Modulation of plant autophagy during pathogen attack

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Highlight

We highlight exciting advances in modulation of autophagy during plant-microbe interactions with a particular focus on reprograming of plant defence-related autophagy by pathogens.

Abstract

In plants, the highly conserved catabolic process of autophagy has long been known as a means of maintaining cellular homeostasis and coping with abiotic stress conditions. Accumulating evidence has linked autophagy to immunity against invading pathogens, regulating plant cell death and antimicrobial defences. In turn, it appears that phytopathogens have evolved ways to not only evade autophagic clearance but also to modulate and co-opt autophagy for their own benefit. In this review, we summarise and discuss the emerging discoveries concerning how pathogens modulate both host and self-autophagy machineries to colonize their host plants, delving into the arms race that determines the fate of inter-organismal interaction.

Keywords:
Autophagy, biotroph, hypersensitive response, innate immunity, Joka2, necrotroph, NLR, PCD, TOR, virus

Abbreviations:
ARGONAUTE 1 (AGO1), ATG8 interacting motif (AIM), AuTophaGy-related genes (ATGs), Bax inhibitor-1 (BI-1), Cauliflower mosaic virus (CaMV), Coiled-Coil-NLR (CNLR), constitutive active RabG3b (RabG3bCA), Cotton leaf curl Multan virus (CLCuMuV), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), hypersensitive response (HR), NONEXPRESSOR OF PATHOGENESIS-RELATED GENES1 (NPR1), nucleotide-binding domain and leucine-rich repeat-containing proteins (NLRs), PAMP/pattern-triggered immunity (PTI), pathogen-associated molecular patterns (PAMPs), phosphatidylethanolamine (PE), phosphatidylinositol-3-kinase (PI3K), programmed cell death (PCD), Pseudomonas syringae pv. tomato strain DC3000 (Pst DC3000), RNA-dependent RNA polymerase 6 (RDR6), RNA-induced silencing complex (RISC), salicylic acid (SA), Suppressor of Gene Silencing 3 (SGS3), Tobacco Mosaic Virus (TMV), Toll/Interleukin-1 receptor-NLR (TNLR), Turnip mosaic virus (TuMV), viral genome-linked protein (VPg)

Submitted on 5th of September 2017

Figure 1. Modulation of autophagy by plant pathogens during infection. (Colour)
Word count: 5177

Introduction

Autophagy is a fundamental cellular digestion process conserved across eukaryotic organisms. Almost all cellular components including large organelles such as the chloroplasts that are 3-10 µm in length can be degraded via autophagy (Xie *et al.*, 2015). Although initially thought to be a mechanism to maintain cell survival under nutrient deprivation, it is now clear that the more than 1.5 billion-year-old process has evolved to counteract various types of physiological and environmental stress conditions. To coordinate diverse cellular activities, autophagy has become specialized to capture specific cargoes and acquired additional non-degradative roles such as non-conventional protein secretion. For instance, in the mammalian immune system, a selective form of autophagy known as xenophagy functions in targeting intracellular pathogens for degradation whereas secretory autophagy mediates cytosol to cell surface delivery of pro-inflammatory cytokines (Knodler and Celli, 2011; Dupont *et al.*, 2011). Although the defence related roles of autophagy in cell autonomous immunity are well established, it is becoming clear that adapted pathogens can subvert and employ host autophagy machinery for their own benefit (Deretic and Levine, 2009).

In plants, previous studies have revealed that autophagy contributes to immunity by regulating the defence hormone levels and the hypersensitive response, a form of programmed cell death that restricts the spread of microbial infection (Liu *et al.*, 2005; Yoshimoto *et al.*, 2009; Coll *et al.*, 2014*b*). However, the molecular mechanisms that underpin defence-related selective autophagy in plants, and how it is manipulated by adapted pathogens are poorly understood. The defence related roles of autophagy against pathogens have been difficult to dissect with standard genetic approaches. This is mainly because autophagy proteins also execute many non-autophagy functions, and autophagy mutants often show pleiotropic effects that perturb plant development and various other cellular processes. Nevertheless, several recent studies which employed pathogen produced proteins that target plant autophagy machinery uncovered novel autophagy related defence components and shed light on the functioning of defence related autophagy (Dagdas *et al.*, 2016; Haxim *et al.*, 2017; Hafrén *et al.*, 2017). In this review, we analyse the emerging role of selective autophagy in plant immunity and delve into how both the host plants and the pathogens modulate autophagy for their own benefit.

Autophagy is a multi-step process that can be highly selective.

While originally described as a bulk, non-selective degradation process that maintains cellular homeostasis under environmental stress conditions (Tsukada and Ohsumi, 1993), more recent studies have demonstrated that autophagy can be a highly selective process. In plants, autophagy contributes to stress tolerance, senescence, development, and immunity (Patel and Dinesh-Kumar, 2008; Vanhee and Batoko, 2011; Lenz *et al.*, 2011; Li and Vierstra, 2012; Teh and Hofius, 2014; Lv *et al.*, 2014).

