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Return to the fetal gene program:

A suggested metabolic link to gene expression in the heart

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Abstract

A hallmark of cardiac metabolism before birth is the predominance of carbohydrate use for energy provision. After birth, energy substrate metabolism rapidly switches to the oxidation of fatty acids. This switch accompanies the expression of “adult” isoforms of metabolic enzymes and other proteins. However, in a variety of pathophysiologic conditions, including hypoxia, ischemia, hypertrophy, atrophy, diabetes, and hypothyroidism, the postnatal heart returns to the “fetal” gene program. These adaptive mechanisms are also a feature of the failing heart muscle, where at a certain point this fetal-like reprogramming no longer suffices to support cardiac structure and function. We advance the hypothesis that in the postnatal heart, metabolic remodeling triggers the process through glycosylation of transcription factors, potentially protecting the stressed heart from irreversible functional impairment and programmed cell death. In other words, we propose a metabolic link to gene expression in the heart.

Keywords

fetal heart; hypertrophy; atrophy; hibernating myocardium; heart failure; glucose; metabolism

Introduction

A common response of the heart to hemodynamic or metabolic stress is the suppression of the post-natal gene program, resulting in a predominance of the fetal gene program.¹ Main features of fetal heart metabolism reemerge and include the preference of carbohydrates over fatty acids as substrates for energy provision in a relatively hypoxic environment. Additional features include the expression of atrial natriuretic factor (ANF), transforming growth factor β (TGF- β), and early response genes, such as *c-myc* and *c-fos*, as well as isoform switches of many other proteins, including metabolic enzymes and sarcomeric proteins (myosin heavy chains and α -actins).

Several questions arise in this context. First, how and why is the fetal gene program reactivated when the heart remodels? Second, how is it possible for such divergent environmental stimuli as pressure overload, hemodynamic unloading, hypoxia, low-flow ischemia, or hormonal imbalances to trigger the same gene program? Third, what are the functional consequences of a predominance of the fetal gene program in the heart?

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Conflicts of interest

The authors declare no conflicts of interest.

Metabolic features of the fetal heart

As the heart grows *in utero* it is exposed to a low oxygen environment, to a gradually increasing hemo-dynamic load, and to a changing metabolic milieu.² The developing heart also undergoes a considerable transformation in its energy needs. Metabolically, the fetal heart relies on carbohydrate substrates, primarily lactate and glucose, as the major sources of adenosine triphosphate (ATP) synthesis, while its ability to oxidize long chain fatty acids is limited.² The consequences of such a metabolic pattern are manifold. Prominent among them are the greater efficiency of carbohydrate substrates per mole of oxygen consumed by the heart, and the rapid mobilization of carbohydrate energy stores when the heart is stressed.³

For the fetal heart, the ultimate stress is birth.⁴ Although immediately after birth glycolysis remains the predominant source of energy, after a brief (24 h) period of starvation there is a sustained shift of substrates from lactate and glucose oxidation to fatty acid oxidation, which is accompanied by changes in the expression of the enzymes of the respective metabolic pathways and a switch to the postnatal “adult” isoforms.

Accordingly, histologic differences between the adult and fetal heart are striking and easily observable. While glycogen occupies about 2% of the cell volume in the adult cardiomyocyte, more than 30% of the cell volume in the fetal cardiomyocyte is occupied by glycogen⁵ (Fig. 1A). The importance of glycogen for the developing heart is underscored by gene-deletion experiments. When glycogen synthase (GS) is genetically ablated in mice, 90% of the animals die perinatally because of severe cardiac malformation.⁶ Thus, glycogen turnover (requiring both glycogen synthase and phosphorylase activity) is necessary for the normal formation of the heart. In contrast, the postnatal adult mammalian myocardium is characterized by an abundance of mitochondria and sarcomeres and only a relatively small amount of glycogen (Fig. 1B).

Another feature of the fetal heart is its dependence on cytosolic NADH-producing glycolytic pathways. Transport of NADH for access to the respiratory chain and across the mitochondrial membrane, which is impermeable to NADH, occurs through transport systems, including the α -glycerophosphate, malate-aspartate, and malate-citrate shuttles. The capacity of these systems is high in the fetal heart and decreases after birth,⁷ implying a developmental shift in control of the NADH redox state. This also helps to maintain high rates of glycolytic flux, in the absence of lactate formation.

