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PPAR Transcriptional Activator Complex Polymorphisms and the Promise of Individualized Therapy for Heart Failure

Neville F. Mistry, MD and **Sharon Cresci, MD**
Washington University School of Medicine, Departments of Medicine, Saint Louis, Missouri

Abstract

The PPAR gene pathway consists of interrelated genes that encode transcription factors, enzymes and downstream targets which coordinately act to regulate cellular processes central to glucose and lipid metabolism. The pathway includes the PPAR genes themselves, other class II nuclear hormone receptor transcription factors within the PPAR family, PPAR co-activators, PPAR co-repressors, and downstream metabolic gene targets. This review focuses on the transcription factors that comprise the PPAR transcriptional activator complex – the PPARs (PPARα, PPARβ, or PPARγ), PPAR heterodimeric partners, such as RXRα, and PPAR co-activators, such as PPARγ coactivator 1α (PGC-1α) and the estrogen related receptors (ERRα, ERRβ, and ERRγ). These transcription factors have been implicated in the development of myocardial hypertrophy and dilated cardiomyopathy as well as response to myocardial ischemia/infarction and, by association, ischemic cardiomyopathy. Human expression studies and animal data are presented as the background for a discussion of the emerging field of pharmacogenetics as it applies to these genes and the consequent implications for the individualization of therapy for patients with heart failure.

Keywords

Pharmacogenetics; Peroxisome Proliferator-activated Receptor; PPAR; PGC-1; ERR; Cardiovascular Disease

INTRODUCTION

Peroxisome proliferator-activated receptors (PPARs) are members of the group II nuclear receptor superfamily. This family of transcription factors has been further subdivided into 3 groups distinguished by the affinity of ligand binding, the size of the ligand binding site, and the existence of known ligands (Table 1) (1–3). The PPARs belong to the group that has a relatively larger ligand-binding pocket with a relatively lower ligand binding affinity compared with the other two groups. These characteristics are thought to allow for binding of more diverse ligands, including metabolic intermediates (fatty acids) and xenobiotics (fibrates, thiazolidinediones) (1–4). In the presence of ligand, PPARα, β or γ binds to its cognate DNA regulatory element as a heterodimer with the retinoid X receptor α (RXRα; Figure 1) (5). Ligand binding results in a conformational change in the nuclear receptor complex that results in the association of co-activators, release of co-repressors and increased transcriptional activation of target genes (3;4;6–11).

Corresponding author: Sharon Cresci, MD, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8086, Saint Louis, MO 63110-1093, Telephone: 314 362 5363, Fax: 314 747-5613, scresci@im.wustl.edu.

Several PPAR co-activators have been described. One such inducible transcriptional co-activator is PPARγ coactivator −1α (PGC-1α) (6;7). PGC-1α is highly expressed in both heart and the adipocyte and has been shown to exert physiologic control on glucose transport and gluconeogenesis as well as fatty acid oxidation and mitochondrial biogenesis (12;13). Another family of PPAR co-activators, known as the estrogen-related receptors (ERRα, ERRβ, and ERRγ), has recently been identified (13;14). ERRα and ERRγ are functional partners of PGC-1α(15–17) and gene expression profiling studies in cardiomyocytes demonstrate that ERRα and ERRγ up-regulate the expression of PPARα and PPARα-regulated genes.(18;19)

The PPARs, and more recently, PPAR-family members and transcription factors that comprise the PPAR transcriptional activator complex, have been the focus of intensive study as potential therapeutic targets in diseases such as diabetes, atherosclerosis and cardiomyopathy. Animal models and human expression data have implicated PPAR transcriptional activator complex genes in three general forms of cardiomyopathy: hypertrophic, diabetic and dilated cardiomyopathy. Additionally animal models have revealed that these genes are involved in the response to myocardial ischemia and infarction, thus likely affecting the development of ischemic cardiomyopathy. As these data represent the foundation for the investigation of genetic and pharmacogenetic associations with these genes, the data relevant to each gene and cardiomyopathic state are reviewed first. The genetic and pharmacogenetic association data with respect to these same phenotypes in patients are then discussed. The intention of this review is to provide the context for understanding the complexity of the PPAR-pharmacologic interaction as the field of PPAR pharmacogenetics, while currently in its infancy, is rapidly developing. Ultimately a better understanding of the genes described here will permit personalized medicine wherein medications are tailored to an individual patient's genotype. Given the extensive data associating PPAR family members with cardiovascular diseases, outcomes, and response to drug therapy these genes offer much promise for further inquiry.