The mechanisms of autophagy are conserved in yeast, plants and metazoans. At its core, more than 30 AuTophaGy-related genes (ATGs), often organised in groups, are responsible for distinct but continuous steps of the autophagic process (Kellner et al., 2017). The central player involved in the 3 steps of autophagosome formation (initiation, expansion and closure) and selective cargo recruitment is the ubiquitin-like protein ATG8 (Slobodkin and Elazar, 2013). Upon activation by stress or recognition of cargo, the serine/threonine kinase, ATG1, in complex with ATG13 mediates formation of the phagophore, the initial membranous cistern involved in autophagosome biogenesis. At the phagophore assembly site, the ATG1

complex activates the phosphatidylinositol-3-kinase (PI3K) complex including other core autophagy proteins ATG6, ATG14 and VPS15, which mediate the nucleation step of autophagosome formation (Kaur and Debnath, 2015). Subsequently, a ubiquitination-like system involving the orchestrated action of ATG7 (E1-activating-like enzyme), ATG3 (E2-conjugating-like enzyme) and the ATG12-ATG5-ATG16 (E3 ubiquitin ligase-like enzyme) complex mediates anchoring of lipidated ATG8 to the outer and inner membrane of the growing phagophore (Hanada et al., 2007, Geng and Klionsky, 2008). ATG8 lipidation involves proteolytic processing of C-terminal residues of proATG8 by ATG4 exposing a terminal glycine residue, which is conjugated to phosphatidylethanolamine (PE) by a ubiquitination like process mediated by ATG7 and ATG3. This enables ATG8 to be anchored into the developing autophagosomal membranes. On the outer membrane of autophagosomes, ATG8 mediates transport and docking of autophagosomes to the lysosomes. The lipidation reaction is reversible; de-conjugation of ATG8s from PE by ATG4 allows recycling of ATG8 to the cytoplasm and enables fusion with lysosomes (Yu et al., 2012).

ATG8 decorating the inner autophagosomal membrane serves as a port for autophagy cargo receptors that recruit selective autophagy cargoes. Cargo receptors bind to ATG8 via a conserved ATG8 interacting motif (AIM) (Ichimura *et al.*, 2008). The AIM motif consists of the consensus sequence starting with one of the aromatic amino acids W/F/Y followed by XX-L/I/V, where X represents any other residue.

ATG8 appears to have gone through a series of duplication events and diversified to encode different isoforms in higher eukaryotes (Shpilka *et al.*, 2011). Although yeast encodes one ATG8 protein, higher plants carry up to 22 ATG8 isoforms that are subdivided into two clades (Kellner *et al.*, 2016). It is believed that different ATG8 isoforms, redundantly and independently of each other, contribute to different selective autophagy processes. However, experimental evidence assigning specific biological functions to different ATG8 isoforms in plants is lacking.

Modulation of autophagic activity in filamentous plant pathogens; autophagy is required for host cell penetration.

Filamentous plant pathogens including fungi and oomycetes pose a major threat to global food security. Many of the aggressive forms, including the rice blast pathogen *Magnaporthe oryzae*, form intimate interactions with their hosts and are highly efficient in penetrating

through preformed plant barriers. For instance, upon germination on the leaf surface, rice blast pathogen forms a dome-shaped cellular structure known as an appressorium that builds-up a massive turgor pressure to breach the host cuticle and mediate subsequent rupture of the cell wall (Talbot, 2003). This step is critical for the pathogen to penetrate host cells and gain access to the nutrient rich environment of the host. Formation of the appressorium requires major changes in cellular organization and formation of a highly specialized apparatus that accumulates glycerol essential to build-up the turgor pressure. The building blocks and energy (glycogen and lipids) for glycerol accumulation are transported from neighbouring conidia cells that undergo autophagy related cell death (Wilson and Talbot, 2009). Hence, autophagy mutants fail to produce proper appressoria and are unable to penetrate the host. Likewise, ATG1 protein is induced in the fungal pathogen *Botrytis cinerea* during host colonization and ATG1 mutants are impaired in appressorium formation [Ren et al., MPMI 2016] supporting the view that autophagy dependency of appressorium formation is widespread in fungi. Consistent with this, knockout mutants for a small Rab GTPase known as MoYPT7 that localizes to the lysosomal membranes, were shown to be impaired in autophagy and appressorium development in *M. oryzae* (Liu *et al.*, 2015) providing a link between autophagy and vesicle transport systems in plant pathogenic fungi. Interestingly, several essential components of the retromer membrane trafficking machinery are also detected on lysosomal membranes. Gene replacement mutants for components of the retromer were shown to be defective in autophagy induction, mobility of glycogen and lipid bodies that are required for developing appressorial pressure, and subsequent host penetration (Zheng *et al.*, 2015). Whether MoYPT7 colocalizes with these retromer components and has retromer related functions to regulate autophagy remains to be determined. In *M. oryzae*, five autophagy proteins (ATG1, ATG2, ATG3, ATG17, and ATG18) displayed increased phosphorylation during appressorium formation while decreased phosphorylation was only observed for a single site on ATG13, implicating post-translational ATG modifications in host cell penetration (Franck *et al.*, 2015). The autophagy process that mediates appressoria maturation does not appear to be affected by deficiency in other forms of autophagy as mitophagy and pexophagy mutants did not affect host penetration and colonization of *M. oryzae*. However, a pexophagy mutant of the anthracnose fungus *Colletotrichum orbiculare* showed host penetration defects following appressoria maturation, indicating some selective autophagy pathways could execute essential tasks during host invasion in diverse filamentous pathogens. Recently, stimulation of autophagy was detected in haustorial mother cells of leaf rust pathogens and found to be essential for host colonization (Liu *et al.*, 2017). How this

increased autophagic activity contributes to host colonization remains unclear. It is possible that autophagy is activated to transport and recycle nutrients absorbed from the host, serve as an alternative secretory system, or mediate host cell penetration.

