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Cardio-onco-metabolism: metabolic remodelling in cardiovascular disease and cancer

Anja Karlstaedt[1], Javid Moslehi[2] ✉ and Rudolf A. de Boer[3] ✉

Abstract | Cardiovascular disease and cancer are the two leading causes of morbidity and mortality in the world. The emerging field of cardio-oncology has revealed that these seemingly disparate disease processes are intertwined, owing to the cardiovascular sequelae of anticancer therapies, shared risk factors that predispose individuals to both cardiovascular disease and cancer, as well the possible potentiation of cancer growth by cardiac dysfunction. As a result, interest has increased in understanding the fundamental biological mechanisms that are central to the relationship between cardiovascular disease and cancer. Metabolism, appropriate regulation of energy, energy substrate utilization, and macromolecular synthesis and breakdown are fundamental processes for cellular and organismal survival. In this Review, we explore the emerging data identifying metabolic dysregulation as an important theme in cardio-oncology. We discuss the growing recognition of metabolic reprogramming in cardiovascular disease and cancer and view the novel area of cardio-oncology through the lens of metabolism.

The new field of cardio-oncology has blossomed because of the rapid growth in novel therapies for cancer. These treatments have revolutionized the overall prognosis and survival of patients with cancer, but cardiovascular and metabolic toxicities can occur[1]. Moreover, the intersection between cancer and cardiovascular disease (CVD) extends beyond toxicology[2]. Indeed, emerging data suggest that CVDs might potentiate cancer (a concept referred to as reverse cardio-oncology)[3]. One emerging aspect of this interaction is the metabolic milieu and metabolic switches that occur in both CVD and cancer. Tumours develop metabolic phenotypes that are distinct from those of adjacent, non-malignant tissue and, while providing cell-autonomous benefits for tumour growth, can also have cardiovascular and metabolic sequelae[4–6]. In addition, shared risk factors such as diabetes mellitus and obesity can predispose individuals to both CVD and cancer[7,8]. This concept has important public health implications and is especially relevant to a growing number of survivors of cancer, who are at high risk of developing CVD[9–13]. Indeed, several lines of evidence indicate that metabolism is a central mechanism in both CVD and cancer. Cross-disciplinary and cooperative research studies between cardiology and oncology are needed to translate findings from animal models to clinical applications, to improve patient care, and to use patient-derived samples for risk stratification and mechanistic studies.

In this Review, we highlight emerging themes in the field of cardio-oncology. We specifically look at these issues from the standpoint of metabolism, focusing on conceptual advances and the latest discoveries in the development of CVDs during tumour progression, with particular attention to how evolving metabolic and immunometabolic dependencies provide opportunities for therapeutic intervention to improve the care of patients with cancer and survivors of cancer[14–16].

Metabolism in cardiac and cancer cells

Metabolism is a defining feature of every living cell, providing energy, biosynthetic intermediates and defence mechanisms against reactive by-products of oxidative metabolism. The variations in metabolic profile between tissues or cells are defined by the metabolic pathways that are being used and the flux rates through these pathways. Cardiomyocytes and cancer cells share a unique capacity to maintain crucial cellular functions during periods of stress[17]. One governing factor is the demand for ATP and macromolecule synthesis in the form of proteins, lipids or complex sugars. The heart achieves a continuous supply of ATP for contractile activities through tight coupling between substrate uptake and oxidation, while maintaining the synthesis of structural proteins and lipids. The primary catabolic demands of cardiomyocytes are met predominantly by using fatty acids, which are preferred over carbohydrates (such as glucose) and amino acids under normal physiological conditions[18–20].

Various forms of stress, including increased physical activity, alterations in the blood composition of

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Key points

- Metabolic remodelling is a defining feature of both cardiovascular diseases and tumours.
- Metabolic dysregulation of cancer cells extends beyond the tumour microenvironment and can lead to both systemic and cardiac-specific consequences.
- Cardiovascular disease and cancer share several risk factors, including diabetes mellitus, dyslipidaemia, cachexia and an impaired immune response.
- Anticancer therapies can result in adverse cardiac events, including acute myocardial infarction and heart failure.
- Targeting metabolic features of cancer cells might limit tumour growth and also protect the heart against adverse remodelling.

nutrients or reduced supply of oxygen, can challenge cardiac metabolism and cause a mismatch between ATP demand and oxidative processes (FIG. 1a). For example, in the failing heart, cardiac metabolism shifts from oxidative phosphorylation to glycolytic ATP provision, which allows cardiac contractile function to be maintained and creates a metabolic profile that is similar to that of tumour cells[4,21]. During heart failure progression, the utilization of amino acids and ketone bodies increases relative to that of fatty acids and carbohydrates[22,23] (FIG. 1b). The degradation of glutamine and ketone bodies leads to the incorporation of carbons into the Krebs cycle via acetyl-CoA.

Switches in metabolism not only have consequences for energy expenditure, but specific substrates can also function as signalling factors. For example, ketone bodies can act as a metabolic fuel, can function as an external signal by binding to cell-surface proteins and can promote epigenetic modifications by increasing the post-translational modification of histones via lysine acetylation[24,25] (FIG. 1c). Likewise, glucose is a primary source of energy, but in excess amounts can be shuttled to the hexosamine pathway, resulting in *O*-linked β-*N*-acetylglucosamine (*O*-GlcNAc) modification of cytoprotective peptides[26,27]. The contribution of glutamine or other amino acids to cardiac energy substrate metabolism under normal physiological conditions is negligible but increases substantially during pathological remodelling and in the failing heart[28,29]. Studies indicate that glutamine-derived carbons are used to maintain ATP provision, whereas glutamine-derived nitrogen is donated for macromolecule synthesis[30]. Branched-chain amino acid catabolism is disrupted during heart failure, in which the oxidation of branched-chain amino acids (valine, leucine and isoleucine) is substantially downregulated, causing the accumulation of catabolic by-products[31,32]. The notion that energy substrates are only a fuel is, therefore, incorrect because it neglects the pleiotropic roles of metabolic factors in the internal milieu.