I. Peroxisome Proliferator-Activated Receptors (PPARs)

A. LEFT VENTRICULAR HYPERTROPHY

Both human and animal studies have demonstrated changes in PPARα expression during the development of left ventricular hypertrophy (LVH) (20–22). In a rat model of progressive LVH and heart failure, the expression of PPARα target genes was downregulated greater than 70% compared to controls (21). Similarly, in a transverse aortic constriction mouse model of pressure-overload induced LVH, PPARα mRNA levels were 39% lower in mice with aortic constriction compared with sham operated mice (22).

Recent supportive evidence for a key role of PPARβ/δ in the development of myocardial hypertrophy derives from the observation that mice with cardiomyocyte-restricted PPARδ deletion develop marked LVH in adulthood (23). In addition, the PPARβ/δ agonist L-165041 inhibits phenylephrine-induced hypertrophy in neonatal rat cardiomyocytes via increased interaction between PPARβ/δ and NF-κB (a transcription factor known to be important in the signaling pathway of myocardial hypertrophy) and decreased expression of NF-κB target genes (24).

Genetic and Pharmacogenetic Associations—The *PPARA* IVS7 2498 G>C polymorphism (located in intron 7 of *PPARA*; 36,354 nucleotides from the translation start site in genomic *PPARA* sequence; 2498 nucleotides downstream from the exon-intron junction) was identified by direct sequencing of a Taq1 restriction fragment length polymorphism generated in the initial cDNA cloning of human *PPARA*(25;26). Given its

location within an intron, the functional consequences of this polymorphism remain unclear (25;26).

The *PPARA* IVS7 2498 polymorphism (designated "*PPARA* intron 7 G/C polymorphism" in the publication) has been associated with left ventricular hypertropy in response to exercise in 144 healthy British army recruits undergoing a 10-week intensive training program. This exercise regimen included upper and lower body strength and endurance training (25). At baseline, age, weight, BMI, blood pressures, and measurements of heart size (determined by cardiac MRI) were similar among all genotype groups (25). Cardiac MRI performed at the commencement and termination of training revealed an increase in LV mass that was largest in CC homozygotes (19.4 +/− 4.2g), intermediate in GC heterozygotes (11.8 +/− 1.9g), and lowest in GG homozygotes (6.7 +/− 1.5; p=0.009 between groups) (25). The genotype effect upon LV mass increase remained significant when adjusted for body surface area (P=.02) (25). No interaction between the effect of genotype and losartan (i.e. pharmacogenetic interaction) was noted in this study.

In a subset of the third MONitoring Trends and Determinants in CArdiovascular Disease (MONICA) Augsburg survey, 1142 German women and men ages 25–74 underwent echocardiographic analysis of LV mass (25;27). *PPARA* IVS7 2498 (designated "*PPARA* intron 7 G/C polymorphism" in the publication) CC homozygote men exhibited significantly higher left ventricular mass index (LVMI) and septal wall thickness than G allele carries (105.7 ± 4.8 g/m^2 in CC; 92.2 ± 1.3 g/m^2 in GC; 91.8 ± 1.0 g/m^2 in GG; p=0.005) (25). *PPARA* IVS7 2498 CC homozygote women displayed a similar trend. In the combined sample of men and women, the hypertrophic effect of CC homozygosity, as measured by LVMI, was significant (25). Hypertension greatly increased the effect of *PPARA* IVS7 2498 genotype in males, with hypertensive C allele homozygote individuals 4 times as likely to have LVH as hypertensive G-allele carriers (25).

B. Dilated Cardiomyopathy

Several studies have implicated PPARα, PPARγ and PPARδ in the development of dilated cardiomyopathy. Sack and colleagues compared explanted left ventricular tissue from cardiac transplant recipients with Class III-IV heart failure to control hearts from patients who died of noncardiac etiologies and found significantly decreased mRNA and protein levels of PPARα target genes MCAD and LCAD in the cardiac tissue from patients with heart failure compared to controls. These findings were confirmed by Razeghi and colleagues who demonstrated a significant downregulation of PPARα target genes MCAD, LCAD, and mCPT-1 mRNA levels in 10 failing hearts of patients undergoing LVAD placement when compared to 9 normally functioning hearts that were not transplanted for technical reasons (28). Furthermore, several investigators have demonstrated that up-regulation of PPARα may be advantageous in heart failure, as administration of the PPARα agonist fenofibrate attenuated cardiac dysfunction in both pig and rat models of heart failure (29;30). While the preponderance of data suggests that PPARα and PPARα target gene expression is downregulated in dilated cardiomyopathy, one study has reported discordant results. When Schupp and colleagues studied explanted hearts from 16 patients with dilated cardiomyopathy undergoing transplant compared with 15 donor hearts (not used for transplantation due to technical reasons) PPARα mRNA expression was significantly increased in the explanted hearts compared to controls (136+/−25.4% vs. control, $p<0.01$) (31). mRNA levels of the PPAR-target gene CPT-1 were observed to have similarly increased levels (147+/−51% vs. control, $p<0.05$) (31). It is interesting to speculate that the differences in these findings may be related to different underlying etiologies of the dilated cardiomyopathic samples used in the studies or to the timing of transplantation with respect to the development of heart failure.

