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# ULK1 Prevents Cardiac Dysfunction in Obesity Through Autophagy-Meditated Regulation of Lipid Metabolism

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Autophagy is essential to maintain tissue homeostasis, particularly in long-lived cells such as cardiomyocytes. Whereas many studies support the importance of autophagy in the mechanisms underlying obesity-related cardiac dysfunction, the role of autophagy in cardiac lipid metabolism remains unclear. In the heart, lipotoxicity is exacerbated by cardiac lipoprotein lipase (LPL), which mediates accumulation of fatty acids to the heart through intravascular triglyceride (TG) hydrolysis.

In both genetic and dietary models of obesity, we observed a substantial increase in cardiac LPL protein levels without any change in messenger ribonucleic acid (mRNA). This was accompanied by a dramatic down-regulation of autophagy in the heart, as revealed by reduced levels of unc-51 like kinase-1 (ULK1) protein. To further explore the relationship between cardiac LPL and autophagy, we generated cardiomyocyte-specific knockout mice for ulk1 (Myh6-cre/ulk1$^{fl/fl}$), Lpl (Myh6-cre/Lpl$^{fl/fl}$), and mice with a combined deficiency (Myh6-cre/ulk1$^{fl/fl}$Lpl$^{fl/fl}$). Similar to genetic and dietary models of obesity, Myh6-cre/ulk1$^{fl/fl}$ mice had a substantial increase in cardiac LPL levels. When these mice were fed a high-fat diet (HFD), they showed elevated cardiac TG levels and deterioration in heart function. However, with combined deletion of LPL and ULK1 in Myh6-cre/ulk1$^{fl/fl}$ Lpl$^{fl/fl}$ mice, HFD feeding did not lead to alterations in levels of TG or diacylglycerol, or in cardiac function. To further elucidate the role of autophagy in cardiac lipid metabolism, we infused a peptide that enhanced autophagy (D-Tat-beclin1). This effectively lowered LPL levels at the coronary lumen by restoring autophagy in the genetic model of obesity. This decrease in cardiac luminal LPL was associated with a reduction in TG levels and recovery of cardiac function.

These results provide clear evidence of the critical role of modulating cardiac LPL activity through autophagy-mediated proteolytic clearance as a potential novel strategy to overcome obesity-related cardiomyopathy.