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Cardio-Onco-Metabolism – Metabolic vulnerabilities in cancer and the heart

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Abstract

Cancer and cardiovascular diseases (CVDs) are the leading cause of death worldwide. Metabolic remodeling is a hallmark of both cancer and the failing heart. Tumors reprogram metabolism to optimize nutrient utilization and meet increased demands for energy provision, biosynthetic pathways, and proliferation. Shared risk factors for cancer and CVDs suggest intersecting mechanisms for disease pathogenesis and progression. In this review, we aim to highlight the role of metabolic remodeling in cancer and its potential to impair cardiac function. Understanding these mechanisms will help us develop biomarkers, better therapies, and identify patients at risk of developing heart disease after surviving cancer.

Keywords

Cardio-oncology; Metabolism; Metabolic remodeling; Tumor metabolism; Oncometabolism; D2-HG

1. Introduction

Cardio-oncology has emerged as a new field due to novel cancer therapies and management which have improved overall survival for patients. In the United States of America, the survival rate of cancer patients has increased on average to 68% in 2019 [1,2]. Especially, the success of modern therapies to target cancer cells has increased the likelihood of survival from childhood cancers [3]. Despite these advancements, survivors are at a higher risk in developing cardiovascular disease (CVDs) and are about 10-times more likely to die from CVDs [4-7]. In fact, the number of cardiac-related deaths in survivors of childhood cancers exceeds those in the average population [8,9]. The cardio-oncology field is based on the principle that altered cellular activities in cancer cells support the development of CVDs, due to shared common risk factors (e.g., diabetes, obesity) and

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interactions at the molecular level in addition to treatment-related toxicities [1,4,9,10]. Metabolic remodeling is considered a hallmark of cancer and heart failure with a systemic impact on the body [11,12]. Recent studies indicate that metabolic alterations in cancer cells - or oncometabolism - contribute to disease progression and increase the risk for cancer survivors to develop CVDs [8,9,13]. How metabolism becomes reprogrammed in cancer cells or cardiomyocytes, how these activities enable other cellular functions, and how metabolic vulnerabilities can be used for therapeutic benefits are among key questions driving research in cardio-oncometabolism. This review covers fundamental principles in cardio-oncometabolism and recent technological advances, with the goal of introducing non-experts to the concepts and motivating ongoing research. Although metabolism has been a critical component of cardiovascular and cancer research for decades, the development of new technologies in mass spectrometry-based metabolite analysis, proteomics, and DNA/RNA sequencing has dramatically expanded our knowledge of the metabolic landscape [14-18]. We specifically focus on conceptual advances and recent discoveries in metabolic intersection between cardiovascular diseases and tumors, with particular attention to how novel techniques can aid metabolic analysis in translational models and how metabolic vulnerabilities in cancer cells can be translated into effective therapies.

2. Metabolic reprogramming in cancer and heart failure

Altered metabolic activities support adaptation in cardiomyocytes and cancer cells during disease progression. Events that modulate metabolism are driven by a shift in nutrient availability, changes in enzymatic activities through modulators, or protein expression. Characterization of metabolic remodeling provides opportunities to predict flux changes and to prevent disease progression by targeting specific pathways. In the heart, these alterations cause organ dysfunction, while in tumors, metabolic remodeling supports the acquisition and maintenance of malignant properties. An essential feature of cancer cells is the production of oncometabolites by deregulated enzymatic activities [19-21]. To understand the impact of tumor metabolism on other systems it is essential to distinguish between ‘metabolic remodeling’ and ‘oncometabolism’. The term ‘metabolic remodeling should be reserved for adaptation using conventional metabolic pathways in cells that respond to stress, tumorigenic mutations, or other factors. In contrast, oncometabolism or oncometabolites refer to metabolic changes that either (i) lead to the accumulation of a metabolite due to a specific mutation in a tumor or (ii) drive malignancy. Cancer cells and cardiomyocytes are adapting to stress by shifting nutrient uptake and utilization. Cancer cells utilize nutrients for macromolecule synthesis and anaplerotic pathways, while cardiomyocytes shift their nutrient uptake to maintain ATP provision and contractile function [12,22,23]. Several recent reviews have comprehensively described the different metabolic approaches cancer cells and cardiomyocytes apply in response to stress [24-28]. In the section below we will highlight some of the core principles of cardiac and cancer cell metabolism.

A classic example of reprogrammed metabolism is the shift from oxidative phosphorylation towards glycolysis during oxygen and nutrient stress. In cancer cells this shift was first described in the 1920s by Otto Warburg, who found that ascites cancer cells increased the uptake of glucose and production of lactate regardless of oxygen availability [29].

