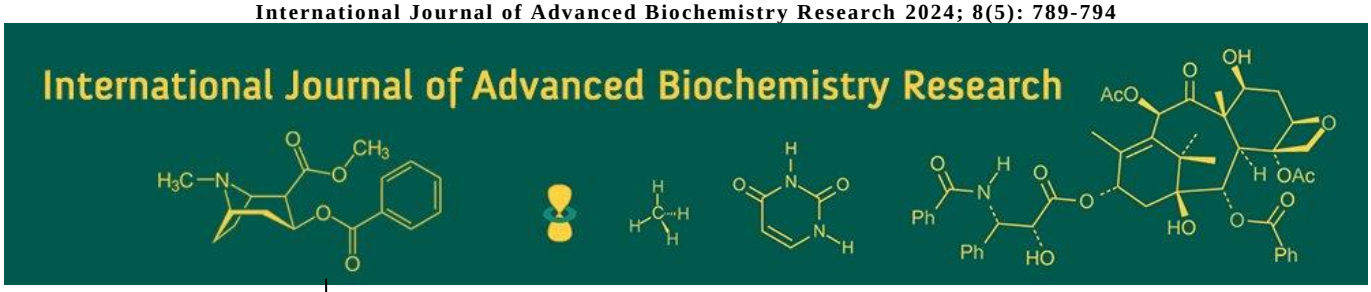

ISSN Print: 2617-4693
ISSN Online: 2617-4707
IJABR 2024; 8(5): 789-794
www.biochemjournal.com
Received: 14-02-2024
Accepted: 17-03-2024

C Shanmugaraj
ICAR - Indian Agricultural Research Institute (IARI), New Delhi, India

V Jaiganesh
TNAU - Citrus Research Station (CRS), Vannikonendal, Tirunelveli, Tamil Nadu, India

HM Akshay Kumar
ICAR - Indian Agricultural Research Institute (IARI), Assam, India

MK Biswas
Palli Siksha Bhavana, Visva-Bharati University, West Bengal, India

Corresponding Author:
C Shanmugaraj
ICAR - Indian Agricultural Research Institute (IARI), New Delhi, India

Deciphering the complex roles of autophagy in plant immunity

C Shanmugaraj, V Jaiganesh, HM Akshay Kumar and MK Biswas

DOI: https://doi.org/10.33545/26174693.2024.v8.i5j.1188

Abstract
Plant defense mechanisms involve a complex network of cellular processes working together to initiate effective immune responses. Autophagy, a fundamental cellular recycling mechanism crucial for responding to nutrient shortages and maintaining cellular balance, has emerged as a key component in plant immunity. Despite recent progress, our understanding of plant autophagy remains limited, and its intricate role in plant defense presents ongoing challenges. This review explores the dual nature of autophagy in plant immunity, highlighting both its beneficial and detrimental effects, as well as how different pathogens exploit this process for their advantage. The diverse role of autophagy in plant immunity emphasizes the need for further investigation and clarification in this area.

Keywords: PTI, ETI, reactive oxygen species, PCD, immunity

Introduction
Plants have developed a sophisticated defense system to protect themselves against pathogen attacks (Jones and Dangl, 2006) [12], (Dangl *et al*., 2013) [3], (Ngou *et al*., 2022) [23]. Pattern-triggered immunity (PTI) is activated when plants recognize conserved microbial components such as fungal chitin or bacterial flagellin through pattern recognition receptors (PRRs) on their cell surfaces. This recognition triggers a cascade of defense responses, including the production of reactive oxygen species (ROS), synthesis of plant hormones, deposition of callose, and alteration of defense-related gene expression (DeFalco and Zipfel, 2021) [4]. However, certain pathogens have evolved strategies to evade PTI by secreting effector proteins into host cells. These effectors manipulate various cellular processes to suppress PTI, promoting pathogenicity (Toruno *et al*., 2016) [30]. In response, plants employ intracellular immune receptors called nucleotide-binding leucine-rich repeat (NLR) proteins, which detect effector presence or activity. This result in effector-triggered immunity (ETI), activating immune signalling pathways that induce programmed cell death, known as the hypersensitive response (HR-PCD). Signalling molecules like salicylic acid (SA) and ROS play roles in initiating and regulating HR-PCD. This targeted cell death confines pathogens, preventing their spread to neighbouring cells (Zhang and Dong, 2022) [41]. Generally, plants have two types of NLRs: Toll-interleukin-1 receptor homology (TIR) domain-containing NLRs (TNLs) and coiled-coil domain-containing NLRs (CNLs). Although PTI and ETI have distinct triggers and characteristics, their interconnectedness is increasingly recognized. The collaboration between these immune responses is crucial in combating plant diseases (Yuan *et al*., 2021) [39], (Ngou *et al*., 2021) [22], (Pruitt *et al*., 2021) [26], (Tian *et al*., 2021) [29].
Autophagy, a conserved process found in all eukaryotes, involves the recycling or degradation of cellular components and malfunctioning organelles within a specialized cellular compartment to maintain cellular equilibrium (Yin *et al*., 2016) [37], (Morishita and Mizushima, 2019) [21]. While there are various types of autophagy, macroautophagy has been extensively studied and is commonly referred to simply as autophagy in scientific discussions. Autophagy is primarily characterized by the formation of autophagosomes, specialized vesicles with double membranes that transport cellular materials for degradation within the plant vacuole or animal lysosomes (Hu and Reggiori, 2022) [11]. Selective autophagy occurs when specific organelles or molecules are targeted for degradation (Marshall and Vierstra, 2018) [20], (Gubas and Dikic, 2022) [5]. In plants, more than 40 autophagy-related (ATG) genes have been identified, each with distinct yet interconnected

