Hijacking of the host SCF ubiquitin ligase machinery by plant pathogens

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INTRODUCTION

Diverse pathogens have evolved virulence factors that mimic host cell functions (Elde and Malik, 2009). This molecular mimicry, presumably acquired through either divergent or convergent evolution, is indispensable for pathogens to exploit or subvert the host cellular processes for efficient infection. A fascinating example of the molecular mimicry is pathogen-encoded F-box proteins. As a component of the SCF (SKP1-CUL1-F-box protein) ubiquitin ligase complex, F-box proteins mediate polyubiquitination of target proteins and the subsequent proteasome-dependent protein degradation in eukaryotic cells (Petroski and Deshaies, 2005; Lechner et al., 2006; Vierstra, 2009; Hua and Vierstra, 2011). Surprisingly, an F-box-coding gene was also found in Agrobacterium tumefaciens, a bacterial pathogen that causes neoplastic crown gall disease in plants (Schrammeijer et al., 2000, 2005) and hijacks the host SCF complex to facilitate bacterial infection (Tzfira et al., 2004). Since this discovery, similar F-box-like effector proteins have been described in many other viral and bacterial pathogens, including a human pathogen Legionella pneumophila (Price et al., 2009; Lomma et al., 2010). Furthermore, a recent bioinformatic analysis identified at least 74 putative F-box proteins encoded by 22 different bacterial species, most of which are known pathogens (Price and Kwak, 2010). This finding further suggests the importance and widespread utilization of pathogen-derived F-box proteins for the infection strategy.

The SCF (SKP1-CUL1-F-box protein) ubiquitin ligase complex mediates polyubiquitination of proteins targeted for degradation, thereby controlling a plethora of biological processes in eukaryotic cells. Although this ubiquitination machinery is found and functional only in eukaryotes, many non-eukaryotic pathogens also encode F-box proteins, the critical subunits of the SCF complex. Increasing evidence indicates that such non-eukaryotic F-box proteins play an essential role in subverting or exploiting the host ubiquitin/proteasome system for efficient pathogen infection. A recent bioinformatic analysis has identified more than 70 F-box proteins in 22 different bacterial species, suggesting that use of pathogen-encoded F-box effectors in the host cell may be a widespread infection strategy. In this review, we focus on plant pathogen-encoded F-box effectors, such as VirF of Agrobacterium tumefaciens, GALAs of Ralstonia solanacearum, and P0 of Poleroviruses, and discuss the molecular mechanism by which plant pathogens use these factors to manipulate the host cell for their own benefit.

Like animals, plants face a challenge to adapt their development and growth to a rapidly changing environment. In particular, preparing for a potential threat from a wide array of pathogens is crucial for survival of plants. Increasing evidence suggests that plants utilize the UPS to recognize and combat pathogen invasion (Zeng et al., 2006; Citovsky et al., 2009). As a part of this defense strategy, plants often exploit the SCF ubiquitin ligase complexes, thereby targeting negative regulators of their own defense response and/or pathogen-derived proteins for degradation (Zeng et al., 2006; Citovsky et al., 2009). Notably, plants encode an unusually large number of F-box proteins, the substrate specificity module of the SCF complex (Gagne et al., 2002; Hua and Vierstra, 2011). For example, the model plant Arabidopsis thaliana possesses almost 700 F-box genes, which represent almost 2.3% of the protein-coding genes (Gagne et al., 2002; Hua and Vierstra, 2011). By comparison, fruit flies and humans encode only 27 and 69 F-box proteins, respectively (Hua and Vierstra, 2011). Furthermore, a maximum-likelihood analysis of codon evolution predicted that most of plant F-box genes are likely subject to positive selection specifically in the C-terminal substrate-binding domains (Thomas, 2006). Such site-specific positive selection in plant F-box genes as well as their high degree of diversity are reminiscent of the major histocompatibility complex (MHC) molecules (Hughes and Nei, 1988, 1989a,b), the membrane-associated proteins that activate immune responses in vertebrates by binding fragments of foreign proteins (i.e., antigens). Based on these evolutionary features shared by plant F-box genes and MHC molecules, it is tempting to speculate that plants may have evolved a diverse array of F-box proteins (hence, a wide variety of different SCF complexes) to enable broad protection against innumerable invading pathogens. If this is the case, it is not surprising that...
Although only a few phytopathogen-encoded F-box proteins have been intensively studied thus far, understanding the role of such an F-box effector during the corresponding pathogen infection process is highly informative to illustrate the molecular arms race between host plants and pathogens. Here, we summarize the basic concepts of the UPS as well as the SCF ubiquitin ligase complex, and provide several case studies on plant pathogen-derived F-box proteins, including VirF of *A. tumefaciens*, GALAs of *Ralstonia solanacearum*, and P0 of Poleroviruses.