These alterations have since been reported in other cancer cells and tumors [30], which led to the perception that the stimulation of glycolysis or 'Warburg Effect' is a common feature of malignancy. However, comprehensive studies of cancer metabolism in vivo show that increased glycolysis may persist longside oxidative metabolism even in the same tumor [31,32]. In the failing heart, glucose is a crucial nutrient overtaking fatty acids in providing energy (ATP) for contraction and maintaining macromolecule synthesis (Fig. 1A) [33]. This metabolic flexibility allows both cancer cells and cardiomyocytes to utilize different substrate classes in biosynthetic pathways while balancing the demands of proliferation (cancer) and contraction (heart). Two critical metabolic pathways that have gained considerable recognition are glutaminolysis, which produces α-ketoglutarate from glutamine, and ketone body degradation, which incorporates carbons from 3-hydroxybutyrate acetoacetate into the Krebs cycle via acetyl-CoA (Fig. 1A). Both pathways are upregulated in different cancer types and cardiomyocytes in the failing heart [34,35]. For example, hypoxic cancer cells can use glutamine to fuel the Krebs cycle, maintain ATP provision, and donate nitrogen for macromolecule synthesis. Likewise, KRAS-driven pancreatic cancer cells show increased autophagic flux and protein degradation to scavenge glutamine and other amino acids for energy provision and cell proliferation [36]. Ketone bodies like 3-hydroxybutyrate and acetoacetate can act both as metabolic fuel and as an external signal through interaction with cell surface receptors [37,38]. Cancer cells take up ketone bodies from adjacent stromal cells, which can be used as precursors for acetyl-CoA and provide carbon flux into the Krebs cycle (Fig. 1A). Recent studies also showed that ketone bodies promote epigenetic modifications through increased histone acetylation [39,40].

The generation of oncometabolites is driven by mutations of metabolic enzymes in a subset of tumors. The list of oncometabolites is currently limited to D-2-hydroxyglutarate (D2-HG), succinate and fumarate [19,20,41]. These metabolites can serve as biomarkers and have a wide-ranging impact on cellular functions by inhibiting or activating endogenous systems. Somatic mutations in isocitrate dehydrogenase (*IDH*) 1 and 2 lead to the increased production of D2-HG, which is a reduced form of the Krebs cycle intermediate α-ketoglutarate (Fig. 1B). Unlike succinate and fumarate, D2-HG is virtually absent in normal tissues but rises to millimolar concentrations in tumors [14,42-45]. Mutations of *IDH1* or *IDH2* are found in about 80% of gliomas, 20% acute myelogenous leukemias, and 10% of colorectal cancers [19,46]. Therefore, D2-HG is used as a biomarker for disease monitoring, and novel inhibitors targeting specific mutants of *IDH1* and *IDH2* are in clinical trials for AML and solid tumors [46-48]. High levels of D2-HG interfere in cancer cells with nonmetabolic activities that require α-ketoglutarate as a co-substrate, including α-ketoglutarate-dependent dioxygenases such as EGLN prolyl 4-hydroxylases (also known as PHDs) and lysine demethylases (KDMs) [21,49,50]. D2-HG promotes transformation in cancer cells via TET enzymes and α-ketoglutarate-dependent dioxygenase. Initial reports suggested that EGLN enzymes are inhibited by D2-HG. However, recent data suggests that D2-HG can also act as an alternative co-substrate and activate certain EGLN enzymes, thus blunting hypoxia-induced stabilization of HIF α D2-HG is able to inhibit specific KDM enzymes resulting in aberrant hypermethylation of histone 3 lysine 9 (H3K9), which, in turn, masks a local H3K9 trimethylation signal and disrupts chromatin signaling [18,51]. Similar,

in the heart, D2-HG has been shown to impair contractile function in the heart through inhibition of the α-Ketoglutarate dehydrogenase and increased H3K9 methylation [14]. How these changes are linked to chromatin remodeling and altered gene expression in the heart is the focus of ongoing studies. The enantiomer L2-HG is not produced by mutant *IDH1* or *IDH2*, but most likely appears during hypoxia or oxidative stress through the noncanonical activities of malate dehydrogenase and lactate dehydrogenase [52]. During hypoxia or acidic conditions, L2-HG is produced in low millimolar concentrations. Both L2-HG and D2-HG can be oxidized back to α-ketoglutarate by two FAD-linked enzymes, L2HG dehydrogenase (L2HGDH) and D2HG dehydrogenase (D2HGDH), respectively. Deficiency of L2HGDH and D2HGDH causes L2-HG and D2-HG aciduria, respectively, and is a rare neurometabolic disease during infancy and childhood [43,44,53-55]. Affected children present with abnormalities, high levels of L2- or D2-HG, neurological abnormalities (e.g., seizures, mental retardation, reduced brain) and cardiomyopathy. A few cases have been reported in which children with L2HGDH deficiency developed malignant brain tumors indicating that L2- and D2-HG impair the similar enzymatic functions and signaling pathways [56,57]. Furthermore, L2-HG production has been linked to renal cell carcinoma due to reduced expression of L2HGDH.

