thousand-fold more sensitive than normal MRS, these techniques still require millimolar concentrations of circulating stable isotope (160). These high concentrations have implications for the biochemical interpretation of signals. Biochemical tracers that operate in the linear uptake or binding regimes require concentrations either much higher or much lower than the Km or Kd for the enzymes or targets under study. Because HP MRS reporters transiently operate near the Km (nonlinear regime) or above, they interrogate the complex interplay between the Km, Vmax, and flux of substrate. Therefore, these reporters could yield highly nonlinear signals. Quantitative modeling to linearize this nonlinear behavior to enable more robust and reproducible data sets is an area of active research. Mechanistically, in the case of ^{13}C-pyruvate, the signal generated is the convolution of blood flow, cellular transport (eg, MCT1) (161), intracellular pyruvate pool, transport into the mitochondria for oxidation to CO2, and export of lactate to the extracellular environment (MCT1/4). Indeed, the heart is one of the only organs with the combination of either a sufficiently small pyruvate pool or sufficiently high flux through the mitochondrial pyruvate carrier protein to observe polarized CO2/bicarbonate (162,163). Despite the high mitochondrial mass of many tumors, CO2/bicarbonate is rarely observed, whereas lactate and even alanine are readily observed. In rats, data suggest that MCT1 and therefore likely pyruvate uptake and metabolism occurs during the process of HF (164,165). In patients and mice, MCT4 has been shown to play a critical and inhibitory role in cardiac hypertrophy (166). The translational role of hyperpolarized MRS in cardio-oncology is of interest; defining the interactions between tumor secreted factors, and pyruvate-lactate transport in the heart might advance our understanding of the direct interactions between cancer and CVD.

Finally, particularly as higher-field magnets become more readily available, and cardiac gating becomes more routine, there may be a resurrection of endogenous MRS of the heart. Boltzmann polarization of ^{31}P can detect and quantify phosphocreatine to ATP ratios, which can help identifying perturbed cardiac metabolism during ischemia (167,168). Measuring these ratios does not directly determine which metabolic pathways are altered in a disease state, but they may serve as early indicators for flux changes both ex vivo and in vivo (167,168). Additionally, these endogenous readouts might well be coupled with metabolic tracers via noninvasive cardiac PET/MRI yielding multidimensional highly orthogonal data sets (169). Such data sets are currently expensive and still inferior to other imaging techniques for cardiac stress tests (170). Nonetheless, these techniques could feed into modern machine learning algorithms to build better predictive models of patient risk and response to therapy (169).

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Future research in cardio-oncology needs to focus on elucidating the mechanisms involved in crosstalk between cardiac and cancer cells (**Central Illustration**). Therefore, the bridge from animal models to human studies is critical to translate findings from basic research into clinical applications. Identification of biomarkers and characterization of cardiac metabolic changes during cancer in animal models and patients to date have yielded some results highlighting a potential role for carnitine, citric acid, and aconitic acid in anthracycline cardiotoxicity; these studies need external validation (171,172). The development of multi-institutional cohort studies and clinical trials with detailed biologic and clinical phenotypic data collection, coupled with recent advances in imaging and metabolic probes will be key to overcome these shortcomings (173). Thus, interdisciplinary collaborations among cardiologists, oncologists, basic researchers, and radiologists will be necessary to advance the field and identify metabolic vulnerabilities for the development of novel therapeutics.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The work was supported by the National Institutes of Health grants K99-HL-141702 (Dr Karlstaedt), R01-HL-148272 (Dr Ky), and U24-CA-220325 (Dr Gammons), Bethesda, Maryland, USA. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Bonnie Ky, Perelman Center for Advanced Medicine, University of Pennsylvania, East Pavilion, 2nd Floor, 3400 Civic Center Boulevard, Philadelphia, Pennsylvania 19104, USA. E-mail: Bonnie.Ky@pennmedicine.upenn.edu. OR Dr Anja Karlstaedt, Department of Cardiology, Smidt Heart Institute, 127 South San Vincente Boulevard, AHSP 9229, Los Angeles, California 90048, USA. E-mail: anja.karlstaedt@csmc.edu.

REFERENCES

1. Ritterhoff J, Young S, Villet O, et al. Metabolic remodeling promotes cardiac hypertrophy by directing glucose to aspartate biosynthesis. Circ Res 2020;126:182–96.

2. Karlstaedt A, Khanna R, Thangam M, Taegtmeyer H. Glucose 6-phosphate accumulates via phosphoglucose isomerase inhibition in heart muscle. Circ Res 2020;126:60–74.

