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Shared weapons of blood- and plant-feeding insects: Surprising commonalities for manipulating hosts

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ABSTRACT

Insects that reprogram host plants during colonization remind us that the insect side of plant–insect story is just as interesting as the plant side. Insect effectors secreted by the salivary glands play an important role in plant reprogramming. Recent discoveries point to large numbers of salivary effectors being produced by a single herbivore species. Since genetic and functional characterization of effectors is an arduous task, narrowing the field of candidates is useful. We present ideas about types and functions of effectors from research on blood-feeding parasites and their mammalian hosts. Because of their importance for human health, blood-feeding parasites have more tools from genomics and other – omics than plant-feeding parasites. Four themes have emerged: (1) mechanical damage resulting from attack by blood-feeding parasites triggers "early danger signals" in mammalian hosts, which are mediated by eATP, calcium, and hydrogen peroxide, (2) mammalian hosts need to modulate their immune responses to the three "early danger signals" and use apyrases, calreticulins, and peroxiredoxins, respectively, to achieve this, (3) blood-feeding parasites, like their mammalian hosts, rely on some of the same "early danger signals" and modulate their immune responses using the same proteins, and (4) blood-feeding parasites deploy apyrases, calreticulins, and peroxiredoxins in their saliva to manipulate the "danger signals" of their mammalian hosts. We review emerging evidence that plant-feeding insects also interfere with "early danger signals" of their hosts by deploying apyrases, calreticulins and peroxiredoxins in saliva. Given emerging links between these molecules, and plant growth and defense, we propose that these effectors interfere with phytohormone signaling, and therefore have a special importance for gall-inducing and leaf-mining insects, which manipulate host-plants to create better food and shelter.

1. Introduction

To colonize and exploit plants, parasites must defeat a multi-layered defense system. The earlier the plant's "danger signaling" is defeated, the better it is for the parasite. Research on plant pathogens has produced a four-part model of plant defense and parasite adaptation (Dangl et al., 2013). The first layer of plant defense involves plants recognizing 'non-self' molecules belonging to the invading organism, which are known as microbe- or herbivore-associated molecular patterns (MAMPs or HAMPs, respectively) (Erb et al., 2012; Heil, 2009; Acevado et al., 2015). This layer of defense also recognizes 'self' molecules arising from damage to plant cells, which are known as damage-associated molecular patterns (DAMPs) (Erb et al., 2012; Heil, 2009; Acevado et al., 2015). Only few DAMPs have been extensively studied in plant-insect interactions and their recognition and associated signaling mechanisms remain unclear (Tanaka et al., 2014). Detection of MAMPs, HAMPs, and DAMPs occurs by pattern recognition receptors (PRRs) located in the plasma membrane. Detection triggers a set of broad-spectrum downstream defense responses, known as pattern-triggered immunity (PTI) (Zipfel, 2014). To counter this first layer of defense, plant parasites have evolved secreted effector proteins, which act in the plant apoplast or cytosol (Dangl et al., 2013). The plant's second layer of defense takes advantage of these effectors by having surveillance systems that detect a specific

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parasite effector, referred to as an *Avirulence* (Avr) effector because it renders the parasite avirulent rather than virulent. The surveillance system relies on plant *Resistance* (R) proteins encoded by plant *Resistance* genes. Detection by the second layer of defense activates effector-triggered immunity (ETI), which is generally seen as more harmful to the parasite than PTI. To counter this second layer of defense, parasites modify the *Avirulence* effector so that detection by the R protein-mediated surveillance system is no longer possible.

Oral secretions of insect herbivores are important recognition cues that can be used by plants to mediate induced defenses (i.e., elicitors). Oral secretions also have important functions for herbivores (i.e., effectors) as some components are instrumental for interfering with plant defense-signaling pathways, altering plant development to modify or create new habitats, and manipulating plant resources (Chung et al., 2013; Consales et al., 2011; Giron and Glevarec, 2014; Nabity et al., 2013). We view elicitors and effectors as overlapping subsets of HAMPs. Salivary effectors may be especially important for organisms that reprogram host plants during colonization, including the leaf-mining insects and gall-inducing insects that are the subjects of many of the papers in this Special Issue. However, in contrast to effectors of plant pathogens, understanding of effectors of plant-feeding insects is in its infancy (Harris et al., 2015). Insights will come from genome sequencing. The first genome sequence of a plant-manipulating insect was published recently for the Hessian fly, *Mayetiola destructor* (Diptera: Cecidomyiidae), (Zhao et al., 2015), which provided evidence for hundreds of transcripts encoding candidate effectors. The four Hessian fly candidate *Avirulence* effector genes that have been identified through genome sequencing and map-based cloning (Aggarwal et al., 2014; Zhao et al., 2015, 2016) exhibit gene-for-gene interactions with four grass *Resistance* genes *H6*, *H9*, *H13* and *H24*. Suppression of the first layer of defense, i.e., PTI, is expected to be an important function of Hessian fly *Avirulence* effectors. Functional studies of the four *Avr* effector candidates are now underway.

Clearly it is an arduous task to clone and functionally characterize even a single effector gene. If plant-manipulating insects produce many effectors, scientists need information to narrow the field of candidates. Where can this information be found? We propose interactions between blood-feeding parasites and their mammalian hosts. Because of their importance for human health, blood-feeding parasites have been studied for a longer time than plant-feeding parasites and have more tools from genomics and related-omics (Fig. 1). Whereas the first genome of a blood-feeding insect was published in 2002, it took more 6 years to publish the genome of the first plant-feeding insect (Fig. 1A). Differences in the chronology of genome sequencing may also be related to genome size, average genome size being smaller for sequenced species of blood-feeding versus plant-feeding insects (Fig. 1B). Sequencing of salivary gland proteomes or transcriptomes (hereafter referred to as sialomes) occurred 5 years earlier for blood-feeding insects (Fig. 1C) than for plant-feeding insects (Fig. 1D).

A number of recent discoveries have shifted attention to DAMPs involved in the earliest events that occur during plant attack by herbivorous insects (Maffei et al., 2007; Zebelo and Maffei, 2015). These include the plant's perception of specific physiological alterations that occur at the attack site, including the release of extracellular ATP (eATP), the elevation of cytosolic calcium concentration ($[Ca^{2+}]_{cyt}$), and the production of reactive oxygen (ROS) and nitrogen (RNS) species (Zebelo and Maffei, 2015). These responses originate at the plant cell plasma membrane, and are triggered by physical damage caused by insect herbivores. These

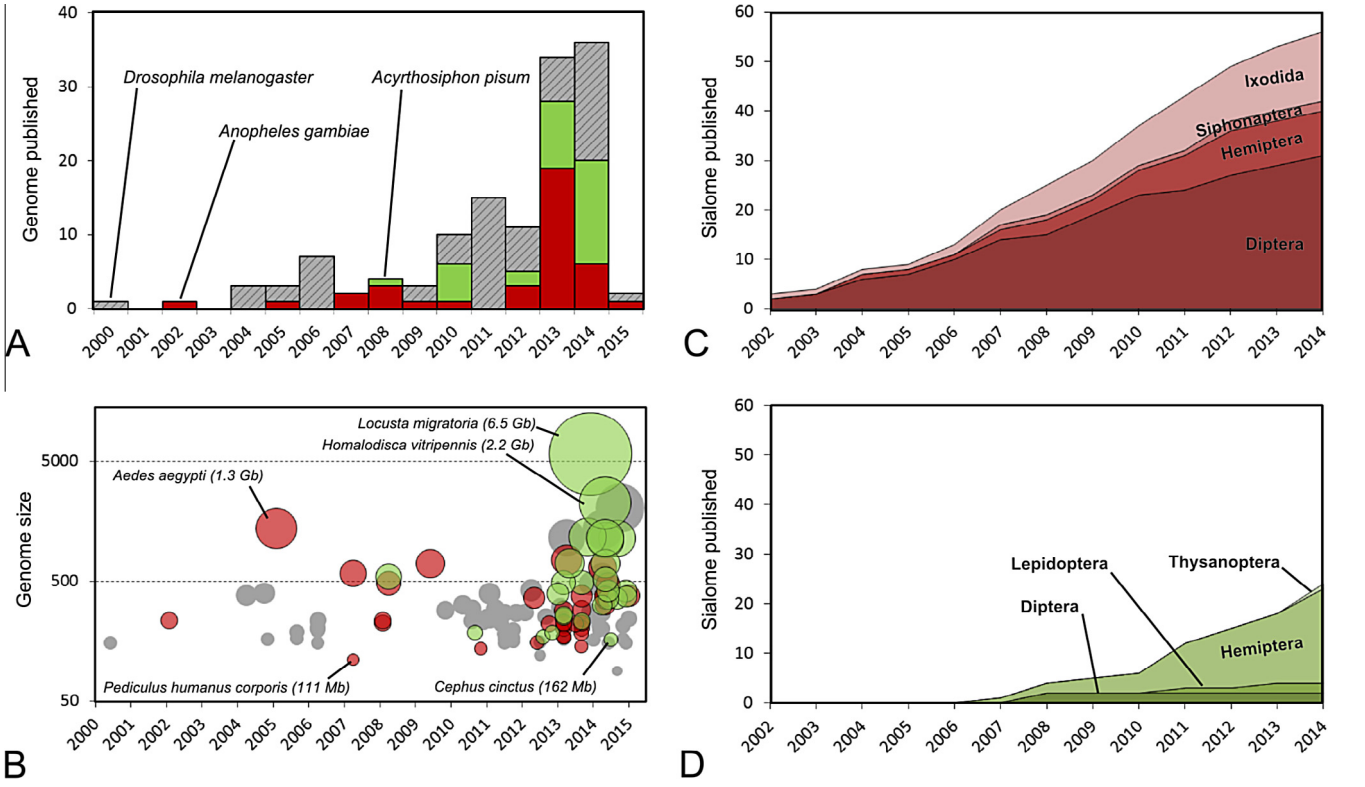

Fig. 1. Comparison of omics studies between blood- and plant-feeding insects. Insect genomes are compared in terms of (A) year of publication and (B) size. Cumulative number of salivary gland proteomes or transcriptomes (here referred to as sialome) published for (C) blood-feeding insects and (D) plant-feeding insects (sources: NCBI and Web of Science). Plant-feeding insects are shown in green, blood-feeding insects in red, and other insects in grey.

events occur seconds to minutes after attack begins and are among the earliest plant defense responses. Interacting downstream networks of protein kinases and phytohormones mediate these early signals and result in concerted gene activation. Electrical signals resulting from early events that occur during plant attack spread through entire wounded leaves and activate jasmonate biosynthesis in leaves distal to wounds (Mousavi et al., 2013).

