Metabolic Determinants of Cardiomyocyte Proliferation

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Abstract

The adult mammalian heart is recalcitrant to regeneration after injury, in part due to the postmitotic nature of cardiomyocytes. Accumulating evidence suggests that cardiomyocyte proliferation in fetal or neonatal mammals and in regenerative non-mammalian models depends on a conducive metabolic state. Results from numerous studies in adult hearts indicate that conditions of relatively low fatty acid oxidation, low reactive oxygen species generation, and high glycolysis are required for induction of cardiomyocyte proliferation. Glycolysis appears particularly important because it provides branchpoint metabolites for several biosynthetic pathways that are essential for synthesis of nucleotides and nucleotide sugars, amino acids, and glycerophospholipids, all of which are required for daughter cell formation. In addition, the proliferative cardiomyocyte phenotype is supported in part by relatively low oxygen tensions and through the actions of critical transcription factors, coactivators, and signaling pathways that promote a more glycolytic and proliferative cardiomyocyte phenotype, such as hypoxia inducible factor 1α (Hif1α), Yes-associated protein (Yap), and ErbB2. Interventions that inhibit glycolysis or its integrated biosynthetic pathways almost universally impair cardiomyocyte proliferative capacity. Furthermore, metabolic enzymes that augment biosynthetic capacity such as phosphoenolpyruvate carboxykinase 2 and pyruvate kinase M2 appear to be amplifiers of cardiomyocyte proliferation. Collectively, these studies suggest that acquisition of a glycolytic and biosynthetic metabolic phenotype is a sine qua non of cardiomyocyte proliferation. Further knowledge of the regulatory mechanisms that control substrate partitioning to coordinate biosynthesis with energy provision could be leveraged to prompt or augment cardiomyocyte division and to promote cardiac repair.

Graphical Abstract

Hyperoxia
ROS
Fatty acid oxidation
Succinate oxidation

Hypoxia
Hif1α
Glycolysis
Glucose oxidation
Pkm2
Pck2
Mevalonate biosynthesis
O-GlcNAcylation
NAD+ biosynthesis
Introduction

Cardiomyocyte death is the principal cause of heart failure, with myocardial infarction (MI) comprising the primary contributor to loss of functional myocytes. Fortunately, advances in risk factor management have decreased rates of MI and acute MI-related fatalities; however, non-lethal cardiac events and significant growth of the elderly population continue to escalate the burden of heart failure. Projections in several countries indicate precipitation of a heart failure epidemic, which comes at the cost of upsurges in morbidity and higher healthcare expenditures.

Notwithstanding prevention, cardiac repair presents a solution to this problem. Cardiac repair involves coordinated phases of extracellular matrix remodeling, neovascularization, and cardiomyocyte repopulation. Successful integration of these processes can lead to a completely regenerated heart. In mammals, cardiac regeneration occurs only in the fetal and early neonatal periods of mammals, when a significant loss of cardiomyocytes is countered by veritable heart regeneration; however, the capacity for cardiomyocyte cytokinesis appears to be lost by day 4 after birth. After this time, the cardiac repair response is limited to replacement fibrosis as well as modest vascular regeneration and remodeling, which are regulated in part by immune cell-mediated mechanisms.

Metabolism influences each process involved in myocardial repair and regeneration. Metabolic pathways provide usable energy as well as the building blocks to build, repair, or remodel cells and tissues. Thus, catabolic and anabolic metabolic pathways must be appropriately synchronized to fulfill specific cellular tasks. For cell proliferation, nucleotide biosynthesis meets the demands for mRNA synthesis and DNA synthesis and repair; amino acid biosynthesis supports protein synthesis; and glycerophospholipid biosynthesis provides the structural components for making new membranes. Because metabolites have strong roles in cell signaling, metabolism also supports the informational architecture of cells and tissues. Although such universal roles of metabolism may be inferred to contribute to cardiac repair, it remains unclear how metabolic changes influence myocyte proliferation. The goal of this minireview is to integrate current information on how intermediary metabolism in the cardiomyocyte contributes to proliferation and to identify hurdles to gainful knowledge in the field of cardiac regeneration. For review of the role of metabolism in other cell types found in the heart (e.g., fibroblasts, endothelial cells) and in broader aspects related to cardiac metabolism and remodeling, the reader is directed to the following reviews.

Metabolic Requirements for Cell Proliferation

Cell division requires biosynthesis of cellular components to form daughter cells. Metabolism and its regulatory networks support this function and also provide usable energy and reducing power to maintain homeostasis and combat stress. Although catabolic processes are important for energy provision to sustain life and fuel work, how anabolic pathways influence cellular processes such as cell growth and proliferation is less well understood. Studies in cancer cells suggest that, although ATP is required for homeostasis, additional ATP does not appear to be required to fuel proliferation. Rather, proliferating cells increase biosynthetic pathway activity. The synthesis of nucleotides, nucleotide sugars, amino acids, and phospholipids integrate tightly with the catabolic pathways that provide ATP to fuel cellular work. In particular, the steps of glycolysis are optimally positioned to balance energy yield with enzyme cost, while concomitantly ensuring operability of ancillary branched pathways for biosynthesis. Indeed, the canonical glycolytic pathway appears to be the shortest pathway that ensures both production of precursors for cellular biomass and a high ATP yield capacity (Fig. 1). Remaining unclear are the regulatory mechanisms that control substrate partitioning to coordinate biosynthesis with energy provision to animate cell proliferation.

