Yap Plays a Crucial Role in the Development of Cardiomyopathy in Lysosomal Storage Diseases

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Rag proteins play a critical role in regulating lysosomal functions. Muscle-specific deletion of RagA and RagB (Rag A/B) results in lysosomal dysfunction, suppression of autophagy, and development of cardiomyopathy, reminiscent of lysosomal storage diseases (LSDs). We investigated the molecular mechanism by which cardiomyopathy is developed in RagA/B knockout (KO) mice. We generated cardiac-specific Rag A/BKO (RagA/BcKO) mice using αMHC-Cre. Similar to the muscle-specific KO mice, RagA/BcKO mice showed prominent cardiac hypertrophy (heart weight (HW)/ tibial length (TL): 12.35 ± 0.41 vs. 7.12 ± 0.15, $p< 0.01$) at 3 months of age. RagA/BcKO mice exhibited significantly greater phospho-histone H3-positive cardiomyocytes than control mice, suggesting that cardiomyocyte proliferation is stimulated in RagA/BcKO mice. However, RagA/BcKO mice exhibited a significantly smaller percentage of fractional shortening (%FS: 23.0 ± 0.82 vs. 45.8 ± 1.06, $p< 0.01$) and significantly greater mortality than control mice (50% vs. 0%, $p<0.01$). RagA/BcKO mouse hearts showed upregulation of β-MHC and α-smooth muscle actin, indicating de-differentiation. Yes-associated protein (YAP) is a transcription co-factor that controls growth and survival and is a key downstream target of the Hippo pathway. YAP associates with p62/SQSTM1 and is degraded through autophagy. YAP is significantly more accumulated (5.9-fold, $p<0.05$) in RagA/BcKO mouse hearts, where autophagy is inhibited and p62/SQSTM1 is accumulated, than in control hearts. In order to elucidate the role of YAP in mediating cardiomyopathy, we crossed RagA/BcKO mice with cardiac-specific heterozygous YAPKO mice. Heterozygous deletion of YAP in RagA/BcKO mice reduced the heart size (HW/ TL: 9.12 ± 0.10 vs. 11.9 ± 0.27, $p< 0.05$) and improved cardiac function (%FS: 35.0 ± 2.89 vs. 24.0 ± 0.58, $p< 0.05$) in RagA/BcKO mice. Pharmacological inhibition of YAP by verteporfin treatment also suppressed cardiac hypertrophy (HW/ TL: 8.92 ± 0.11 vs. 12.09 ± 0.30, $p< 0.05$) and heart failure (%FS: 33.3 ± 2.29 vs. 23.3 ± 0.63, $p< 0.05$) in RagA/BcKO mice. These results indicate that YAP plays a crucial role in the development of cardiomyopathy in RagA/BcKO mice, a mouse model of LSDs.

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