3. Young ME, Laws FA, Goodwin GW, Taegtmeyer H. Reactivation of peroxisome proliferator-activated receptor alpha is associated with contractile dysfunction in hypertrophied rat heart. J Biol Chem 2001;276:44390–5.

4. Young ME, Yan J, Razeghi P, et al. Proposed regulation of gene expression by glucose in rodent heart. Gene Regul Syst Bio 2007;1:251–62.

5. Sheng S, Chen D, Van Eyk JE. Multidimensional liquid chromatography separation of intact proteins by chromatographic focusing and reversed phase of the human serum proteome: optimization and protein database. Mol Cell Proteomics 2006; 5:26–34.

6. Agnetti G, Kaludercic N, Kane LA, et al. Modulation of mitochondrial proteome and improved mitochondrial function by biventricular pacing of dyssynchronous failing hearts. Circ Cardiovasc Genet 2010;3:78–87.

7. Karlstaedt A, Zhang X, Vitrac H, et al. Oncometabolite d-2-hydroxyglutarate impairs alpha-ketoglutarate dehydrogenase and contractile function in rodent heart. Proc Natl Acad Sci U S A 2016;113:10436–41.

8. Avraham S, Abu-Sharki S, Shofti R, et al. Early cardiac remodeling promotes tumor growth and metastasis. Circulation 2020;142:670–83.

9. Meijers WC, Maglione M, Bakker SJL, et al. Heart failure stimulates tumor growth by circulating factors. Circulation 2018;138:678–91.

10. Koelwyn GJ, Newman AAC, Afonso MS, et al. Myocardial infarction accelerates breast cancer via innate immune reprogramming. Nat Med 2020;26: 1452–8.

11. Hopkins BD, Pauli C, Du X, et al. Suppression of insulin feedback enhances the efficacy of PI3K inhibitors. Nature 2018;560:499–503.

12. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 2014;64:83–103.

13. Leerink JM, de Baat EC, Feijen EAM, et al. Cardiac disease in childhood cancer survivors. J Am Coll Cardiol CardioOnc 2020;2(3):363–78.

14. Lipshultz SE, Landy DC, Lopez-Mitnik G, et al. Cardiovascular status of childhood cancer survivors exposed and unexposed to cardiotoxic therapy. J Clin Oncol 2012;30:1050–7.

15. Mariotto AB, Rowland JH, Yabroff KR, et al. Long-term survivors of childhood cancers in the United States. Cancer Epidemiol Biomarkers Prev 2009;18:1033–40.

16. Strongman H, Gadd S, Matthews A, et al. Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers: a population-based cohort study using multiple linked UK electronic health records databases. Lancet 2019;394:1041–54.

17. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271–89.

18. Nathan PC, Greenberg ML, Ness KK, et al. Medical care in long-term survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol 2008;26:4401–9.

19. Ryan TD, Nagarajan R, Godown J. Pediatric cardio-oncology: development of cancer treatment-related cardiotoxicity and the therapeutic approach to affected patients. Curr Treat Options Oncol 2019;20:56.

20. Lenihan DJ, Fradley MG, Dent S, et al. Proceedings from the Global Cardio-Oncology Summit. J Am Coll Cardiol CardioOnc 2019;1:256–72.

21. Cramer L, Hildebrandt B, Kung T, et al. Cardiovascular function and predictors of exercise capacity in patients with colorectal cancer. J Am Coll Cardiol 2014;64:1310–9.

22. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med 2014;371: 2488–98.

23. Akbay EA, Moslehi J, Christensen CL, et al. D-2-hydroxyglutarate produced by mutant IDH2 causes cardiomyopathy and neurodegeneration in mice. Genes Dev 2014;28:479–90.

24. Pavlova NN, Thompson CB. The emerging hallmarks of cancer metabolism. Cell Metab 2016; 23:27–47.

25. Li F, Wang Y, Zeller KI, et al. Myc stimulates nuclearly encoded mitochondrial genes and mitochondrial biogenesis. Mol Cell Biol 2005;25: 6225–34.

26. Viale A, Pettazzoni P, Lyssiotis CA, et al. Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function. Nature 2014;514:628–32.

27. Gopal YN, Rizos H, Chen G, et al. Inhibition of mTORC1/2 overcomes resistance to MAPK pathway inhibitors mediated by PGC1alpha and oxidative phosphorylation in melanoma. Cancer Res 2014;74:7037–47.

28. Sancho P, Burgos-Ramos E, Tavera A, et al. MYC/PGC-1alpha balance determines the metabolic phenotype and plasticity of pancreatic cancer stem cells. Cell Metab 2015;22:590–605.

