Metabolic Coordination of Physiological and Pathological Cardiac Remodeling

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Abstract: Metabolic pathways integrate to support tissue homeostasis and to prompt changes in cell phenotype. In particular, the heart consumes relatively large amounts of substrate not only to regenerate ATP for contraction but also to sustain biosynthetic reactions for replacement of cellular building blocks. Metabolic pathways also control intracellular redox state, and metabolic intermediates and end products provide signals that prompt changes in enzymatic activity and gene expression. Mounting evidence suggests that the changes in cardiac metabolism that occur during development, exercise, and pregnancy as well as with pathological stress (eg, myocardial infarction, pressure overload) are causative in cardiac remodeling. Metabolism-mediated changes in gene expression, metabolite signaling, and the channeling of glucose-derived carbon toward anabolic pathways seem critical for physiological growth of the heart, and metabolic inefficiency and loss of coordinated anabolic activity are emerging as proximal causes of pathological remodeling. This review integrates knowledge of different forms of cardiac remodeling to develop general models of how relationships between catabolic and anabolic glucose metabolism may fortify cardiac health or promote (mal)adaptive myocardial remodeling. Adoption of conceptual frameworks based in relational biology may enable further understanding of how metabolism regulates cardiac structure and function. (_Circ Res_. 2018;123:107-128. DOI: 10.1161/CIRCRESAHA.118.312017.)

Key Words: exercise ■ glucose ■ heart failure ■ hypertrophy ■ mitochondria ■ pregnancy ■ systems biology

Metabolism is a unifying link between tissue form and function. Despite the general recognition that metabolism is the means by which organisms use matter and energy to develop, grow, and maintain the fabric of their being, the mechanisms of how metabolism and changes therein accomplish this feat are unclear. Difficulties answering this question are due in part to the multifaceted nature of causation invoked by the individual parts and coordinated activities of the metabolic network. For example, integrated with ATP production and biosynthesis are the regulation of intracellular redox state (ie, pyridine nucleotide ratios, $NAD(P)^+/NAD(P)H$), and the coordination of cellular signals (Figure 1). Although it is evident that intermediary metabolism is required for energy provision and imparts a material form of causation, for example, biomolecule synthesis, how inter-regulation of anabolic and catabolic pathways of metabolism achieve a metabolic state that permits or activates phenotypic changes remains vague, especially in the heart.

The heart was an organ of choice for seminal metabolic studies.[1] Its high ATP demand is fulfilled primarily by oxidative phosphorylation, which contributes to ≈95% of its ATP requirements; the remaining 5% is derived primarily from substrate-level phosphorylation in glycolysis.[2–4] To support its energetic needs, the heart uses multiple substrates, which compete for catabolism (Figure 2).[1,5,14–27] The reader is directed to Taegtmeyer et al[19] as a resource for the models and methods used to investigate cardiac metabolism and for the role of protein turnover in cardiac remodeling. For information on the circadian elements of cardiac metabolism, we direct the reader to several excellent reviews.[28–30] Here, we attempt to synthesize current understanding of how intermediary metabolism regulates physiological growth and pathological hypertrophy of the heart and to address difficult conceptual issues about the causative role of metabolism in tissue remodeling and repair.

Role of Metabolism in Exercise-Induced Cardiac Growth

Exercise-induced increases in cardiac size were initially identified in the late 1890s,[31,32] and they were first described in the 1950s.[33] This form of cardiac hypertrophy occurs primarily in highly trained athletes, is relatively mild (≈10%–20% increase in heart mass), and is reversible on prolonged cessation of exercise.[34] It is accompanied by unchanged or marginally enhanced systolic and diastolic function.[35] Exercises that promote sustained increases in cardiac output (eg, endurance running) cause an eccentric form of cardiac remodeling, whereas exercises that increase systemic arterial pressures (eg, weight lifting) often promote concentric

Nonstandard Abbreviations and Acronyms	
AKT	protein kinase B
AMPK	AMP-activated protein kinase
BCAA	branched-chain amino acid
BDH1	β-hydroxybutyrate dehydrogenase 1
DCA	dichloroacetate
FFA	free fatty acid
FGF21	fibroblast growth factor 21
FoxO1	forkhead box O1
GLP	glycero(phospho)lipid synthesis pathway
GLUT1	glucose transporter 1
GLUT4	glucose transporter 4
GPAT	glycerol 3-phosphate acyltransferase
GPCR	G-protein–coupled receptor
GPD1	glycerol 3-phosphate dehydrogenase 1
HBP	hexosamine biosynthetic pathway
HIF1α	hypoxia-inducible factor 1α
IGF-1	insulin-like growth factor 1
mTOR	mammalian target of rapamycin
O-GlcNAc	β-linked *N*-acetylglucosamine
PDK4	pyruvate dehydrogenase kinase 4
PFK1	phosphofructokinase 1
PFK2	6-phosphofructokinase/fructose-2,6-bisphosphatase
PGC1α	peroxisome proliferator–activated receptor γ coactivator 1α
PPAR	peroxisome proliferator–activated receptor
PPP	pentose phosphate pathway
SBP	serine biosynthesis pathway
TGF-β	transforming growth factor β

Figure 1. Primary functions of metabolism. Schematic summarizing the importance of metabolism for useable energy (ATP production), the synthesis of cellular building blocks (Biosynthesis), control of NAD(P)$^+$/NAD(P)H pools (Control of redox state), and regulation of signals in the cell, which includes allosterism, metabolite signaling, and post-translational protein modifications (Signaling).

hypertrophy.[36,37] Although adaptation of the heart to exercise is generally beneficial—protecting the heart from ischemia-reperfusion injury[38,39] and increasing stroke volume[40]—it may be maladaptive by promoting fibrosis,[41] deleterious ventricular remodeling,[42] or atrial or ventricular fibrillation.[43,44] Nevertheless, exercise can lead to cardiac adaptations, which broadly applied to healthy and diseased populations, improves health, and complements exercise-induced increases in health span.[45–47]

As may be expected, the physical exertion occurring with exercise has robust effects on cardiac function and metabolism. Exercise increases left ventricular contractile power and myocardial oxygen consumption 3- to 10-fold above resting rates.[20,48,49] The increases in myocardial oxygen consumption are caused by elevated ADP concentrations, which drive oxidative phosphorylation to regenerate ATP at higher rates.[50] Changes in cardiac substrate catabolism provide the fuel for increased energy demands and are dependent on several integrated factors including workload, circulating hormones, and substrate availability and abundance. Importantly, the acute changes in metabolism that occur during exercise are different from the chronic changes that occur after adaptation. We discuss these issues below, concluding with evidence of how changes in metabolism may be involved in exercise-induced cardiac growth.

Workload-Dependent Effects During Exercise

During exercise, changes in cardiac preload, heart rate, and afterload synergize to increase workload, which augments
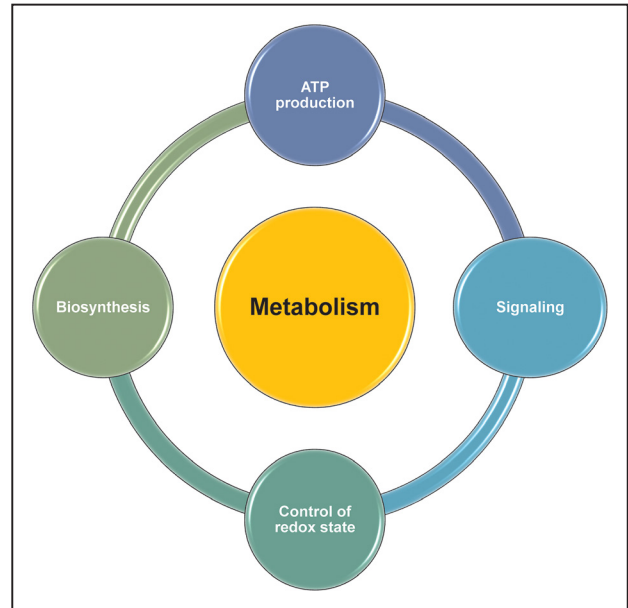
energy demand and influences substrate metabolism. On the basis of studies of ex vivo perfused hearts, this increase in workload is sufficient to increase myocardial carbohydrate and fatty acid catabolism.[22,51–55] Further evidence that workload is sufficient to change substrate metabolism in vivo comes from studies of atrial pacing, which increases cardiac work without affecting circulating substrates. Atrial pacing causes the heart to use more fatty acids,[56] and it also increases glucose and lactate uptake in proportion to myocardial energy demand.[57]

Increases in circulating and local catecholamines elevate heart rate and inotropy during exercise and further contribute to changes in cardiac metabolism.[3,58] Both epinephrine and norepinephrine, which increase episodically with exercise, can promote oxidation of endogenous (triglycerides, glycogen)[59] and exogenous carbon substrates (eg, free fatty acids [FFAs], glucose, pyruvate, branched-chain amino acids [BCAAs]).[60–62] In the working heart, epinephrine increases glucose catabolism[17,62,63] at least in part via the activation of phosphofructokinase.[54,64,65] Nevertheless, as reviewed by Opie,[3] cardiac glucose utilization may decrease with catecholamines, especially in vivo when other substrates are available and abundant.