The most striking change occurring at birth is the shift from the relatively hypoxic fetal environment to an oxygen-rich environment with activation of transcriptional regulatory circuits controlling mitochondrial biogenesis. Emerging evidence indicates that the postnatal gene-regulatory circuit involves the actions of the nuclear receptor peroxisome proliferator-activated receptor alpha (PPAR- α) and its coactivator the PPAR- γ coactivator 1 (PGC-1 α).⁸ In a “feed-forward” mechanism, PPAR- α is activated by ligand binding of long chain fatty acids and regulates the expression of multiple genes controlling both fatty acid uptake and oxidation. PPAR- α is also a key factor in the transcriptional regulation of substrate preference in the heart. PGC-1 α promotes mitochondrial biogenesis and the activation of PPAR- α , which leads to an increase of muscle carnitine palmitoyl transferase I (mCPT I) expression and activity as well as other target genes.

The postnatal “switch” from fetal to adult isoforms of metabolic and other proteins is most likely related to the switch in the physiologic environment. During the immediate postnatal period, plasma glucagon levels increase and plasma insulin levels fall to a very low range of concentrations,⁹ while the heart rapidly adapts to oxidizing fatty acids. However, the heart retains its ability to change back to a “fetal” mode of metabolism when it is stressed and

when it remodels. The heart's ability to mobilize the "carbohydrate reserve" is critical for its adaptation to stress and tied to a number of metabolic signals. It is our hypothesis that altered metabolic fluxes like activation of glycogenolysis and glucose transport give rise to metabolic signals during the adaptive induction of the fetal gene program (Fig. 2). This concept includes the "nutrient sensing" of genes together with those encoding the contractile proteins of the heart.

Contractile proteins of the fetal heart

The expression pattern of many sarcomeric proteins in the fetal heart also undergoes major isoform switches at birth. Changes in the proportion of myosin heavy chain (MHC) isoforms seem to be directly related to the level of mechanical performance and efficiency of the heart as it switches from fetal to postnatal circulation. In mouse ventricle, MHC- β is the predominant isoform in the developing heart, but during early postnatal development it is replaced by MHC- α .¹⁰ In humans, however, MHC- β isoform is predominantly expressed in the ventricle throughout life from fetus to adult, regardless of the stage of development.^{11,12} There also is inter-species variability, specifically in the ratio of α - to β MHC isoforms associated with contractile function and the speed of cross-bridge formation. Myocardium of small animals with faster heart rates (e.g., mice and rats) predominately contains the V1 form ($\alpha\alpha$) of MHC and myocardium of guinea pigs and rabbits predominately expresses V3 ($\beta\beta$) MHC, but possesses small amounts of the V1 and V2 ($\alpha\beta$) forms, whereas bovine and human myocardium contain less than 10% V1.¹³ Because of this "hierarchy" in myosin isoform expression, it has been suggested that changes in the proportion of cardiac MHC isoforms are directly related to the level of mechanical performance of the heart. Both isoforms are downregulated in the fetal and failing human heart.¹⁴

Human skeletal α -actin and titin isoforms are also developmentally regulated. In the fetal and neonatal heart α -skeletal actin predominates, whereas in the adult heart α -cardiac actin does.¹¹ Fetal hearts express higher amounts of compliant titin isoforms (N2BA1/N2BA2), which are eventually replaced by adult isoforms during postnatal development.¹⁵ In diseased hearts a shift in coexpression of titin isoforms has been reported with a higher N2BA/N2B ratio in human dilated cardiomyopathy and a lower N2BA/N2B ratio in a pacing-induced canine heart failure model.¹⁶

Several transcription factors have been identified as regulating differentiation and growth of the developing heart, including GATA4, NFAT, Csx/Nkx2.5, SRF, MEF2, Hand1/2, and Smad.¹⁷ Some of those are specifically involved in sarcomerogenesis and expression of different myofibrillar isoforms, and all have been shown to be involved in hypertrophic growth in adult heart. In the fetal mouse heart, the MHC- β gene is expressed under the control of Nkx-2.5, MEF-2C, and GATA-4/5/6. After birth, thyroid hormone induces expression of MHC- α and inhibits expression of MHC- β .¹⁸ While microRNAs may act as negative regulators of gene expression¹⁹ and microRNAs have been implicated as a cue for fetal reprogramming in heart failure, a metabolic link to the regulation of gene expression may exist in the heart as well.^{20,21} Whether microRNAs are affected by glucose or glucose metabolism is not known at this time.