The networked pathways of metabolism provide conduits that direct nutrients toward multiple fates. In the cell, these biochemical networks obey the second law of thermodynamics and rise to the challenge of partitioning free energy across numerous metabolic steps to meet requirements for biosynthesis and usable energy. Particularly important are reactions that control levels of metabolites that lie at branchpoint sites. Examples of these include glucose 6-phosphate (G6P), fructose 6-phosphate (F6P), dihydroxyacetone phosphate, and 3-phosphoglycerate, which provide precursors for pyruvate or enter ancillary pathways such as the pentose phosphate pathway (PPP), the hexosamine biosynthetic pathway (HBP), the glycerolipid synthesis pathway, and serine synthesis pathway: some of these pathways branch further to direct carbon flow to additional fates. It is worth noting that these ancillary pathways appear to carry significant flux in the heart, given that at least 50% of glucose entering the myocardium and cardiomyocytes is partitioned for glycogen storage or biosynthetic pathways. Nevertheless, it remains unclear how cells partition glucose-derived carbon to balance energy demand with biosynthetic need. Although non-equilibrium enzymes in glycolysis such as phosphofructokinase and pyruvate kinase are known to influence carbon fate, the formation of metabolic enzyme complexes (e.g., metabolons) that foster metabolic channeling also contribute to glucose carbon partitioning. Understanding the interplay of these mechanisms and how they contribute to cell growth and proliferation is an exciting goal for the future.

In addition to partitioning of glucose-derived carbon to biosynthetic pathways, proliferating cells appear to use alternative means of driving carbon toward biosynthesis. Beyond glucose, glutamine contributes to core metabolic functions that support proliferation, as do branched chain amino acids, lactate, serine, and glycine, all of which can provide material...
resources required for replication. Also important to biosynthesis and cell division are key enzymes that link metabolism in the mitochondrial and cytosolic compartments or that influence glucose catabolic rate. For example, the gluconeogenic enzyme, phosphoenolpyruvate carboxykinase 2 (Pck2), is commonly expressed in proliferating cells and drives carbon in the Krebs cycle into the glycolytic pathway, where it can be allocated for biosynthetic reactions. Moreover, expression of pyruvate kinase (Pkm) splice variants have been shown to influence cell proliferation. Like Pck2, Pkm2 can help maintain the glycolytic intermediate pool, although this does not occur via the shuttling of carbon from the Krebs cycle; rather, Pkm2 is enzymatically slower than the Pkm1 variant and promotes accumulation of phosphoenolpyruvate and enriches or maintains levels of glycolytic intermediates. These intermediates can then be allocated to ancillary biosynthetic pathways, where they contribute to building block synthesis and NADPH regeneration, both of which are required for cell growth and proliferation.

Cardiomyocyte Metabolism in the Fetal Mammalian Heart

Unlike the adult mammalian heart, cardiomyocytes in the fetal heart are capable of avid growth and division, which is associated with a unique metabolic state. The fetal heart appears to depend mostly on glucose and lactate for energy, with lactate both released and taken up by the myocardium. In the growing fetus, the high reliance of the heart on glycolysis is a product of several factors, including but not limited to: a hypoxic environment; lower mitochondrial abundance and disorganized mitochondrial structure compared with adult heart; lower mitochondrial abundance and disorganized mitochondrial structure compared with adult heart; lower fetal circulation of fatty acids and lower fat oxidation capacity of fetal cardiac mitochondria; and a relatively low circulatory workload.
Figure 2. Metabolic phenotypes of fetal and adult cardiomyocytes. Fetal mammalian cardiomyocytes appear more reliant on glycolysis for energy compared with adult myocytes, which supply the majority of their ATP demand by oxidizing fatty acids. In addition, the fetal heart has been suggested to accumulate glycogen to higher levels and have higher pentose phosphate pathway (PPP) activity. Because end products of biosynthetic pathways are required for daughter cell formation, it is also expected that fetal hearts synthesize relatively more nucleotides and have higher hexosamine biosynthetic pathway (HBP), glycerolipid synthesis pathway (GLP), and serine biosynthesis pathway activity (SBP) than the adult heart.

Table 1. Evidence for a role of metabolism in cardiomyocyte proliferation.

| Metabolic pathway | Intervention | Highlights | Reference |
|-------------------|--------------|------------|-----------|
| Glycolysis        | Pdk4         | Deletion of Pdk4 promotes cardiomyocyte proliferation, decreases DNA damage, improves cardiac repair after MI | 77         |
| Glucose oxidation | Fatty acid availability | Fatty acid deficient milk extends post-birth cardiomyocyte proliferation window | 77         |
| Fatty acid        | Sdh          | Provision of succinate inhibits cardiomyocyte proliferation and cardiac regeneration; Inhibition of Sdh promotes cardiomyocyte cell cycle entry and augments cardiac regeneration after MI | 80         |
| availability      |              |            |           |
| Hypoxia           | Hif1α        | Hypoxia diminishes ROS and promotes cardiomyocyte proliferation and regeneration after MI; Deletion of Hif1α downregulates glycolytic genes, decreases cardiomyocyte proliferation, and impairs cardiac development | 62,81-85   |
|                  | Pkm2         | Pkm2 overexpression promotes cardiomyocyte proliferation, improves cardiac function after MI, and activates the pentose phosphate pathway | 90         |
|                  | ErbB2        | Activates glycolysis and promotes cardiomyocyte proliferation and cardiac repair | 118,126    |
| Anabolic pathways | Simvastatin   | Inhibits the mevalonate pathway, which is important for isoprenoid synthesis, and impairs cardiomyocyte proliferation | 95         |
|                   | Oga          | Overexpression of OGA, which is associated with the HBP, prevents cardiomyocyte cell cycle entry and progression | 100        |
|                   | Nampt        | Knockdown of NAMPT diminishes cardiomyocyte cell cycle entry and progression | 100        |
|                   | Pck2         | Overexpression of Pck2 augments 4F-triggered cardiomyocyte proliferation | 100        |

