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Review

Innate immune memory in plants

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ABSTRACT

The plant innate immune system comprises local and systemic immune responses. Systemic plant immunity develops after foliar infection by microbial pathogens, upon root colonization by certain microbes, or in response to physical injury. The systemic plant immune response to localized foliar infection is associated with elevated levels of pattern-recognition receptors, accumulation of dormant signaling enzymes, and alterations in chromatin state. Together, these systemic responses provide a memory to the initial infection by priming the remote leaves for enhanced defense and immunity to reinfection. The plant innate immune system thus builds immunological memory by utilizing mechanisms and components that are similar to those employed in the trained innate immune response of jawed vertebrates. Therefore, there seems to be conservation, or convergence, in the evolution of innate immune memory in plants and vertebrates.

Contents

Abbreviations: Arabidopsis, Arabidopsis thaliana; Avr, avirulence; BTH, benzo(1,2,3)thiadiazole-7-carbothioic acid *S*-methyl ester; HR, hypersensitive response; JA, jasmonic acid; NHR, nonhost resistance; NPR1, nonexpresser of PR genes 1; Pip, pipecolic acid; SA, salicylic acid; SAR, systemic acquired resistance; WIR, wound induced resistance.

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1. Introduction: the plant immune system

Plants are a rich source of nutrients and that is why they host a diversity of microbes on their shoot (stem, leaves, and reproductive structures) and root. They are protected from microbial infection by a waxy cuticle atop their shoot or, in case of perennials, by a protective periderm that mainly consists of dead cork cells. Would-be pathogens overcoming these barriers encounter a multilayered immune system comprising constitutive and inducible defenses. In contrast to jawed vertebrates, plants did not evolve mobile immune cells nor did they develop an adaptive immune system. Nonetheless, plants are capable of deploying various innate immune responses to ward off pathogens and remember previous infection.

1.1. Nonhost resistance

Nonhost resistance (NHR) is the most prevalent form of plant immunity. NHR enables a plant species to ward off microbes and viruses that cause infectious diseases on other species of plant [1,2]. NHR is extraordinarily powerful and utilizes both constitutive and inducible defenses [3,4]. The former comprise, for example, the waxy cuticle and suberized cork cells, whereas the latter encompass the accumulation of antimicrobial secondary metabolites, such as the so-called phytoalexins (Greek for 'plant defender') [5]. Inducible defenses are being activated, e.g. upon recognition of microbe-associated molecular patterns (MAMPs) by pattern recognition receptors (PRRs) at the plant cell surface [6] and downstream cellular signaling. In contrast to mammals [7], plants do not seem to possess intracellular PRRs [8].

NHR is thought to result from multiple defense mechanisms that are supposedly regulated by even more defense-related genes [9,10]. Presently known key players of NHR to nonadapted fungi in the reference plant thale cress (*Arabidopsis thaliana*, hereafter called *Arabidopsis*) are plasma membrane-localized ATP-binding cassette (ABC) transporter PENETRATION (PEN) 3 (also called PDR8 or ABCG36) and myrosinase PEN2. The two proteins cooperate while activating, and presumably exporting, one or more antimicrobial plant secondary metabolite(s), such as glucosinolates [11–13]. In *Arabidopsis*, loss of PEN3 results in susceptibility to some nonadapted microbial pathogens, alters susceptibility to adapted infectious bacteria, and attenuates the hypersensitive response (HR, a programmed cell death response in plants) and fungal race-specific disease resistance [12,14–17]. Upon inoculation, PEN3 focally accumulates at sites of attempted fungal penetration, underneath papillae (appositions to the plant cell wall that serve as structural penetration barriers), and in extracellular encasements surrounding fungal feeding organs – so-called haustoria [12,18,19]. Focal PEN3-GFP accumulation was also seen after inoculation of transgenic *Arabidopsis* plants with adapted (infectious) bacteria or upon treatment with flg22, a MAMP in bacterial flagellin (see below) [16,19]. Upon *Arabidopsis* challenge with flg22, fungal xylanase, or the peptide RALF, PEN3 is being phosphorylated [20,21], possibly by Ca^{2+}-dependent protein kinase 10 [22]. Although it is unclear whether PEN3 phosphorylation is important to PEN3 function, it is suggestive of a kinase-dependent signaling pathway regulating PEN3 activity in the *Arabidopsis* immune response [20]. A recent study disclosed the Ca^{2+}-interacting protein calmodulin 7 as a PEN3 interactor crucial to *Arabidopsis* NHR [23] also suggesting a role of Ca^{2+}-dependent protein kinases in NHR.