Metabolic signals as regulators for a coordinated stress response in heart

Metabolic remodeling

The adult heart responds to a wide spectrum of stressors (including pressure overload, unloading, ischemia, hypothyroidism, and metabolic dysregulation) by remodeling its metabolic and contractile machinery. The initial response to stress, irrespective of the stressors, is a change in fluxes through pathways of energy substrate metabolism. We

propose that metabolic signals precede, trigger, and sustain the return to the fetal gene program.

The exact mechanisms by which this switch of energy substrates leads to changes at the transcriptional level of regulatory proteins and enzymes involved in glucose and fatty acid metabolism are not known. We propose that altered glucose homeostasis within the cardiomyocyte acts as a central mechanism for the regulation of gene expression in response to environmental stresses via activation of the hexosamine biosynthetic pathway and glycosylation of transcription factors (Fig. 3). This hypothesis finds support in the effects of substrates and diet on cardiac gene expression.²¹ It also finds support in the patterns of metabolic gene expression in the failing and non-failing human heart.

Transcript levels of glucose transporter GLUT1, GLUT4, pyruvate dehydrogenase kinase 2 (PDK2), muscle-glycogen synthase (mGS), mCPT-I, medium chain acyl-CoA dehydrogenase (MCAD), and acetyl-CoA carboxylase (ACC) are all higher in the non-failing adult human heart than in the fetal heart.^{14,22} In the failing human heart, expression of these metabolic genes decreases to the same levels as in the fetal heart. In the hypertrophied heart, DNA binding activities and nuclear expression of repressors like specificity protein 1/3 (Sp1/3) and chicken ovalbumin upstream promoter transcription factor (COUP-TF) are similar to the normal fetal mouse heart.²² Teleologically this may be related to better energy efficiency of glucose oxidation that could preserve contractile function during those disease states.²³ Glucose flux also mediates transcriptional regulation of metabolic enzymes in hepatocytes via the generation of a signaling molecule, xylulose 5-phosphate, by the hexose monophosphate shunt pathway. The heart may possess a mechanism similar to the one in the liver.²⁴

As previously mentioned, “footprints” of the fetal and remodeled heart muscle include the abundance of glycogen. In the oxygen-deprived state, glycogen stores in the heart are associated with increased survival.²⁵ There are several mechanisms for the protective effects of glycogen on heart.²⁶ Shunting of intracellular free glucose into glycogen protects cellular proteins from excess glycosylation and the effects of glucotoxicity (very much like shunting of fatty acid metabolites into triglycerides protects the cell from the effects of lipotoxicity). Secondly, switching from the highly aerobic metabolism of fatty acids to the less aerobic metabolism of glucose appears to be a necessary prerequisite for immediate cell survival. Glycolysis, or the conversion of glucose to lactate, has been implicated as the source of ATP for fueling ion pumps, including those involved in calcium cycling. Without these acute adaptive changes in metabolism, the resultant “energy deficit” leads to contractile dysfunction and ultimately to cell death, either by apoptosis or necrosis. It is reasonable to assume that glycogen increases survival by acting as a fuel source during conditions of decreased substrate uptake (e.g., in the hibernating myocardium of ischemic cardiomyopathy).