4F, 4 factors, ie, cyclin D1, cyclin B1, Cdk1, and Cdk4; HBP, hexosamine biosynthetic pathway; Hif1α, hypoxia-inducible factor 1α; Nampt, nicotinamide phosphoribosyl transferase; Oga, protein O-GlcNAcase; Pck2, phosphoenolpyruvate carboxykinase 2; Pdk4, pyruvate dehydrogenase kinase 4; Pkm2, pyruvate kinase M2; Sdh, succinate dehydrogenase.
The fetal heart also accumulates glycogen to relatively high levels, and the early neonatal heart has higher levels of glutamine, which influences mTOR activation to help drive cardiogenesis. Because tissue accretion requires carbohydrates derived from glucose for making nucleotides, amino acids, and glycero-phospholipids, it is expected that the developing heart has high requirements for biosynthetic processes. Interestingly, this high anabolic demand occurs in the setting of progressively higher cardiac work load. In mice, the heart commences contraction at day 8 of gestation (40% of the gestation period), and in humans, contraction begins around day 22 of gestation or even earlier (equating to 8% of the overall gestation period). The heart grows in size during gestation in proportion with rising plasma volume and body weight. Thus, it appears that the fetal mammalian heart has an extraordinary ability to coordinate anabolic processes for growth with energy-providing processes for physical work.

That the fetal and early neonatal heart maintains the ability to regenerate cardiomyocytes also suggests a high level of metabolic robustness, which refers to the capacity to maintain metabolic homeostasis and tissue function in the face of external or internal perturbations. This is likely a consequence of the high reliance of the fetal heart on glycolysis, the steps of which ensure energy provision, while also maintaining sufficient levels of glycolytic precursors for biosynthesis. Beyond the fact that the fetal heart has high PPP activity and high levels of oxidative PPP enzymes, little is known about biosynthetic pathway activity in the fetal heart, the extent to which it differs from the adult heart, and which specific aspects of the fetal heart metabolic configuration contribute to cell cycle entry and exit.

Influence of Metabolic Interventions on Mammalian Cardiomyocyte Proliferation

Although many studies investigating the metabolic requirements of proliferating cells have focused on cancer cell biology, accumulating evidence supports the relevance of metabolic changes to regenerative capacity of the heart (Table 1). Loss of the proliferative capacity of mammalian cardiomyocytes in adulthood is associated with a post-birth switch from predominantly glycolysis to mitochondrial oxidative phosphorylation and the use of fatty acids for energy. Interestingly, feeding fatty acid-deficient milk to neonatal mice was found to extend the post-birth cardiomyocyte cell cycle activity window for up to 14 days after birth, which suggests that free fatty acid availability and fatty acid oxidation could influence the maturation of cardiomyocytes. In support of this, cardiac-specific pyruvate dehydrogenase kinase 4 (Pdk4) deletion (which increases glucose oxidation and could supplant the use of fats for energy) increased cardiomyocyte proliferation. It is possible that increasing glucose oxidation and inhibiting fatty acid oxidation promotes a phenotype amenable to proliferation by decreasing reactive oxygen species (ROS) production.

A recent study highlighted the role of succinate in regulating cardiomyocyte cell cycle entry. Injection of succinate in neonatal mice for 7 days after MI was shown to inhibit cardiomyocyte proliferation and cardiac regeneration. Furthermore, injection of malonate, an inhibitor of succinate dehydrogenase, was shown to extend the proliferation window of neonatal cardiomyocytes. Daily injections of malonate in adult mice promoted adult cardiomyocyte cell cycle re-entry, revascularization, and heart regeneration after MI. These changes were associated with metabolic reprogramming, leading to higher levels of some glycolytic and pentose phosphate pathway intermediates. These changes are interesting in light of the fact that glycolytic intermediates are used for several biosynthetic pathway products, which are required for daughter cell formation.

Hypoxia and its associated changes in metabolism also influence cardiomyocyte division and have been shown to contribute directly to the cell cycle. The relatively low blood oxygenation level of the fetal environment is conducive to cardiomyocyte proliferation, as the transition to the oxygen-rich postnatal environment has been suggested to promote reactive oxygen species (ROS) generation and cardiomyocyte cell cycle arrest, leading to loss of regenerative potential. Moreover, exposure of adult mice to hypoxia diminishes ROS and allows cardiomyocyte cell cycle reentry and cardiac regeneration after MI. Concordant with these findings are studies showing that hypoxia promotes proliferation of cardiomyocytes in culture and in human cardiomyocytes in vitro and in vivo. Thus, the processes of metabolism influenced by hypoxia are likely important in cardiogenesis.

