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Current Insights into the Primary Carbon Metabolic Flux that Occurs in Plants Undergoing a Defense Response

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ABSTRACT

The precise control of photoassimilate production, partitioning, and storage is a crucial process during plant growth and development. An excess of carbohydrates mediates important regulatory processes, including the down-regulation of source-specific genes and the up-regulation of sink-specific gene repertoires. Such source-to-sink transitions occur also in plant cells infected with biotrophic pathogens. A growing body of evidence now indicates that successful plant defense responses are accomplished by the reprogramming of a diverse set of cellular pathways that are associated with an increased demand for energy. Notably, it is frequently observed that cell wall-bound invertase (CW-INV) activity is rapidly induced at the infection site, indicating an early metabolic transition of host cells to overcome the invading pathogen. The shift from housekeeping to defense metabolism is also evident on the basis of microarray-based global transcript analysis. However, the intimate relationship between the changes in primary carbon metabolism and defense responses in plants remains poorly understood. In our present review, we focus on the current knowledge of this phenomenon with respect to the reprogramming of primary carbon metabolism and its potential role in the reinforcement of defense mechanisms in infected plants.

Keywords: carbon metabolism, cell wall invertase, defense response, hexokinase, sink, source, sugar
Abbreviations: AATP; ATP/ADP transporter; **Avr**, avirulence; **CAB**, chlorophyll-a/b-binding protein; **C-INV**, cytosolic INV; **CW-INV**, cell wall invertase; **ETI**, effector-triggered immunity; **HR**, hypersensitive response; **HXK**, hexokinase; **HXT**, hexose transporter; **PAMP**, pathogen-associated molecular pattern; **PCD**, programmed cell death; **PD**, plasmodesmata; **PR**, pathogenesis-related; **PTI**, PAMP-triggered immunity; **R**, resistance; **RbcS**, Rubisco small subunit; **ROS**, reactive oxygen species; **TTSS**, type III secretion system; **SAR**, systemic acquired resistance; **SUT**, sucrose transporter; **VIGS**, virus-induced gene silencing

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INTRODUCTION

Photosynthesis in higher plants provides most living organisms with basal food and fuel via the conversion of light energy into chemical energy. In addition to being a fundamental source to fuel carbon and energy metabolism, sugars have also emerged as potential signaling molecules that regulate gene expression during normal plant growth and development, and during plant defense responses (Jang *et al*. 1997; Smeekens 1998; Rolland *et al*. 2001; Leon and Sheen 2003; Gibson 2005; Biemelt and Sonnewald 2006; Penna *et al*. 2006; Rolland *et al*. 2006). On the basis of the ratio between sugar uptake and export, plant tissues can be divided into sink and source tissues. Whereas sink tissues require a net import of assimilates, source tissues produce excess assimilates which are then allocated to competing sinks. Sink and source tissues are not static but change according to environmental and developmental signals. Hence, an appropriate regulation of the sink-to-source transition of assimilates is required for normal plant growth and development, as well as for a fortified defense response in plants infected with pathogens.

Alterations in carbon partitioning in plants faced with various stresses act as new signals that balance the portioning or reduction of stress-induced damage. A timely source-to-sink transition in pathogen-infected tissues is thus extremely important for plant defense responses, as invading pathogens may also benefit from an elevated availability of assimilates, which might facilitate an easier exploitation of nutrients from the host cells. Thus, during the early phases of infection, a change in carbon flux towards sink metabolism of pathogen-infected tissues might be critical for the establishment of a successful defense response.

Several reports have now described global gene expression pattern changes in plants after pathogen attack (Chou *et al*. 2000; Tao *et al*. 2003; Craigon *et al*. 2004; Zipfel *et al*. 2004), but so far little attention has been paid to the relationship between primary carbon metabolism and the plant

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defense response. In particular, plants generally activate multiple defense responses upon pathogen invasion, leading to a diverse cellular reprogramming that is closely associated with an increased demand for energy. On the basis of chlorophyll fluorescence imaging and sugar level assays, some analyses of photosynthesis and carbohydrate metabolism have been performed during host-pathogen interactions (Scharte *et al*. 2005; Swarbrick *et al*. 2006). These studies have indicated that the timely activation of pathways generating and utilizing soluble hexoses, via both enhanced cell wall invertase (CW-INV) activity and plasma membrane hexose transporter (HXT), may play a crucial role in maintaining a successful robust defense response in pathogen-infected host tissue.