Circulating Substrates During Exercise

Although an increase in cardiac workload has been associated with an increase in glucose uptake and oxidation in the myocardium,[22,51,66,67] results from several in vivo and ex vivo studies support the notion that glucose uptake and oxidation are diminished when concentrations of lactate and FFAs are increased to the levels occurring with exercise.[22,67–69] During exercise, plasma FFA levels can increase to 2.4 mmol/L,[70] due in large part to catecholamine-activated lipolysis in adipose
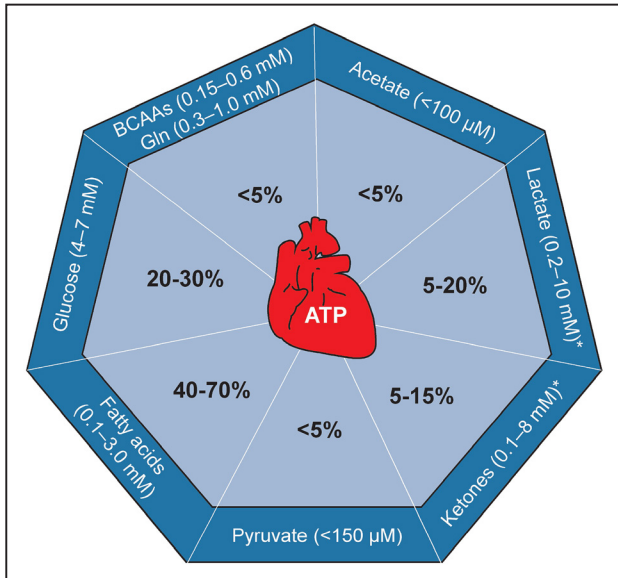
Figure 2. Overview of metabolic substrates used for cardiac ATP production. Schematic representing the physiological range of circulating substrates (dark blue) and the utilization of those substrates by the heart for ATP production (light blue). The percentages in bold represent the expected cardiac reliance on each substrate by the normal heart under physiological conditions. The range of physiological circulating levels were primarily from the HMDB database (www.hmdb.ca). *Lactate and ketone levels, when elevated to high levels (eg, during exercise or dietary interventions), may influence cardiac metabolism more than that estimated here (eg, for lactate[5–9]; for ketone bodies[10–13]). BCAA indicates branched-chain amino acid.

tissue. The increase in circulating FFA stimulates fatty acid uptake and utilization during exercise.[71–73] During intense exercise, circulating lactate levels also increase remarkably (to up to 10 mmol/L), due in large part to glycolytic activity of skeletal muscle. This is important because the myocardium is a net lactate consumer[71,74–76] and because myocardial lactate uptake and utilization correlate positively with arterial lactate concentration.[5,6,66] During exercise, the contribution of lactate to total oxidative metabolism may account for the majority of cardiac substrate utilization,[6–9] and in rat heart, high lactate levels, such as occurs during exercise, contribute to nearly 40% of ATP production.[5] Compared with the sedentary state, even relatively low-intensity exercise increases the contribution of lactate oxidation to overall myocardial oxidative metabolism.[66] Lactate may also enhance fat oxidation in the heart,[22] which would increase the capacity of the heart to generate ATP under high workloads.

During certain types of intense exercise, such as weightlifting, or with prolonged endurance exercise, arterial glucose concentrations can diminish,[70,77] whereas high-intensity aerobic exercise may increase blood glucose levels.[67] Interestingly, exercise-mediated increases in arterial glucose do not seem to be associated with an increase in cardiac glucose uptake, as indicated by studies using 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography.[67] During exercise in humans, myocardial glucose uptake and oxidation increase significantly at low-to-moderate intensities[66] but may diminish at higher intensities.[67] Moreover, studies in both humans and animal models suggest that exercise can lower oxygen extraction ratios

for glucose and decrease glucose uptake and utilization.[68,69] These findings suggest that exercise can increase or decrease both circulating glucose levels and myocardial glucose use in a manner dependent on the type, intensity, or duration of exercise. Yet, compared with other circulating substrates, plasma glucose concentrations remain relatively constant.[78]

Cardiac Metabolism in the Exercise-Adapted State

Compared with cardiac metabolic changes during exercise, the metabolic changes that occur in the exercise-adapted state are relatively less well studied. Data addressing this issue are predominantly from ex vivo perfused heart preparations. Adaptation to swim training was shown to increase the rates of glycolysis, glucose oxidation, and fat oxidation in the perfused mouse heart, suggesting that most major catabolic pathways are higher in the exercise-adapted state.[79] Although studies in treadmill exercise-adapted mice seem congruent with these findings (at least with respect to cardiac glycolysis),[80] glycolysis was found to be diminished in exercise-adapted rats, yet myocardial glucose and palmitate oxidation were higher compared with hearts from sedentary controls.[38] In another study, a moderate-intensity treadmill regimen showed no effect on glucose oxidation, palmitate oxidation, or myocardial oxygen consumption, whereas a high-intensity, interval style regimen resulted in higher glucose oxidation, lower palmitate oxidation, and a net decrease in myocardial oxygen consumption.[81] Reasons for discrepancies could be because of model-specific factors (eg, mouse strain, type of exercise) or differences in perfusion protocols (eg, substrate levels, addition of hormones, time of day[28]).

Information from metabolomic studies and knowledge of circulating substrates and hormones could help elucidate the metabolic state of the exercise-adapted heart in vivo. Snapshot metabolite abundance data show that hearts of voluntary wheel-trained mice have lower levels of some acylcarnitine and polar carboxylate species[82]; however, metabolomic analysis of treadmill-trained mice showed relatively few changes.[80] Such discrepancies could be because of different exercise models, mouse strains, or tissue acquisition protocols. Regardless, the elevated levels of plasma FFA that occur in the exercise-adapted state[83,84] would be thought sufficient to increase myocardial fat catabolism. Moreover, hormones that regulate exercise adaptation, for example, IGF-1 (insulin-like growth factor 1)[85] and neuregulin 1,[86,87] remain elevated in the exercise-adapted state and are likely to increase glucose uptake and utilization.[88–90] Metabolic changes caused by these hormones are mediated at least in part by AKT (protein kinase B),[88,90–92] which can activate the myocardial form of 6-phosphofructokinase/fructose-2,6-bisphosphatase (PFK2) and augment glycolysis.[91,93] IGF-1 may also influence cardiac energy demand and metabolism via its mild inotropic effects.[94,95] Of note, recent findings suggest that exercise augments levels of circulating extracellular vesicles, which may deliver metabolic enzymes to recipient cells, thereby altering tissue metabolism.[96–98]

Metabolic Causes of Exercise-Induced Cardiac Adaptations

Several mechanisms have been suggested to explain how exercise-induced metabolic changes drive cardiac adaptations.

These include changes in metabolite signaling, metabolism-mediated changes in gene expression, and coordination of biosynthetic pathways.

Metabolite-Mediated Signaling

Previous studies show that metabolites regulate the activities of kinases important for cardiac hypertrophy and growth. For example, the cellular fuel gauge AMPK (AMP-activated protein kinase), which senses intracellular levels of AMP and ATP,[99] is activated during exercise.[100,101] With excessive energy demand, AMPK is activated to increase glucose and fatty acid catabolism and to inhibit protein synthesis, thereby augmenting ATP levels.[102] Relatively little is known about how AMPK regulates cardiac adaptation to exercise; however, the enzyme has been shown to modulate sinoatrial node behavior to promote the adaptive bradycardia characteristic of the exercise-adapted state.[103] It is also likely to modulate mitochondrial abundance and quality control in response to exercise, as studies in other contexts show that AMPK activates PGC1α (peroxisome proliferator–activated receptor γ coactivator 1α)[104,105] and mitophagy.[106] Also, AMPK antagonizes pathological hypertrophy,[102,107,108] yet its constitutive activation can cause deleterious cardiac remodeling.[109]

Metabolites of glucose and fat metabolism may also be important regulators of exercise-induced cardiac growth. Changes in intracellular glucose-6-phosphate levels can regulate mTOR (mammalian target of rapamycin),[110–112] which is implicated in cardiac adaptation to exercise.[34] Also, palmitoleate (C16:1n7) liberated during exercise via adipose tissue lipolysis promotes cardiac growth, potentially by activating GPCRs (G-protein–coupled receptors), prohypertrophic kinases such as Akt, or nuclear receptors.[113] The cardiac growth-stimulating effect of palmitoleate is reminiscent of the robust, fatty acid–induced growth of the python heart, which occurs after a large meal.[114] The fact that numerous classes of metabolites have cognate GPCRs[115] provides potential mechanisms by which local or systemic changes in circulating metabolites initiate or sustain cardiac growth.

Metabolism-Mediated Changes in Gene Expression With Exercise

Although episodic bouts of strenuous physical activity are known to elicit adaptive changes in skeletal muscle gene expression,[47] less is known about how exercise impacts gene expression in the heart. Decreases in glucose catabolism occurring in the later stages of relatively vigorous exercise[80] seem to be important for expression of genes that promote physiological cardiac growth. Low PFK1 activity caused by expression of a cardiac-specific, kinase-deficient PFK2 transgene (Glyco^Lo mice) seems sufficient to partially phenocopy the exercise-adapted heart and to regulate genes (eg, *Cebpb*, *Cited4*[116,117]) required for exercise-induced cardiac growth.[80,118] Activation of the exercise gene program in Glyco^Lo mice occurs in the absence of Akt activation,[80] which normally regulates physiological cardiac growth.[34,45,119] This suggests that periodic, exercise-mediated decreases in glycolysis may be a proximal propagator of the growth program.

