Mechanisms involved in the pathogenesis of *Candidatus* Liberibacter asiaticus and possible molecular bases of tolerance in citrus

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Abstract. Huanglongbing (HLB) is considered the most destructive citrus disease in the world, caused by *Candidatus* Liberibacter asiaticus (*C*Las) and spread by the vector *Diaphorina citri*. HLB has generated economic losses in the citrus industry worldwide. All commercial citrus varieties are susceptible to this disease. The intracellular nature of *C*Las, a strict intracellular parasite limited to the phloem, makes the phytopathological studies of HLB difficult. The “omic” tools, applying comparative analysis with a massive approach, have been useful to describe the interactions between the pathogenic agent and different citrus species, increasing the knowledge about the molecular basis of *C*Las pathogenicity and host responses to the infection. However, many processes involved in the complex interaction *C*Las-citrus are not fully understood yet. This review summarizes some of the main findings related to the pathogenicity mechanisms of *C*Las at the molecular level, as well as the transcriptomic, metabolic, and proteomic responses to the infection induced in tolerant or susceptible citrus varieties. This knowledge is necessary for the design and implementation of new strategies for the sustainable management of this disease.

Keywords: Huanglongbing, immune response, omics, phytohormones, susceptibility, tolerance.

Citrus (genus: *Citrus*, family: *Rutaceae*, subfamily: *Aurantoideae*) are fruit crops of worldwide economic importance. Their optimal development zone lies between 35 and 40° north and south latitude, that is, in the tropical and subtropical areas (Gottwald, 2010; Liu *et al.*, 2012; Nehela *et al.*, 2018). Citrus production is affected by the incidence of a wide variety of pests and diseases, among which Huanglongbing (HLB), greening or yellow dragon of citrus, stands out as the most destructive disease worldwide, causing billions of dollars in losses each year (Timmer *et al.*, 2000; Singerman and Rogers, 2020).

Plants that contract this disease develop a series of characteristic symptoms: yellow shoots in some parts of the crown, thinning of the affected branches, few fruits, asymmetric mottling with yellow islands, and accumulation of starch in the leaves, which tend to be thicker, corky, enlarged, leathery and with yellow veins. These symptoms are similar to those caused by different types of nutritional deficiency such as zinc deficiency. The fruits show uneven coloration, reduced size, reverse ripening starting at the stem, deformation, premature fall of fruit, and seed abortion. The coverage of the root system is also affected by reducing the formation of secondary roots, which decreases the uptake of minerals from the soil (Esquivel-Chávez *et al.*, 2012; Robles-González *et al.*, 2013; da Graça *et al.*, 2016; Nehela and Killiny, 2020b).

Huanglongbing affects commercial plantations by increasing the mortality rate of trees, reducing yield and fruit quality, and increasing production costs (Farnsworth *et al.*, 2014). The yield can be reduced from 30% to zero, depending on the intensity of the disease. The fruits become small and acidic, with juice low in degrees Brix, which makes it difficult to place them on the market (Bassanezi *et al.*, 2009). In Florida, a 23% reduction in citrus production was reported from 2006 to 2011, a loss of more than 1.7 billion dollars and 8,000 direct and indirect jobs (Hodges and Spreen, 2012). The number of citrus growers in Florida decreased from 7,389 in 2002 to 2,775 in 2017. In addition, the number of juice processing plants fell from 41 to 14, while the number of packing plants fell from 79 to 26 in the same period of time (Singerman and Rogers, 2020).

In Mexico, there are few reports of the impact of HLB. The state of Colima has been one of the most affected by HLB, damaging almost 5,000 hectares that had to be replanted. The most affected crop was Mexican lime, the production of which fell by more than 84,000 tons, causing a net economic loss of more than 300 million pesos (Granados-Ramírez and Hernández-Hernández, 2018). In Yucatán, Flores-Sánchez *et al.* (2015) pointed out that symptomatic diseased trees showed a reduction in fruit weight of 17.3% and a reduction in juice volume of 18.6%. Based on these data, a loss of 2.4 t ha^{-1} was estimated. Salcedo *et al.* (2011) and Hernández-Hernández *et al.* (2019) suggested that in a high-impact scenario for HLB, more than 19 million jobs could be lost throughout the country and the loss in orange production could reach 1.8 million t.

The strategies for the management of HLB include early efforts to stop the advance of the disease in plantations by eliminating diseased plants (Martini *et al.*, 2015) and the use of certified plants (Bové, 2012), as well as foliar applications of insecticides (Boina and Bloomquist, 2015) or biological control of the vector (Álvarez *et al.*, 2016). They include also recently developed technologies such as thermotherapy (Hoffman *et al.*, 2013) and the generation of resistant transgenic plants (Dutt *et al.*, 2015; Ventura-Medina *et al.*, 2019; Soares *et al.*, 2020). Given that the HLB disease is already established in most commercial plantations throughout the world, the strategies currently being evaluated aim to extend the productive life of infected trees. These strategies include agronomic management and complementary fertilization programs (Xia *et al.*, 2011; Uthman *et al.*, 2020; Atta *et al.*, 2021; Hernández-Morales *et al.*, 2021), as well as the use of resistance inducers (Hu *et al.*, 2018; Trinidad-Cruz *et al.*, 2019; Flores-de la Rosa *et al.*, 2021), antimicrobial peptides (SAMPs) (Huang *et al.*, 2021), antibiotics (Killiny *et al.*, 2020), and phytohormones (Tang *et al.*, 2021; Ma *et al.*, 2022). Frontier technologies such as gene editing using CRISPR may also be a viable alternative for the management of HLB (Song *et al.*, 2017).

However, the development of effective and sustainable strategies to reduce the impact of HLB requires a thorough understanding of the mechanisms involved in the interaction between *C*Las and citrus plants, as well as identifying the genetic and molecular factors involved in the *C*Las pathogenesis process and in the defense and tolerance responses of citrus plants. In the last decade, the use of the so-called "omics" tools has made it possible to identify *C*Las virulence factors and some of the molecular bases potentially involved in the infection and pathogenesis processes (Dalio *et al.*, 2017; Coyle *et al.*, 2018). Transcriptomic, proteomic and metabolomic responses differentially expressed in infected plants of tolerant and susceptible varieties have also been described to identify the mechanisms involved in tolerance to HLB (da Graça *et al.*, 2016; Dalio *et al.*, 2017; Coyle *et al.*, 2018; Curtolo *et al.*, 2020a; Yao *et al.*, 2020).

The present work reviews the state of the art on the molecular mechanisms and metabolic processes associated with the *C*Las-citrus interaction. Special attention is given to the Asian variant because it is the predominant species in Mexico and the world, and to those elements on which future strategies for the sustainable management of HLB disease can be developed, such as the molecular recognition of plant pathogens, differences in transcriptomic/proteomic/metabolomic responses between susceptible and tolerant varieties, hormonal modulation of defense responses, and the relationship between metabolic/physiological changes in plants and the development of symptoms in susceptible varieties.

For the new technologies under development to be adopted in the field, it is necessary to provide access to this information not only to the scientific community, but also to government officials, technicians, agricultural producers, and society in general.

The causal agent of HLB and its transmission. HLB is caused by gram-negative bacteria of the genus *Liberibacter*, obligate pathogens that colonize the phloem cells of infected plants and which cannot be isolated on artificial media using traditional microbiological techniques (a *Candidatus* species) (Fleites *et al.*, 2014; Merfa *et al.*, 2019). However, it has been possible to obtain axenic cultures of this species through the use of bioreactors (Ha *et al.*, 2019). Based on the geographic distribution and sequence characteristics of the 16S rDNA (ribosomal DNA) gene, four species associated with the HLB disease have been proposed: *Candidatus* Liberibacter asiaticus (*C*Las), *Ca.* L. americanus (*C*Lam), *Ca*. L. africanus (*C*Laf), and *Ca.* L. caribbeanus (*C*Lca) (Jagoueix *et al.*, 1994; Thapa *et al.*, 2020). Transmission of the disease occurs through infected grafts and, to a greater extent, through vector insects such as *Trioza erytreae* (Del Guercio; Hemiptera: Triozidae) in the African continent, *Diaphorina citri* (Hemiptera: Liviidae) in the Asian and American continents (Bové, 2006), and *Cacopsylla citrisuga* in China (Cen *et al.*, 2012).

The transmission process of HLB by *D. citri* begins when the vector acquires the *C*Las bacterium by feeding on the sap of a diseased tree. The bacterial cells pass from the intestine to the hemolymph, then to the salivary glands, where they remain in a latent state inside the vector (3-20 days) and reproduce before being transmitted to new plants (Ammar *et al.*, 2016). The bacterial cells spread to most insect organs, multiplying in vacuoles associated with the endoplasmic reticulum (Ghanim *et al.*, 2017). Insects pass the bacteria from diseased to healthy trees in subsequent feedings (Hall *et al.*, 2013). Pelz-Stelinski and Killiny (2016) indicated that the transmission of *C*Las to a healthy plant can occur even after only 30 min of feeding on a diseased tree. When the bacterium is transmitted to a new plant through the insect's stylet into the phloem of tender shoots, it spreads through the vascular tissue to the entire plant in a heterogeneous manner, including leaves, stems, roots, floral tissues, fruits, and seeds, even though there are no reports of vertical transmission from seeds to seedlings (Tatineni *et al.*, 2008; Bagio *et al.*, 2020). However, *C*Las colonization is limited to the phloem. The appearance of symptoms is a slow process, lasting between 6 and 9 months from the experimental inoculation by grafting or vector-induced infection (Folimonova *et al.*, 2010).

The development of HLB and its epidemiology depends on the spatiotemporal convergence of a susceptible host, a virulent pathogen, a vector, and favorable environmental conditions (Francl, 2001). The density of the host and the vector, as well as the dominance of the wind, are crucial factors for the dispersal of the primary inoculum, but so are anthropogenic activities (Flores-Sánchez *et al.*, 2017). For this reason, we consider that the producer or controller of the agroecosystem should be included in the tetrahedron of the disease described by Dik and Albajes (1999) (Figure 1), since he is responsible for the timely use of all available technical strategies to avoid the spread and reduce the impact of the HLB disease (Pérez-Zarate *et al.*, 2016; Pérez-Zarate *et al.*, 2020).

The pathogenesis mechanisms of *C*Las (how the pathogen causes damage to susceptible plants) are still unknown. Figure 1 shows an overview of some of the possible biochemical and molecular events subsequent to the transmission of *C*Las: Plants recognize the presence of the bacterium by detecting molecules secreted by it (PAMPs and/or effectors). These molecules are recognized by plants through transmembrane receptors (PRRs) and/or cytoplasmic receptors (NLRs). The detection of the bacterium by the plant leads to the activation of internal signaling cascades that involve the participation of second messengers such as calcium (Ca^{2+}), the electrolyte flow through the plasma membrane, production of reactive oxygen species (ROS), and nitric oxide. This, in turn, leads to the activation of mitogen-activated protein kinases (MAPKs) (Coyle *et al.*, 2018). Signaling cascades target transcription factors (TFs) that modulate the expression of multiple genes, including those involved in local and systemic defense and immunity processes. Transcriptional changes are also manifested in metabolic and physiological changes associated with the activity of phytohormones and that eventually lead to the development of the characteristic symptoms of the HLB disease.

Innate immunity in plants: PTI, ETI, and SAR. To better understand the molecular and metabolic events that have been proposed as possibly involved in the *C*Las-citrus interaction, the present work first summarizes an overview of the defense responses described in model plant-pathogen relationships. Figure 2 shows that the innate immune system of plants acts in two ways: a) It begins by recognizing pathogens through *pathogen pattern-recognition receptors* or PRRs (*Pattern*

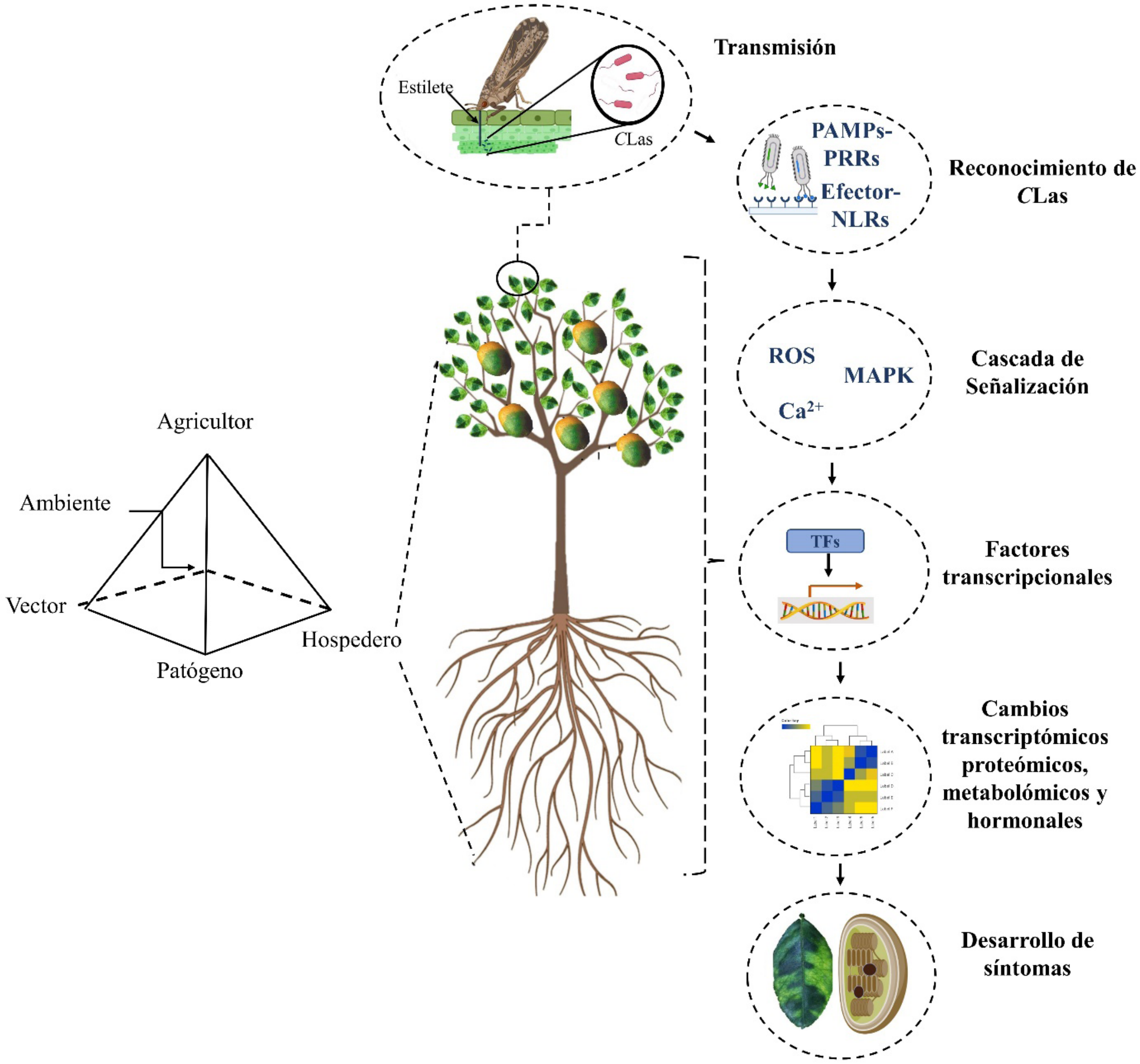

Figure 1. Components of the HLB disease tetrahedron, as well as consecutive events from the transmission and perception of the disease, to intracellular signaling processes, gene response, and eventual development of symptoms. PAMPs: Pathogen-associated molecular patterns, PRRs: PAMP recognition receptors, NLRs: Nucleotide-binding domain receptors with leucine-rich repeats, ROS: Reactive Oxygen Species, MAPK: Mitogen-activated protein kinases, Ca^{2+}: ions of calcium, TFs: Transcriptional factors. The meaning of further abbreviations can be found in Table 2.

