LC3/GABARAP interaction with cardiolipin: Implications for mitophagy

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Mitochondria are essential organelles for the regulation of cellular energy homeostasis and cell death. The elimination of damaged mitochondria through selective autophagy (mitophagy) is therefore critical for maintaining proper cellular functions. How the cell recognizes dysfunctional cellular components which should be degraded is still unclear. The phospholipid cardiolipin (CL) has been proposed to play a role in selective mitochondrial degradation. CL externalization to the outer mitochondrial membrane would act as a signal for the autophagic machinery to start the process, in which the LC3B protein would be involved. This protein belongs to LC3/GABARAP family, composed of the six orthologs of yeast protein Atg8 identified as yet in mammals. The existence of this variety of closely related proteins raises the question of whether each of them has a different role in autophagy, either in the selection of cargos or in the various steps of autophagosome biogenesis. In order to explore which of the orthologs could be involved in mitophagy, we have performed a quantitative analysis of CL interaction with the LC3/GABARAP family members LC3A, LC3B, LC3C, GABARAP, GABARAPL1, GABARAPL2, using model membranes. Furthermore an *in vivo* approach has been carried out to determine the co-localization of these proteins with mitocondria in cells, upon induction of mitophagy by rotenone, a mitochondrial complex I inhibitor that induces CL externalization to the outer mitochondrial membrane. We have observed that LC3A, LC3B and LC3C but not GABARAP or GABARAPL2 interact with CL-containing vesicles. Moreover, in human glioblastoma cells rotenone-induced autophagy leads to LC3B translocation to mitochondria and subsequent delivery of mitochondria to lysosomes. Our results support the notion that each human Atg8 ortholog might play a specific role in different autophagic processes.

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