

Have you seen?

Unsaturated fatty acid-induced non-canonical autophagy: unusual? or unappreciated?

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The breakdown of cellular components via autophagy is crucial for cellular homeostasis. In this issue of *The EMBO Journal*, Niso-Santano *et al* (2015) report the important observation that feeding cells with saturated or unsaturated fatty acids triggers mechanistically distinct autophagic responses. Feeding cells saturated fatty acid induced the canonical, BECN1/PI3K-dependent autophagy pathway. Conversely, the unsaturated fatty acid oleate triggered autophagic responses that were independent of the BECN1/PI3K complex, but that required a functional Golgi system.

See also: **M Niso-Santano *et al*** (April 2015)

We all understand that maintaining an orderly household requires timely removal of accumulated garbage and, for the environmentally conscious among us, the recycling of waste items from which useful materials can be recovered and reused. Cells engage in analogous activities, and autophagy is an integral part of the larger waste recycling strategy. Autophagy, the process of cellular “self-digestion”, was initially described by Christian de Duve, was outlined in molecular terms primarily by Yoshinori Ohsumi and colleagues, and was initially characterized as a cellular strategy for maintaining proteostasis and responding to nutrient stress (Deter *et al*, 1967; Mizushima *et al*, 2011). While such a self-consumption system has its uses, it needs to be tightly regulated to avoid autophagy-mediated cell death. More than 30 autophagy gene products are therefore involved in the

tightly choreographed biogenesis of the membrane structures that enclose the cargo to be degraded and recycled, and this process is under negative control by the TOR nutrient sensor kinase (Mizushima *et al*, 2011).

Definition of what constitutes canonical versus non-canonical is driven by historical precedent above all else. For the purposes of this discussion, the canonical autophagy pathway is characterized by a complex series of membrane biogenetic steps that result in formation of the autophagosome (i.e. the structure that engulfs and sequesters the cytoplasmic cargo marked for degradation) (Fig 1). The Beclin/phosphatidylinositol-3-phosphate (BECN/PI3K) complex is recruited to the nascent autophagosome where it produces a pool of phosphatidylinositol-3-phosphate, thereby marking the forming membrane for targeting to lysosomes. This phosphoinositide pool also organizes the events that culminate in lipidation of the autophagy protein LC3 in preparation for fusion of the double-membrane autophagosome to lysosomes. Lipidation of LC3 is a signature autophagic event, and it became apparent early on that autophagy was not solely a nutrient scavenging pathway, but one that also efficiently clears damaged organelles from the cytoplasm (Dunn *et al*, 2005; Youle & Narendra, 2011).

The ability of autophagy to sequester and clear large particles from the cytoplasm has broader implications as evidenced by the discovery of non-canonical autophagy pathways. One such example involves host defense strategies in the ever-escalating arms race between host and pathogen where

phagocytes evolved a dedicated plasma membrane-localized autophagy pathway that channels incoming pathogens into rapidly maturing autophagosomes (Levine, 2005; Mehta *et al*, 2014). This pathway counters the strategies used by intracellular pathogens to encourage their entry into cells and to subsequently inhibit maturation of conventional phagolysosomes so that these organelles are co-opted as suitable microenvironments for pathogen propagation. These immune response applications are classified as non-canonical autophagy pathways because the action is initiated at the plasma membrane, and the operant autophagosomes are systems enclosed by a single membrane. While the pathway remains dependent on the BECN/PI3K complex, it is neither dependent on components of the canonical autophagy pre-initiation complex nor is it subject to control by the TOR nutrient sensor kinase (Mehta *et al*, 2014). Such a non-canonical LC3-associated phagocytosis pathway (LAP) more generally promotes immune responses by facilitating antigen presentation, by regulating interferon production, and by dampening inflammation potential by clearing cell corpses (Mehta *et al*, 2014) (Fig 1).

The non-canonical pathway described by Niso-Santano *et al* (2015) shares some features with LAP in that it too does not require the canonical pre-initiation machinery for autophagosome formation. It is fundamentally distinct from the LAP pathways, however, as it demands a functional Golgi system, and is independent of any BECN/PI3K requirement (Fig 1). While a BECN/PI3K-independent autophagic response had