In the heart, metabolic changes are directly linked to organ dysfunction or preservation, whereas in tumours, metabolic remodelling supports the acquisition and maintenance of malignancy. Cancer cells alter metabolic pathways by balancing catabolic and anabolic requirements to meet cellular homeostatic, bioenergetic and biosynthetic requirements (FIG. 1b). These findings have led to the perception that cancer cells have a defined metabolic profile, but in vivo studies of cancer metabolism have challenged this view[33,34]. The Warburg effect, characterized by a preference for glycolysis and increased secretion of lactate, even in the presence of oxygen, is an example of oncogenic remodelling in many proliferating cancer cells[35,36]. Although the initial interpretation was that oxidative metabolism is deficient in tumours, subsequent studies demonstrated that cancer cells retain their capacity for mitochondrial respiration with increased glycolysis, suggesting that the regulation of glycolysis is impaired[37].

Studies indicate that the metabolic phenotype of tumours is heterogeneous, dynamic and flexible, and this view is supported by insights from advanced technologies, including mass spectrometry-based metabolomics and proteomics, functional genomics and computational metabolic flux analyses in mouse models of cancer and patients with cancer[33,38–41]. Furthermore, metabolic phenotypes in tumours evolve as the tumour progresses from premalignant lesions to locally invasive and eventually metastatic cancer. Oncogene-driven expression of nutrient transporters[42,43], autophagic degradation of proteins and organelles[44] and environmental factors through the tumour microenvironment influence metabolic differences between tumours, and can also give rise to regional heterogeneity within a single tumour[34,38,41].

Tumorigenic variants in *KRAS*, *TP53* and *MYC* (encoding GTPase KRas, cellular tumour antigen p53 and MYC proto-oncogene protein, respectively) drive metabolic remodelling in cancer cells by accommodating the increased demand for nutrients to support cell proliferation[42,43,45,46]. Variants in *KRAS* can increase the expression of amino acid transporter SLC7A5 and autophagic flux, thereby supporting the higher demand for protein synthesis in proliferating cancer cells[42]. Likewise, p53 and MYC control various metabolic pathways and transporter activities for nutrients. p53 is a central component of cellular stress response pathways, and various forms of stress (including nutrient deprivation) can lead to p53 activation via the AKT–mTOR signalling pathway and AMP-activated protein kinase[47,48]. Nucleocytoplasmic malate dehydrogenase 1 has been shown to bind to and activate p53 in response to glucose deprivation, leading to increased oxidative metabolism[49]. Oncoproteins of the MYC family are crucial drivers of malignancy and are deregulated in up to 70% of human cancers through several mechanisms, including genetic variants, super-enhancer activation, aberrant upstream signalling and altered protein turnover[45,46,50]. Studies have demonstrated that increased MYC expression drives metabolic regulation of macromolecule synthesis and building blocks (such as lipids, nucleic acids and proteins) to sustain increased cancer cell proliferation[51]. KRAS, p53 and MYC directly affect the transcription of glycolytic enzymes[52,53]. In particular, MYC modulates the expression of glucose transporter SLC2A1, lactate exchange via monocarboxylate transporter 1 (MCT1) and MCT2, and several glycolytic enzymes[21,54]. Together, these studies indicate the tight link between metabolism and gene expression regulation to control the adaptation of cancer cells to stress.

Shared risk factors for CVD and cancer

CVD and cancer share several risk factors, including diabetes, dyslipidaemia, cachexia and an impaired immune response[14,15,55]. In patients with obesity and diabetes, the plasma availability of glucose is increased, the abundance and composition of plasma lipids are altered, insulin regulation is disrupted and the levels of inflammatory cytokines are upregulated[56–58]. Likewise, cancer is a systemic disease that affects the cardiovascular system through several factors, including the release of small molecules, modulation of immune cell activity and metastatic lesions.

CVD and cancer frequently coincide in the same patient and often complicate each other. To date, much of the focus in cardio-oncology has been on the cardiovascular complications developed during cancer progression and as a result of cancer treatment[59,60]. However, the reverse can also be true, and patients with CVD have been shown to be at increased risk of developing cancer (reverse cardio-oncology[3]), as reviewed previously[61,62].

Multiple pathways and mechanisms have been proposed for the comorbidity of CVD and cancer[2,3,62–66]. First, CVD and cancer share environmental risk factors, including obesity, smoking and a sedentary lifestyle[7,67,68]. Furthermore, traditional cardiovascular risk factors, such as dyslipidaemia and hypertension, can also be associated with the development of cancer — commonly used 10-year risk scores for atherosclerotic CVD are also predictive of incident cancer[8]. This finding emphasizes that the risk factors for CVD and cancer overlap.

