Another face of cell death

Comment on: Sheibani S, et al. Cell Cycle 2014; 13: 138–47; PMID:24196447; http://dx.doi.org/10.4161/cc.26885

Luis A Rokeach*, Mehdi Jbel, and Dominic Dulude; Department of Biochemistry and Molecular Medicine; Université de Montréal; Montréal, Québec, Canada; *Email: luis.rokeach@umontreal.ca; http://dx.doi.org/10.4161/cc.27302

For multicellular organisms, cell death can be as important as life itself. Programmed cell death (PCD) plays key roles during embryonic development by eliminating superfluous cells. In adult organisms, the homeostasis of tissues partly depends on eliminating damaged cells by PCD; otherwise, severe consequences can ensue. For instance, failure to eliminate damaged cells may lead to cancer.

The term programmed in PCD implies the orderly intervention of gene products in the execution of cell death following an intrinsic or an extrinsic signal. PCD also infers regulated forms of death as opposed to accidental. As such, it is possible to alter the net outcome of PCD by genetically modifying the levels/activities of the intervening gene products.

Initially, PCD was classified into 3 major types: apoptosis, autophagic cell death, and programmed necrosis.[1] This classification was based mostly on morphological differences between cells committed to these different forms of PCD. More recently, the inclusion of biochemical markers in the classifications of PCD has portrayed a more complex picture, composed of different facets of cell death, each involving diverse modules of the 3 main suicide pathways.[2]

Interestingly, in this issue of *Cell Cycle*, Sheibani et al.[3] report a new form of PCD that they call "liponecrosis." In previous work, the authors have assessed the effect of palmitoleic acid (POA) on the viability of *Saccharomyces cerevisiae*, and have demonstrated that a short exposure (2 h) to this fatty acid severely reduces clonogenicity.[4,5]

In the current work, the authors investigate the death mechanism induced by exposure to POA. Previously, they observed that a *pex5Δ* mutation, which impairs peroxisomal fatty acid oxidation, enhanced the POA-death phenotype. This observation suggested that healthy mitochondria might be required to protect cells from this type of death, leading to the hypothesis that macromitophagy could be involved in the defense against POA-induced lethality. To test this hypothesis, the authors examined the *ATG32* gene that is specifically involved in macromitophagy.[6,7] The results were conclusive; an *atg32Δ* strain is more sensitive to death triggered by POA. Interestingly, the reduction of cell viability by the POA mechanism appears to progress with the chronological age of a yeast cell, indicating that it is an age-related modality of cell death. Atg1p is a serine/threonine kinase protein kinase that orchestrates macroautophagy; the en masse degradation of components and organelles of the cell.[8] Macroautophagy has a pro-survival function against apoptotic death, by eliminating damaged molecules and organelles, which are the cause of apoptosis. As the authors show, the *atg1Δ* mutation significantly reduces clonogenic survival of yeast cells submitted to apoptosis induced by exposure to H_2O_2. In stark contrast, the knock-out of the Atg1p encoding gene reduces the lethality induced by POA; indicating its role in the execution of this form of death. Moreover, that POA-triggered death can be altered genetically indicates that it is a form of PCD.

But how is POA-induced death related to the known major forms of PCD? Rather interestingly, POA-induced mortality significantly differs from the currently known major forms of PCD, i.e., apoptosis, regulated necrosis, and autophagic cell death. In fact, liponecrosis presents a unique set of characteristic death markers: (1) Unlike apoptotic cells, liponecrotic cells do not show nuclear fragmentation nor phosphatidylserine exposure on the cell membrane; (2) Unlike necrotic cells, liponecrotic cells do not exhibit plasma membrane rupture; (3) Like necrotic cells, however, liponecrotic cells do show increased permeability to propidium iodide (PI); (4) In contrast to cells undergoing autophagic death, liponecrotic cells do not display massive cytoplasmic vacuolization. However, both types of death depend on Atg1p; (5) As a unique feature of liponecrotic death, cells accumulate large numbers of lipid droplets (LD), a hallmark that has not been observed in another types of cell death. LD serve as deposition sites for non-esterified fatty acids and sterols. According to Sheibani et al., LD protect cells from liponecrotic death, and functional mitochondria are needed for the accumulation of LD, as mitochondria produce the energy needed for this pro-survival mechanism. In this context, macromitophagy would maintain a population of functional mitochondria for such a survival process.