29. Faubert B, Li KY, Cai L, et al. Lactate metabolism in human lung tumors. Cell 2017;171: 358–71.e9.

30. Hensley CT, Faubert B, Yuan Q, et al. Metabolic heterogeneity in human lung tumors. Cell 2016;164:681–94.

31. Lin X, Hong S, Huang J, Chen Y, Chen Y, Wu Z. Plasma apolipoprotein A1 levels at diagnosis are independent prognostic factors in invasive ductal breast cancer. Discov Med 2017;23:247–58.

32. Masri S, Papagiannakopoulos T, Kinouchi K, et al. Lung adenocarcinoma distally rewires hepatic circadian homeostasis. Cell 2016;165: 896–909.

33. Borniger JC, Walker WH Ii, Surbhi, et al. A role for hypocretin/orexin in metabolic and sleep abnormalities in a mouse model of non-metastatic breast cancer. Cell Metab 2018;28:118–29.e5.

34. Leone RD, Zhao L, Englert JM, et al. Glutamine blockade induces divergent metabolic programs to overcome tumor immune evasion. Science 2019; 366:1013–21.

35. Chen H, Orozco LD, Wang J, et al. DNA methylation indicates susceptibility to isoproterenol-induced cardiac pathology and is associated with chromatin states. Circ Res 2016; 118:786–97.

36. Rivera CM, Ren B. Mapping human epigenomes. Cell 2013;155:39–55.

37. Onuchic V, Hartmaier RJ, Boone DN, et al. Epigenomic deconvolution of breast tumors reveals metabolic coupling between constituent cell types. Cell Rep 2016;17:2075–86.

38. Fulop N, Marchase RB, Chatham JC. Role of protein O-linked N-acetyl-glucosamine in mediating cell function and survival in the cardiovascular system. Cardiovasc Res 2007;73:288–97.

39. Wright JN, Collins HE, Wende AR, Chatham JC. O-GlcNAcylation and cardiovascular disease. Biochem Soc Trans 2017;45:545–53.

40. Stocker PJ, Bennett ES. Differential sialylation modulates voltage-gated Na+ channel gating throughout the developing myocardium. J Gen Physiol 2006;127:253–65.

41. Zacchi LF, Schulz BL. N-glycoprotein macroheterogeneity: biological implications and proteomic characterization. Glycoconj J 2016;33: 359–76.

42. Ashwood C, Waas M, Weerasekera R, Gundry RL. Reference glycan structure libraries of primary human cardiomyocytes and pluripotent stem cell-derived cardiomyocytes reveal cell-type and culture stage-specific glycan phenotypes. J Mol Cell Cardiol 2020;139:33–46.

43. Gudmundsdottir T, Winther JF, de Fine Licht S, et al. Cardiovascular disease in adult life after childhood cancer in Scandinavia: a population-based cohort study of 32,308 one-year survivors. Int J Cancer 2015;137:1176–86.

44. Kang Y, Assuncao BL, Denduluri S, et al. Symptomatic heart failure in acute leukemia patients treated with anthracyclines. J Am Coll Cardiol CardioOnc 2019;1:208–17.

45. DiNardo CD, Propert KJ, Loren AW, et al. Serum 2-hydroxyglutarate levels predict isocitrate dehydrogenase mutations and clinical outcome in acute myeloid leukemia. Blood 2013;121:4917–24.

46. Mardis ER, Ding L, Dooling DJ, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. N Engl J Med 2009;361: 1058–66.

47. Wang JH, Chen WL, Li JM, et al. Prognostic significance of 2-hydroxyglutarate levels in acute myeloid leukemia in China. Proc Natl Acad Sci U S A 2013;110:17017–22.

48. Janin M, Mylonas E, Saada V, et al. Serum 2-hydroxyglutarate production in IDH1- and IDH2-mutated de novo acute myeloid leukemia: a study by the Acute Leukemia French Association group. J Clin Oncol 2014;32:297–305.

49. Kranendijk M, Struys EA, Salomons GS, Van der Knaap MS, Jakobs C. Progress in understanding 2-hydroxyglutaric acidurias. J Inherit Metab Dis 2012;35:571–87.

50. Kranendijk M, Struys EA, van Schaftingen E, et al. IDH2 mutations in patients with D-2-hydroxyglutaric aciduria. Science 2010;330:336.

51. Kranendijk M, Struys EA, Gibson KM, et al. Evidence for genetic heterogeneity in D-2-hydroxyglutaric aciduria. Hum Mutat 2010;31:279–83.

52. Zheng L, MacKenzie ED, Karim SA, et al. Reversed argininosuccinate lyase activity in fumarate hydratase-deficient cancer cells. Cancer Metab 2013;1:12.