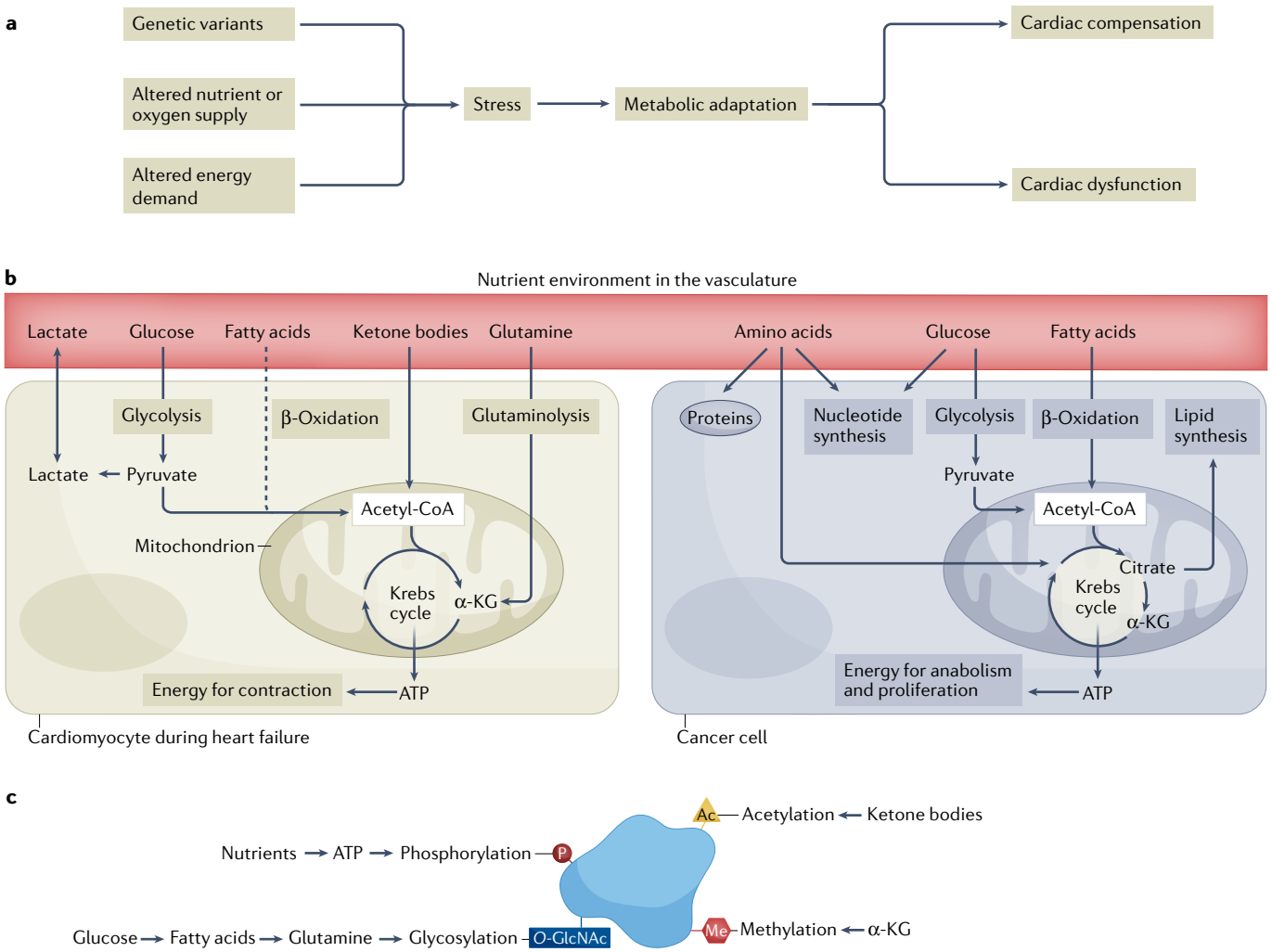

Fig. 1 | **The central role of metabolic remodelling in cardiovascular disease and cancer. a** | An overview of the metabolic consequences of stressors to the heart, which initially might be compensated for, but in the long term lead to dysfunction of the heart. **b** | In adult cardiomyocytes (left), the main source of fuel under normal physiological conditions is fatty acids. Stress initiates a shift in nutrient utilization away from fatty acid oxidation (dashed line) and towards glucose, ketone bodies or amino acids (such as glutamine) as sources of energy. These dynamic changes ensure continued ATP provision and maintenance of cardiac contractile function. In cancer cells (right), metabolic reprogramming supports successful adaptation to acquired mutations during tumorigenesis. Both catabolic and anabolic processes are maintained to ensure ATP provision and macromolecule synthesis during tumour growth. **c** | Post-translational modifications of proteins are linked to energy substrate metabolism and have a key role in the regulation of signalling, gene expression, protein stability and interactions, and enzyme kinetics. Ac, acetyl; α-KG, α-ketoglutarate; Me, methyl; *O*-GlcNAc, *O*-linked β-*N*-acetylglucosamine; P, phosphate.

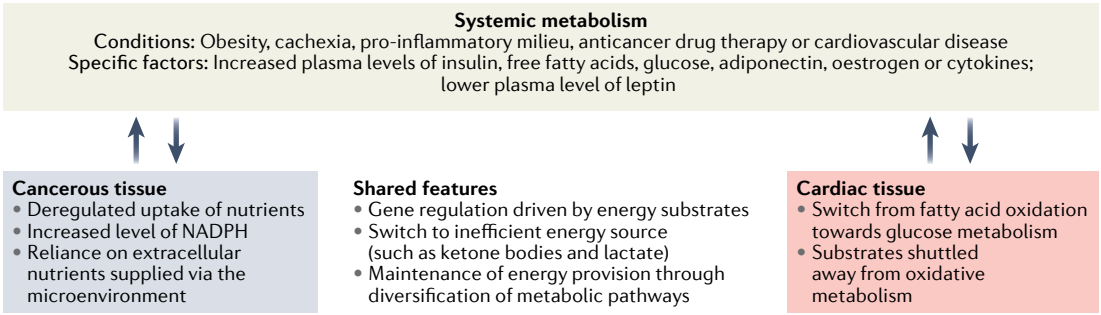

Fig. 2 | **Metabolism bridges cancer and cardiovascular disease.** Several metabolic stressors and perturbations, including obesity and cachexia, prompt the production and release of metabolic and inflammatory signal peptides and molecules. These systemic effects are accompanied by distinct differences as well as shared features in cardiac tissue and in cancer cells.

Second, shared genetic variants might explain the connection between CVD and cancer. Specific inherited genetic variants (for example, in genes encoding components of the WNT signalling pathway, the DYRK protein kinase family and the methionine pathway) have been associated with both incident cancer and incident CVD, such as coronary artery disease and heart failure[69,70]. Moreover, clonal haematopoiesis of indeterminate potential (CHIP), which is caused by certain somatic mutations in haematopoietic stem cells, has been identified as a shared risk factor for the onset and development of both CVD and cancer[71–73]. CHIP increases the risk of blood cancers, cardiometabolic diseases and microvascular dysfunction[74,75]. Remarkably, the risk of cardiovascular events is doubled in patients with CHIP[76]. Approximately 80% of the mutations occur in genes encoding epigenetic regulators, such as *DNMT3A* and *TET2* (REFS[77–79]). Somatic mutations in *DNMT3A* and *TET2* contribute to the development of atherosclerosis through increased endothelial inflammation driven by molecular interactions between circulating clonal monocytes and macrophages and the endothelium[80]. TET2-deficient macrophages have increased IL-1β secretion, which modulates endothelial cell adhesion and vascular permeability[81]. Heritable and acquired risk factors, including age, unhealthy lifestyle behaviours (for example, smoking and obesity), inflammatory conditions and exposure to anticancer therapies, are associated with an increased prevalence of CHIP[82]. For example, the incidence of CHIP among patients treated with stem cell transplantation for lymphoma was nearly 30%[71]. Although CHIP greatly increases the risk of haematological malignancies, the main cause of death in individuals with CHIP is atherosclerotic CVD[6,74,76]. Whether CHIP is a causal risk factor for CVD or simply reflects the accumulation of somatic mutations during biological ageing has been debated. However, it has been established that the presence of CHIP alters the function of immune cells, such as macrophages, which at least partly explains the increased propensity to develop coronary artery disease and its complications, as well as adverse myocardial remodelling[76,77,79]. Furthermore, *DNMT3A* mutations increase platelet production, which can be accompanied by increased platelet functionality, leading to a higher risk of cardiovascular events[83].