roles in autophagy regulation (Tang and Bassham, 2018) [27]. Mutations in ATG genes can impact not only autophagy but also various cellular and developmental processes (Levine and Kroemer, 2019) [16]. The autophagy process consists of several stages, starting with initiation and progressing through nucleation, elongation, completion, and ultimately, the fusion of autophagosomes with the vacuole or lysosome. This facilitates the delivery and subsequent degradation or recycling of cargoes. Numerous studies have demonstrated the significant reliance of plant immunity on the effective functioning of plant autophagy. Moreover, pathogens employ various strategies to manipulate autophagy to subvert host immunity. This review explores the diverse aspects of the relationship between autophagy and plant defense mechanisms, including the roles of autophagy in enhancing plant immunity and the tactics used by pathogens to influence autophagy.

Roles of autophagy in PRR-mediated defence

In Arabidopsis, autophagy regulates the levels of FLAGELLIN-SENSING 2 (FLS2), a receptor kinase crucial for pattern recognition, which detects bacterial flagellin and activates pattern-triggered immunity (PTI) through orosomucoid (ORM) proteins (Zipfel *et al*., 2004) [43], (Yang *et al*., 2019) [36]. ORM proteins act as autophagy receptors, facilitating the degradation of FLS2 via autophagy. Reduction of ORM expression through RNAi or CRISPR-Cas9 in orm1 and orm2 mutant plants resulted in excessive FLS2 accumulation and heightened PTI response upon infection with *Pseudomonas syringae* pv. *tomato* strain DC3000 (Pst DC3000). Conversely, elevated ORM levels led to decreased FLS2 levels and increased susceptibility to Pst DC3000 infection. Furthermore, increased ORM expression in atg7-2 and atg10-1 mutants did not affect FLS2 accumulation and conferred resistance against Pst DC3000, in contrast to wild-type plant's response (Yang *et al*., 2019) [36]. This research underscores the inhibitory role of autophagy in FLS2-triggered PTI by promoting FLS2's autophagic degradation. While ORMs did not influence other pattern recognition receptor (PRR)-mediated signalling pathways examined, it prompts further investigation into autophagy's potential involvement in regulating PRR levels through different targeting mechanisms and selective degradation.

BAK1 acts as a co-receptor for various pattern recognition receptors (PRRs), crucial for initiating immune responses by facilitating the activation of immune signalling pathways (DeFalco and Zipfel, 2021) [4]. Recent findings reveal that BAK1 has a negative regulatory impact on ATG18a's functions post *Botrytis cinerea* infection (Zhang *et al*., 2021) [40]. ATG18a plays a pivotal role in plant defense against *B. cinerea* by aiding autophagy-mediated degradation and enhancing the expression of the defense-related transcription factor WRKY33 (Lai *et al*., 2011) [13]. During the plant's defense against *B. cinerea*, BAK1 phosphorylates and hampers ATG18a activity. In the absence of BAK1 function, ATG18a experiences decreased phosphorylation, resulting in heightened autophagy and improved resistance against *B. cinerea* (Zhang *et al*., 2021) [40]. This study illuminates a novel connection between PRR-mediated defense mechanisms and autophagy, showcasing how the immune system regulates autophagy to modulate pathogen-triggered defense responses.

Autophagy's dual function in immune-triggered cell demise

Autophagy plays a dual role in plant defense mechanisms, contributing to both survival and cell death processes. Research suggests that the outcome is influenced by various factors, including the type of pathogens, the plant's developmental stage, and the specific defense mechanisms activated. Typically, when a plant's NLR detects pathogen-derived effectors, it initiates the ETI reaction, leading to localized cell death at the infection site and thus limiting pathogen spread (Jones and Dangl, 2006) [12], (Zhang and Dong, 2022) [41].