**THE UBIQUITIN/26S PROTEASOME SYSTEM**

Post-translational modifications regulate the molecular function of target proteins by modulating their activity, stability, localization, and affinity to other molecules. Among many known post-translational modifications, addition of ubiquitin moieties (i.e., ubiquitination) is known to be a highly complex process regulated by numerous cellular factors, and plays an essential role in diverse biological processes.

Ubiquitin is a 76-amino acid polypeptide that is highly conserved among eukaryotes. As its name suggests, ubiquitin is ubiquitously expressed in virtually all types of eukaryotic cells. Covalent attachment of ubiquitin to its target protein is mediated by a reaction cascade involving three classes of enzymes: ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3) (Petroski and Deshaies, 2005; Vierstra, 2009; Hua and Vierstra, 2011; Figure 1). The sequential reactions start with ATP-dependent activation of ubiquitin by an E1 enzyme, resulting in formation of a high energy thioester linkage between a cysteine residue present in E1 and the C-terminal glycine residue of ubiquitin. This activated ubiquitin is then transferred to another cysteine residue in an E2 enzyme, and subsequently conjugated to a lysine residue in the target protein with the help of a substrate-specific ubiquitin ligase (E3). E3 ligases are classified into two groups, depending on their mode of action.RING finger-type E3 ligases transfer a ubiquitin moiety directly from E2 to a lysine residue of the target protein. HECT-type E3 ligases conjugate ubiquitin in two steps: first, a ubiquitin moiety is transferred from E2 to the HECT domain of a HECT-type E3 ligase and, then, to a lysine residue of the target protein. Lys11- or Lys48-linked polyubiquitination targets the substrate for 26S proteasome-dependent protein degradation.

![The ubiquitin/26S proteasome system (UPS).](image)

The UPS not only facilitates removal of misfolded proteins, but also regulates a plethora of cellular processes by targeting regulatory proteins for selective degradation. Furthermore, the UPS is also known to play a key role in host immune responses against invading pathogens (Zeng et al., 2006; Citovsky et al., 2009). For instance, some plant virus-encoded movement proteins (MPs), the essential factors for the cell-to-cell spread of viral infection, are targeted for degradation by the UPS (Reichel and Beachy, 2000; Druegeon and Jupin, 2002). Similarly, the viral RNA-dependent RNA polymerase (RdRp), which is required for genome replication of positive-strand RNA viruses, is also degraded by the UPS in plant cells (Camborde et al., 2010). These examples illustrate the importance of the defensive role of the UPS in host–pathogen interactions and imply that the host UPS represents a challenge that pathogens need to overcome for successful infection.

**THE SCF COMPLEX**

The role of E3 ubiquitin ligases in the UPS is substantial as these enzymes determine substrate specificity by selectively recruiting target proteins to the ubiquitination machinery. Among the
E3 families, the SCF complex is by far the largest and best characterized class of E3 ligases. The SCF complex is comprised of cullin 1 (CUL1), S-phase kinase-associated protein 1 (SKP1), RING-box 1 (RBX1), and an F-box protein (Petroski and Deshaies, 2005; Lechner et al., 2006; Vierstra, 2009; Hua and Vierstra, 2011; Figure 2). In this multi-protein complex, CUL1 serves as a scaffold that tethers SKP1 and RBX1 to its N-terminal and C-terminal domains, respectively. An F-box protein, which confers substrate specificity to the SCF complex, directly interacts with SKP1 via its F-box domain whereas RBX1 functions as the docking site for E2 ubiquitin-conjugating enzymes. Most, but not all, F-box proteins harbor an additional interaction domain that brings specific target proteins in close proximity to the catalytic core of the SCF complex (Gagne et al., 2002).