Recognition Receptors) located on the surface of membrane cells. These receptors detect molecules produced by microorganisms known as microbe- or pathogen-associated molecular patterns (MAMPs or PAMPs). Upon detecting the pathogen, PRRs trigger the so-called *PAMP-Triggered Immunity* (PTI). b) Intracellular receptors called Nucleotide-binding domain Leucine-rich repeat containing Receptors (NLR) detect pathogen molecules, called effectors, that have penetrated the cell. These

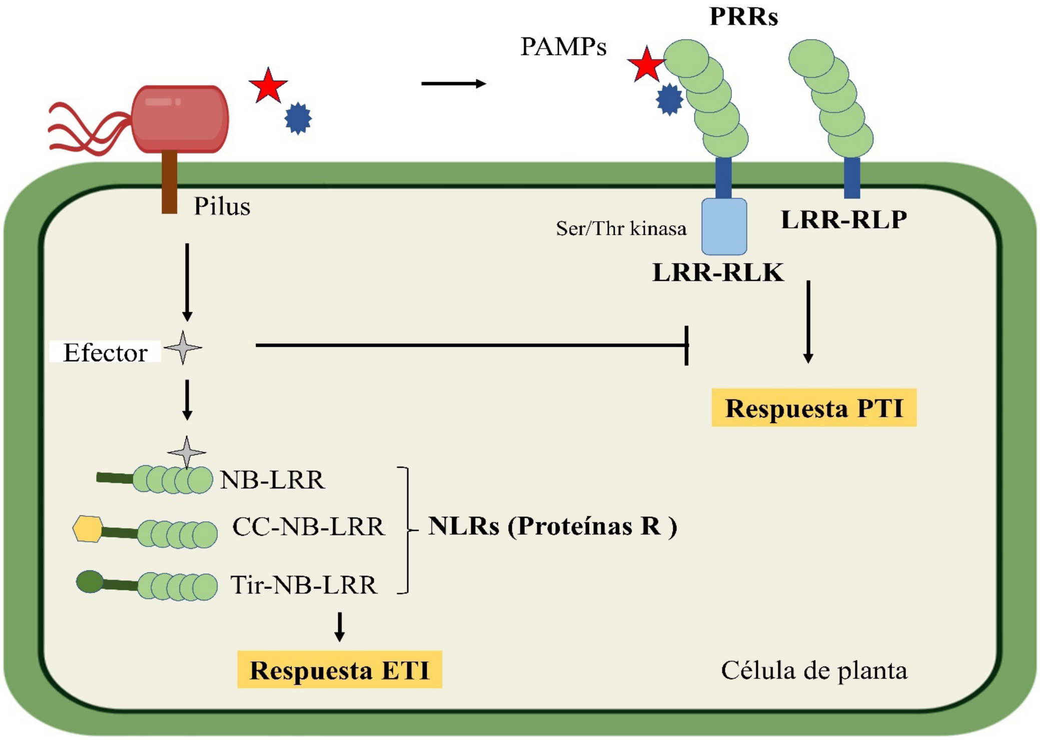

Figure 2. Activation pathways of the plant immune system before the attack of pathogens; structure of the transmembrane receptors for the recognition of pathogens, and intracellular receptors for the recognition of effectors in citrus. Adapted from Dodds and Rathjen (2010) and Dalio *et al*. (2017). ETI: Effector-triggered immunity; NLRs: Nucleotide-binding oligomerization domain (NOD)-like receptors with leucine-rich repeats; Tir: Domain homologous to Toll or interleukin-1 receptors; CC: coiled-coil domain LRR: Leucine-rich repeats; NB: Nucleotide-binding site; PAMPs: Pathogen-associated molecular patterns; PRRs: Pattern recognition receptors; PTI: PAMP Triggered Immunity; RLK: Receptor-like kinase; RLP: Receptor-like protein; Ser/Thr kinase: Serine/Threonine kinase.

virulence factors or effectors directly or indirectly modify plant processes to increase the chances of survival of the pathogen. The detection of effectors by NLRs triggers the so-called Effector-Triggered Immunity (ETI).

In 2006, Jones and Dangl proposed a model of four sequential "zig-zag" phases in which: 1) the initial innate PTI response, induced by PAMPs, is manifested through signaling cascades, transcriptional induction of genes in response to pathogens, ROS production, and cell wall reinforcement at infection sites, all of which are part of the first immunity barrier, slowing down the colonization of new tissues. 2) To break through the PTI and colonize the host, successful virulent pathogens use pathogenicity effectors that can interfere with PTI, preventing its activation or inhibiting its mechanisms. This leads to an Effector Triggered Susceptibility (ETS), which in turn leads to the development of the disease in the plant. However, 3) if any NLR-type plant intracellular receptor recognizes and neutralizes any pathogen effector, the ETI is triggered through the reactivation of signaling cascades and the eventual expression of defense genes. For this reason, the receptor is called a resistance protein (R). ETI is an immune response similar to PTI, but more rapid and intense, leading to disease resistance and usually to a hypersensitivity response (HR) involving cell death at the site of infection (Jones and Dangl, 2006). This interaction, in which a plant resistance gene specifically recognizes a complementary pathogen virulence gene (Durrant and Dong, 2004; Kaloshian, 2004), triggering apoptosis mechanisms (formerly called gene by gene hypothesis), eventually derives in phase 4), in which the pathogen, by natural selection, eliminates or diversifies the recognized effector and/or acquires additional virulence factors that allow it to again evade the immune response of the plant. The latter eventually co-evolves through the selection of new R proteins, which are not always receptors and which again trigger the ETI.

The gene-by-gene resistance hypothesis (Flor, 1971), currently included in the ETI, states that host plants contain dominant resistance genes (R), highly conserved in the plant kingdom, that encode proteins that specifically recognize, directly or indirectly, complementary products of pathogen genes called of avirulence (avr). This interaction leads locally to HR and subsequently to the activation of signaling pathways that culminate in the induction of systemic acquired resistance (SAR).

SAR is an innate immune response that protects uninfected plant parts from a distance. It is a long-lasting and effective response against a wide variety of pathogens after an initial local infection (Thilmony *et al.*, 1995; Fu and Dong, 2013). Plants with SAR are primed to activate a faster and more effective defense response if the same pathogen attacks a second time. This immune response depends on mobile systemic signals, possibly lipid in nature, which transmit from a distance the message that the plant is being invaded by a possible pathogen (Durrant and Dong, 2004). ISR (Induced systemic resistance) is a response similar to SAR but induced by non-pathogenic microorganisms that are part of the microbiota associated with plants. PTI and ETI induce SAR, which is why the latter is considered a secondary resistance response, induced after the appearance of necrosis associated with a hypersensitivity response. Systemic resistance can be elicited by substances that mimic the presence of the microorganisms that induce the mobile signal. SAR is characterized by the accumulation of salicylic acid (SA) and its methylated derivative MeSA, as well as genes encoding pathogenesis-related (PR) proteins with antimicrobial activity, such as chitinases or glucanases. The expression of PRs is regulated by NPR1, or nonexpressor of pathogenesis-related proteins, a key factor that changes to its active form when interacting with SA in the cytoplasm. Active NPR1 enters the cell nucleus to interact with transcriptional factors that activate the transcription of PR genes (Pieterse *et al.*, 2014).

PAMPs are highly conserved molecules among microorganisms, essential for their functions. They are secreted into the extracellular space and their epitopes are detected by plants as foreign molecules. PAMPs include lipopolysaccharides (LPS) (He *et al.*, 2007) such as the bacterial lipid A, as well as antigenic oligosaccharides and peptidoglycans from Gram-positive bacteria (Schwessinger and Zipfel, 2008). The best characterized PAMP is flagellin, a flagellar motility protein that triggers PTI and whose epitope of 22 amino acids in the N-terminal domain (flg22) is highly conserved (Schwessinger and Zipfel, 2008).

The effectors or virulence factors of successful pathogens that suppress PTI by mimicking or inhibiting cellular functions include phytotoxins, extracellular polysaccharides and various proteins secreted by the type III secretion system TTSS or T3SS (Jones and Dangl, 2006; He *et al.*, 2007).

Plant cells have receptors that perceive various environmental signals, including those from pests and pathogens. PRR receptor proteins located on the surface of the cytoplasmic membrane detect PAMPs (Figure 2) (Jones and Dangl, 2006). Albert *et al.* (2020) classify PRRs as receptor-like kinases (RLKs) or receptor-like proteins (RLPs), both of which contain ectodomains with ligand-binding capacity (Figure 3). Ectodomains are extracellular domains located outside the cell that come into contact with pathogens or their effectors, which leads to signal transduction into the cell (Restrepo-Montoya *et al.*, 2020). The structure of RLKs comprises an N-terminal extracellular domain with a transmembrane region, and a C-terminal intracellular domain with kinase activity (Shiu and Bleecker, 2001; Dalio *et al.*, 2017). RLPs have a transmembrane domain and an N-terminal extracellular domain but lack the intracellular kinase domain (Shiu and Bleecker, 2001).

As for the NLR receptors that detect pathogen effectors, they contain a variable N-terminal domain, a nucleotide binding site (NBS), and a domain with leucine-rich repeats (LRR) with a variable number of repeats and composition (Figure 2). The N-terminus is responsible for the interaction with signaling complexes and the NBS domain functions as ATPase and regulates oligomerization, while the LRR domain participates in protein-protein interaction and effector recognition (Alder *et al.*, 2005). The N-terminus of NLRs can alternatively present the Toll/interleukin-1 (TIR) or the CC (Coiled-coil) domain.

The immune response in citrus against HLB. When infected with *C*Las, plants of susceptible varieties such as *Citrus sinensis* (sweet orange) have been reported to present an overexpression of defense genes such as callose synthase (*CscalS*), which leads to callose deposition and programmed cell death at the infection site due to the effect of oxidative damage caused by ROS (Pitino *et al.*, 2017). It is presumed that the programmed cell death has the objective of preventing the general spread of the bacterium throughout the plant. However, the clogging of the phloem tubes possibly contributes to the accumulation of starch in leaves, which leads to the development of foliar symptoms as a result of anatomical and histochemical changes in the mesophyll and phloem. These changes include cell wall thickening in phloem cells, increased cell division (hyperplasia) of the phloem parenchyma, increase in the total area of the vascular system (xylem and phloem) and in the protein content of the phloem, such as PP1 and PP2, which participate in the blockage of the phloem during infection (Albrecht and Bowman, 2012; Esquivel-Chávez *et al.*, 2012; Koh *et al.*, 2012; Granato *et al.*, 2019).

Attempts have been made to explain the interaction between *C*Las and susceptible citrus plants, which gives rise to HLB symptoms, according to the zig-zag model of Jones and Dang (2006). Curtolo *et al.* (2020a) reported that the interaction of *C*Las PAMPs triggers an effective PTI during the asymptomatic state, associated with the production of gibberellins (GA) and SA. Subsequently, the *C*Las effectors interfere with the PTI or enable the pathogen to obtain nutrients and spread throughout the plant, giving rise to the ETS and eventual expression of symptoms. The activation of ETI in the plant is associated with the activation of genes responsible for the accumulation of callose and phloem protein 2 (PP2), which results in anatomical alterations and clogging of the phloem tubes, which in turn could trigger cell death by HR to prevent the widespread propagation of *C*Las throughout the plant (Jain *et al.*, 2019; Achor *et al.*, 2020). This also leads to phloem dysfunction and prevents the flow and distribution of photoassimilates throughout the vascular system, causing the accumulation of starch in mesophyll chloroplasts, accumulation of sucrose and glucose