Decarboxylation and reduction of α-ketoglutarate causes the production of succinate and subsequently fumarate. Both metabolites are structurally similar to α-ketoglutarate and can act as competitive inhibitors to α-ketoglutarate-dependent dioxygenases. Loss-of-function mutations of the succinate dehydrogenase (SDH) and fumarate hydratase (FH) cause the accumulation of succinate and fumarate, respectively. SDH and FH mutations have been described in a wide range of solid tumors including paraganglioma, gastrointestinal stromal tumors, renal cell carcinoma, as well as hereditary paraganglioma-pheochromocytoma (45) and leiomyomatosis. Limited clinical evidence indicates that germline mutations of SDH or FH are associated with cardiac impairment including dilated cardiomyopathy and arrythmias. Currently it is not clear to what extend loss-of-function mutations in both enzymes impair cardiac function. Like D2-HG, accumulation of succinate and fumarate disrupt DNA repair [18,58] and interfere with dioxygenase activities and inhibit the prolyl hydroxylase family of enzymes causing epigenetic remodeling in cancer cells [21,59]. Inhibition of prolyl hydroxylases leads to the stabilization of HIF-1α during normal oxygen supply [50,60,61]. Studies in human renal cell carcinoma indicate that fumarate covalently binds to sulfhydryl groups in glutathione, enhancing ROS and HIF-1α signaling [62,63]. Together succinate and fumarate act as tumor suppressors via canonical and non-canonical functions, which directly oppose mitotic signaling or promote apoptosis. Beyond the fundamental role of oxidative metabolism to maintain ATP provision, IDH and SDH activities are critical in regulating mitochondrial function and cell signaling during nutrient and oxygen limitation. Recent preclinical studies indicate that fumarate reduction and succinate oxidation are feasible by the SDH complex and depend on the availability of oxygen [64]. Likewise, reductive carboxylation of α-ketoglutarate through the reverse function of IDH1 or 2 has been shown in cancer cells with defective mitochondrial metabolism (Fig. 1C) [31], and implicated in the cardiac metabolic remodeling during D2-HG producing tumors [14]. It will be critical for future studies to investigate the

functions of these wildtype enzymes in the heart to understand the full extent of metabolic dysregulation during cancer.

3. Metabolism and cardiotoxicity of chemotherapies

Chemotherapy remains one of the most common therapeutic options for various cancer types, specifically in solid tumors at the advanced disease stage, resistance, or non-compliance to immunotherapy, and after surgical removal of the tumor [65]. The development of antimetabolites (e.g., 5-Fluorouracil and oxaliplatin) and anthracyclines (e.g., doxorubicin) have revolutionized the treatment of patients with leukemia as well as colorectal, lung, and breast cancer. Although these therapies are efficacious for the treatment of various types of cancer, severe cardiotoxicity and therapy resistance remain ongoing clinical problems [65]. Common adverse cardiovascular effects observed in chemotherapy were comprehensively reviewed elsewhere [65], and encompass a wide range of CVDS, including myocarditis, hypertension, arrhythmias, and heart failure. Each adverse effect can impair short-and long-term quality of life and overall therapy outcome in cancer patients and survivors.

New strategies to overcome these problems focus on the unique metabolic phenotype of cancer cells, which present actionable metabolic vulnerabilities [66]. Furthermore, alternative adjuvant therapies alongside specific chemotherapies may help prevent, limit, or improve the risk of developing CVDs in cancer patients and survivors. From a therapeutic perspective, genetically defined metabolic alterations in cancer cells provide opportunities for pharmacologic modulation and allow combination with existing therapies (Table 1). One of the most promising examples are *IDH1* and *IDH2* mutations in AML which cause production of the oncometabolite D2-HG and persistent metabolic alterations. The clinical efficacy of ivosidenib (Tibsovo) and enasidenib (Idhifa), two small molecule inhibitors targeting *IDH1* and *IDH2* mutations inhibitors, has been demonstrated in AML patients, and clinical trials in solid tumors (e.g., glioblastomas and cholangiocarcinoma) are currently pending (Table 1). In addition, recent studies indicate that non-mutant *IDH1* overexpression is a common metabolic adaptation by glioblastomas, which - like its mutant *IDH1* counterpart - causes tumor growth and therapy resistance [67]. These findings may provide therapeutic opportunities beyond *IDH1*- and *IDH2*-mutant tumors.

