

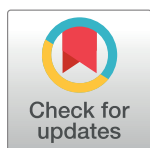
PEARLS

Effectors of plant-colonizing fungi and beyond

Simon Uhse, Armin Djamei*

Gregor Mendel Institute (GMI), Austrian Academy of Sciences, Vienna BioCenter (VBC), Vienna, Austria

* armin.djamei@gmi.oeaw.ac.at



Plant–microbe interactions have evolved over hundreds of millions of years, generating a diversity of interactions covering a broad continuum from pathogenic to mutualistic coexistence. Although these different lifestyles have different needs, they all bear in common the use of secreted molecules, termed “effectors”, that enable microbes to interact with their hosts and to influence the outcome of the interaction. Effectors are not distinguished by sharing similar chemical properties but are instead defined by their function within the biological context of an interaction. To understand effectors, one needs to understand the coevolutionary forces that shape them. The host defense system is a major selection force that eradicates pathogens with a nonadapted effector repertoire. Reciprocally, host plants only survive the evolutionary race if they have been selected to recognize and defend against invading pathogens. This ongoing coevolution creates complex interdependencies between the effector repertoire of microbes, their effectome, and the host susceptibility machinery and defense system of their host plants. This review will summarize recent advances made in the field of effector studies in filamentous plant-colonizing microbes.

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Effector gene expression—Being in the right place at the right time

Each produced effector can be considered as an investment that needs to pay off by giving a selective advantage to the invader, at least from time to time across generations, to be kept in the population. As many effectors are tools that redirect host metabolism and development, their dosage and timing should be controlled to achieve an optimal, balanced result, especially in the case of biotrophs, which need to retain the viability of their host. Evidence for the tight control of effector synthesis and their place and mode of secretion has been provided from various filamentous pathogens [1–4]. Lifestyle switches, e.g., from biotrophic to necrotrophic, or host switches require profound changes in the applied effector cocktail [5]. The same is true when changing environments within the host, e.g., by moving between organs, as exemplified for the biotrophic maize pathogen *Ustilago maydis* [6]. Growing evidence supports the view that adapting the composition of produced effectors to external cues and developmental requirements is a general feature of interspecies interactions. Infection-phase-specific expression of putative effectors has been demonstrated by transcriptomic time-course experiments, among others, in the obligate biotrophic poplar leaf rust *Melampsora larici-populina* [7]; the hemibiotrophic fungus *Colletotrichum higginsianum*, which causes anthracnose during *Arabidopsis thaliana* infection [8]; the obligate biotrophic barley fungus *Blumeria graminis* [9]; the root mutualistic fungus *Serendipita indica* (former *Piriformospora indica*) [5]; and the maize-infecting biotroph *U. maydis* [10]. Adaptation of effector secretion and/or expression may even be cell-type-specific, although this hypothesis lacks experimental support, likely because of technical challenges. An emerging concept is that adaptation of effector expression is not limited to developmental programs of the pathogen or infection strategies in different hosts or plant organs but also occurs when the host plant

is challenged by abiotic stresses. Transcriptomic studies on rice under mild drought stress showed that the hemibiotrophic fungus *Magnaporthe oryzae* transcriptionally downregulates the majority of its putative effectors despite being more successful in colonizing the stressed plants [11]. All these examples of adapted effector expression imply that specific environmental signals must be perceived during colonization by the invading microbes. On the pathogen side, very little is known about what these external signals are and how they are perceived, especially after infection [12, 13]. As misregulation of effectors has been shown to reduce pathogenicity in various pathogens, manipulating effector expression via these external cues could be an elegant way to interfere with pathogen infections [4, 14]. Studying the underlying regulatory networks controlling effector expression is an important future research direction.

Enigmatic effector translocation and place of action

A common hallmark of effectors is that they are, in one way or the other, secreted. Their place of action is therefore either in the interphase between the microbe and the host cell (apoplastic effectors) or inside the host cell (translocated/symplastic effectors). The term “symplastic effector” embodies the idea that translocated effectors might not be restricted to a single cell and includes all possible places of action within plant cells. Similar to the spreading of effectors within the symplast, effectors might diffuse within the apoplast and therefore act on several cells. Within these two compartments, further subcompartments can be delimited. Within the apoplast, effectors have been identified that bind fungal cell wall components, potentially to protect their degradation or recognition by plant pattern-recognition receptors [15, 16]. Other effectors act in the biotrophic interphase, e.g., as inhibitors of apoplastic proteases or to bind pathogen-associated molecular patterns (PAMPs) to reduce recognition [17, 18].

We are not aware of any effector being identified with targets associated with the host plasma membrane from the apoplastic side, and only a few have been identified acting from the cytosolic side at the membrane, likely because of technical limitations in identifying these interactions [19–21].