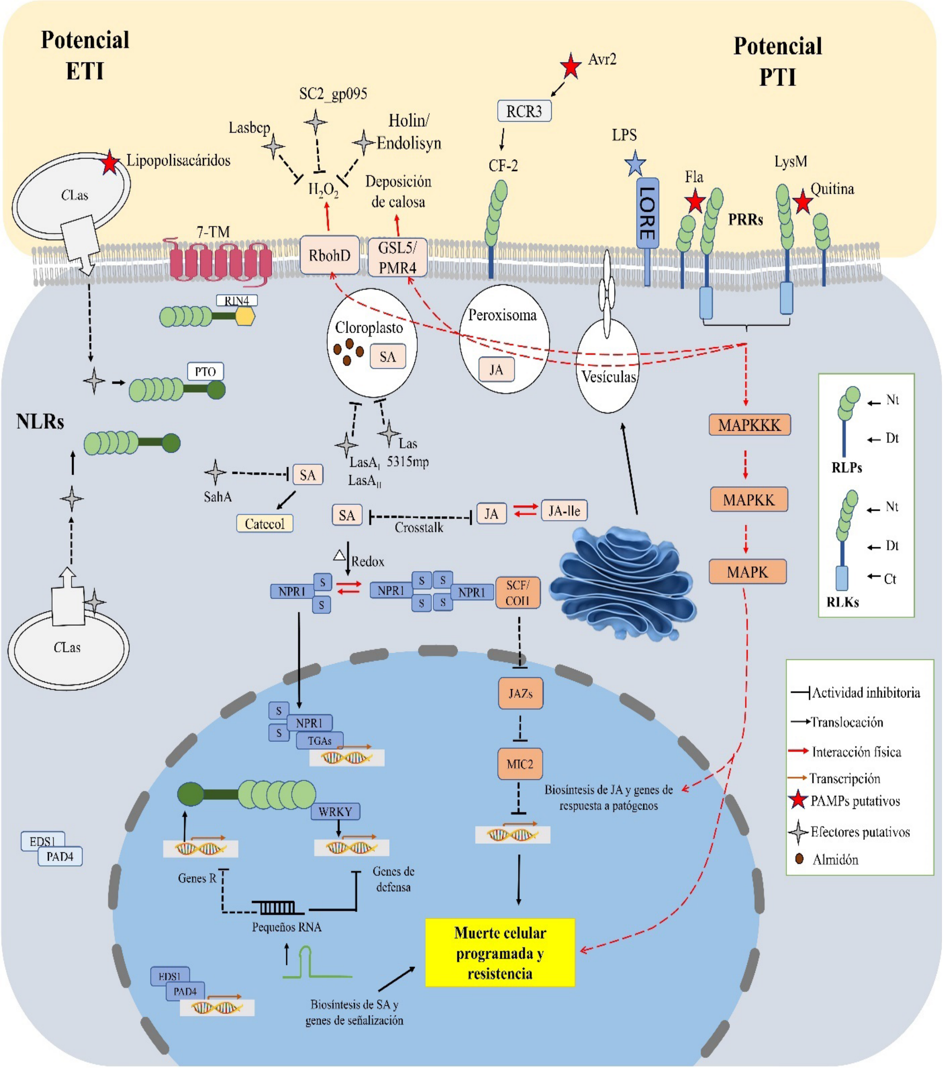

Figure 3. Immune response model in citrus, including the participation of possible *C*Las effectors. Since the effectors are still hypothetical, they are shown in gray, as in the original diagram. Adapted from Panstruga *et al.* (2009) and da Graça *et al.* (2016). AVR2: Avirulence effector 2; CF-2: Tomato receptor homologous to the resistance gene of *Cladosporium fulvum*; Ct: C-terminus; Dt: Transmembrane domain; EDS1/PAD4: Protein dimer that increases susceptibility to disease and its phytoalexin-deficient coregulator; ETI: Effector-triggered immunity; Fla: Flagellin, GSL5/PMR4: Glucan synthase-like 5 (callose synthase)/powdery mildew resistant 4; H_2O_2: Hydrogen peroxide; JA: Jasmonic acid; JA-Ile: Jasmonyl-Isoleucine; JAZ: Jasmonate ZIM domain; LPS: Lipopolysaccharides; LysM: Lysine motifs; MAPKs: Mitogen-activated protein kinases; MIC2: bHLH-like transcription factor; NLRs: Nucleotide oligomerization domain (NOD)-like receptors with leucine-rich repeats; NPR: Nonexpressor of pathogenesis-related genes; Nt: N-terminus end; PRRs: Pathogen recognition receptors; PTI: PAMP-triggered immunity; PTO: A serine/threonine kinase that confers resistance to *Pseudomonas syringae* pv. Tomato; RbohD: Respiratory burst oxidase homologous protein D; RCR3: Extracellular tomato cysteine protease homologous to papain-like Cys-proteases; RIN4: RPM1-interacting protein 4; RLK: Receptor-like kinase; SA: Salicylic acid; SahA: Salicylate hydroxylase effector; SCF/COI1: SCF(COI1) ubiquitin ligase; TGAs: bZIP-like transcription factors; WRKY: WRKY-like transcription factors; 7-TM: Receptors with 7 transmembrane domains.

in leaf cells (Koh *et al.*, 2012; Manzanilla-Ramírez *et al.*, 2019), rupture of thylakoid membranes, and chlorophyll degradation. All of this, together with a phytohormonal imbalance and oxidative stress, contribute to the development of late HLB symptoms in susceptible citrus plants (da Graça *et al.*, 2016).

Some putative PAMPs have been identified in the *C*Las genome using the same approach, and transcriptional studies have found evidence that the expression of receptor-like kinases (RLKs) is induced on the cell surface upon infection, which suggests the ability of citrus cells to recognize *C*Las PAMPs and initiate a signaling cascade that leads to PTI (Zou *et al.*, 2012; Hao *et al.*, 2013; Aritua *et al.*, 2013; Mafra *et al.*, 2013; Wei *et al.*, 2021). The identification of numerous molecules homologous to innate immunity elicitors, as well as to components of the defense and signaling responses in citrus, has led to the proposal of a "potential ETI" as part of the immune response to *C*Las infection (da Graça *et al.*, 2016).

Possible PAMPs and Effectors identified in *C*Las. To date, conclusive mechanisms of *C*Las pathogenicity in citrus have not been established, mainly due to the difficulty of cultivating this bacterium in the laboratory to perform pathology tests. The alternative has been to use close relatives such as *Liberibacter crescens*, *Agrobacterium* sp., and *Sinorhizobium* sp. to heterologously express *C*Las effectors or homologous genes (Dalio *et al.*, 2017; Jain *et al.*, 2019; Andrade *et al.*, 2020).

The whole genome sequencing of *C*Las by Duan *et al.* (2009) revealed that, among the genes potentially involved in the pathogenicity of the bacterium, 57 of them are involved in cell envelope and lipopolysaccharide biogenesis, which means that they could function as PAMPs. In addition, another 30 are involved in flagella biosynthesis. Zou *et al.* (2012) demonstrated that the 452-amino acid protein that is homologous to flagellin contains the flg22 domain and functions as a PAMP (Figure 3). Furthermore, flg22 can differentially trigger the citrus defense response in resistant and susceptible citrus plants (Shi *et al.*, 2017). However, Andrade *et al.* (2020) reported that these genes are not expressed in plants. Moreover, many PAMPs that are present in other pathogens are absent from the *C*Las genome. Thus, it has been suggested that *C*Las may have evolved to reduce the inducement of PTI (Duan *et al.*, 2009; Li *et al.*, 2017). This hypothesis considers that, since the inoculation route of the *D. citri* vector is intracellular and goes directly to the phloem (the only tissue affected by *C*Las infection), the pathogen may avoid the initial PTI response of the plant due to the fact that PRR receptors detect PAMPs only on the outside of the cell.

According to the model, once *C*Las enters the plant, it uses effectors to modulate some cell functions of the host to successfully multiply and colonize phloem cells. Effectors play a crucial role in the pathogenicity of *C*Las by restricting the activity of the plant immune system or interfering with the development processes of the host (Iqbal *et al.*, 2020). The sequencing of the *C*Las genome revealed the presence of proteins derived from a type I secretion system (T1SS) and a general secretion system (Sec) that are considered important for *C*Las virulence. However, the authors of that work reported that secretion genes commonly found in other pathogenic bacteria were not found in *C*Las. A gene potentially encoding the serralysin protein was also found. This protein is associated with T1SS and potentially acts as a virulence factor, participating in protein degradation (Cong *et al.*, 2012). Several computational tools can be used for the identification of possible pathogenicity effectors, such as http://prodata.swmed.edu/

liberibacter_asiaticus/curated/, a public website that allows one to view the most relevant results of a bioinformatic analysis that identifies possible factors of *C*Las virulence (Cong *et al.*, 2012). In recent years, important progress has been made in the functional evaluation of *C*Las pathogenicity factors and their role in the infection process in citrus plants. Figure 3 shows the possible *C*Las pathogenesis factors identified so far, as well as the defense responses they induce in plants. The characterization of some of the various effectors under study is described below.

Liu *et al.* (2019) pointed out that *C*Las secretes proteins with still unknown functions, and that the CLIBASIA_00460 protein could be associated with the pathogenicity of this bacterium since its overexpression in tobacco leaves is known to cause programmed cell death. The authors also showed that CLIBASIA_00460 was expressed at significantly higher levels in *C*Las infecting citrus than in positive psyllids. These findings, together with those from previous studies (Pitino *et al*., 2016), led them to conclude that this protein can act as a *C*Las virulence factor. Furthermore, Hao *et al.* (2013) reported that the hypothetical $LasA_I$ and $LasA_{II}$ proteins share structural features with families of transporters and have been detected in mitochondria when heterologously expressed in plants. Morphological changes have been observed in mitochondria and chloroplasts from overexpressing plants. Thus, it is hypothesized that $LasA_I$ and $LasA_{II}$ could manipulate energy production in the plant during infection. Clark *et al.* (2018) pointed out that the Sec1 effector of *C*Las inhibits the activity of papain-like cysteine proteases (PLCPs), which are produced by citrus plants as part of their defense response, associated with SAR. It has also been reported that CLIBASIA_RS00445 encodes the bacterioferritin protein (LasBCP), which belongs to the 1-Cys peroxiredoxin family and is essential for the survival and colonization of *C*Las in plants. The bacterioferritin protein degrades hydrogen peroxide (H_2O_2) and has specificity for organic peroxides (Singh *et al.*, 2017; Jain *et al.*, 2018), potentially affecting ROS signaling and activity as a defense mechanism. Jain *et al.* (2019) observed that LasBCP expression in citrus leaves was associated with a transcriptional decrease in oxylipin biosynthesis, thereby repressing ROS-induced lipid peroxidation. The authors also reported that LasBCP attenuates plant defense signaling mediated by jasmonic acid (JA) and salicylic acid (SA). Pitino *et al.* (2016) transiently expressed the Las5315 effector in *Nicotiana benthamiana* chloroplasts. This produced heavy callose depositions and cell death three days after inoculation. Pitino *et al.* (2017) also observed higher levels of H_2O_2 and adenosine triphosphate (ATP) in diseased leaves, compared to healthy ones. In 2018, Pitino *et al.* demonstrated that *C*Las infection caused an accumulation of starch in *N. benthamiana* leaves, similar to what has been observed in citrus trees infected with HLB. They also demonstrated that the transiently expressed effector Las5315 caused a 6- to 8-fold increase in starch accumulation, which was associated with low expression of starch-degrading plant enzymes, such as alpha-glucosidase, alpha-amylase, and glycosyl hydrolase. Jain *et al.* (2015) reported that the *C*Las protein SC2_gp095 was associated with negative transcriptional regulation of RBOHB proteins, which are essential in H_2O_2-mediated defense signaling. Ying *et al.* (2019) reported the presence of the CLIBASIA_00470 proteins, which is associated with the alteration of the host protein profile through the degradation of defense proteins mediated by ubiquitin. Furthermore, Wang and Trivedi (2013) and Li *et al.* (2017) reported the presence of the functional salicylate hydroxylase (SahA) enzyme in the *C*Las genome, which converts the SA produced by infected plants into catechol, which in turn inactivates the signaling pathway that induces systemic resistance. Other possible virulence factors of the *C*Las genome are present in two prophages, one an excision prophage (SC1) and the other a chromosomally integrated prophage. Both prophages encode two proteins with peroxidase activity (SC1_gp035 and SC1_gp110) that are similar to endolysin and holin, respectively. These proteins may protect the bacterium from ROS produced by the plant during infection (Fleites *et al.*, 2014). Vahling *et al.* (2010) reported the presence of the nttA (nucleotide transporter protein) gene that encodes an ADP/ATP translocase that alters intracellular ATP levels, which suggests that *C*Las imports ATP from its environment. Furthermore, *C*Las contains genes related to the Zn, Mn and Fe transport system (Znu #1, Znu #2), to ABC transporters (ZnuA1, ZnuB1, ZnuC1) and other periplasmic transporters (ZnuA2, ZnuB2, ZnuB2-2, Znu-C2), which suggests that *C*Las may import nutrients from its immediate environment (Vahling-Armstrong *et al.*, 2012; Sharma *et al.*, 2015, 2016).

In sum, there is no clarity regarding the existence of PAMPs in *C*Las, but there is a wide diversity of possible effectors for which there is evidence that they can trigger defense responses in citrus.

Putative PRR and NLR receptors in citrus. Despite the economic importance of citrus cultivation and its coexistence with a wide variety of pathogens, no citrus PRR has been functionally well characterized. However, some RLKs and RLPs appear to have a role in pathogen perception and in triggering innate immunity (Dalio *et al.*, 2017). Using bioinformatics, Magalhaes *et al.* (2016) identified in *C. clementina* and *C. sinensis* a total of 300 and 297 proteins, respectively, that are homologous to PRR receptors of the LRR-RLKs subfamily. Furthermore, Aritua *et al.* (2013) performed a microarray analysis and reported that, upon *C*Las infection, *C. sinensis* plants overexpressed 12 genes that are homologous to receptors present in rice (*Xa21*) and tomato (*Hcr2-5D* and *Cf-2.2*), a gene that encodes the SR160 receptor, homologs to the FERONIA (FER) receptor kinase, cell wall-associated kinases (WAK) and WLK family genes (similar to WAK genes). They also reported a negative regulation of receptor-like kinase homologs such as ERECTA and of a receptor similar to protein kinase 1, which have been described in Arabidopsis and crops such as corn and rice, where they participate in communication between the cell wall and the plasma membrane, mediating the transduction of signals to the intracellular compartment when their extracellular domains are activated (Hurni *et al.*, 2015; Hu *et al.*, 2017a). Furthermore, Fu *et al.* (2016) conducted a transcriptomic profile of *C. sinensis* and reported a large number of transcripts that were differentially expressed before the inoculation of *C*Las (RLP6, RLP9, RLP13, RLP14, RLP15, and RLP45), in addition to RLKs similar to LRR-K, WAKs, and proteins with a domain of unknown function 26 (DUF26).

Regarding the recognition of effectors by citrus plants with NLR-type receptors, the presence of possible resistance genes (R) homologous to these receptors has been reported in the sequenced genomes of *Citrus sinensis* and *C. clementina* (Wang *et al.*, 2015). Mafra *et al.* (2013) evaluated the response of *C. sinensis* to *C*Lam infection using microarrays and reported, in addition to the presence of transcripts encoding proteins similar to PRRs (RLP12), the differential expression of NBS-LRR pathogen recognition genes and lysin motif receptor-like kinases (CERK1). The transcriptomic analysis (CitEST) of sequences expressed in citrus plants in response to different species of pathogens under different growth conditions, showed the presence of a large number (137) of putative R genes with a structure similar to NBS-LRR, CC-NBS-LRR, and TIR-NBS-LRR, as well as the presence of resistance proteins of the transmembrane family 7 (7-TM) (Guidetti-Gonzalez and Carrer, 2007; Dalio *et al.*, 2017). Moreover, studies that compare the transcriptional profiles of healthy and HLB-infected plants have found that the differential expression of multiple NBS-LRR genes is potentially involved in the perception of *C*Las effectors (Kim *et al.*, 2009; Aritua *et al.* 2013; Mafra *et al.*, 2013; Nwugo *et al.*, 2013). The overexpression of the *CsSAMT1* gene in transgenic *C. sinensis* plants has been associated with the induction of receptor kinase expression, particularly TIR-NBS-LRR-like receptors (Zou *et al.*, 2021), in addition to an increased expression of genes for defense and resistance to HLB disease. *CsSAMT1* encodes salicylic acid methyltransferase (SAMT), which catalyzes the formation of methylsalicylic acid (MeSA) from salicylic acid. MeSA is essential for signaling the SA-mediated systemic acquired response (SAR) when a pathogen attacks. Despite the correlation of the expression profiles of putative NLRs with the infection process of HLB, the role of these receptors that functionally interact with *C*Las effectors and promote defense in resistant plants has not yet been proven.