Cardiomyocyte restricted PPARγ knockout mice develop a dilated cardiomyopathy that is felt to be a consequence of reduced superoxide dismutase 2 (32), however when investigators compared the expression of PPARγ mRNA in ventricular samples from patients with dilated cardiomyopathy and controls, similar levels were observed (33). Mice with cardiomyocyte restricted PPARδ deletion develop a dilated cardiomyopathy after 4 months that is thought to be lipotoxic in nature (23) but no studies of PPARδ expression in human tissue have been performed to date.

C. Diabetic Cardiomyopathy

The PPAR genes have been implicated in the development of diabetic cardiomyopathy in animal models (34). The expression and activity of PPARα are increased in the hearts of both rat and mouse models of insulin-deficient and insulin-resistant diabetes. Mice with cardiac-restricted overexpression of PPARα have a cardiac phenotype, characterized by an increased dependence on fatty acid oxidation and a decreased dependence on glucose oxidation, similar to that seen in patients with diabetes(35;36). The hearts from mice with cardiac-restricted overexpression of PPARα also demonstrate features of diabetic cardiomyopathy including ventricular hypertrophy and systolic dysfunction compared to non-transgene controls (36).

Genetic and Pharmacogenetic Associations—While no genetic or pharmacogenetic associations of PPAR gene polymorphisms and development of diabetic cardiomyopathy have been reported to date, there are numerous reports of SNPs in these genes being associated with the onset, progression and severity of DM itself. For example, the common *PPARG* Pro12Ala SNP (located in exon B which is present only in adipocyte-specific isoforms of PPARγ) has been associated with the risk of developing DM in multiple populations of different ethnicity (37–42) and a SNP in the promoter of *PPARA* has been shown to influence the onset and progression of type 2 DM (43). Furthermore, associations have been observed between SNPs in these genes and differences in response to medications that are commonly used to treat type 2 DM. For example, the *PPARG* Pro12Ala SNP and *PPARG* haplotype have been reported to influence response to thiazolidinedione therapy in patients with DM (44;45) and the *PPARG* Pro12Ala SNP has been associated with the development of peripheral edema in patients with type 2 diabetes treated with the dual-acting PPARalpha/gamma agonist ragaglitazar (46).

D. Ischemic Cardiomyopathy

Both PPARα and PPARγ may have important roles in the myocardial response to ischemia. Experimental animal models suggest that if PPARα is upregulated during myocardial ischemia and reperfusion, left ventricular contractile function deteriorates, microinfarction and intramyocardial triglyceride deposition develop, and there is a significantly diminished recovery of cardiac function (20;47). Further supporting the deleterious role of PPARα during ischemia/reperfusion, PPARα-null mice have better recovery in ventricular function after ischemia/reperfusion compared to their wild-type littermates (48).

PPARγ also affects the myocardial response to ischemia and infarction, but its effects appear to be dependent on the timing of its expression. Upregulation of PPARγ in the post-infarction period appears to be deleterious. When the PPARγ agonist thiazolidinedione rosiglitazone was given to rats in the post infarction period (more than 6 hours after infarction), there was significantly increased mortality compared with controls (49). In contrast, there is evidence that upregulation of PPARγ may be protective in the pre-infarction period. When Zucker diabetic fatty rats were pretreated with rosiglitazone for 8 days prior to ischemia/reperfusion or myocardial infarction, the number of apoptotic cardiomyocytes was decreased by 58% and myocardial infarct size was decreased by 46%

(50). Similar results were found when hypercholesterolemic rabbits were pretreated with rosiglitazone before being subjected to ischemia/reperfusion (51).