In plants, the SCF complex has been shown to regulate a multitude of developmental processes (Lechner et al., 2006; Vierstra, 2009; Hua and Vierstra, 2011). Indeed, different SCF complexes are involved in signaling pathways of almost all plant hormones, including auxin, gibberellins, jasmonic acid, etc. (Santner and Estelle, 2010). In addition, the SCF complex plays a critical role in plant pathogen interactions (Zeng et al., 2006; Citovsky et al., 2009). One such example is the involvement of the ACIF1 gene in disease resistance in tomato and tobacco (van den Burg et al., 2008). Silencing of the ACIF1 gene in tobacco compromises the host defense responses to Tobacco mosaic virus (TMV) as well as to the bacterial pathogen Pseudomonas syringae (van den Burg et al., 2008). In tomato, knockdown of ACIF1 attenuates resistance against the pathogenic fungus Cladosporium fulvum (van den Burg et al., 2008). The Arabidopsis homologs of ACIF1 are also implicated for defense responses as simultaneous knockdown of three ACIF1 homologs alters expression of defense-responsive genes, including those coding for pathogenesis-related (PR) proteins (van den Burg et al., 2008). Thus, the F-box protein ACIF1 and the SCFACIF1 complex may serve as a conserved, integral part of plant defense against various pathogens, from viruses to bacteria to fungi.

The role of the SCF complex in plant pathogen interactions is also exemplified by the rice defense-related F-box (OsDRF1) protein (Cao et al., 2008). Expression of the OsDRF1 transcripts is induced by infection of the rice blast fungus Magnaporthe grisea, as well as by treatment of benzothiadiazole (BTH), a chemical inducer of plant defense responses (Cao et al., 2008). Interestingly, overexpression of OsDRF1 in tobacco transgenic plants leads to enhanced disease resistance to Tomato mosaic virus (ToMV) and P. syringae (Cao et al., 2008). These results suggest that the potential OsDRF1-containing SCF complex (SCF OSDRF1) may positively regulate plant defense responses against diverse pathogens.

The SCF complex functions not only as a positive regulator but also as a negative regulator of plant defense responses. For instance, the Arabidopsis F-box protein CPR1 (Constitutive Expresser of PR Genes 1, also known as CPR30) is involved in negative regulation of plant immunity via the UPS (Gou et al., 2009, 2011; Cheng et al., 2011). The CPR1-containing SCF complex (SCFCPR1) mediates degradation of at least two resistance (R) proteins, SNC1 (Suppressor of npr1-1 Constitutive 1) and RPS2 (Resistance to P. syringae 2), both of which are critical immune receptors that recognize pathogen invasion (Cheng et al., 2011; Gou et al., 2011). Consistent with this negative role of SCFCPR1, loss-of-function mutations in CPR1 lead to enhanced resistance to P. syringae (Gou et al., 2009, 2011) as well as the oomycete pathogen Hyaloperonospora arabidopsidis (Cheng et al., 2011).

Utilization of the SCF complex in plant defense responses should exert selective pressure on pathogens toward evolution of counter-defense strategies by which they can subvert or co-opt the host SCF machinery. Indeed, increasing evidence suggests that several plant pathogens, such as A. tumefaciens, R. solanacearum, and Poterovirus, hijack the host SCF complex for their own benefits by translocating or expressing their own F-box effectors in the host cell (Tzfira et al., 2004; Angot et al., 2006; Baumberger et al., 2007; Bortolamiol et al., 2007; Table 1). Moreover, recent bioinformatic analyses revealed that many other plant pathogens also encode F-box-like proteins (Angot et al., 2007; Price and Kwaik, 2010; Table 1), suggesting that hijacking of the host SCF machinery through this molecular mimicry may be a widespread infection strategy. To better understand the plant pathogen molecular arms race revolving around the SCF complex, we summarize recent advances in the studies of phytopathogen-encoded F-box effectors.
**Table 1 | Summary of F-box proteins encoded by plant pathogens.**