What has been summarized so far, illustrated in Figure 3, represents a significant advance in the understanding of the possible PAMPs and virulence factors or effectors of *C*Las, and of their mechanisms to elicit or block immunity in citrus. However, further research is needed to carry out a functional characterization of putative citrus PRR receptors and R proteins antagonistic to *C*Las effectors. This would allow a better understanding of the pathways of PTI and ETI activation that are proposed to be induced in citrus plants infected with HLB.

HLB as an immune-mediated disease, an alternative view. It is generally considered that the protection of plants against most pathogens depends on the innate immune system that gives rise to PTI, ETI, or both, as well as on the systemic signals that emanate from the infection site, giving rise to the SAR (da Graça *et al.*, 2016). However, the differential classification between PTI and ETI, based on model plant-pathogen interactions, does not always fit the great diversity of existing plant-pathogen interactions, and there is little clarity about the chemical or functional differentiation between PAMPs and effectors. Moreover, the plant responses associated with PTI and ETI often converge or overlap (Bart *et al.*, 2011). Therefore, the differentiation between PAMPs/Effectors, types of receptors and types of immunity can only be conceptual.

Likewise, it is assumed that plant diseases are a direct result of the impact of pathogenicity factors on the causal or effector agents, such as toxins, enzymes that degrade the cell wall, and pathogen biofilms that obstruct the flow of photosynthetic products, among others. However, in the case of HLB, the mechanisms through which *C*Las damages infected plants are not clear and no pathogenic factors have been confirmed as directly responsible for the disease symptoms. On the contrary, Ma *et al.* (2022) recently proposed that HLB is mediated by the immune system and that the symptoms are caused by the plant's own chronic and systemic immune responses, indirectly caused by the pathogen (*a pathogen-triggered immune disease*) by inducing chronic and excessive overproduction of ROS, which causes the death of phloem cells. This is based on a) genomic and experimental evidence that *C*Las does not have pathogenicity factors that directly cause HLB symptoms. b) The fact that the presence of *C*Las in new leaves of infected *C. sinensis* trees triggers an immune response and cell death in the phloem tissues. The immune response includes an increase in the production of ROS (H_2O_2), callose deposition, starch accumulation before the visible appearance of yellowing, and the expression of PR proteins as immunity markers. c) The death of companion cells and sieve tubes in the phloem, mediated by HLB, seems to be triggered by the high levels of ROS produced both in young leaves in the early stages of infection and mature leaves and stems. This is consistent with the fact that the involvement of oxidative stress in HLB has been suggested by many studies. d) *C*Las infection significantly alters the expression of pathways related to oxidative stress, including both the negative regulation of antioxidant enzyme homologs and the overexpression of possible membrane NADPH-oxidases or RBOHs (Respiratory burst oxidative homologs) that, according to the analysis of the expression profiles reported in transcriptomic studies of *C. sinensis*, participate in other plants in the generation of ROS after the recognition of PAMPs. e) The same analysis of multiple transcriptomic studies has also revealed that there are expression changes in homologs of genes associated with the immune response, including the induction of tens of NLRs. The immune responses triggered by *C*Las have been widely described (Zou *et al.*, 2012; Li *et al.*, 2017; Clark *et al.*, 2018) and this hypothesis suggests that these responses are directly responsible for causing the damage associated with HLB, a process similar to what happens in human immune diseases.

Transcriptomic, proteomic and metabolomic responses in citrus plants tolerant or susceptible to *C*Las infection. The hypothesis described above was proposed based on the responses and symptoms observed in citrus plants susceptible to HLB. However, even though all citrus plants are affected by HLB to a greater or lesser degree, it has been reported that some species or varieties exhibit differentiated tolerance to the disease (Folimonova *et al.*, 2009). Oranges, mandarins, and tangelos are highly susceptible, but grapefruit, lemon, and sour orange show some degree of tolerance, with slower symptom expression and continued growth even during the infection (Folimonova *et al.*, 2009; Albrecht and Bowman, 2012). To date, no citrus varieties or commercial scion-rootstock combinations resistant to HLB have been reported, nor have specific resistance genes to *C*Las been identified, possibly because in evolutionary terms it is a recent disease (100 years) and citrus plants have not yet developed such resistance (Bové, 2006; Gottwald, 2010). Although the selection of hybrids described as resistant was reported recently (crosses between *Citrus sunki* ex Tan and *Poncirus trifoliata* Raf. cv Rubidoux), and a chitinase gene was proposed as a possible resistance gene (Curtolo *et al.*, 2020a; b), there is no further information regarding their behavior and productivity in the field.

The identification of defense mechanisms against HLB in tolerant varieties and possible resistant hybrids will allow to propose better management alternatives for HLB, even for susceptible citrus plants. It will also open the possibility of generating genetically improved varieties. Various works using data mapping to evaluate the expression of quantitative trait loci (eQTL) in citrus trees infected with *C*Las support the hypothesis that the tolerance to HLB shown by some varieties is polygenic (Huang *et al.*, 2018; Soratto *et al.*, 2020; Curtolo *et al.*, 2020b; Hu *et al.*, 2021).

Species, varieties, hybrids, and stem/rootstock combinations with different degrees of tolerance or susceptibility have been used individually or comparatively to determine their transcriptomic, proteomic, and metabolic responses to *C*Las infection. This has been done to identify differentially accumulated molecules presumably associated with different levels of tolerance to infection (Table 1). A comprehensive analysis of these studies suggests that citrus plants with different levels of tolerance to HLB, show changes in gene expression and the accumulation of proteins and metabolites when infected with *C*Las. These changes vary between genotypes, including receptor homologs, resistance proteins, transcription factors, antioxidant enzymes, the metabolization of carbohydrates, amino acids and fatty acids, phytohormones, the cell wall and other metabolic pathways. Thus, the susceptibility or tolerance of a particular genotype could be associated with the under- or over-expression of a set of genes and certain metabolic pathways. Below, we describe response patterns that are differentially affected by *C*Las infection in citrus plants, depending on the level of tolerance of the variety. The patterns are grouped according to the possible function of the molecules involved during the immunity process.

Receptors: changes in the expression of possible PRR recognition receptors have been reported in susceptible varieties. These changes include the negative regulation of some transmembrane receptors homologous to RLKs, cysteine-rich kinases, FERONIA-like receptor kinases, serine/threonine/kinase-like receptors, and kinases with leucine-rich repeats (Curtolo; *et al.*, 2020a), suggesting a possible late recognition of *C*Las. However, the same authors, and also Hu *et al.* (2017b), reported an upregulation of other receptor kinases possibly related to the response to biotic stress, such as the LRR receptor-like serine/threonine-protein kinase GSO1, ERL2, and an RLP similar to protein 12, which may recognize PAMPs and trigger PTI. In tolerant varieties infected with *C*Las, an increase in the expression of homologs to PRRs such as the flagellin receptors CiFLS2-1 and CiFL2-2 has been reported, related to the activation of PTI and resistance to bacteria in citrus plants (Shi *et al.*, 2017). Other potential receptors overexpressed in tolerant varieties include RLK homologs such as the G-type lectin receptor-S, cysteine-rich receptor kinase, serine/threonine/protein kinase, and leucine-rich repeat transmembrane kinase (Hu *et al.*, 2017a; Curtolo *et al.*, 2020a). The expression of these genes could be associated with the recognition, signaling and activation of response genes against *C*Las; however, their role as receptors remains to be demonstrated experimentally.

REDOX state homeostasis: Despite the importance of ROS in defense and signaling during pathogenesis processes, and against HLB in particular, a decrease in reducing compounds (e.g. thioredoxin), antioxidant enzymes (e.g. superoxide dismutase (Cu/Zn-SOD), and peroxidases (POD4) was observed in susceptible varieties. These are all crucial components in the reduction of oxidative damage caused by ROS (Hu *et al.*, 2017a). Thus, these varieties would be exposed to oxidative stress triggered by the plant's defenses to face the *C*Las infection, leading to an ETS. In contrast, tolerant varieties showed a higher expression of glutathione S-transferase (Wang *et al.*, 2016), glutaredoxin genes such as GRXC6, GRXC9 and GRXS9, and peroxidases (Cu/Zn-SOD and POD4) (Hu *et al.*, 2016, 2017a). Furthermore, these varieties also show the induction of biosynthesis genes that encode Fe(II) 2-oxoglutarate dioxygenase, which catalyzes numerous oxidative reactions in cells and participates in the biosynthesis (GA and Ethylene) and catabolism (Aux and SA) of phytohormones, as well as in the biosynthesis of secondary metabolites and thioredoxin, a protein of the Trx antioxidant system (Albrecht and Bowman, 2012). This means that these tolerant varieties might have more protection against damage caused by oxidative stress and by the immune system itself when induced by ROS signaling pathways.

Table 1. Transcriptomic, metabolic and/or proteomic studies of citrus plants with different levels of tolerance to infection with *C*Las.

Variedad	Tipo de estudio y Referencia	Ejemplos de transcritos, proteínas o metabolitos diferencialmente expresados potencialmente relacionados con la tolerancia o susceptibilidad
Limón Lisboa (*C. limon*) ^{MT} vs Naranja Navel (*C. sinensis*)^{S}. Porta injerto: Carrizo citrange (X *Citroncirus webberi*)^{T}.	-Plantas en invernadero. -Inoculación mediante injerto. -Evaluación de expresión transcriptómica, metabolómica y proteómica. -Comparación entre hojas de plantas sanas y enfermas de limón vs Naranja. (Chin *et al*., 2021)	-*C*Las indujo la disrupción del metabolismo de cítricos tanto en la variedad tolerante como en la susceptible a nivel de transcritos, proteínas, metabolitos y micronutrientes: -Mayor acumulación de micronutrientes (Cu^{2+} y K^{+}) en hojas de plantas de limón y menor concentración de Mg^{2+}, Cu^{2+}, Fe^{2+} y Ca^{2+} en hojas de naranja infectadas con *C*Las. -Expresión diferenciada de proteínas relacionadas con fotosíntesis, respuesta de defensa, inhibidores de tripsina tipo Kunitz, degradación de quitina y glucólisis en hojas positivas a *C*Las, respecto a plantas sanas. -Mayor cantidad de Azúcares, aminoácidos y otros compuestos en hojas enfermas de naranjas respecto a limón. -Mayor expresión de transcritos de degradación de quitina en hojas de limón infectadas respecto a hojas infectadas de naranja. -En un estado pre-sintomático, la fotosíntesis fue afectada en menor grado en limón respecto a naranja. -Transcritos de inhibidores de proteasas (PI) se expresaron en mayor medida en hojas de limón respecto a naranja. -Mayores cambios metabólicos en naranja respecto a limón.
Mandarina Sugar belle^{T} (*C. reticulata* x *Minneola tangelo*)^{T} vs Mandarina Murcott (*C. reticulata* Blanco)^{S}. Porta injerto: Naranjo agrio (*Citrus aurantium* L.)^{MT}.	-Plantas en invernadero. -Inoculación mediante injerto. -Evaluación metabolómica. -Comparación entre hojas de plantas sanas y enfermas de Sugar belle vs Murcott. (Suh *et al*., 2021)	-Algunas vías metabólicas (síntesis de aspartato, glutamato, purinas y biosíntesis de fitohormonas como auxinas y citoquininas) se incrementaron en el grupo tolerante tanto en plantas sanas como enfermas, pero no metabolitos relacionados con ácido salicílico (ácido salicílico, ácido salicílico β-D-glucosido y ácido 2, 3-dihidroxibenzoico). -Las vías catabólicas asociadas al metabolismo productor de energía se incrementaron en el grupo tolerante. -Los autores sugieren que en la variedad tolerante el patrón asociado a la tolerancia está asociado con el crecimiento continuo y regeneración del floema; por el contrario, en la variedad susceptible se expresó una respuesta de defensa directa.
C. sinensis^{S}*, C. sunki*^{S}*, P. trifoliata*^{T}*,* 21 híbridos (tres grupos^{S,T,R}) obtenidos de la cruza de *C. sunki* x *Poncirus Trifoliata.* Porta injerto: Lima Rangpur (*C. limonia*)^{MT}.	-Plantas en invernadero. -Inoculación mediante injerto. -Evaluación transcriptómica. -Comparación entre hojas de plantas sanas y enfermas de variedades susceptibles (*C. sinensis*, *C. sunki* y grupo susceptible), tolerantes (*P. trifoliata* y grupo tolerante) y resistente (grupo resistente). (Curtolo *et al*., 2020a)	-Las variedades susceptibles mostraron la expresión diferencial de un gran número de genes respecto a variedades tolerantes. Respecto a los híbridos, todos los grupos mostraron expresión diferenciada de genes, sin embargo, el grupo tolerante mostró la mayor expresión de genes, respecto a los grupos resistente y susceptible. Muchos de los genes diferencialmente expresados fueron regulados negativamente en plantas enfermas respecto a plantas sanas. -En *P. trifoliata* y el grupo resistente se observó una mayor expresión de receptores de reconocimiento como: *receptor cinasa rico en cisteína*, *proteína cinasa serina/treonina, cinasa transmembranal-LRR y* LRR-RLK, respecto a las variedades susceptibles. -En genotipos tolerantes y resistentes, *C*Las indujo la expresión de genes relacionados con la degradación de giberelinas, en comparación con genotipos susceptibles. -La expresión de factores transcripcionales WRKY se relacionó con los mecanismos de defensa genética en *P. trifoliata*. -Respecto a los genes de defensa, el gen *endoquitinasa B* se expresó en mayor medida en el grupo resistente. -En *P. trifoliata* se expresaron genes relacionados con lignina y fenilpropanoides como ácido *cafeico O-metiltransferasa*, *chalcona sintasa* y *feruloil orto-hidroxilasa 1* entre otros. -En *P. trifoliata* se observó una modulación génica a nivel de floema como respuesta a *C*Las, sin la deposición de calosa que ocurre en variedades susceptibles. -En variedades tolerantes no se observó inducción de genes relacionados con la síntesis de almidón.