The metabolic periodicity caused by regular exercise could be important for maintaining or improving mitochondrial health. During exercise, cardiac mitochondria undergo fission, which seems to enhance their function.[120] Mitochondrial fission could regulate myocardial substrate utilization because, in other cell systems, mitochondrial fission may increase fatty acid oxidation and diminish glucose oxidation.[121] It remains unclear how mitochondrial fission and fusion integrate with substrate utilization in the heart; however, periodic episodes of both mitochondrial fragmentation and substrate utilization are likely important because loss of mitochondrial dynamics accelerates mitochondrial senescence and compromises mitochondrial quality,[122,123] and constitutively high or low glycolytic rates cause mitochondrial dysfunction.[80] Interestingly, the mechanisms of mitochondrial adaptations to exercise seem distinct from those that cause cardiac growth,[79,124] which could explain why constitutively low rates of glycolysis engage the cardiac growth program, yet cause mitochondrial dysfunction.[80] Nevertheless, how exercise-induced metabolic periodicity integrates with mitochondrial dynamics and quality control remains unclear.

Coordination of Myocardial Biosynthetic Pathways

Exercise-induced cardiac growth would be thought to require coordinated changes in metabolism to couple synthesis of structural materials with the activation of critical gene programs that foster myocyte hypertrophy. In simple organisms such as bacteria, pathways ancillary to glycolysis interconvert metabolites of sugar to the biomass required for cell growth and function via the simplest biochemical paths, indicating the presence of an optimality principle that underlies the structure of central carbon metabolism.[125] The regulation of rate-limiting steps of glycolysis, especially the PFK and pyruvate kinase steps, are likely critical for achieving the metabolic pathway flux configurations necessary for physiological cardiac growth (Figure 3). In several cell types, PFK regulates pentose phosphate pathway (PPP) flux, which influences proliferative capacity and sensitivity to oxidative stress.[126–129] Elegant modeling studies in the adult heart suggest that PFK strongly regulates the PPP and the polyol pathway.[130] Indeed, in cardiac myocytes, PFK activity coordinates flux through the PPP, the hexosamine biosynthetic pathway (HBP), and the glycerophospholipid synthesis pathway (GLP) by modulating glucose carbon entry into these pathways and by regulating the synthesis of amino acids (eg, aspartate) from Krebs cycle intermediates.[131] Metabolomic studies indicate that PFK has far-reaching effects on not only ancillary pathways of glucose metabolism but also several amino acid and lipid metabolic pathways.[80]

Relatively less is known about how key steps of glycolysis regulate other ancillary pathways such as the HBP, which can regulate the function and survival of cardiomyocytes.[132,133] This is important to understand in the context of exercise because transient changes in the HBP and O-linked β-*N*-acetylglucosamine (O-GlcNAc) levels occur with changes in physical activity.[134–137] Although the extent to which the PFK step influences the serine biosynthesis pathway (SBP) remains unclear, the pyruvate kinase node seems capable of regulating both the SBP[138] and the PPP.[139,140] The SBP is likely an important link among metabolism, epigenetic programming, and changes in cardiac structure and function because, by
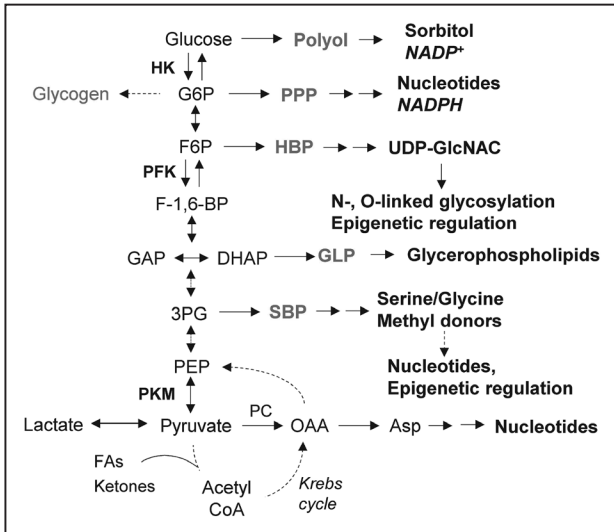
Figure 3. Schematic of glycolysis and ancillary glucose metabolism pathways. Once glucose enters the cell, it can enter the polyol pathway or it can be phosphorylated to form glucose-6-phosphate (G6P), which isomerizes to fructose-6-phosphate (F6P). The F6P is then phosphorylated by phosphofructokinase (PFK)—the major rate-limiting and committed step in glycolysis—to fructose-1,6-bisphosphate (F-1,6-BP). These reactions comprise the preparatory phase of glycolysis and use ATP. In addition, glycolytic metabolites in this phase of glycolysis serve as precursors to the pentose phosphate pathway (PPP), the hexosamine biosynthetic pathway (HBP), and the glycogen synthetic pathway. The payoff phase commences with the splitting of F-1,6-BP into dihydroxyacetone phosphate (DHAP) and glyceraldehyde-3-phosphate (GAP). DHAP is a precursor for the glycerolipid pathway (GLP), important for the synthesis of glycerophospholipids. GAP is oxidized and phosphorylated to 1,3-bisphosphoglycerate. The formation of 3-phosphoglycerate (3PG) then provides precursors for the serine biosynthesis pathway (SBP), which yields serine and glycine and intersects with one-carbon metabolism to regulate the abundance of epigenetic modifiers such as methyl donors and α-ketoglutarate. HK indicates hexokinase; OAA, oxaloacetate; PC, pyruvate kinase; PEP, phosphoenolpyruvate; PFK, phosphofructokinase; and PKM, pyruvate kinase M.

modulating one-carbon metabolism, it regulates the formation of methyl donors required for DNA methylation reactions.[141] Nevertheless, it would seem that stable isotope tracing in vivo is required to understand in greater detail how exercise coordinates biosynthesis reactions in the myocardium.

Summary

Exercise acutely increases cardiac workload, elevates catecholamine levels, and augments circulating levels of fatty acids and lactate. Although lower intensity exercise seems to increase myocardial glucose catabolism, relatively high-intensity, prolonged exercise may diminish glucose catabolism and initiate mitochondrial fission and augment mitochondrial function. Decreases in PFK activity seem particularly important for coordinating glucose-derived carbon for anabolic processes and for activating the *Cebpb/Cited4* cardiac growth program. Temporary accumulation of intracellular metabolites such as AMP and glucose-6-phosphate may promote mitochondrial biogenesis and activate mTOR, respectively, to initiate physiological myocyte hypertrophy. Acute or more prolonged elevations in particular plasma FFAs (eg, C16:1n7) initiate cardiac

growth by poorly understood mechanisms, and elevations of hormones (eg, IGF-1, neuregulin 1) important for cardiac adaptation help coordinate anabolic metabolism with the signaling pathways critical for growth (eg, Akt; Figure 4). Nevertheless, it remains unclear how exercise-induced changes in metabolism couple the synthesis of structural materials to the activation of adaptive gene programs and how metabolic changes in the heart integrate with mitochondrial dynamics. Moreover, it remains to be tested whether glucose metabolism, its intermediates, or its end products are important for exercise-induced cardiac angiogenesis, as they are in other organs[142] or contexts.[143,144] Last, it is unclear whether changes in metabolism regulate exercise-induced myocyte proliferation[145] or are involved in exercise-mediated activation of cardiac progenitor cells.[87]

Metabolism and Pregnancy-Induced Cardiac Remodeling

Like exercise, pregnancy promotes a reversible increase in cardiac mass. Studies in the 1930s and 1940s demonstrated that pregnancy increases stroke volume, heart rate, and cardiac output.[146,147] In the 1970s, the routine use of echocardiography contributed to the finding that pregnancy causes a reversible form of cardiac hypertrophy, referred to as pregnancy-induced cardiac growth.[148] Later studies showed that this remodeling was eccentric in nature and develops during the second and third trimesters of pregnancy.[149–151] The degree to which the myocardium hypertrophies during pregnancy may exceed that typically occurring with exercise, with left ventricular masses increasing by as much as 50%; however, the maternal heart weight to body weight ratio can actually decrease due to the robust increase in body mass occurring in the third trimester.[152–155] Interestingly, pregnancy is commonly associated with mild systolic and diastolic dysfunction,[149,151,152,156] longer QT-interval dispersion, and a higher risk for arrhythmias during labor.[157,158] Late pregnancy may even increase vulnerability to myocardial ischemia-reperfusion injury.[159,160] Nevertheless, the mild cardiac dysfunction during pregnancy is usually not of concern because it reverses in the postpartum period.[161] This fact, combined with the increase in angiogenesis,[162,163] lack of fibrosis,[151,162,164,165] and protection against some forms of stress[166–168] in the pregnancy-adapted heart, help to assign pregnancy-induced cardiac growth as a physiological form of hypertrophy.

