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Rambo and Heart Failure

Murakawa T, Yamaguchi O, Hashimoto A, Hikoso S, Takeda T, Takafumi Oka, et al. Bcl-2-like protein 13 is a mammalian Atg32 homologue that mediates mitophagy and mitochondrial fragmentation. **Nature Communications, 2015;6:7527.http://doi.org/6cn**

The Bcl-Rambo protein (also known as Bcl2-L-13) received its name from a group of Japanese scientists because it was thought to participate in activating apoptotic cell death. However, it seems that the "Rambo" movie character protein counterpart has actually been misjudged. New research shows for the first time that Bcl-Rambo protein may not be so "violent" after all, and might actually be involved in protective processes implicated in heart failure.

Mitochondria are subcellular organelles that generate energy through oxidative phosphorylation. Dysregulated mitochondrial activity results in generation of reactive oxygen species, causing damage to DNA and proteins. Thus, mitochondrial "quality control" is essential for normal cellular homeostasis. Autophagy is responsible for mitochondrial "quality control". There are two types of autophagy, non-selective and selective autophagy. Non-selective autophagy sequesters bulk cytoplasm and organelles; in contrast, selective autophagy targets proteins or organelles with specific cargos, such as mitochondria and peroxisomes. The degradation of damaged mitochondria is called mitophagy. This cellular process may be triggered by nutrient restriction and also under low oxygen. It may be aimed to eliminate dysfunctional mitochondria or as "quality control" in case of defective biogenesis, to avoid damaged mitochondria from producing excessive reactive oxygen species with potential harmful effects for the rest of the cell. Finally, mitophagy can be a normal process in the development of some cells; for example, it is necessary for reticulocyte conversion into erythrocytes or for lymphocyte T maturation. An abnormally high mitophagy rate is seen in some diseases, as Parkinson´s disease and heart failure, which might be relevant in the pathogeny of both diseases.

The present study revealed that Bcl2-L-13 (Rambo) protein is localized in the external mitochondrial membrane and interacts with other proteins facilitating mitophagy. Although the exact mechanism by which Bcl2-L-12 mediates mitophagy is not fully understood, the authors speculate that Bcl2-L-13 recruits LC3 protein to the surface of mitochondria leading to the formation of a mitochondria-specific autophagosome (mitophagosome). Thus, it is possible that Bcl1-L-13 induces mitophagy as a consequence of mitochondrial fragmentation; however, further studies are needed to elucidate this point.

We now know for the first time that the Bcl-Rambo protein is implicated in the process of mitophagy in mammalian cells. Since mitophagy is involved in heart failure, there is need to know more about molecules and participating pathways to search for a treatment. The discovery of the importance of Bcl-Rambo protein goes in this direction and represents an important step towards the understanding of the disease processes at the cellular level. The investigation, published in Nature Communications, will open the doors to develop new therapies to improve the prognosis of individuals suffering from heart failure.