Type III secretion signals from bacteria and RXLR-dEER or LXLFLAK motifs from oomycetes are predicted to be translocation signals (although in case of RXLR-dEER, its role in uptake is under debate [22]), which make the prediction of symplastic effectors possible in these systems [23, 24]. For fungi, RXLR-like signals leading to translocation of fungal effectors have been controversially discussed but have not been confirmed [25, 26]. Experimental evidence for translocation has been generated either directly by fusing fluorescent proteins to effectors [27] or through immunoelectron-microscopy approaches [28, 29] or are inferred by cytosolic resistance gene (R-gene)-based recognition of avirulence (Avr) effectors [30]. Experimental results for the rust symplastic effector AvrM indicate a host-cell autonomous translocation [29, 31], which implies that AvrM harbors intrinsic biochemical properties mediating its translocation. In contrast to this, the effector Avr2 of *Fusarium oxysporum* does not show such properties but instead requires a pathogen-derived trigger for translocation [32]. The differences observed between pathosystems make it likely that the mechanisms of translocation into the host cell might differ between fungal species and potentially even between different symplastic effectors within a species [27–29, 33]. After translocation into the host cell, symplastic effectors might target specific host compartments. Transgenic production of effector proteins without signal peptides in plant cells have indicated specific localization for effectors in the nucleus, nucleoli, chloroplasts, mitochondria, and discrete cellular bodies [34, 35].

Effector functions—Avoid the alarm, activate what serves, and inhibit what harms

The functions that need to be covered by an effectome reflect the challenges presented by the host immune machinery and mirror the specific needs of the pathogen and its lifestyle. While effectors of biotrophs often function in suppression of host immunity, the necrotrophic fungus *Cochliobolus victoriae* targets a defense-associated thioredoxin TRX-h5 guarded by the NB-LRR protein LOV1 via the toxin effector victorin. The LRR recognition leads to host defense responses, conferring disease susceptibility to the necrotroph [36].

Looking at so-far-identified effector functions, one can identify different modes of action serving the strategies for successful host invasion illustrated in Fig 1.

The self-binder and self-modifier

Effectors with a defensive mode of action either sequester potential microbe-associated molecular patterns (MAMPs) or modify their cell walls upon penetration to minimize recognition. Examples include the chitin-oligomer-chelating LysM effectors Ecp6 of *Cladosporium fulvum* or the Slp1 LysM effector of *M. oryzae* [18, 37]. Another effector passively protects from antimicrobial counter attack [16, 38].

The inhibitor

Many effectors have classic inhibitory activities, e.g., against immune-related proteases, glucanases, or peroxidases, but also against intracellular signaling components to interfere with defense-related signaling processes [39–42]. Inhibition of the Jasmonic-acid-triggered degradation of PtJAZ6 by the MiSSP7 *Laccaria bicolor* effector is an example of signaling suppression by a mutualistic fungus [43].

The activator

Only a few effectors have been identified that clearly fall into the activator category, probably as evolution of inhibitory activity is more likely. The NUDIX hydrolase effector Avr3b of *Phytophthora sojae* and the deregulated, secreted chorismate mutase Cmu1 of *U. maydis* are examples [28, 44]. Some activating effectors function by interfering with the deactivation or degradation of their interacting host protein, thereby acting positively, although they are basically an inhibitor type of effector. One example is the *U. maydis* effector Tin2, which stabilizes the maize kinase TKK1 by inhibiting its degradation [33].

Most effector functions are usually inferred via the host interaction partners, as many effectors show low conservation on the sequence level because of high selection pressure to evade host recognition. One conceptual restriction is that effectors might interact with host molecules either to target and manipulate them or to use them as part of the host cellular machinery to reach their final destination. For example, an effector with a nuclear localization signal might interact with Importin α to enter the host nucleus, but its ultimate target might be the inhibition of a specific host transcription factor. Some effectors have a broader target spectrum, as exemplified by EPIC2B, a cystatin-domain-containing, protease-inhibiting effector from *Phytophthora infestans* [45]. Other effectors show a high degree of specificity even when they target members of expanded protein families, as is the case for the *M. oryzae* effector AvrPii, which targets specific vesicle-tethering Exo70 subunits involved in host immune responses, or the *P. infestans* effector PexRD54, which targets a specific autophagy-modulating ubiquitin-like ATG8 family member [46, 47].