However, in randomized clinical trials, effects on cardiovascular outcomes for the 2 available TZDs are divergent. The PROactive trial, a randomized, double-blind outcome study in patients with type 2 DM and a history of macrovascular disease managed with diet and/or oral pioglitazone (52), demonstrated a reduction in the frequency of death, non-fatal MI, and cerebral infarction (53). Consistent with these observations, a meta-analysis of clinical trials demonstrated a significant reduction in death, MI, or stroke in patients with DM randomized to pioglitazone compared with placebo (54). In contrast, a meta-analysis including 42 clinical trials in DM patients demonstrated a significant 43% increased risk of MI and 64% increased risk of cardiovascular mortality in patients randomized to rosiglitazone compared with placebo (55). Additional data suggest that the effects of PPARα agonist drugs are equally complex and confusing. In contrast to the hyperglycemia seen in animal models where PPARα agonists are administered, in clinical trials administration of PPARα agonists to patients with DM results in a decrease in serum glucose levels and an apparent decrease in progression of coronary atherosclerosis (56).

Genetic and Pharmacogenetic Associations—Associations between the *PPARA* IVS7 2498 G>C polymorphism, atherosclerosis, and adverse cardiac events have been investigated. In the Lopid Coronary Angiography Trial (LOCAT - a study in 395 Finnish men less than 70 years old), *PPARA* IVS7 2498 C allele carriers had a significantly greater progression of coronary atherosclerosis compared with GG homozygotes with similar progression in both treated and untreated groups (no genotype-by-treatment interaction) (57). Among healthy middle aged men in the second Northwick Park Health Study (NPHS2), the *PPARA* IVS7 2498 CC genotype showed a trend toward greater incidence of ischemic events (myocardial infarction or coronary revascularization) (HR 1.83; 95%CI 0.96–3.51; p=0.07) (57).

We have recently investigated the influence of*PPARA* IVS7 2498 genotypeon clinical outcomes in response to β-blocker therapy in patients admitted to the hospital with acute coronary syndromes(58). Mortality and cardiac rehospitalization through 1 year were assessed in 735 patients with acute coronary syndromes and significantly different outcomes associated with β-blocker therapy were observed according to *PPARA* IVS7 2498 genotype (p = 0.002 for interaction). Multivariable analysis, adjusting for propensity of BB therapy and all factors that differed by *PPARA* IVS7 2498 genotype, demonstrated that among ACS patients homozygous for the *PPARA* IVS7 2498 GG genotype, discharge on β-blocker therapy was associated with a 48% relative risk reduction in cardiac rehospitalization (HR 0.52, 95% CI 0.32–0.86; p=0.011). Discharge on β-blocker therapy in carriers of the *PPARA* IVS7 2498 C allele was associated with a nearly 3-fold relative increase in the risk of cardiac rehospitalization (HR 2.92, 95% CI 1.32–6.92; p=0.015; genotype interaction p=0.0005). We further demonstrated that PPARα mRNA expression in cardiac tissue from 34 hearts with normal left ventricular ejection fraction determined by echocardiography and no history of myocardial dysfunction donated for orthotopic cardiac transplantation but declined for reasons related to size or ABO blood type mismatch was significantly greater in the *PPARA* IVS7 2498 GG homozygote individuals compared to the *PPARA* IVS7 2498 GC heterozygote individuals (none of the individuals were CC homozygotes; 1.20 ± 0.30 vs. 0.94 ± 0.40 respectively; p = 0.04). To further explore the effect of increased PPARα expression on β-adrenergic responsiveness, we studied changes in heart rate and contractility in response to incremental doses of the β sympathomimetic dobutamine in transgenic mice with cardiac specific overexpression of PPARα (an animal model that mimicked the relative differences in cardiac PPARα expression demonstrated by our mRNA expression experiments in humans) (58). We found that, compared to non-transgene littermates,

transgenic mice with cardiac specific overexpression of PPARα had a blunted response to incremental doses of dobutamine and proposed that *PPARA* IVS7 2498 C allele carriers have less of a general response to β-adrenergic stimulation compared to GG homozygote individuals, thereby reducing or eliminating the expected benefit derived from β-blocker therapy after acute coronary syndromes and potentially unmasking hazardous effects (58).

The *PPARA* Leu162Val SNP, located in the DNA binding region of PPARα and thought to confer differences in ligand-responsive activation of PPARα(59;60), has been associated with serum triglyceride, total cholesterol, LDL-cholesterol, and apolipoprotein B and C-III levels in small scale clinical studies (61–63). However when the association of the PPARA Leu162Val polymorphism with the risk of atherosclerosis was investigated in 3,012 healthy middle aged men in NPHS2, or in 395 Finnish men less than 70 years old from the LOCAT study, no association with variations in serum lipids were found (57). Nevertheless, the Val162 allele carriers had less progression of atherosclerosis in both treated and untreated groups in LOCAT (no interaction of drug treatment with genotype was noted) (57).