Our understanding of the role of autophagy in oomycete pathogens remains mostly unexplored due to technical difficulties in genetic transformation of these organisms. However, a recent study demonstrated that autophagy related genes are induced during infection along with an increase in autophagic activity. Silencing of the PsATG6a gene in *Phytophthora sojae* reduces its ability to colonize the host plant (Chen *et al.*, 2017). Finally, host autophagy could also be important for beneficial microbes. For instance, in the mycorrhizal fungus *Glomus intraradices*, transcripts of genes encoding plant core autophagy proteins ATG8f and ATG4a were found to be upregulated in both cortical cells and arbuscule-containing cells of mycorrhiza-colonized roots (Gaude *et al.*, 2012). However, it remains unknown whether the upregulation of autophagic activity in mycorrhizal fungus is essential for formation of symbiotic relationship or arbuscules.

Autophagy deficiency leads to perturbations in plant immunity and in defence related cell death.

To prevent penetration attempts of filamentous pathogens and to protect against various other invaders, plants rely on innate immunity. This involves detection of microbes, activation of counter-invasion mechanisms, and subsequent accumulation of defence related components at the sites of invasion. The detection of microbes is achieved by surface localized or intracellular immune receptors. Surface-localized recognition receptors recognize pathogen-associated molecular patterns (PAMPs) and activate so-called PAMP/pattern-triggered immunity (PTI) (Jones and Dangl, 2006). To counteract PTI and interrupt other plant processes, adapted pathogens deploy effector proteins at the cell surface or inside the host cells. Nevertheless, some specialized surface immune receptors and a set of cytoplasmic/intracellular immune receptors known as nucleotide-binding domain and leucine-rich repeat-containing (NLRs) proteins can sense effector proteins. Activation of NLRs initiate effector-triggered immunity that is often accompanied by HR related cell death (Duxbury *et al.*, 2016; Wu *et al.*, 2017). The recognition of effectors by NLRs is mostly indirect and frequently involves modulation of host proteins targeted by effectors guarded by the NLRs. Hence, accurate deployment of immune receptors, guardees and defence

components at particular sites and in correct amounts is critical not only for immune recognition but also for execution of downstream mechanisms leading to pathogen elimination.

In metazoans, the role of autophagy in selective clearance of intracellular pathogens and defence related non-conventional secretion is well-documented (Deretic and Levine, 2009; Dupont *et al*., 2011). Although there are debates on whether autophagy can be manipulated to serve pathogens, autophagy cargo receptors and adaptors as well as components that generate eat-me signals for pathogen clearance are well defined (Deretic and Levine, 2009; Zaffagnini and Martens, 2016). In contrast, the role of autophagy in plant immunity remains poorly understood. Autophagy has been implicated in execution of HR and its local restriction. The precise molecular mechanisms and pathways are the subject of controversy in the literature. Most of our knowledge originates from studies that aim to block bulk autophagy rather than selective autophagy components. Nevertheless, some recent insights on the role of selective autophagy in plant immunity are emerging.

Earlier studies revealed that autophagy enhances hypersensitive cell death induced by avirulent pathogens, whereas it restricts unnecessary spread of cell death throughout the uninfected tissue (Patel and Dinesh-Kumar, 2008). Silencing of autophagy genes including *PI3K/VPS34*, *ATG3*, and *ATG7* or expression of an ATG6/Beclin1 antisense transgene in tobacco plants carrying a resistance gene against the *Tobacco mosaic virus* (TMV) leads to uncontrolled spread of HR beyond primary virus infection sites. The unrestrained spread of HR in autophagy deficient plants also occurred upon treatment with elicitors from diverse pathogens. This phenomenon is also observed in ATG6-deficient Arabidopsis (*Arabidopsis thaliana*) challenged with *Pseudomonas syringae* pv. *tomato* DC3000 (*Pst DC3000*) harbouring the effector protein AvrRpm1 recognised by the RPM1 disease resistance protein. Consistently, Arabidopsis *atg* (*atg5, atg7, atg10* and *atg18a*) loss of function mutants showed uncontrolled spread of cell death when challenged with the necrotrophic fungal pathogens *Alternaria brassicicola* or *B. cinerea* (Lai *et al*., 2011; Lenz *et al*., 2011).