Metabolic Changes in the Maternal Heart During Pregnancy

Studies from the early 1990s showed that pregnancy is associated with a progressive decrease in myocardial glucose utilization.[169–172] Although pregnancy can mildly decrease circulating glucose levels, the levels of ketone bodies, nonesterified FFAs, lactate, and triglycerides are higher during pregnancy.[169,170,172–175] Thus, heightened levels of competing substrates might be sufficient to explain diminished cardiac glucose utilization during pregnancy. Nevertheless, recent findings illustrate that the hormonal environment of pregnancy promotes metabolic remodeling, which spares glucose at the expense of increased fat catabolism.[173] In particular, progesterone was shown to increase the expression of PDK4 (pyruvate dehydrogenase kinase 4), leading to the inhibition of glucose oxidation and elevated rates of fat oxidation.[173] A separate study showed that elevated levels of FGF21 (fibroblast growth
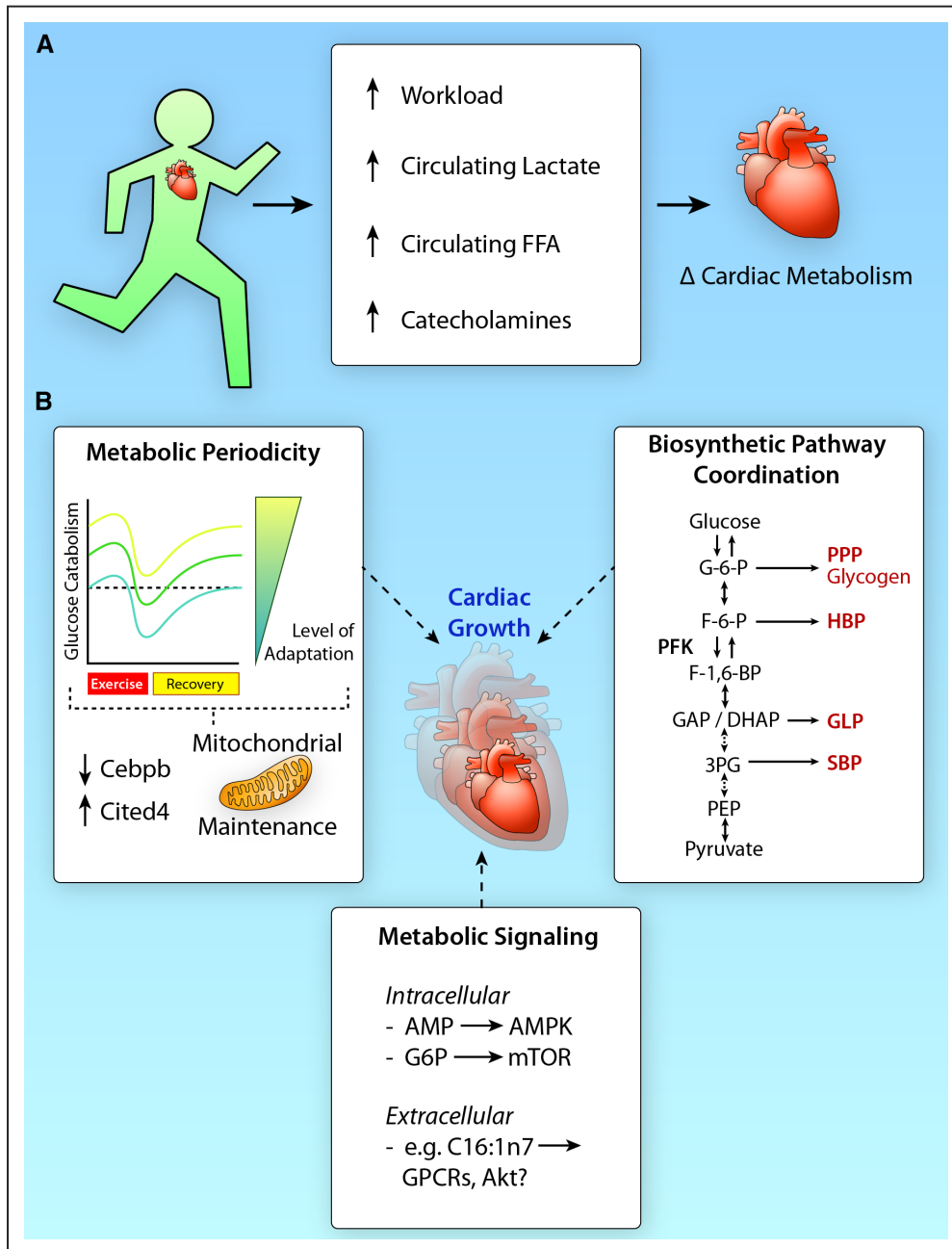
Figure 4. Metabolic mechanisms of exercise-induced cardiac growth. A, During exercise, changes in cardiac workload, circulating substrates, and hormones influence cardiac metabolism. The catabolic pathways invoked and the degree by which cardiac metabolism changes are dependent on the type and duration of exercise. **B,** Metabolic mechanisms that integrate to promote cardiac growth: exercise may diminish the activity phosphofructokinase (PFK), which leads to diminished glucose catabolism (ie, decreased glycolysis and glucose oxidation). In the exercise-adapted, resting state, glucose catabolism appears elevated above the untrained state. Such periodicity in glucose metabolism seems to regulate the exercise gene program, that is, by decreasing *Cebpb* expression and augmenting levels of *Cited4*. In addition, the metabolic periodicity caused by exercise may influence mitochondrial dynamics and help maintain healthy pools of mitochondria. The PFK step of glycolysis is important for coordinating the activity of ancillary biosynthetic pathways, which not only provide material causes for cardiac growth but may also influence the epigenetic landscape. Changes in the intracellular abundance of metabolites such as AMP and glucose-6-phosphate (G6P) may directly activate key kinases involved in cardiac adaptation. Also, circulating metabolites [eg, palmitoleate (C16:1n7)] may activate signaling pathways that promote cardiac growth. 3PG indicates 3-phosphoglycerate; F-1,6-BP, fructose-1,6-bisphosphate; F6P, fructose-6-phosphate; FFA, free fatty acids; GAP, glyceraldehyde-3-phosphate; GLP, glycero(phospho)lipid synthesis pathway; HBP, hexosamine biosynthetic pathway; and SBP, serine biosynthesis pathway. Illustration credit: Ben Smith.

factor 21) during pregnancy also induce PDK4 and increase fatty acid oxidation in the heart.[176] Similarly, endothelial nitric oxide synthase, which is commonly upregulated or activated with exercise,[39,177,178] activates fatty acid oxidation and inhibits glucose oxidation in the hearts of pregnant dogs.[179]

Metabolic Causes of Pregnancy-Induced Cardiac Growth

The diminishment in myocardial glucose catabolism during pregnancy seems important for cardiac growth. Overcoming PDK4-mediated inhibition of glucose oxidation with

dichloroacetate prevents pregnancy-induced increases in cardiac mass.[173] The sparing of glucose-derived carbon for ancillary biosynthetic pathways is a simple explanation for how a switch to fat oxidation could facilitate cardiac growth. Interestingly, genes for glycerolipid synthesis are upregulated in the heart during pregnancy,[180] which further supports the idea that glucose-derived carbon, if directed toward biosynthesis rather than ATP production, may promote cardiac growth. How pregnancy affects other pathways ancillary to glycolysis (eg, the PPP, HBP, and SBP) in the heart and how they integrate to contribute to cardiac growth remain interesting questions to address. Nevertheless, the finding that decreases in glucose oxidation seem to be required for pregnancy-induced cardiac growth[173] is concordant with findings in the context of exercise, where episodic decreases in glucose catabolism seem to drive metabolic changes and gene programs required for physiological growth.[80] Of note, FGF21, which is increased in pregnancy and by supporting fatty acid oxidation could diminish myocardial glucose oxidation,[176] is also induced by exercise.[181–183] Thus, it is possible that FGF21 promotes pregnancy- and exercise-induced cardiac growth by similar metabolic mechanisms.

Summary

Increased myocardial metabolic demand during pregnancy is associated with integrated changes in circulating substrates and hormones and metabolic remodeling of the heart. The levels of circulating FFAs, triglycerides, ketone bodies, and lactate tend to increase, which drives their uptake and catabolism in the heart. Furthermore, hormones such as progesterone and FGF21 upregulate PDK4, which diminishes glucose oxidation and promotes the oxidation of competing substrates. The decrease in glucose catabolism seems to be causative in pregnancy-induced cardiac growth because pharmacological activation of glucose oxidation prevents the increases in cardiac mass associated with pregnancy (Figure 5). Although it is likely that decreases in glucose catabolism spare glucose for the anabolic reactions needed for myocyte growth, how biosynthetic pathways change with pregnancy remains unexamined. Moreover, the roles of metabolism in epigenetic reprogramming, metabolite signaling, and redox balance remain unclear in the context of pregnancy-induced cardiac growth.

The Developing Heart and Metabolism

Two key events that promote high metabolic demand occur during fetal development: organ and body growth, and maturation and differentiation.[184] The heart begins to maintain circulation early in embryonic development, with mouse hearts contracting regularly at 40% of gestation (days 8 of 20) and human hearts at 8% of gestation (days 22 of 280)[185] or perhaps even earlier.[186] During gestation, the heart grows in size but does so in proportion with rising plasma volume and body weight.[184] As expected, these changes coincide with remarkable alterations in cardiac metabolism, and several studies support a causal role of the unique metabolic properties of early life in the development and growth of the heart.