The *PPARG* Pro12Ala polymorphism is located in exon B of *PPARG* which is specific to PPARγ2, the PPARγ isoform restricted to adipose tissue (39). Compared with the PPARG Pro12 variant, *in vitro* DNA binding assays have demonstrated that the PPARG Ala12 variant has lower binding affinity for a PPAR responsive element and transient transfection experiments demonstrate that the PPARG Ala12 variant has decreased PPARγ-activation of a reporter construct in response to ligand (39). Several studies have suggested an association of this polymorphism with carotid atherosclerosis, coronary artery disease and/or myocardial ischemic events, however, not all studies have agreed on the direction of the association (64–66).

In individuals enrolled in the Physicians' Health Study (14,916 men followed for a mean of 13.2 years) (67), the PPARG Pro12Ala polymorphism was genotyped in 523 individuals who developed a myocardial infarction and in 2092 controls obtained through a nested case-control design (66). Of those individuals who developed a myocardial infarction, the frequency of PPARG Ala12 allele carriers was significantly less than in the controls, with a decreased risk of subsequent MI (hazard ratio HR=0.77; 95% CI 0.60–0.98; p=0.034) (66). This relationship held even after controlling for traditional cardiac risk factors.

The association of this polymorphism with cardiovascular risk was also assessed in 2016 (all Caucasian) patients with type 2 DM from the genetic portion of the continually updated dataset known as the Diabetes Audit and Research in Tayside Scotland database (Go-DARTS) (65). A borderline, non-significant association of the Ala12 allele with non-fatal MI or revascularization (HR 0.54; 95%CI 0.27–1.08; p=0.08) was observed for the entire group. Subgroup analysis demonstrated a significant association if patients younger than 70 years old at time of enrollment were assessed separately (HR 0.43; CI 0.18–0.99; p=0.05) or if patients younger than 70 year old at time of enrollment with no prior history of stroke, MI or revascularization were evaluated for time to first event (HR 0.21; CI 0.06–0.69; p=0.01) (65).

More recently, association of PPARG Pro12Ala genotype with the risk of coronary artery disease was assessed prospectively in women enrolled in the Nurses' Health Study (8 years mean follow-up) and in men (6 years mean follow-up) enrolled in the Health Professionals Follow-Up Study (64) 249 women and 266 men were identified who had a myocardial infarction. Nested case-controls, matched for age, smoking status and phlebotomy date, were used for comparison. This study demonstrated that, in contrast to the Physicians' Health Study, men carriers of the Ala12 allele had an increased risk of MI or cardiac death (Relative Risk RR=1.44; CI 1.00–2.07; p=0.05). There was no statistical difference in

nonfatal MI or fatal CHD in women carriers of the Ala12 allele (Relative Risk RR=1.17; CI 0.82–1.68; p=0.39) (64). When data were pooled for men and women, carriers of the Ala12 allele had an increased risk of MI or cardiac death (Relative Risk RR=130; CI 1.00–1.67; p=0.05) and, when stratified by body weight, men and women with a body mass index ≥ 25kg/m^2 had a 1.68 fold increase in risk (CI 1.13–2.50; p=0.01) (64). While the results from these studies may seem contradictory, there are obvious differences in study design, patient cohorts, primary end-points and power. In addition, it is possible that geographic and ethnic differences in allele frequencies may contribute to variability in the study findings.

The *PPARG* 54,347 C>T (also referred to as *PPARG* 1431C>T and PPARG c.161C>T) polymorphism is a synonymous C>T substitution in nucleotide 161 of exon 6 (54,347 nucleotides from the translation start site in genomic *PPARG* sequence) (68). As exon 6 is found in all isoforms of PPARγ, it has been proposed that associations of this polymorphism may be more informative that those of isoform specifc polymorphisms (69). No functional information on this polymorphism is available to date. The *PPARG* 54,347 C>T polymorphism has been associated with the extent of coronary artery disease by angiography (69), carotid intima media thickness (70) and incidence of myocardial infarction among individuals younger than age 50 (71).