Third, inflammation is a central driver in both CVD and cancer. The CANTOS trial[84] evaluated the use of canakinumab, a human monoclonal antibody to IL-1β, in >10,000 patients with previous myocardial infarction and a blood level of high-sensitivity C-reactive protein of ≥2 mg/dl. Compared with placebo, canakinumab treatment was associated with a significantly lower rate of recurrent cardiovascular events, independent of LDL-cholesterol levels[84]. Strikingly, canakinumab treatment also reduced the incidence of lung cancer, although this outcome was a secondary end point of the trial[85]. Prospective studies evaluating the efficacy of canakinumab are ongoing, but the results from the CANTOS trial suggest that targeting inflammation can both reduce the risk of CVD and limit tumour growth. The use of other compounds that interfere with IL-1 signalling, such as anakinra (a recombinant and slightly modified version of the human protein IL-1 receptor antagonist), has also been associated with reductions in both cardiovascular events[86] and cancer events[87]. In addition, the use of generic anti-inflammatory drugs, such as colchicine, is effective in reducing CVD events[88,89], although the efficacy in patients with cancer is uncertain. Clearly, inflammation itself is heterogeneous, but the emerging data that inflammation has a central role in both CVD and cancer calls for a greater understanding of the underlying mechanisms.

Cancer metabolism and cardiovascular remodelling

Metabolic dysregulation of cancer cells can extend beyond the tumour microenvironment and lead to both systemic and cardiac-specific consequences (FIG. 2). The best evidence for tumour-intrinsic factors causing cardiovascular dysregulation comes from variants in genes encoding metabolic enzymes that can lead to cancer but which can also have systemic repercussions (FIG. 3). For example, somatic mutations in *IDH1* and *IDH2* (encoding cytosolic isocitrate dehydrogenase [NADP] (IDH1) and mitochondrial isocitrate dehydrogenase [NADP](IDH2), respectively) have been identified in gliomas (82%), acute myeloid leukaemia (15%), colorectal cancer (10%) and prostate cancer (1–3%)[90,91]. Variants in *IDH1* and *IDH2* lead to excessive accumulation of the oncometabolite D-2-hydroxyglutarate

(D2-HG) in cancer cells and subsequent release into the bloodstream. D2-HG promotes epigenetic modifications via inhibition of α-ketoglutarate-dependent dioxygenases, which in turn provides a benefit to tumours for growth and proliferation[92–94] (FIG. 4). In addition, multiple preclinical studies have shown that D2-HG affects the cellular functions of non-malignant cells. Increased production and release of D2-HG by cancer cells with *IDH1* or *IDH2* variants impairs oxidative metabolism via inhibition of the α-ketoglutarate dehydrogenase and inhibits ATP provision and cardiac contractile function[4,95]. Additionally, D2-HG contributes to an immunosuppressive milieu by impairing the immune cell response via inhibition of T cell activation and proliferation[96,97]. Together, these systemic effects might explain observations that show an association between the presence of *IDH1* or *IDH2* variants in patients with leukaemia and reduced left ventricular function, especially after chemotherapy with anthracyclines, which has cardiotoxic effects[98]. The effects of D2-HG are enantiomer-specific and can be reversible, offering the potential for compounds that block variants of IDH1 or IDH2 to have antitumour activity.

The overall effect of cancer on the cardiovascular system depends on the size of the tumour, its vascularization, the shielding of the tumour from the invaded organ(s) (for example, by the presence of a capsule) and several other factors. This concept has been most studied for the oncometabolite D2-HG. The production and release of D2-HG has been directly linked to the development of cardiomyopathy and neurological disorders[4,5]. 2-Hydroxyglutaric acidurias are a heterogeneous group of genetic diseases that are characterized by the accumulation of D2-HG or L-2-hydroxyglutarate (L2-HG) in bodily fluids and which are caused by variants in *D2HGDH* (encoding mitochondrial D2-HG dehydrogenase), *L2HGDH* (encoding mitochondrial L2-HG dehydrogenase), *IDH2* or *SLC25A1* (encoding the mitochondrial tricarboxylate transport protein). The mitochondrial D2-HG and L2-HG dehydrogenases catalyse the conversion of D2-HG and L2-HG, respectively, to α-ketoglutarate. Loss-of-function variants in *D2HGDH* or *L2HGDH* cause an accumulation of D2-HG or L2-HG, respectively, and impairment of endogenous enzymatic systems[99]. Children with these variants have a wide range of neurological disorders as well as dilated or hypertrophic cardiomyopathy[100]. Interestingly, adult patients with 2-hydroxyglutaric aciduria syndrome often harbour heterozygous germline variants in *IDH2* in addition to variants in *D2HGDH* or *L2HGDH*, resulting in even higher levels of D2-HG and L2-HG and a substantially increased risk of cardiomyopathy[101,102]. In adult mice, global induction of variant *Idh2* expression (and the subsequent increase in plasma D2-HG and L2-HG levels) resulted in dilated cardiomyopathy, muscular dystrophy and white matter abnormalities throughout the central nervous system[5]. Hearts from these mice accumulated glycogen and had smaller and fewer mitochondria than hearts from healthy control mice[5]. Remarkably, implantation of tumour xenografts harbouring an *IDH2* variant also resulted in cardiac abnormalities[5], suggesting that D2-HG and L2-HG can act in a paracrine fashion to cause cardiotoxicity.