In *Nicotiana benthamiana* plants containing the N protein, resistance against Tobacco mosaic virus (TMV) is conferred. Upon TMV infection, it triggers hypersensitive response-programmed cell death (HR-PCD), containing TMV within the infection site (Whitham *et al*., 1994) [34], (Liu *et al*., 2002) [19]. However, when the plant's version of ATG6/Beclin1, essential for autophagosome formation, was silenced in N-containing plants, HR-PCD expanded beyond the infected area, affecting nearby healthy tissue and systemic leaves. Similar outcomes were observed with the suppression of other crucial autophagy-related genes, such as ATG3, ATG7, and VPS34 (Liu *et al*., 2005) [18]. These findings suggest that in cells lacking autophagy, the signals promoting cell death during HR-PCD are not contained, indicating a supportive role of immunity-induced autophagy in promoting cell survival.

A similar expansion of cell death was observed in Arabidopsis plants with silenced ATG6 genes at four weeks of age upon infection with the hemibiotrophic pathogen Pst DC3000 carrying the AvrRpm1 effector gene (Pst-AvrRpm1) (Patel and Dinesh Kumar, 2008) [25]. Furthermore, Arabidopsis plants with atg5-1 genes knocked out exhibited uncontrolled cell death in response to Pst-AvrRpm1 infection (Yoshimoto *et al*., 2009) [38]. These findings indicate that autophagy triggered by immunity plays a critical role in promoting cell survival by eliminating signals that induce cell death, such as HR-PCD.

In mammalian biology, the equilibrium between cell survival and cell demise is governed by proteins from the B-cell lymphoma 2 (Bcl-2) family, comprising both anti-apoptotic and pro-apoptotic members such as BAX (BCL2-associated X) and BAK (BCL2 antagonist/killer), which also influence autophagy processes (Levine and Kroemer, 2019) [16]. In contrast to mammals, plants lack equivalents to Bcl-2, BAX, or BAK proteins. Nevertheless, they possess a conserved protein termed Bax inhibitor 1 (BI-1)-like protein, which acts as a suppressor of cell death (Henke *et al*., 2011) [8]. In plants, BI-1 interacts with ATG6, and this interaction is crucial for triggering autophagy during resistance mediated by the N TNL against TMV (Xu *et al*., 2017) [35]. Inhibition of BI-1 resulted in elevated levels of TMV-GFP and heightened cell death, indicating that BI-1 is vital for initiating autophagy to mitigate cell demise. In contrast to its conventional role in inhibiting cell death, the overexpression of BI-1 induces cell death in plants, and this process of cell demise depends on the presence of autophagy. These findings underscore the dual function of plant BI-1 in promoting and restraining cell death. Although the mechanism governing the transition between these roles remains incompletely understood, it is likely that autophagy, which is also governed by BI-1, plays a pivotal role in this process.

Cytoplasmic glyceraldehyde-3-phosphate dehydrogenases (GAPDH) play a role in regulating autophagy in plants. In *Nicotiana benthamiana*, GAPDH acts as an inhibitor of autophagy by interacting with ATG3. When GAPDH is suppressed, there is an increase in hypersensitive response-programmed cell death (HR-PCD) when N interacts with Tobacco Mosaic Virus (TMV), as well as enhanced resistance to virulent strains such as Pst DC3000 and *P. syringae* pv. *tabaci* (Han *et al*., 2015) [7]. Similarly, Arabidopsis plants lacking GAPDH exhibit higher levels of reactive oxygen species (ROS) and sustained autophagy. These mutant plants show increased HR-PCD when exposed to Pst-AvrRpt2 and demonstrate inherent resistance to Pst DC3000 infection (Henry *et al*., 2015) [9]. Overall, GAPDH acts as a suppressor of immunity-induced cell death and basal resistance, potentially through its inhibitory effects on plant autophagy.