An interesting model of transient adaptation to the fetal program is hypobaric hypoxia. Exposure to *in vivo* hypobaric hypoxia triggers a large number of complex physiologic responses in the right ventricle. Not surprisingly, with hypoxia there is an early downregulation of PPAR α -regulated gene expression, suggesting a substrate switch from fatty acid to glucose use.²⁷ There is also downregulation of SERCA 2a, another energy-conserving mechanism. When compensatory mechanisms (e.g., an increase in hematocrit) restore normoxic conditions, the adult transcriptional profile including PPAR α -regulated gene expression is restored together with normal structure and function.²⁸

Another example of return to the fetal gene program is the heart in diabetes.^{29,30} Surprisingly, the metabolic stress observed in both clinical and experimental diabetes is

associated with reactivation of markers of the fetal gene program in the heart (ANF, MHC isoform switches, GLUT isoform switches, and activation of *c-myc* and *c-fos*).²⁹ We have proposed that in the heart of diabetic patients or animals the relative imbalance of glucose uptake and oxidation results in increased flux through the hexosamine biosynthetic pathway and the glycosylation of transcription factors.²¹ Indeed, when compared to the non-diabetic heart failure patient, diabetic heart failure patients show a greater decrease in MHC- α , GLUT4, and MEF2C expression and less of a decrease in PPAR α and MCAD and uncoupling protein 3 (UCP3).³¹

Sarcomeric remodeling

During the process of adaptation, myosin isoform expression will change to maintain an appropriate contractile force. In rat models of pressure/volume overload, a decrease in the MHC- α isoform and an increase in the MHC- β isoform have been shown. However, in human heart, MHC- β is the major isoform throughout life.^{12,32} A decrease in MHC- α expression (mRNA) and content (protein) in the failing human left ventricle³³ and a relative increase of MHC- β expression in the left ventricle of patients with cardiomyopathy have been reported.³⁴ While MHC- β expression was also decreased in the failing heart compared with the non-failing heart, the ratio of MHC- β /MHC- α increased because of a greater repression of MHC- α .¹⁴ Indeed, even small decreases in the MHC- α isoform can influence contractility and cardiac output.³³ Forced glucose uptake both *ex vivo* and *in vivo* results in *mhc* isoform switching. Restricting dietary glucose prevents *mhc* switching in hearts of rats subjected to pressure overload-induced hypertrophy (Fig. 4).

In other words, glucose availability correlates with *mhc* isoform switching under all conditions investigated. A potential mechanism by which glucose affects gene expression is through O-linked glycosylation of specific transcription factors. The enzyme glutamine fructose-6-phosphate amidotransferase (GFAT) is the rate-limiting step for flux through the hexosamine biosynthetic pathway and UDP-N-acetylglucosamine biosynthesis, the main metabolite in protein glycosylation. Ascending aortic constriction increased intracellular levels of UDP-N-acetylglucosamine, and the expression of *gfat2*, but not *gfat1*, in the rat heart. Although the results require further confirmation, they are in support of glucose-regulated gene expression in the heart, and the involvement of glucose metabolites in isoform switching of sarcomeric proteins characteristic for the fetal gene program.²¹ It has also been shown that glycosylation increases the stability of the transcription factor Sp1, which is activated by increased glucose availability and pressure overload, and regulates reversion to the fetal isoform program during cardiac hypertrophy. Moreover, feeding rats a high-fat, low-carbohydrate diet blocks *mhc* isoform switching in models of pressure overload including Dahl salt-sensitive rats³⁵ and rats with aortic constriction.²¹

Cell survival in the fetal and stressed postnatal heart

Myocardial hibernation is perhaps the most dramatic example of programmed cell survival, an adaptive state of reduced myocardial contractile function in response to a reduction of myocardial blood flow.³⁶ A metabolic characteristic of hibernating myocardium is the switch from fat to glucose metabolism, accompanied by reactivation of the fetal gene program. As in the fetal heart, the glycogen content of hibernating myocardium is dramatically increased. This supports the idea of a direct link between metabolic pathways and pathways of both cell death and cell survival.

The fetal gene program supports the activation of innate cell-survival pathways in the heart. One anti-apoptotic, cardioprotective, signaling pathway occurs via PI3-kinase and Akt activated mammalian target of rapamycin (mTOR) and P70S6 kinase.^{37,38} Akt plays a key role in regulating cardiomyocyte growth and survival.³⁹ Overexpression of constitutively

active Akt raises myocardial glycogen levels and protects against ischemic damage *in vivo* and *in vitro*. Akt is also a modulator of metabolic substrate use.⁴⁰ Phosphorylation of GLUT4 by Akt promotes its translocation and increases glucose uptake.⁴¹ Akt also inhibits fatty acid oxidation through inhibition of PPAR- α /PCG-1-dependent transcription.⁴² Reactivation of PPAR- α in a model of hibernating myocardium worsens contractile function, induces microinfarction, and increases intramyocardial triglyceride deposits,⁴³ indicating the importance of a return to the fetal metabolic gene profile as a protective mechanism for the cardiomyocyte.