Table 1. Continue...

Variedad	Tipo de estudio y Referencia	Ejemplos de transcritos, proteínas o metabolitos diferencialmente expresados potencialmente relacionados con la tolerancia o susceptibilidad
Naranja dulce (*C. sinensis*)^{S}. Porta injerto: Carrizo citrange (*C. sinensis* x *Poncirus trifoliata*)^{MT}. Plantas sanas vs enfermas.	-Plantas en invernadero. -Inoculación mediante injerto. -Evaluación transcriptómica en raíz de plantas sanas y enfermas. -Tratamientos de fertilización a base de macro y micro nutrientes. -Cuatro tratamientos de fertilización: 1) árboles sanos con fertilización (HLY-F), 2) árboles enfermos con fertilización (HLB-F), 3) árboles sanos sin fertilización (HLY-NF) y 4) árboles enfermos sin fertilización (HLB-NF). (Shahzad *et al*., 2020)	-Ante la condición de deficiencia nutricional nueve genes codificantes de: tranferencia de fosfoglicéridos, proteínas de la famila HPP, proteínas similares a dedos de zinc (Ran BP2/NZF), HVA22 homologo C, dominio barrel A/B sensible al estrés, peroxidasas, transportadores de zinc y receptores LRR se expresaron de forma diferenciada en raíces de plantas inoculadas con HLB. -Ante la fertilización (una semana después) genes relacionados con transporte de iones, crecimiento y desarrollo de raíz, cambios anatómicos, muerte celular y apoptosis, se expresaron de manera diferenciada en raíces de plantas enfermas vs sanas. -Las plantas enfermas mostraron mayor eficiencia en la toma de nutrientes, sin embargo, el volumen de raíz fue menor que en plantas sanas, lo que limita la toma de nutrientes. -Los macronutrientes secundarios y micronutrientes son metabolizados en una tasa mayor en plantas enfermas. -Los autores sugieren que un suministro constante de fertilización con dosis ligeramente superiores a las recomendadas de macro nutrientes secundarios y micronutrientes sería beneficioso para el manejo de árboles enfermos con HLB.
Naranja Valencia (*C. sinensis*)^{S}. Porta injertos: Swingle (*Citrus paradisi* x *Poncirus trifoliata*)^{S} y 46x20-04-48 (*C. grandis* x *C. reticulata*)^{T}.	-Plantas cultivadas en una parcela. -Inoculación mediante *D. citri*. -Evaluación proteómica en pulpa de frutos sintomáticos y asintomáticos (ambos HLB+). Comparación: porta injerto tolerante vs susceptible vs fruto sintomático vs fruto asintomático. Grupo de sanas vs enfermas. (Yao *et al*., 2020)	-La naranja valencia mostró diferencias en las características del fruto y el perfil de expresión de proteínas ante la infección de *C*Las, tanto en el portainjerto susceptible como el tolerante: 525 proteínas tuvieron una regulación negativa en frutos del portainjerto Swingle y 257 en 46x20-04-48, respecto a los testigos sanos. -En Swingle se encontró una regulación negativa de proteínas asociadas a la biosíntesis de aleno óxido sintasa y a la señalización de jasmonatos como SKP1 (proteína cinasa asociada a fase S), ASK2 (similar a SKP1), RUB1 (similar a ubiquitina), proteínas de choque térmico HSP70T-2 y HSP90.1, subunidades del proteosoma como RPN8A y RPT2a y receptores para tráfico vesicular (SNAREs). -Se propone que las proteínas reguladas negativamente relacionadas a la vía de señalización de jasmonato y tráfico vesicular, podrían relacionarse con la sensibilidad de Swingle.
Naranja Valencia (*C. sinensis*)^{S}.	-Plantas en invernadero. -Plantas sanas vs plantas inoculadas mediante injerto vs plantas infestadas con *D. citri*. -Evaluación metabolómica en hojas. -Aplicación de melatonina exógena. (Nehela y Killiny, 2020a)	-La infección con *C*Las y la infestación con *D. citri* incrementó los niveles endógenos de melatonina y reguló positivamente sus genes de biosíntesis como *TDC* (tirosina decarboxilasa), *T5H* (triptamina-5-hidroxilasa), *SNAT* (serotonina N-acetiltransferasa), *ASMT* (N-Acetilserotonina O-metiltransferasa) y *COMT* (ácido cafeico O-metiltransferasa) en hojas de naranja Valencia. -El incremento en los niveles endógenos de melatonina se correlacionó positivamente con el contenido de ácido salicílico. -La aplicación exógena de melatonina potenció el contenido de fitohormonas asociadas a estrés (salicilatos, auxinas, ácido *trans*-jasmónico y ácido abscísico), así como la transcripción de los genes de sus biosíntesis. -La aplicación de melatonina disminuyó significativamente los títulos de *C*Las en hojas sintomáticas de *C. sinensis.* -Se propone a la melatonina como mediador de la respuesta de defensa de cítricos contra HLB mediante la modulación vías de señalización de fitohormonas.
14 variedades de cítricos clasificadas en cuatro grupos de acuerdo con su grado de tolerancia a *C*Las^{F}.	-Plantas en invernadero. -Plantas sanas. -Evaluación metabolómica de savia del floema de brotes colectados en tres alturas del dosel. -Tolerantes vs susceptibles. (Killiny, 2017)	-La variedad tolerante *Citrus latipes* tuvo niveles altos de γ-ABA, ácido L-aspártico, L-asparaginasa, L-Treonina, L-Valina, ácido fumárico, maltosa y fructosa. -La galactosa, *β*-L-arabinopiranosa, arabinosa, sorbosa y los ácidos orgánicos, se correlacionaron negativamente con la tolerancia. -El ácido fumárico, *α*-D-galactopiranosa, α-D-manopiranosa, maltosa, manosa y disacáridos se correlacionaron positivamente con la tolerancia de los cítricos a *C*Las.

Table 1. Continue...

Variedad	Tipo de estudio y Referencia	Ejemplos de transcritos, proteínas o metabolitos diferencialmente expresados potencialmente relacionados con la tolerancia o susceptibilidad
US-812^{T}, US-897^{T}, US-942^{T}, *C. sinensis*^{S}, *C. Paradisi* (Duncan)^{S}, *C. paradisi* (Ruby Red)^{S}.	-Plantas sanas en invernadero vs plantas enfermas cultivadas en parcela. -Inoculación natural mediante *D. citri.* -Evaluación transcriptómica en hojas. -Tolerantes vs susceptibles. (Rawat *et al*., 2017)	Mayor actividad de los genes PtCDR2 y PtCDR8, relacionados con la activación constitutiva de respuesta de defensa en *P. trifoliata* infectadas con *C*Las, respecto a variedad es susceptibles.
Mandarina Sun Chu Sha^{T} vs Pomelo Duncan^{S}	-Plantas en invernadero. -Evaluación transcriptómica en hojas. -Aplicación exógena del péptido Flg22 en hojas. -Tolerante vs susceptible. (Shi *et al*., 2017)	-La aplicación de Flg22 indujo la expresión de 86 genes en el genotipo de mandarina tolerante, de los que destacan citocromo P450, glicoproteínas ricas en hidroxiprolina y proteínas de resistencia a enfermedades. -24 horas después del tratamiento se encontró una mayor expresión de genes *EDR1, EDS1, NDR1, PBS1, RAR1* y *SGT1*, biosíntesis de fenilpropanoides (*PAL1*), reguladores transcripcionales de PRs (NPR2 y NPR3), inductores de SAR (*AZI1)* y genes de patogenicidad (RdRp1) en el genotipo tolerante. Por otro lado, en el genotipo susceptible solo se indujo la expresión de un gen PR (*PR1*).
Varetas tolerantes de lima Kaffir (*C. hystrix*)^{T} vs naranja dulce 'pineapple' (*C. sinensis*)^{S}. Porta injerto: Carrizo citrange (*C. sinensis* x *P. trifoliata*)^{T}. Inoculo: Pomelo Guanximiyou (*C. grandis*)^{NR}.	-Plantas en invernadero. -Inoculación mediante injerto. -Evaluación transcriptómica en hojas. -Tolerante vs susceptible. (Hu *et al*., 2017b)	-Se encontró una respuesta diferenciada en el metabolismo de carbohidratos, procesos fotosintéticos, metabolismo de la pared celular, metabolismo secundario, procesos de oxido-reducción en *C. hystrix* respecto a *C. sinensis*. -Los autores no encontraron cambios en la síntesis de almidón y procesos fotosintéticos en *C. hystrix*, por el contrario, éstas vias fueron reguladas positivamente en *C. sinensis*. -Familias de proteínas similares a celulosa sintasa que participan en la síntesis de la pared celular se expresaron en mayor medida en *C. hystrix*, respecto a *C. sinsensis*. -Genes involucrados en rutas del metabolismo secundario se expresaron en *C. hystrix* y reprimidos en *C. sinensis.* -La expresión de peroxidasas (Cu/Zn-SOD y POD4) se asociaron con la tolerancia de *C. hystrix a C*Las, probablemente por su actividad como proteínas de detoxificación de ROS.
Limón mexicano (*C. aurantifolia*)^{MT} vs lima Persa (*C. latifolia*)^{MT} vs naranja dulce (*C. sinensis*)^{S}.	-Plantas en parcela bajo condiciones de temporal. -Infección natural con *D. citri.* -Evaluación proteómica de hojas de árboles infectados con HLB. -Árboles sintomáticos vs a sintomáticos. (Torres *et al*., 2017)	-Mayor expresión de proteínas totales en limón mexicano infectado con *C*las. -Mayor actividad enzimática de fenilalanina amonio liasa (PAL) en naranja dulce infectada con *C*Las. -La actividad α-amilasa fue mayor en limón persa.
13 variedades de cítricos clasificadas en cuatro grupos de acuerdo con su grado de tolerancia a *C*Las^{F}.	-Plantas en invernadero. -Plantas sanas. -Evaluación metabolómica en hojas. -Tolerantes vs susceptibles. (Killiny e Hijaz, 2016)	-La mayoría de los aminoácidos encontrados en la savia del floema como fenilalanina, tirosina, triptófano, valina, leucina, histidina, lisina, cisteína, metionina, serina y glutamato se relacionaron positivamente con la tolerancia de cítricos a *C*Las. -Los ácidos orgánicos se correlacionaron negativamente con la tolerancia y los ácidos grasos no mostraron correlación.

Table 1. Continue...

Variedad	Tipo de estudio y Referencia	Ejemplos de transcritos, proteínas o metabolitos diferencialmente expresados potencialmente relacionados con la tolerancia o susceptibilidad
C. volkameriana^{MT}*, C. sinensis* (Nabel)^{S}, patrón *C. sinensis* x *Poncirus trifoliata*^{T}. Inoculo: *C. limon.*	-Plantas en invernadero -Inoculación mediante injerto. -Análisis proteómico de nervaduras y peciolos. -Tolerante vs susceptible. (Martinelli *et al*., 2016)	-En el genotipo susceptible, la enfermedad del HLB inhibió la fotosíntesis, la ruta de isoflavonas, síntesis de tetrapirrol, metabolismo de galactosa. Disminuyó la biosíntesis de ácidos grasos y metabolismo de nitrógeno, además, se incrementó la degradación de aminoácidos, metabolismo de lípidos, jasmonatos, proteínas PR y metabolismo de ácido linoleico. -En el genotipo tolerante disminuyó la actividad de isoprenoides, unión de ARN y activación de aminoácidos. Además, incremento en el metabolismo de galactosa, modificaciones en la pared celular y proteínas de choque, también, se activaron tres proteínas involucradas en la transducción de señalización de auxinas y cuatro glutation S-transferasas. -En ambos cultivares se expresaron receptores cinasa tipo LRR ante la infección de *C*Las.
Tres híbridos de Toronja Jackson (R20T17, R20T18 y R19T17)^{T} vs tres híbridos de Toronja Marsh (R19T23, R19T24 y R20T24)^{S}.	-Plantas cultivadas en campo. -Infección natural con *D. citri.* -Análisis transcriptómico en brotes jóvenes. -Tolerantes vs susceptibles. (Wang *et al*., 2016)	-Sobre expresión de genes SAUR y NPR1 relacionados con la resistencia sistémica en los híbridos tolerantes, respecto a susceptibles. -Expresión diferenciada de genes asociados a la pared celular, tetrapirrol y metabolismo secundario entre los híbridos tolerantes y susceptibles. -Mayor expresión de genes de patogénesis (PR) en la variedad tolerante. -La expresión de genes asociados a la pared celular como celulosa sintasa y transferasa, celulasa, expansinas y pectín esterasas se relacionaron con el desarrollo de síntomas en la variedad susceptible. -La mayor expresión de genes asociados a receptores RLK se presentó en la variedad tolerante. -Los mayores cambios encontrados a nivel de sobre expresión de factores transcripcionales se observaron en la variedad susceptible. -Se encontró una baja expresión de genes relacionados a la biosíntesis de brasinoesteroides en la variedad tolerante.
I: Mandarina Cleopatra (*C. reticulata*)^{S}, vs híbrido US-897 (*C. reticulata* 'Cleopatra' x *P. trifoliata* 'Dragón volador')^{T}. II: Mandarina Cleopatra (*C. reticulata*)^{S} vs Carrizo citrange (*C. sinensis* x *P. trifoliata*)^{T}, US-802 (C. *grandis* 'Siamese pummelo' x *P. trifoliata* 'Gotha Road')^{T}, US-812 (*C. reticulata* 'Sunki' x *P. trifoliata* 'Benecke')^{T}, US-897, US-942 (*C. reticulata* 'Sunki' x *P. trifoliata* 'Flying Dragon')^{T}.	-Estudio en invernadero. -Inoculación mediante injerto. -Evaluación metabólica en hojas. -Cinco híbridos tolerantes vs un cultivar susceptible. -Plantas sanas vs enfermas. -Dos experimentos independientes. (Albrecht *et al*., 2016)	-I: Ante la infección de *C*Las el híbrido tolerante US-897 mostró altos niveles de palatinosa, carbohidratos, (glucosa, fructosa y rafinosa), ácido hidroxicinámico, ácido láurico y algunos otros compuestos desconocidos. Además, la mandarina cleopatra mostró mayores niveles de arginina, sinefrina, ornitina citrulina y prolina, además, ácidos orgánicos (ácido sacárico, ácido pirrol-2-carboxílico y ácido maleico) y aminoácidos (lisina, tirosina y glicina), así como, compuestos desconocidos. Los metabolitos se expresaron de forma diferenciada en plantas infectadas respecto a sanas y fue mayor en Cleopatra respecto a US-897. -II: Los metabolitos que se expresaron en mayor cantidad en el cultivar susceptible fueron inulobiose, trans-4-Hidroxiprolina y prolina, además, también se encontró una menor expresión de treitol, rafinosa, ácido isotreónico, salicina, ácido α-cetoglutárico, galactinol, glucosa y fluctosa. El único metabolito encontrado en altas concentraciones en cuatro de los seis cultivares (Cleopatra, Carrizo, US-802, US-812) fue la prolina, además, en los mismos cultivares el ácido 2-hidroxiglutárico, ácido α-cetoglutárico, salicina, además, de metabolitos de estructura desconocida se expresaron en menor cantidad. -Los autores señalan que la tolerancia a la enfermedad del HLB no parece estar asociada con la acumulación de altas cantidades de metabolitos como respuesta la infección.
Naranja Valencia y Hamling (*C. sinensis*)^{S}.	-Plantas cultivadas en campo. -Infección natural con *D. citri.* -Evaluación metabolómica en frutos. -Plantas sanas, plantas sintomáticas y asintomáticas (ambas HLB+). (Chin *et al*., 2014)	-Diferencias en la concentración de metabolitos como fenilalanina, histidina, limonina y sinefrina se encontraron frutos provenientes de árboles sanos y asintomáticos respecto a frutos de árboles sintomáticos. -La concentración de fructosa, glucosa, sacarosa y prolina fue menor en comparación con testigos sanos. -Los autores señalan que los estudios metabólicos podrían ser útiles para detectar árboles enfermos en estados iniciales de la enfermedad.

