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Lamp-1 overexpression rescues cardiomyopathy in Lamp-2 deficient cells by correcting cellular lysosomal function

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Danon disease is a rare disorder characterized by a clinical triad of hypertrophic cardiomyopathy, skeletal myopathy and mental retardation, which is caused by a mutation in the gene encoding lysosome-associated membrane protein 2 (Lamp-2). *Lamp*2 KO mice, the mouse model of Danon disease, have massive hypertrophic cardiomyopathy and mild myopathy. In hepatocytes, reduced lysosomal protein degradation and retarded autophagic process were reported.

In this study, we examined whether the phenotype of Lamp-2 deficiency can be rescued by overexpression of Lamp-1, which is a homologue molecule with 37% identity in amino acid to Lamp-2. We generated *Lamp1*-Tg mice, in which Lamp-1 was overexpressed in various organs and crossed with *Lamp*2 KO mice (*Lamp2*KO*Lamp1*-Tg). In our results, cardiomyocyte hypertrophy and fibrosis was observed in *Lamp*2 KO mice. In contrast, *Lamp2*KO*Lamp1*-Tg showed remarkable improvement in these phenotypes. These results indicate that overexpression of *Lamp1* can rescue cardiomyopathy in *Lamp2* KO mice.

Using fibroblasts from wild-type, *Lamp*2KO, and *Lamp2*KO*Lamp1*-Tg mice, we analyzed the lysosomal function and autophagic process at cellular level. Degradation of long-lived proteins was impaired in *Lamp2*KO cells, however the rate of degradation was recovered with overexpression of Lamp-1. Starvation-induced autophagic flux and its progression were measured by using acidotropic dye tracer, Lysotracker. Autophagic flux was not different among three mouse cells, while retardation of autophagic progression was observed in only *Lamp2*KO cells. Electron microscopic analysis also supported this finding.

Our results indicate that overexpression of Lamp-1 rescues the autophagic progression as well as lysosomal function in *Lamp2*KO cells.

ダノン病は、リソソーム膜タンパク質のひとつ **LAMP2** の変異が原因でおこる遺伝性筋疾患である。リソソームは細胞内のタンパク質分解に重要な役割をはたす小器官で、その膜の大部分は **LAMP2** と **LAMP1** という構造的に類似したタンパク質で構成されている。本研究で我々は、ダノン病モデルマウスである **LAMP2** 欠損マウスに、**LAMP1** を過剰に発現させることで、ダノン病の治療の可能性を報告した。