Several large-scale randomized trials conducted over the last two decades among patients with increased risk of cardiovascular disease, and perhaps especially those with type 2 DM, have demonstrated that statin treatment significantly reduces cardiovascular events (72–78). Although the physiologic mechanism of interaction between these pharmacologic agents and PPAR is not fully understood, it has been proposed that at least some of the cardiovascular effect of statins may result from increased expression and activation of PPARα and PPARγ(79;80).

Chen et al investigated whether a multi-locus haplotype association study combining information from all of the PPAR polymorphisms into a combined model would result in new insights into PPAR pharmacogenetics in the Lipoprotein and Coronary Atherosclerosis Study (LCAS; a randomized, placebo-controlled study of 429 subjects, 35–70 years old, with at least one 30–75% diameter stenosis on coronary angiography and LDL-cholesterol of 115–190 mg/dL despite diet) cohort assessing response to fluvastatin (81). 372 individuals were genotyped for seven PPAR polymorphisms (*PPARA* Leu162Val, *PPARA* −35,089 A>C, *PPARG* Pro12Ala, *PPARG* 54,347 C>T (designated “*PPARG* 161 C>T” in the publication), *PPARG* 25,506 C>T, *PPARD* −87 T>C (designated “*PPARD* 294 T>C” in the publication), *PPARD* −4401 C>T) and the change in serum lipids and progression of coronary artery disease (quantified by changes in lumen diameter and development of new coronary lesions) in response to fluvastatin was assessed (81). *PPARD* haplotypes were associated with significantly different changes in plasmid lipids and significantly different mean number of new coronary lesions in response to treatment with fluvastatin (81). *PPARG* haplotype was associated with significantly different changes in minimum lumen diameter (p=0.009) in response to fluvastatin treatment(81).

II. PPARγ Coactivator 1(PGC-1α)

PGC-1α acts as a coactivator to PPARs and other hormone receptors involved in the regulation of cellular energy metabolism and has a similar tissue expression pattern (expression of PGC-1α is enriched in tissues with high oxidative capacity including skeletal muscle, brown adipose tissue, and the heart). PGC-1α is thought to be the intersect point for the complex regulation of cellular energy balance, acting to “fine-tune” nuclear hormone receptor activity and orchestrating the response to multiple physiologic stimuli.

PGC-1α null mice have yielded interesting insights into the cardiac role of PGC-1α. PGC-1α null mice have been shown to have reduced systolic function (82) as well as diminished heart rate response to exercise and β-adrenergic stimulation. Thus PGC-1α regulation of cardiomyocyte metabolism implicates a role for this coactivator in cardiomyopathy.

A. Left Ventricular Hypertrophy

Given its integral role as a PPARα co-activator, it seems likely that PGC-1α would play a role in cardiac hypertrophy. Animal models have not directly addressed hypertrophy in relation to PGC-1α expression, however, in mouse models of chronic pressure overload (a model of LVH) PGC-1α levels are downregulated along with PPARα target genes (83). Human data suggests a role for PGC-1α in hypertrophic cardiomyopathy (HCM)(84).

Genetic and Pharmacogenetic Associations—Two PGC-1α gene (*PPARGC1*) polymorphisms have been associated with the development of HCM (84). The *PPARGC1* Gly482Ser (G>A) and *PPARGC1* Thr394Thr (C>T) SNPs were studied in 270 Chinese patients with hypertrophic cardiomyopathy (LV wall thickness >13 mm) and 894 healthy controls. Of note these SNPs are not in linkage dysequilibrium. *PPARGC1* Ser482 allele frequency was significantly higher in HCM patients than in controls (84). Regression analysis controlling for age, sex, blood pressure, and BMI revealed an Odds Ratio for HCM of 1.52 (1.11–2.11) for *PPARGC1* Ser482 carriers (84). The *PPARGC1* Ser482 allele was also associated with increased maximum wall thickness in HCM patients (20.7 vs 19.1 mm; $p < 0.05$) (84). The CC genotype of the *PPARGC1* Thr394Thr SNP was more common in HCM patients than in controls (59.3 vs 49.7%; $p < 0.05$), suggesting a recessive effect of the C allele (84). After multivariable regression analysis accounting for age, sex, BMI, and blood pressure, an odds ratio for HCM of 1.49 was noted for patients with CC homozygosity. The CC genotype was also associated with increased maximal wall thickness in HCM patients. Interestingly the *PPARGC1* Ser482 and *PPARGC1* Thr394Thr polymorphisms, when studied in 2486 hypertensive Chinese patients, were not associated with LVH (present in nearly 50% of these patients). The *PPARGC1* Gly482Ser SNP was also studied in 2656 Danish patients, ages 41–71 as part of the DanMONICA study (85). Again no significant interaction between *PPARGC1* Gly482Ser genotype and LV mass index was noted.