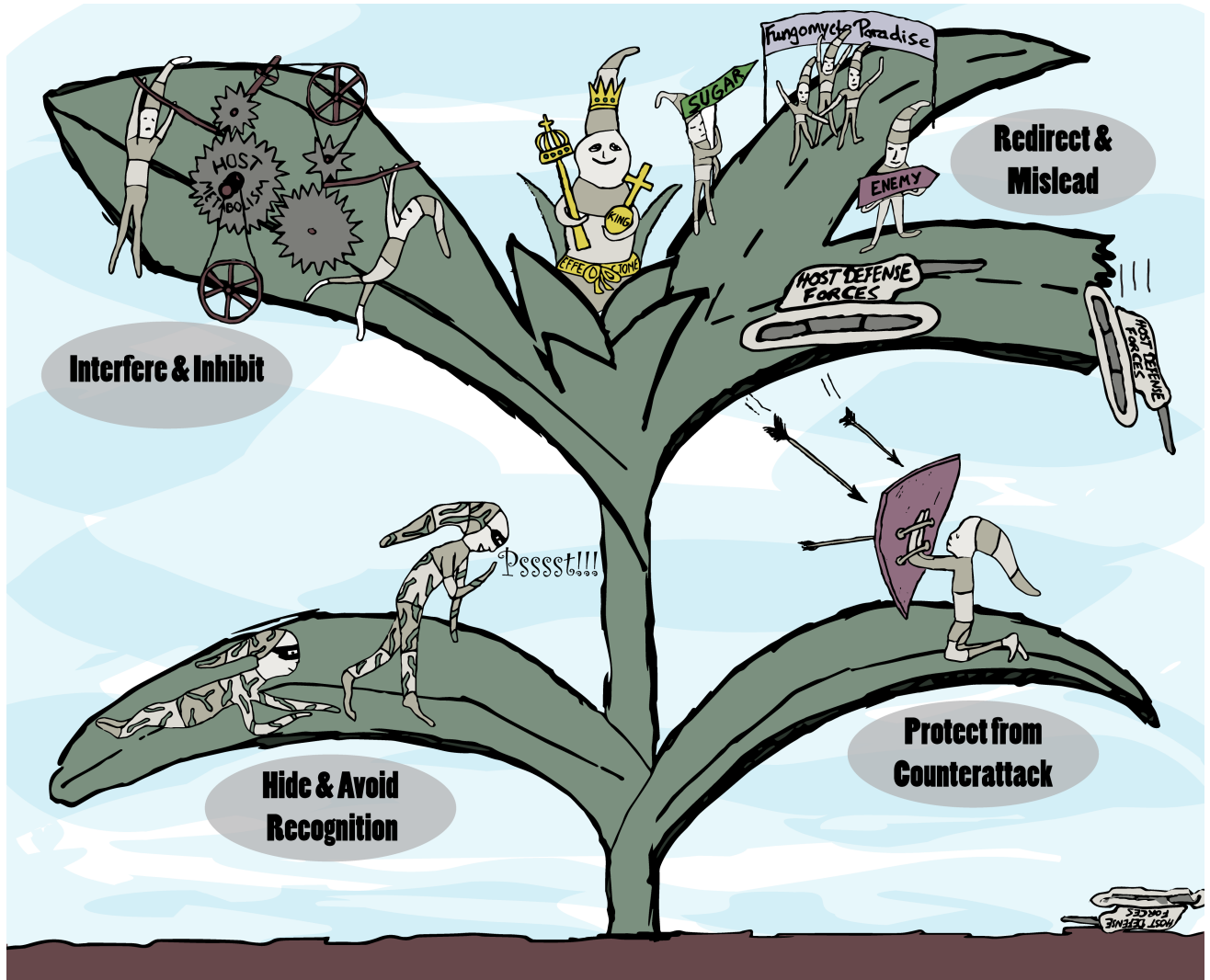


Fig 1. Strategies for successful host invasion. Plant-colonizing microbes employ effectors fulfilling various functions during the host invasion, which are visualized symbolically in this cartoon. Different modes of action (self-binding and self-modifying, activating or inhibiting activities) of effectors described in the text may be applied to serve the listed strategies (text on grey oval background).

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Large-scale effector/host ORFome interaction screens demonstrated that effector targets are usually well-connected cellular hubs [48, 49]. Furthermore, these and other studies revealed that effectors often converge on the same host targets [50]. This goes hand in hand with independent observations that many effector deletion strains do not show any observable virulence defect, potentially a reflection of functional redundancy [51]. Functional redundancy likely provides robustness to host-colonization success and could be considered a sign that the target is of specific importance for a successful interaction. This is supported by a correlation between converging effector-target-deletion plants often showing altered immune-response phenotypes [49].

The decoy-domain fusions found in many nucleotide binding domain and leucine-rich repeat receptor (NLR) proteins might represent effector-target mimics. This, among others, has been experimentally validated for the WRKY domain containing NLR RRS1-R [52]. Therefore, sensor domains fused to NLRs might serve as an informative way to preselect

common effector targets [53]. While effectors also target directly defense components, they more commonly target defense modulators, e.g., by exploiting antagonistic hormone pathways that promote both growth and development, thereby inhibiting immunity [48]. This could be a coevolutionary consequence of the host immune system being less able to detect manipulation of modulators that are involved in various processes beyond immunity.

Outlook

Within the context of the host metabolism, effectors act as alien molecules, overrunning feedback control systems that usually maintain homeostasis [33]. For this reason, they are valuable dominant acting molecular tools. Effectors teach us not only about the molecular defense machinery of the host but often disclose the wiring between immunity, growth, and developmental host pathways. Like a molecular language, effectors coevolve with the host population the invader needs to communicate with. Our understanding of this language is still in the early stages, and thousands of effectomes await to be understood. However, being able to translate this language will likely reward us with immense payback both in strategies for preventing pathogen infections and tools for understanding plant biology.

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