1.2. MAMP- and effector-triggered immunity and their interplay

The activation of inducible plant defense responses is triggered, for example, upon activation of cell surface-localized PRRs by evolutionary conserved MAMPs. This induced plant disease resistance is referred to as MAMP-triggered immunity (MTI) or, less accurate, pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI). Probably the most prominent example of MAMP/PRR interaction is the activation of the leucine-rich repeat receptor kinase (LRR-RK) FLAGELLIN-SENSING2 (FLS2) by bacterial flagellin [24,25]. FLS2 recognizes a N-terminal, immunogenic epitope of 22 amino acids in flagellin, referred to as flg22 [24,25]. Flg22 binding to FLS2 induces immediate recruitment of BAK1, a LRR-RK acting as a coreceptor for flg22, that is required to fully activate flg22-triggered immunity [26]. Other prominent MAMP/PRR pairs with a role in plant defense are the bacterial elongation factor Tu (EF-Tu)/EFR (another LRR-RK duo), the fungal chitin/CERK1 (*Arabidopsis*) and chitin/CEBiP (rice) pairs [26,27].

MTI typically wards off multiple microbes, no matter whether infectious or not, likely because of the conserved nature of MAMPs across diverse species, genera, families, orders, or even classes of pathogens [28,29]. Thus, to no one's surprise MTI is a likely key component of NHR [29–31]. Consistent with its broad spectrum of activity, MTI is associated with complex downstream signaling and excessive transcriptional reprogramming [8,31–33]. Recent studies suggested that endogenous danger/damage-associated molecular patterns (DAMPs) help amplifying MTI to establish a robust systemic plant immune response [34–38].

Bacterial pathogens that during evolution adapted to a given plant species suppress MTI by secreting, via their type III secretion system, effector molecules that impair MTI signaling [39–41]. This then causes so-called effector-triggered susceptibility (ETS) in the plant [6,42–46]. Different from bacteria, pathogenic oomycetes and fungi seem to secrete effector proteins from their haustorium [47–49].

Another component of plant defense is based on the direct or indirect recognition of pathogen effectors, previously called avirulence (Avr) proteins, by appropriate plant resistance (R) proteins. The direct interaction of effectors with R proteins leads to so-called gene-for-gene immunity [50,51]. In the indirect recognition of pathogen effectors, watchdog R proteins guard the integrity of cellular proteins, and when they sense modification or degradation of these proteins by appropriate effectors, they will initiate plant defense. This scenario has conceptually been described in the so-called guard hypothesis [6,52–56]. Independent of whether pathogen effectors are recognized directly or indirectly, their perception causes intense and highly robust effector-triggered immunity (ETI). In plants, ETI is often, although not always associated with HR [57–59], a localized programmed cell death response supposed to avoid spread of biotroph pathogens to the healthy tissue of plant. Both, MTI and ETI are associated with complex defense signaling which includes reactive oxygen species release, mitogen-activated protein kinase (MPK) activation, plant hormone synthesis and signaling, metabolic changes, excessive transcriptional reprogramming, and the synthesis and accumulation of phytoalexins and other secondary metabolites [6,60–62]. MTI and ETI trigger very similar transcriptional reprogramming in the plant, independent of the origin of the MAMP or effector [27,63]. However, the transcriptional ETI response usually is faster, stronger, and/or more prolonged than MTI-associated gene expression [60,62–64]. Thus, although quantitatively different, MTI and ETI seem to act in concert when conferring plant immunity [6]. Very recent studies suggested strong similarity of defense responses associated with MTI and ETI in both animals and plants. While in the latter ETI is known since many years, research in the animal field just recently provided some mechanistic insight into ETI [51,65–70].

Despite many similarities in the defense responses associated with MTI and ETI in animals and plants, the latter do not possess adaptive immunity. The absence of an adaptive immune response likely forced plants to evolve a multiplicity of PRRs, whereas