We review evidence that three classes of insect-produced molecules, i.e., apyrases, calreticulins and peroxiredoxins, act as effectors by interfering with host 'danger signals' that begin with eATP. We show the origins of this idea in research on mammals and their blooding-feeding parasites. After reviewing the consensus model of mammal–parasite interactions, we present the emerging model of plant-parasite interactions to show how plant-feeding insects might also interfere with "early danger signals" of hosts by deploying apyrases, calreticulins and peroxiredoxins in saliva. Given emerging links between these molecules and plant growth and defense, we propose that effectors disrupting the plant's early signaling could interfere with phytohormone signaling. This is of special importance for gall-inducing and leaf-mining insects, which manipulate their host-plant leading to better food and shelter.

2. Early danger signaling in animal and plant hosts

During the earliest stages of attack, signaling molecules are highly conserved among eukaryotes (Hernández-Oñate and Herrera-Estrella, 2015). Three signaling molecules appear to be especially important (Heil and Land, 2014): extracellular ATP (eATP), calcium (Ca^{2+}), and hydrogen peroxide (H_2O_2) (Fig. 2).

2.1. The animal model of early danger signaling

2.1.1. First danger signal: host-generated eATP (Fig. 2A)

The idea that eATP functions as a danger signal began when Burnstock proposed in 1972 that eATP was a neurotransmitter (Burnstock, 2012a, 2012b). This proposal was considered outrageous by most animal physiologists and continued to be controversial until the 1990s, when the first purinergic receptors (P2X and P2Y receptors) shown to detect eATP were finally cloned and characterized (Burnstock, 2012a,b). Today the purinergic pathway mediated by eATP is recognized as a major signaling pathway in animals and an important mechanism to control various cell functions, in particular immunity (Burnstock, 2012a; Riteau et al., 2012).

Rupture of the cell membrane of attacked cells provides a simple mechanism for eATP release (Fig. 2A). A secondary release of eATP occurs through activation of eATP-gated ion channels (i.e., P2X receptors). Increased levels of eATP activate other P2X and P2Y receptors at the cell surface (autocrine activation) and/or in adjacent cells (paracrine activation) (Praetorius and Leipziger, 2009).

After release, eATP interacts with specific P2X and P2Y receptors or is degraded (see Section 3) via different ecto-ATPases, including ectonucleoside triphosphate diphosphohyrolases, to di- and monophosphates, and then by 5′-nucleotidase to adenosine (Yegutkin, 2008). The fifteen known P2 receptors are activated by eATP or other nucleotides, such as UTP and UDP-glucose, and fall into two families. P2X receptors are ATP-gated cationic channels that facilitate downhill fluxes of Na^+, K^+ and Ca^{2+} upon ATP binding (ionotropic receptors). P2Y receptors are coupled to G proteins that elevate cytoplasmic levels of Ca^{2+} and cAMP by activation of phospholipase C and adenylyl cyclase, respectively (metabotropic receptors) (reviewed in Burnstock, 2012b). Numerous subtypes of these two families of P2 purinergic receptors are present in every animal cell that is involved in the wound response, e.g., immune cells, erythrocytes, platelets and skin cells, including keratinocytes, endothelial cells and fibroblasts (reviewed in Burnstock, 2012b).

2.1.2. Second danger signal: eATP → Ca^{2+} (Fig. 2A)

Increases in eATP concentrations ([eATP]) occurring at the attack site result in the elevation of cytoplasmic Ca^{2+} and the mobilization of Ca^{2+} from endoplasmic and organellar reserves (Cordeiro and Jacinto, 2013) (Fig. 2A). This wound-induced calcium burst represents the earliest identified signal following wounding and orchestrates release of cytokines and chemokines that rapidly recruit immune cells to repair damaged tissues (Razzell et al., 2013). The Ca^{2+} wave propagates to neighboring cells via GAP junctions to activate the expression of defense factors that reduce harm from the parasite and/or prevent further attack (Cordeiro and Jacinto, 2013). Accumulating evidence implicates calcium as a key intracellular signal or messenger modulating the expression of cellular functions involved in inflammation, platelet aggregation and wound healing processes (Lansdown, 2002).

2.1.3. Third danger signal: Ca^{2+} → H_2O_2 (Fig. 2A)

The $[Ca^{2+}]_{cyt}$ burst activates synthesis of reactive oxygen species, in particular the production of H_2O_2 (Fig. 2A). This occurs through activation by the wound-induced elevation in $[Ca^{2+}]_{cyt}$ of the enzymes NADPH oxidase (NOX) and dual oxidase (DUOX) (Cordeiro and Jacinto, 2013). Long-distance whole organism signaling results from the simple diffusion of H_2O_2 away from the wound (Suzuki and Mittler, 2012). As a consequence, release of this danger signal by damaged tissues recruits the first inflammatory blood cells to the wound within minutes and contributes to activation of downstream genes involved in the host immune system (Razzell et al., 2013).

In animals, the defensive importance of H_2O_2 is its capability to kill bacteria. NOX is responsible for phagocyte respiratory bursts in neutrophils, eosinophils, monocytes/macrophages, as well as fibroblasts, cardiomyocytes, hematopoietic stem cells, and endothelial cells. H_2O_2 also acts as a signal that propagates through tissues during inflammatory responses. Wounding of epithelial cell membranes leads to an influx of calcium in adjacent cells. Calcium binding to the EF-hand domain of DUOX may then generate hydrogen peroxide (Wittmann et al., 2012).

2.2. The plant model of early danger signaling

2.2.1. First danger signal: host-generated DAMP eATP (Fig. 2B)

The idea that eATP might also be a danger signal for plants came 30 years after eATP was proposed as a neurotransmitter in animals (Demidchik et al., 2003). However, the idea sat dormant because there was no evidence for the existence of plant homologs of animal P2X and P2Y receptors for eATP (Tanaka et al., 2010). Supporting evidence only came recently with the discovery of the DORN1 receptor for eATP in *Arabidopsis thaliana* (Choi et al., 2014). This demonstrated that plants, like animals, detect the onset of attack by using eATP (Fig. 2B). Suppression of DORN1 reduces resistance in *A. thaliana* to plant pathogens (Choi et al., 2014). [eATP] initially increases at the attack site due to membrane disruption in wounded cells. A subsequent release of eATP by adjacent unattacked cells also occurs, possibly through exocytosis and/or transmembrane transport (Tanaka et al., 2010). Because the eATP signal is self-generated rather than a signal that arises from the attacking organism, it is considered to be a DAMP rather than a MAMP or HAMP (Tanaka et al., 2014). Long after the idea was finally accepted by animal biologists, eATP is now recognized by plant biologists as a central signaling molecule in plant biotic and abiotic stress responses (Cao et al., 2014; Clark et al., 2014; Heil and Land, 2014).