53. Salminen A, Kauppinen A, Hiltunen M, Kaarniranta K. Krebs cycle intermediates regulate DNA and histone methylation: epigenetic impact on the aging process. Ageing Res Rev 2014;16:45–65.

54. Chouchani ET, Pell VR, Gaude E, et al. Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS. Nature 2014;515:431–5.

55. Unruh D, Zewde M, Buss A, et al. Methylation and transcription patterns are distinct in IDH mutant gliomas compared to other IDH mutant cancers. Sci Rep 2019;9:8946.

56. Morin A, Goncalves J, Moog S, et al. TET-mediated hypermethylation primes SDH-deficient cells for HIF2alpha-driven mesenchymal transition. Cell Rep 2020;30:4551–66.e7.

57. Tannahill GM, Curtis AM, Adamik J, et al. Succinate is an inflammatory signal that induces IL-1beta through HIF-1alpha. Nature 2013;496:238–42.

58. Sadagopan N, Li W, Roberds SL, et al. Circulating succinate is elevated in rodent models of hypertension and metabolic disease. Am J Hypertens 2007;20:1209–15.

59. Taegtmeyer H. Metabolic responses to cardiac hypoxia. Increased production of succinate by rabbit papillary muscles. Circ Res 1978;43:808–15.

60. van Diepen JA, Robben JH, Hooiveld GJ, et al. SUCNR1-mediated chemotaxis of macrophages aggravates obesity-induced inflammation and diabetes. Diabetologia 2017;60:1304–13.

61. Gonzalez H, Hagerling C, Werb Z. Roles of the immune system in cancer: from tumor initiation to metastatic progression. Genes Dev 2018;32:1267–84.

62. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.

63. Gilliland TM, Villafane-Ferriol N, Shah KP, et al. Nutritional and metabolic derangements in pancreatic cancer and pancreatic resection. Nutrients 2017;9(3):243. https://doi.org/10.3390/nu903024

64. Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. Cell Metab 2012;16:153–66.

65. Evans WJ, Morley JE, Argiles J, et al. Cachexia: a new definition. Clin Nutr 2008;27:793–9.

66. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12:489–95.

67. Ungefroren H, Witte D, Fiedler C, et al. The role of PAR2 in TGF-beta1-induced ERK activation and cell motility. Int J Mol Sci 2017;18(12):2776.

68. Lok C. Cachexia: the last illness. Nature 2015;528:182–3.

69. Kim HS, Mendiratta S, Kim J, et al. Systematic identification of molecular subtype-selective vulnerabilities in non-small-cell lung cancer. Cell 2013;155:552–66.

70. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med 2018;378:2386–98.

71. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood 2017;130:722–31.

72. Totzeck M, Schuler M, Stuschke M, Heusch G, Rassaf T. Cardio-oncology - strategies for management of cancer-therapy related cardiovascular disease. Int J Cardiol 2019;280:163–75.

73. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963;1:785–9.

74. Piao L, Fang YH, Parikh K, Ryan JJ, Toth PT, Archer SL. Cardiac glutaminolysis: a maladaptive cancer metabolism pathway in the right ventricle in pulmonary hypertension. J Mol Med (Berl) 2013;91:1185–97.

75. Bedi KC Jr., Snyder NW, Brandimarto J, et al. Evidence for intramyocardial disruption of lipid metabolism and increased myocardial ketone utilization in advanced human heart failure. Circulation 2016;133:706–16.

76. Allard MF, Schonekess BO, Henning SL, English DR, Lopaschuk GD. Contribution of oxidative metabolism and glycolysis to ATP production in hypertrophied hearts. Am J Physiol 1994;267:H742–50.

77. Davila-Roman VG, Vedala G, Herrero P, et al. Altered myocardial fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy. J Am Coll Cardiol 2002;40:271–7.

78. Schroeder MA, Lau AZ, Chen AP, et al. Hyperpolarized (13)C magnetic resonance reveals early- and late-onset changes to in vivo pyruvate metabolism in the failing heart. Eur J Heart Fail 2013;15:130–40.

79. Riehle C, Abel ED. Insulin signaling and heart failure. Circ Res 2016;118:1151–69.

80. Badolia R, Ramadurai DKA, Abel ED, et al. The role of nonglycolytic glucose metabolism in myocardial recovery upon mechanical unloading and circulatory support in chronic heart failure. Circulation 2020;142:259–74.

81. Raez LE, Papadopoulos K, Ricart AD, et al. A phase I dose-escalation trial of 2-deoxy-D-glucose alone or combined with docetaxel in patients with advanced solid tumors. Cancer Chemother Pharmacol 2013;71:523–30.