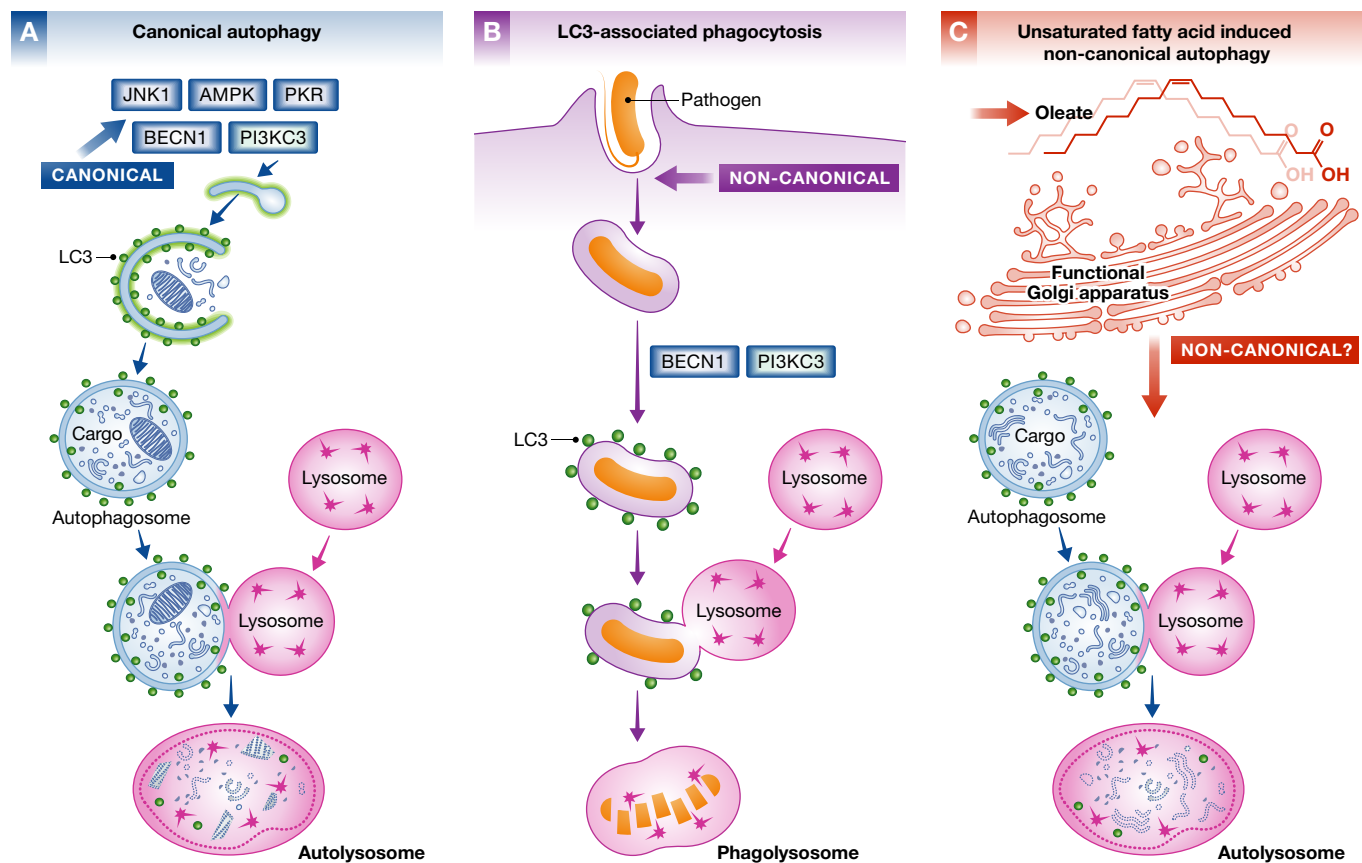


Figure 1. Canonical and non-canonical autophagy pathways.

Canonical autophagic pathway (A) involves different components than the LC3-associated phagocytosis pathway (B) and the oleate-induced non-canonical autophagic pathway (C).

previously been described in the context of promoting death of cells unable to resolve stress (Galluzzi *et al*, 2015), the pathway described by Niso-Santano *et al* (2015) seems different. It is responsive to TOR-mediated control, and this would be a curious feature for a pathway dedicated to removal of a failed cell. Clues as to why the pathway described by Niso-Santano and colleagues exists might be forthcoming from demonstrations that a non-immune system version of LAP is critical in the retinal epithelium for phagocytosis of shed photoreceptor outer segments, that is, a high flux membrane turnover system intrinsic to the normal biology of rod and cone cells (Kim *et al*, 2013). Interestingly, this LAP executes a significant recycling function for salvaging retinoids from spent outer segments so as to maintain chromophore homeostasis in the retinal pigment epithelium. Thus, the non-canonical autophagy pathway described by Niso-Santano *et al* (2015) might represent an ancient mechanism for the recycling of

critical lipophiles from damaged membranes and exogenous sources. Perhaps there exists a series of privileged autophagic systems, devoted to just such purpose, that operate in an organelle-specific manner. Such parallel autophagic recycling systems might contribute to the difficulties confronting experimental identification of the birth organelle for autophagosomal membranes (Lamb *et al*, 2013).

The demonstration that unsaturated fatty acids such as oleate induce non-canonical autophagic pathways that are conserved from yeast to mammals further expands the already impressive versatility of autophagy. It also provokes interesting questions regarding the physiological roles of such a curious non-canonical autophagy and awaits a better molecular characterization of the underlying pathway. The ancient origins of this non-canonical pathway argue some fundamental function and suggest the cardinal features of the pathway are not so much unusual as they are unappreciated.

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