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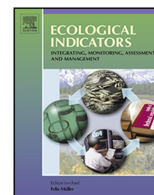

Autophagy in response to environmental stresses: New monitoring perspectives

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Autophagy, an evolutionarily conserved process of cellular homeostasis in all eukaryotes, has been heavily implicated in many aspects of human health and diseases. However, its pivotal roles, particularly in stress and adaptive responses in other species in the environment, have perhaps not received the attention they deserve. Autophagy processes may underlie important ecological phenomena such as coral bleaching, as well as various forms of responses and adaptations to environmental forcing and deterioration. Investigating and assessing autophagy responses in the contexts of environmental stresses and ecological changes would therefore be important. Such investigations in indicator organisms could provide valuable parameters for ecosystems health assessment. Understanding autophagy responses in ecologically important species could also be useful in efforts of species and biodiversity conservation.

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1. Autophagy – a brief molecular and cell biology background

Autophagy is a rather broad term for eukaryotic cellular processes whereby cytoplasmic and membranous contents are first enclosed in a double-membrane autophagosome, then subsequently degraded at the vacuoles or lysosome (Yang and Klionsky, 2010). The autophagic process could appear non-selective, or it could specifically target damaged cellular organelles (such as mitochondria, termed mitophagy) as well as invading pathogens (termed xenophagy). As an evolutionarily conserved process from yeast to humans, autophagy plays critical roles in cellular homeostasis during embryonic development, as well postnatal cell survival and death. In human biomedicine, autophagy is known to underlie a multitude of physiological processes, while impairment of autophagic activities is prominently associated with a myriad disease conditions such as cancer (Rosenfeldt and Ryan, 2011), neurodegeneration (Banerjee et al., 2010) and metabolic/cardiovascular disorders (Ouimet, 2013), all of which impinges on ageing and longevity (Gelino and Hansen, 2012). An understanding of its basic molecular components and mechanisms, as well as how these may be dysfunctional in disease contexts, are therefore research topics that are being intensely pursued (Ohsumi, 2014).

Autophagy is executed by a network of molecular factors that mediates autophagosome formation, maturation and eventual fusion with the degradative compartments, namely lysosome (in animal cells) or vacuole (in yeast and plant). The process of autophagy could be experimentally induced in cells and tissues by physiological stresses or nutrient starvation. The actually cellular membrane source for autophagosome formation remains controversial, and autophagosomal membrane could potentially be derived from the endoplasmic reticulum (ER), Golgi apparatus, endosomal or even mitochondrial membranes (Tanida, 2011; Lamb et al., 2013; Chan and Tang, 2013). Recent work has indicated that ER-mitochondrial contact sites are major locales of autophagosome generation (Hamasaki et al., 2013). In spite of the confusion associated with its membrane origin, the molecular components required for autophagy are well characterized. A specific set of Autophagy (Atg) related proteins were first identified by genetic screens in yeast (Reggiori and Klionsky, 2002). These Atg proteins form and function in various molecular complexes in a complicated and often non-linear fashion (Simonsen and Tooze, 2009; Yang and Klionsky, 2010; Klionsky, 2013). The Atg1/unc51-like kinase 1 (ULK1) complex (Wong et al., 2013), containing Atg1/ULK1, Atg17, and dephosphorylated Atg13 is an upstream effector of autophagic signalling. The complex is functionally connected to the target of rapamycin (TOR) (Zoncu et al., 2011) and AMP-activated kinase (AMPK) modulated nutrient-sensing pathways (Yuan et al., 2013). This Atg1/ULK1 complex recruits other Atg proteins to the autophagosome assembly sites to initiate the formation of the pre-autophagosmal membrane/phagophore as seen in yeast cells, or

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isolation membrane (IM) in mammalian cells (Hayashi-Nishino et al., 2009).

Another Atg complex consisting of the class III phosphatidylinositol-3 (PI3)-kinase Vps34, Atg6/beclin1, Vps15/p150 and Atg14/Atg14L, acts in autophagosome generation through local production of phosphatidylinositol 3-phosphate (PI_3P) (Axe et al., 2008; Walker et al., 2008) in the inner surface of the phagophore/IM. These two Atg complexes act in a cooperative manner. For example, ULK1 could phosphorylate Atg6/beclin1, thus activating the Vps34 lipid kinase (Russell et al., 2013). The membrane PI_3P generated engages other Atg proteins such as the Atg18 and Atg21 (or their mammalian homologues WD-40 repeat containing protein that Interacts with Phosphatidyinositols (WIPI) 1 and 2) (Polson et al., 2010) that act as scaffolds, thus generating a membrane platform for accumulation of autophagosomal contents and subsequent phagophore/IM growth and maturation.

The subsequent expansion and eventual closure of the phagophore/IM to form a free double membrane vesicle is dependent on two ubiquitin-like conjugation processes, leading to the formation of phosphatidylethanolamine (PE) conjugates (Noda et al., 2008). The E1-like Atg7 and E2-like Atg10 catalyze the conjugation of the ubiquitin-like protein Atg12 to Atg5, and facilitate the subsequent formation of the Atg16L-containing complex (Fujita et al., 2008). This Atg5–Atg12–Atg16L complex acts like an E3-ligase to promote the recruitment of another ubiquitin-like protein Atg8/microtubule-associated protein 1A/1B light chain 3 (LC3, the cytoplasmic form, non-lipidated form is often designated as LC3-I) to PE on the membrane (Fujita et al., 2008). The Atg8/LC3-PE conjugate (LC3-II) on the membrane facilitates autophagosome formation likely by facilitating membrane elongation. Being an autophagosome specific marker, labelling and detection of cytoplasmic and membrane-associated LC3 (or exogenously expressed tagged GFP-LC3) is a simple and popular method for monitoring autophagy progression (Tanida et al., 2008). In the end, autophagosomes fuses with the late endosome or lysosome/vacuole, and this fusion has been shown to involve a known component of membrane fusion machinery, namely the SNAP receptor syntaxin 17 (Itakura et al., 2012; Hegedűs et al., 2013).

