Journal of Molecular and Cellular Cardiology 55 (2013) 130–138

Contents lists available at SciVerse ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Review article

Metabolic stress in the myocardium: Adaptations of gene expression

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ARTICLE INFO

Article history:
Received 30 April 2012
Received in revised form 5 June 2012
Accepted 13 June 2012
Available online 21 June 2012

Keywords:
Diabetic cardiomyopathy
Pathological hypertrophy
Ischemia–reperfusion
Nuclear receptor transcription factor
Histone deacetylation
miRNA
Protein translation

ABSTRACT

The heart is one of the highest ATP consuming organs in mammalian organisms. Its metabolic function has evolved a remarkable degree of efficiency to meet high demand and plasticity in response to varying changes in energy substrate supply. Given the high flux of energy substrates and the centrality of their appropriate use for optimal cardiac function, it is not surprising that the heart has intricate signaling mechanisms through which it responds to metabolic stress. This review focuses on the changes in gene expression in myocardial and vascular tissues during metabolic stress that affect mRNAs and subsequent protein synthesis with an eye toward understanding the manner in which these changes effect adaptive and maladaptive responses of the heart. This article is part of a Special Issue entitled "Focus on Cardiac Metabolism".

Contents

1. Introduction

To maintain bioenergetic homeostasis, the myocardium is poised to reconfigure its metabolic program during states that alter caloric content and abundance, hemodynamic load, and oxygenation. Cytoplasmic signal transduction cascades and nuclear programming drive mechanisms that regulate protein synthesis and turnover, organelle function, and metabolic flux. The purpose of this review is to reveal the myocardial adaptations of gene regulation that are enlisted during three commonly-encountered states of metabolic stress: (1) metabolic substrate excess and diabetes; (2) pressure overload; and (3) ischemia–reperfusion. Evidence for these adaptations comes from physiological studies of humans and rodent models as well as from biochemical and genetic analyses of the various cell types resident in the heart. We will focus on dynamic gene regulation that directly influences metabolic flux and substrate selection in these contexts, and will integrate DNA-bound transcription factors with chromatin modifications, non-coding RNA regulatory mechanisms, and translational regulation.

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doi:10.1016/j.yjmcc.2012.06.008

2. Cellular responses to states of myocardial metabolic stress

While omnivorous and metabolically flexible, the normal heart predominantly exploits the high-energy yield of fatty acid β-oxidation to generate ATP for its mechanical, electrical, and homeostatic activities [1,2]. However, prolonged ingestion of excess calories through overnutrition increases delivery of fatty acids and undermines systemic lipid homeostasis secondary to insulin resistance. The heart is initially able to increase fatty acid oxidation, but when this capacity is exceeded, fatty acids are diverted to neutral lipid pools and to alternate metabolic fates within the myocardium. These responses contribute to metabolic inflexibility, bioenergetic inefficiency, insulin resistance of the myocardium itself, cellular damage and contractile dysfunction [3–6]. Moreover, these metabolic abnormalities may underlie, in part, increased heart failure and worse outcomes in coronary artery disease that significantly impact morbidity and mortality in diabetes [7–9]. Metabolic adaptations of the myocardium to caloric excess and diabetes are classically accompanied by gene expression programs that support increased cellular processing of fatty acids: uptake and esterification to CoA (CD36, fatty acid transport protein 1, and long-chain acyl-CoA synthetase 1), intracellular transport (fatty acid binding protein), esterification to glycerol backbones (glycerol-3-phosphate acyltransferase and diacylglycerol acyltransferase), and β-oxidation [carnitine palmitoyltransferase 1 (CPT1) and medium chain acyl-CoA dehydrogenase]. Furthermore, augmentation of the mRNAs encoding mediators of mitochondrial uncoupling (mitochondrial thioesterase 1, uncoupling proteins 2 and 3) and inhibition of glucose oxidation (pyruvate dehydrogenase kinase 4) are also observed [5,10,11]. Related shifts in gene expression occur in the setting of nutrient deprivation, when the myocardium becomes highly dependent on fatty acids and ketone bodies, reducing its glucose utilization [12].

