The Relationship Between KLF5 and PPARα in the Heart

It’s Complicated

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The heart consumes a significant amount of ATP to maintain its contractile performance, and fatty acid oxidation (FAO) serves as a primary source of energy in the adult heart. Research in the past several decades has demonstrated that the nuclear receptor family, in particular peroxisome proliferator-activated receptor α (PPARα), is a major transcriptional mechanism regulating expression of proteins involved in fatty acid metabolism. Although much progress has been made in understanding the functional role of PPARα in cardiac physiology and disease, less is known about the regulation of PPARα itself. PPARα-mediated transcriptional cascades are determined by the level of PPARα expression as well as its activity. Long chain fatty acids and synthetic ligands, such as fibrates, increase the transcriptional activity of PPARα in multiple cell types, including cardiac myocytes. The endogenous ligands of PPARα are still debated but evidence indicates that they may be associated with triglyceride lipolysis. Expression of PPARα in the heart changes during the development, and under multiple pathological conditions, including heart failure and diabetes mellitus. However, the mechanism(s) underlying these changes are poorly understood. In this issue of Circulation Research, Drosatos et al report that Krüppel-like factor 5 (KLF5) regulates the transcription of PPARα in the heart (Figure).

KLFs are a family of zinc-finger DNA-binding proteins known to be heavily involved in gene expression during development, but their role in adult organ/tissue is just begun to be revealed. KLF5 has been shown to regulate lipid metabolism in noncardiac tissue, such as lung development and adipogenesis. In the heart, KLF5 was found to promote cardiac hypertrophy by driving platelet-derived growth factor-A expression and transactivating insulin-like growth factor 1 (IGF-1) in fibroblasts. Using both gain- and loss-of-function approaches, Drosatos et al in this study showed that KLF5 regulates the expression of PPARα in the heart. A binding site of KLF5 was mapped to the promoter region of PPARα. ChIP assay demonstrated the binding of KLF5 to the site in the cardiac muscle cell line (HL-1) during adenovirus-mediated overexpression of KLF5, which is associated with increased PPARα expression (Figure). Furthermore, cardiac-specific deletion of KLF5 in mice led to decreased expression of PPARα and its target genes with concomitant decrease of FAO. The evidence collectively identifies KLF5 as a positive regulator of FAO in the heart via the transcription of PPARα.

Does the regulation of PPARα by KLF5 play a role in heart disease? The study examined 2 pathological conditions in which PPARα was downregulated in the heart, sepsis, and diabetes mellitus. In mouse models of both type I (streptozotocin injection) and type II (db/db and ob/ob mice) diabetes mellitus, the study found a nice parallel change of KLF5 and PPARα expression in the heart. It also showed that the downregulation of KLF5-PPARα in the early stage of diabetes mellitus could be restored by normalizing blood glucose levels (Figure). The relationship of hyperglycemia and KLF5 expression, however, seemed to be more complex in these models because a rebound of KLF5-PPARα level occurred at later stage of diabetes mellitus, despite persistent hyperglycemia. Future studies determining the causal relationship and the molecular mechanisms are clearly warranted. Nevertheless, these observations provide an interesting new direction to dissect the regulation of PPARα in the diabetic heart. Although increased FAO has been consistently observed in diabetic hearts, the level of PPARα varies significantly depending on the model and the severity of disease. It is worth testing whether the biphasic change of KLF5–PPARα is another regulator of FAO in the diabetic heart and hence a new target for modulating cardiac metabolism in diabetes mellitus.

PPARα expression is downregulated in the heart in sepsis, which however, was found negatively correlated with KLF5 level. A previous study by the same group showed that c-Jun N-terminal kinase activation during sepsis was responsible for decreases in FAO through PPARα downregulation. Here, they further demonstrated in HL-1 cells treated with lipopolysaccharide that activated c-Jun bound to the same promoter region as KLF5 of the Ppara gene, with c-Jun outcompeting KLF5 leading to suppression of PPARα (Figure). This is an excellent example illustrating the complexity of a delicate molecular dance in the transcriptional regulation. The relative role of each specific regulatory mechanism is dependent on the contribution of other mechanisms, which are probably disease specific. In the clinical setting, sepsis has historically been considered primarily a disorder of acute inflammation, but this paradigm is under reconsideration after several anti-inflammatory interventions failed to improve patient outcomes. The role of metabolic failure in sepsis and cardiac metabolism
Direct measurements of metabolic fluxes are thus necessary for the normalization of PPARα levels and accumulation of lipids in the myocardium of cKO at older age, suggesting defective energy metabolism despite the normalization of PPARα and its target gene expression. Direct measurements of metabolic fluxes are thus necessary to further dissect the metabolic mechanisms responsible for contractile dysfunction in cKO.

This work adds a much needed insight into how PPARα gene expression is regulated in the heart, but also raises many additional questions. The authors showed clearly that KLF5 and c-Jun have opposing regulatory actions on PPARα expression in cKO hearts. This is especially important because of the fact that PPARα and downstream gene expression returns to normal levels after 9 months of age in the cKO hearts when reduced ATP content and increased triglyceride deposition occur; pointing to potential consequences of KLF5 loss outside of PPARα down-regulation. The authors did indeed identify significant gene expression changes of many pathways in cKO hearts. Microarray data showed that deletion of KLF5 led to increase expression of 228 genes and decrease expression of 79 genes with the compliment and coagulation cascade pathway being the most affected, suggesting a much broader effect of KLF5 deficiency outside of PPARα regulation and opened up a swath of possibilities by which KLF5 deletion would affect cardiac function.

As with all good science, this line of investigation has opened the door for additional studies. Future experiments will be needed to fully elucidate the mechanism of cardiac dysfunction caused by KLF deficiency, as well as the significance of KLF5-mediated control of PPARα expression in diabetic cardiomyopathy and heart failure. It is exciting to speculate that the regulation of PPARα by KLF5 will be significant in the well-documented downregulation of FAO in heart failure, possibly opening up KLF5 activators or mimetics as a therapeutic target for heart failure.

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None.

References


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