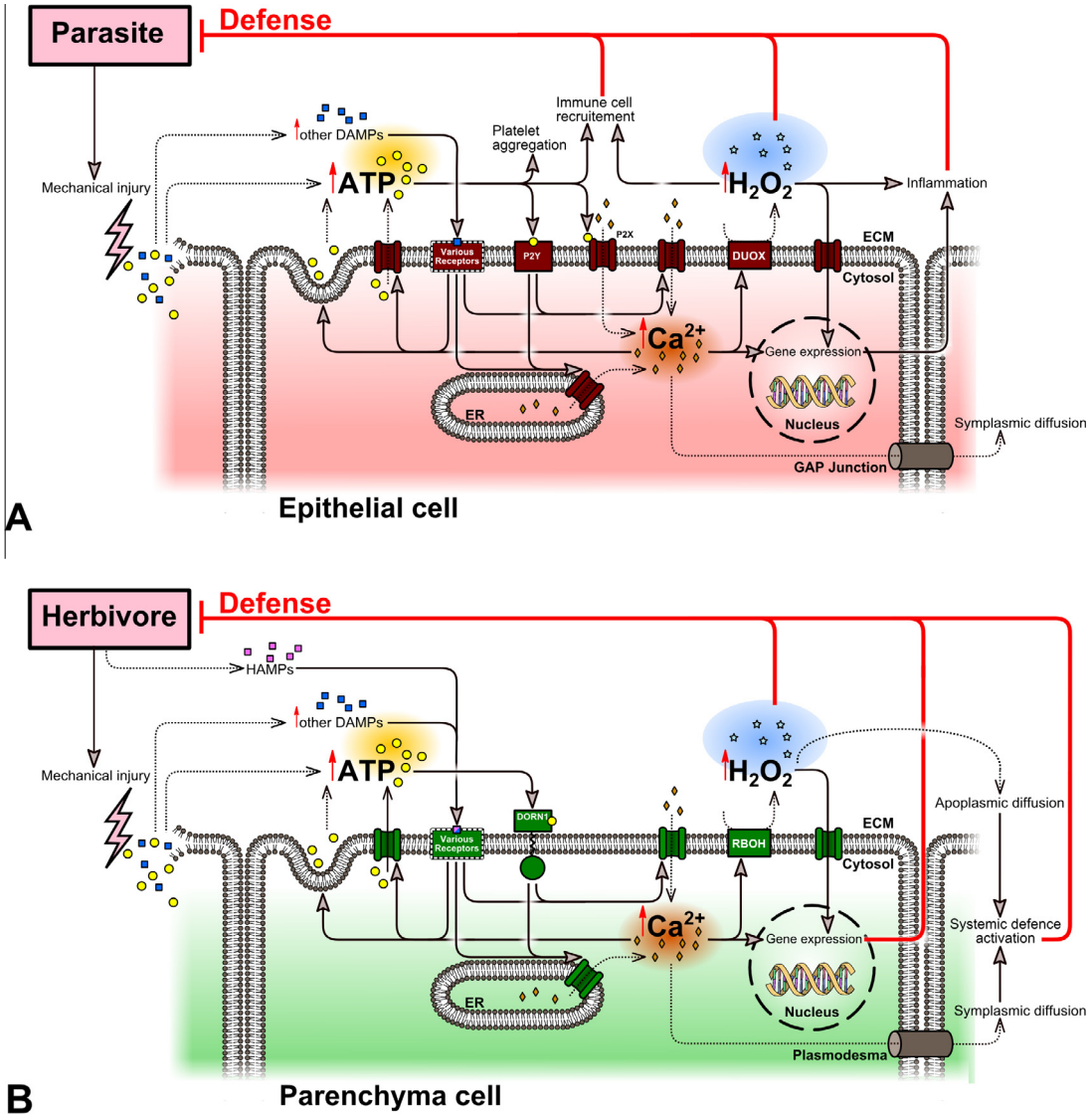

Fig. 2. Early signaling in animals and plants after parasite attack. In both animals (A) and plants (B), attack by parasites results in release of extracellular ATP (in yellow), increase of intracellular calcium (Ca^{2+}, in orange) and production of hydrogen peroxide (H_2O_2, in blue) in the extracellular medium (ECM). This three-step early signaling cascade ultimately leads to an activation of host defenses and altered physiological processes that impairs establishment and survival of the parasite.

2.2.2. Second danger signal: eATP → Ca^{2+} (Fig. 2B)

During the past two decades, research on plant cells has provided evidence that the spatial and temporal changes in $[Ca^{2+}]_{cyt}$ (referred to as the 'calcium signature') that are caused by a given biotic agent contribute to the specificity of the biological outcome (Lecourieux et al., 2006; Maffei et al., 2007). Indeed, the calcium ion is now firmly established as a secondary messenger in numerous plant signaling pathways (Zebelo and Maffei, 2015). However, only rarely have connections been made between alterations in [eATP] induced by herbivory and changes in calcium levels (Choi et al., 2014; Heil and Land, 2014). The immediate response to the increase of [eATP] is the triggering of Ca^{2+} uptake from the extracellular medium (Fig. 2B). The released ATP is recognized by plasma membrane-localized receptors, such as DORN 1 in *Arabidopsis*, which in turn can elevate $[Ca^{2+}]_{cyt}$ (Choi et al., 2014). Elevation of $[Ca^{2+}]_{cyt}$ also stimulates Ca^{2+} mobilization from endoplasmic and organellar reserves (Zebelo and Maffei, 2015). Additionally, HAMPs (reviewed in Zebelo and Maffei, 2015) induce an increase in the membrane permeability to Ca^{2+} leading to an increase of $[Ca^{2+}]_{cyt}$. The resulting Ca^{2+} wave propagates to neighboring cells via plasmodesmata thereby initiating downstream events that presumably lead to appropriate plant defense responses (Zebelo and Maffei, 2015). Ca^{2+}-sensor proteins, such as calmodulin (CaM), CaM-like proteins (CML), calcineurin B-like proteins (CBLs) and calcium-dependent protein kinases (CPKs), detect Ca^{2+} signals and subsequently regulate downstream targets to advance the signal transduction cascade (Du et al., 2011).

2.2.3. Third danger signal: Ca^{2+} → H_2O_2 (Fig. 2B)

ROS, including H_2O_2, have been unequivocally shown to participate in plant responses to insects, especially against aphids (Kerchev et al., 2012; Maffei et al., 2007; Torres, 2010). As in animals, the $[Ca^{2+}]_{cyt}$ burst activates the production of H_2O_2 through NOX (Fig. 2B). In plants, the NOX homologs have been named RBOH (respiratory burst oxidase homologs) (Zebelo and Maffei, 2015). In *Arabidopsis*, a Ca^{2+}-signaling network regulates the formation of ROS. After interaction with CBL calcium sensors, interacting protein kinases (CIPKs) enhance the activity of the NADPH oxidase RBOH via phosphorylation (Drerup et al., 2013; Kimura et al., 2013). In plants, because the extracellular wave of H_2O_2

auto-propagates along with the Ca^{2+} wave and therefore spreads throughout the plant, H_2O_2 constitutes a rapid and systemic signaling pathway (Gilroy et al., 2014). Peroxidases use H_2O_2 as a substrate to catalyze diverse products that inhibit root growth through peroxidase-catalyzed wall cross-linking reactions (cross-linking of phenolic compounds to proteins and polysaccharides) and lignin formation (Lim et al., 2014). These stress-induced morphogenic responses reinforce the wall and are associated with increased resistance to insect herbivores and pathogens (Hu et al., 2012; Suzuki and Mittler, 2012).

Based on the animal model (Fig. 2A), there could be additional role for H_2O_2 in plants (Fig. 2B). In animal cells H_2O_2 functions as an early danger signal that controls the expression of various genes involved in cellular defense mechanisms (including the transcription nuclear factor kappa NFk-beta) in order to minimize tissue injury, improve wound healing, and prevent secondary microbial infections (van der Vliet and Janssen-Heininger, 2014).

3. Modulation of danger signals by hosts and parasites

Organisms need to manage their self-generated danger signals in order to maintain rapid and highly effective downstream defenses while preventing possible deleterious effects caused by over-activated defense mechanisms (Ray et al., 2012). For example, a hyper-active immune system creates fitness costs for plants that have not been attacked by pathogens (Eichmann and Schäfer, 2015). The need for hosts to modulate their own self-generated danger signals creates an opportunity for the host's enemies. Because hosts and their enemies use the same early signaling molecules (including eATP, Ca^{2+} and H_2O_2), they may also share similar molecular factors to modulate their own danger signals as homologies or as converging solutions to similar problems (Heil and Land, 2014; Schultz, 2002; Schultz and Appel, 2004). These molecules can be secreted and applied to the host to interfere with early danger signaling during colonization. Finally, because the molecules have functions other than modulating danger signals, this opens the way for the enemy to use these molecules to manipulate these other host functions, such as modification of growth and source-sink relationships.

3.1. Modulation of eATP by apyrase

Modulation of the eATP danger signal could be achieved, by any of the following mechanisms: (1) reducing/stopping the generation of eATP, (2) reducing the longevity of the generated eATP signal, (3) interfering with the functioning of the eATP receptors, and/or (4) interfering with downstream signaling pathways triggered by detection of the eATP signal, such as the eATP-associated increase in $[Ca^{2+}]_{cyt}$ and the Ca^{2+}-generated increase in H_2O_2. In animals and plants, a diverse array of extracellular enzymes helps control [eATP]. Among them, apyrases play a major role (Clark and Roux, 2011). The majority of characterized apyrases are ecto-apyrases anchored in the plasma membrane with their active site pointing out into the extracellular matrix of cells (Wu et al., 2007).

3.1.1. Apyrase function for the mammalian host (Fig. 3A)

Apyrases (or ATP-diphosphohydrolases) are a class of enzymes that hydrolyze ADP and ATP to AMP (Meyerhof, 1945; Plesner, 1995) (see Fig. 3). There are three families of apyrases: the cell-surface CD39 apyrase (Knowles, 2011) and the Cimex-type apyrases (Valenzuela et al., 1996), both of which are ecto-nucleoside triphosphate diphosphohydrolases (NTPDases), and the ecto-5′-nucleotidases (Champagne et al., 1995).

Functionally, extracellular apyrases have been implicated in the maintenance of blood fluidity (Smith et al., 2002). They are important for the termination of purinergic receptor-mediated responses, including platelet recruitment, activation and aggregation, as well as the regulation of hemostasis and thromboregulation that prevents excess clot formation and vessel occlusion (Zimmermann et al., 2012). In vertebrates, apyrases are also key regulators of neurotransmission and blood pressure (Zimmermann et al., 2012).