After invasion, plant pathogens deploy one of three main strategies to utilize the host as a food source: necrotrophy, biotrophy, or hemibiotrophy (Hammond-Kosack and Jones 1997; Schulze-Lefert and Panstruga 2003; Glazebrook 2005). In this review, we have put a particular emphasis on the specialized nature of biotrophic plant-pathogen interactions, in which the invading organisms subvert the metabolic processes to favor their growth and reproduction, and the plant cells remain alive throughout the infection.

SOURCE-TO-SINK TRANSITION OF PLANT TISSUES INFECTED WITH BIOTROPHIC PATHOGENS

Light is obviously a tremendously important environmental factor during plant growth and development, but has also been found to play a key role in the innate immune response of plants to infection. For example, the expression of a rice pathogenesis-related (*PR*) gene, *OsPR1b*, was found to be enhanced under high light (Agrawal *et al*. 2000). Light is also required in plants for the activation of systemic acquired resistance (SAR), the induction of defense genes, and the regulation of programmed cell death (PCD) (Bechtold *et al*. 2005; Chandra-Shekara *et al*. 2006). Moreover, analysis of the *Arabidopsis* phytochrome photoreceptor mutants *phyA* and *phyB* showed an altered response to the activation of SA-induced *PR* gene expression and a hypersensitive response (HR) (Genoud *et al*. 2002). The plant Toll/Interleukin1 Receptor-Nucleotide Binding Site-Leucine-Rich Repeat (TIR-NBS-LRR) family members have also been widely reported as disease resistance proteins with a similarity to animal toll-like receptors (Holt *et al*. 2003). Notably, in a similar manner to animal TIR domain proteins, the dual role of an NBS-LRR protein in both photomorphogenic development and defense response has been uncovered during the analysis of the *Arabidopsis* constitutive shade-avoidance mutant *csa1* (Faigón-soverna *et al*. 2006). In addition, silencing of the psbO subunit of the oxygen-evolving complex in photosystem II led to increased virus replication in tobacco, again suggesting an important role for light in disease resistance responses in plants (Abbink *et al*. 2002).

While the impact of light on plant defense in terms of molecular response to biotic attack has been underscored (Roberts and Paul 2006), the importance of rapid changes of both light-dependent gene expressions and primary carbon metabolic flux in pathogen-infected photosynthetic tissues is less well understood. It has been shown that the light-dependent expression of genes encoding chlorophyll-a/b-binding protein (CAB) appears to be strongly disrupted in rapeseed cell culture with 2.0% sucrose (Harter *et al*. 1993). This carbohydrate accumulation in cultured cells has been demonstrated to result in a source-to-sink transition, thereby suppressing the expression of photosynthetic genes (Koch 1996; Ehness *et al*. 1997; Roitsch *et al*. 2003; Li *et al*. 2006; Osuna *et al*. 2007). Similarly, both the inhibition of photosynthesis-related gene expression and reduced photosynthetic activities have been commonly observed in pathogen-infected tissues (Chou *et al*. 2000; Scharte *et al*. 2005). In *Arabidopsis* infected with a biotrophic pathogen *Albugo candida*, quantitative imaging of chlorophyll fluorescence revealed that the rate of photosynthesis declines progressively in the invaded regions of the leaf (Chou *et al*. 2000). During tobacco-*Phytophthora nicotianae* interaction, photosynthetic flux was also evidently reallocated from CO_2 assimilation in favor of photorespiration (Scharte *et al*. 2005). In this study, chlorophyll fluorescence imaging demonstrated that reduction in photosynthesis and defense reactions are highly localized processes, which occur in single mesophyll cells. Consistently, expression of photosynthetic genes such as *CAB* and *Rubisco small subunit* (*RbcS*) was repressed in pathogen-infected tissues. As a common feature, a rapid accumulation of soluble sugars such as sucrose, glucose, and fructose was observed in host tissues undergoing defense response. Moreover, treatment with soluble sugars or sugar analogs induces the expression of plant defense- or stress-related genes (Johnson and Ryan 1990; Herbers *et al*. 1996a; Ehness *et al*. 1997; Price *et al*. 2004; Thibaud *et al*. 2004). These results suggest that an increased level of soluble sugars is positively correlated with the plant defense response upon pathogen attack. Considering that the expression of photosynthetic genes is inversely correlated with the initiation of plant defense responses, the rapid accumulation of sugars often observed in pathogen-infected tissues is likely to be caused by redirection of assimilates to the infection site, rather than an enhanced production of photoassimilates. A summary of the coordinated regulation of photosynthesis-, defense- and primary carbon metabolism-related genes is shown in **Table 1**.