Plant autophagy may contribute to promoting cell death in certain interactions between plants and pathogens. For example, in Arabidopsis, the TNLs RPS4 and RPP1 recognize the AvrRps4 effector from Pst DC3000 and the AvrAtr1 effector from the oomycete *Hyaloperonospora arabidopsidis*, respectively. Similarly, the CNLs RPM1 and RPS2 recognize the effectors AvrRpm1 and AvrRpt2 from Pst. When these effectors are successfully recognized, it triggers HR-PCD. However, in mutants such as atg7-1 and atg9-1, HR-PCD inhibition occurs following infection with Pst-AvrRps4 and *H. arabidopsidis* race Noco2, as shown by electrolyte leakage assays. The involvement of autophagy in promoting cell death seems to have some specificity, as minimal decrease in electrolyte leakage was observed in atg7-1 and atg9-1 mutants following infection with Pst-AvrRpm1, or in atg5-1 and atg7-2 mutants after infection with Pst-AvrRpt2 (Hofius *et al*., 2009) [10]. However, when looking at cell death individually, the HR-PCD triggered by Pst-AvrRpm1 was inhibited in 2-week-old atg5-1 and atg18a mutant plants (Coll *et al*., 2014) [1]. Furthermore, catalase, an antioxidant enzyme, seems to act before autophagy in inducing cell death by Pst-AvrRpm1 (Hackenberg *et al*., 2013) [6]. These findings provide evidence supporting the involvement of autophagy in the cell death initiated by specific NLRs when pathogens infect young plants.

Autophagy's dual function in disease associated cell demise

Cell death associated with diseases typically involves necrotic cell demise, which is triggered by necrotrophic pathogens such as *B. cinerea* exploiting host vulnerability. Apart from its function in promoting cell survival during immunity-induced cell death, autophagy also contributes to regulating disease-associated cell death. In a study by Patel and Dinesh Kumar (2008) [25], Arabidopsis ATG6 RNAi lines displayed uncontrolled proliferation of cell death induced by disease when infected with virulent Pst DC3000. Similarly, mutations in atg5-1, atg10-1, atg18a-1, and atg18a-2 (ATG18a RNAi) in Arabidopsis plants led to the expansion of disease-linked cell death and increased susceptibility to infection by the necrotrophic fungus *Alternaria brassicicola*, as demonstrated by Lenz *et al*. (2011) [15]. Additionally, Arabidopsis lines with mutations in atg5-1, atg7-2, atg7-3, atg18a-1, and atg18a-2 exhibited heightened cell death related to disease and were more susceptible to infection by the necrotrophic fungus *B. cinerea*, as shown in a study by Lai *et al*. (2011) [13]. These investigations provide evidence supporting the beneficial role of autophagy in defense against necrotrophic pathogens. On the contrary, plants carrying the atg2-2 mutation displayed enhanced immunity towards *Golovinomyces cichoracearum*, an obligate biotrophic fungus responsible for powdery mildew (Wang *et al*., 2011) [33]. This improved resistance in atg2-2 plants was accompanied by increased expression levels of defense-related genes like PR1, PR2, and PR5, alongside higher concentrations of salicylic acid (SA) and reactive oxygen species (ROS). Similarly, mutations in other autophagy-related genes such as atg5-1, atg7-1, and atg10-1 also demonstrated heightened resistance against *G. cichoracearum*, comparable to the atg2-2 plants. These findings suggest that autophagy may have a negative impact on defense mechanisms against this particular obligate biotrophs.

Members of the Bcl-2-associated athanogene (BAG) family play a crucial role in governing cell death mechanisms (Thanthrige *et al*., 2020) [28]. In Arabidopsis, BAG6 is implicated in controlling cell death associated with disease upon infection by *B. cinerea*. Normally, Arabidopsis plants of the Col-0 wild-type variety display localized cell death symptoms at the site of *B. cinerea* inoculation. However, Arabidopsis mutants lacking the BAG6 gene exhibit rapid extension of cell death beyond the inoculation site, rendering them more susceptible to *B. cinerea*. The ability of BAG6 to confer resistance against *B. cinerea* depends on its cleavage by the aspartyl protease APCB1 (Aspartyl Protease Cleaving BAG). Interestingly, introducing a cleavage-resistant form of BAG6 into bag6 mutants does not restore resistance against *B. cinerea*. In response to *B. cinerea* infection and cleaved BAG6 presence, autophagy is activated, which is crucial for initiating immune responses and inducing autophagic cell death to contain *B. cinerea* at the infection site (Li *et al*., 2016) [17]. These findings highlight the role of BAG6 in promoting plant immune responses through the regulation of host autophagy and, consequently, pathogen-induced cell death.

