SIRT1, a protein deacetylase, contributes to mitophagy by promoting autophagosome-lysosome fusion in the cardiomyocyte.

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Background: Damaged mitochondria is removed by autophagy. This process includes engulf of mitochondria by autophagosomes and degradation of autophagosomes by lysosomes. We recently reported that activation of SIRT1, a protein deacetylase, promotes autophagosome degradation and reduces damaged mitochondria in the heart of a mouse model of muscular dystrophy. Here, we examined how SIRT1 participates in mitochondrial autophagy (mitophagy) in the cardiomyocyte.

Methods and Results: Mitophagy was induced by CCCP (20 μM), a mitochondrial uncoupler, in H9c2 cardiomyocytes. Western blotting showed that levels of succinate dehydrogenase B and cyclophilin F, mitochondrial proteins, were reduced by CCCP. These reductions in mitochondrial proteins were significantly blocked by siRNA-mediated SIRT1 knockdown (KD). CCCP increased level of LC3-II, an autophagosome marker; however, LC3-II level was rather increased in SIRT1 KD cells, suggesting a role of SIRT1 in autophagosome degradation. Mitophagosomes defined as autophagosomes (LC3 dots) including fragmented mitochondria (Tomm20) in immunostaining were increased by CCCP. In contrast, SIRT1 KD promoted accumulation of mitophagosomes compared with control cells, suggesting disturbance of mitophagosome clearance. Finally, CCCP-induced autophagosome-lysosome fusion analyzed by colocalization of LC3 dot and LAMP1, a lysosome marker, was significantly suppressed by SIRT1 KD.

Conclusion: These findings suggest that SIRT1 plays a role in mitophagy at autophagosome-lysosome fusion in cardiomyocytes.