General Metabolic Signatures of the Developing and Fetal Heart

The developing heart is reliant on glycolysis for energy. The glycolytic phenotype of the fetal heart seems to be the product of a hypoxic environment, the substrates available to the fetus, low mitochondrial abundance, low fat oxidation capacity of fetal cardiac mitochondria, and a low circulatory workload. The fetal heart also accumulates glycogen in high concentrations.[187] This setting, combined with activation of certain developmental programs, empowers metabolism with an exceptional ability to synthesize nascent myocardial tissue and maintain ATP production. The most conspicuous change in cardiac metabolism occurring with the transition to the neonatal period is a switch from glycolysis to oxidative phosphorylation.[188,189]

Substrates Available to the Developing Heart

The umbilical circulation provides the principal avenue by which the fetus procures substrates from the placenta and maternal environment; however, the substrates available to the fetus for energy provision and for tissue accretion differ from that in the maternal circulation. Although glucose crosses the placenta by facilitated diffusion (and thus can be strongly influenced by maternal blood glucose concentrations[190,191]), the levels of lactate, amino acids, and fatty acids are regulated at distinct levels. Arterial glucose concentrations in fetal lambs have been reported to be ≈1.1 mmol/L. It is likely that the reason for these relatively low levels is rapid uptake and utilization of glucose by fetal tissues. In the newborn lamb, arterial glucose concentration rises to ≈5.5 mmol/L. In contrast, lactate is 1.1 to 1.4 mmol/L in both the fetus and the newborn and falls below mmol/L levels when approaching adulthood.[192,193] Circulating levels of ketone bodies, triglycerides, and fatty acids are much lower in the fetus (eg, <100 µmol/L) compared with that of newborns (where concentrations range from ≈200 to 500 µmol/L),[192] which, at least for fatty acids, is due in part to poor placental transfer.[187]

Consistent with substrate availability, the fetal heart depends primarily on glucose and lactate for energy,[192–194] with lactate simultaneously released and taken up by the myocardium.[193] It has been estimated that glucose catabolism accounts for 50% to 75% of oxygen utilization in the entire fetus,[187,195] and lactate oxidation may account for up to 32%.[196] Interestingly, lactate oxidation in the fetal heart is attenuated by supply of fatty acids, but not glucose,[193] which could insinuate a role of glucose beyond ATP production. Glucose uptake in the fetal heart becomes progressively more dependent on insulin during gestation.[197,198] After birth, it seems that insulin-dependent glucose uptake is important for normal cardiac growth and maturation because cardiomyocyte-specific deletion of the insulin receptor decreases cardiac size by up to 30%.[199]

Metabolic Causes of Cardiac Growth and Remodeling During Development

Tissue accretion requires carbons derived from glucose for making biomolecules (eg, nucleotides, amino acids, glycerophospholipids), which insinuates relatively high activity of ancillary biosynthetic pathways of glucose metabolism. Indeed, the fetal heart has high PPP activity[200] and shows higher levels of key enzymes in the oxidative PPP than the adult heart.[201] Glucose also provides carbon for the glycerol backbone of phospholipids, key for membrane expansion in times of growth. After birth, the neonatal mammalian heart, despite its increasing ability to catabolize fatty acids and ketone bodies
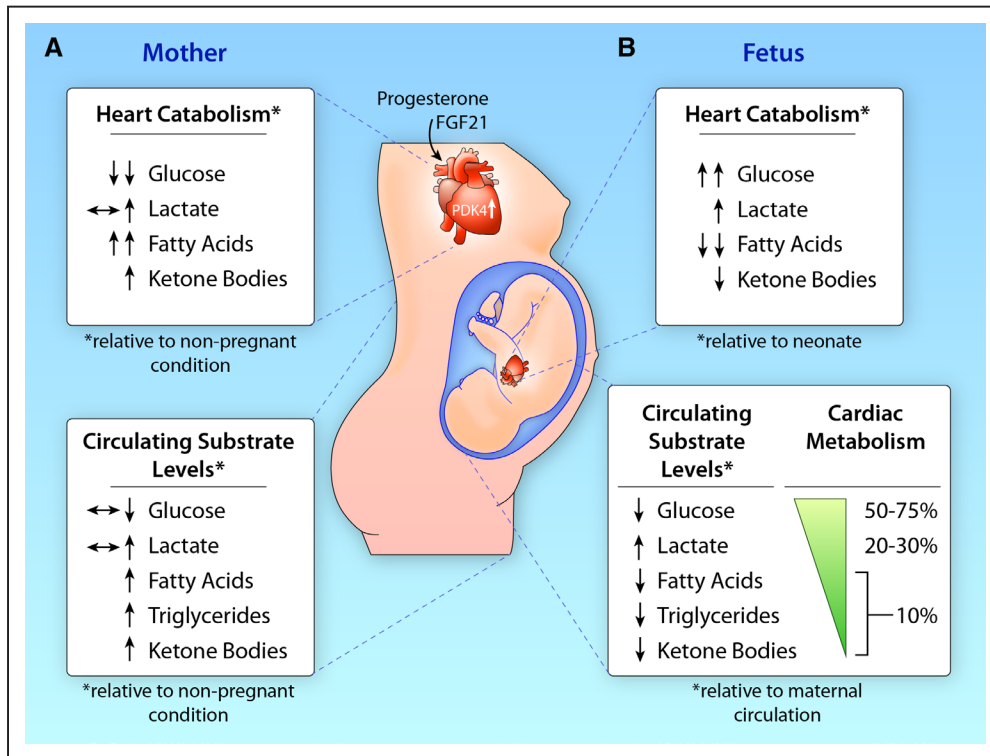
Figure 5. Metabolic changes induced by pregnancy. Heart catabolism in the mother and fetus are driven not only by intrinsic metabolic programs in the heart (eg, progesterone-dependent PDK4 [pyruvate dehydrogenase kinase 4] upregulation in the maternal heart) but also by changes in circulating substrate levels. Shown are the directional changes compared with a relevant context (denoted by the *). FGF21 indicates fibroblast growth factor 21. Illustration credit: Ben Smith.

for energy,[189,192] also maintains relatively high glucose uptake, which provides carbon material for cardiac growth.

The high reliance of the developing heart on glucose for energy and biosynthesis suggests that changes in glucose metabolism or impairments in the switch to oxidative metabolism could affect cardiac development. In the embryonic heart, hypoglycemia causes abnormal looping, disorganizes developmental layers, and decreases myocardial thickness; it also diminishes heart rate and vascularity.[202] Furthermore, hypoglycemia in newborns is associated with cardiomegaly and heart failure.[203] Maternal hyperglycemia is also associated with congenital cardiac defects and pathological hypertrophy.[204] Interestingly, high levels of glucose may inhibit cardiac maturation by promoting excessive nucleotide biosynthesis through the PPP.[205] Such findings provide preliminary support for the hypothesis that defects in the developing heart associated with poor maternal glucose control are caused by dysregulated biosynthetic pathway activity.

Delay or inhibition of the switch to oxidative metabolism in the neonatal period seems to promote pathological remodeling. For example, deletion of mitofusins 1 and 2, key regulators of mitochondrial morphology, causes pathological remodeling and heart failure postnatally in mice.[206] We can infer that the loss of mitochondrial function in such models prevents the switch from glycolytic to mitochondrial metabolism that normally occurs after birth.[189,207] This is supported by data from experiments interrogating the role of HIF1α (hypoxia-inducible factor 1α), which unifies the upregulation of the glycolytic machinery with the downregulation of oxidative

capacity. In the absence of HIF1α, fetal cardiomyocytes have a diminished ability to use glucose and become quiescent,[208] whereas deletion of the E3 ubiquitin ligase *Vhl* during midgestation hyperactivates HIF1α, promotes a constitutive glycolytic phenotype, prevents cardiac maturation, and leads to heart failure.[209]

Changes in the epigenetic landscape are also important for transcriptional programming during cardiac development. Deletion or loss of function of numerous histone acetyltransferase, deacetylase, methyltransferase, and demethylase enzymes is sufficient to influence cardiac development. Similarly, disrupting the balance of DNA methylation and demethylation dysregulates cardiogenesis or remodeling in the fetal or neonatal periods.[210–213] The primary methyl donors for post-translational methylation modifications, that is, S-adenosyl methionine, derive from dietary methyl group consumption and from the 5-methyl tetrahydrofolate generated in the folate cycle.[214] Cofactors and metabolites of both glucose metabolism and the Krebs cycle may also contribute to epigenetic regulation of cardiac development. For example, the end product of the HBP, that is, uridine diphosphate *N*-acetylglucosamine,[215] is required for O-GlcNAcylation of histones,[216,217] which can regulate transcription and the self-renewal genes Oct4 and Sox2.[218] In addition, the abundance of several other cofactors and metabolites, including but not limited to NAD+, FAD (flavin adenine dinucleotide), acetyl CoA (coenzyme A), α-ketoglutarate, and 2-hydroxyglutarate, regulates protein modifications and epigenetic enzyme activity to influence gene transcription.[214,219] The relative contribution

of the metabolic pathways that contribute to epigenetic programming in cardiogenesis, development, and neonatal heart growth remains to be determined.

Summary

The fetal heart is reliant on glucose and lactate for energy and as carbon sources for biosynthesis (Figure 5). Circulating levels of common competing substrates such as triglycerides, fatty acids, and ketone bodies are relatively low in the fetus. Insulin-dependent glucose uptake seems to manifest in the last third of gestation, when it becomes important for normal cardiac growth and maturation. The switch from glycolysis to oxidative phosphorylation in the neonatal period is fundamental to continued physiological growth of the heart. Moreover, steady levels of circulating glucose are important for normal cardiac remodeling and maturation. Although early cardiac development coincides with relatively high activity of some ancillary pathways of glucose metabolism such as the PPP, there is little extant information on the changes, relative importance, and regulation of other biosynthetic pathways in the fetal and neonatal periods. How changes in metabolism affect the epigenetic landscape in the fetal and neonatal periods also remain unclear.

Role of Metabolism in Pathological Cardiac Remodeling

Pathological remodeling has diverse origins, including pressure overload, volume overload, myocardial infarction, metabolic diseases (eg, diabetes mellitus), and aging. Remodeling in each case may be remarkably different, and the metabolic causes for each may be different as well. Because of the numerous reviews on substrate catabolism in pathological remodeling[21,207,220,221]), we frame the primary issues for which there is consensus and controversial topics, and we discuss the evidence for how changes in intermediary metabolism may influence pathological remodeling.