New clinical opportunities may arise also from the contribution of different nutrients to tumor growth and common risk factors (e.g., diabetes and obesity). Two promising strategies have emerged that focus on (i) increasing nutrient uptake and oxidation (e.g., glucose) and (ii) reduce metabolic risk factors (e.g., diabetes, obesity). Several studies have shown that coupling of glucose uptake and oxidation improves cardiac function in heart failure models [82-85]. Upon transport across the cell membrane, glucose is rapidly phosphorylated to glucose-6 phosphate and converted to pyruvate in the glycolysis. Pyruvate is further decarboxylated in the Krebs cycle facilitating provision of ATP via oxidative phosphorylation. Mismatch between oxygen supply and ATP demand limits pyruvate flux into the Krebs cycles causing an accumulation of glycolytic intermediates. Recent studies have shown that metabolic flux through glycolysis is tightly regulated at several steps including glucose-6 phosphate and dihydroxyacetone phosphate [22]. Glycolytic

intermediates can funnel into anabolic pathways to support de novo synthesis of nucleotides or proteins [86]. Thus, both glycolysis and Krebs cycle function support macromolecular synthesis. A case in point is the development of drugs that target insulin or glucose transporter activities [87,88]. The phosphatidylinositol-3-kinase (PI3K) pathway plays a critical role in the regulation of signaling pathways and integrates stimuli from hormones (e.g., insulin), cytokines and growth factors which bind to receptor coupled tyrosine kinases [89,90]. PI3K mutations have been identified in several tumors, f.exp. breast, endometrial and brain cancer [87]. Alterations during malignancy lead to excessive PI3K signaling resulting in tissue growth and increased glucose metabolism in cancer cells. Pharmacologic strategies targeting PI3K hold the promise to disrupt this cascade and suppress tumor growth [71, 72]. The challenge is to develop therapies that target the dysregulation of PI3K/insulin signaling in tumors without disrupting normal tissues and wildtype isoforms. Several PI3K inhibitors that entered clinical trials target both mutated and wildtype isoforms of PI3K that mediate insulin response in muscle, liver, and fat, which causes a corresponding increase in blood glucose levels and upregulation of pancreatic insulin release (Table 1) [87]. In certain patients these compensatory mechanisms reactivate PI3K signaling in cancer cells which promotes tumor growth and causes therapy resistance [71]. An improved selectivity of PI3K inhibitors hold the promise of reducing hyperglycemia and systemic metabolic dysregulation, thus reducing therapy resistance.

Oncogenic driver mutaions in PI3K [91], KRAS or BRAF promote downstream activation of the mammalian target of rapamycin complex (mTORC) 1 and 2. Hyperactivation of mTORC1 and 2 is observed in different types of solid tumors including brain, breast, lung, colon, and liver [92,73]. Two mTOR inhibitors, everolimus and temsirolimus, are clinically approved for the treatment of advanced renal cell carcinoma (Table 1). Several ATP-competitive mTOR inhibitors have entered clinical trials for the treatment of solid tumors. These inhibitors class compete with the binding of ATP and target both mTORC1 and 2. Recent clinical trials indicate that several inhibitors show promising results in the treatment of primary effusion lymphoma and non-Hodgkin B cell lymphoma [74,75]. Furthermore, dual inhibition of PI3K/mTOR holds the promise of reducing tumor growth and chemoresistance of cancer cells. Several drugs targeting both PI3K and mTOR are currently in phase I and II clinical trials [93]. Unfortunately, most clinical trials reported dose-limiting toxicities (e.g., myocardial ischemia, hyperglycemia, and fatigue) or no clinical activity which have limited clinical applications [94].

Another metabolic vulnerability in cancer cell progression is the increased reliance on fatty acid synthesis in the advanced stages of the disease. The expression of fatty acid synthase and ATP-dependent citrate lyase (ACLY) are significantly increased in metastatic breast cancer, colorectal carcinoma, and pancreatic tumors. Recent studies suggest that there is a limited lipid availability in solid tumors, making cancer cells dependent on de novo synthesis to proliferate over time [95]. Disrupting acetyl-CoA synthesis via ACLY inhibitor bempedoic acid in preclinical models of ovarian cancer, prostate cancer, colorectal cancer, and cervical cancer decreased tumor progression in mice and improved the efficacy of chemotherapies in otherwise resistant cancer cells (Table 1) [96,97]. Together, the advantage of these strategies is that these metabolic treatments are specific and have shown to be very effective. A challenge arises in advancing metabolic therapies to the clinic. Targeting

fatty acid oxidation by inhibiting carnitine palmitoyltransferase I (CPT1) or transcriptional regulation has shown an effect in some tumors. Pharmacologic modulation of fatty acid oxidation by selective inhibition of carnitine palmitoyltransferase 1 (CPT1) [98] and 3-ketoacyl coenzyme-A thiolase (3-KAT) [99,100] or activation of peroxisome proliferator-activated receptor (PPAR) α (Table 1) [101] have shown promising results in tumors. However, in the treatment of heart failure, CPT1 inhibitors have not been successful due to severe side effects raising the question of how to prevent cardiotoxicity with otherwise effective metabolic therapeutic interventions [102,103].