Table 1. Continue...

Variedad	Tipo de estudio y Referencia	Ejemplos de transcritos, proteínas o metabolitos diferencialmente expresados potencialmente relacionados con la tolerancia o susceptibilidad
Naranja Valencia (*C. sinensis*)^{S}.	-Plantas cultivadas en campo. -Infección natural con *D. citri.* -Expresión transcriptómica en hojas maduras, hojas inmaduras y cáscara de frutos inmaduros. -Sintomáticas vs asintomáticas vs sanas. (Martinelli *et al*., 2013)	-La infección de *C*Las afectó la expresión de factores transcripcionales (TFs) como AP2-EREBP, factores de dominio MYB, dedos de zinc tipo C2H2 y WRKY en hojas inmaduras, sin embargo, ante la aparición de síntomas los TFs CAL1, AGL14, LBD37, ERF23 y ERF26 fueron menos abundantes. -En hojas maduras la infección afectó la transcripción de genes de las familias AP2-EREBP, MYB, bZIP, AS2, ABI3/VP1, y WRKY. -En frutos sintomáticos se sobre expresaron genes asociados a la fotosíntesis, metabolismo de sacarosa y rafinosa, además, de regulación negativa de genes de biosíntesis de almidón. -Los genes asociados con la respuesta de defensa sistémica fueron mayormente afectados en hojas inmaduras.
Limón (*C. lemon*)^{MT}. Porta injerto: Pomelo Duncan (*C. paradisi*)^{S}.	-Plantas en invernadero. -Inoculación mediante injerto. -Evaluación proteómica en hojas. -Plantas enfermas vs sanas. (Nwugo *et al.*, 2013)	-En plantas de limón infectadas se mostró la acumulación diferencial de 27 proteínas, incluyendo incremento de almidón sintasa y una disminución en proteínas asociadas con fotosíntesis. -La infección de *C*Las afectó negativamente la expresión de proteínas de respuesta a estrés como chaperonas, homeostasis celular y proteínas de respuesta a patógenos, lectina, quitinasa I y miraculina. Además, regulación negativa de proteínas asociadas con procesos fotosintéticos como RuBisCO y fotosistema I entre otras.
Híbrido US-897 (*C. reticulata* x *P. trifoliata*)^{T} vs Mandarina Cleopatra (*C. reticulata)*^{S}. Inoculo: C. *sinensis*^{S}.	-Plantas en invernadero. -Inoculación mediante injerto. -Evaluación transcriptómica en hojas. -Resistete vs susceptible. -Enfermas vs sanas. (Albrecht y Bowman, 2012)	-Sobreexpresión de 326 genes en el genotipo susceptible respecto al híbrido tolerante US-897. -Mayor expresión de reguladores transcripcionales (TF) Myb tipo HH, mayor acumulación de almidón y carencia de expresión de proteínas de la familia Thioredoxina en Cleopatra respecto al híbrido US-897. -En el híbrido US-897 se observó mayor expresión de genes que codifican enzimas relacionadas con la biosíntesis de metabolitos secundarios como 2-oxoglutarato dioxigenasa dependiente de Fe(II), respecto a la mandarina Cleopatra y a los testigos sanos.
Naranja Madam Vinous (C. sinensis)^{S}, Pomelo Duncan (*C. paradisi*)^{S}, Carrizo citrange (x *Citroncirus webberi*)^{T} y *Poncirus trifoliata*^{T}.	-Plantas en invernadero. -Inoculación mediante injerto. -Evaluación metabólica en hojas. -Tolerantes vs susceptibles. (Cevallos-Cevallos *et al*., 2012)	-Las variedades susceptibles mostraron mayores niveles de aminoácidos como: L-prolina, L-serina y L-ácido aspártico y de ácidos orgánicos como butanodióico y tetradecanóico y acumulación de galactosa. -En Pomelo Duncan se encontraron altos niveles de galactosa con respecto a Carrizo y *P. trifoliata*. -Las variedades tolerantes mostraron mayores niveles de L-glicina y manosa respecto a variedades susceptibles. En pomelo Duncan se observaron cambios significativos en mioinositol en brotes maduros y L-prolina y xilosa en brotes tiernos.
Limón rugoso (*Citrus jambhiri*)^{T} vs Naranja Madam Vinous (*C. sinensis*)^{S}. Infeccion con: Carrizo citrange (*C. sinensis* x *P. trifoliata*)^{T}.	-Plantas en invernadero. -Inoculación mediante injerto. -Evaluación transcriptómica en hojas. Tolerante vs susceptible. (Fan *et al*., 2012)	-Expresión diferenciada de genes relacionados con funciones de la pared celular y un grupo de genes codificantes de β-1, 3-Glucanasa en la variedad tolerante. -Mayor expresión de genes en limón rugoso que en naranja en una etapa inicial de infección y menor en una etapa avanzada de infección. -El limón rugoso mostró menores afectaciones al floema que la naranja.

^{F}Clasificación de Folimonova *et al*., 2009: ^{I}Inconsistente, ^{MT}Moderadamente tolerante, ^{NR}No reportado, ^{R}Resistente, ^{S}Susceptible, ^{T}Tolerante, ^{V}Variable.

Resistance genes and proteins: In susceptible genotypes, genes homologous to pathogenesis genes (PR) do not show major changes in the presence of the bacterium. Shi *et al.* (2017) pointed out that in Duncan grapefruit, *C*Las infection induced only the expression of the PR1 gene homolog, while three PR1 genes were induced in tolerant Jackson grapefruit trees (Wang *et al.*, 2016). Furthermore, a tolerant variety of Sun Chu Sha mandarin treated with Flg22 showed a higher expression of NPR2 and NPR3, which regulate the expression of PRs (Shi *et al.*, 2017). The constitutive resistance gene (CDR1) was expressed to a lesser extent in the susceptible varieties of Cleopatra mandarin, compared to the hybrid US-897 (Albrecht and Bowman, 2012) and *C. sinensis* (Rawat *et al.*, 2017). In contrast, tolerant varieties and hybrids of *Poncirus* showed high levels of expression of CDR1, CDR2, and CDR8 (Rawat *et al.*, 2017; Curtolo *et al.*, 2020a). Furthermore, Shi *et al.* (2017) reported that when treated with Flg22, tolerant mandarin plants showed a higher expression of genes associated with resistance compared to susceptible Grapefruit trees. Those genes included *EDR1* (increased resistance to diseases), *EDS1* (increased susceptibility to diseases), *NDR1* (non-breed specific disease resistance), *PBS1* (avrPphB effector sensing kinase), RAR1 (required for Mla12 resistance), and SGT1 (suppressor of the G2 allele of skp that promotes HR).

Transcription factors: The WRKY and MYB families have been considered crucial regulators of the defense response of plants against pathogens. In susceptible varieties such as *C. sinensis* and *C. reticulata*, multiple TFs from the WRKY family were positively regulated by *C*Las infection, compared to the hybrid US-897 (Albrecht and Bowman, 2012; Fu *et al.*, 2016). Curtolo *et al.* (2020a) reported that around two hundred transcription factors are less or more highly expressed in susceptible varieties of citrus plants infected with *C*Las, while only five or two are differentially expressed in the tolerant species *P. trifoliata* or the resistant hybrid, respectively. This huge difference in the number of affected transcription factors suggests that developmental and metabolic processes are only affected in susceptible varieties, not in tolerant ones. Furthermore, Curtolo *et al.* (2020a) found that, in susceptible varieties, most of the WRKYs with identified changes were repressed by *C*Las infection, although they are different from those reported by Fu *et al.* (2016). Some WRKY were induced in the tolerant hybrids of *P. trifoliata*, including those related to the MAPK-mediated defense response. Other TFs were suppressed, particularly those with a SCL domain (Scarecrow). The authors suggested that some WRKYs might be associated with genetic resistance mechanisms of *P. trifoliata*; however, their participation in the induction of immune responses and/or tolerance mechanisms has not yet been demonstrated.

Defense genes expressed in phloem potentially associated with HLB symptoms: In most of the studies on the subject, susceptible varieties showed obstruction by callose associated with increased expression of genes related to callose synthesis, and of phloem proteins such as PP2-B15. The latter are proposed to participate, together with callose, as a physical barrier that prevents the dispersion of *C*Las, but also causes alterations in the phloem flow. Genes encoding phloem crystalloid proteins that participate in the occlusion of sieve tubes, such as SEOc and SEOd, are also induced by *C*Las infection (Curtolo *et al.* 2020a). Carbohydrate metabolism is also widely affected in HLB-susceptible varieties, showing overexpression of starch biosynthesis genes such as starch synthase (glgA) and starch branching enzyme II, as well as deletion of starch-degrading enzyme genes such as a- and β-amylases (Martinelli *et al.*, 2016; Hu *et al.*,

Table 2. Meaning of abbreviations commonly used in the literature and in this review.

Abreviación	Significado	Descripción y/o función molecular, bioquímica y/o fisiológica
ABI3/VP1	Factor transcripcional Insensible al ABA 3 *(abscisic acid insensitive3*) / Viviparous1.	Participa en la regulación transcripcional durante el crecimiento, desarrollo y respuestas al estrés abiótico mediando respuestas al ABA.
AGL14	Factores transcripcionales AGL (*Agamous-like*).	Genes homeóticos florales tipo MADS-box.
AP2-EREBP	Factores transcripcionales tipo APETALA 2 / proteínas que unen elementos de respuesta al etileno (*ethylene-responsive element binding proteins*).	Factores transcripcionales de genes que participan diversos procesos en plantas como crecimiento, desarrollo y en la respuesta a estrés.
AS2	Factor transcripcional AS2 (hojas asimétricas).	Participa en la formación de un complejo represores de transcripción de genes KNOX.
Avr2	Efector de avirulencia 2.	Factor de virulencia que puede inhibir varias Cys proteasas requeridas para la defensa basal de las plantas, incluyendo RCR3. Juega un papel como factor de avirulencia disparando respuestas de inmunidad en plantas que contienen el gen de resistencia I-2.
bZIP	Factor transcripcional con dominio tipo cierre de leucinas (*basic leucine zipper*).	Participa en la regulación de transcripción de genes de desarrollo, crecimiento, estrés biótico y abiótico en plantas.
C2H2	Proteínas con dedos de zinc C2H2 (2 Cisteínas y 2 histidinas).	Participan en diversos procesos en plantas, incluyendo la regulación transcripcional de genes de resistencia a estrés.
Ca^{2+}	Iones de calcio.	Segundo mensajero en la respuesta inmune de las plantas.
CAL1	Factores transcripcionales CAL (CAULIFLOWER) tipo MADS-box.	Participan en la regulación de la transcripción de genes que se expresan en procesos fisiológicos como la floración.
CC	Hélice superenrollada (*Coiled coi*l).	Dominios de proteínas formados por 2-7 α hélices enroscadas como hilos de una cuerda.
CCAAT-HAP2	Factor de unión CCAAT/ subunidad HAP2.	Factores transcripcionales que participan en diversos procesos durante el desarrollo de las plantas, incluyendo senescencia y respuestas a estrés.
Cf-2	Receptor de tomate homólogo al gen de resistencia de *Cladosporium fulvum*.	Participa en el reconocimiento de PAMPs e inicia la transducción de señales intracelulares.
*C*Las	*Candidatus* Liberibacter asiaticus.	Patógeno causal de la enfermedad del HLB, cepa asiática.
Ct	Extremo C terminal.	En los PRRs es un dominio intracelular que participa en la señalización de la percepción de PAMPs hacia el interior de la célula.
Dt	Dominio transmembranal.	Parte de del PRRs que atraviesa la bicapa de la membrana.
EDS1/PAD4	Dímero de la proteína que incrementa la susceptibilidad a enfermedad y su coregulador deficiente a fitoalexina (*Enhanced Disease Susceptibility1/ Phytoalexin Deficient* 4).	Proteínas tipo lipasa que coadyuvan con receptores LRR activando cascadas de señalización y confieren inmunidad a patógenos.
ERF23, 26	Factor de respuesta a etileno (*Ethylene response factors*)	Factores transcripcionales que regulan la expresión de genes en respuesta a etileno, incluyendo respuestas al ataque de patógenos.

Table 2. Continue...

