Abstract: The novel mitophagic receptor protein bcl2-like protein 13: new insights for the molecular mechanisms of the pathogenesis of heart disease

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Cardiac function highly depends on energy generated by mitochondria, which are injured by various stresses such as pressure overload or aging. Damaged mitochondria in failing hearts are removed by a mitochondria-specific autophagy, called mitophagy. Dysregulation of mitophagy is implicated in the pathogenesis of heart disease such as heart failure. Mitochondrial morphologies change continuously through actions of mitochondrial dynamics (fission and fusion) and mitophagy is closely associated with mitochondrial fission to make mitochondria engulfable size by autophagosomes.

Atg32 is an essential protein for mitophagy in yeast. Some molecules have been reported to be involved in mitophagy, such as Parkin, FUNDC1 and Bnip3l. However, no Atg32 homologue has been identified in mammalian cells. We hypothesized that an unknown mammalian mitophagy receptor will share the molecular features with Atg32. By screening a public protein database for Atg32 homologues, we identified Bcl-2-like protein 13 (Bcl2-L-13).

Initially, we examined the function of Bcl2-L-13 in cardiomyocytes from 1-day-old Wistar rats. Forty-eight hours after infection of cardiomyocytes with an adenoviral vector expressing Bcl2-L-13, mitochondrial fragmentation was induced. In contrast, knockdown of Bcl2-L-13 induced mitochondrial elongation.

We carried out further investigation into functions of Bcl2-L-13 using cell lines. Bcl2-L-13 is localized at the mitochondrial outer membrane and bound to LC3 through the WXXI motif and induced mitochondrial fragmentation and mitophagy. In Bcl2-L-13, the BH domains are important for mitochondrial fragmentation, while the WXXI motif facilitates mitophagy. Bcl2-L-13 induces mitochondrial fragmentation in the absence of Drp1 which is the master regulator of mitochondrial fission, while it induces mitophagy in Parkin-deficient cells.

Next, we investigated physiological function of Bcl2-L-13. Knockdown of Bcl2-L-13 attenuated CCCP (carbonyl cyanide m-chlorophenyl hydrazone) -induced fragmentation and mitophagy. CCCP upregulated the phosphorylation level of Bcl2-L-13 Ser272 and Ser272Ala mutant showed less ability for inducing mitophagy. Considering of these, phosphorylation of this protein may regulate its activity. Furthermore, Bcl2-L-13 completely restored mitophagy in atg32-deficient yeast, suggesting that Bcl2-L-13 is a mammalian functional homologue of Atg32.

Our findings thus offer novel insights into molecular mechanisms of the pathogenesis of heart disease.