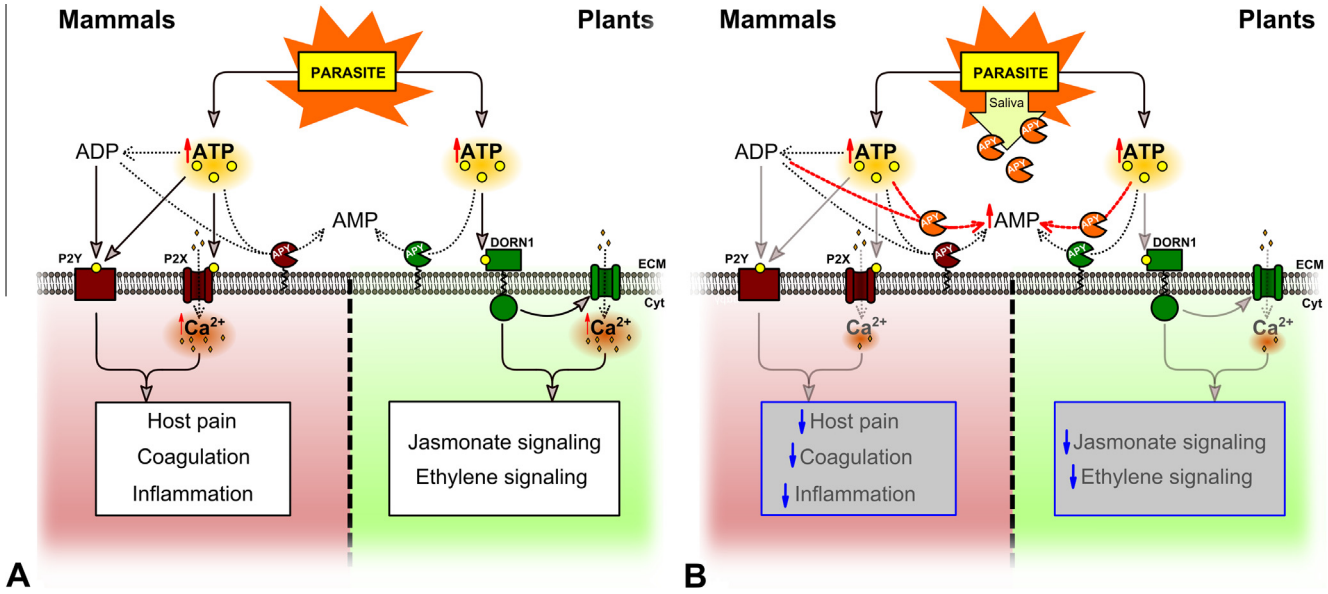

Fig. 3. Major effects of secreted apyrase on the host's eATP signaling pathway. (A) Wounding induces an increase in [eATP] both in animal (in red) and plant cells (in green). This danger signal is perceived by P2X and P2Y receptors in animals, and by the DORN1 receptor in plants. In both cases, it triggers an increase in $[Ca^{2+}]_{cyt}$, a secondary messenger that activates the specific host defensive responses shown in boxes. (B) The presence of ecto-apyrases anchored in the plasma membrane in the lumen regulates the magnitude and the duration of the response to the danger signal eATP. Injection of salivary apyrase (in orange) by parasites can alter wound-induced cellular responses in ways that benefit the parasite.

3.1.2. Apyrase function for blood-feeding parasites (Fig. 3B and Table S1)

Apyrases are major antihemostatic effectors of hematophagous insects (Ribeiro and Garcia, 1980; Ribeiro et al., 1984, 1985b). They are found in the salivary secretions of every group of blood-feeding arthropods, including mosquitoes, ticks, bed bugs, and triatomine bugs (Table 1). Salivary expression of these proteins evolved several times (Hughes, 2013) and genes encoding apyrases are under a strong positive selection in *Anopheles* mosquitoes (Arcà et al., 2014).

By disrupting local purinergic signaling, salivary apyrases decrease host defenses and facilitate better nutrition for the parasite. ATP hydrolysis has an anti-inflammatory effect in some tissues where it inhibits chemotaxis and degranulation of mast cells, neutrophils and eosinophils (Gounaris and Selkirk, 2005). Since ATP is the neurotransmitter at P2X receptors whose activation induces pain, eATP hydrolysis reduces the pain signal associated with attack by blood-feeding enemies. The subsequent degradation of ADP, a factor that induces platelet aggregation, improves access of blood-feeders to food by preventing the obstruction of the injured vessel. These properties make apyrases key salivary effectors of blood-feeders.

Three classes of apyrases have been characterized in blood-feeding insects (Table S1). The 5′-nucleotidases are the most common. They are expressed in the salivary glands of most flies (order Diptera) belonging to the suborder Nematocera (mosquitoes, black flies, biting midges and frog-biting flies, Ribeiro et al., 2010a), as well as brachyceran flies (e.g., the tsetse fly and the horse fly, Caljon et al., 2010; Ma et al., 2009), triatomine bugs (Ribeiro et al., 2012a), and ticks (Francischetti et al., 2009). Salivary apyrases of fleas belong to the CD39 class of apyrases (Andersen et al., 2007; Ribeiro et al., 2012c). Finally, the Cimex-type apyrases are specifically found in salivary secretions of bed bugs (Valenzuela et al., 1996) and sandflies (Anderson et al., 2006; Charlab et al., 1999; Hostomská et al., 2009). Species of endoparasitic nematodes and platyhelminths produce all three classes of apyrases (Gounaris, 2002; Hewitson et al., 2013; Liu and Weller, 1992; Levano-Garcia et al., 2007; Nisbet et al., 2011; Zarlenga et al., 2011).

Additional references were used to create Tables 1 and S1 (Alves-Silva et al., 2010; Andersen et al., 2009; Arcà et al., 2007; Assumpção et al., 2008, 2011, 2012; Bussacos et al., 2011; Calvo et al., 2004, 2006, 2007, 2010a,b; Cheeseman, 1998; Cupp et al., 1994; Da'dara et al., 2014a,b; Dong et al., 2012; Faudry et al., 2004, 2006; Field et al., 1999; Francischetti et al., 2008a,b, 2010; Gounaris et al., 2004; Hamasaki et al., 2009; Hewitson et al., 2011; Hostomská et al., 2009; Jariyapan et al., 2006, 2007; Jex et al., 2014; Karim et al., 2011; Kato et al., 2006, 2010; Kerlin and Hughes, 1992; Lehiy and Drolet, 2014; Liyou et al., 2000; Manque et al., 2012; Mans et al., 1998a,b, 2000, 2008; Marinotti et al., 1996; Martín-Martín et al., 2012, 2013a,b; Moreira-Ferro et al., 1999; Oliveira et al., 2006; Reno and Novak, 2005; Ribeiro, 2000; Ribeiro et al., 1985a, 1986, 1989, 1990, 2004a,b, 2010b, 2011, 2012b; Rohoušová et al., 2012; Santos et al., 2007; Sarkis et al., 1986; Stutzer et al., 2009; Sun et al., 2006; Valenzuela et al., 1998, 2001, 2002b, 2003, 2004).

3.1.3. Apyrase function for the plant host (Fig. 3A)

Plant cells, like animal cells, release ATP into their extracellular matrix when they are mechanically stimulated, wounded, or engaged in growth (Kim et al., 2006; Wu et al., 2007). Extracellular ATP can induce diverse downstream changes that influence not only plant defense but also plant growth and stomatal aperture (Clark et al., 2011, 2014). Control of [eATP] is important because extensive depletion of eATP can result in loss of cell viability (Chivasa et al., 2005) and because eATP regulates plant growth (Demidchik et al., 2003; Jeter et al., 2004). Dose–response experiments show there is an optimal [eATP] for growth, above and below which growth is inhibited (Clark and Roux, 2011). One explanation is that increased [eATP] can lead to inhibition of auxin transport leading to the accumulation of growth-inhibitory levels of auxin (Liu et al., 2012). eATP-mediated mechanisms for inhibiting plant growth also include increased cross-linking in cell walls as a result of the accumulation of H_2O_2 and lignin (Lim et al., 2014).

In plants, the recent identification of the DORN1 eATP receptor in *A. thaliana* has stimulated interest in the study of plant apyrases (Choi et al., 2014). Apyrases help control [eATP] and play a key role in the regulation of growth (Wu et al., 2007), and modulation of responses to biotic and abiotic stresses (Clark et al., 2014; Lim et al., 2014). In *Arabidopsis*, inhibition of apyrases blocks pollen germination and suppresses growth of diverse tissues (Clark et al., 2010; Wolf et al., 2007; Wu et al., 2007). There is also growing evidence in support of a role for apyrases in the regulation of biotic interactions and biotic stress responses, including impaired nodulation in legumes when apyrase activity is reduced (Tanaka et al., 2011a, 2011b) or impaired plant defense in pea when treated with a chemical inhibitor of apyrase activity (Amano et al., 2012).

3.1.4. Apyrase function for plant parasites (Fig. 3B and Table S1)

The idea that plant parasites might use apyrases to manipulate eATP and related functions in host plants is relatively new. After discovering that plants make apyrases in order to modulate their own self-generated eATP, Lim et al. (2014) proposed that pathogens and insect herbivores also generate their own apyrases, which are applied to the plant during colonization and interfere with danger signals at wound sites that begin with increases in eATP. This has been demonstrated in *Helicoverpa zea* caterpillars where ATP-hydrolyzing enzymes have been identified in the salivary gland, leading to a high ATPase activity in saliva (Wu et al., 2012). Among these enzymes, a member of the 5′-nucleotidase family of apyrases used by mosquitoes to circumvent host responses has been identified (Wu et al., 2012). Expression of ATP hydrolyzing enzymes in the *Escherichia coli* heterologous system and application of purified expressed apyrase, ATP synthase or ATPase 13A1 to wounded tomato leaves suppressed plant defenses. ATP hydrolyzing enzymes found in the saliva of *H. zea* suppressed glandular trichome production and expression of defensive genes regulated by JA and ET pathways. This most likely resulted from interference with the plant early signaling pathway that begins with increases in eATP, a strategy potentially used by pathogens and insect herbivores to successfully colonize and exploit plants (Lim et al., 2014).

The idea that insect herbivores use apyrase to interfere with danger signaling in plants is further supported by the identification of apyrases in the salivary secretions of several other herbivores (Tables 1 and S1). The 5′-nucleotidases that are secreted by the caterpillar *H. zea* (Wu et al., 2012) were predicted to be in salivary secretions of the white fly *Bemisia tabaci* (Su et al., 2012), and the green rice leafhopper *Nephotettix cincticeps* (Matsumoto et al., 2014). However, for the latter species, the secretion of apyrases was not confirmed by the sialoproteome (Hattori et al., 2015). Cimex-type apyrases have been predicted to be in the oral secretions of thrips *Frankliniella occidentalis* (Stafford-Banks et al., 2014), the Hessian fly *M. destructor* (Chen et al., 2008), and *B. tabaci* (Su et al., 2012).