However, different studies did not find any uncontrolled spread of pathogen-associated cell death following inoculation with the avirulent pathogens in Arabidopsis *atg5, atg7, atg9* and *atg18a* mutants (Hofius *et al*., 2009; Coll *et al.*, 2014*b*). In contrast, cell death was reduced and delayed in Arabidopsis upon challenge by the avirulent *Pst* DC3000 (*AvrRps4*) or the avirulent isolate Noco2 of the oomycete pathogen, *Hyaloperonospora arabidopsidis* (Hofius *et al.*, 2009). The controversy in the execution of HR under autophagy deficiency is attributed

to the age of the plants used in different studies; although 7-8 week old plants had spreading cell death upon activation of HR as previously described, younger plants (4-5 weeks) showed a slight delay but no symptoms of trailing PCD (Yoshimoto *et al.*, 2009). The enhanced PCD in old plants was shown to be due to increased defence hormone salicylic acid (SA) levels where the SA transducer NONEXPRESSOR OF PATHOGENESIS-RELATED GENES1 (NPR1) is essential. Nevertheless, it is now widely accepted that spreading HR observed in older autophagy mutants is due to enhanced cellular stress build-up over time.

An earlier study found that the latency in execution of the HR occurred upon activation of Toll/Interleukin-1 receptor-NLR (TNLR) type but not Coiled-Coil-NLR (CNLR) types of cytoplasmic immune receptors providing the first clue on the specificity of the perturbation of HR during autophagy deficiency (Hofius *et al.*, 2009). However, a subsequent study found that HR triggered by activation of the CNLR, RPM1, is also suppressed in an autophagy deficient background (Coll *et al.*, 2014*b*). Interestingly, a constitutive active mutant form of the small GTPase RabG3b (RabG3bCA) was shown to mimic autophagy mutants in leading to spreading PCD upon HR activation. However, in contrast to autophagy mutants, RabG3bCA accelerated PCD occur much faster, and is stimulated non-specifically by both a TNLR and a CNLR. Although RabG3bCA was shown to promote autophagic activity, whether the accelerated PCD triggered by the mutant is due to perturbation in autophagy remains to be elucidated. It is possible that RabG3b contributes to acceleration of PCD via recently described parallel independent cell death pathways (Coll *et al.*, 2011).

As autophagy is branched to execute specialized cellular tasks in different conditions, identifying links between diverse cellular activities and autophagy should help understanding the complicated role of autophagy in plant HR associated cell death. Recently, cytosolic glyceraldehyde-3-phosphate dehydrogenase (GAPDH) the key enzyme in the glycolytic pathway with various other moonlighting functions, was found to interact with ATG3 and negatively regulate ATG3 triggered autophagy (Han *et al.*, 2015*a*). In contrast, Bax inhibitor-1 (BI-1), a highly conserved cell death and ER stress regulator, was found to interact with ATG6 and positively regulate autophagy (Xu *et al.*, 2017). Intriguingly, depletion of GAPDH, that enhances autophagy or depletion of BI-1 that supresses autophagy, both activated TMV-triggered HR on plants carrying the TNLR type resistance gene *N* (Han *et al.*, 2015*b*; Xu *et al.*, 2017). Moreover, *GAPDH* silencing did not lead to any change in HR cell death symptoms induced by *Pst* DC3000 unlike the previously described autophagy mutants. These conflicting differences in activation of HR compared to previous observations could be attributed to the non-autophagy related roles of the genes that are studied.

Nevertheless, it appears that autophagy deficiency does not significantly influence the outcome of the incompatible interactions in most instances. This notion is further validated in a more recent study which showed that autophagy deficiency, metacaspase AtMC1 deficiency, or both combined, leads to suppression of HR in Arabidopsis challenged with avirulent pathogens but does not give rise to susceptibility (Coll *et al.*, 2014*a*).

Whether autophagy actively plays a direct role on NLR-mediated HR cell death remains unclear. First, as discussed earlier, additional non-autophagy related functions of many of the targeted genes makes it difficult to derive precise conclusions. Secondly, shutting down autophagy fully will lead to defects in multiple cellular processes and uncontrolled accumulation of components that are toxic. For instance, autophagy mediates programmed recycling of damaged organelles such as chloroplasts and mitochondria (Michaeli and Galili, 2014). The uncontrolled release of death signals from these damaged organelles, such as the reactive oxygen species and cytochrome c, can trigger accelerated cell death upon further stress. Particularly, it has been shown that entire photo-damaged chloroplasts are targeted to central vacuole for degradation, whereas immobile non-active forms accumulate in autophagy mutants (Izumi *et al.*, 2017). A build-up stress and damage in aging chloroplasts which cannot be cleared up by autophagy, can lead to uncontrolled release of chloroplast-generated salicylic acid (SA) precursors to the cytosol. In line with this, mutations in the chloroplast-targeted SA biosynthetic SID2 (salicylic acid induction deficient 2) prevented uncontrolled spread of HR in Arabidopsis (Yoshimoto *et al.*, 2009; Coll *et al.*, 2014*a*).