Hypoxia-inducible factor 1α (Hif1α) is stabilized by low oxygen environments and promotes a metabolic phenotype amenable to cardiomyocyte proliferation. Hif1α is expressed early in embryonic stages, and Hif1α deletion in mice promotes death at E10.5, which manifests as a defect in cardiac development. Moreover, deletion of Hif1α downregulates glycolytic metabolism genes and decreases fetal cardiomyocyte proliferation. Interestingly, a rare population of cardiomyocytes in the adult heart has been shown to have stable Hif1α expression and to contribute to basal cardiomyocyte turnover. Intersecting with Hif1α is the transcription factor Meis1, which increases in the heart after birth and augments the expression of several cyclin-dependent kinase inhibitors (eg, p15, p16, and p21), leading to cardiomyocyte cell cycle arrest. Because Meis1 influences expression of Hif1α-regulated genes, it is likely that it also plays a key role in regulating levels of metabolic enzymes conducive to cardiomyocyte proliferation.

Similar to its effect in cancer cells, the glycolytic enzyme Pkm2 has also been shown to influence cardiomyocyte proliferation. Interestingly, Pkm2 is expressed in cardiomyocytes during development and immediately after birth, but is lost in the transition to adulthood, thereby paralleling loss of cardiomyocyte proliferative capacity. Cardiomyocyte-specific Pkm2 deletion during development was found to reduce cardiomyocyte cell number and diminish markers of the cell cycle. Gain-of-function studies suggest that cardiomyocyte-specific Pkm2 overexpression in models of MI promote cardiomyocyte cell division and significantly improve cardiac function and long-term survival. Interestingly, Pkm2 upregulation in cardiomyocytes was shown to activate the PPP and lower oxidative stress. Conversely, a separate study suggested an antiproliferative function for Pkm2 in cardiomyocytes after MI. The reasons for discrepancies between these studies remain unclear; however, it is interesting that both studies found an interaction between Pkm2 and β-catenin in regulating cardiomyocyte cell cycle entry, especially in light of the importance of β-catenin to energy metabolism in cardiomyocytes. The interaction between...
Pkm2 and β-catenin is also required for recruitment of both proteins to the promoter of the cyclin D1 gene, suggesting non-metabolic roles for Pkm2 in activation of the cell cycle as well. Of interest, Pkm2 also functions as a transcriptional co-activator by interacting directly with Hif1α, highlighting feedback loops between metabolism and the transcriptional machinery.

High-throughput screening has been useful for understanding other ways that metabolism contributes to mammalian cardiomyocyte proliferation. In an effort to find a core proliferation program, screening in a human cardiac organoid platform revealed small molecules with pro-proliferative actions that activated the mevalonate pathway and the cell cycle network. The mevalonate pathway is an anabolic pathway that converts acetyl-CoA into isopentenyl pyrophosphate, the essential building block of all isoprenoids, important for cholesterol synthesis and as precursors for protein prenylation. The pathway is known to be important for proliferation and to affect the G1 and S phases of the cell cycle. Indeed, the pro-proliferative effect of the small molecules was inhibited by simvastatin, which inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase, an essential enzyme in the mevalonate pathway.

Similarly, another screening strategy identified a cocktail of cell cycle genes that, once expressed, activate the cardiomyocyte cell cycle in 15%-20% of adult rodent cardiomyocytes as well as in human iPSC cardiomyocytes and to promote cardiac regeneration in mice after MI. Cell cycle induction using 4F also promoted cytokinesis in vivo, as indicated using fate-mapping MADM mice. In a trial for preclinical application of 4F, Abouleisa et al cloned a polycistronic non-integrating lentivirus encoding 4F in which each factor is driven by the TNNT2 promoter (TNNT2-4F-NIL), leading to transient and specific activation of the cardiomyocyte cell cycle. Intramyocardial injection of TNNT2-4F-NIL improved systolic function and reduced scar size after ischemia-reperfusion in rats and pigs compared with respective controls. Interestingly, transduction of the heart or human iPSC cardiomyocytes with 4F remarkably decreases expression of several genes important in fatty acid oxidation and increases expression of genes required for nucleotide, phospholipid, and amino acid biosynthesis, suggesting a shift from catabolic to anabolic pathway activity. Indeed, respiration studies and stable isotope metabolomics revealed that 4F decreases mitochondrial oxidative phosphorylation and promotes partitioning of glucose-derived carbon to ancillary biosynthetic pathways of glucose metabolism, including NADP+, hexosamine, phospholipid, and serine biosynthetic pathways. Furthermore, pharmacological or genetic interventions that diminish NADP+ synthesis, serine synthesis, or protein O-GlcNAcylation decreased 4F-mediated cell cycle entry. Interestingly, overexpression of Pck2, which is known to support biosynthetic pathway activity in other cell types, further augmented 4F-initiated cardiomyocyte proliferation. Because Pck2 and Pkm2 have both been shown to augment biosynthesis and to promote cardiomyocyte proliferation, it is possible that they work in tandem through the phosphoenolpyruvate cycle to coordinate metabolism to meet the demands of proliferating cells. Collectively, these findings suggest that induction of the cell cycle is associated with acquisition of a biosynthetic metabolic phenotype, sourced largely by glycolytic intermediates.