82. Wu R, Wyatt E, Chawla K, et al. Hexokinase II knockdown results in exaggerated cardiac hypertrophy via increased ROS production. EMBO Mol Med 2012;4:633–46.

83. Warburg O. Origin of cancer cells. Article in German. Oncologia 1956;9:75–83.

84. Warburg O. On respiratory impairment in cancer cells. Science 1956;124:269–70.

85. Warburg O. On the origin of cancer cells. Science 1956;123:309–14.

86. Kato T, Niizuma S, Inuzuka Y, et al. Analysis of metabolic remodeling in compensated left ventricular hypertrophy and heart failure. Circ Heart Fail 2010;3:420–30.

87. McMurtry MS, Bonnet S, Wu X, et al. Dichloroacetate prevents and reverses pulmonary hypertension by inducing pulmonary artery smooth muscle cell apoptosis. Circ Res 2004;95:830–40.

88. McCommis KS, Douglas DL, Krenz M, Baines CP. Cardiac-specific hexokinase 2 overexpression attenuates hypertrophy by increasing pentose phosphate pathway flux. J Am Heart Assoc 2013;2:e000355.

89. Liao R, Jain M, Cui L, et al. Cardiac-specific overexpression of GLUT1 prevents the development of heart failure attributable to pressure overload in mice. Circulation 2002;106:2125–31.

90. Chambers KT, Leone TC, Sambandam N, et al. Chronic inhibition of pyruvate dehydrogenase in heart triggers an adaptive metabolic response. J Biol Chem 2011;286:11155–62.

91. McMullen JR, Shioi T, Huang WY, et al. The insulin-like growth factor 1 receptor induces physiological heart growth via the phosphoinositide 3-kinase(p110alpha) pathway. J Biol Chem 2004;279:4782–93.

92. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–38.

93. Park EJ, Lee JH, Yu GY, et al. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell 2010;140:197–208.

94. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009;16:1103–23.

95. Abdel-Wahab AF, Mahmoud W, Al-Harizy RM. Targeting glucose metabolism to suppress cancer progression: prospective of anti-glycolytic cancer therapy. Pharmacol Res 2019;150:104511.

96. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science 2009;324:1029–33.

97. Yu L, Lu M, Jia D, et al. Modeling the genetic regulation of cancer metabolism: interplay between glycolysis and oxidative phosphorylation. Cancer Res 2017;77:1564–74.

98. Sack MN, Rader TA, Park S, Bastin J, McCune SA, Kelly DP. Fatty acid oxidation enzyme gene expression is downregulated in the failing heart. Circulation 1996;94:2837–42.

99. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res 2000;86:580–8.

100. Gao D, Ning N, Niu X, Hao G, Trimetazidine Meng Z. a meta-analysis of randomised controlled trials in heart failure. Heart 2011; 97:278–86.

101. Razani B, Zhang H, Schulze PC, et al. Fatty acid synthase modulates homeostatic responses to myocardial stress. J Biol Chem 2011;286: 30949–61.

102. Zhao S, Torres A, Henry RA, et al. ATP-citrate lyase controls a glucose-to-acetate metabolic switch. Cell Rep 2016;17:1037–52.

103. Dean EJ, Falchook GS, Patel MR, et al. Preliminary activity in the first in human study of the first-in-class fatty acid synthase (FASN) inhibitor, TVB-2640. J Clin Oncol 2016;34. 2512-2512.

104. Lee L, Campbell R, Scheuermann-Freestone M, et al. Metabolic modulation with perhexiline in chronic heart failure: a randomized, controlled trial of short-term use of a novel treatment. Circulation 2005;112:3280–8.

105. Kaimoto S, Hoshino A, Ariyoshi M, et al. Activation of PPAR-alpha in the early stage of heart failure maintained myocardial function and energetics in pressure-overload heart failure. Am J Physiol Heart Circ Physiol 2017;312:H305–13.

106. Kalender A, Selvaraj A, Kim SY, et al. Metformin, independent of AMPK, inhibits mTORC1 in a rag GTPase-dependent manner. Cell Metab 2010;11:390–401.

107. Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. Diabetologia 2017;60:1620–9.

108. Bergmark BA, Bhatt DL, McGuire DK, et al. Metformin use and clinical outcomes among patients with diabetes mellitus with or without heart failure or kidney dysfunction: observations from the SAVOR-TIMI 53 trial. Circulation 2019;140: 1004–14.

109. Nielsen R, Moller N, Gormsen LC, et al. Cardiovascular effects of treatment with the ketone body 3-hydroxybutyrate in chronic heart failure patients. Circulation 2019;139:2129–41.

110. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019; 381:1995–2008.

111. Kosiborod MN, Jhund PS, Docherty KF, et al. Effects of dapagliflozin on symptoms, function, and quality of life in patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial. Circulation 2020;141:90–9.

112. Ferrannini E, Baldi S, Frascerra S, et al. Shift to fatty substrate utilization in response to sodium-glucose cotransporter 2 inhibition in subjects without diabetes and patients with type 2 diabetes. Diabetes 2016;65:1190–5.

113. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, et al. Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. J Am Coll Cardiol 2019;73:1931–44.

114. Martinez-Outschoorn UE, Lin Z, Whitaker-Menezes D, Howell A, Sotgia F, Lisanti MP. Ketone body utilization drives tumor growth and metastasis. Cell Cycle 2012;11:3964–71.

115. Cohen CW, Fontaine KR, Arend RC, Soleymani T, Gower BA. Favorable effects of a ketogenic diet on physical function, perceived energy, and food cravings in women with ovarian or endometrial cancer: a randomized, controlled trial. Nutrients 2018;10(9):1187.

116. Klement RJ, Champ CE, Kammerer U, et al. Impact of a ketogenic diet intervention during radiotherapy on body composition: III–final results of the KETOCOMP study for breast cancer patients. Breast Cancer Res 2020;22:94.

117. Martin-McGill KJ, Marson AG, Tudur Smith C, et al. Ketogenic diets as an adjuvant therapy for glioblastoma (KEATING): a randomized, mixed methods, feasibility study. J Neurooncol 2020; 147:213–27.

118. Andre F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 2019;380:1929–40.

119. Juric D, Janku F, Rodon J, et al. Alpelisib plus fulvestrant in PIK3CA-altered and PIK3CA-wild-type estrogen receptor-positive advanced breast cancer: a phase 1b clinical trial. JAMA Oncol 2019; 5:e184475.

120. Mayer IA, Abramson VG, Formisano L, et al. A phase Ib study of alpelisib (BYL719), a PI3Kalpha-specific inhibitor, with letrozole in ER+/HER2- metastatic breast cancer. Clin Cancer Res 2017;23:26–34.

121. Das M, Ellies LG, Kumar D, et al. Time-restricted feeding normalizes hyperinsulinemia to inhibit breast cancer in obese postmenopausal mouse models. Nat Commun 2021;12:565.

122. Cienfuegos S, Gabel K, Kalam F, et al. Effects of 4- and 6-h time-restricted feeding on weight and cardiometabolic health: a randomized controlled trial in adults with obesity. Cell Metab 2020;32:366–78.e3.

123. Watanabe K, Nagao M, Toh R, et al. Critical role of glutamine metabolism in cardiomyocytes under oxidative stress. Biochem Biophys Res Commun 2021;534:687–93.

124. Peyton KJ, Liu XM, Yu Y, Yates B, Behnammanesh G, Durante W. Glutaminase-1 stimulates the proliferation, migration, and survival of human endothelial cells. Biochem Pharmacol 2018;156:204–14.

125. Schoonjans CA, Mathieu B, Joudiou N, et al. Targeting endothelial cell metabolism by inhibition of pyruvate dehydrogenase kinase and glutaminase-1. J Clin Med 2020;9(10):3308.

126. Lee JS, Kang JH, Lee SH, et al. Dual targeting of glutaminase 1 and thymidylate synthase elicits death synergistically in NSCLC. Cell Death Dis 2016;7:e2511.

127. Hollinger KR, Smith MD, Kirby LA, et al. Glutamine antagonism attenuates physical and cognitive deficits in a model of MS. Neurol Neuroimmunol Neuroinflamm 2019;6(6):e609.

128. Nedelcovych MT, Kim BH, Zhu X, et al. Glutamine antagonist JHU083 normalizes aberrant glutamate production and cognitive deficits in the EcoHIV murine model of HIV-associated neurocognitive disorders. J Neuroimmune Pharmacol 2019;14:391–400.

129. Hage FG, ALJaroudi WA. Review of cardiovascular imaging in the Journal of Nuclear Cardiology in 2017. Part 2 of 2: myocardial perfusion imaging. J Nucl Cardiol 2018;25:1390–9.

130. Pirro M, Simental-Mendia LE, Bianconi V, Watts GF, Banach M, Sahebkar A. Effect of statin therapy on arterial wall inflammation based on 18F-FDG PET/CT: a systematic review and meta-analysis of interventional studies. J Clin Med 2019;8(1):118.

