The Histone Methyltransferase Smyd1 is a Novel Transcriptional Regulator of Cardiac Fatty Acid Metabolism in Mice

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Epigenetic control of metabolism in the healthy and diseased heart remains poorly understood. We recently demonstrated that chromatin-bound Smyd1, a muscle-specific histone methyltransferase, is significantly upregulated in a mouse model of pressure overload-induced heart failure (HF) and that inducible, cardiac-specific Smyd1 knock-out (Smyd1-KO) mice develop cellular hypertrophy and fulminate HF. Bioinformatic analysis of transcripts differentially regulated in these mice revealed that cardiac metabolism was the most perturbed biological function in the heart. However, it was not clear whether alterations in cardiac metabolism were a direct consequence of Smyd1 deletion or were secondary to developed HF. Here we hypothesized that Smyd1 directly regulates cardiac metabolism; the effects of which should be detectable in Smyd1-KO mice before overt cardiac dysfunction. To test this hypothesis we performed unbiased metabolomic analysis of Smyd1-KO mice using GC/MS and MS/MS (n=9 control, n=10 KO) combined with targeted gene expression analysis. Our results showed significant changes in the metabolic profile of Smyd1-KO mice at the earliest time point (3 weeks after tamoxifen treatment) in which Smyd1 protein expression was significantly reduced while cardiac function remained normal. The most profound difference, in energetics-associated pathways in these mice, was found in fatty acid β-oxidation, manifested by the decreased myocardial content of carnitine and free fatty acids and downregulation of their transporters, OCTN2 and CD36. In addition, mRNA levels of the PPAR-α complex (PPAR-α;RXR-α;PGC-1α), an established regulator of fatty acid β-oxidation, and its target genes (CPT1b;CD36;Acox1;MCAD) were significantly reduced in Smyd1-KO mice prior to the onset of cardiac dysfunction (all $p<0.05$). To identify whether Smyd1 directly controls gene expression of PPAR-α, we examined the PPAR-α loci using chromatin-immunoprecipitation followed by qPCR and observed significant binding of Smyd1 upstream of the PPAR-α transcriptional start site. Overall, this study identifies Smyd1 as a novel regulator of fatty acid metabolism and suggests that Smyd1 controls cardiac energetics directly by regulating gene expression of PPAR-α.

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