A second pharmacologic strategy focuses on reducing risk factors for cancer patients. In recent years there is increasing awareness for shared risk factors in cancer and heart failure, especially obesity and diabetes [104-108]. Suppression of androgen or estrogen in endocrine therapies during breast or prostate cancer has improved clinical outcomes. However, endocrine therapy is associated with treatment-related side effects that can increase the risk for cardiovascular morbidity and mortality through hormonal alteration of blood lipid profiles, insulin resistance, and diabetes. For example, metformin, a pleiotropic antidiabetic agent, reduces cardiovascular death among patients with type 2 diabetes mellitus [109] and reduces plasma levels of insulin, as well as insulinlike growth factor 1 (IGF-1). Similar effects have been observed in cancer patients, where metformin therapy has been shown to reduce mortality, tumor growth and limit adverse effects from the chemotherapy [110-113]. Therefore, metformin can be used as a complementary therapeutic agent for cancer treatment and preventing CVDs. Ketogenic diets and intermittent fasting have shown cardiovascular benefits in both pre-clinical models and human trials [114-119]. Both dietary regimens are associated with reduced blood glucose levels, insulin resistance, and inflammation, limiting tumor growth and reducing risk factors associated with CVDs and cancer. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a novel class of oral anti-hyperglycemic drugs that have been approved for the treatment of diabetes mellitus [76,77]. Currently three selective SGLT2 inhibitors are FDA approved: canagliflozin (Invokana), dapagliflozin (Fraxiga) and empagliflozin (Jardiance). SGLT2 inhibitors reduce renal tubular glucose reabsorption, which causes a reduction in blood glucose levels [120,121]. In patients with type 2 diabetes mellitus, SGLT2 inhibitors have shown to lower blood glucose levels and body weight without impacting cardiovascular safety [122,76]. Adverse events in SGLT2 inhibitors are wide ranging including hypoglycemia and ketoacidosis. Preclinical studies indicate that SGLT2 inhibition is efficacious in slowing tumor growth in murine models of obesity [77] and tumors with high expression of SGLT2, including lung adenocarcinoma [123]. Challenges arise in identifying patients most likely to benefit from metabolic therapies and modifying risk factors that are known to contribute to cancer and cardiovascular diseases. Close collaborations between basic researchers and clinicians are necessary to address if these metabolic therapies are advantageous and to develop new therapeutic approaches for cancer and heart failure patients.

4. Innovative technologies for discovery-oriented approaches

Recent advances in our understanding of cardiac metabolic remodeling during cancer have been driven by advanced technologies that allow us to measure genomic, proteomic, and metabolomic information accurately. The detection and quantification

of metabolites (metabolomics) is necessary to understand the molecular mechanism of disease developments and adverse therapy effects. Furthermore, biomarker discovery is critical in providing risk stratification for patients and to develop clinical protocols for treatments [124]. It is important to distinguish metabolite quantification (metabolomics) from measuring metabolic activities or flux analysis. It is not possible to interfere alterations in metabolic flux from metabolite levels alone [22,125]. Changes in metabolite levels may derive either from processes that directly affect the synthesis or removal of a given metabolite, f.exp. through altered transporter or enzyme activities. Combining metabolomics with flux analysis through tracers or computational techniques provides a comprehensive assessment of metabolic alterations [126,127]. The analysis of metabolites is commonly realized through nuclear magnetic resonance (NMR) or mass spectrometry coupled to gas or liquid chromatography (GC/LC-MS) (Fig. 2). Targeted (hypothesis--driven) metabolomics detects ions from known metabolites, while untargeted (hypothesis-generating) metabolomics records all ions within a specific mass range, including ions belonging to structurally novel metabolites. Therefore, targeted metabolomics may cover a few hundred metabolites whereas untargeted metabolomics allows the detection of thousands of molecules. Here, the limitation is the biological interpretation of unknown metabolites and lack of validation through standards. The development of higher resolution mass spectrometry and implementation of data analysis platforms (e.g., Reactome) have improved accessibility of metabolomics approaches for a broad range of cancer and cardiovascular studies. Especially the detection and quantification of lipids has dramatically expanded. Lipids are a diverse class of molecules that are gaining potential as therapeutic targets in disease states such as cancer and cardiovascular diseases. The analysis of lipids (lipidomics) poses a unique analytical challenge within the field of metabolomics because many lipid species are structural isomers. MS alone cannot distinguish between structural isomers and requires complementary separation methods. Recent advances in MS and separation techniques have enabled the discrimination of isomers [128-130]. However, currently there is no single analytical technique that can resolve the entire metabolome and lipidome including isomers. The development of ion mobility-mass spectrometry (IM-MS) for metabolomic and lipidomic analyses allows to quantify structural alterations based on headgroup, acyl chain length, and the degree of unsaturation [131-135].