Evidence for a Role of Metabolism in Non-Mammalian Regenerative Models

Numerous non-mammalian species have been used as models of cardiac regeneration. Lower vertebrates, such as zebrafish and newts, regenerate their hearts through a coordinated process of cardiomyocyte dedifferentiation, proliferation, migration, and redifferentiation. In studies that have examined metabolism, glycolysis has been identified as a metabolic pathway critical to the proliferative cardiomyocyte response to injury. Single-cell RNA sequencing approaches showed that proliferating cardiomyocytes in the border zone of the cryoinjured zebrafish heart have a distinct transcriptome characterized by downregulated mitochondrial genes and upregulated glycolytic genes. This metabolic reprogramming to a glycolytic phenotype was found to be required for regeneration and is triggered by neuregulin 1/ErbB2 signaling, which is known to be important in mammalian cardiomyocyte regeneration. Interestingly, ErbB2 was found in zebrafish to activate glycolysis and promote trabeculation, and loss of Pkm2 impaired trabeculation. Similarly, another study showed that transcripts for enzymes in glucose metabolism, eg, pyruvate kinase and pyruvate dehydrogenase kinase, are increased in zebrafish heart tissue bordering the damaged area and that inhibition of glycolysis decreases cardiomyocyte proliferation following injury. Less metabolic information is available from other non-mammalian models; however, in newts, a hedgehog-triggered network of genes regulate heart regeneration, characterized in part by upregulation of the Mycn gene, which is known to promote glycolysis. Collectively, these data suggest that a
switch to a more glycolytic phenotype is a fundamental feature of cardiomyocyte proliferation. That even more fundamental models of tissue regeneration (e.g., planarians) show the same glycolytic signature during tissue regeneration suggests that changes in glycolysis, and likely the biosynthetic pathways it sources, are generalizable features of regenerating tissue.

Summary and Future Directions
The collective results from studies in models of cardiac regeneration indicate that conditions of relatively low fat oxidation, low ROS production, and high glycolysis are conducive for cardiomyocyte division. Although this metabolic phenotype appears to be evident in fetal and neonatal mammals, it is lost soon after birth. The proliferative cardiomyocyte phenotype is upheld physiologically in part by relatively low oxygen tensions and through the actions of critical transcription factors such as Hif1α and the Hippo-Yap and Nrg1-ErbB2 pathways, all of which remodel metabolism to a more glycolytic state. Because cellular building blocks (e.g., nucleotides, amino acids, phospholipids, cholesterol) are required for the production of daughter cells, it is not surprising that biosynthetic pathway activation is also required for cardiomyocyte proliferation (Fig. 3).

Although the chemical logic of glycolysis provides branchpoint metabolites for several biosynthetic pathways, it remains unclear how proliferating cells partition substrate-derived carbon for material growth versus energy provision. Addressing this knowledge gap requires understanding how distinct metabolic enzymes coordinate the biosynthetic and transcriptional programs required for cardiac regeneration. Also required is fundamental knowledge of how biosynthetic pathways change during mitotic stages of heart development and whether poorly understood processes such as metabolic channeling influence cardiomyocyte proliferation. Harnessing such knowledge could provide the means to augment regenerative responses in the injured heart.

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Conflict of Interest
T.M.A.M. declared patent holder and stock ownership with Tenaya Therapeutics. The other authors indicated no financial relationships.

Author Contributions
R.A.: conception and design, manuscript writing, final approval of manuscript; T.M.A.M., B.G.H.: conception and design, financial support, manuscript writing, final approval of manuscript.

Data Availability
No new data were generated or analyzed in support of this research.

References
1. Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med. 2010;362(23):2155-2165. https://doi.org/10.1056/NEJMoa0908610.
2. Khera R, Pandey A, Ayers CR, et al. Contemporary epidemiology of heart failure in fee-for-service medicare beneficiaries across healthcare settings. Circ Heart Fail. 2017;10(11):e004402.
3. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. Circulation. 2019;139(10):e56-e528. https://doi.org/10.1161/CIR.0000000000000659.
4. Danielsen R, Thorgeirsson G, Einarsson H, et al. Prevalence of heart failure in the elderly and future projections: the AGES-Reykjavik study. Scand Cardiovasc J. 2017;51(4):183-189. https://doi.org/10.1080/14017431.2017.1311023.
5. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6(3):606-619. https://doi.org/10.1161/HCJHE.0b013e318291329a.
6. Chan YK, Turtle C, Ball J, et al. Current and projected burden of heart failure in the Australian adult population: a substantive but still ill-defined major health issue. BMC Health Serv Res. 2016;16(1):501. https://doi.org/10.1186/s12913-016-1748-0.
7. Okura Y, Ramadan MM, Ohno Y, et al. Impending epidemic: future projection of heart failure in Japan to the year 2055. Circ J. 2008;72(3):489-491. https://doi.org/10.1253/circj.72.489.
8. Savarese G, Lund LH. Global public health burden of heart failure. Card Fail Rev. 2017;3(1):7-11. https://doi.org/10.15420/cfr.2016:25:2.
9. Soonpaa MH, Kim KK, Pajak L, et al. Cardiomyocyte DNA synthesis and binucleation during murine development. Am J Physiol. 1996;271(5 Pt 2):H2183-H2189. https://doi.org/10.1152/ajpheart.1996.271.5.H2183.
10. Porrello ER, Mahmoud AI, Simpson E, et al. Transient regenerative potential of the neonatal mouse heart. Science. 2011;331(6020):1078-1080. https://doi.org/10.1126/science.1200708.
11. Shammas NW, Moss AJ, Sullebarger JT, et al. Acquired coronary angiogenesis after myocardial infarction. Cardiology. 1993;83(3):212-216. https://doi.org/10.1159/000175972.
12. Huwer H, Rissland J, Vollmar B, et al. Angiogenesis and microvascularization after cryothermia-induced myocardial infarction: a quantitative fluorescence microscopic study in rats. Basic Res Cardiol. 1999;94(2):85-93. https://doi.org/10.1007/s003950050130.
13. Bing RJ. Myocardial ischemia and infarction: growth of ideas. Cardiovasc Res. 2001;51(1):13-20. https://doi.org/10.1016/s0008-6363(01)00250-4.
14. Nahrendorf M, Swirski FK, Aikawa E, et al. The healing myocardium sequentially mobilizes two monocyte subsets with divergent and complementary functions. J Exp Med. 2007;204(12):3037-3047. https://doi.org/10.1084/jem.20070885.
15. Chen B, Frangogiannis NG. Immune cells in repair of the infarcted myocardium. Microcirculation. 2017;24(1):e12305. https://doi.org/10.1111/mic.12305.
16. Gibb AA, Lazaropoulos MP, Elrod JW. Myofibroblasts and fibrosis: mitochondrial and metabolic control of cellular differentiation. Circ Res. 2020;127(3):427-447. https://doi.org/10.1161/CIRCRESAHA.120.316958.
17. Li X, Sun X, Carmeliet P. Hallmarks of endothelial cell metabolism in health and disease. Cell Metab. 2019;30(3):414-433. https://doi.org/10.1016/j.cmet.2019.08.011.
18. Falkenberg KD, Rohenova K, Luo Y, et al. The metabolic engine of endothelial cells. Nat Metab. 2019;1(10):937-946. https://doi.org/10.1038/s42255-019-0117-9.
19. Gibb AA, Hill BG. Metabolic coordination of physiological and pathological cardiac remodeling. Circ Res. 2018;123(1):107-128. https://doi.org/10.1161/CIRCRESAHA.118.312017.
p. 24. Noor E, Eden E, Milo R, et al. Central carbon metabolism as a minimal biochemical walk between precursors for biomass and energy. *Mol Cell*. 2010;39(5):809-820. https://doi.org/10.1016/j.molcel.2010.08.031.