In addition, inefficient degradation of ubiquitinated protein aggregates, enhanced ER stress and cell death were also observed in autophagy mutants (Munch *et al.*, 2014). Accumulation of protein aggregates will put more pressure on proteasomes which are themselves degraded by autophagy when damaged (Waite *et al.*, 2016). Therefore, variation in cell death activation by different types of immune receptors could also be due to differential accumulation of immune receptors themselves and/or other components such as their guardees as well as avirulence products. Thus, variation in cell death activation by different types of immune receptors can be attributed to cumulative effects of various independent distorted cellular processes. Autophagy cargo receptors or adaptors that specifically participate in these processes would be necessary to identify the precise role of autophagy in HR-associated cell death.

Autophagy deficiency in host plants favours pathogens with necrotrophic lifestyle over biotrophic; one man's heaven is another man's hell.

Apart from the conflicting views on activation of plant cell death upon infection with avirulent pathogens, there is generally an agreement regarding the role of autophagy in basal immunity depending on the lifestyle of the infectious agent. A number of studies have provided convincing evidence attributing a positive role of autophagy activation in resistance against necrotrophic pathogens (Lai *et al.*, 2011; Lenz *et al.*, 2011; Katsiarimpa *et al.*, 2013). This is not surprising as the autophagy-deficient plants are more sensitive to cell death induction and devoid of potential autophagy-related defences, which could favour necrotrophic pathogen lifestyle. This essential role played by autophagy in immunity against necrotrophic pathogens is further supported by the discovery of the host autophagy-suppressing mechanisms employed by the necrotrophic fungal pathogen *Sclerotinia sclerotiorum* (Kabbage *et al.*, 2013).

In contrast, autophagy mutants generally display increased resistance to biotrophic pathogens. This is mainly believed to be due to defects originating from general shutdown of plant autophagy machinery leading to enhanced SA accumulation and impaired cellular survival under stress conditions (Han *et al.*, 2011). However, it is possible that a selective form of autophagy also contributes to basal immunity against biotrophic pathogens, which is masked by pleiotropic effects of autophagy deficiency. Consistent with this view, selective autophagy cargo receptor NBR1/Joka2 was found to contribute to defence against the hemibiotrophic Irish potato famine pathogen *Phytophthora infestans* (Dagdas *et al.*, 2016). Interestingly, similar to plant-biotroph interactions, autophagy proteins PI3K, ATG6 and Target Of Rapamycin (TOR) were also implicated in plant symbiotic relationships (Estrada-Navarrete *et al.*, 2016; Nanjareddy *et al.*, 2016).

The autophagy machinery exerts a crucial antiviral role and mediates clearance of viruses in metazoans (Shoji-Kawata and Levine, 2009) In contrast, some viruses avoid autophagic clearance and manipulate autophagy to propagate and replicate (Dong and Levine, 2013). Although autophagy contributes to antiviral defence in plants, underlying molecular mechanisms are poorly understood (Shoji-Kawata and Levine, 2009). More recently however, autophagy has been shown to have a more direct antiviral function in plants, degrading viral proteins associated with dsRNA-induced RNA silencing, an essential immune evasion strategy used by viral phytopathogens (Agius *et al.*, 2012; Nakahara *et al.*, 2012). It appears

that in plant antiviral immunity, autophagy takes on a more direct function, targeting viral particles and proteins for degradation.

Selective autophagy contributes to plant defence; catch me if you can.

Currently, very little is known about the mechanisms involved in defence-related selective autophagy and the strategies employed by the pathogens to evade it. Recent discoveries on defence related roles of selective autophagy sparked excitement and interest the in plant autophagy field (Nakahara *et al.*, 2012; Dagdas *et al.*, 2016; Haxim *et al.*, 2017; Hafrén *et al.*, 2017).

An earlier study found that tobacco calmodulin-like protein rgs-CaM (also known as NtCAM) targets viral RNA silencing suppressors for degradation by autophagy (Nakahara *et al.*, 2012). However, how rgs-CaM mediates selective autophagic clearance of viral particles remains unclear. A different study showed that *Cotton leaf curl Multan virus* (CLCuMuV) encoded protein βC1 is degraded by autophagy through recruitment to autophagosomes by directly interacting with the host ATG8 proteins (Haxim *et al.*, 2017). βC1-ATG8 interaction did not involve any AIMs and did not require autophagy cargo receptor NBR1/JOKA2. Intriguingly, a single amino acid mutation in βC1-ATG8 interaction interface abolished autophagic clearance of the viral protein. However, it is puzzling how several different ATG8 isoforms have evolved to bind βC1 to mediate its autophagic degradation. Whether ATG8s evolved to recognize βC1 and natural βC1 alleles that avoid ATG8 binding exist, remains to be elucidated.

A different study showed NBR1/Joka2 can target *Cauliflower mosaic virus* (CaMV) non-assembled and virus-forming capsid proteins for degradation through the autophagic pathway in Arabidopsis (Hafrén *et al.*, 2017). In response, the virus attempts to avoid degradation by forming inclusion bodies (virus factories), which help the sequestration and assembly of capsid proteins. However, as a result of the evolutionary arms race, viruses have developed a balanced infection rate not to kill the host plant too fast to enable and ensure spread to other hosts (Clavel *et al.*, 2017; Hafrén *et al.*, 2017; Haxim *et al.*, 2017).