| Pathogen            | F-box protein | Target protein | Proposed role in infection                                                                 | Reference                                      |
|---------------------|---------------|----------------|------------------------------------------------------------------------------------------|------------------------------------------------|
| **BACTERIAL PATHOGEN** |               |                |                                                                                          |                                                 |
| Agrobacterium       | VirF          | VIP1           | Interacts with the Arabidopsis SKP1. Facilitates the T-complex uncoating by destabilizing the host factor VIP1 as well as its associated T-strand coating protein VirE2 | Schrammeijer et al. (2001), Tzfira et al. (2004) |
| Ralstonia solanacearum | GALA family | N/D            | At least four (GALA1, 5, 6, 7) out of seven members of this protein family interact with the Arabidopsis SKP1. Possess partially overlapping roles in enhancing infection of Arabidopsis and tomato. GALA7 is a host range factor required for virulence in Medicago truncatula | Angot et al. (2006) |
| Pseudomonas syringae | YP_273421    | N/D            | N/D                                                                                      | Angot et al. (2007), Price and Kwaik (2010)    |
| Pseudomonas savastanoi | ZP_07003893 | N/D            | N/D                                                                                      | Price and Kwaik (2010)                         |
| Xanthomonas axonopodis | NP_641107   | N/D            | N/D                                                                                      | Price and Kwaik (2010)                         |
| Xanthomonas campestris | YP_362537   | N/D            | N/D                                                                                      | Price and Kwaik (2010)                         |
| Xanthomonas fuscans | ZP_06706287 | N/D            | N/D                                                                                      | Price and Kwaik (2010)                         |
| Xanthomonas albilineans | YP_003375967 | N/D            | N/D                                                                                      | Price and Kwaik (2010)                         |
| **VIRAL PATHOGEN**   |               |                |                                                                                          |                                                 |
| Polerovirus group   | P0            | AGO1           | Interacts with the Arabidopsis SKP1. Counteracts the host RNA silencing-mediated antiviral defense by targeting AGO1 for degradation | Pazhouhandeh et al. (2006), Baumberger et al. (2007), Bortolamiol et al. (2007) |
| [e.g., Beet western yellows virus (BWYV) and Cucurbit aphid-borne yellows virus (CABYV)] |               |                |                                                                                          |                                                 |
| Faba bean necrotic yellows virus (FBNYV) | Clink       | N/D            | Contains an LxCxE motif required for the interaction of animal virus oncoproteins with the cell cycle regulator pRB. Interacts with the human pRB as well as the Medicago sativa SKP1 in vitro. Involvement in viral infection is still unknown | Aronson et al. (2000) |

*The names of F-box proteins or their NCBI accession numbers are indicated. N/D, not determined.*

**VirF of AGROBACTERIUM**

Agrobacterium tumefaciens-encoded VirF is the first F-box protein that was identified in prokaryotes and proved functional in eukaryotic host cells (Schrammeijer et al., 2001; Tzfira et al., 2004). Agrobacterium is a phytopathogenic soil bacterium that causes neoplastic growths (crown gall tumors) on various plant species by transferring and integrating its own genetic materials into the host genomes. This Agrobacterium-mediated genetic transformation has been considered to represent the only known natural example of trans-kingdom gene transfer until a recent study using cultured human cells showed that the zoonotic pathogen Bartonella hense- lae is also capable of mobilizing its DNA into the eukaryotic host (Schröder et al., 2011). Furthermore, under laboratory conditions, Agrobacterium can genetically transform virtually any eukaryotic species, from fungi to human cells (Bundock et al., 1995; Piers et al., 1996; Kunik et al., 2001; Lacroix et al., 2006).

The infection process of Agrobacterium is regulated by many bacterial factors as well as the host cellular components (Tzfira and Citovsky, 2006; Gelvin, 2010; Pitzschke and Hirt, 2010; Figure 3). First, Agrobacterium activates expression of virulence (Vir) proteins in response to phenolic compounds exuded from wounded plant tissues. Among the induced Vir proteins, VirD1 and VirD2 mediate generation of a single-stranded copy of transferred DNA (T-DNA), a specific DNA segment of the bacterial tumor-inducing (Ti) plasmid. The resulting mobilized single-stranded (ss) DNA molecule, termed T-strand, is then delivered into the host cell via the type IV secretion system composed of the VirB and VirD4 proteins. Within the plant cell, the T-strand is thought to exist as a nucleoprotein complex called T-complex, in which its 5’ end is covalently attached to one VirD2 molecule and the entire length of the T-strand is coated with numerous molecules of the ssDNA binding protein VirE2, another bacterial effector exported into the host cell (Sheng and Citovsky, 1996; Gelvin, 2000; Tzfira and Citovsky, 2000, 2002; Zupan et al., 2000). Furthermore, the host VirE2-Interacting Protein 1 (VIP1) directly binds to VirE2 and facilitates the nuclear import of T-DNA as well as its subsequent targeting to the host genome (Tzfira et al., 2001; Li et al., 2005; Lacroix et al., 2008).