131. Alpert NM, Guehl N, Ptaszek L, et al. Quantitative in vivo mapping of myocardial mitochondrial membrane potential. PLoS One 2018;13: e0190968.

132. Madak JT, Neamati N. Membrane permeable lipophilic cations as mitochondrial directing groups. Curr Top Med Chem 2015;15:745–66.

133. Zielonka J, Joseph J, Sikora A, et al. Mitochondria-targeted triphenylphosphonium-based compounds: syntheses, mechanisms of action, and therapeutic and diagnostic applications. Chem Rev 2017;117:10043–120.

134. Ehrenberg B, Montana V, Wei MD, Wuskell JP, Loew LM. Membrane potential can be determined in individual cells from the Nernstian distribution of cationic dyes. Biophys J 1988;53: 785–94.

135. Sharma V, Beatty A, Wey SP, et al. Novel gallium(III) complexes transported by MDR1 P-glycoprotein: potential PET imaging agents for probing P-glycoprotein-mediated transport activity in vivo. Chem Biol 2000;7:335–43.

136. Nekolla SG, Reder S, Saraste A, et al. Evaluation of the novel myocardial perfusion positron-emission tomography tracer 18F-BMS-747158-02: comparison to 13N-ammonia and validation with microspheres in a pig model. Circulation 2009;119: 2333–42.

137. Yalamanchili P, Wexler E, Hayes M, et al. Mechanism of uptake and retention of F-18 BMS-747158-02 in cardiomyocytes: a novel PET myocardial imaging agent. J Nucl Cardiol 2007;14: 782–8.

138. Klabunde RE. Cardiac electrophysiology: normal and ischemic ionic currents and the ECG. Adv Physiol Educ 2017;41:29–37.

139. Oizel K, Gratas C, Nadaradjane A, Oliver L, Vallette FM, Pecqueur C. D-2-Hydroxyglutarate does not mimic all the IDH mutation effects, in particular the reduced etoposide-triggered apoptosis mediated by an alteration in mitochondrial NADH. Cell Death Dis 2015;6:e1704.

140. Fu X, Chin RM, Vergnes L, et al. 2-Hydroxyglutarate inhibits ATP synthase and mTOR signaling. Cell Metab 2015;22:508–15.

141. Piwnica-Worms D, Chiu ML, Budding M, Kronauge JF, Kramer RA, Croop JM. Functional imaging of multidrug-resistant P-glycoprotein with an organotechnetium complex. Cancer Res 1993;53:977–84.

142. Karamanlidis G, Lee CF, Garcia-Menendez L, et al. Mitochondrial complex I deficiency increases protein acetylation and accelerates heart failure. Cell Metab 2013;18:239–50.

143. O'Farrell AC, Evans R, Silvola JM, et al. A novel positron emission tomography (PET) approach to monitor cardiac metabolic pathway remodeling in response to sunitinib malate. PLoS One 2017;12:e0169964.

144. Vlachopoulos CV, Koutagiar IP, Georgakopoulos AT, et al. Lymphoma severity and type are associated with aortic FDG uptake by 18F-FDG PET/CT imaging. J Am Coll Cardiol CardioOnc 2020;2:758–70.

145. Thorens B, Mueckler M. Glucose transporters in the 21st century. Am J Physiol Endocrinol Metab 2010;298:E141–5.

146. Richter EA, Hargreaves M. Exercise, GLUT4, and skeletal muscle glucose uptake. Physiol Rev 2013;93:993–1017.

147. Szablewski L. Glucose transporters in healthy heart and in cardiac disease. Int J Cardiol 2017;230:70–5.

148. Tsai HJ. Functional organization and evolution of mammalian hexokinases: mutations that caused the loss of catalytic activity in N-terminal halves of type I and type III isozymes. Arch Biochem Biophys 1999;369:149–56.

149. Caraco C, Aloj L, Chen LY, Chou JY, Eckelman WC. Cellular release of [18F]2-fluoro-2-deoxyglucose as a function of the glucose-6-phosphatase enzyme system. J Biol Chem 2000;275:18489–94.

150. Kim MJ, Lee CH, Lee Y, et al. Glucose-6-phosphatase expression-mediated [(18)F]FDG efflux in murine inflammation and cancer models. Mol Imaging. Biol 2019;21:917–25.

151. Qu W, Zha Z, Ploessl K, et al. Synthesis of optically pure 4-fluoro-glutamines as potential metabolic imaging agents for tumors. J Am Chem Soc 2011;133:1122–33.

152. Huang Y, Liu S, Wu R, et al. Synthesis and preliminary evaluation of a novel glutamine derivative: (2S,4S)4-[(18)F]FEBGln. Bioorg Med Chem Lett 2019;29:1047–50.