25. Melendez-Hevia E, Waddell TG, Heinrich R, et al. Theoretical approaches to the evolutionary optimization of glycolysis--chemical analysis. *Eur J Biochem*. 1997;244(2):527-543. https://doi.org/10.1111/j.1432-1033.1997.tb00527.x.

26. Gibb AA, Hill BG. Metabolic coordination of physiological and pathological cardiac remodeling. *Circ Res*. 2018;123(1):107-128. https://doi.org/10.1161/CIRCRESAHA.118.321017.

27. Wisneski JA, Gertz EW, Neese RA, et al. Metabolic fate of extracted glucose in normal human myocardium. *J Clin Invest*. 1985;76(5):1819-1827. https://doi.org/10.1172/JCI12174.

28. Gertz EW, Wisneski JA, Stanley WC, et al. Myocardial substrate utilization during exercise in humans. Dual carbon-labeled carbohydrate isotope experiments. *J Clin Invest*. 1988;82(6):2017-2025. https://doi.org/10.1172/JCI13822.

29. Gibb AA, Lorkiewicz PK, Zheng YT, et al. Integration of flux measurements to resolve changes in anabolic and catabolic metabolism in cardiac myocytes. *Biochem J*. 2017;474(16):2785-2801. https://doi.org/10.1042/BCJ20170474.

30. Russell RR 3rd, Cline GW, Guthrie PH, et al. Regulation of exogenous and endogenous glucose metabolism by insulin and acetateacetate in the isolated working rat heart. A three tracer study of glycolysis, glycogen metabolism, and glucose oxidation. *J Clin Investig*. 1997;100(11):2892-2899. https://doi.org/10.1172/JCI119938.

31. Willebrands AF, van der Veen KJ. Influence of substrate on oxygen consumption of isolated perfused rat heart. *Am J Physiol*. 1967;212(6):1529-1535. https://doi.org/10.1152/ajplegacy.1967.212.6.1529.

32. Goodwin GW, Cohen DM, Taegmeyer H. [5-3H]glucosylate overestimates glucolytic flux in isolated working rat heart: role of the pentose phosphate pathway. *Am J Physiol Endocrinol Metab*. 2001;280(3):E502-E508. https://doi.org/10.1152/ajpendo.2001.280.3.E502.

33. Cortassa S, Caceres V, Bell LN, et al. From metabolomics to fluxomics: a computational procedure to translate metabolite profiles into metabolic fluxes. *Biophys J*. 2015;108(1):163-172. https://doi.org/10.1016/j.bpj.2014.11.1857.

34. Park JO, Rubin SA, Xu YF, et al. Metabolic concentrations, fluxes and free energies imply efficient enzyme usage. *Nat Chem Biol*. 2016;12(7):482-489. https://doi.org/10.1038/nchembio.2077.

35. Pedley AM, Benkovic SJ. A new view into the regulation of purine metabolism: the purinosome. *Trends Biochem Sci*. 2017;42(2):141-154. https://doi.org/10.1016/j.tibs.2016.09.009.

36. Pareek V, Sha Z, He J, et al. Metabolic channeling: predictions, deductions, and evidence. *Mol Cell*. 2021;81(18):3775-3785. https://doi.org/10.1016/j.molcel.2021.08.030.

37. Fulghum KL, Audam TN, Lorkiewicz PK, et al. In vivo deep network tracing reveals phosphofructokinase-mediated coordination of biosynthetic pathway activity in the myocardium. *J Mol Cell Cardiol*. 2022;162:32-42.