Metabolism is dynamic and heterogenous even within the same tissue. Capturing metabolic alterations is challenging and require the development of *in vitro* and *ex vivo* models that facilitate metabolic studies and mimic the complexity of *in vivo* systems in a lab-based setting [36,32]. *Ex vivo* working heart perfusions have been a cornerstone of cardiovascular research for decades [136], which allow mimicking physiologic nutrient and hemodynamic conditions. Perfusion techniques are limited by throughput and experiment duration. Therefore, cell culture models are often used to complement discovery-based research. However, *in vitro* culture models of murine or human induced pluripotent stem cell-derived cardiomyocytes are limited in a classic 2D culture setting [137]. Similar, a lack of efficacy in some cancer models and use of 3-D cell culture models have limited drug discoveries [138]. Recent efforts aim to implement physiologically relevant cell culture models with new media formulations [139] and define standards for the evaluation of in vitro models. The PREDECT consortium (https://www.imi.europa.eu) aims to compare and

better characterize *in vitro* models for cancer research, especially models that attempt to study the complexity of human cancers through 3-D cultures [140]. Recent development of high-throughput experimental models in cardiovascular research that mimic cardiac structure may provide clinically relevant discoveries [137,141]

A powerful tool to measure metabolic changes are metabolic flux studies, which use stable isotope tracers (e.g., ^{13}C, ^{15}N, or ^{2}H) or radioisotope probes (e.g., ^{14}C, ^{18}F) to track flow through metabolic pathways (Fig. 2) [142-145]. Labeled nutrients (e.g., [U-^{13}C]glucose) are supplied to cells or animals through media, food, water supplementation, or direct infusion into the bloodstream. The extent and distribution of labeling within metabolites allow determining which pathways or reactions are differentially active in response to stress or mutations. Combining this information with additional data, including oxygen consumption or nutrient uptake rates, allows determining flux rates across metabolic networks. Stable isotope tracer studies allow assessing the dynamic range of metabolic remodeling that cannot be determined from metabolite levels alone. Theoretical concepts and mathematical approaches in stable isotope tracer analysis have been reviewed extensively elsewhere [125]. Several recent studies have begun to use stable isotopes to investigate cardiac metabolism *in vivo* [146-149]. Because stable isotopes do not undergo radioactive decay, they are safe for administration to both animals and human subjects. A recent study by Ritterhof et al. using ^{15}N and ^{13}C stable isotope tracing showed that glucose but not glutamine contributed to increased biosynthesis of aspartate during cardiac hypertrophy [148]. Similarly, Neinast et al. used in vivo isotope tracing to quantify branched chain amino acid oxidation (BCAA) in healthy and insulin-resistant mice [147]. Systemic administration of ^{15}N or ^{13}C-labeled nutrients through intermittent or continuous infusions has been shown to generate intermediary metabolites in the heart during various disease models [147,149]. Likewise, recent studies have used stable isotopes to investigate metabolism in intact tumors as part of clinical studies [23,36,95]. Metabolic dependencies evolve during tumorigenesis and heart failure. Thus, metabolic properties diverge over time and cause mixed metabolic phenotypes even within the same tumor or organ [23,25]. Administration of ^{13}C-labeled nutrients (e.g., lactate) has proven to be valuable to demonstrate that human non-small lung tumors metabolize glucose simultaneously through glycolysis and oxidative decarboxylation in the Krebs cycle [23,32].

The integration of different types of data is critical to understand the systems-wide impact of cancer and cardiac remodeling during diseases. Combining computational approaches with analytical techniques allows researchers to build both experimental platforms and understand metabolic vulnerabilities during disease progression (Fig. 2). Machine learning algorithms allow the identification of patterns and regulation for the unbiased analysis of large-scale data sets [150-152]. These approaches have been successfully applied to improve risk evaluation in cardiovascular patients [150], estimation of the cardiac ejection fraction from input echocardiogram [151], or evaluation of electrocardiograms [153]. The American Heart Association recently established the Precision Medicine Platform in a collaboration with Amazon Web Service [154]. This platform allows the dissemination and analysis of large-scale clinical data (see https://precision.heart.org/). Another application for machine learning and other computational approaches is the detection and functional analysis of metabolite-protein interactions [152]. Metabolic adaptation is regulated by enzyme

activity, changes in the abundance of proteins, or metabolic self-regulation [152,155]. The dynamic relationship between enzyme function and metabolites has been studied extensively, but only a fraction of metabolic enzymes have been purified and characterized. Here, mathematical modeling allows the identification of potential therapeutic targets while providing insight into the complex relationship between metabolites and proteins [152,156,157]. Biochemical reactions can be represented through metabolic networks and mathematical equations based on established knowledge. Together these systems-based approaches enable conceptualization of experimental data and testing biological hypotheses *in silico*. The integration of stable isotope tracers with computational modeling allows the estimation of flux distributions and provides theoretical explanations for observed label patterns for given metabolic intermediates [14,22,125].