Once the T-complex reaches the host chromatin, the coating VirE2 and VIP1 proteins are most likely removed from the...
**FIGURE 3** | Involvement of F-box proteins in Agrobacterium infection.

_Agrobacterium_ exports a single-stranded copy of T-DNA (T-strand) as well as virulence (Vir) effector proteins into plant cell. Within plant cell, T-strand is assembled into a nucleoprotein complex (T-complex) in which one VirE2 molecule is attached to the 5′ end of the T-strand and multiple VirE2 molecules coat the entire length of the T-strand. In addition, the plant factor VIP1 directly interacts with VirE2 and guides the T-complex into the host cell nucleus. Once the T-complex enters the nucleus, it is presumably disassembled by an SCF complex containing VirF as an F-box component. The SCF<sup>VirF</sup> complex mediates polyubiquitination of VIP1, thereby targeting VIP1 as well as its associated VirE2 for 26S proteasome-dependent degradation. In plant species that do not require VirF for full virulence, _Agrobacterium_ most likely also utilizes the host F-box protein VBF for the T-complex uncoating. As a defense strategy, the host plants destabilize VirF via the ubiquitin/26S proteasome system (UPS), presumably using an as yet unidentified plant SCF complex. Another exported effector, VirD5, counteracts this host-induced degradation of VirF by directly binding to and stabilizing VirF, T-strand, resulting in release of the “naked” DNA molecule as a substrate for integration. Presumably, this uncoating process is mediated by VirF (Tzfira et al., 2004), another bacterial effector that is translocated into the host cell independently of the T-strand (Vergunst et al., 2000; 2005) and localizes to the host cell nucleus by as yet unknown mechanism (Tzfira et al., 2004; Figure 3). The _Agrobacterium_ F-box effector VirF has been shown to interact with the plant SKP1 through the F-box domain (Schrammeijer et al., 2001), suggesting that VirF functions as a component of the SCF complex in plant cell (Schrammeijer et al., 2001; Tzfira et al., 2004). Although VirF does not possess any additional protein interaction domains, which are usually found in many F-box proteins, it directly binds VIP1 and targets it for 26S proteasome-dependent degradation in plant and yeast cells (Tzfira et al., 2004). In addition, VirE2, which is associated with VIP1, is indirectly destabilized by VirF at least in a heterologous yeast system (Tzfira et al., 2004). The degradation of VIP1 and VirE2 is indeed mediated by the VirF-containing SCF complex (SCF<sup>VirF</sup>) because this degradation does not occur in yeast mutant cells that do not express functional SKP1 (Tzfira et al., 2004). Together, these observations suggest that _Agrobacterium_ hijacks the host SCF machinery for efficient infection with the help of the bacterial F-box effector. It remains unknown how _Agrobacterium_ controls the timing of the SCF<sup>VirF</sup>-mediated T-complex uncoating, but the proposed role of VirF during _Agrobacterium_ infection illustrates the strategic importance of molecular mimicry by pathogen-encoded F-box effectors.

The paradox of the infection strategy using VirF is, however, that F-box proteins are inherently unstable due to their own degradation mediated by the autocatalytic mechanism (Zhou and Howley, 1998; Galan and Peter, 1999) or other E3 ligases (Ayad et al., 2003; Guardavaccaro et al., 2003; Margottin-Goguet et al., 2003). Thus, _Agrobacterium_, which delivers only the VirF protein molecules but not the virF gene into the host cell, faces a challenge to protect VirF against detrimental degradation. Most likely, this is achieved by another translocated effector of _Agrobacterium_, VirD5, that directly binds to and stabilizes VirF, which otherwise undergoes rapid degradation via the host UPS (Magori and Citovsky, 2011; Figure 3). This degradation of VirF is likely mediated by an unknown plant E3 ligase, but not the autocatalytic mechanism because mutations in the F-box, a domain required for autoubiquitination, do not stabilize the VirF protein (Magori and Citovsky, 2011). Although it remains elusive whether the host-induced degradation of VirF is actually associated with bona fide plant defense responses, these observations illustrate a novel type of host–pathogen molecular arms race, in which both sides compete for the control of the stability of pathogen-encoded F-box effectors.