Overview of the Metabolic Changes in the Hypertrophied and Failing Heart

During pathological remodeling, the heart switches to a fetal gene program[222] and modifies its substrate preference from fatty acids to glucose[223–225]; however, these changes in cardiac metabolism are not sharply defined. For example, in humans with pathological hypertrophy or heart failure, fatty acid uptake and oxidation may be diminished,[226–229] augmented,[230–232] or unchanged.[233] Contrasting reports could be because of differences in disease severity, as indicated by studies that correlate functional impairment with fat utilization.[228,229] Consistent with this idea, decreases in fatty acid oxidation are suggested to be a late-stage heart failure phenomenon in dogs and rats.[234,235] Such decreases in fat oxidation are associated with diminished expression of genes involved in fatty acid uptake or mitochondrial β-oxidation[236–238] and decreased oxidation of fatty acid substrates by isolated mitochondria.[239,240] Although an increase in glucose oxidation may temporally supplant losses in fat oxidation capacity,[241] changes in substrate reliance are typically associated with a lower capacity for oxidative metabolism, higher glycolytic rates, and lower levels of high-energy phosphate reserves.[2,21,23] Some studies suggest

that actual rates of glycolysis and glucose oxidation are decreased,[242] due in part to myocardial insulin resistance[242–245] or to decrements in mitochondrial oxidative capacity.[246] Nevertheless, it seems that the consensus is that the heart decreases its capacity for fat oxidation and increases its reliance on glycolysis for energy.

The failing heart also shows marked changes in ketone and BCAA metabolism. Not only are circulating ketone bodies higher in the context of heart failure,[247,248] but the expression of genes important for ketone metabolism is increased in the failing heart.[249,250] Ketone bodies have a pronounced inhibitory effect on the rate of glucose use,[10,11,251] suggesting that they are oxidized in preference to glucose, and if in sufficient abundance, they diminish myocardial fat uptake and utilization. Although BCAAs contribute to <5% of myocardial oxygen consumption[24] (possibly because of relatively low expression of BCAA catabolism enzymes[252]), BCAAs and their metabolites are elevated in the failing heart,[244] which seems due in part to their diminished catabolism.[253,254]

Metabolic Mechanisms of Pathological Remodeling in Heart Failure

Are the metabolic changes that occur in the context of pathological remodeling adaptive or maladaptive? As detailed below, evidence from genetic and pharmacological models of altered myocardial metabolism provides clues, but the answer is not fully clear and several issues remain to be addressed.

Glucose Uptake

Changes in glucose uptake occur in the hypertrophied and the failing heart. Although decreased responsiveness to insulin is a relatively early event in pressure overload–induced hypertrophy[242] and heart failure,[244] multiple models of hypertrophy show an increased rate of glucose uptake and glycolysis.[255–258] These changes are consistent with increased reliance on GLUT1 (glucose transporter 1)-dependent glucose transport and a switch to a fetal metabolic profile.[259,260] In the context of pressure overload, constitutive cardiomyocyte-specific overexpression of GLUT1 prevents left ventricular dilatation and heart failure,[261] whereas inducible short-term GLUT1 overexpression attenuates mitochondrial dysfunction and fibrosis, but exacerbates cardiac hypertrophy.[262] Deletion of GLUT1 does not accelerate or worsen pressure overload–induced heart failure.[263] Deletion of the insulin-responsive glucose transporter, GLUT4, in the heart abolishes insulin-stimulated glucose uptake, yet increases glucose uptake in a GLUT1-dependent manner.[264] In the absence of any stressor, GLUT4-deleted mice show a compensated form of cardiac hypertrophy at baseline, but in response to pressure overload, they show more severe contractile dysfunction; in response to exercise, they show higher levels of fibrosis and apoptosis.[264,265] These findings suggest that increasing the availability of glucose in the heart could regulate the hypertrophic program and attenuate myocardial dysfunction, but that loss of insulin-dependent glucose uptake is pathological.

Handling of Glucose by the Glycolytic Machinery

Overexpression of hexokinase 2, which generates glucose-6-phosphate, partially prevents cardiac hypertrophy, potentially by increasing PPP activity and NADPH production.[266] Changes

in PFK activity are also sufficient to regulate cardiomyocyte ancillary biosynthetic pathway activity[131] and cardiac remodeling.[80,267,268] Whereas low rates of glycolysis drive a form of remodeling redolent of the exercise-adapted heart,[80] constitutive activation of PFK and heightened glycolysis promotes a mild, dilated form of cardiomyopathy.[80,267] The corollary of this finding could be that the high PFK activity observed in the pressure-overloaded heart[257] is causal to heart failure. The pyruvate kinase step in glycolysis may be important for regulating cardiac health as well. Elevated expression of the PKM2 splice variant has been suggested to be a signature of heart failure.[269] Nevertheless, it remains unclear whether changes in pyruvate kinase activity affect cardiac remodeling. This seems important because, whereas PKM1 is constitutively active, PKM2 activity is regulated through allosterism (eg, glycolytic intermediates, alanine, serine), protein-protein interactions (eg, with tyrosine-phosphorylated proteins), and post-translational modifications (eg, phosphorylation, acetylation, oxidation). These mechanisms of regulation elicit either an active, tetrameric form of PKM2 or a relatively inactive, dimeric form, the latter of which appears in several cell types to have transactivator or protein kinase functionalities.[270] In the context of cancer, PKM2 regulates ancillary biosynthetic pathway activity, thereby contributing to cancer cell growth.[270,271] This could be germane to cardiac health because, under some conditions, the heart demonstrates footprints of cancer cell metabolism.[272]

Ancillary Biosynthetic Pathways in the Hypertrophied and Failing Heart

Approaches to understand the importance of particular ancillary pathways of glucose metabolism to pathological remodeling have yielded mixed results. Most studies to assess how the PPP regulates cardiac responses to stress or affects remodeling have done so by modulating the activity of glucose-6-phosphate dehydrogenase, which converts glucose-6-phosphate and $NADP^+$ to 6-phosphogluconolactone and NADPH.[273] Although this enzyme is important to maintain cellular redox status and contractile function in myocytes and may be important for diminishing ischemia-reperfusion injury,[274,275] it may also worsen heart failure by fueling production of superoxide by NADPH oxidase.[276,277] Beyond the context of O-GlcNAc, little is known about how the HBP affects cardiac health. The vast majority of studies show that modulating levels of O-GlcNAcylated proteins affects cardiac responses to injury and heart failure.[215,278–280] It should be noted that O-GlcNAc levels are not necessarily linked to corresponding changes in HBP flux[281] and that the end product of the HBP, that is, uridine diphosphate-*N*-acetylglucosamine, is used for other reactions as well (eg, *N*-glycosylation,[282] glycosylphosphatidylinositol anchoring[283]). There seems to be much more to learn about how both the HBP and the PPP affect cardiac remodeling and heart failure.

Little knowledge exists for how ancillary pathways deriving from 3-carbon intermediates of glycolysis (eg, the GLP and the SBP) influence pathological remodeling. Interestingly, expression of HIF1α has been shown not only to upregulate glycolytic genes in pathological hypertrophy, but, by transcriptionally activating PPARγ (peroxisome proliferator–activated receptor α), to induce the expression of rate-limiting enzymes in the GLP, that is, GPD1 (glycerol 3-phosphate

dehydrogenase 1) and GPAT (glycerol 3-phosphate acyltransferase).[284] This could affect both triacylglycerol and phospholipid levels in the heart. It is notable that the activity of PFK, which poises the 6-carbon sugar backbone for lysis by aldolase, may regulate GLP flux.[131,285] The importance of the SBP and its regulation in cardiac hypertrophy and failure is a completely untapped area of inquiry. This is surprising given the fact that the SBP can modulate the levels of substrates important for epigenetic reactions (ie, α-ketoglutarate, 5-methyl tetrahydrofolate).[141,286] Interestingly, in fibroblasts, TGF-β (transforming growth factor β)—which promotes myofibroblast transdifferentiation[287]—not only increases glycolysis[288] and glutaminolysis[289] but upregulates major enzymes in the SBP as well.[290] This is important because the SBP is responsible for the biosynthesis of glycine, which constitutes one third of collagen. Accordingly, genetically or pharmacologically diminishing SBP prevents collagen synthesis by fibroblasts.[290]

BCAA Metabolism in Heart Failure

High levels of both extracellular and intracellular BCAAs could be detrimental to cardiac function. Perfusion of rat hearts with relatively high levels of leucine and isoleucine causes systolic dysfunction[291] and has a general cardiodepressant effect.[292] Excessive levels of BCAAs and their catabolites inhibit the activities of α-ketoglutarate and pyruvate dehydrogenases and mitochondrial respiration.[254,293–295] Similarly, deletion of protein phosphatase 2Cm[296] elevates BCAA catabolites, causes progressive cardiac dysfunction, and worsens cardiac outcomes in response to pressure overload.[254] Promoting BCAA catabolism by giving an inhibitor of BCKD (branched chain alpha- ketoacid dehydrogenase) kinase improves cardiac function.[254,295] It remains unclear why the heart responds to insult or injury by diminishing BCAA catabolism. Because BCAAs stimulate protein synthesis and promote anabolism, it is possible that decreases in catabolism occur to augment intracellular levels of BCAAs, which are required for anabolic processes involved in cardiac hypertrophy. Of the BCAAs, leucine seems the most potent at promoting a positive nitrogen balance and accelerating protein synthesis in the heart.[297,298] Mechanistically, BCAAs stimulate mTOR, which is a major signaling regulator of anabolism and processes such as autophagy, proliferation, and survival.[299]