Other ATP-hydrolyzing enzymes could also be used to circumvent the plant's early danger signaling, such as the ATP synthase and the ATPase 13A1 found in *H. zea* saliva (Wu et al., 2012). While ATPase activity was also measured in the saliva of the three aphids *Acyrthosiphon pisum*, *Megoura viciae* and *Myzus persicae*, no apyrases were identified in their sialome. This suggests that the enzymatic activity is due to ATPases other than apyrase (Vandermoten et al., 2014).

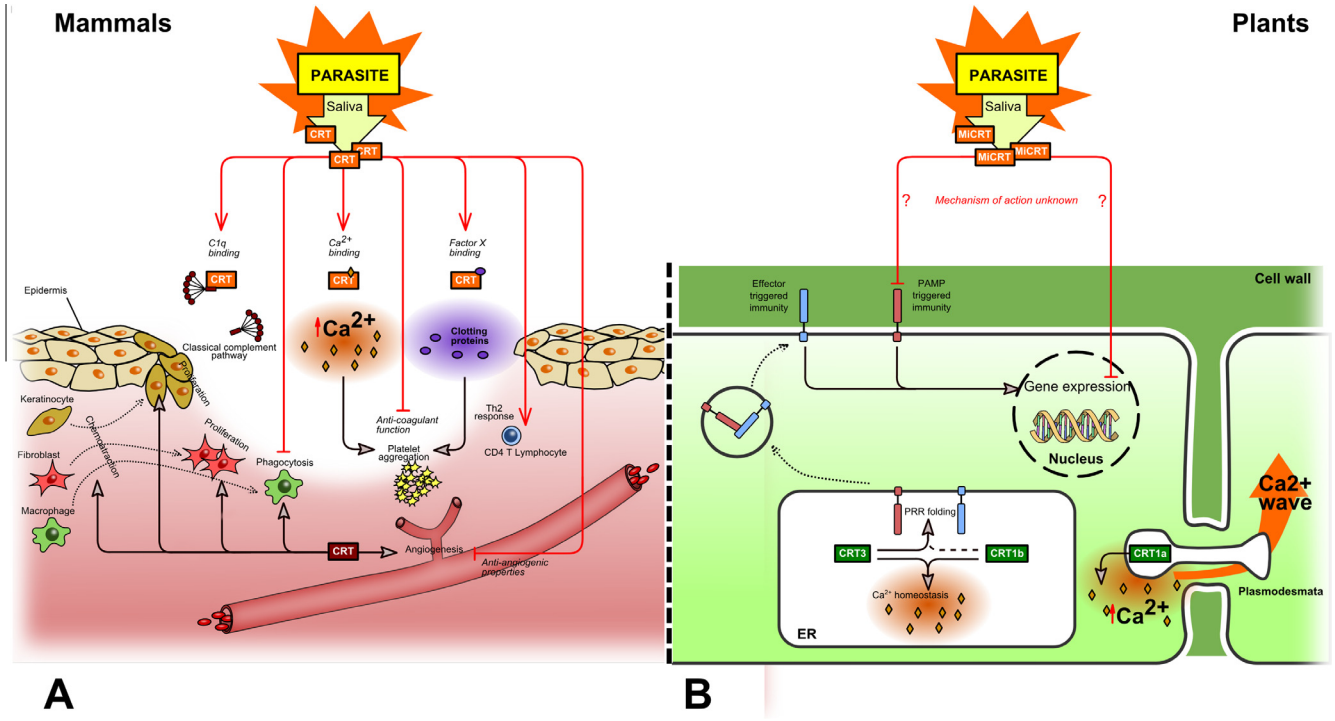

Fig. 4. Major effects of secreted calreticulin on the host's immunity and Ca^{2+} signaling pathway. Parasite attack induces a release of extracellular Ca^{2+} in animal tissues (A) and an increase of $[Ca^{2+}]_{cyt}$ in plant cells (B). In animals (A), this signal activates platelet aggregation at the wounding site. In plants, $[Ca^{2+}]_{cyt}$ signals propagate to neighboring cells and activate cell defense. The host's calreticulin (in dark red) is an angiogenic factor and a chemoattractant of phagocytes, keratinocytes and fibroblasts and stimulates phagocytosis and proliferation of the two last cell types. The parasite's calreticulin (in orange) binds Ca^{2+}, the classical complement C1q and the coagulant factor *X* and thus inhibits Ca^{2+} signals, the complement pathway and coagulation. It also activates Th2 response and reduces angiogenesis. The three plant calreticulins have different roles (B). CRT3 and CRT1b are found in endoplasmic reticulum (ER) and regulate Ca^{2+} homeostasis in this compartment and the LRR folding. CRT1a is in the smooth ER at the plasmodesmata and may regulate Ca^{2+} flux towards the neighboring cell. The calreticulin secreted by *Meloidogyne incognita* (MiCRT, in orange) alters PAMP triggered immunity and inhibits the expression of defense gene.

3.2. Modulation of Ca^{2+} Homeostasis by calreticulins

3.2.1. Calreticulin (CRT) function for the mammalian host (Fig. 4A)

CRTs are calcium-binding proteins. In mammals, they are key factors regulating Ca^{2+} homeostasis and gene expression (Wang et al., 2012). They are actively involved in cellular stress responses, including the wound healing process (Gold et al., 2010) (Fig. 4A). The cell-surface form of calreticulin (ectocalreticulin) possesses a 124-residue domain (CRT S-domain). This domain is a C1q receptor and prevents the formation of C1, inhibiting activation of the classical pathway of complement system (Lynch et al., 2002).

3.2.2. Calreticulin (CRT) function for blood-feeding parasites (Fig. 4A and Table S2)

Among the CRTs of mammalian parasites, a CRT secreted by the causal agent of Chagas disease, *Tripanozoma cruzi*, is the best studied. Discovered in 1999 (Labriola et al., 1999), TcCRT is central to the host–parasite interaction, inhibiting the activation of the earliest stages of the complement system and by interacting directly with endothelial cells, a result being inhibition of angiogenesis (Ramírez et al., 2011) (Fig. 4A). It was also shown recently that TcCRT is a strong activator of wound healing, promoting endothelial cell proliferation five times more efficiently than human CRT (Ignacio Arias et al., 2015). CRTs have also been identified in secretions of parasites that interact with hosts over a longer time period (Table 1). The C1q inhibition function was found in several CRTs secreted by nematodes and other helminth species that are human parasites (Kasper et al., 2001; Suchitra and Joshi, 2005; Yadav et al., 2014). CRTs also have been identified in the saliva of numerous tick species. Functional tests showed that CRT recombinant of *Amblyomma americanum* binds C1q, but apparently it does not inhibit the activation of the classical complement pathway (Kim et al., 2015). In blood-feeding insects, CRTs are present in the salivary secretions of two fleas (Jaworski et al., 1996) and two mosquito species (Arcà et al., 2005; Ribeiro et al., 2007). Their presence suggests a possible interaction with endothelial cells and with host immune systems. However, functional characterization is lacking.

Additional references were used to create Tables 1 and S2 (Alarcon-Chaidez et al., 2007; Aljamali et al., 2009; Chmelař et al., 2008; Ferreira et al., 2002; Guillou et al., 2007; Jaworski et al., 1995; Jex et al., 2014; Joshi et al., 1996; Martínez-Ibeas et al., 2013; Ribeiro et al., 2011; Rzepecka et al., 2009; Valenzuela et al., 2002b; Wang et al., 2009; Xu et al., 2004; Zhu et al., 2010).

3.2.3. Calreticulin (CRT) function for the plant host (Fig. 4B)

CRTs are highly conserved among animals and plants. In plants, their physiological functions are less understood but are often linked with responses to biotic and abiotic stress (Kim et al., 2013). More specifically, CRT3 is involved in both PAMP-triggered immunity (PTI) and in effector-triggered immunity (ETI) (Tintor and Saijo, 2014). CRT1a and CRCT1b are involved in defense mechanisms, modulating plasmodesmata permeability to Ca^{2+} (Demchenko et al., 2014; Sager and Lee, 2014; De Storme and Geelen, 2014) (Fig. 4B) and regulating the salicylic acid (SA) immune response (Qiu et al., 2012).

3.2.4. Calreticulin function for plant parasites (Fig. 4B and Table S2)

Considering the importance of CRT in host/parasite interactions in animals and in plant immunity, it can be postulated that plant

parasites use CRTs to modulate plant defenses (Fig. 4B) (Tables 1 and S2). However, data on CRTs of plant parasites are scarce. The only CRT that *has been functionally characterized* is one secreted by the root-knot nematode *Meloidogyne incognita* (MiCRT), which appears to suppress PTI, the plant's first line of defense (Dubreuil et al., 2009; Jaouannet et al., 2012). CRTs have been found in the sialomes of five plant-feeding insects, including the pea aphid *A. pisum* (Carolan et al., 2011), the Russian wheat aphid *Diuraphis noxia* (Nicholson et al., 2012), the gall-inducing Hessian fly *M. destructor* (Chen et al., 2008), and the beet armyworm *Spodoptera exigua* (Afshar et al., 2013). Among them, three (*A. pisum*, *D. noxia* and *M. destructor*) are relatively sessile compared to the caterpillar of *S. exigua* and two (*A. pisum* and *D. noxia*) are phloem-feeders. For phloem-feeders, injection of saliva containing calcium-binding proteins like CRT may help maintain phloem circulation to facilitate insect feeding and nutrition (Will et al., 2013). This idea is supported by recently observed increases in transcripts encoding CRTs during feeding by phloem-feeders (Foyer et al., 2015). CRTs may also contribute to the establishment of the nutritive tissue induced by gall-inducing insects through interactions with the downstream phytohormone signaling pathways (see Section 4).

Additional references were used to create Tables 1 and S2 (Li et al., 2011; Peng et al., 2013).