In vivo preclinical imaging via positron emission tomography (PET), computer tomography (CT), and magnetic resonance imaging (MRI) can provide noninvasive and longitudinal assessment of metabolic alterations (Fig. 2). Imaging techniques for small animals are the same as in clinical setting and enable translational studies. Commonly used tracers for PET imaging are ^{18}F or ^{n}C-labeled nutrients including 2-^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) or amino acid tracers such as O-(2-^{18}F-fluoroethyl)-L-tyiosine (^{18}F-FET) and (S-^{n}C-methyl)-L-methionine (^{11}C-MET). These radio-labeled probes allow measuring transporter activities for nutrients (e.g., ^{18}F-FDG) or incorporation of nutrients into macromolecules (e.g., ^{11}C-MET). Clinical applications for these probes range from detecting, grading, and delineating the occurrence of solid tumors or cardiac injury to evaluating the response to treatment. Integrating imaging with metabolomics in preclinical murine models of cancers has identified new molecular targets and biomarkers for tumor detection. The novel PET probe ^{18}F-flurpiridaz (Lantheus) has a high affinity to mitochondrial complex I, thus yielding information about myocardial perfusion and mitochondria mass. Additionally, labeling of glutamine via ^{18}F-glutamine is emerging from preclinical research into clinical practice. In tumors upregulating the expression of glutamine transporters such as SLC1A5 [158], glutamine probes can be used to monitor the efficacy of glutaminase inhibitors. Likewise, SLC1A5 protein levels are downregulated in the failing heart thus ^{18}F-glutamine allows longitudinal clinical studies and evaluation of disease progression.

5. Conclusions and current challenges

Substantial progress has been made in recent years toward understanding the mechanisms of cardiac remodeling during cancer. First, several risk factors are shared between cancer and CVDs. Diabetes and obesity impact overall patient survival in both populations. Second, metabolic reprogramming is essential for adaptation in cancer and the failing heart to maintain macromolecule synthesis, growth, and energy provision. Third, alterations in key metabolic intermediates can affect cellular signaling, epigenetic remodeling, and gene expression through allosteric inhibition of enzymes, covalent modifications, or posttranslational modifications of proteins. Fourth, targeting metabolic pathways may reduce the cardiotoxicity of chemotherapies and prevent long-term cardiac remodeling. The field has expanded historic observations like the Warburg effect by combining technologies (e.g., mass spectrometry and sequencing) with computational analysis and machine learning algorithms. Challenges arise from modeling human tumors and organs in cell culture.

Direct analysis of flux distributions in the beating heart is necessary to provide translational data and bridge the gap between preclinical and clinical studies. Ultimately understanding the metabolic interactions between tumors and the heart will open new avenues for risk stratification of patients and the development of new therapeutic strategies.

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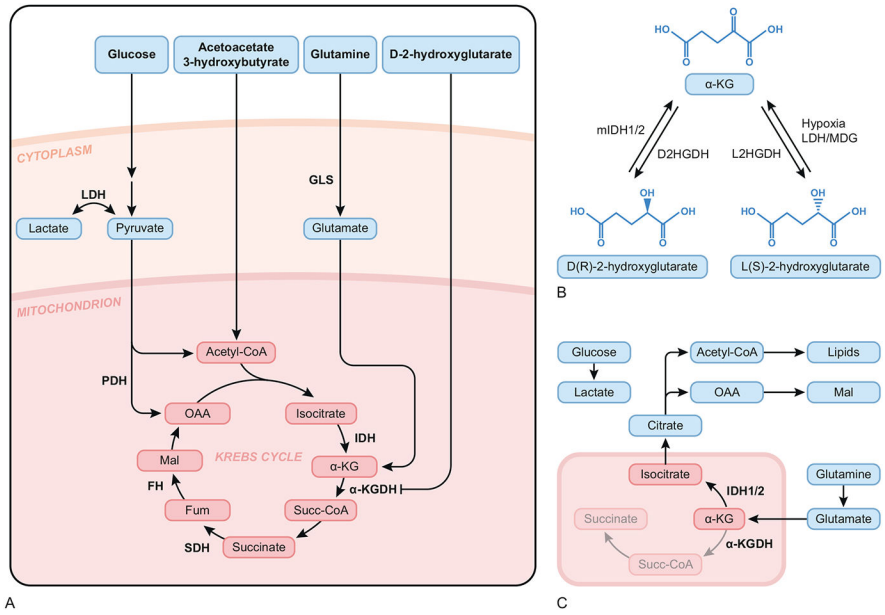

Fig. 1.