It should be noted that VirF was originally identified as a bacterial host range factor, the function of which is required for _Agrobacterium_ infection in some, but not all, plant species (Hooykaas et al., 1984; Melchers et al., 1990; Jarchow et al., 1991; Regensburg-Tuink and Hooykaas, 1993). For example, _Agrobacterium_ strains lacking the virF gene exhibit substantially attenuated infectivity on tomato and tree tobacco ( _Nicotiana glauca_; Hooykaas et al., 1984; Melchers et al., 1990), while such strains still exhibit wild-type virulence on _Arabidopsis_ (Zaltsman et al., 2010). Thus, in plant species that are susceptible to the VirF-lacking strains, _Agrobacterium_ may utilize a host F-box protein as an alternative to VirF. Consistent with this notion, an _Arabidopsis_ F-box protein, VIP1-Binding F-box protein (VBF), was shown to substitute for the VirF function during _Agrobacterium_ infection (Zaltsman et al., 2010; Figure 3). Similarly to VirF, VBF interacts with the plant SKP1, and promotes proteasomal degradation of VIP1 as well as VirE2 (Zaltsman et al., 2010). Interestingly, the VBF transcripts are upregulated in _Arabidopsis_ upon inoculation with _Agrobacterium_ (Ditt et al., 2006) and fungal pathogens (Li et al., 2006). This, in turn, suggests that _Agrobacterium_ may co-opt the plant defense responses to facilitate the T-complex uncoating and, hence, successful infection.

**GALAS OF RALSTONIA**

Another phytopathogenic bacterium _R. solanacearum_ causes a lethal wilting disease on more than 200 plant species, which belong to as many as 50 families (Schell, 2000). This unusually wide host range may be related to a diverse array of effector proteins that _Ralstonia_ potentially uses during the infection process. Indeed,
The F-box domain of P0 not only abolishes the interaction between P0 and SKP1, but also significantly reduces accumulation of the viral RNAs in the host plants (Pazhouhandeh et al., 2006), indicating that P0 is a bona fide F-box protein essential for viral infectivity. The potential targets of the SCF\textsuperscript{P0} complex include ARGONAUT1 (AGO1), the catalytic component of the RISC complex (Baumberger et al., 2007; Bortolamiol et al., 2007). P0 directly interacts with AGO1 and targets it for degradation in the host cell (Baumberger et al., 2007; Bortolamiol et al., 2007). Indeed, transient expression of P0 in Nicotiana benthamiana or Arabidopsis leads to substantial reduction in the AGO1 protein levels (Baumberger et al., 2007; Bortolamiol et al., 2007). Consistent with this result, ectopic expression of P0 in transgenic Arabidopsis plants elicits pleiotropic developmental abnormalities that are reminiscent of ago1 mutants (Bortolamiol et al., 2007). Together, these observations reveal a novel counter-defense strategy, in which viral pathogens disrupt the host RNA silencing through targeted degradation of AGO1. The P0 protein of Poleroviruses is the first evidence that not only bacterial pathogens but also viral pathogens have evolved to encode their own F-box proteins and hijack the host SCF machinery to enhance infection efficiency.

CONCLUSION

Host–pathogen interactions represent a never-ending arms race between host organisms defending against unwanted invaders, and pathogens countering the host defense system. Due to their short generation times and large population sizes, bacterial, and viral pathogens are thought to evolve much faster than multicellular, eukaryotic hosts (Arber, 2000). In addition, horizontal gene transfer, a process in which different prokaryotic species exchange their genetic materials, further speeds up evolution of pathogens (Arber, 2000). Thus, it is not surprising that pathogens, rather than hosts, seem to dominate the battle by constantly updating their infection strategies. In particular, use of F-box effectors within host cells illustrates how elaborate pathogens are when infecting their hosts. Hijacking the host SCF machinery by pathogens makes biological sense because the SCF complex plays a key role in host defense responses in many cases. Furthermore, due to the essential function of the SCF complexes in diverse cellular processes, hosts cannot modify this ubiquitin ligase system just to evade pathogen attack, further allowing for evolution of pathogen-encoded F-box proteins. Ever since the discovery of the Agrobacterium VirF protein, many additional pathogen-encoded F-box effectors have been identified, and at least several of them have been demonstrated to play an indispensable role in pathogenicity. How widespread is this infection strategy? How have pathogens evolved such eukaryotic F-box effectors? How have the F-box effectors affected evolution of host defense systems? With the advent of the discovery and studies of pathogen-encoded F-box proteins, we are beginning to understand the true complexity of host–pathogen interactions.

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Phytopathogen-encoded F-box proteins

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