Abreviación	Significado	Descripción y/o función molecular, bioquímica y/o fisiológica
ETI	Inmunidad mediada por efectores (*effector-triggered immunity*).	Se activa ante la interacción y reconocimiento específico entre productos de genes de avirulencia de patógenos y los correspondientes genes de resistencia de las plantas
Fla	Flagelina.	Proteína principal del flagelo de bacterias, que actúa como PAMP y al ser reconocida por PRRs elicita la respuesta de defensa de las plantas.
GSL5/PMR4	Glucano sintasa *like* 5 (calosa sintasa) / resistente al moho polvoriento 4.	Participa en la síntesis y deposición de calosa.
HLB	Huanglongbing.	Enfermedad de los cítricos causada por bacterias del género *Candidatus* Liberibacter.
JA	Ácido jasmónico.	Fitohormona que participa en la respuesta de defensa ante insectos como *D. citri*
JA-lle	Jasmonil-isoleucina	Conjugado de JA y el aminoácido isoleucina que participa en la vía de señalización de defensa mediada por SA/JA.
JAZ	Dominio ZIM de jasmonato (*Jasmonate ZIM-domai*n).	Dominio de proteínas involucradas diversos procesos de plantas, incluida la respuesta de defensa participando en la señalización de JA.
LBD37	Dominio de proteínas límite de órganos laterales LOB (*protein Lateral Organ boundaries*).	Familia de factores transcripcionales específicos de plantas que participan en la regulación de genes de desarrollo, respuesta a patógenos y metabolismo de nitrógeno y antocianinas.
LORE	Elicitación reducida específica para lipopolisacáridos. (*lipooligosaccharide-specific reduced elicitation*).	PRR tipo receptor cinasa de lectina G, que reconoce lipopolisacáridos o PAMPs tipo ácidos grasos 3-OH de cadena mediana de bacterias dando lugar a una respuesta inmune.
LPS	Lipopolisacaridos.	Componente de la membrana de bacterias que participa como factor de virulencia que interactua con los receptores LORE de la superficie celular.
LRR	Repeticiones ricas en leucina (*leucine-rich repeats*).	Dominios proteícos con repeticiones ricas en el amioácido leucina, participan en la interacción proteína-proteína.
LysM-RLK	Receptor tipo RLK con motivos de lisina.	Receptores cinasa con motivos extracelulares que interactúan con MAMPs activando respuestas en plantas que conducen a simbiosis o defensa contra patógenos.
MAMPs/ PAMPs	Patrones moleculares asociados a microorganismos/patógenos (*microbe- or pathogen-associated molecular patterns*).	Moléculas señal provenientes de bacterias como lipopolisacáridos, flagelina o lipoproteínas detectados por los receptores.
MAPK	Proteínas cinasa activadas por mitógenos (*Mitogen-activated protein kinas*e).	Participan en la transducción de señales en la respuesta inmune de las plantas.
MIC2	Factor transcripcional.	Factor transcripcional bHLH (basic helix-loop-helix) que regula la transcripción de genes que responden a la señal de JA.
MYB	Factores transcripcionales tipo MYB.	En plantas participan en numerosos procesos, incluyendo la regulación de las respuestas a hormonas y a estrés.
NBS	Sitio de unión a nucleótido (*Nucleotide-binding sit*e).	El dominio NBS en genes R (NBS-LRR) es responsable de la unión e hidrólisis de ATP para la señalización al detectar patógenos.
NPR1	Gen supresor de patogénesis (*Non-expressor of pathogenesis-related genes* 1).	Cofactor transcripcional que actúa como regulador maestro de la resistencia sistémica adquirida (SAR) mediada por SA.
Nt	Extremo N terminal.	En los PRRs el Nt es un dominio extracelular que participa en el reconocimiento de PAMPs para iniciar la señalización.

Table 2. Continue...

Abreviación	Significado	Descripción y/o función molecular, bioquímica y/o fisiológica
PRRs	Receptores de reconocimiento de patógenos (*Pattern Recognition Receptor*s).	Receptores celulares que perciben a moléculas asociadas a patógenos.
PTI	Inmunidad desencadenada por PAMPs (*PAMP-triggered immunit*y).	Activación de genes de defensa ante el reconocimiento de PAMPs y posterior señalización.
PTO	Serina/treonina cinasa que confiera resistencia a *Pseudomonas syringa*e pv tomato.	Gen de resistencia que participa en el reconocimiento de proteínas Avr, transducción de señalización y activación de respuesta de defensa.
RbohD	Proteina D homóloga a oxidasa del *burst* respiratorio (*respiratory burst oxidase homolog protei*n).	Proteína transmembranal que ante la percepción de PAMPs por los receptores, se fosforila y participa en la producción de ROS.
RCR3	Cisteina-proteasa extracelular de tomate homóloga a las Cys-proteasas similares a papaína.	Proteasa extracelular que actúa como correceptor formando un complejo con el PAMP Avr2 para unirse al receptor Cf-2 y disparar la respuesta de hipersensibilidad HR.
RIN4	Proteína que interactúa con RPM1 (*RPM1-interacting protein* 4).	Proteína de membrana que interactúa con efectores de patogenicidad y se une a proteínas de resistencia como RPM1 lo que activa la respuesta inmune.
RLK	Receptor similar a cinasa (*receptor-like kinase*s).	Proteínas transmembranales con extremo C-terminal intracelular. Participan en el reconocimiento de PAMPs e inician la transducción de señales fosforilando otras moléculas.
RLP	Receptor similar a proteínas (*Receptor-like protein*s).	Proteínas transmembranales que carecen de extremo C-termial intracelular. Participan en el reconocimiento de PAMPs en inician la transducción de señales.
ROS	Especies reactivas a oxígeno (*Reactive oxigen species*).	Moléculas derivadas del oxígeno molecular altamente oxidantes que participan en la vía de señalización y respuesta inmune.
SA	Ácido salicílico.	Fitohormona que participa en la respuesta de defensa de cítricos ante *C*Las.
SCF/COI1	SCF/COI1 ubiquitin ligasa.	Complejo mediador de la degradación de JAZ.
7-TM	Receptores transmembranales 7.	Proteínas receptoras con 7 dominios transmembranales que atraviesan la bicapa de la membrana celular y responden a estímulos extracelulares.
Ser/Thr kinasa	Serina/Treonina cinasa.	Enzima que fosforila el hidroxilo (-OH) de la Serina o Treonina. En los receptores RLK es un dominio intracelular con participación en la transducción de señales para la respuesta de defensa de las plantas.
TGAs	Factores transcripcionales tipo bZIP (*basic leucine zippe*r).	Forma un complejo transcripcional con NPR1 para inducir la transcripción de genes de defensa PR1.
TIR	Dominio homólogo a receptores de Toll o interleucina-1 (*Toll/Interleukin-1 receptor)*.	Dominio N-terminal de receptores NBS-LRR, con repeticiones de leucina que interactúan con los efectores de patógenos.
WRKY	Factores transcripcionales tipo WRKY.	Factores transcripcionales que activan o reprimen la transcripción de genes de muchos procesos en plantas, incluidas las respuestas de defensa.

2017b; Curtolo *et al.*, 2020a). In tolerant genotypes, on the contrary, callose-induced phloem occlusion has not been observed and callose synthase genes have not been found overexpressed in the *P. trifoliata* hybrid reported as resistant (Curtolo *et al.* 2020a), even though there was modulation of phloem protein genes. Furthermore, carbohydrate metabolism is altered to a lesser degree in *P. trifoliata*, according to Curtolo *et al.* (2020a), while Hu *et al.* (2017b) reported the expression of an α amylase (AAM) gene associated with starch degradation in the tolerant variety *C. hystrix*. The different profiles of genes that affect phloem flow in susceptible and tolerant genotypes suggest that tolerant varieties can suppress the defense response to *C*Las infection, thus avoiding phloem blockage and the accumulation of starch in chloroplasts. This explains in part why these varieties do not express foliar symptoms.

Photosynthesis: A decrease in the expression of proteins involved in photosynthetic reactions has been observed in susceptible plants, in accordance with the yellowing symptoms at the foliar level. The overexpressed proteins include the chlorophyll a/b binding protein of the light-harvesting complex II, the photosystem II protein that contains the psbP domain and the O-subunit of photosystem I. In tolerant species, such as *H. hystrix*, the genes that encode these proteins were not affected by *C*Las infection (Albrecht and Bowman, 2012; Hu *et al.*, 2017a; Curtolo; *et al.*, 2020a).

Cell wall: The reinforcement of the cell wall is one of the initial defense responses of plants against the attack of pathogens. Susceptible citrus varieties infected with *C*Las showed a negative regulation of genes related to cell wall functions such as lignin biosynthesis (Curtolo *et al.*, 2020a), which is essential for cell wall rigidity. They also showed a greater expression of genes associated with metabolism and cell wall disruption, such as cellulose synthase, cellulase, expansins, pectin esterases, and pectin-methyltransferases (Martinelli *et al.*, 2016; Wang *et al.*, 2016; Curtolo *et al.*, 2020a). These changes suggest that *C*Las colonization could be faster in susceptible varieties due to a less rigid cell wall. In tolerant varieties, on the contrary, the biosynthesis pathway of lignin and its precursors is one of the most overexpressed, including genes such as caffeic acid O-methyltransferase, feruloyl ortho hydroxylase, hydroxycinnamoyl transferase, and the laccase precursor (Curtolo *et al.*, 2020a), which is involved in lignin degradation and was found highly induced in *P. trifoliata*. A gene involved in pectin degradation showed decreased expression. Increased expression of β-1,3-Glucanase (Chin *et al.*, 2021) and cellulose synthase-like proteins (CSLA2 and CSLA9) (Hu *et al.*, 2017a) was also reported. It is suggested that the changes associated with the structure of the cell wall in tolerant varieties could contribute to the reinforcement of physical barriers that curb the invasion by *C*Las (Hu *et al.*, 2017a).

Other defense genes and metabolites: The endochitinase gene B was differentially expressed in hybrid varieties considered resistant to *C*Las by Curtolo *et al.* (2020a). Endochitinases play an important role as bactericides, and some can break peptidoglycan chains, leading to the lysis of bacterial cells (De Medeiros *et al.*, 2018). This hybrid shows very few transcriptomic changes when infected with *C*Las, compared to the parent variety and other tolerant hybrids. The authors proposed that the endochitinase gene plays the role of resistance gene in this genotype. Furthermore, the transcription of many genes that participate in the phenylpropanoid biosynthesis pathway was affected, unlike what was observed in susceptible varieties (Curtolo *et al.*, 2020a). Phenylalanine ammonia lyase (PAL) participates in the biosynthesis of important molecules for plant defense such as phenylpropanoids, lignin and SA. For that reason, it has been proposed that PAL participates in disease resistance by mediating the production of antimicrobial compounds and signaling molecules. However, in the susceptible variety *C. sinensis* infected with *C*Las, PAL levels increased above the levels detected in moderately tolerant varieties such as *C. aurantifolia* and *C. latifolia* (Torres *et al.*, 2017). Furthermore, Curtolo *et al.* (2020a) observed the induction of lipid transport protein homologs in susceptible varieties and hybrids, which could inhibit the growth of pathogens. Thymol is a metabolite recognized for its antimicrobial properties (Kachur and Suntres, 2020). Killiny *et al.* (2017) reported that the tolerant Sugar belle mandarin showed a higher concentration of thymol and its precursors (γ-terpinene and p-cymene), compared to susceptible varieties such as Duncan grapefruit, Dancy tangerine, Minneola tangelo, and Clementina mandarin. Heat shock proteins (HSP) participate in the defense response of plants to biotic and abiotic stress, protecting other proteins from denaturation and regulating their folding, localization, agglomeration and degradation under stress conditions (Balfagón *et al.*, 2018). In the tolerant hybrid US-897, a differentiated expression of HSP70 and HSP20 has been reported with respect to the susceptible Cleopatra mandarin, although with similar expression values between healthy and diseased plants of each cultivar (Albrecht and Bowman, 2012).

Phytohormones: The increase of endogenous levels of phytohormones has been reported in susceptible citrus trees infected with *C*Las. The participation of phytohormones as defense signals is well known, including salicylates (SAs), jasmonates (JAs), abscisic acid (ABA), and auxins (AUX), as well as their biosynthesis genes. In contrast, lower levels of ethylene (ET) have been observed in diseased fruits compared to healthy fruits (Rosales and Burns, 2011; Nehela *et al.*, 2018). Signaling triggered by phytohormones during defense processes can activate or repress transcription factors that regulate the transcription of immunity genes.

Regarding SAs, Nehela *et al.* (2018) reported abundance of benzoic acid, trans-cinnamic acid and salicylic acid in susceptible citrus plants. However, there are no other reports on the expression of SAs in HLB-tolerant citrus plants. Furthermore, there are reports of negative regulation of salicylate-carboxyl methyltransferase (SAMT) produced by Me-SA (Zou *et al.*, 2012) and of UDP-Glycosyltransferase, which modulates the levels and distribution of endogenous signaling molecules (Albrecht and Bowman *et al.*, 2012). In tolerant plants such as the Sun Chu Sha mandarin, Shi *et al.* (2017) reported that *C*Las infection induces genes related to SA metabolism such as PAL1 and AZI1 (mobile metabolite required for SAR, induced by azelaic acid and associated with the accumulation of SA in infections). However, Curtolo *et al.* (2020a) did not find important changes in the transcription of genes related to SA biosynthesis in tolerant genotypes. Suh *et al.* (2021) reported an increased expression of the metabolic pathways of hormone biosynthesis, except for SA, which was downregulated in tolerant plants. The authors suggested that the reduction of SA could be associated with the defense strategy of these cultivars, avoiding the immune response that generates symptoms. Regarding jasmonates, Yao *et al.* (2020) found a negative regulation of jasmonic acid biosynthesis and signaling genes in symptomatic Valencia orange fruits, such as allene-oxide cyclase 3 and 4 (AOC3 and AOC4). In infected leaves of susceptible varieties, Curtolo *et al.* (2020a) did not find large changes in jasmonate-related transcripts.

Regarding gibberellins (GAs), in susceptible genotypes, Curtolo *et al.* (2020a) reported the induction of biosynthesis genes and decreased transcription of proteins that participate in their degradation. The opposite was observed in the tolerant *P. trifoliata* genotype, where the expression of biosynthesis genes was decreased and key genes for the degradation of GAs were overexpressed. The gene induced by gibberellins was one of the most negatively affected. Gibberellins are considered modulators of SA signaling during the response to pathogens. The authors proposed that GAs play a relevant role in the *C*Las-citrus interaction, affecting plant physiology and symptom development. However, these transcription results differ from the proposal of Ma *et al.* (2022) about treating susceptible diseased trees with GAs to alleviate oxidative damage by ROS and to manipulate flowering and premature fruit drop (Tang *et al.*, 2021). Field tests are required to assess the participation and effect of GAs on the development of symptoms.

