A recent study unveils a fascinating role for an intracellular lipase in cardiac myocytes. The new results demonstrate that liberation of lipid species from myocyte neutral lipid stores results in activation of the nuclear receptor peroxisome proliferator-activated receptor \(\alpha\) (PPAR\(\alpha\)) and the transcriptional coactivators, PPAR\(\gamma\) coactivator 1 (PGC-1) \(\alpha\) and \(\beta\), chief regulators of cardiac mitochondrial fat burning capacity. Deficiency of this lipase in mice causes a cardiomyopathy with myocyte lipid accumulation and mitochondrial dysfunction.

The adult mammalian heart burns enormous quantities of fatty acids (FA) to meet its high energy demand. FA import, storage, and oxidation must be tightly coordinated to maintain cardiac myocyte lipid balance while yielding sufficient fuel supply. Significant progress has been made in the delineation of gene regulatory networks involved in the coordinate control of myocyte FA uptake and oxidation. The PPARs, which belong to a family of nuclear receptor transcription factors, have been shown to regulate the expression of almost every protein and enzyme involved in cellular FA import and oxidation pathways, the latter taking place in the mitochondria, and to a lesser extent in peroxisomes. The PPARs are activated by endogenous lipid ligands, the identity of which remains unknown in the myocyte. However, little is known about the regulatory mechanisms that link myocyte lipid storage with downstream pathways involved in FA catabolism.

A recent study by Haemmerle et al.\(^2\) sheds light on how the myocyte neutral lipid storage depot communicates with downstream FA utilization pathways. The results of this study suggest that in contrast to the commonly held dogma, myocyte lipid storage is not simply an inert reservoir but actually serves to instruct downstream FA oxidation pathways involved in FA catabolism.

The ATGL-deficient heart also exhibited mitochondrial derangements, including reduced mitochondrial DNA levels, increased size of individual mitochondria, and diminished expression of proteins involved in the activity of complex I and II of the electron transport chain. Moreover, the respiratory capacity of mitochondria isolated from the subasascular fraction of ATGL-deficient hearts was significantly reduced. The mitochondrial abnormalities of the ATGL-deficient heart was shown to be associated with a markedly reduced expression of the transcriptional coactivators PGC-1\(\alpha\) and \(\beta\), inductive “boosters” of a subset of transcription factors, including the PPARs, known to control mitochondrial biogenesis and the coordinate expression of virtually all mitochondrial proteins. Therefore, ATGL deficiency not only leads to a reduction in the capacity for FA oxidation via loss of PPAR\(\alpha\) function but also deactivates the gene regulatory circuitry that controls mitochondrial biogenesis and function in myocytes. Taken together, these results suggested that loss of this lipase function causes an "energy-starved" heart with expanded lipid stores leading to cardiomyopathy.

It was important for Haemmerle et al.\(^2\) to determine whether the observed reduction in PPAR activity in the ATGL-deficient heart was a cause of, or secondary to, the cardiomyopathy. Indeed, it is well known that the capacity for
Fat oxidation is reduced in many forms of heart failure. To address this question, a series of “rescue” strategies in mice were conducted. First, cardiac-specific transgenic overexpression of ATGL in the context of whole-body ATGL deficiency was shown to rescue the cardiac metabolic and functional derangements. Second, exogenous administration of known activators of PPARα but not PPARβ/δ rescued the cardiac phenotype of the ATGL-deficient mice. The PPARα specificity of this latter finding is somewhat surprising, given that both PPARα and PPARβ/δ are highly expressed in the heart and play important roles in regulating genes involved in cardiac lipid and energy metabolism. These results strongly suggest that loss of PPARα signaling is at the root of the cardiomyopathy caused by ATGL deficiency and, surprisingly, that additional pathways exist for the generation of PPARβ/δ ligands in the heart.

This study provides surprising new insights into the mechanisms whereby the cardiac myocyte matches FA import, storage, and utilization. Previous dogma held that myocyte neutral lipid storage droplets simply store excess FA prior to β-oxidation in the mitochondrion. However, the results of the study by Haemmerle et al. suggest that the myocyte neutral lipid depot plays a critical and dynamic role in matching lipid import and storage with oxidation. This is accomplished by the generation of biologically active lipid species that signal to the PPAR/PGC-1 gene regulatory circuit, which in turn controls the capacity for FA utilization and mitochondrial function (Figure). Given that the lipid droplet storage depot presumably changes size and characteristics based on rates of import and utilization, it is a logical barometer or “lipostat” for orchestrating intracellular lipid balance by signaling to downstream catabolic pathways. These new findings also suggest that FA imported into the cardiac myocyte do not directly serve as endogenous activators of PPARα. This latter finding is consistent with that of a study in liver demonstrating that PPARα is activated by newly synthesized lipid ligand rather than FA species that are imported into the hepatocyte. It is tempting to speculate that the specific endogenous lipid ligands for the PPARs are cell-specific, possibly generated by distinct metabolic pathways, each of which could serve as tissue-specific therapeutic targets for modulating fuel and energy metabolism.

What are the clinical implications of these new findings? First, there are known genetic defects in ATGL that cause neutral lipoid storage disease (NLSD) in humans. NLSD leads to cardiomyopathy and hepatic dysfunction characterized by intracellular lipid accumulation. The heart disease of NLSD is often severe, requiring cardiac transplantation. The results of the Haemmerle study suggest that future studies aimed at determining whether activation of the PPARα pathway could prove useful in NLSD may be warranted. Second, it is well known that many acquired forms of heart failure are associated with a reduction in the capacity of the heart to oxidize FA, mitochondrial dysfunction, and, in some cases, myocyte lipid accumulation. The latter is especially true for the cardiac dysfunction that occurs within the setting of obesity and diabetes. Is it possible that the cardiac metabolic and functional abnormalities described in this recent study are relevant to the pathogenesis of common metabolic heart disease? Interestingly, similar to the ATGL-deficient heart, PGC-1 deficiency and mitochondrial dysfunction have been linked to the development of acquired forms of heart failure. However, in the case of the diabetic heart, there is evidence that PPARα is chronically activated, at least in the early stages, contributing to the development of a “lipotoxic” cardiomyopathy. It is likely that further dissection of the mechanisms unveiled in this study could lead to new therapeutic options.

These new results raise several interesting questions that open new avenues for future investigation relevant to the control of cardiac fuel and energy metabolism. First, by what mechanism does PGC-1 signaling become deactivated, leading to mitochondrial dysfunction in the ATGL-deficient heart? It is certainly possible that PPARα itself activates the expression of the PGC-1 genes. Alternatively, biologically active species generated from the neutral lipid storage depot could act on the expression and activity of PGC-1 coactivators. Second, what is the basis for the PPARα versus PPARβ/δ specificity in this response? Are only PPARα ligands generated by hydrolysis of intracellular neutral lipids?
Or do other lipases generate PPAR\(\beta/\delta\) ligands from this depot? Third, is the rescue affected by the administration of pharmacological PPAR\(\alpha\) activators due to mechanisms within the heart or via extracardiac systemic effects? This latter question deserves additional exploration given that the observed rescue by exogenous PPAR\(\alpha\) activators was described for generalized rather than cardiac-specific ATGL-deficient animals.\(^2\)

In summary, the study by Haemmerle et al\(^2\) has unveiled new roles for ATGL and the myocyte lipid storage depot. Dissection of the mechanisms controlling the dynamic nature of the cardiac neutral lipid reservoir show great promise for further elucidation of the mechanisms involved in the control of cardiac myocyte lipid and energy homeostasis relevant to the metabolic basis of myocardial diseases.

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