Finally, selective autophagy has recently been found to contribute to defence against the oomycete *Phytophthora infestans.* Overexpression of NBR1/Joka2 limits pathogen growth whereas its depletion leads to enhanced pathogen growth (Dagdas *et al.*, 2016). How NBR1/Joka2 mediates defence related selective autophagy remains to be elucidated. It is

possible that NBR1/Joka2 associates with defence related cargoes to regulate their autophagic clearance or secretion. A new study revealed that NBR1/Joka2 labelled puncta accumulates around the haustoria of *P. infestans* suggesting that NBR1/Joka2 could mediate deployment of defence related cargoes to pathogen interface or it is further manipulated by the pathogen to remain inactive (Dagdas *et al.*, 2017 BioRxiv).

Reprogramming of host autophagy by pathogens: avoiding immunity and rerouting cellular resources?

In metazoans, there is ample evidence for modulation of autophagy by invading pathogens. In particular, manipulation of autophagy for nutrients is an emerging theme employed by a diverse range of microbes. For example, *Toxoplasma gondii* induces autophagy to promote its parasitic growth, while it prevents fusion of autophagosomes with the parasitophorous vacuole that it resides in, a process which can lead to destruction of the parasite (Wang *et al.*, 2009; Muniz-Feliciano *et al.*, 2013). Although inhibition of autophagy decreases *T. gondii* replication, supplementing exogenous amino acids rescued this phenotype (Wang *et al.*, 2009). Interestingly, several other mammalian pathogens were also found to manipulate host cell autophagy for nutrient uptake while evading autophagic degradation via different mechanisms (Wang *et al.*, 2009; Niu *et al.*, 2012; Steele *et al.*, 2015). These findings suggest a beneficial role for host cell autophagy in the development of the parasites. Although the precise role of autophagy in supporting intracellular fitness of these pathogens remains unknown, nutrient acquisition is proposed as a potential explanation.

In contrast to animal pathosystems, our knowledge in modulation of host autophagy by plant pathogens is limited. Several recent studies provided insights into how pathogens can modulate plant autophagy for their own benefit. The clues to co-option of host autophagy by plant pathogens were first discovered in plant-polerovirus interactions. A viral RNA silencing suppressor from polerovirus, P0 has been reported to mediate autophagic degradation of ARGONAUTE 1 (AGO1), an essential component of the RNA-induced silencing complex (RISC) (Derrien *et al.*, 2012, Baumberger *et al.*, 2007). The precise mechanisms by which P0 coordinates autophagic clearance of AGO1 are not clear. Interestingly, P0 carries an F box domain, typically implicated in ubiquitination of target proteins for degradation. Whether P0 acts as a canonical cargo receptor connecting AGO1 to ATG8 or if it functions as an adaptor

to link AGO1 to autophagy indirectly via autophagy cargo receptors remains to be determined.

A recent study demonstrated that host calmodulin-like protein NbCaM, induced by geminivirus encoded βC1 protein, serves as a susceptibility factor to mediate autophagic clearance of components of the plant RNA silencing machinery (Li *et al.*, 2017). NbCAM interacts with and promotes autophagic degradation of *N. benthamiana* Suppressor of Gene Silencing 3 (NbSGS3), a protein that functions alongside RNA-dependent RNA polymerase 6 (RDR6) to mediate dsRNA synthesis (Fukunaga and Doudna, 2009). The SGS3/RDR6 complex has been known to be targeted by various virulence factors including a viral genome-linked protein (VPg) from *Turnip mosaic virus* (TuMV). VPg leads to destruction of the complex by eliminating SGS3 through both autophagy and the proteasome (Cheng and Wang, 2016). Thus, viruses have evolved diverse strategies to interfere with host RNA silencing machinery by stimulating autophagic degradation of essential host components. It would be interesting to discern whether NbCAM or VPg have ATG8 binding capacities like autophagy cargo receptors or if they require NBR1/Joka2, or a yet uncharacterized cargo receptor, for SGS3 depletion.

A new study revealed an interesting interplay between plant autophagy and CaMV. It appears that CaMV might form viral inclusion bodies in an effort to avoid immune clearance mediated by host selective autophagy (Hafrén *et al.*, 2017). Remarkably, whereas NBR1 mediates autophagic depletion of viral particles, a virus-triggered NBR1-independent autophagy pathway prevents extensive cell death. Thus, it is proposed that by delaying host cell suicide, the virus gains extra time to be picked up by transmission vectors (Hafrén *et al.*, 2017). On the other hand, an independent study suggested that CaMV encoded viral suppressor P6 protein that interacts with TOR kinase (Schepetilnikov *et al.*, 2011), promotes TOR activation to suppress oxidative burst and salicylic acid dependent autophagy (Zvereva *et al.*, 2016). Although how CaMV coordinates these contrasting processes in host autophagy regulation remains unclear, it appears that this particular virus has developed multiple ways to simultaneously suppress host selective autophagy while modulating the process for its own replicative purposes.

