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COMMENTARY

Membrane dynamics in autophagosome biogenesis

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ABSTRACT

Bilayered phospholipid membranes are vital to the organization of the living cell. Based on fundamental principles of polarity, membranes create borders allowing defined spaces to be encapsulated. This compartmentalization is a prerequisite for the complex functional design of the eukaryotic cell, yielding localities that can differ in composition and operation. During macroautophagy, cytoplasmic components become enclosed by a growing double bilayered membrane, which upon closure creates a separate compartment, the autophagosome. The autophagosome is then primed for fusion with endosomal and lysosomal compartments, leading to degradation of the captured material. A large number of proteins have been found to be essential for autophagy, but little is known about the specific lipids that constitute the autophagic membranes and the membrane modeling events that are responsible for regulation of autophagosome shape and size. In this Commentary, we review the recent progress in our understanding of the membrane shaping and remodeling events that are required at different steps of the autophagy pathway.

This article is part of a Focus on Autophagosome biogenesis. For further reading, please see related articles: 'ERES: sites for autophagosome biogenesis and maturation?' by Jana Sanchez-Wandelmer et al. (*J. Cell Sci.* **128**, 185-192) and 'WIPI proteins: essential PtdIns3*P* effectors at the nascent autophagosome' by Tassula Proikas-Cezanne et al. (*J. Cell Sci.* **128**, 207-217).

KEY WORDS: Atg, PtdIns3*P*, Autophagosome, Phagophore

Introduction

Macroautophagy, hereafter referred to as autophagy, is the best characterized form of autophagy and has been implicated in a diverse set of physiological and pathophysiological conditions. Autophagy was for a long time considered to be a non-selective cell survival process, involving random sequestration of cytoplasmic material into forming autophagosomes, but it is now evident that autophagy also plays an essential quality control function by selective removal of damaged or dysfunctional organelles, as well as protein aggregates and pathogens (Stolz et al., 2014). The pathway initiates with the nucleation of a double-membraned structure (the phagophore, also called the isolation membrane), which expands to engulf cytoplasm into a double-membraned vesicle (autophagosome). Fusion of the autophagosome with lysosomes leads to degradation of the sequestered material and the recycling of degradation products into new macromolecules (Klionsky and Codogno, 2013; Lamb et al., 2013) (Fig. 1).

A large number of autophagy-related (Atg) proteins have been identified and found to be essential for both the non-selective and selective types of autophagy (see Box 1) (Klionsky et al., 2011). Recent progress in the field has made it clear that Atg proteins act together with general membrane trafficking components, such as coat proteins, soluble N-ethylmaleimide-sensitive factor (NSF) attachment protein receptor (SNARE) proteins and RAB proteins. Membrane shaping and remodeling are required at several steps of the autophagy pathway (for general principles on the generation of membrane curvature, see Box 2) and these processes appear to be tightly regulated by lipid modifying enzymes, membrane sculpting and remodeling proteins, lipid-binding effector proteins and protein kinases and phosphatases. This Commentary will focus on recent progress in our understanding of the early membrane modeling events in phagophore biogenesis, such as those involved in the nucleation process and the role of phosphatidylinositol (PtdIns) 3-phosphate (PtdIns3*P*) and other lipids, as well as later steps of phagophore expansion and closure, including tethering and fusion reactions to obtain the membrane composition and curvature of the functional autophagosome. Finally, we briefly discuss the membrane dynamics and modeling events occurring in selective autophagy. For detailed reviews of the complex hierarchy of Atg proteins and their regulation upon induction of autophagy, see Lamb et al., 2013; Mizushima et al., 2011 and Box 1.

Membrane modeling events in the early autophagy response: formation of the phagophore

The phagophore membrane

The phagophore is a small cup-shaped membrane precursor formed upon induction of autophagy, and its origin and identity have been a matter of debate for decades (Tooze, 2013). Recent studies of Atg proteins in yeast and mammalian cells have contributed substantially to our understanding of the mechanisms involved in phagophore formation, but the constitutive lipid species and membrane modeling proteins involved in determining phagophore shape and size are still mostly unknown.

It is generally agreed that phagophores are formed *de novo* by nucleation on a preexisting membrane (for recent reviews, see Abada and Elazar, 2014; Hamasaki et al., 2013b; Lamb et al., 2013; Shibutani and Yoshimori, 2014). In yeast, the phagophore membrane has been found to originate from a single origin near the vacuole, called the pre-autophagosomal structure (PAS) (Suzuki and Ohsumi, 2010). In higher eukaryotes, phagophore nucleation might occur at different locations in the cell, but it is now largely accepted that, at least upon starvation, phagophores nucleate at an intricate membranous structure, termed the omegasome (due to its resemblance to the Greek letter omega in electron microscopy pictures). Omegasomes were originally identified as endoplasmic reticulum (ER)-associated spots labeled

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