Autophagy under attack

Pathogens target proteins involved in autophagy to inhibit immune responses in plants.

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The Irish potato famine was responsible for more than one million deaths and the emigration of one million people from Europe in the 1840s (Andrivon, 1996). Today, the microbe that caused the famine, an oomycete called Phytophthora infestans, continues to cause serious outbreaks of disease in potato crops. Traditional control measures, such as fungicides and breeding for resistance, often have only marginal success in combating the disease, especially when the climate favors the growth and development of P. infestans (Fry and Goodwin, 1997). Now, in eLife, Sophien Kamoun, Tolga Bozkurt and colleagues – including Yasin Dagdas and Khaoula Belhaj as joint first authors – report how they carried out a screen for plant molecules that interact with effectors from P. infestans (Dagdas et al., 2016). The experiments were carried out in the leaves of tobacco, which is a commonly used plant model, and show that an effector called PexRD54 targets a process called autophagy in plant cells.

Autophagy is a complex “self-eating” process that occurs when plant and other eukaryotic cells experience certain stresses – for example, due to a shortage of nutrients or a change in environmental conditions. During autophagy, cell material is broken down to supply the building blocks needed to maintain essential processes (Li and Vierstra, 2009). More recently, autophagy has been implicated in a variety of other situations, including restricting the growth and spread of invading microbes. A growing body of evidence suggests that autophagy plays a dual role both in promoting the survival of cells and in triggering cell death.

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Related research article
Dagdas YF, Belhaj K, Maqbool A, Chaparro-Garcia A, Pandey P, Petre B, Tabassum N, Cruz-Mireles N, Hughes RK, Sklenar J, Win J, Menke F, Findlay K, Banfield MJ, Kamoun S, Bozkurt TO. 2016. An effector of the Irish potato famine pathogen antagonizes a host autophagy cargo receptor. eLife 5:e10856. doi: 10.7554/eLife.10856

Image
PexRD54 is a protein that interferes with the process that plant cells use to destroy damaged or unwanted proteins.
During autophagy, cell materials are sequestered by structures called autophagosomes and then delivered to acidic cell compartments where the material is degraded and recycled. In addition to supporting the bulk degradation of cell materials, it was recently shown that autophagy allows the selective removal of cellular components that are damaged or no longer needed. In selective autophagy, the sequestered material is loaded into autophagosomes by specific interactions between receptor proteins and specific autophagy proteins, such as the ATG8 proteins (Stolz et al., 2014, Lamb et al., 2013).

Dagdas, Belhaj et al. found that PexRD54 interferes with the activity of a potato cargo receptor called Joka2. PexRD54 out-competes Joka2 to bind to an ATG8 protein and stimulate the formation of an autophagosome in the plant cell (Figure 1). In doing so, the oomycete cleverly reduces the loading of specific types of cargo into autophagosomes and thus limits the plant defense response.

The reported observations expand upon studies of mammalian pathogens that also harbor effectors that interfere with autophagy (Table 1). Taken together, this work provides a template for future investigations into the ways in which effectors subvert host plant defenses. However, a number of interesting questions remain unanswered. For example, how do cargo receptors work? How are they regulated? What is the nature of the cargo in the autophagosomes and how does it regulate immune responses? In addition, our understanding of the mechanisms that control selective autophagy remain incomplete. How is the selectivity regulated, and what other cell mechanisms might be subverted by effectors? Phytophthora diseases can have devastating effects, but as this study illustrates, they can also illuminate and advance
Table 1. Mammalian pathogens that express proteins that interfere with host autophagosome biogenesis or function.

| Domain | Pathogen | Host | Effector | Activity | Refs |
|--------|----------|------|----------|----------|------|
| Virus  | HIV virus | human | Nef1     | Inhibits host autophagy | Campbell et al., 2015 |
|        | CMV virus | human | Trs1     | Inhibits host autophagy | Chaumorcel et al., 2012 |
| Dengue virus | mammal | NS4A    | Upregulation of autophagy | McLean et al., 2011 |
| Bacteria | Legionella | mammal | RavZ     | Cleaves an Atg8 protein from pre-autophagosomes | Choy et al., 2012, Horenkamp et al., 2015 |
|         | Coxiella  | mammal | Cig2     | Disrupts interactions between acidic compartments and host autophagosomes | Newton et al., 2014 |
|         | Salmonella | mammal | SseL     | Inhibits selective autophagy of cytosolic aggregates | Mesquita et al., 2012 |
|         | Anaplasma phagocytophilum | mammal | Ats-1    | Hijacks a pathway that activates autophagy to promote its growth inside cells | Niu et al., 2012 |
|         | Vibrio parahaemolyticus | mammal | VopQ     | Creates pores in acidic compartments in host cells | Sreelatha et al., 2013 |
| Eukaryote | Phytophthora | plant | PexRD54  | Inappropriately activates the formation of autophagosomes | Dagdas et al., 2016 |

our understanding of fundamental cellular processes.

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