153. Salabei JK, Lorkiewicz PK, Holden CR, et al. Glutamine regulates cardiac progenitor cell metabolism and proliferation. Stem Cells 2015;33:2613–27.

154. van Geldermalsen M, Wang Q, Nagarajah R, et al. ASCT2/SLC1A5 controls glutamine uptake and tumour growth in triple-negative basal-like breast cancer. Oncogene 2016;35:3201–8.

155. Kennel PJ, Liao X, Saha A, et al. Impairment of myocardial glutamine homeostasis induced by suppression of the amino acid carrier SLC1A5 in failing myocardium. Circ Heart Fail 2019;12:e006336.

156. Hesketh RL, Brindle KM. Magnetic resonance imaging of cancer metabolism with hyperpolarized (13)C-labeled cell metabolites. Curr Opin Chem Biol 2018;45:187–94.

157. Keshari KR, Wilson DM. Chemistry and biochemistry of 13C hyperpolarized magnetic resonance using dynamic nuclear polarization. Chem Soc Rev 2014;43:1627–59.

158. Chaumeil MM, Najac C, Ronen SM. Studies of metabolism using (13)C MRS of hyperpolarized probes. Methods Enzymol 2015;561:1–71.

159. Bhattacharya P, Ross BD, Bunger R. Cardiovascular applications of hyperpolarized contrast media and metabolic tracers. Exp Biol Med (Maywood) 2009;234:1395–416.

160. Dutta P, Pando SC, Mascaro M, et al. Early detection of pancreatic intraepithelial neoplasias (PanINs) in transgenic mouse model by hyperpolarized (13)C metabolic magnetic resonance spectroscopy. Int J Mol Sci 2020;21(10):3722.

161. Rao Y, Gammon S, Zacharias NM, et al. Hyperpolarized [1-(13)C]pyruvate-to-[1-(13)C] lactate conversion is rate-limited by monocarboxylate transporter-1 in the plasma membrane. Proc Natl Acad Sci U S A 2020;117:22378–89.

162. Lau AZ, Chen AP, Ghugre NR, et al. Rapid multislice imaging of hyperpolarized 13C pyruvate and bicarbonate in the heart. Magn Reson Med 2010;64:1323–31.

163. Cunningham CH, Lau JY, Chen AP, et al. Hyperpolarized 13C metabolic MRI of the human heart: initial experience. Circ Res 2016;119:1177–82.

164. Johannsson E, Lunde PK, Heddle C, et al. Upregulation of the cardiac monocarboxylate transporter MCT1 in a rat model of congestive heart failure. Circulation 2001;104:729–34.

165. Gabriel-Costa D, Cunha TF, Paixao NA, et al. Lactate-upregulation of lactate oxidation complex-related genes is blunted in left ventricle of myocardial infarcted rats. Braz J Med Biol Res 2018;51:e7660.

166. Cluntun AA, Badolia R, Lettlova S, et al. The pyruvate-lactate axis modulates cardiac hypertrophy and heart failure. Cell Metab 2021;33(3):629–48.e10.

167. Buchthal SD, den Hollander JA, Merz CN, et al. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. N Engl J Med 2000;342:829–35.

168. Conway MA, Bristow JD, Blackledge MJ, Rajagopalan B, Radda GK. Cardiac metabolism during exercise in healthy volunteers measured by 31P magnetic resonance spectroscopy. Br Heart J 1991;65:25–30.

169. Purvis LAB, Valkovic L, Robson MD, Rodgers CT. Feasibility of absolute quantification for (31) P MRS at 7 T. Magn Reson Med 2019;82:49–61.

170. Bakermans AJ, Bazil JN, Nederveen AJ, et al. Human cardiac (31)P-MR spectroscopy at 3 Tesla cannot detect failing myocardial energy homeostasis during exercise. Front Physiol 2017;8:939.

171. Asnani A, Shi X, Farrell L, et al. Changes in citric acid cycle and nucleoside metabolism are associated with anthracycline cardiotoxicity in patients with breast cancer. J Cardiovasc Transl Res 2020;13:349–56.

172. Armenian SH, Gelehrter SK, Vase T, et al. Carnitine and cardiac dysfunction in childhood cancer survivors treated with anthracyclines. Cancer Epidemiol Biomarkers Prev 2014;23:1109–14.

173. Rhee J-W, Ky B, Armenian SH, Yancy CW, Wu JC. Primer on biomarker discovery in cardio-oncology. J Am Coll Cardiol CardioOnc 2020;2:379–84.

KEY WORDS cancer, cardio-oncology, heart failure, metabolism, oncometabolism