In individuals with somatic mutations in *IDH1* or *IDH2*, paracrine or endocrine effects can be the cause of cardiac remodelling, but in other situations, inherited genetic variants can directly cause metabolic dysregulation. Biallelic loss-of-function variants in *VHL* (encoding von Hippel–Lindau disease tumour suppressor), which are typical in renal cell carcinoma and haemangioblastoma, are an example of how metabolic reprogramming facilitates the development of cancer and can lead to cardiac sequelae[103,104] (FIG. 4). von Hippel–Lindau syndrome, characterized by germline variants in *VHL*, predisposes patients to a multitude of vascular tumours, including retinal angiomas and cerebellar haemangioblastomas[103]. Furthermore, patients with specific homozygous variants in *VHL* can have polycythaemia and cardiopulmonary abnormalities, including increased basal ventilation, pulmonary vascular tone and heart rate responses at baseline, and these abnormalities are accentuated by hypoxia[105,106]. During exercise, these patients have early and marked phosphocreatine depletion and acidosis in skeletal muscle, greater accumulation of lactate in the blood and reduced maximum exercise capacity[107]. Transgenic mice with the same *Vhl* variants have increased glycolysis and a decreased phosphocreatine to ATP ratio in the heart, consistent with impaired oxidative metabolism[108]. A case study described a patient with a point mutation in *VHL* that was associated with reduced growth rate, persistent hypoglycaemia and limited exercise capacity, with gene expression changes that reprogrammed carbohydrate and lipid metabolism, impaired mitochondrial respiratory function in skeletal muscle and uncoupled oxygen consumption from ATP production[109]. Finally, cardiac-specific deletion of *Vhl* in mice can lead to progressive heart failure and premature death, with a subset of mice developing malignant cardiac tumours with features of rhabdomyosarcoma and the capacity to metastasize[110].

The protein product of *VHL* functions as an E3 ubiquitin ligase of hypoxia-inducible factor 1α (HIF1α), which promotes proteasome-mediated degradation of HIF1α (and of the related protein, HIF2α) during normoxia. In hypoxia, HIF1α and HIF2α are stable and heterodimerize with HIF1β (also known as ARNT protein)

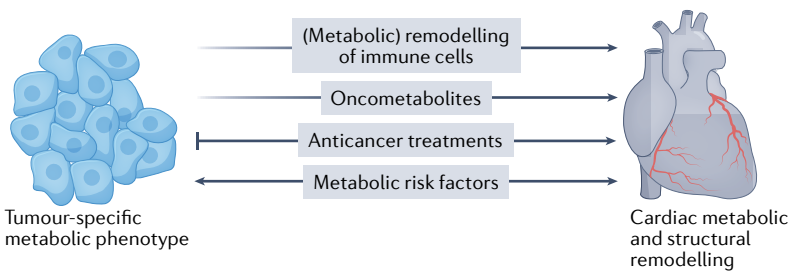

Fig. 3 | **Putative mechanisms of cardio-onco-metabolic remodelling.** The presence of cancer and/or the use of anticancer therapies can provoke changes in the organism, such as remodelling of immune cells, that affect the heart. Furthermore, specific oncometabolites, such D-2-hydroxyglutarate and succinate, can affect the heart tissue directly. Metabolic risk factors can cause cardiovascular disease as well as exacerbate tumour proliferation and cancer progression.

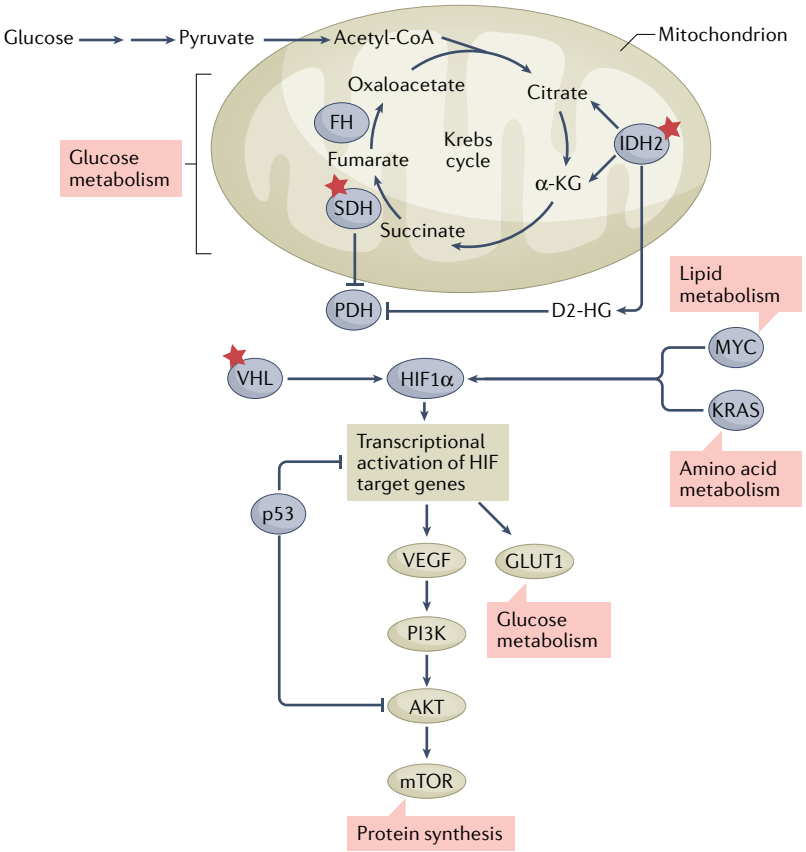

Fig. 4 | **Accumulation of somatic mutations changes the metabolic profile of tumours and influences the cardiovascular system.** Variants (indicated by red stars) in *IDH1* or *IDH2*, encoding cytosolic isocitrate dehydrogenase [NADP] (IDH1) and mitochondrial isocitrate dehydrogenase [NADP] (IDH2), cause increased production and release of the oncometabolite D-2-hydroxyglutarate (D2-HG). D2-HG promotes epigenetic modifications and tumorigenesis. Variants in *VHL*, encoding von Hippel–Lindau disease tumour suppressor (VHL), are associated with vascular tumours by interference with the hypoxia-inducible factor 1α (HIF1α)–vascular endothelial growth factor (VEGF) pathway. Likewise, variants in succinate dehydrogenase (SDH)-encoding genes increase malignant remodelling and affect transcriptional regulation. α-KG, α-ketoglutarate; AKT, RACα serine/threonine-protein kinase; FH, mitochondrial fumarate hydratase; GLUT1, glucose transporter type 1; KRAS, GTPase KRas; mTOR, mechanistic target of rapamycin; MYC, MYC proto-oncogene protein; p53, cellular tumour antigen p53; PDH, pyruvate dehydrogenase; PI3K, phosphoinositide 3-kinase.