Emerging Themes for Therapy

How can we modify metabolism in the failing heart to optimize anabolic processes while maintaining adequate energy for contraction? Promoting fatty acid utilization could be an approach that spares glucose-derived carbon for anabolic reactions and ensures sufficient ATP production. In support of this idea, deletion of acetyl CoA carboxylase 2 increases fat oxidation, diminishes glucose oxidation, and prevents pathological remodeling caused by pressure overload.[300] Similarly, preserving fatty acid oxidation prevents diastolic dysfunction caused by angiotensin II infusion.[301] Overexpression of medium-chain acyl-coenzyme A dehydrogenase, a key β-oxidation enzyme, is sufficient to both promote physiological cardiac growth and prevent pressure overload–induced pathological remodeling.[302] This seems important because medium-chain acyl-coenzyme A dehydrogenase is diminished in the human

failing heart,[236] and its deletion in mice causes cardiomyopathy.[303] Dietary interventions that regulate fatty acid availability for myocardial catabolism also affect the trajectory of heart failure. For example, dietary augmentation of fatty acids in the context of heart failure decreases glucose oxidation and improves cardiac function,[304–306] and FFA withdrawal decreases myocardial efficiency in heart failure patients.[307]

Augmenting myocardial ketone body oxidation also seems to be beneficial in the context of heart failure. That ketone levels are higher in patients with heart failure,[247,248] combined with the fact that cardiac ketone utilization is elevated in heart failure patients[249] and in mice with heart failure,[250] suggest that ketone bodies provide an alternative fuel for the heart under pathological conditions. Ketone bodies have a pronounced inhibitory effect on the rate of glucose use,[10,11,251] suggesting that they are oxidized in preference to glucose. The increase in ketone utilization in the failing heart is due not only to elevated circulating levels of ketone bodies but also to increased expression of genes important for ketone catabolism.[249,250] Increased ketone use in the context of heart failure seems advantageous because overexpression of a rate-limiting enzyme in ketone catabolism, that is, BDH1 (D-β-hydroxybutyrate dehydrogenase 1), prevents maladaptive remodeling caused by pressure overload.[308] Correspondingly, interventions that decrease ketone oxidation (eg, deletion of succinyl-CoA: 3-ketoacid CoA transferase) worsen cardiac function and hypertrophy in response to stress.[309] Collectively, these findings support the thesis that augmenting fat or ketone utilization prevents or delays heart failure, potentially by sparing glucose-derived carbon for anabolic reactions.

At first glance, the findings of other genetic and of pharmacological studies are difficult to square with the simple idea that increasing the availability of glucose carbon for biosynthesis preserves cardiac function. For example, increasing fatty acid oxidation by overexpressing PPARα decreases glucose oxidation and impairs cardiac function, causes hypertrophy, and seems to mimic some of the facets of the diabetic heart.[310,311] However, it should be noted that nearly every genetic intervention targeting PPARs in the heart (with the exception of PPARβ/γ) causes impaired cardiac function or deleterious remodeling.[220] This is not surprising given that PPARs play highly integrated and essential roles in metabolism, transcription, differentiation, and organelle abundance.[312–314]

Dichloroacetate (DCA), which augments glucose oxidation by activating the pyruvate dehydrogenase complex,[315] was shown in rats to delay transition of cardiac hypertrophy to heart failure. These effects of DCA were associated with increases in energy reserves, glucose uptake, and glucose oxidation and activation of the PPP and diminished oxidative stress.[316] Clinical studies seem consistent with findings in rodent models and show that DCA increases stroke volume and improves myocardial efficiency.[317,318] Inhibition of fatty acid oxidation using compounds such as etomoxir, perhexiline, and trimetazidine seems to have effects similar to that of DCA.[21] That DCA increases glucose oxidation yet also augments PPP flux suggests that higher glucose catabolism does not always equate with lower glucose carbon allocation into biosynthetic pathways. It is possible that these pharmacological compounds optimize myocardial metabolism in the hypertrophied or failing heart by diminishing aerobic glycolysis, thereby preventing loss of glucose-derived carbon as lactate. Beneficial unintended effects is another possibility. For example, dichloroacetate causes overproduction of acetyl CoA, hyperacetylation of histone H3K9 and H4, and differential gene expression, which may form the molecular basis of its effects on the heart.[319] The beneficial effects of compounds such as trimetazidine may be due in part to systemic improvements in insulin sensitivity.[320]

The Heart in Diabetes Mellitus

Pathological remodeling of the diabetic heart also seems to have metabolic underpinnings. The defining structural and functional characteristics of the diabetic heart are left ventricular hypertrophy and diastolic dysfunction,[321] which are associated with higher rates of fatty acid[15,322,323] and ketone oxidation,[324] and lower rates of glucose oxidation, glycolysis,[322,323] and lactate oxidation.[322,325] These metabolic changes seem to be the product of higher circulating fatty acids and ketone bodies, increased fatty acid transport, decreased insulin sensitivity, downregulation of glucose transporters, elevated levels of PDK4, higher malonyl-CoA decarboxylase activity, and lower acetyl CoA carboxylase and PFK activities.[20,322,326–329] Associated with the metabolic phenotype of the diabetic heart are metabolic inflexibility, lipotoxicity (eg, accumulation of triacylglycerols, diacylglycerols, ceramide, long chain acyl CoAs, acylcarnitines), glucotoxicity, mitochondrial dysfunction, and cardiac insulin resistance.[20,330,331]

The mechanisms by which metabolic changes modulate pathological remodeling in the diabetic heart remain largely unclear; however, oversupply of fatty acids and insulin resistance could be entwined causal features. For example, cardiac insulin resistance is associated with relocation of fatty acid transporters to the cell membrane,[332–335] and reduction in their abundance can diminish diet-induced cardiac insulin resistance.[336] Moreover, overexpression of proteins regulating fatty acid uptake promotes a form of lipotoxic cardiomyopathy.[337,338] Interestingly, the metabolic stress associated with diabetes mellitus was shown to activate FoxO1 (forkhead box O1), and deletion of FoxO1 in cardiomyocytes shifted substrate utilization more toward glucose, decreased lipid accumulation in the heart, improved insulin sensitivity, and prevented diabetic cardiomyopathy.[339] Both glucotoxicity and lipotoxicity in the diabetic heart are commonly associated with elevated levels of advanced glycation end products and reactive oxygen species, the latter of which occurs in large part via mitochondrial dysfunction.[20,321,340]

Ancillary Biosynthetic Pathway Activity in the Diabetic Heart

It is commonly thought that conditions of diabetes mellitus increase HBP flux, which leads to constitutive, deleterious increases in uridine diphosphate *N*-acetylglucosamine levels and O-GlcNAc–modified proteins.[215,278,341] Evidence for changes in other ancillary pathways in the diabetic heart is relatively scant; however, diabetes mellitus seems to decrease myocardial PPP flux[342] and to increase polyol pathway flux.[343] Changes in the PPP seem important because pharmacologically increasing PPP activity prevents pathological cardiac remodeling and improves ventricular function in diabetic mice.[344] Concerning the importance of the polyol pathway, increasing or decreasing levels of aldose reductase has remarkable effects on cardiac glucose
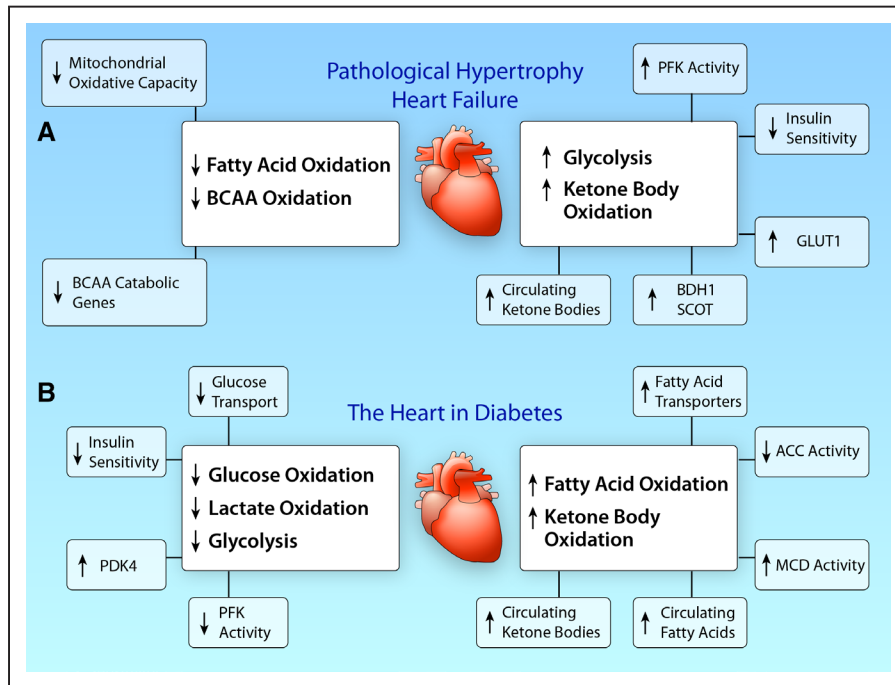
Figure 6. Changes in substrate catabolism associated with pathological cardiac remodeling. A, Metabolic changes in the hypertrophied and failing heart: glycolysis and ketone oxidation are higher and fatty acid oxidation and branched-chain amino acid (BCAA) oxidation are lower in the hypertrophied and failing heart. This appears to be caused by decreases in mitochondrial oxidative capacity, BCAA catabolic gene expression, and insulin sensitivity, and increases in phosphofructokinase (PFK) activity, glucose transporter 1 (GLUT1) expression, β-hydroxybutyrate dehydrogenase (BDH) and succinyl CoA:3-oxoacid CoA-transferase (SCOT) abundance. Moreover, higher circulating levels of ketones may also contribute to the diverse metabolic changes occurring during hypertrophy and heart failure. **B**, Metabolic changes in the diabetic heart: fatty acid and ketone oxidation are higher, and glucose/lactate oxidation and glycolysis are lower in the diabetic heart. This appears to be caused by decreased insulin sensitivity, elevated circulating levels of fatty acids and ketone bodies, alterations in substrate transport, higher pyruvate dehydrogenase kinase 4 (PDK4) abundance, lower PFK activity, lower acetyl CoA carboxylase (ACC) activity, and higher malonyl-CoA decarboxylase (MCD) activity. Illustration credit: Ben Smith.