Pathological hypertrophy commonly occurs in response to pressure (e.g., hypertension, aortic coarctation) or volume (e.g., left-to-right shunt) overload, or after myocardial infarction. The compensated hypertrophic phase is accompanied by marked changes in gene expression, and is considered an adaptive response to diminish wall stress associated with increased strain [13]. Pathological hypertrophy is coordinated by cytoplasmic signal transduction cascades, including multiple arms of the mitogen-activated protein kinase pathway, the calcineurin pathway, the PKA and PKC pathways, the phosphatidylinositol 3-kinase (PI3K)/Akt/glycogen synthase kinase (GSK) pathway, and the Ca^{2+}/calmodulin-dependent protein kinase II pathway, all of which are engaged by both 'stretch' sensors, and by locally-produced and systemically circulating neuroendocrine mediators. In turn, these pathways transduce a subset of their signals to the nucleus, resulting in marked reprogramming of the cardiomyocyte at the level of gene expression and chromatin structure. From prognostic, physiological, and molecular mechanistic perspectives, it is important to differentiate pathological from the process of physiological hypertrophy, which occurs in trained athletes. While the cytoplasmic and nuclear signaling pathways engaged by these programs are distinct, there is overlap. Details of the metabolic shifts that differentiate these two forms of hypertrophy were recently reviewed [14,15]. In particular, the serine/threonine kinase Akt, downstream of insulin/insulin receptor substrate/PI3K signaling, serves as an integrative node in the development of physiological and pathological forms of hypertrophy. When constitutively active (via myristoylation) Akt1 is conditionally overexpressed in cardiomyocytes in vivo, the heart initially exhibits an adaptive growth phase with preserved systolic function and enrichment of myocardial transcripts that are associated with physiological growth [16,17]. Moreover, cardiomyocyte Akt1 is required for the development of physiological hypertrophy [18]. Conversely, chronic constitutive Akt1 activation results in the development of pathological hypertrophy that includes fibrosis, altered homeostasis of glucose uptake, and systolic dysfunction [16,19] — but Akt1 knockout mice also develop an exacerbated form of pathological hypertrophy [18]. The provocation of similar phenotypes in both absence and excess of discrete cellular signals is not uncommon, as this review will highlight, creating challenges in the development of targeted therapies.

Classically-described alterations of gene expression during cardiac hypertrophy include induction of the encoded fetal sarcomeric isoforms, the natriuretic peptides, mediators of inflammation and fibrosis, glycolysis, and apoptosis [20]. While the time course of measured metabolic shifts in the pathologically hypertrophied heart remain debated, fatty acid β-oxidation becomes reduced, and this diminution is accompanied by decreased mRNA abundance of encoded enzymes in the pathway, including CPT1. While reduction of glucose oxidation rates appears to be a later component in the evolution from compensated to decompensated hypertrophy, glycolysis rates, and its encoded mediators, are increased [15]. Interestingly, anaplerotic entry of pyruvate into the tricarboxylic acid (TCA) cycle, relative to entry rates of pyruvate through acetyl-CoA into the cycle via citrate synthase, is augmented in hypertrophied hearts, which can be linked to increased expression of the cytoplasmic isoform of the malic enzyme [21]. In the failing heart, rates of oxidative metabolism and indices of normal mitochondrial function are both reduced, as the heart becomes more reliant on the lower yield glycolytic pathway [5,15,22,23].

Much of the myocardial metabolic response to acute ischemia occurs through signaling cascades independent of changes in gene expression: increased peripheral lipolysis and mobilization of free fatty acids, activation of the AMP-activated protein kinase (AMPK), cardiomyocyte plasma and mitochondrial inner membrane remodeling due to phospholipase activation, impairment of fatty acid β-oxidation and oxidative phosphorylation, and shifts of intracellular ionic and redox potentials [5]. Acute reperfusion is associated with re-activation of β-oxidation. In the post-infarction remodeling phase, myocardial β-oxidation is reduced, which can be linked to reduced expression of mediators of fatty acid transport and oxidation [24]. Numerous transcription factors influence remodeling post ischemia or infarction. Taken together, modifications of gene regulation fundamentally reprogram cell function and adaptation to multiple forms of metabolic stress.

3. Adaptation to metabolic stress by transcription factors

3.1. Nuclear receptor transcription factors

A plethora of transcription factors coordinate the metabolic responses to stress in the myocardium (Table 1). The peroxisome proliferator-activated receptors (PPARs), nuclear receptor transcription factors that bind to site-specific DNA sequences as heterodimers with retinoid X receptors (RXR), serve as integrated coordinators of multiple forms of metabolic stress. For PPARs, *cis*-elements are organized as repeated 'half-site' hexad sequences separated by a single nucleotide, with one half-site bound per monomer of the PPAR–RXR complex [25]. These 'direct repeat 1' elements are commonly encountered in the promoters of genes encoding mediators of fatty acid transport and β-oxidation [26]. Constitutively, PPARs repress transcription through interaction with a complex of co-repressor histone deacetylates (HDACs), maintaining chromatin in a condensed conformation. When fatty acid and eicosanoid ligands bind PPARs and induce conformational changes in the PPAR–RXR heterodimer, co-repressors are released, and co-activator histone acetyltransferases are recruited, opening chromatin and favoring transcriptional activation in a site-specific manner [25,27]. Three mammalian PPAR family members, PPARα, PPARδ, and PPARγ, are encoded by distinct genes, and exhibit unique tissue distributions and ligand specificities — PPARα, is a target for the hypolipidemic fibrate drug class, and PPARγ is a target for insulin-sensitizing thiazolidinediones [28]. All three PPARs are expressed in cardiomyocytes to varying extents, and demonstrate overlapping and distinct properties in the context of metabolic stress, which will be described below.

Genetic gain- and loss-of-function tools have provided insight into the roles of these nuclear receptors in cardiovascular pathophysiology. When specifically overexpressed in cardiomyocytes of transgenic mice using an