The remodeling process of the atrophied heart also includes a return to the fetal gene program.⁴⁴ Similar changes in gene expression, cell signaling, and metabolism in the atrophy of unloading and in pressure overload-induced hypertrophy suggest that atrophy is not a simple reversal of pressure-induced hypertrophy. We propose that either increased or decreased mechanical stress induces a local environment of hypoxia and a concerted mechanism of adaptation by isoform switching in energy-providing and energy-consuming pathways, which drives the adaptation of myocardial energetics to changes in energy demand. Unloading-induced remodeling is an active metabolic process, which involves both protein synthesis and degradation. Unloading the heart reduces cardiac mass by a self-limited process and limits energy expenditure by preserving the expression of fetal isoforms of proteins regulating myocardial energetics. In other words, opposite changes in workload result in structural adaptation (remodeling), which causes induction of a similar transcriptional response. Therefore, expression of the fetal gene program is purely adaptive and does not imply, *per se*, irreversible cell damage. In fact, it is cardioprotective.

Conclusions

The prevailing opinion among the community of heart-failure physiologists remains that a return to the fetal gene program is detrimental and a hallmark for progressive decline in cardiac function.⁴⁵ We have reviewed here evidence supporting the hypothesis that these changes in gene expression are an adaptive process, possibly triggered by glucose-derived metabolic signals. The process is associated with survival rather than destruction of the heart. The exact mechanisms underlying the transition from adaptation to cardiomyocyte dysfunction involve isoform switches of sarcomeric proteins, which requires further investigation. However, we propose that metabolic signals arising from the metabolism of energy-providing substrates become the “regulators of regulators” of gene expression. Specifically, we suggest that metabolic signals arising from glucose metabolism trigger a coordinated response to stress, which includes the return to the fetal gene program. In other words, there may be a metabolic link to gene expression in the heart.

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Figure 1.

Transmission electron micrograph of mammalian left ventricular myocardium from (A) a 5-month-old human fetus and (B) an adult dog. (A) Note the vast number of large, highly-branched molecules of glycogen, which appear as very dark cytoplasmic granules found mostly in the form of β -granules (scan courtesy of Dr. Visvan Navaratnam, University of Cambridge, UK). Also note (B) the large number of mitochondria in the adult canine myocardium at 1:1800 magnification (scan courtesy of Dr. Barry Van Winkle, University of Texas Health Science Center at Houston).

Figure 2.

Proposed mechanism of metabolic remodeling. Under a wide spectrum of stressors (pressure overload, unloading, ischemia, diabetes), the heart alters its metabolism and uses less commonly used pathways (hexosamine biosynthetic pathway), leading to an accumulation of metabolic signals that triggers the induction of the fetal gene program. (Modified from Young *et al.*⁴⁶)

Figure 3.

Proposed mechanism of altered glucose homeostasis leading to changes in gene expression. When excess glucose is presented to hearts under certain environmental stressors (pressure overload, unloading, ischemia, diabetes), glucose homeostasis is altered. Excess glucose enters the glycolytic pathway, but it also may be stored as glycogen or shunted into the hexosamine biosynthetic pathway leading to protein glycosylation of transcription factors, inducing the return to the fetal gene program to protect the heart. (Modified from Young *et al.*²¹)

Figure 4.

Effects of altered carbohydrate and fat availability on *mhc* α (A) and *mhc* β (B) expression, and on the ratio of *mhc* α /*mhc* β (C) in hypertrophied (banded) rat hearts. Rats were placed on either a high-carbohydrate/low-fat (HC/LF) diet or on a low-carbohydrate/high-fat (LC/HF) diet. (Adapted from Young *et al.*²¹)