B. Dilated Cardiomyopathy

PGC-1α has recently been demonstrated to play a role in the development of dilated cardiomyopathy in animal models (12). Transgenic mice with cardiomyocyte-restricted constitutive overexpression of PGC-1α developed cardiomegaly with four chamber enlargement, severely reduced global contractile function and marked edema by 6 weeks of age (12). Histological section from left ventricular tissue revealed sarcomeric disruption, mild fibrosis and expansion of enlarged mitochondria (12). No genetic or pharmacogenetic associations with PGC-1α and the development of dilated cardiomyopathy have been reported to date.

C. Diabetic Cardiomyopathy

PGC-1α has also been implicated in the development of diabetic cardiomyopathy in animal models (34). The expression and activity of PGC-1α are increased in the hearts of two mouse models of diabetes (mice rendered diabetic by streptozotocin or leptin receptor deficiency) (36). Interestingly the association between PGC-1α and insulin resistance itself remains unclear. While studies focused on skeletal muscle would suggest a protective role, studies on pancreatic β cells suggest that PGC-1α reduces insulin secretion (86;87).

Genetic and Pharmacogenetic Associations—The Gly482Ser SNP of *PPARGC1A* (associated with hypertrophic cardiomyopathy, as discussed above) has been associated with the risk of developing type 2 DM and diabetic retinopathy in Caucasians (88;89).

III. Estrogen Related Receptors (ERRs)

ERRs were originally identified in a search for nuclear hormone receptors related to the estrogen receptors. Although downstream targets of ERR are incompletely understood to date, given that ERRs bind to the same nuclear hormone receptor binding site consensus sequence that the estrogen receptor binds they are thought to potentially have many of the same targets and effects as the estrogen receptors. As discussed above, ERRα and ERRγ have recently been recognized as important PPAR co-activators (13;14) as well as functional partners of PGC-1α(15–17). Gene expression profiling studies in cardiomyocytes demonstrate that ERRα and ERRγ up-regulate the expression of PPARα and PPARα-regulated genes(18;19).

A. Left Ventricular Hypertrophy

ERRα and ERRγ are thought to have a significant role in myocardial hypertrophy. ERRα mRNA levels are reduced in mice subjected to transient aortic constriction when compared to sham-operated controls, suggesting a role in the response to pressure overload (90). Mice null for ERRα have no significant difference in total body weight, but have significantly lower LV mass to body weight ratio when compared to wild-type mice (90). ERRγ is thought to have a similar role as ERRα in the myocardial hypertrophic response to pressure overload, however, direct binding to DNA may be required for ERRγ as mice with ERRγ lacking a DNA binding domain are characterized by lower LV mass to body weight ratio as well as conduction abnormalities (91).

Genetic and Pharmacogenetic Associations—To date, no genetic or pharmacogenetic associations of polymorphisms within the genes encoding ERRα and ERRγ (*ESRRA* and *ESRRG*, respectively) with ventricular hypertrophy have been reported. However, associations with hypertrophy have been described for two close relatives, the estrogen receptor α (*ESR1*) (92–95) and estrogen receptor β (*ESR2*) (96) genes. It seems likely that similar associations will be reported with the ERRs in the future.

B. Ischemic Cardiomyopathy

To date, there is no animal or human expression data that analyzes the role of ERRs in the myocardial response to ischemia. However, investigators have noted a genetic association of a polymorphism in the related gene *ESR1* and the extent of coronary artery disease (92;93).

IV. Retinoid X Receptor α (RXRα)

As described earlier, PPARs heterodimerize with RXRα and bind to their cognate DNA regulatory elements. While studies relating RXRα to cardiomyopathic phenotypes do not currently exist, an RXRγ polymorphism has been associated with significantly higher indices of coronary stenosis in 105 patients with suspected coronary artery disease undergoing coronary angiography (97). This same polymorphism has been associated with familial combined hyperlipidemia(97).

DISCUSSION

The ultimate goal of pharmacogenetics is to define the genetic determinants of individual drug responsiveness and thereby provide personalized treatment to each individual. This review has discussed the growing body of data reporting the association of PPAR activator

complex gene polymorphisms with cardiomyopathic phenotypes. To date, however, there are a limited number of important studies that have explored the interaction between PPAR activator complex gene variants and pharmacotherapy and even less that have explored the interaction between these variants and pharmacotherapy administered to treat heart failure. These studies, taken together, represent the beginning of a promising area of targeted genotype analysis as a potential guide to new drug development in the treatment of cardiomyopathy and heart failure.