to function as a master transcription factor for the induction of hundreds of genes that are crucial for the cellular and systemic response to hypoxia. Tumours with *VHL* variants have aberrant activation of HIF2α and, therefore, show many of the hallmarks of hypoxia[111]. HIF2α (the HIF isoform specifically implicated in renal cell carcinoma) activates the transcription of genes encoding angiogenic growth factors (such as members of the vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) families) as well as genes encoding metabolism-related protein (such as the glucose transporter type 1), thereby changing the metabolic phenotype of affected tumours[112,113]. Belzutifan, a small-molecule inhibitor of HIF2α, has been approved for the treatment of patients with von Hippel–Lindau syndrome[114]. In a mouse xenograft model of renal cell carcinoma, inhibitors of HIF2α blocked the angiogenic and metabolic targets of HIF2α, demonstrating on-target antitumour activity[112,115]. Interestingly, in mouse models with the specific variants in *Vhl* that result in polycythaemia, treatment with a HIF2α inhibitor reversed the cardiopulmonary phenotypes associated with the genetic variant[116]. The spectrum of cardiopulmonary abnormalities that are associated with *VHL* variants is a demonstration of the genotype–phenotype correlations that occur between cancer-associated variants and cardiovascular metabolism.

The systemic and cardiac effects of the presence in tumours of other inherited or somatic variants in genes encoding metabolic enzymes are less clear. Biallelic (germline or somatic) loss-of-function variants in genes encoding subunits of succinate dehydrogenase (SDH) can cause rare conditions that comprise 2% of mitochondrial respiratory chain disorders[117] (FIG. 4). SDH forms complex II of the mitochondrial electron transport chain and couples the oxidation of succinate to fumarate in the Krebs cycle to the transfer of electrons to the terminal acceptor ubiquinone in the electron transport chain. The four subunits of the SDH complex are encoded by *SDHA*, *SDHB*, *SDHC* and *SDHD* in the nucleus. Genetic variants in one or more subunits predispose individuals to a variety of tumours, including phaeochromocytoma, paraganglioma, gastrointestinal stromal tumours, haemangioblastoma and papillary renal cell carcinoma[117–122]. Germline variants in SDH-encoding genes are associated with the complete loss of enzymatic function and mitochondrial accumulation of succinate[123]. The cardiac phenotypes of patients who have tumours with variants in SDH-encoding genes are yet to be defined in a large population, but case reports suggest that these variants are associated with severe myopathy, most notably dilated cardiomyopathy with impaired left ventricular function[124–128].

Like D2-HG, succinate is considered to be an oncometabolite, and drives genome-wide hypermethylation and transcription factor activation via inhibition of α-ketoglutarate-dependent dioxygenases and HIF1α prolyl hydroxylases[122,123]. However, whether succinate drives tumorigenesis and acts as a metabolic signal during malignancy remains to be determined. Increased plasma succinate levels are associated with CVDs and increased inflammation, as well as ischaemia–reperfusion injury[129,130]. Preclinical studies suggest that succinate release from cancer cells activates an immune response and cellular signalling via succinate receptor 1 (REFS[131,132]). Despite these promising preclinical studies, further research is needed to explain the cardiometabolic phenotype associated with variants in SDH-encoding genes.

A more general effect of cancer on the cardiovascular system is cancer-associated cachexia, a debilitating condition characterized by skeletal muscle wasting and loss of adipose tissue, which substantially contributes to morbidity and mortality[133,134]. Many factors contribute to cancer-induced muscle wasting, including altered protein and energy metabolism and chronic inflammation[134–136]. Pro-inflammatory cytokines, including tumour necrosis factor, IL-1β and IL-6, which are produced either by cancer cells or by immune cells in response to the tumour, interfere with appetite signals

in the anterior hypothalamus and increase the metabolic rate[137]. Increased net protein breakdown and increased oxidation of branched-chain amino acids are characteristic features of solid tumours, and result in decreased plasma amino acid concentrations[42,138]. Accordingly, monitoring of plasma amino acid levels (for example, glutamine) has emerged as a pretreatment risk stratification tool[138], and controlling amino acid availability is a promising therapeutic intervention[139,140].

Metabolic effects of anticancer therapies

Anticancer therapies can induce CVD via several mechanisms, including direct cardiotoxicity, effects on the vasculature, and perturbations to cardiovascular and immune homeostasis[141–144]. In addition, a subset of anticancer therapies can have substantial metabolic effects, which can either manifest systemically or cause organ-specific perturbations (for example, in the heart). Traditional anticancer therapies, such as anthracyclines and radiation, have long been known to be associated with cardiovascular sequelae, including cardiomyopathy and cardiac ischaemia[145]. Because of the non-specific mechanisms of action of these therapies, the cardiotoxicities can involve direct cell death and also metabolic sequelae. For example, preclinical models suggest multiple mechanisms of anthracycline-mediated cardiotoxicity, with several studies indicating metabolic perturbations, such as impairment of mitochondrial biogenesis and iron metabolism and effects on transcription factors that regulate metabolism, including HIF[60,146,147]. Cardiotoxicity can also occur with therapy with antimetabolites, such as 5-fluorouracil, a synthetic analogue of uracil that inhibits thymidylate synthase, thereby limiting the availability of thymidine nucleotides for DNA synthesis. Although 5-fluorouracil is an effective anticancer treatment, cardiotoxicity can result from vascular spasms[148]. Androgen deprivation therapy (with the use of drugs such as leuprolide), which is a mainstay of treatment for prostate cancer, can cause systemic metabolic sequelae, including hyperglycaemia, hypertriglyceridaemia, increased adiposity and decreased lean body mass[149].

An improved understanding of the specific pathways that are dysregulated in cancer has led to the development of more targeted therapies, but these therapies have been associated with more diverse metabolic dysregulation. For example, given that specific kinases become aberrantly activated in different types of malignancy, kinase inhibitors have emerged over the past two decades as important forms of anticancer treatment[59]. Kinase inhibitors can generally be divided into antibodies and small molecules. Small-molecule inhibitors bind to receptor kinases intracellularly, inhibiting the catalytic activity of tyrosine kinases by allosteric inhibition or by directly interfering with the binding of ATP to a structurally unique pocket. However, because the ATP-binding pocket can be similar on more than one kinase receptor, small-molecule inhibitors can target more than one kinase. For this reason, whereas biologic agents (such as antibodies) are often fairly specific, small molecules can be promiscuous and result in off-target inhibition of kinases other than the intended target[150]. Depending on the kinases affected, metabolic dysregulation can arise.