The Role of autophagy in the regulation of SA and ROS levels

Salicylic acid (SA) and reactive oxygen species (ROS) act as protective elements in plants and are tightly regulated (Zhang and Dong, 2022) [41]. SA operates as a crucial hormone in signalling defense mechanisms upon pathogen detection, leading to its synthesis and accumulation. ROS are also generated in response to pathogen recognition and play a significant role in signalling defense responses, although excessive ROS levels can cause cellular damage. Both SA and ROS are involved in regulating hypersensitive response-programmed cell death (HR-PCD). Studies have demonstrated that autophagy negatively regulates the accumulation of SA and ROS. Arabidopsis plants lacking the ATG5 gene (atg5-1) exhibited increased SA accumulation and elevated expression of SA-responsive genes when infected with Pst DC3000. Similar results were observed in atg2-1 and atg5-1 mutants, which also showed higher levels of hydrogen peroxide (H_2O_2). The spread of cell death observed in atg5-1 mutants in response to Pst-AvrRpm1 was suppressed when SA-related pathways were deactivated (Yoshimoto *et al*., 2009) [38]. Comparable outcomes were found in atg2-2 plants when challenged with the powdery mildew pathogen *G. cichoracearum*. These

mutants displayed increased resistance to the pathogen but also showed symptoms of autoimmunity, including inhibited growth and premature aging. Disabling SA signalling in atg2-2 mutants alleviated autoimmunity symptoms and reduced resistance to powdery mildew (Wang *et al*., 2011) [33]. Autophagy appears to downregulate the SA-ROS amplification signalling pathway, mediating HR-PCD (Zhang *et al*., 2020) [42]. Arabidopsis mutants such as atg5-1, atg10-1, atg18a-1, and atg18a-2 showed enhanced resistance to Pst DC3000 infection and accumulated higher levels of SA. However, their response to the necrotrophic pathogen *A. brassicicola* differed, resulting in larger necrotic lesions without significant changes in ROS production (Lenz *et al*., 2011) [15]. This highlights the complex interplay between SA, ROS, and autophagy in plant defense mechanisms, which is influenced by the characteristics of pathogens.

Microbial manipulation of autophagy

Manipulation of the autophagy pathway by effectors derived from different pathogens appears to be a common strategy to enhance their disease-causing potential. This underscores the pivotal role of autophagy in determining the outcomes of infections and in the ongoing evolutionary battle between pathogens and plants. The success of bacterial infections in plants hinges on the pathogen's ability to circumvent the host's immune defenses. While extensive research has focused on bacterial effectors and their interactions with various biological pathways in plants, recent efforts have shed light on effectors capable of modulating plant autophagy. Type 3 effectors from Pst DC3000 disrupt the ubiquitin-proteasome system (UPS), a crucial pathway for protein degradation in eukaryotic cells, to heighten their virulence (Ustun *et al*., 2016) [32]. Nevertheless, the Pst effectors failed to impede the UPS in the atg5-1 knockout mutant, highlighting the significance of pathogen-induced autophagy in disturbing the plant UPS. Additionally, HopM1 has been recognized as an effector that promotes host autophagy. However, NBR1, an autophagic cargo receptor, mitigated the impact of HopM1 by decreasing water-soaked lesions and bacterial propagation (Ustun *et al*., 2018) [31]. Collectively, Pst DC3000 exploits host autophagy through the HopM1 effector to degrade the UPS, facilitating bacterial proliferation and infection. Conversely, plants counteract HopM1's actions through NBR1-mediated selective autophagy, targeting unidentified specific proteins. The Pst DC3000 effector HrpZ1 induces autophagy in plants, aiding disease progression by interacting with various Arabidopsis ATG8 isoforms, hinting at its potential role in manipulating the host's autophagy pathway. Further research unveiled that HrpZ1 boosts autophagy by enhancing ATG4b protease activity, crucial for modifying ATG8 during autophagosome formation. Besides triggering autophagy, certain bacterial effectors suppress it to bolster bacterial virulence. For instance, the *Pseudomonas* effector HopF3 interacts selectively with a subset of Arabidopsis ATG8 proteins, inhibiting autophagy. Expression of HopF3 in Arabidopsis atg5-1 mutants diminished the heightened virulence of Pst DC3000 seen in normal plants, underscoring the pivotal role of host autophagy in HopF3-mediated virulence. Similar to HopF3, the Pst DC3000 effector AvrPtoB suppresses autophagy by targeting the ATG1 kinase, a key initiator of autophagy. AvrPtoB disrupts ATG1 phosphorylation, dampening autophagy while enhancing bacterial virulence (Lal *et al*., 2020) [14].

Similar to bacteria, oomycete pathogens employ effector proteins to impede host immunity. One such effector, PexRD54 found in *Phytophthora infestans*, contains two predicted ATG8 interacting motifs (AIMs). One of these AIMs, in conjunction with the host small GTPase Rab8a, which plays a crucial role in vesicle trafficking, is essential for the interaction between PexRD54 and ATG8CL. This interaction facilitates the integration of the effector into autophagosomes, disrupting the interaction between ATG8CL and the autophagy cargo receptor Joka2, a tobacco counterpart of NBR1. Ultimately, this mechanism strengthens defense against *P. infestans* infection (Dagdas *et al*., 2016) [2], (Pandey *et al*., 2021) [24].