3.2.5. Calreticulin function for parasitoid wasps (Table S2)

Interestingly, CRTs are also present in the venom of numerous endoparasitoid wasps (Tables 1 and S2) (reviewed by Asgari and Rivers, 2011). In *Cotesia rubecula*, a CRT copy was identified in symbiotic Polydnavirus sequences, suggesting an important role in silencing of host immunity (Asgari et al., 2003). This function was confirmed in *C. rubecula* (Zhang et al., 2006) and more recently also in *Pteromalus puparum* (Wang et al., 2013) and *Cotesia plutellae* (Cha et al., 2015). In these endoparasitic wasps, venom CRT acts as an inhibitor of host hemocyte spreading, which is a common measure of immune fitness, and cellular encapsulation, highlighting the similarities of CRT function for insect parasites of insects and insect parasites of mammals.

Additional references were used to create Tables 1 and S2 (Crawford et al., 2008; Dorémus et al., 2013a; Goecks et al., 2013; De Graaf et al., 2010; Rivers et al., 2009; Zhu et al., 2010).

3.3. Modulation of H_2O_2 by peroxiredoxins

3.3.1. Peroxiredoxin (PRX) function for the mammalian host

PRXs are enzymes that reduce H_2O_2 to H_2O and oxidize thioredoxins (Sharapov et al., 2014). This class of enzymes was discovered and isolated in 1968 in human erythrocytes and has since been found in all kingdoms of life, from prokaryotes to eukaryotes. In mammals, there are six PRXs that are expressed in many organs and tissues where they have mainly an anti-oxidant function (Sharapov et al., 2014).

3.3.2. Peroxiredoxin (PRX) function for blood-feeding parasites (Table S3)

An important oxidative challenge for hematophagous parasites is the excess of heme that is generated by feeding on blood and leads to production of toxic products of lipid peroxidation via ROS (Graça-Souza et al., 2006). Many kinds of ROS detoxification enzymes are secreted by animal parasites, including ten species of parasitic worms (Chandrashekar et al., 2000; Donnelly et al., 2008; Hewitson et al., 2008; Hudson et al., 2011; Lu et al., 1998; Moreno et al., 2011; Nguyen et al., 2013; Sangpairoj et al., 2014), three mosquito species (Francischetti et al., 2002; Ribeiro et al., 2007; Valenzuela et al., 2002a), and six tick species (Díaz-Martín et al., 2013; McNair et al., 2009; Oliveira et al., 2013; Ribeiro et al., 2006;

Table 1
Apyrases, calreticulins and peroxiredoxins in parasite secretions. Numbers correspond to the number of species with a recorded presence of a protein in their secretions sensu lato (secretion for nematodes, platyhelminthes and protozoa, saliva for plant- and blood-feeding arthropods and venom for parasitoid wasps) and those in bold represent the number of species for which the protein activity was characterized. For details, see Tables S1–S3.

		Animal parasite Saliva/secretions	Herbivore Saliva/secretions	Parasitoid Venom
		Saliva/secretions	Saliva/secretions	Venom
Apyrases	Diptera	30 (**20**)	1	
	Lepidoptera		1 (**1**)	
	Hymenoptera			1
	Hemiptera	9 (**3**)	3	
	Thysanoptera (thrips)		1	
	Ixodida (ticks)	9 (**4**)		
	Siphonaptera (fleas)	2 (**2**)		
	Nematoda	7 (**4**)		
	Platyhelminths	1 (**1**)		
	Protozoa	1 (**1**)		
Calreticulins	Diptera	2	1	
	Lepidoptera		1	
	Hymenoptera			9 (**3**)
	Hemiptera		2	
	Ixodida (ticks)	9 (**1**)		
	Siphonaptera (fleas)	2		
	Nematoda	5 (**4**)	3 (**1**)	
	Platyhelminths	3		
	Protozoa	2 (**1**)		
Peroxiredoxins	Diptera			
	Lepidoptera		2	
	Hymenoptera			3
	Hemiptera		2	
	Ixodida (ticks)	6 (**1**)		
	Nematoda	5 (**3**)	3 (**2**)	
	Platyhelminths	5 (**4**)		
	Protozoa	4 (**1**)		

Tirloni et al., 2014; Tsuji et al., 2001). PRX anti-oxidant activity has only been characterized in seven parasitic worm species (Chandrashekar et al., 2000; Hong et al., 2013; Hudson et al., 2011; Kwatia et al., 2000; Lu et al., 1998; Sangpairoj et al., 2014; Sekiya et al., 2006), and one tick species (Tsuji et al., 2001) (Tables 1 and S3).

Additional references were used to create Tables 1 and S3 (Alger et al., 2002; Donnelly et al., 2005; Dorémus et al., 2013b; Liao et al., 2011; Lu et al., 1998; Sayed and Williams, 2004; Valenzuela et al., 2002b, 2003).

3.3.3. Peroxiredoxin (PRX) function for the plant host

Genome sequencing of *A. thaliana* (Arabidopsis Genome Initiative, 2000) led to the identification of the first plant PRX (Sharapov et al., 2014). PRXs regulate oxidative stress, in particular in the case of abiotic stress protection (Vidigal et al., 2013). They also have a role in the regulation of metabolism, redox signaling and gene expression and some PRXs have a chaperone function (Dietz, 2011).

3.3.4. Peroxiredoxin (PRX) function for plant parasites (Table S3)

Despite the presence of PRXs in the saliva of two aphid species (Cooper et al., 2011), two lepidopteran species (Afshar et al., 2013; Celorio-Mancera et al., 2011) and one dipteran species (Chen et al., 2008), none of these PRXs secreted by herbivorous insects has been functionally characterized (Tables 1 and S3). Interestingly, PRX is a virulence factor of *Meloidogyne incognita* (Dubreuil et al., 2011) suggesting that PRX, in combination with apyrases and calreticulins, may contribute to circumvent early "danger signals" of plants.

Additional references were used to create Tables 1 and S3 (Li et al., 2011; Robertson et al., 1999; Shinya et al., 2013).

4. Implications of similarities between plant and animal early signaling

Common attack strategies and tactics across phylogenetically diverse parasites are frequently observed, regardless of whether the host is a plant or an animal (Schultz, 2002; Schultz and Appel, 2004). We have shown striking similarities between the early signal transduction pathways of plant and animal immune systems with regard to the danger molecules involved in perception of parasites and the molecular factors used to modulate these danger signals. While some of these similarities may represent homologies (shared ancestral traits), others may represent adaptive convergence (similar solutions to face analogous threats) possibly resulting sometimes from symbiotic associations and/or lateral gene transfer (Heil and Land, 2014; Schultz, 2002).

4.1. Implications for the evolution of host–parasite interactions

From an evolutionary point of view, similarities in early signaling between distant kingdoms like plants and animals argues for an ancient origin of eATP, Ca^{2+} and H_2O_2 messengers, which is confirmed by phylogeny (Heil and Land, 2014). Fig. 5 illustrates a point we wish to make about the host's three messengers. The Spanish patriots executed by the French soldiers in Goya's painting "Tres de Mayo" (1814, Prado Museum) cannot escape their fate. The three messengers are similar to the patriots in being "*stationary targets*". We propose that they are stationary because hosts cannot replace their eATP-based early signaling system, i.e., there is no other signaling system that has a redundant function. It follows that countering the action of the parasites' manipulation of this early danger signaling via apyrases, calreticulins, and peroxiredoxins is far more constrained than countering the action of parasite effectors that target downstream events.

4.2. Implications for insect nutrition

Interestingly, the ribonucleotides ATP and ADP are known to be strong phagostimulants for mosquitoes, triatomines bugs and other hematophagous insects (Friend and Smith, 1977; Romero and Schal, 2014). ATP is released by the strong shear stress imposed on the red blood cells (Wan et al., 2008). Damage to vessels at the feeding site caused by insects' mouthparts may also promote ATP release by injured platelets and/or cytoplasm of endothelial cells. Body fluids ingested by hematophagous insects are evaluated by taste receptors located into the alimentary channel, with detection of eATP by receptors located near the cibarium triggering sustained feeding (Bernard, 1974).

Despite the fact that ribonucleotides are rarely included in feeding assays for plant-feeding insects (Schoonhoven and van Loon, 2002), they have been shown to stimulate feeding in a number of species. Adenine and adenosine are phagostimulants for the alfafa weevil, *Hypera postica* (Hsiao, 1969), and the armyworm, *Spodoptera exigua*, as well as other *Spodoptera* species (Ma, 1977; Ma and Kubo, 1977). A number of different ribonucleotides have also been shown to stimulate feeding in the Mediterranean fruit fly, *Ceratitis capitata* (Galun, 1989). The diverse phylogenetic positions of these three insect groups suggest that the phagostimulatory role of ATP may be widespread among phytophagous insects.

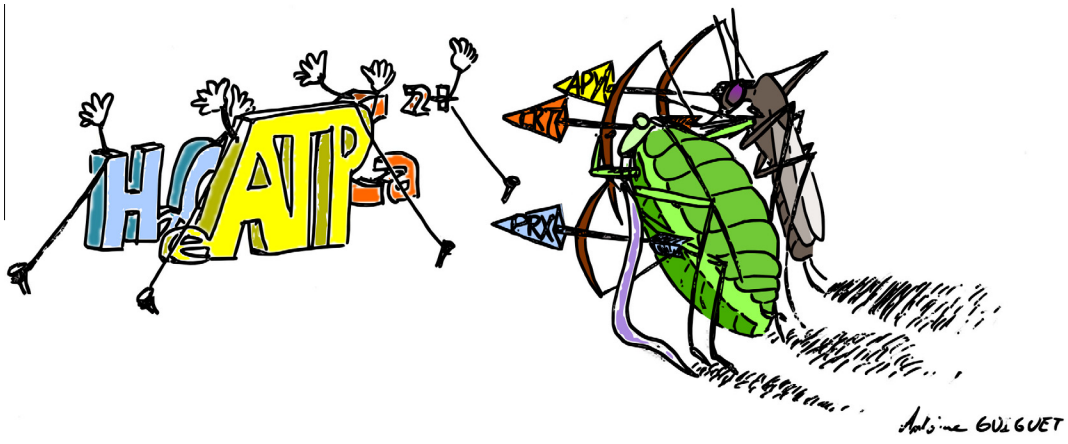

Fig. 5. eATP, Ca^{2+} and H_2O_2: "stationary targets" for parasites. Evolutionary constraints maintain the stability of the three messengers in hosts, facilitating sustainable targeting by parasite factors like apyrases (APY), calreticulins (CRT) or peroxiredoxins (PRX). The image was inspired by "Tres de Mayo", painted by Francisco de Goya in 1814.