38. White E. Exploiting the bad eating habits of Ras-driven cancers. *Genes Dev*. 2013;27(19):2063-2071. https://doi.org/10.1101/gad.228112.113.

39. DeBerardinis RJ, Chandel NS. Fundamentals of cancer metabolism. *Sci Adv*. 2016;2(5):e1600200. https://doi.org/10.1126/sciadv.1600200.

40. Montal ED, Dewi R, Bhalla K, et al. PEPCK coordinates the regulation of central carbon metabolism to promote cancer cell growth. *Mol Cell*. 2015;60(4):571-583. https://doi.org/10.1016/j.molcel.2015.09.025.

41. Vincent EE, Serghisichev A, Griss T, et al. Mitochondrial phosphoenolpyruvate carboxykinase regulates metabolic adaptation and enables glucose-independent tumor growth. *Mol Cell*. 2015;60(2):195-207. https://doi.org/10.1016/j.molcel.2015.08.013.

42. Vander Heiden MG, Locasale JW, Swanson KD, et al. Evidence for an alternative glycolytic pathway in rapidly proliferating cells. *Science*. 2010;329(5998):1492-1499. https://doi.org/10.1126/science.1188015.

43. Lunt SY, Muralidhar V, Hossios AM, et al. Pyruvate kinase isozform expression alters nucleotide synthesis to impact cell proliferation. *Mol Cell*. 2015;57(1):93-107. https://doi.org/10.1016/j.molcel.2014.10.027.

44. Nakamura M, Bhatnagar A, Sadoshima J. Overview of pyridine nucleotides review series. *Circ Res*. 2012;111(5):604-610. https://doi.org/10.1161/CIRCRESAHA.111.247924.

45. Fessel JP, Oldham WM. Pyridine dinucleotides from molecules to man. *Antioxid Redox Signal*. 2018;28(3):180-212. https://doi.org/10.1089/ars.2017.2120.22. https://doi.org/10.1089/ars.2017.2120.22.

46. Hossios AM, Vander Heiden MG. The redox requirements of proliferating mammalian cells. *J Biol Chem*. 2018;293(20):7490-7498. https://doi.org/10.1074/jbc.M117.000239.

47. Jones DP, Sies H. The redox code. *Antioxid Redox Signal*. 2015;23(9):734-746. https://doi.org/10.1089/ars.2015.6247.

48. Xiao W, Wang RS, Handy DE, et al. NAD(H) and NADP(H) redox couples and cellular energy metabolism. *Antioxid Redox Signal*. 2018;28(3):251-272. https://doi.org/10.1089/ars.2017.2121.

49. Lunt SY, Vander Heiden MG. Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. *Annu Rev Cell Dev Biol*. 2011;27:441-464. https://doi.org/10.1146/annurev-cellbio-092910-154237.

50. Fan J, Ye J, Kamphorst JJ, et al. Quantitative flux analysis reveals folate-dependent NADPH production. *Nature*. 2014;510(7504):298-302. https://doi.org/10.1038/nature13236.

51. Haubner BJ, Schneider J, Schweigmann U, et al. Functional recovery of a human neonatal heart after severe myocardial infarction. *Circ Res*. 2016;118(2):216-221. https://doi.org/10.1161/CIRCRESAHA.115.307017.

52. Vivien CJ, Hudson JE, Porrello ER. Evolution, comparative biology and ontogeny of vertebrate heart regeneration. *NPJ Regen Med*. 2016;1:16012. https://doi.org/10.1038/npjregened.2016.12.

53. Lam NT, Sadek HA. Neonatal heart regeneration: comprehensive literature review. *Circulation*. 2018;138(4):412-423. https://doi.org/10.1161/CIRCULATIONAHA.118.036468.

54. Fisher DJ, Heymann MA, Rudolph AM. Myocardial oxygen and carbohydrate consumption in fetal lambs in utero and in adult sheep. *Am J Physiol*. 1980;238(6 Pt 2):H399-H405. https://doi.org/10.1152/ajpheart.1980.238.6.H399.

55. Bartelds B, Gratama JW, Knoester H, et al. Perinatal changes in myosin isoform expression alters nucleotide synthesis to impact cell proliferation. *Circ Res*. 2001;89(10):298-308. https://doi.org/10.1161/01.res.89.10.298.

56. Zbranek J, Hutter SM, Konkle ME, et al. Evolutionary biology and ontogeny of vertebrate heart regeneration. *Int J Mol Sci*. 2016;17(12):2812. https://doi.org/10.3390/ijms17122812.
Menendez-Montes I, Abdisalaam S, Xiao F, et al. Mitochondrial fatty acid utilization increases chromatin oxidative stress in cardiomyocytes. Proc Natl Acad Sci USA. 2021;118(34):e2101674118.

Lim GB. Inhibiting fatty acid oxidation promotes cardiomyocyte proliferation. Nat Rev Cardiol. 2020;17(5):266-267. https://doi.org/10.1038/s41569-020-0361-4.

Bae J, Salamon JR, Brandt EB, et al. Malonate promotes adult cardiomyocyte proliferation and heart regeneration. Circulation. 2021;143(20):1973-1986. https://doi.org/10.1161/CIRCULATIONAHA.120.049952.

Nakada Y, Canseco DC, Ther S, et al. Hypoxia induces heart regeneration in adult mice. Nature. 2017;541(7636):222-227. https://doi.org/10.1038/nature20173.