In the ongoing evolutionary battle between plants and pathogens, it is evident that pathogens have developed tactics to manipulate or exploit the autophagy pathway, thus enhancing their ability to cause disease. This manipulation is often achieved through microbial effectors, with some effectors stimulating autophagy while others inhibit it. Additionally, certain effectors compete for interaction with host autophagy components without disrupting the overall autophagic process. Despite these variations, the ultimate goal of enhancing pathogen virulence remains consistent. However, only a limited number of effectors have been identified as directly disrupting autophagy. Across various kingdoms, numerous effectors from pathogens have been observed to interact with ATG proteins, yet their precise mechanisms for regulating autophagy remain incompletely understood. Understanding their functions and how plants respond to these effectors would provide valuable insights into the interplay between autophagy and plant immunity.

Conclusion

Autophagy serves as a vital mechanism for recycling when organisms face various stresses, especially under conditions of nutrient scarcity. Disruption of autophagy can result in abnormalities in the growth and function of eukaryotic organisms. Evidence is mounting to suggest a connection between autophagy and plant defense against pathogens. Several studies have illustrated that mutations or suppression of different ATG genes affect how plants defend against pathogens through both the PTI (Pathogen-Associated Molecular Pattern Triggered Immunity) and ETI (Effector Triggered Immunity) pathways. In terms of PTI and basal resistance, plants with altered ATG genes have shown diverse responses to various virulent pathogens, with some exhibiting increased resistance and others demonstrating reduced resistance. Changes in the host's defense mechanisms have been linked to modifications in key elements of basal resistance and the equilibrium of immune receptors. In the realm of Effector Triggered Immunity (ETI), autophagy plays a critical role in regulating Hypersensitive Response-Programmed Cell Death (HR-PCD). Autophagy can have both pro-death and pro-survival functions during ETI-mediated PCD in response to pathogen attack. However, it is important to recognize that discrepancies observed in studies of both PTI and ETI may stem from differences in pathogen types and specific genotypes of plant ATG mutants. This suggests potential involvement of individual ATGs in other biological pathways associated with autophagy. Numerous host factors participating in the pathway from pathogen recognition to the initiation of autophagy and HR-PCD have been identified. Nonetheless, understanding their precise roles

and mechanisms of action within this pathway, as well as identifying any additional unknown contributors, will require further investigation to complete the puzzle. Despite occasional inconsistencies, pathogens have developed tactics to enhance their virulence by influencing plant autophagy. Overall, the dual role of autophagy in plant immunity highlights the complexity of this relationship and emphasizes the extensive exploration still needed in this field.