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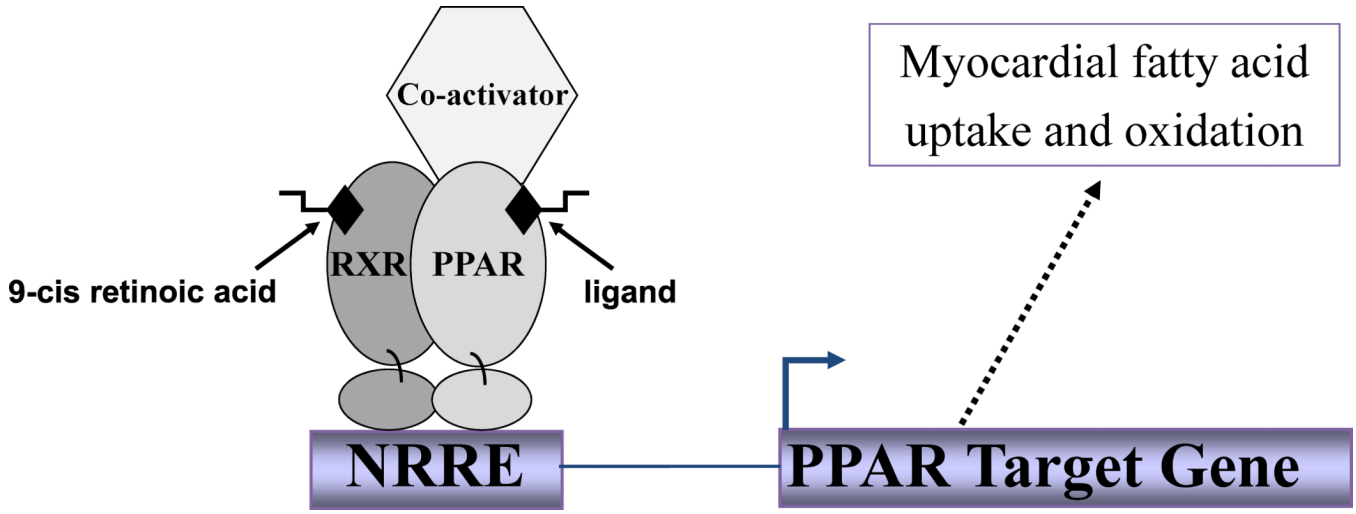

Figure 1.
Schematic of the PPAR transcriptional activator complex. PPAR-RE (PPAR response element) represents the DNA sequence that PPAR binds.

Table 1

Nuclear Hormone Receptors stratified by ligand

Endocrine Receptors - High affinity binding sites; Ligands are hormonal lipids
Estrogen Receptor α,β (ERα,β)
Progesterone Receptor (PR)
Androgen Receptor (AR)
Glucocorticoid Receptor (GR)
Mineralocorticoid Receptor (MR)
Thyroid Receptor α, β (TRα, β)
Vitamin D Receptor (VDR)
Retinoic Acid Receptor α, β (RAR α, β)
Adopted Orphan Receptors – Low affinity binding sites; Ligands are dietary lipids
Peroxisome Proliferator Activated Receptor α, β/δ, γ (PPAR α, β/δ, γ)
Retinoid X Receptor α, β, γ (RXR α, β, γ)
Liver X Receptor α, β (LXR α, β)
Farnesoid X Receptor (FXR)
Pregnane X Receptor (PXR)
Constitutive Androstane Receptor (CAR)
Orphan Receptors – Unknown Ligands
Steroidogenic Factor 1 (SF-1)
Liver Receptor Homlogue 1 (LRH 1)
DAX-1
Small Heterodimer Partner (SHP)
TLX
Photoreceptor Cell-specific Nuclear Receptor (PNR)
Nerve Growth Factor Inducible-B α, β,γ (NGFI-B α,β,γ)
RAR-related Orphan Receptor α,β,γ (ROR α,β,γ)
Estrogen Related Receptor α,β,γ (ERR α,β,γ)
RVR α,β,γ (RVR α,β,γ)
Germ Cell Nuclear Factor (GCNF)
Testicular Orphan Receptor (TR 2,4) Hepatocyte Nuclear Factor 4 (HNF4)
Chicken Ovalbumin Upstream Promoter Transcription Factor α, β, γ (COUP-TF α, β, γ)