Hashimoto K, Kodama A, Honda T, et al. Fam64a is a novel cell cycle promoter of hypoxic fetal cardiomyocytes in mice. Sci Rep. 2017;7(1):4486. https://doi.org/10.1038/s41598-017-04823-1.

Ye L, Qu L, Feng B, et al. Role of blood oxygen saturation during post-natal human cardiomyocyte cell cycle activities. JACC Basic Transl Sci. 2020;5(5):447-460. https://doi.org/10.1016/j.jatbs.2020.02.008.

Iyer NV, Kotch LE, Agani F, et al. Cellular and developmental control of O2 homeostasis by hypoxia-inducible factor 1 alpha. Genes Dev. 1998;12(2):149-162. https://doi.org/10.1101/gad.12.2.149.

Compernelle V, Brusselmann K, Franco D, et al. Cardiac bifida, defective heart development and abnormal neural crest migration in embryos lacking hypoxia-inducible factor-1alpha. Cardiovase Res. 2003;60(3):569-579. https://doi.org/10.1016/j.cardiores.2003.07.003.

Guimaraes-Camboa N, Stowe J, Aneas I, et al. HIF1alpha represses cell stress pathways to allow proliferation of hypoxic fetal cardiomyocytes. Dev Cell. 2015;33(5):507-521. https://doi.org/10.1016/j.devcel.2015.04.021.

Kamura W, Xiao F, Canseco DC, et al. Hypoxia fate mapping identifies cycling cardiomyocytes in the adult heart. Nature. 2015;523(7559):226-230. https://doi.org/10.1038/nature14582.

Mahmoud AI, Kocabas F, Muralidhar SA, et al. Meis1 regulates postnatal cardiomyocyte cell cycle arrest. Nature. 2013;497(7448):249-253. https://doi.org/10.1038/nature12054.

Kocabas F, Zheng J, Ther S, et al. Meis1 regulates the metabolic phenotype and oxidant defense of hematopoietic stem cells. Blood. 2012;120(25):4963-4972. https://doi.org/10.1182/blood-2012-05-432260.

Magadm A, Singh N, Kurian AA, et al. Pkm2 regulates cardiomyocyte cell cycle and promotes cardiac regeneration. Circulation. 2020;141(15):1249-1265. https://doi.org/10.1161/CIRCULATIONAHA.119.043067.

Hauck L, Dadson K, Chauhan S, et al. Inhibiting the Pkm2/b-catenin axis drives in vivo replication of adult cardiomyocytes following experimental MI. Cell Death Differ. 2020;28(4):1398-1417. https://doi.org/10.1038/s41418-020-00669-9.

Balatsky VV, Vaskivskyi VO, Myronova A, et al. Cardiac-specific beta-catenin deletion dysregulates energetic metabolism and mitochondrial function in perinatal cardiomyocytes. Mitochondrion. 2021;60:59-69. https://doi.org/10.1016/j.mito.2021.07.005.

Yang W, Xia Y, Ji H, et al. Nuclear Pkm2 regulates beta-catenin transcription upon EGFR activation. Nature. 2011;480(7373):118-122. https://doi.org/10.1038/nature10598.

Luo W, Hu H, Chang R, et al. Pyruvate kinase M2 is a PHD3-stimulated coactivator for hypoxia-inducible factor 1. Cell. 2011;145(3):732-744. https://doi.org/10.1016/j.cell.2011.03.054.

Mills RJ, Parker BL, Quaife-Ryan GA, et al. Drug screening in human PSC-cardiac organoids identifies pro-proliferative compounds acting via the mevalonate pathway. Cell Stem Cell. 2019;24(6):895-907.e6. https://doi.org/10.1016/j.stem.2019.03.009.

Quesney-Huneveus V, Galich HA, Siperstein MD, et al. The dual role of mevalonate in the cell cycle. J Biol Chem. 1983;258(1):378-385.
114. Zhang X, Qiao Y, Wu Q, et al. The essential role of YAP
110. Enzo E, Santinon G, Pocaterra A, et al. Aerobic glycolysis tunes
109. Menini S, Iacobini C, de Latouliere L, et al. Diabetes promotes
108. Nokin MJ, Durieux F, Peixoto P, et al. Methylglyoxal, a glycolysis
104. Wang J, Liu S, Heallen T, et al. The Hippo pathway in the heart:
103. Stark R, Pasquel F, Turcu A, et al. Phosphoenolpyruvate cycling
102. Katz J, Rognstad R. Futile cycles in the metabolism of glucose.
101. Hue L. The role of futile cycles in the regulation of carbohydrate
99. Abouleisa RRE, Salama ABM, Ou Q, et al. Transient cell
98. Mohamed TMA, Ang Y-S, Radzinsky E, et al. Regulation of cell
97. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
96. YAP/TAZ transcriptional activity.
95. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
94. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
93. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
92. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
91. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
90. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
89. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
88. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
87. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
86. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
85. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
84. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
83. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
82. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
81. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
80. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
79. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
78. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
77. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
76. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
75. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
74. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
73. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
72. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
71. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
70. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
69. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
68. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
67. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
66. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
65. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
64. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
63. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
62. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
61. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
60. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
59. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
58. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
57. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
56. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
55. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
54. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
53. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
52. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
51. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
50. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
49. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
48. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
47. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
46. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
45. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
44. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
43. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
42. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
41. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
40. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
39. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
38. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
37. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
36. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
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32. Lasuncion MA, Martinez-Botas J, Martin-Sanchez C, et al. Cell cycle
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