References

1. Coll NS, Smidler A, Puigvert M, Popa C, Valls M, Dangl JL. The plant metacaspase AtMC1 in pathogen triggered programmed cell death and aging: functional linkage with autophagy. Cell Death Differ. 2014;21:1399-408. https://doi.org/10.1038/cdd.2014.50
2. Dagdas YF, Belhaj K, Maqbool A, Chaparro-Garcia A, Pandey P, Petre B, *et al*. An effector of the Irish potato famine pathogen antagonizes a host autophagy cargo receptor. eLife. 2016;5:e10856. https://doi.org/10.7554/eLife.10856
3. Dangl JL, Horvath DM, Staskawicz BJ. Pivoting the plant immune system from dissection to deployment. Science. 2013;341:746-751. https://doi.org/10.1126/science.1236011
4. DeFalco TA, Zipfel C. Molecular mechanisms of early plant pattern-triggered immune signaling. Mol Cell. 2021;81:4346. https://doi.org/10.1016/j.molcel.2021.07.029
5. Gubas A, Dikic I. A guide to the regulation of selective autophagy receptors. FEBS J. 2022;289:75-89.https://doi.org/10.1111/febs.15824
6. Hackenberg T, Juul T, Auzina A, Gwizdz S, Malolepszy A, Van Der Kelen K, *et al*. Catalase and NO CATALASE ACTIVITY1 promote autophagy dependent cell death in Arabidopsis. Plant Cell. 2013;25:4616-4626. https://doi.org/10.1105/tpc.113.117192
7. Han S, Wang Y, Zheng X, Jia Q, Zhao J, Bai F, *et al*. Cytoplastic glyceraldehyde-3-phosphate dehydrogenases interact with ATG3 to negatively regulate autophagy and immunity in *Nicotiana benthamiana*. Plant Cell. 2015;27:1316-1331. https://doi.org/10.1105/tpc.114.134692
8. Henke N, Lisak DA, Schneider L, Habicht J, Pergande M, Methner A. The ancient cell death suppressor BAX inhibitor-1. Cell Calcium. 2011;50:251-260. https://doi.org/10.1016/j.ceca.2011.05.005
9. Henry E, Fung N, Liu J, Drakakaki G, Coaker G. Beyond glycolysis: GAPDHs are multi-functional enzymes involved in regulation of ROS, autophagy, and plant immune responses. PLoS Genet. 2015;11:e1005199. https://doi.org/10.1371/journal.pgen.1005199
10. Hofius D, Schultz-Larsen T, Joensen J, Tsitsigiannis DI, Petersen NHT, Mattsson O, *et al*. Autophagic components contribute to hypersensitive cell death in Arabidopsis. Cell. 2009;137:773-783. https://doi.org/10.1016/j.cell.2009.02.036
11. Hu Y, Reggiori F. Molecular regulation of autophagosome formation. Biochem Soc Trans. 2022;50:55-69. https://doi.org/10.1042/BST20210819
12. Jones JD, Dangl JL. The plant immune system. Nature. 2006;444:323-329. https://doi.org/10.1038/nature05286
13. Lai Z, Wang F, Zheng Z, Fan B, Chen Z. A critical role of autophagy in plant resistance to necrotrophic fungal pathogens. The Plant Journal. 2011;66:953-968. https://doi.org/10.1111/j.1365-313X.2011.04553.x
14. Lal NK, Thanasuwat B, Huang PJ, Cavanaugh KA, Carter A, Michelmore RW, *et al*. Phytopathogen effectors use multiple mechanisms to manipulate plant autophagy. Cell Host Microbe. 2020;28:558-571.e6. https://doi.org/10.1016/j.chom.2020.07.010
15. Lenz HD, Haller E, Melzer E, Kober K, Wurster K, Stahl M, *et al*. Autophagy differentially controls plant basal immunity to biotrophic and necrotrophic pathogens. The Plant Journal. 2011;66:818-830. https://doi.org/10.1111/j.1365-313X.2011.04546.x
16. Levine B, Kroemer G. Biological functions of autophagy genes: a disease perspective. Cell. 2019;176:11-42. https://doi.org/10.1016/j.cell.2018.09.048
17. Li Y, Kabbage M, Liu W, Dickman MB. Aspartyl protease-mediated cleavage of BAG6 is necessary for autophagy and fungal resistance in plants. Plant Cell. 2016;28:233-47. https://doi.org/10.1105/tpc.15.00626
18. Liu Y, Schiff M, Czymmek K, Talloczy Z, Levine B, Dinesh-Kumar SP. Autophagy regulates programmed cell death during the plant innate immune response. Cell. 2005;121:567-77. https://doi.org/10.1016/j.cell.2005.03.007
19. Liu Y, Schiff M, Marathe R, Dinesh-Kumar SP. Tobacco Rar1, EDS1 and NPR1/NIM1 like genes are required for N-mediated resistance to tobacco mosaic virus. The Plant Journal. 2002;30:415-429. https://doi.org/10.1046/j.1365-313x.2002.01297.x
20. Marshall RS, Vierstra RD. Autophagy: the master of bulk and selective recycling. Annu Rev Plant Biol. 2018;69:173-208. https://doi.org/10.1146/annurev-arplant-042817-040606
21. Morishita H, Mizushima N. Diverse cellular roles of autophagy. Annu Rev Cell Dev Biol. 2019;35:453-75. https://doi.org/10.1146/annurev-cellbio-100818-125300
22. Ngou BP, Ahn HK, Ding P, Jones JD. Mutual potentiation of plant immunity by cell-surface and intracellular receptors. Nature. 2021;592(7852):110-5. https://doi.org/10.1038/s41586-021-03315-7
23. Ngou BP, Ding P, Jones JD. Thirty years of resistance: Zig-zag through the plant immune system. The Plant Cell. 2022;34(5):1447-1478. https://doi.org/10.1093/plcell/koac041
24. Pandey P, Leary AY, Tumtas Y, Savage Z, Dagvadorj B, Duggan C, *et al*. An oomycete effector subverts host vesicle trafficking to channel starvation-induced autophagy to the pathogen interface. eLife. 2021;10:e65285.https://doi.org/10.7554/eLife.65285
25. Patel S, Dinesh-Kumar SP. Arabidopsis ATG6 is required to limit the pathogen-associated cell death response. Autophagy. 2008;4:20-27. https://doi.org/10.4161/auto.5056
26. Pruitt RN, Locci F, Wanke F, Zhang L, Saile SC, Joe A, *et al*. The EDS1-PAD4-ADR1 node mediates Arabidopsis pattern-triggered immunity. Nature. 2021;598:495-499. https://doi.org/10.1038/s41586-021-03829-0
27. Tang J, Bassham DC. Autophagy in crop plants: what's new beyond Arabidopsis? Open Biol. 2018;8:180162. https://doi.org/10.1098/rsob.180162