The TOR modulation appears to be a common target for invading plant pathogens as the bacterial wilt pathogen *Ralstonia solanacearum*, deploys the AWR5 effector to inhibit TOR related activity and stimulate autophagy in yeast (Popa *et al.*, 2016). It remains unclear if AWR5 has the same effect on autophagy in plants and if so, whether AWR5 directly or indirectly inhibits TOR, and what benefit the pathogen gains by activation of autophagy.

Interestingly, during symbiosis, TOR expression is upregulated and its promoter activity can be observed in growing infection threads, nodule primordial cells and Rhizobium infected cells in mature nodules. RNAi-mediated silencing of TOR caused an arrest of infection thread within root hair cells and reduction in nodule number and ability to fix nitrogen. A further ultrastructural study showed that in the TOR RNAi nodules, rhizobium-infected cells are smaller and contain abundant autophagosomes but fewer, less-developed symbiosomes. It was suggested that upon TOR suppression, activation of autophagy treats the bacterial symbiont as an intruder and leads to abortion of symbiosis (Nanjareddy *et al.*, 2016). This is in a way reminiscent to the innate immune response against intracellular pathogens (Jo *et al.*, 2013).

Finally, filamentous plant pathogens also appear to be proficient modulators of host autophagy. Many filamentous pathogens including *P. infestans,* vigorously reprogram cellular trafficking through secretion of effector proteins through hyphal extensions that grow into the host cells known as haustoria (Bozkurt *et al.*, 2011, 2015). Remarkably, *P. infestans* RXLR effector PexRD54 has evolved a canonical AIM to bind potato ATG8CL isoform with 10 fold increased affinity compared to ATG8IL isoform, which suggests a selective perturbation in the host autophagy machinery (Dagdas *et al.*, 2016). Through this motif, the effector depletes NBR1/Joka2 from ATG8CL complexes and antagonizes the defence-related autophagy coordinated by NBR1/Joka2. Interestingly, PexRD54 boosts formation of ATG8CL autophagosomes suggesting co-option of plant autophagy by *P. infestans* (Dagdas *et al.*, 2016). Moreover, during infection, PexRD54/ATG8CL autophagosomes are diverted towards the haustoria. It is proposed that PexRD54 might recruit beneficial cargo that either replaces or neutralizes defence-related cargo targeted to pathogen interface (Dagdas *et al.*, 2017 BioRxiv). Nevertheless, the mechanisms that facilitate re-routing of autophagosomes to pathogen contact sites, and the nature of the autophagy cargo sequestered by PexRD54 and Joka2 are of great interest as they will help clarify pathogen's efforts to subvert host autophagy.

Thus, although as a common strategy pathogens try to avoid or suppress autophagy-related defences, some viruses, bacteria, and filamentous plant pathogens appear to develop strategies to stimulate autophagy. A provocative hypothesis is that these parasites hijack the host autophagy machinery to promote recycling of host cellular resources to absorb nutrients using the plant cell machinery in a similar manner as certain animal pathogens (Heaton and Randall, 2010; Niu *et al.*, 2012; Steele *et al.*, 2015).

Concluding remarks

A lot remains to be addressed surrounding autophagy in plants, how it contributes to immunity and how pathogens have developed means to modulate it for their own benefits. Up until recently, the bulk of the information about the molecular mechanisms of autophagy stem from studies done in *atg* knockout mutants. Being such a key cellular homeostatic, membrane trafficking and alternative secretory process, knocking out fundamental components of the autophagic machinery inevitably leads to unspecific pleiotropic effects. As a result, it is hard and often misleading to draw specific conclusions regarding molecular functions of autophagy. The study of plant microbial interactions proves to be especially problematic when using general *atg* mutants as it introduces a pathogenic organism in turn triggering various immune responses, often leading to additional unspecific effects such as uncontrolled spread of cell death. Instead, more precise approaches such as targeting individual host cargo receptors and autophagic adaptors or using pathogen effectors as molecular probes would give us a clearer insight into the intricate molecular mechanisms of autophagy in plant microbial interactions.

Acknowledgments

This work made possible by funding from the Biotechnology and Biological Sciences Research Council (BB/M002462/1 and BB/M011224/1), the BBSRC doctoral training program, the Royal Thai Government scholarship, the Imperial College Schrödinger Scholarship Scheme, the TUBITAK & British Council Newton-Katip Çelebi Fund and the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET).

