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Review article

The PPAR trio: Regulators of myocardial energy metabolism in health and disease

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Abstract

Common causes of heart failure are associated with derangements in myocardial fuel utilization. Evidence is emerging that metabolic abnormalities may contribute to the development and progression of myocardial disease. The peroxisome proliferator-activated receptor (PPAR) family of nuclear receptor transcription factors has been shown to regulate cardiac fuel metabolism at the gene expression level. The three PPAR family members (alpha, beta/delta and gamma) are uniquely suited to serve as transducers of developmental, physiological, and dietary cues that influence cardiac fatty acid and glucose metabolism. This review describes murine PPAR loss- and gain-of-function models that have shed light on the roles of these receptors in regulating myocardial metabolic pathways and have defined key links to disease states including the hypertensive and diabetic heart.

Keywords: Murine model; Peroxisome proliferator-activated receptor (PPAR); Cardiomyopathy; Metabolism; Transcription; Fatty Acid; Glucose; Diabetes

Contents

1. Introduction: a primer on myocardial fuel metabolism in health and disease

In order to function as a constant pump, the mammalian heart must produce vast amounts of ATP under diverse nutritional and physiological conditions. The heart is a metabolic omnivore, using multiple fuel sources to satisfy these enormous energy demands. The healthy adult heart,

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predominantly reliant on fatty acids, is capable of switching to a glucose-predominant substrate utilization pattern under certain conditions, such as the postprandial state [1]. The flexibility to utilize multiple fuels according to availability and physiological demands is believed to be important for normal cardiac function.

It has long been observed that pathologic states are associated with derangements in myocardial fuel utilization patterns. Pathologic cardiac hypertrophy and congestive heart failure caused by pressure overload are examples of states in which the myocardium switches to using predominantly glucose as the chief energy substrate [2]. This metabolic reprogramming is commonly referred to as a "fetal" shift due to the fact that during the embryologic development, the myocardium relies predominantly on glycolysis and lactate metabolism for ATP production [1]. Conversely, the diabetic myocardium relies largely, and at times, exclusively on fatty acids as the main energy substrate with the contribution by glucose to ATP production being minimal [3–7]. The central question of whether these fuel metabolic derangements are "bystanders" of the underlying disease process or directly contribute to the etiology of pathologic cardiac remodeling is the focus of intense debate and investigation. The best evidence to support a causal role for metabolic derangements in the development of cardiac dysfunction is the observation that children with genetic defects in fatty acid oxidation (FAO) enzymes, which forces the heart to rely on glucose, often develop cardiomyopathy [8].

Evidence has emerged that the capacity for myocardial fatty acid utilization is determined, at least in part, at the gene regulatory level, providing a mechanism for reprogramming the expression of enzymes involved in fuel utilization pathways in response to diverse dietary and physiological conditions, and in disease states. This review focuses on one of these gene regulatory pathways, the family of transcriptional regulators termed the peroxisome proliferator-activated receptors (PPARs). Special emphasis will be given to studies aimed at defining the function of PPAR family members in the normal and diseased heart in vivo, based on the development and characterization of mouse models in which the expression of individual PPARs has been altered in the hearts of mice.

2. The PPAR family of nuclear receptors: ligand-activated transcriptional regulators of cellular fuel metabolism

The PPARs are members of the nuclear hormone receptor superfamily. Upon binding with their cognate ligands, PPARs form heterodimers with 9-*cis* retinoic acid-activated receptors (RXRs) and bind to DNA response elements in target gene promoter regions (Fig. 1). There are three members of the PPAR family (α, β/δ, γ) with distinct but overlapping spatial, temporal and regulated expression patterns. PPARα is enriched in tissues with high capacity for FAO, such as heart, brown adipose tissue, slow-twitch skeletal muscle, and liver [9,10]. PPARβ (also known as PPARδ) is ubiquitously expressed, with relatively high levels of expression in heart, skeletal muscle and brain [9] and also participates in regulation of FAO [11,12]. Finally, PPARγ is adipose-enriched [9] and plays a vital role in adipocyte differentiation and fat storage [13–16]. Although the endogenous ligands for the individual PPARs have not been established with certainty, it appears that long-chain fatty acids and their metabolites likely serve as activating endogenous ligands.

Given that PPARs are responsive to fatty acid ligands and regulate the expression of genes involved in cellular lipid metabolism, they are uniquely suited to serve as transducers of developmental, physiological, and dietary cues to the control of cardiac fuel metabolism. The PPARs are also ideal pharmacologic targets because they possess large hydrophobic ligand-binding sites that can be activated by diverse compounds. Indeed, several well-known pharmacologic agents, such as lipid-lowering (fibrates) and insulin-sensitizing drugs (thiazolidinediones or TZDs) activate PPARα and PPARγ, respectively. The triglyceride-lowering effects of fibrates are related, in part, to PPARα-driven increases in fatty acid oxidation in the liver, leading to suppression of very low density lipoprotein (VLDL) secretion [17,18]. TZDs, commonly used PPAR agonists, agonize PPARγ and increase the capacity for fat storage in adipose tissue, alleviating the effects of lipolysis on muscle and hepatic insulin resistance [19]. There is also evidence that PPARs exert anti-inflammatory effects which may also contribute to insulin-sensitizing and possibly cardioprotective effects, but this aspect of PPAR biology is beyond the scope of this review (reviewed in

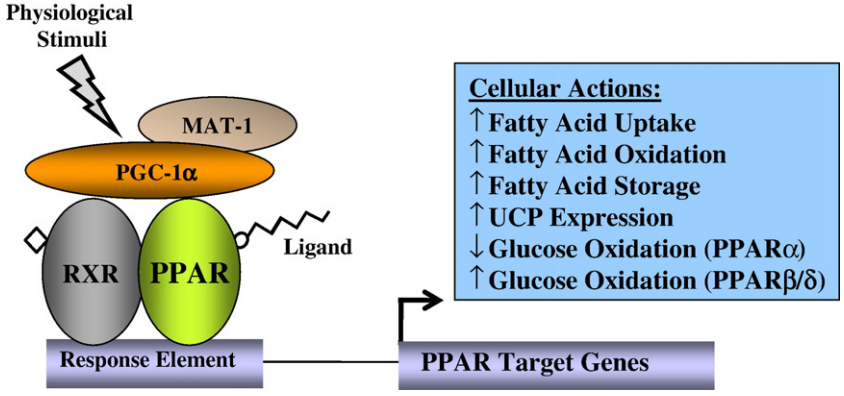

Fig. 1. The PPAR family of transcription factors forms dimers with RXRs and, upon binding cognate DNA response elements on target gene promoter regions, activates the transcription of target genes. The transcriptional activity of the PPARs is influenced by binding of endogenous ligands and protein coactivators such as PGC-1 and its regulator MAT-1. Some of the major actions of PPARs in the heart are shown in the box. Note that some of the actions are PPAR subtype-specific. UCP, uncoupling protein.