metabolism[345] and cardiac structure, function, and recovery from ischemia.[346] Diabetes mellitus also diminishes the efficacy of cardiac mesenchymal cells to repair the heart,[347,348] which may in part be because of heightened glycolytic activity and impaired or uncoordinated flux through the PPP, HBP, and GLP.[285] In support of this idea, augmenting PPP flux in the diabetic heart increases diabetic cardiac progenitor cell abundance and proliferation.[349]

Summary
Cardiac remodeling in the hypertrophied and failing heart is associated with progressive decreases in fatty acid and BCAA oxidation and increases in cardiac reliance on glucose and ketone bodies for energy (Figure 6). Coordinated development of cardiac insulin resistance, upregulation of Glut1, activation of PFK, elevations in circulating ketone bodies and ketone oxidation enzymes, and downregulation of the fatty acid and BCAA oxidation machinery integrate to establish this metabolic phenotype. Findings from genetic mouse models suggest that enhancement of glucose uptake and increases in ketone utilization are beneficial in pressure overload–induced or infarct-induced remodeling and that activation of PFK and downregulation of fatty acid and BCAA oxidation are maladaptive. The mechanisms contributing to cardiac dysfunction in diabetes mellitus continue to be controversial; however, cardiac insulin resistance, lipotoxicity, and glucotoxicity remain defining features. Overall, the collective evidence suggests that loss of homeostasis in glucose metabolism and altered relationships between anabolic and catabolic pathways of glucose metabolism are defining features of most forms of pathological remodeling.

Conceptual Issues and Future Directions
The knowledge reviewed here suggests that changes in metabolism play a critical role in myocardial remodeling. Particularly conspicuous are findings in the contexts of exercise, pregnancy, and development, which suggest that proper handling of glucose-derived carbon for anabolic reactions is critical for physiological cardiac growth. Correspondingly, inefficient or uncoordinated handling of glucose appears central to pathological remodeling (Figure 7). Given that at least 50% of glucose entering the heart is reserved for storage or anabolism,[66,76,131,251,350,351] understanding how glucose carbons are allocated to ancillary biosynthetic pathways seems important. These pathways are critical for not only the synthesis of cellular building blocks but for also modulating specific pathways of cell signaling and the epigenetic landscape. Nevertheless, the multifaceted levels of causality intrinsic to metabolism present a paradox for understanding the extent to which changes in metabolism trigger healthy adaptations or promote functional decline.

Adoption of a systems-level approach within a relational biology conceptual framework appears required to forge new ground. Although several frameworks have emerged as candidates, all must deal with the fact that metabolism contains self-referencing components and circular pathways of causal relationships. For example, in the 1970s, Maturana and
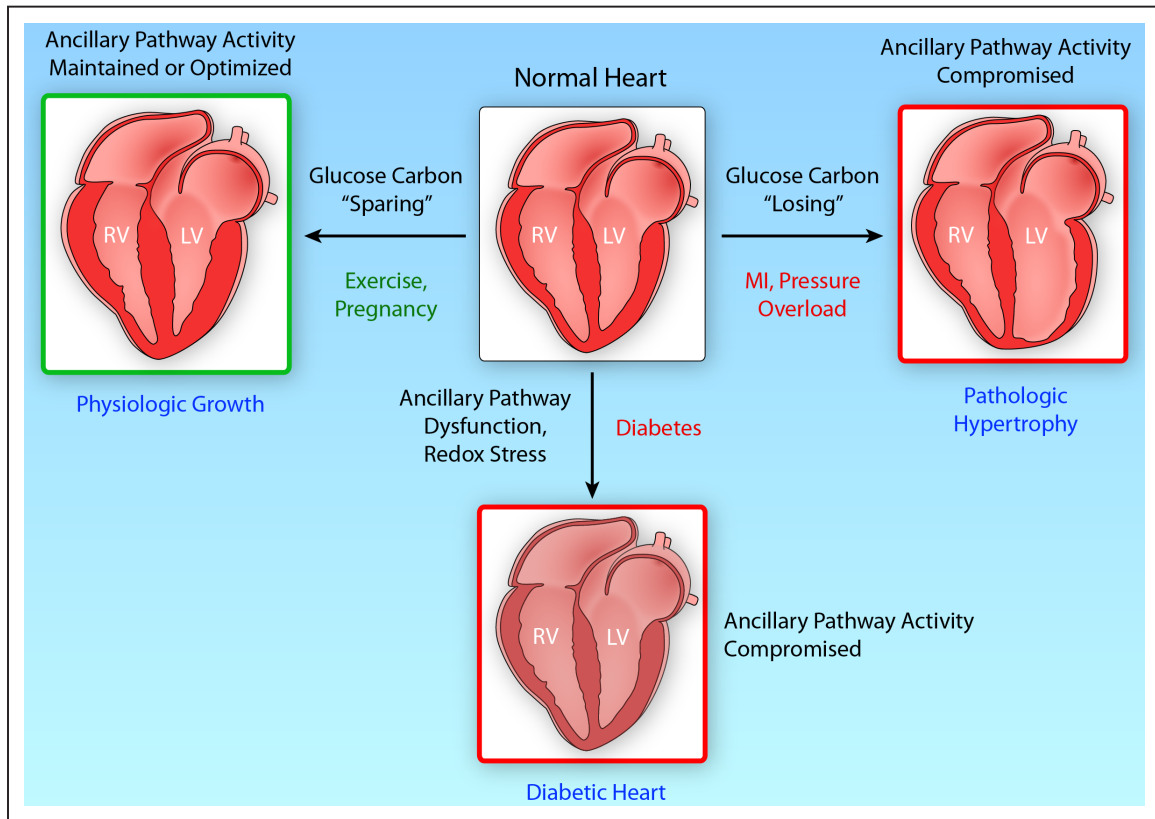
Figure 7. Generalized model of how metabolism regulates cardiac health and remodeling. Stimuli that promote physiological cardiac growth (eg, exercise, pregnancy) augment fatty acid, ketone, and lactate catabolism, which collectively supplant glucose as a metabolic fuel. In contrast, conditions that instigate pathological remodeling are characterized by metabolic changes that dysregulate glucose uptake and increase reliance of the heart on glucose for fuel. The metabolic changes may cause either adaptive or maladaptive remodeling by modulating the activity of ancillary biosynthetic pathways of glucose metabolism. In the context of diabetes mellitus, excess substrate may cause ancillary biosynthetic pathway dysfunction and redox stress, which could contribute to the development of cardiomyopathy. Illustration credit: Ben Smith.

Varela[352,353] introduced autopoiesis as a framework for describing biological systems. From its etymology, the term autopoiesis means self (auto) creation (poiesis). It can be defined as a network of processes that produce the components required for maintaining the bounded and organized systems of cells, organs, tissues, or organisms.[354] Nevertheless, this term is commonly derided for being solipsistic,[355] and the suffix, -poiesis, could be confused with terms also bearing the suffix (eg, hematopoiesis). Regardless, some of its conceptual implications may be useful for understanding how relationships between different ontologies (eg, metabolic relationships, transcriptional responses) or orders (eg, cell, organ, and environmental crosstalk) of systems integrate to promote growth and health.[356] Similarly, Robert Rosen's Metabolism-Repair/Replacement systems approach is theorized capable of explaining the dynamic relationships between pathways and how they support life.[357,358] In particular, Metabolism-Repair/Replacement systems involve mathematical expressions that focus on the interplay between the material and efficient causes in metabolism.

Although both Metabolism-Repair/Replacement systems and autopoiesis are highly abstract, they both suggest that the metabolome is continuous with the proteome, transcriptome, and genome, which we commonly compartmentalize and linearize for simplicity. Moreover, a distinguishing feature of both frameworks is the development of ideas behind life's capacity for self-organization, in opposition to entropic forces. However, despite their wide range and scope, neither autopoiesis nor Metabolism-Repair/Replacement systems fully capture the interconnectedness of metabolism with cell structure and function or with environmental interactions.[359] Perhaps in the short term, working toward a more defined and precise understanding of how metabolic pathway relationships change under physiological and pathological conditions would be most productive. This knowledge could guide efforts to understand the regulatory mechanisms that give rise to the metabolic flux configurations that cause or influence tissue remodeling.

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