For example, small-molecule inhibitors targeting VEGF and PDGF receptors have been rapidly developed for the treatment of many forms of cancer, including kidney cancer[143,151]. These therapies are often associated with hypertension and are associated with mild cardiomyopathy[152–154]. VEGF is widely expressed in cardiac tissue, and inhibition of VEGF signalling can impair the growth, development and repair of cardiac tissue[155,156]. In addition, therapy with VEGF inhibitors can be associated with relative hypoglycaemia, although isolated cases of severe hypoglycaemia have been reported[157]. In experimental models, sunitinib (a small-molecule, multi-targeted receptor tyrosine kinase inhibitor) prevented and reversed diabetes in mice as a result of 'on-target' inhibition of both PDGF and VEGF signalling[158,159]. Interestingly, therapy with imatinib, which is primarily used to inhibit tyrosine protein kinase ABL1, which is activated in certain forms of leukaemia, is also associated with hypoglycaemia in experimental models and in patients[160–163]. Imatinib does not target VEGF receptors but was initially developed as a PDGF receptor inhibitor, which contributes to the changes in blood glucose levels, although the specific mechanisms are uncertain[158,164]. VEGF inhibitor therapy can lead to mild cardiomyopathy, which is often reversible after drug discontinuation[152,165]. Mechanistically, this cardiomyopathy arises owing to direct inhibition of VEGF and PDGF, resulting in microvascular dysfunction and stabilization of HIF and downstream targets[166,167]. In accordance with this mechanism, mice in which HIF is genetically stabilized also develop cardiomyopathy, which is reversible when the transgene is turned off[168,169]. Similarly, phosphoinositide 3-kinase (PI3K) inhibitors are associated with hyperglycaemia[143]. This adverse effect is expected, because PI3K is an important modulator of insulin signalling and lipid homeostasis[162]. Although the metabolic complications associated with VEGF or PI3K inhibitor therapies are often 'on-target' (that is, caused by the direct inhibition of the intended kinase target), the mechanisms of toxicity associated with other kinase inhibitors are less clear. Nilotinib, an ABL1 kinase inhibitor that is used in the treatment of some forms of leukaemia, is associated with hyperglycaemia and subsequent vascular disease[162]. The association between nilotinib and hyperglycaemia is presumably an off-target effect, because other ABL1 kinase inhibitors are not associated with hyperglycaemia, and imatinib is even associated with hypoglycaemia[163].

In the past decade, intense efforts have been made to target the metabolism of the tumour or the tumour microenvironment in the treatment of cancer. Many of these efforts have been precision-based. For example, ivosidenib (an IDH1 inhibitor previously known as AG-120) and enasidenib (an IDH2 inhibitor previously known as AG-221) have been approved by the FDA for the treatment of patients with relapsed or refractory acute myeloid leukaemia and variants in *IDH1* or *IDH2*, respectively[170,171]. These drugs are currently being tested in patients with other types of cancer with variants in *IDH1* or *IDH2*, including glioma, cholangiocarcinoma

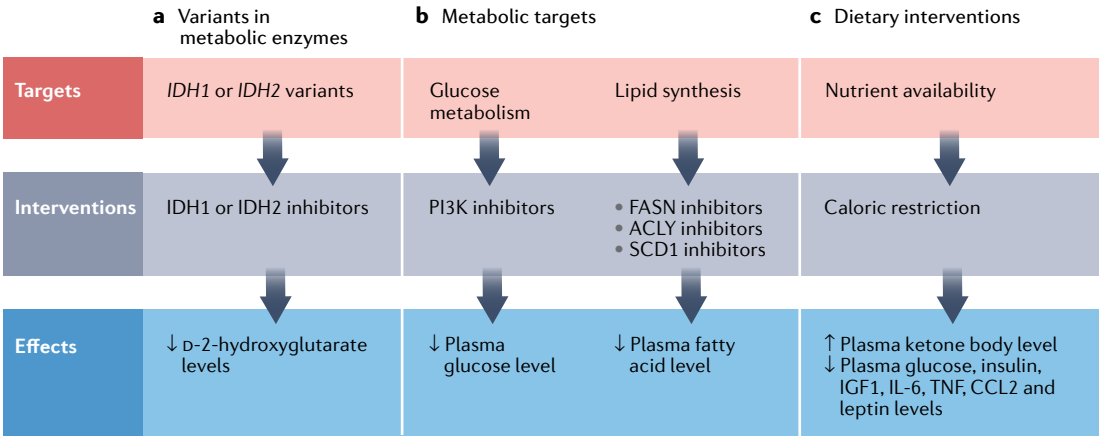

Fig. 5 | **Metabolic targets and interventions in cardiovascular disease and cancer. a** | Inhibitors targeting variant forms of cytosolic isocitrate dehydrogenase [NADP] (IDH1) or mitochondrial isocitrate dehydrogenase [NADP] (IDH2) are efficacious in patients with acute myeloid leukaemia. **b** | Inhibitors of the phosphoinositide 3-kinase (PI3K) pathway or of fatty acid synthase (FASN), ATP–citrate synthase (ACLY) or stearoyl-CoA desaturase 1 (SCD1) lower plasma levels of glucose or fatty acids and might have beneficial effects in patients with cardiovascular disease or cancer. **c** | Caloric restriction has beneficial effects in patients with cardiovascular disease or cancer via its pleiotropic effects on various metabolic and inflammatory components. CCL2, C-C motif chemokine 2; IGF1, insulin-like growth factor 1; TNF, tumour necrosis factor.

and chondrosarcoma[170–173]. Any adverse sequelae of these therapies are currently uncertain because of their recent approval, although given that ivosidenib and enasidenib target only mutant IDH1 and IDH2, respectively, any effect on wild-type IDH enzymes in normal organs, including the heart, should be minimal. Interestingly, prolongation of the corrected QT interval (QTc) on the surface electrocardiogram, which increases the risk of ventricular arrhythmia, was a serious and unexpected adverse effect associated with ivosidenib in both preclinical and clinical testing[174]. Indeed, >25% of patients who were treated with ivosidenib had QTc prolongation, although only 8% required treatment interruption or dose reduction[174].