*C*Las infection causes alterations in AUX-mediated signaling in susceptible varieties, such as the negative regulation of SAUR72 genes (small RNA positively regulated by auxin) and IAA1 (indoleacetic acid-induced protein 1 that represses the function of ARFs, transcription factors that respond to AUX). It also lowers the expression of negative regulators of auxin synthesis, which could lead to increased expansin expression and cell wall disruption (Hu *et al.*, 2017b). Curtolo *et al.* (2020a) reported that many genes related to auxins and ethylene were differentially expressed in susceptible citrus plants. This included the overexpression of auxin-induced genes and the downregulation of auxin-responsive factors. In the tolerant species *P. trifoliata*, neither of those pathways were affected. However, Wang *et al.* (2016) reported a negative regulation of genes similar to DMR6 (Downy Mildew Resistance 6) in the tolerant Jackson grapefruit. These DMR6 gene participates in ethylene biosynthesis and has been classified as an immunity suppressor in Arabidopsis. The authors also reported an increased expression of auxin response genes (SAUR), which could contribute to a lower expression of expansin. The upregulation of the ethylene-responsive transcription factor and the EIN3-binding F-box protein 1 was also observed (Wang *et al.*, 2016; Hu *et al.*, 2017b).

Melatonin (MEL) may also play an important role as a mediator of the defense response to *C*Las infection by modulating the biosynthesis of other phytohormones. A higher concentration of MEL has been reported in tolerant varieties (Nehela and Killiny, 2020a). Furthermore, the exogenous application of MEL increased the endogenous content of phytohormones associated with the stress response (salicylates, auxins, trans-jasmonic acid, and abscisic acid), for which the authors concluded that MEL is a mediator of the defensive response of plants against HLB (Nehela and Killiny, 2020a).

Simple carbohydrates, amino acids, and organic acids: Carbohydrate metabolism is affected to a greater extent in citrus varieties susceptible to *C*Las, mainly in the initial stages of infection. Hu *et al.* (2017b) reported that the transcription of starch biosynthetic genes such as glycogen synthase (glgA) is induced in *C. sinensis* by *C*Las infection and that the expression of genes involved in their degradation decreased. In the tolerant genotype of *C. hystrix*, these genes did not undergo significant changes when infected by *C*Las. Killiny (2017) reported that the tolerant varieties showed a higher concentration of α-D-galactopyranose, α-D-mannopyranose, maltose and disaccharides, while organic acids were found increased in susceptible varieties. Albrecht *et al.* (2016) reported an increase in saccharic acid, pyrrole-2-carboxylic acid, and maleic acid in susceptible varieties. Cevallos-Cevallos *et al.* (2012) observed an increase in the levels of butanedioic or succinic acid. Furthermore, an increase in the concentration of amino acids such as lysine, tyrosine, and glycine was reported in susceptible varieties of Cleopatra mandarin infected with *C*Las (Albrecht *et al.*, 2016), and of proline, serine and aspartic acid in Madam Vinous orange (Cevallos-Cevallos *et al.*, 2012). Tolerant citrus varieties also expressed a greater amount of amino acids such as phenylamine, tyrosine, tryptophan, valine, leucine, histidine, lysine, cysteine, methionine, serine, glutamate (Killiny and Hijaz, 2016), glycine, and mannose (Cevallos-Cevallos *et al.*, 2012), while Suh *et al.* (2021) reported that glutamate and aspartate metabolism pathways were upregulated.

Transporters: According to Curtolo *et al.* (2020a), the genes related to the transport of carbohydrates, amino acids and ions (e.g., including zinc transporter genes) are among the most affected by *C*Las in susceptible citrus varieties, compared to tolerant ones.

In summary, the general conclusion from the comparison of results reported in various omics studies is that relatively few pathways and functions change their expression in tolerant plants infected by *C*Las, while many are affected in susceptible plants, in both cases at the transcriptomic, proteomic and metabolomic levels. In some tolerant citrus varieties, there could be a more efficient *C*Las-specific recognition and detoxification system that prevents damage caused by ROS and by the response of the immune system against infection. Furthermore, these varieties seem to increase energy-producing metabolism, favoring continuous growth and phloem regeneration (Deng *et al.*, 2019). Phytohormone signaling seems to be different from what occurs in susceptible varieties. It might be mediated by jasmonates and by the suppression of auxin signaling and gibberellin degradation, leading to a rapid and efficient defense response through the synthesis of phenylpropanoids, endochitinases and the strengthening of the cell wall, in addition to preventing events that lead to phloem dysfunction and derived symptoms (Curtolo *et al.*, 2020a). Alternatively, tolerant varieties might not respond to the presence of *C*Las, or even suppress the immune response, establishing a coexistence system with the bacterium in which the plant does not reprogram its gene expression or alter its proteomic and metabolic profiles, avoiding damaging itself during the defense process, which would be in accordance with the proposal of Ma *et al.* (2022) regarding that HLB is a disease caused by the immune system of the plant. In this sense, da Graça *et al.* (2016) proposed that in tolerant and hybrid varieties, the immune response elicited by possible *C*Las virulence factors is a “potential ETI”, since there is not enough evidence that these varieties display an ETI.

Relationship between metabolic and hormonal changes and HLB symptoms. In the event of *C*Las infection, infected trees of susceptible citrus species respond with a wide range of physiological processes, resulting in the appearance of characteristic symptoms associated with increased bacterial concentration. Figure 4 summarizes how the imbalance and signaling of phytohormones, the alteration of metabolites such as carbohydrates, pigments and polyamines, or of signaling molecules such as gamma aminobutyric acid (GABA) and ROS (H_2O_2), could be related to the development of physiological or developmental symptoms associated with HLB, such as early flowering, leaf and fruit deformities, or seed abortion (Kim *et al.*, 2009; Shen *et al.*, 2013). This coincides with Rosales and Burns (2011), who reported that the presence of ABA was four times higher in the peel of *C. sinensis* fruits with HLB, and that the content of indoleacetic acid (IAA) was significantly higher in deformed areas of the peel.

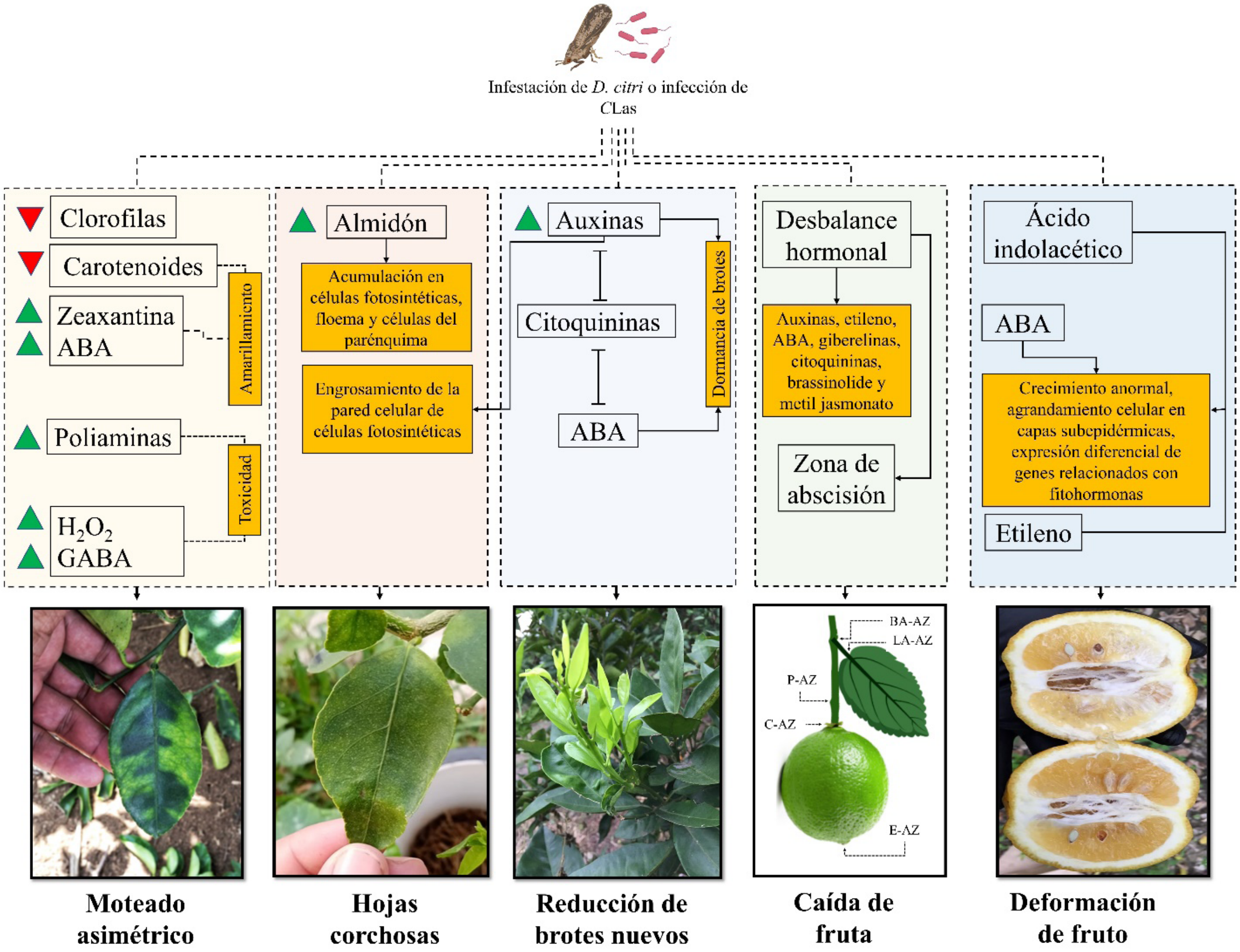

Figura 4. Metabolic and phytohormonal imbalances in citrus plants when infected by *C*Las or infested by *D. citri* and their possible relationship with the characteristic symptoms of the disease, such as asymmetric mottling, corky leaves, reduced shoots, premature drop and fruit deformation. Adapted from Nehela and Killiny (2020a). BA-AZ= Basal abscission zone, LA-AZ= Laminar abscission zone; P-AZ= Peduncle abscission zone; C-AZ= Calyx abscission zone; E-AZ= Style abscission zone; ABA= Abscisic acid; H_2O_2 = Hydrogen peroxide; GABA= Gamma aminobutyric acid.

Premature fruit drop is also a symptom commonly associated with HLB. Zhao *et al.* (2019) found that this symptom is related to hormonal signaling, the defense response, and secondary metabolism. They reported the expression of genes related to the synthesis and signaling of ethylene, as well as jasmonic acid. In addition, ethylene and jasmonic acid levels were significantly higher, while those of abscisic acid were significantly lower in fallen fruits from diseased trees compared to fruits from healthy trees. In this regard, Nehela and Killiny (2020b) pointed out that premature fruit drop could be related to an alteration in the homeostasis of metabolism in the abscission zones (AZ) of the fruit, which is associated with limited availability of carbohydrates and with the regulation of cell division processes (Figure 4).

The decrease in the number of shoots during the advanced stages of the disease has also been associated with a hormonal imbalance, particularly in the auxin/cytokinin ratio, as well as an increase in abscisic acid levels. Asymmetric mottling is associated with an increase in zeaxanthin accumulation and a decrease in pigments such as chlorophyll and carotenoids (Killiny and Nehela, 2017b). In addition, the infection with *C*Las induces the production of polyamines, which is related to the accumulation of H_2O_2 and abscisic acid in leaves. Even though *C*Las manages to survive the toxicity of H_2O_2, the accumulation of high amounts of H_2O_2 eventually becomes toxic to leaf tissues and causes asymmetric mottling (Pitino *et al.*, 2017; Killiny and Nehela, 2020).

The accumulation of starch in photosynthetic cells, phloem sieve tubes and parenchyma cells in petiole leaves is related to the corky leaves symptom (Whitaker *et al.*, 2014). Nehela and Killiny (2020b) reviewed the involvement of various citrus metabolites in the development of HLB symptoms. The authors pointed out that metabolites play a vital role in the development of HLB symptoms in citrus plants by modulating carbohydrate metabolism, phytohormone homeostasis, and antioxidant pathways, or by interacting with other metabolic pathways involving amino acids, leaf pigments, and polyamines (Figure 4).

All of the above shows that the exogenous application of hormones in the field could be a viable alternative to correct the phytohormonal and metabolic imbalances of diseased plants, in addition to enhancing systemic defense pathways (Nehela and Killiny, 2020a; Tang *et al.*, 2021; Ma *et al.*, 2022). Tests under controlled conditions, with the different varieties, are required to thoroughly understand the participation of phytohormones and determine the appropriate management strategy to contain the development of the disease.

Future prospects. The study, using omic tools, of the interaction between *C*Las and different citrus species with a greater or lesser degree of susceptibility to HLB, has allowed us to understand some of the genetic and biochemical resources used by, on the one hand, the pathogen to improve its ability to colonize plant tissues, and, on the other hand, infected plants to maintain cellular homeostasis. A complex signaling network induced by potential effectors of the bacteria is established in the *C*Las-citrus relationship, causing substantial changes such as plant defense responses, including metabolic imbalances of amino acids, organic acids, phytohormones, polyamines, and secondary metabolites. This signaling network also causes the participation of transcription factors, and regulatory and defense proteins, which, together, determine the capacity of tolerance or susceptibility to infection of citrus plants.

A thorough understanding of the etiology of the disease and the mechanisms of susceptibility versus tolerance clarifies the alternatives for the design of HLB management strategies in the field. These strategies include the application of micronutrients, antioxidants, phytohormones, elicitors, and regulators of the immune response or growth promoters that prolong the productive life of infected trees. Another strategy is to develop genetically improved varieties, by conventional, molecular or gene editing methods, that overexpress receptors or other resistance genes to confer the plants a systemic response that prevents infection, or genes that modulate the immune response of plants and mitigate the effect of ROS, or that control the pathogen as antimicrobial peptides. The various strategies to be implemented must be adapted to the different species and varieties of citrus plants, as well as to the characteristics of the various citrus-producing regions.

Although progress has been made in understanding the complex pathogen-host relationship of the HLB pathosystem, the destructive capacity of the disease increases the need for applied research to understand not only the molecular, metabolic, and genetic factors associated with HLB, but also the effect of the association with other diseases such as VTC, and the effect of the environment and sociocultural aspects on the management of HLB. The perception of producers about the disease and management strategies, as well as their knowledge about the pest or the proper use and management of pesticides, influences the effectiveness of the agents used to control *D. citri* (Pérez- Zarate *et al.*, 2016; Hernández-Landa *et al.*, 2017; Pérez-Zarate *et al.*, 2020). Thus, the development and adoption of management alternatives in the Mexican countryside, including innovative technologies and sustainable management, requires that frontier knowledge be transferred efficiently, quickly, and in an accessible manner to producers and technicians from specialized government agencies to reinforce the front-line in the battle for managing Huanglongbing in Mexico.

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