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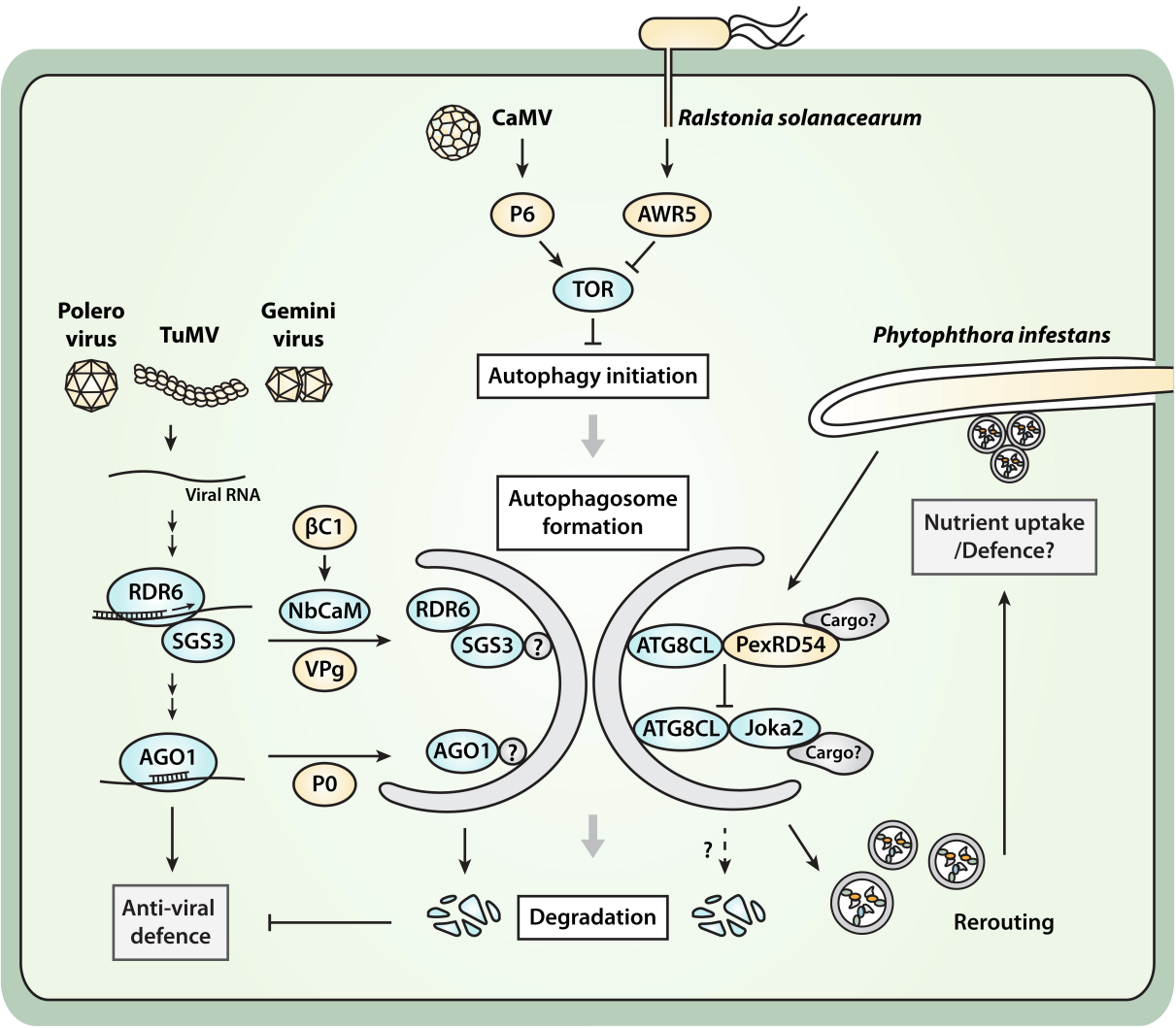
Figure 1. Modulation of autophagy by plant pathogens during infection.

Autophagy plays a vital role against invading plant pathogens. As a result, microbes have evolved means to evade and even modulate autophagy for their own benefit during infection. The polerovirus RNA silencing suppressor P0 mediates autophagic degradation of ARGONAUTE 1 (AGO1), an essential component of the RNA-induced silencing complex. It remains unknown whether P0 acts as an ATG8 binding cargo receptor or as an autophagic adaptor, trafficking AGO1 to a host cargo receptor for degradation. The *Turnip mosaic virus* (TuMV) protein VPg mediates autophagic degradation of the host Suppressor of Gene Silencing 3 (SGS3)/RNA-dependent RNA polymerase 6 (RDR6) complex. Furthermore, the geminivirus protein βC1 induces the host susceptibility factor NbCaM that mediates autophagic degradation of the SGS3/RDR6 complex.

The oomycete pathogen *Phytophthora infestans* secreted effector PexRD54 outcompetes the plant defence related cargo receptor Joka2 for binding of the core autophagy protein ATG8CL, in turn stimulating autophagosome formation. These ATG8CL autophagosomes appear to be rerouted to the pathogen interface for a yet unknown purpose.

The *Cauliflower mosaic virus* (CaMV) protein P6 has been found to promote activation of the host Target of Rapamycin (TOR) to inhibit activation of oxidative burst and salicylic acid dependent autophagy through an unknown mechanism. Interestingly, the *Ralstonia solanacearum* protein AWR5 has been found to directly or indirectly inhibit activation of TOR to instead stimulate autophagy during infection.


CaMV
Ralstonia solanacearum
P6
AWR5
TOR
Autophagy initiation
Polero virus
TuMV
Gemini virus
Viral RNA
Phytophthora infestans
Autophagosome formation
Nutrient uptake /Defence?
βC1
RDR6
SGS3
NbCaM
VPg
AGO1
P0
RDR6
SGS3
?
AGO1
?
ATG8CL
PexRD54
Cargo?
ATG8CL
Joka2
Cargo?
?
Anti-viral defence
Degradation
Rerouting