Finally, immunotherapies have revolutionized anticancer treatment in the past decade[175]. Immunotherapies include a broad range of novel drugs, from antibodies and other biologic agents, including immune checkpoint inhibitors and bispecific T cell engagers, to cell-based therapies, such as chimeric antigen receptor T cell therapies. Immune checkpoint inhibitors can cause inflammatory toxicities, including myocarditis[176]; however, adverse effects can also include metabolic toxicities, including diabetes[177]. Cellular therapies can result in cytokine release syndrome, which can manifest with mild to life-threatening symptoms, including severe hypotension and vascular leak[175,178–180]. Although the mechanisms of these cardiovascular toxicities are not clear, metabolic perturbations resulting from cytokine release syndrome could contribute to systemic toxicities.

Targeting metabolism in CVD and cancer

Given that metabolic pathways are altered in both CVD and cancer, specific treatments that target metabolic features might be beneficial in both conditions. Genetically defined metabolic phenotypes contribute mechanistically to tumour transformation and are potential therapeutic targets. Targeting these metabolic signatures by inhibiting enzymatic functions or through dietary interventions holds the promise to alter tumour metabolite availability and influence cancer cell growth. Incorporating pharmacological and interventional treatments targeting metabolism might improve the efficacy of existing anticancer treatments and might also reduce the overall risks associated with cancer-associated CVD. Given the various possibilities, we restrict the following discussion to some specific examples.

First, variants in genes that encode metabolic enzymes are important drivers of tumour initiation and growth and can be targeted therapeutically. This paradigm has been successfully applied to tumours with variants in IDH-encoding genes. The clinical efficacy of inhibitors of mutant IDH1 and IDH2 has been demonstrated in patients with acute myeloid leukaemia[151], and clinical trials in patients with advanced cholangiocarcinoma or chondrosarcoma have shown increased progression-free survival with the IDH1 inhibitor ivosidenib compared with placebo[181,182] (FIG. 5). IDH1 inhibitors provide new options for patients with unresectable, metastatic and/or refractory cancer who have no other treatment options. Another benefit of IDH1 inhibitors is the significant reduction in plasma D2-HG concentrations, which might improve the D2-HG-mediated metabolic alterations observed in these patients[181].

Second, obesity, diabetes and dyslipidaemia have established systemic manifestations, such as increased inflammation, which might explain their widespread and profound effects on the organism. Interventions that reverse the deleterious effects of these metabolic stressors might have beneficial effects on the risk of CVD and cancer. Dietary interventions have been proposed as another effective strategy to target cancer cells and reduce the risk of CVD (FIG. 5). Fasting is the most extreme approach to reset an organism's metabolism and has been shown to have positive effects in cancer prevention and treatment in mice[183]. Just 1 day of fasting per week delays spontaneous tumorigenesis in p53-deficient mice[184]. Fasting is associated with decreases in plasma

glucose, insulin and insulin-like growth factor 1 levels, which might partly explain the salutary effects of fasting[185–187]. Furthermore, fasting is followed by a period of abnormally high cellular proliferation, which is characterized by the activation of cellular repair pathways and is driven by the replenishment of growth factors during refeeding to reverse atrophic cellular remodelling[183,184]. No clinical data are currently available to advocate intermittent fasting in patients with cancer, but several trials are underway. Low glycaemic diets have been shown to reduce lipid metabolism and tumour growth[188]. Bariatric surgery, another drastic intervention to reduce obesity, has been shown to have long-term preventive effects on incident CVD and cancer[189]. Other examples of therapies that modify metabolism are drugs to reduce serum cholesterol levels, such as statins, which are extremely effective in preventing coronary and cerebrovascular events[190]. However, the effects of statins on the incidence of cancer are uncertain, but are likely to be neutral according to a meta-analysis[190].

Combining metabolic inhibitors with anticancer therapies holds the promise to improve the efficacy and durability of existing treatments for patients with cancer, while also protecting the heart. Several approved metabolic therapies target lipid synthesis, but their clinical applications have been limited. Some tumours rely on glucose metabolism during the early stages of the disease. The use of PI3K inhibitors targeting glucose homeostasis and metabolism has been successful in the treatment of a subset of cancers, including breast cancers[191,192] (FIG. 5). Inhibition of PI3K can lead to both decreased cancer cell proliferation and increased cellular death[191]. However, the use of PI3K inhibitors has been limited in some patients owing to fulminant hypoglycaemia and therapy resistance. Depending on the tumour profile, compensatory signalling mechanisms result in hyperinsulinaemia, causing increased tumour growth and treatment failure[191,192].

Some types of tumour, such as breast cancer, rely on fatty acid synthesis in the advanced stages of the disease[193]. Targeting de novo fatty acid synthesis by inhibition of fatty acid synthase has been proposed as a promising therapeutic strategy in HER2$^+$ breast cancer with brain metastasis[193]. Likewise, inhibitors of stearoyl-CoA desaturase and ATP–citrate synthase in tumours with increased lipid synthesis (such as colorectal cancers and pancreatic cancer) have shown promising results in preclinical studies[194–196]. The cardiovascular risk associated with these therapies is uncertain, but evidence from previous clinical trials suggests that these therapies are likely to be associated with increased risks of adverse cardiovascular events, perhaps owing to metabolic dysregulation[149]. Risk stratification of patients on the basis of existing metabolic risk factors, the tumour profile, cell-specific drug delivery and cardiac remodelling is necessary.

Conclusions

Metabolic adaptation in CVD and cancer is complex and dynamic. The causes of these metabolic changes are multifactorial, including intrinsic and extrinsic factors to both normal and diseased tissue. These complexities introduce challenges to elucidating how cancer cells affect other organs and potentially impair their function. Additional studies are necessary to predict metabolic signatures that can be therapeutically targeted and the potential systemic effects of these therapies. CVDs have emerged as a leading cause of death in survivors of cancer, prompting questions about how tumours alter cellular states beyond their own direct environment. The metabolism of cancer cells and cardiomyocytes seems to be different at first glance, but closer examination of the cellular processes shows that similar stress-response pathways exist in cardiomyocytes and certain types of tumour. Furthermore, tumours impose metabolic stress on the heart, which causes distinct metabolic phenotypes. Understanding the processes by which metabolic processes remodel is likely to provide new avenues of therapeutic interventions and to improve our understanding of cardiac adaptation. To move the field forwards, we need to harness new technologies in metabolic imaging and stable isotope tracer analysis, and to develop models that provide a bridge between preclinical discoveries and clinical translation.

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