28. Thanthrige N, Jain S, Bhowmik SD, Ferguson BJ, Kabbage M, Mundree S, *et al*. Centrality of BAGs in plant PCD, stress responses, and host defense. Trends Plant Sci. 2020;25:1131-1140. https://doi.org/10.1016/j.tplants.2020.04.012
29. Tian H, Wu Z, Chen S, Ao K, Huang W, Yaghmaiean H, *et al*. Activation of TIR signalling boosts pattern triggered immunity. Nature. 2021;598:500-503. https:doi.org/10.1038/s41586-021-03987-1
30. Toruno TY, Stergiopoulos I, Coaker G. Plant-pathogen effectors: cellular probes interfering with plant defenses in spatial and temporal manners. Annu Rev Phytopathol. 2016;54:419-441. https://doi.org/10.1146/annurev-phyto-080615-100204
31. Ustun S, Hafren A, Liu Q, Marshall RS, Minina EA, Bozhkov PV, *et al*. Bacteria exploit autophagy for proteasome degradation and enhanced virulence in plants. Plant Cell. 2018;30:668-685. https://doi.org/10.1105/tpc.17.00815
32. Ustun S, Sheikh A, Gimenez-Ibanez S, Jones A, Ntoukakis V, Bornke F. The proteasome acts as a hub for plant immunity and is targeted by *Pseudomonas* type III effectors. Plant Physiol. 2016;172:1941-1958. https://doi.org/10.1104/pp.16.00808
33. Wang Y, Nishimura MT, Zhao T, Tang D. ATG2, an autophagy-related protein, negatively affects powdery mildew resistance and mildew-induced cell death in Arabidopsis. The Plant Journal. 2011;68:74-87. https://doi.org/10.1111/j.1365-313X.2011.04669.x
34. Whitham S, Dineshkumar SP, Choi D, Hehl R, Corr C, Baker B. The product of the Tobacco mosaic-virus resistance gene-N - similarity to Toll and the interleukin-1 receptor. Cell. 1994;78:1101-1115. https://doi.org/10.1016/0092-8674(94)90283-6
35. Xu G, Wang S, Han S, Xie K, Wang Y, Li J, *et al*. Plant Bax inhibitor-1 interacts with ATG6 to regulate autophagy and programmed cell death. Autophagy. 2017;13:1161-1175. https://doi.org/10.1080/15548627.2017.1320633
36. Yang F, Kimberlin AN, Elowsky CG, Liu Y, Gonzalez-Solis A, Cahoon EB, *et al*. A plant immune receptor degraded by selective autophagy. Mol Plant. 2019;12:113-123. https://doi.org/10.1016/j.molp.2018.11.011
37. Yin Z, Pascual C, Klionsky DJ. Autophagy: machinery and regulation. Microbial Cell. 2016;3:588-596. https://doi.org/10.15698/mic2016.12.546
38. Yoshimoto K, Jikumaru Y, Kamiya Y, Kusano M, Consonni C, Panstruga R, *et al*. Autophagy negatively regulates cell death by controlling NPR1-dependent salicylic acid signaling during senescence and the innate immune response in Arabidopsis. Plant Cell. 2009;21:2914-2927. https://doi.org/10.1105/tpc.109.068635
39. Yuan M, Jiang Z, Bi G, Nomura K, Liu M, Wang Y, *et al*. Pattern-recognition receptors are required for NLR-mediated plant immunity. Nature. 2021;592(7852):105-9. https://doi.org/10.1038/s41586-021-03316-6
40. Zhang B, Shao L, Wang J, Zhang Y, Guo X, Peng Y, *et al*. Phosphorylation of ATG18a by BAK1 suppresses autophagy and attenuates plant resistance against necrotrophic pathogens. Autophagy. 2021;17:2093-20110. https://doi.org/10.1080/15548627.2020.1810426
41. Zhang X, Dong X. Life-or-death decisions in plant immunity. Curr Opin Immunol. 2022;75:102169. https://doi.org/10.1016/j.coi.2022.102169
42. Zhang Y, Wang HL, Li Z, Guo H. Genetic network between leaf senescence and plant immunity: crucial regulatory nodes and new insights. Plants (Basel). 2020;9:495. https://doi.org/10.3390/plants9040495
43. Zipfel C, Robatzek S, Navarro L, Oakeley EJ, Jones JD, Felix G, *et al*. Bacterial disease resistance in Arabidopsis through flagellin perception. Nature. 2004;428:764-767. https://doi.org/10.1038/nature02485