Metabolic pathways that regulate cardiac adaptation. (A) Glucose metabolism generates glycolytic intermediates that support ATP provision and cell growth. Glutamine and ketone bodies (acetoacetate and 3-hydroxybutyrate) provide carbons to the Krebs cycle at different points allowing generation of mitochondrial α-KG and acetyl-CoA, respectively. The oncometabolite D-2-hydroxyglutarate inhibits α-KGDH which impairs mitochondrial redox signaling and ATP provision. (B) Point mutation of IDH1 and 2 cause reduction of α-KG to D-2-hydroxyglutarate. Hypoxia or noncanonical function of LDH and MDH leads to the formation of L-2-hydroxyglutarate. Both L-2- and D-2-hydroxglutarate can be converted to α-KG via FAD-dependent L/D2HG dehydrogenase activities. (C) Reductive carboxylation of α-KG to citrate via reverse function of IDH1 or 2. Abbreviation: α-KG, α-ketoglutarate; α-KGDH, α-ketoglutarate dehydrogenase; DCA, dichloroacetate; Fum, fumarate; FH, fumarate hydratase; GLS, glutaminase; HK, hexokinase; IDH, isocitrate dehydrogenase; LDH, lactate dehydrogenase; Mal, Malate; MDH, Malate dehydrogenase; OAA, oxaloacetate; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; Succ, Succinyl-CoA; SDH, succinate dehydrogenase

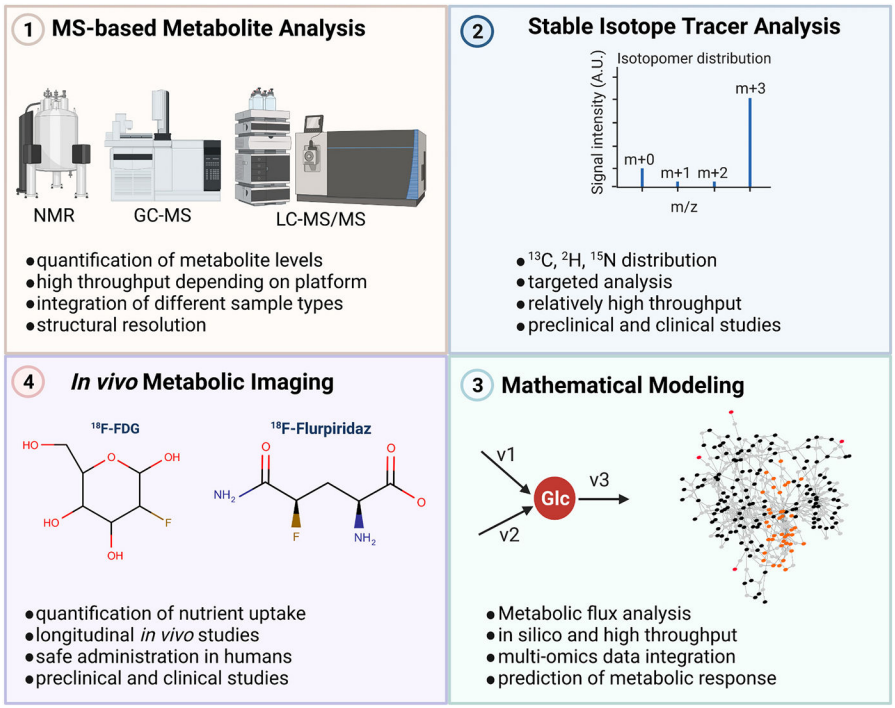

Fig. 2.

Technologies to assess metabolic alterations in preclinical and clinical models.

Table 1

Approved drugs with cardio-oncometabolic benefits or side effects.

Target	Approved drugs	Indication	Cardiovascular side effects	References
mIDH1	Ivosidenib	Acute myeloid leukemia, metastatic cholangiocarcinoma	Long QT syndrome, cardiomyopathy	[45,68-70]
mIDH2	Enasidenib	Acute myeloid leukemia		
PI3K	Alpelisib	HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer	Tachycardiac, increased CVD risk (hyperglycemia)	[71,72]
	Copanlisib	Relapsed follicular lymphoma		
mTOR	Everolimus	Advanced renal cell carcinoma, neuroendocrine tumors, advanced HR-positive, HER2 negative breast cancer	Hyperglycemia, dyslipidemia, arrythmia, cardiomyopathy	[73-75]
	Temsirolimus	Advanced renal cell carcinoma		
SGLT2	Dapagliflozin	Chronic kidney disease, Diabetes Mellitus Type II, Heart Failure	Euglycemic ketoacidosis, hypotension	[76,77]
	Canagliflozin	Chronic kidney disease, Diabetes Mellitus Type II		
ACLY	Bempedoic acid	Adjunct therapy for heterozygous familial hypercholesterolemia, atherosclerotic cardiovascular disease	Increased risk for myocardial infarction, stroke	[78,79]
CPT1	Irinotecan	Metastatic carcinoma of the colon or rectum	Cardiotoxcity, impaired oxidative metabolism	[80,81]