This creates a paradoxical role for apyrases. On the one hand they facilitate insect nutrition by inhibiting the wound response. On the other hand, they contribute to the degradation of phagostimulant molecules. Investigations of the timing and/or localization of apyrase secretion may help resolve this apparent paradox.

4.3. Implications for plant signal highjacking and interference by plant-manipulating insects

Arthropods that parasitize plants have come to genomics and all of the –omics relatively recently compared with blood-feeding insects (Fig. 1). Low-cost generation sequencing provides an opportunity to "catch up". On the other hand, understanding the vast amounts of data resulting from this effort will be a daunting task. Plant-feeding arthropods are extremely diverse in their style of attack and have diverse requirements for successful colonization. Some, like caterpillars, attack rapidly and feed quickly, sometimes moving on to other plants to complete their growth. Others like aphids and mites take a more subtle approach during attack and are less mobile. A third group, comprising gall-inducing and leaf-mining insects, exhibits intricate interactions that involve reprogramming of the host plant, with new tissues benefiting the parasite at the expense of the plant.

Mining the large data sets that will result from the various –omics technologies will benefit from focusing on key effectors, such as those we have discussed in this review through comparisons between blood-feeding and plant-feeding insects. The fact that early danger signaling molecules and mechanisms underlying their regulation are shared by plant and animal hosts offers the opportunity for plant parasites to manipulate or mask the plant defensive signal. This, in turn, opens the way for manipulation that could ultimately lead to the extraordinary, and sometimes extravagant, phenotypes induced by gall-inducing (and to a lesser extent leaf-mining) insects. To date Hessian fly is the only gall-inducing insect for which both the genome and salivary gland transcriptome are published (Chen et al., 2008, 2010; Zhao et al., 2015). The near future will see an increasing number of genomes and sialomes published from a wide range of plant-manipulating insects.

Based on genome sequencing and via map-based cloning, four candidate effectors have been identified in the Hessian fly, *M. destructor* (Aggarwal et al., 2014; Zhao et al., 2015, 2016). RNA-interference-knockdown of the gene (*vH13*) encoding one of the effectors confirmed that knockdown of that gene allows avirulent larvae to survive on *H13*-resistant plants. This suggests that the *vH13*-encoded protein is an *Avr*-encoded effector, a protein that elicits effector-triggered immunity (ETI) when secreted into plant cells that harbor a corresponding *Resistance* (*R*) gene. In plant pathogens, *Avr*-encoded effectors are often involved in defeating the plant's basal defense system (PTI) (Dangl et al., 2013). For all four HF *Avr* genes, loss-of-function mutations permit the insect to escape the ETI elicited by the corresponding *R* gene in resistant plants. This suggests that the function of the four *Avr*-encoded effectors for the insect is to modulate plant defense or plant growth. Nevertheless, the specific functions of *vH6*, *vH9*, *vH13* and *vH24* are not currently known. They may or may not interfere with plant early danger signaling. If they do, it does not seem to be related to the functions of apyrases, calreticulins and peroxiredoxins that are proposed in this paper. The *vH24*-encoded effector possibly interferes with downstream signaling steps by counteracting the protein kinase activities involved in the phytohormone signaling that is associated with biotic stress (Zhao et al., 2016). *vH6* and *vH9* are suspected to contain F box domains and leucine-rich repeats (Zhao et al., 2015) that are known to interact with certain phytohormones. Therefore, it is more likely that the currently identified Hessian fly effectors are involved in downstream events rather than disruption of the plant's early danger signaling. Interestingly, *vH13* and *vH24* were not detected in the transcriptome of first-instar salivary glands (Chen et al., 2008, 2010). However, after their discovery based on genome sequencing and map-based cloning, their transcription in the larval salivary glands was demonstrated (Aggarwal et al., 2014; Zhao et al., 2016). This indicates that transcriptome analyses do not always reveal the full set of effectors used by insects to attack their host-plants. Thus, dynamic approaches may be required to capture the entire set of effectors used in plant-insect interactions.

Our analysis of the sialome of the Hessian fly (Chen et al., 2008, 2010) revealed one salivary apyrase, one calreticulin and one peroxiredoxin that could be involved in the control of eATP, Ca^{2+} and H_2O_2 danger signals, thus modulating key aspects of the plant physiology relevant for the gall induction. Apyrase activity has also been demonstrated to be 1.7 to 5 times greater in the globose galls of *Calliandra brevipes* than in non-galled tissues (Detoni et al., 2012) suggesting a key role of this early signaling disruptor (and others) in plant reprogramming induced by plant-manipulating insects. Whether increased apyrase activity results from the production of apyrase by the galling-insect remains to be determined in this system.

5. Disruption of early danger signals and phytohormone signaling

We propose that disruption of the plant's early signaling through the enemy's production of apyrases and other disruptors could significantly interfere with plant phytohormone signaling and contribute to successful colonization by plant-manipulating insects. Experimental data from a number of systems support the role of phytohormones in gall induction and formation as well as in physiological alterations induced by leaf-miners (reviewed in Bartlett and Connor, 2014; Giron et al., 2013, 2016; Tooker and Helms, 2014). Auxins and Cytokinins (CKs) are central to these interactions, but modulation of the plant defensive hormones such as jasmonic acid (JA), ethylene (ET), salicylic acid (SA) and abscisic acid (ABA) also frequently occurs (Bartlett and Connor, 2014; Tooker and Helms, 2014; Zhang et al., 2016). Various plant parasites have been shown to directly deliver phytohormones to the plant to disrupt plant defenses, to divert plant resources and/or to redirect cell development to generate new structures (Giron and Glevarec, 2014; Jameson, 2000; Kästner et al., 2014; Pertry et al., 2009, 2010; Yamaguchi et al., 2012). In insects, it is believed that salivary secretions and oviposition fluids produced by larvae and/or adults contribute to the delivery of phytohormones directly to the plant, and insect-associated symbionts may play a key role in the production/delivery of these effectors (Body et al., 2013, 2014; Mapes and Davies, 2001a, 2001b; Tooker and Helms, 2014; Yamaguchi et al., 2012). It cannot be excluded that insects also may act directly on the plant's hormone biosynthesis, degradation, transport or signaling pathways to alter the phytohormonal balance (Schaller et al., 2015; Zhang et al., 2016).

5.1. Balancing auxin and CK levels

Auxins and CKs are complementary rather than opposing forces in regulating plant growth and development. The function of these hormones and their role in plant biotic interactions are mediated through complex auxin/CKs crosstalk during biosynthesis, degradation, transport and signaling (El-Showk et al., 2013; Pernisova et al., 2011; Schaller et al., 2015; Vanstraelen and Benková, 2012). They act together dynamically to confer distinct cell fates, regulating myriad developmental responses that can ultimately lead to organogenesis (Schaller et al., 2015). Above ground, CKs

promote the proliferation of undifferentiated cells while auxins act to induce differentiation and organ outgrowth.

Because auxins and CKs lie at the very core of molecular mechanisms controlling the balance between the rate of cell division and differentiation, they have long been hypothesized to be involved in insect-induced plant phenotypes such as galls and green-islands (photosynthetically active green patches in otherwise senescent leaves induced by several leaf-miner and gall-inducer insect species). It has now been demonstrated that some insect herbivores have evolved an ability to manipulate plant hormones for their own benefit and some species might even synthesize these phytohormones de novo (Giron et al., 2013; Tooker and Helms, 2014; Yamaguchi et al., 2012). There are many examples of higher levels of auxin (mostly indole-3-acetic acid, IAA, the main auxin found in plants) and CK concentrations within plant galls and leaf mines (Giron et al., 2007; Mapes and Davies, 2001a, 2001b; Straka et al., 2010; Tooker and De Moraes, 2011a, 2011b). These higher levels may contribute to the induction of key features of galls/mines, such as the formation of a nutritive tissue, the delay of senescence, and the translocation of nutrients towards the insect feeding site.

Emerging from this review, additional mechanisms could be at play to ensure the increase of auxins and CKs required to generate galls and other insect-induced phenotypic responses. eATP released by wounding strongly inhibits polar auxin transport leading to the accumulation of growth-inhibitory levels of auxin (Liu et al., 2012). ATP-hydrolyzing enzymes such as apyrases, by reducing levels of eATP, could contribute to auxin distribution thus increasing the growth rate of specific cells and tissues, impacting, as a consequence, levels of essential components of gall induction and development (Liu et al., 2012; Schaller et al., 2015; Tanaka et al., 2014). Additionally, this could also modulate plant defense and prevent wound-healing processes (Lim et al., 2014; Tanaka et al., 2014).