Although the autophagy process utilizes a set of molecular machineries that appear independent of those that modulate membrane transport and trafficking in eukaryotes, there are considerable points of intersection between these two major process governing intracellular membrane dynamics. Clear examples in support of such a notion comes from discoveries of the involvement of the Rab GTPases in autophagy (Chua et al., 2011; Ao et al., 2014; Szatmári and Sass, 2014). Like intramembrane transport in eukaryotes, autophagy is a process that is just as evolutionary ancient and conserved amongst all eukaryotic clades.

2. Autophagic responses in environmental forcing

As an evolutionarily conserved cellular process, autophagy is expected to occur in multiple tissues of all eukaryotic species, particularly during starvation and stress. While classical invertebrate genetic models such as *Caenorhabditis elegans* and *Drosophila melanogaster* have been extensively used to study its molecular components, work on autophagy in non-human species and invertebrates from an ecological or environmental perspective has been somewhat lacking. The paragraphs below highlight some of the more prominent examples of how autophagy and related processes have been investigated from such perspectives.

2.1. Autophagy in coral bleaching

Reef-building corals form extensive marine habitats that harbour rich and diverse communities. Those cnidarians host mutualistic symbionts in the form of dinoflagellate algae of the genus *Symbiodinium* (commonly termed zooxanthellae) (Davy et al., 2012). The reef structures that harbour rich and diverse marine ecosystems are of great value in coastal ecosystem services. The breakdown of this symbiosis, manifested as a loss of algal photosynthetic pigments and often the endosymbiont itself, has devastating effects on host viability and coral reef integrity. Phenomenally termed coral bleaching, the breakdown of coral–algae symbiosis is due to a variety of biotic and abiotic environmental stresses, some of these have clear links to anthropogenic activities (Anthony et al., 2008; Hoegh-Guldberg and Bruno, 2010; Ban et al., 2014). These environmental stresses are threatening to drive some reef ecosystems to the brink of species extinction (Huang, 2012; Hughes et al., 2014). The molecular and cellular events underlying coral bleaching have been a subject of intensive investigation and debate (Douglas, 2003; Weis, 2008). A plethora of studies have highlighted the importance of reactive oxygen species (ROS) production by the photosynthetic apparatus of the zooxanthellae resulting from elevated temperature and light stress (Downs et al., 2002; Lesser, 2006; Weis, 2008; Tolleter et al., 2013; Perez and Weis, 2006). ROS, nitric oxide (NO) and consequential peroxynitrite production by host coral cells may play complementary roles (Perez and Weis, 2006; Hawkins et al., 2013) in triggering mechanisms that lead to loss of the zooxanthellae. Loss of the endosymbiont may occur via several different pathways, including apoptotic death (Franklin et al., 2004; Dunn et al., 2007; Tchernov et al., 2011; Hawkins et al., 2013) or expulsion by some form of exocytosis (Weis, 2008; Fujise et al., 2014). However, an important, and in some cases probably predominant mechanism of endosymbiont demise, may be autophagic degradation by the host.

Cnidarians recruit *Symbiodinium* likely via a phagocytic process, although whether the process has any selectivity compared to a general mode of phagocytosis is poorly understood. In any case, the phagosomes harbouring designate endosymbionts are somehow prevented from full maturation (i.e. fusion with the lysosomes). While not fully profiled for most coral species, studies in the sea anemone *Aiptasia pulchella* have shown that while early endosomal localized Rab GTPases ApRab4 and ApRab5 are associated with phagosomes harbouring live zooxanthellae, the late endosomal ApRab7 and recycling endosome ApRab11 were largely excluded from these (Chen et al., 2003, 2004, 2005; Hong et al., 2009). The symbiosome vacuole has an acidic pH compared to the host cytoplasm, attesting to its endosomal identity (Venn et al., 2009). Phagocytosed *Symbiodinium* may therefore manipulate host endosomal trafficking, reminiscent of what intracellular pathogenic bacteria do (Alix et al., 2011; Stein et al., 2012), to ensure survival and subsequent establishment of the symbiosome (Rands et al., 1993; Venn et al., 2009; Hill and Hill, 2012). In stable symbiosis, a cell specific symbiont density that differs between cell types and species needs to be maintained. Should endosymbiont proliferation produce excess individuals, these may be expelled or degraded. Importantly, these homeostatic processes may be dysregulated during stress. Downs et al. (2009) have documented that temperature stress induces autophagic responses in *Pocillopora damicornis*, and shown that the symbiosome could be transformed into a digestive organelle bearing the autophagosome marker Rab7 and containing lysosomal acid phosphatase, this was termed “symbiophagy”. Symbiophagy would be analogous to the process whereby mutualistic or parasitic *Wolbachia* bacteria populations are controlled in infected arthropods and nematodes (Voronin et al., 2012), and more broadly analogous to the xenophagy of invading pathogens (Wileman, 2013).

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