The authors integrate their findings into a working model, part of which is reproduced in the accompanying figure. Distinctive regulatory features in this model are the roles of the autophagy gene Atg32p in providing healthy mitochondria for cell survival, and Atg1p as an orchestrator in liponecrotic PCD.

In future directions, it will be of interest to elucidate how the particular features of liponecrotic death integrate with other modules of the PCD network. It will be also interesting to fathom how these findings in the *S. cerevisiae* model translate into human health and diet (**Fig. 1**).
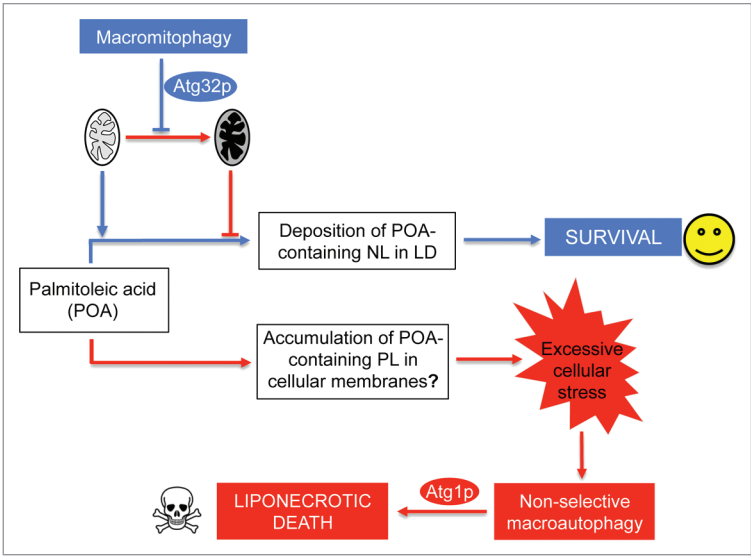
Figure 1. Red arrows indicate pro-death processes; blue arrows indicate pro-survival processes; red Atg1p symbolizes its pro-death role; blue Atg32p indicates its pro-survival role; functional mitochondria are symbolized in pale gray, and dysfunctional mitochondria are symbolized as dark gray and black.

References

1. Kroemer G, et al.; Nomenclature Committee on Cell Death. Cell Death Differ 2005; 12(Suppl 2):1463-7; PMID:16247491; http://dx.doi.org/10.1038/sj.cdd.4401724
2. Galluzzi L, et al. Cell Death Differ 2012; 19:107-20; PMID:21760595; http://dx.doi.org/10.1038/cdd.2011.96
3. Sheibani S, et al. Cell Cycle 2014; 13; http://dx.doi.org/10.4161/cc.26885
4. Goldberg AA, et al. Aging (Albany NY) 2010; 2:393-414; PMID:20622262
5. Burstein MT, et al. Cell Cycle 2012; 11:3443-62; PMID:22894934; http://dx.doi.org/10.4161/cc.21754
6. Kanki T, et al. Dev Cell 2009; 17:98-109; PMID:19619495; http://dx.doi.org/10.1016/j.devcel.2009.06.014
7. Okamoto K, et al. Dev Cell 2009; 17:87-97; PMID:19619494; http://dx.doi.org/10.1016/j.devcel.2009.06.013
8. Reggiori F, et al. Genetics 2013; 194:341-61; PMID:23733851; http://dx.doi.org/10.1534/genetics.112.149013