5.2. Counteracting JA- and SA-mediated plant defenses

In many plants, herbivory stimulates the production of JA and ethylene while other organisms stimulate the production of SA (Erb et al., 2012). It has also been recently recognized that hormones such as auxins and CKs can also influence plant defensive responses (Bari and Jones, 2008; Erb et al., 2012; Giron et al., 2013; Robert-Seilaniantz et al., 2007). Gall-inducing and leaf-mining insects include both chewing and piercing/sucking mouthparts. Sometimes there are even dramatic changes in morphology associated with a switch of larval feeding modes between successive instars (known as hypermetamorphosis, Body et al., 2014). JA- and SA-mediated plant defenses target these herbivores (Tooker and Helms, 2014; Zhang et al., 2016) and several lines of evidence suggest that plant-manipulating insects can counteract these defenses. IAA is known to inhibit JA- and SA-mediated defenses (Davies, 1995; Erb et al., 2012; Tooker and De Moraes, 2011a,b; Tooker and Helms, 2014). The ability of gall-inducing insects to manipulate IAA and/or CK levels – potentially and partially through direct effects of eATP – may contribute to counteracting JA- and SA-mediated downstream anti-herbivore defenses. Because JA can also inhibit the influence of CKs and auxins (Ueda and Kato, 1982), avoiding JA production most likely preserves auxin- and CK-mediated effects required for the successful development of galling and leaf-mining insects, including effects on vascular tissue differentiation, assimilate partitioning, and cell division and growth. Consistent with this hypothesis are data on several gall-inducers and leaf-miners showing that insects induce increased levels of IAA or CKs in galls and mines but fail to induce higher levels of JA or SA and their associated downstream defenses (Mapes and Davies, 2001a,b; Tooker and De Moraes, 2007, 2008, 2009, 2011a,b; Zhang et al. 2016; Glevarec, Giron et al., unpublished results).

Insects could presumably regulate phytohormonal levels through apyrase-mediated decreases in eATP levels. For instance, release of eATP at wounding sites can induce the expression of genes encoding biosynthetic enzymes for JA and ET (Jeter et al., 2004; Song et al., 2006) and contribute to activate additional plant defense systems such as the production of plant secondary metabolites, the production of glandular trichomes, the secretion of extrafloral nectar, and the synthesis and release of volatile compounds (Heil et al., 2012; Maffei et al., 2007; Tanaka et al., 2014; Tooker and Helms, 2014). This could directly impact the herbivore or stimulate the recruitment of predatory insects (Heil et al., 2001; De Moraes et al., 1998, 2001). JA and ET have also been postulated to activate specific wound responsive genes that further promote wound healing (Asahina et al., 2011). ATP hydrolyzing enzymes such as apyrases can inhibit the JA pathway (Wu et al., 2012). The suppression of JA-regulated defense gene expression by ATP degrading enzymes may be due to the depletion of ATP required to complete normal physiological responses, a direct inhibitory effect on the JA pathway or an indirect effect through the upregulation of SA-dependent plant defenses acting via a negative crosstalk on JA (Wu et al., 2007). Reducing [eATP] can also reduce downstream levels of ROS that have begun to be recognized as pivotal redox-based signaling molecules in the plant defense response. ROS such as H_2O_2 can also activate lipoxygenases to initiate the biosynthesis of oxylipins such as JA.

Finally, interference with local early signaling events may prevent GLR-mediated long-distance wound signaling that control the production of jasmonates in undamaged leaves (Mousavi et al., 2013). GLR genes have been implicated in mediating calcium influx in response to the perception of microbe-associated molecular patterns (MAMPs) and damage-associated molecular patterns (DAMPs) (Mousavi et al., 2013). Interestingly, GLRs in plants are related to genes important for synaptic activity in animals suggesting again a deeply conserved function for these genes in organ-to-organ wound signaling. Blocking events that precede (e.g., release of eATP), or follow (e.g., elevation of $[Ca^{2+}]_{cyt}$) plasma membrane depolarization could minimize or prevent the GLR-mediated propagation of electrical activity leading to the distal expression of defense genes. Concomitant effects of apyrases, calreticulins and peroxiredoxins could thus contribute to inhibit JA production at the wounding site and in undamaged distal plant tissues.

ROS accumulation is involved in the plant defense system and can impact the establishment of galling insects as demonstrated by the rapid and prolonged accumulation of H_2O_2 in wheat (*Triticum aestivum*) at the attack site during incompatible interactions with Hessian fly (*M. destructor*) larvae (Liu et al., 2010). But the accumulation of ROS can also play a major role in determining the extent of tissue alterations during gall morphogenesis (Carneiro et al., 2014; Oliveira et al., 2016). At the phase of gall maturation in the galls of *Northotrioza myrtoidis*, the concomitant lignification and ROS accumulation in outermost cell layers of the gall cortex could play a defensive role for the gall-inducer to prevent or minimize pathogen and predator attack (Carneiro and Isaias, 2014; Carneiro et al., 2014; Stone and Schönrogge, 2003). Temporal and spatial regulation of ROS and other plant defensive compounds is thus expected to be finely tuned. Presence or absence of ATP, Ca^{2+} and H_2O_2 regulatory enzymes in insect salivary secretions, the dynamics of their release and the localization of their delivery to the plant at the cellular level are most likely to be determinant factors in the fate of compatible or incompatible interactions between plant-manipulating insects and their host-plant.

5.3. Regulating ABA-mediated effects

ABA-mediated plant defenses are likely to be involved against galling and leaf-mining insects (Tooker and Helms, 2014; Zhang et al., 2016). It is however unclear how ABA levels vary in galled/mined tissues compared to uninfected plant tissues and how leaf-miners and gall-inducers potentially modulate ABA levels in galls and mines (Tokuda et al., 2013; Tooker and De Moraes, 2011a; Zhang et al., 2016). In addition to their possible effects described above, ATP hydrolyzing enzymes may also contribute to reduce or neutralize ABA-mediated effects.

Cell breakage is a simple mechanism for ATP release that could be caused by herbivore attack (wounding) or pathogen-induced cell lysis (necrosis). ABA can also trigger ATP release during plant stress response (Tanaka et al., 2014) and play a very important role in plant resistance against insect herbivores through a modulation of JA-driven defense responses (Bodenhausen and Reymond, 2007; Erb et al., 2012; Mondego et al., 2010; Thaler and Bostock, 2004). ABA also acts as an antagonist of CKs (Jacqmard et al., 1995) and plays a key role in senescence and abscission-promoting effects, two processes of great importance for sessile organisms such as leaf-mining and gall-inducing insects (Lim et al., 2007).

ABA also triggers a signaling cascade in guard cells that results in stomatal closure and inhibits stomatal opening (Clark et al., 2011). CKs and auxin have been shown to inhibit ABA-induced stomatal closure by enhancing ethylene production in *Arabidopsis* that will increase the osmotic pressure in the guard cells (Tanaka et al., 2006). eATP-mediated ROS accumulation also leads to stomatal closure (García-Mata and Lamattina, 2001; Bright et al., 2006; Desikan et al., 2006). In contrast to these effects, apyrase, whose levels correlate with conditions that favor stomatal opening (Clark et al., 2011), may help gall-inducers and leaf-miners to control their microenvironments by modulating humidity, temperature and gas exchange between the ambient air and the atmosphere within plant tissues (Pincebourde and Casas, 2014, 2016; Pincebourde et al., 2006). Insect salivary effectors can also suppress the induction of wound-responsive genes by interfering with the induction of water-stress-related defenses, thus leading to enhanced herbivore performance (Consales et al., 2011).

6. Conclusions

Understanding of effectors used by herbivorous insects is just beginning to emerge (e.g., Acevado et al., 2015; Giron et al., 2016; Zhao et al., 2016). In-depth functional approaches are now required to determine the mechanisms that contribute to plant manipulation. RNA-seq and proteomic approaches, along with RNA interference (RNAi), will be used to identify and characterize a greater number of candidate effectors. This will eventually enable comparative approaches across a diverse set of plant-manipulating organisms. We expect to find convergent mechanisms. Likewise, the technical progress made in the past decade also opens the way to unravel how plants fine-tune their defense machinery to mount appropriate herbivore-specific responses. The extent to which herbivore-induced production of plant defenses is promoted by 'self' signals from damaged cells (DAMPs) versus 'non-self' signals from HAMPS (including effectors) is an unresolved question (Erb et al., 2012). How do insect effectors interact with the two layers of plant defense, i.e., PTI and ETI? Future studies will require deciphering the relative contribution of these two signaling pathways in plant defense against herbivorous insects and whether insect salivary effectors involved in plant early-signaling interference also reduce HAMP-induced plant resistance. Because insects are likely to regulate phytohormonal levels through the production of apyrases and other disruptors, suppressing early defense pathways is likely to inactivate (or at least mitigate) additional plant defense systems and to contribute to the successful colonization.

Promising developments can also be expected in relation to plant- and insect-associated microorganisms. Some of the mechanisms discussed in our review play a role in establishing interactions between plants and their beneficial symbiotic microorganisms. Thus, apyrases are essential for rhizobial and mycorrhizal symbiosis presumably due to their ability to modulate eATP levels (Tanaka et al., 2014). In legumes, bacterial symbionts may control infection and nodulation through regulation of apyrase activity using Lipochitooligosaccharide Nod factors (Day et al., 2000; Kalsi and Etzler, 2000; Tanaka et al., 2014). Increased apyrase activity suppresses ATP-mediated defenses thus enhancing plant colonization. On the other hand, microbial symbionts of plant-feeding insects are now recognized as important "hidden players" in insect-plant interactions (Biere and Bennett, 2013; Frago et al., 2012; Gutzwiller et al., 2015; Sugio et al., 2015) and can directly or indirectly interfere with a number of components of plant metabolism (Body et al., 2013; Giron et al., 2013; Sugio et al., 2015; Zhu et al., 2014). Herbivores possess diverse microbes in their digestive systems and salivary glands that can modify oral secretions. Whether insect symbionts interfere with the plant-early defense signaling and/or directly deliver apyrases remains to be seen. Future research will provide valuable insights for understanding mechanisms of plant manipulation by insects and the roles played by their associated symbionts.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jinsphys.2015.12.006.

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