COMPETITION BETWEEN PLANTS AND INVADING PATHOGENS FOR SUGARS

Biotrophic plant pathogens, including fungi, bacteria and viruses, have evolved a tremendous number of sophisticated strategies to exploit their host nutrients. As an integral part of their life cycle, biotrophic fungal pathogens enter their host cells and initiate specialized intracellular infection structures (Schulze-Lefert and Panstruga 2003; O'Connell and Panstruga 2006). Haustoria then develop as side branches from intercellular, intracellular and epicuticular hyphae. Both hyphae and haustoria remain outside the plant plasma membrane. The plant-fungal pathogen interface is believed to function as a key area of nutrient uptake by these pathogens and an important site of export for pathogen effector molecules into host cells. Diverse gram-negative bacteria have evolved a type III secretion system (TTSS) which delivers effector proteins into the cells of their hosts in order to optimize the environment for bacterial growth (Grant *et al*. 2006). Plant viruses can also adapt and optimize the host metabolism for their own benefit and exploit inter- and intracellular connection systems to facilitate their systemic spread (Boevink and Oparka 2005).

Extracellular sugars are believed to play a pivotal role in plant-microbe interactions. Hexoses have been shown to act as regulatory molecules controlling diverse essential processes such as photosynthesis, senescence, and pathogen defense (Sheen 1990; Goldschmidt and Huber 1992; Jang and Sheen 1997; Perata *et al*. 1997; Smeekens and Rook 1997; Wingler *et al*. 1998; Pego *et al*. 2000; Smeekens 2000; Rolland *et al*. 2001, 2006). They are also believed to act as signaling molecules that regulate the expression of sink-specific and defense-related genes to induce diverse cellular reprogramming in pathogen-infected plants. The effective induction of a plant defense response thus requires a sufficient supply of metabolites and energy. In this regard, the high sugar resistance phenomenon was proposed, that is characterized by an enhanced plant defense response through an elevated level of soluble sugars (Horsfall and Dimond 1957). It has also been shown that the resistance of plants to pathogens is largely dependent upon the sugar levels in the infected leaf tissues (Herbers *et al*. 1996b). Consistently, sugar treatment of tissues or elevated sugar levels in transgenic plants activates the expression of *PR* genes (Johnson and Ryan 1990; Herbers *et al*. 1996a).

Table 1 Regulation of the transcripts of sink metabolism, defense response, and photosynthesis enzymes by sugars and stress-related stimuli[1].

Stimulus	Gene regulation[2]	Special features	Plant	Reference
Induction of sink metabolism				
Suc	*SUSY* (+)[3]	ND[4]	Potato	Salanoubat and Belliard 1989
Agrobacterium tumefaciens	*SUSY* (+), *CW-INV* (+)	Redirection of carbohydrate delivery for tumor growth	Castor bean (*Ricinus communis*)	Wächter *et al*. 2003
Glc, and 6-deoxyGlu[5]	*CW-INV* (+)	ND	*Chenopodium*	Roitsch *et al*. 1995
Chitosan[6], Benzoic acid, Endothall[7,]	*CW-INV* (+)	Induction of defense-related genes	*Chenopodium*	Ehness *et al*. 1997
Potato virus Y	*CW-INV* (+)	Increased soluble sugar; Sugar-mediated and SA-independent viral resistance	Tobacco	Herbers *et al*. 2000
Albugo candida	*CW-INV* (+)	Decreased starch, and increased level of sucrose, glucose, and fructose; decreased chlorophyll content in infected leaves	*Arabidopsis*	Chou *et al*. 2000
Magnaporthe grisea	*CW-INV* (+)	Induction of defense response *PBZ1*	Rice	Cho *et al*. 2005
Blumeria graminis	*CW-INV* (+)	Accumulation of hexoses in infected tissues accompanied with up-regulation of PR 1	Barley	Swarbrick *et al.* 2006
Induction of defense response				
Soluble sugars	*PI* (+)	*PI* expression induced by Suc, Glu, Fru, and Mal, but not Man	Potato	Johnson and Ryan 1990
Glc, Endothall	*PAL* (+)	Activation of protein kinases that phosphorylate the myelin basic protein	*Chenopodium*	Ehness *et al*. 1997
Fungal elicitor	*PAL* (+), *CHS* (+)	ND	Parsley	Chappell and Hahlbrock 1984
Fungal elicitor (*Collectotrichum lindemuthianum*), wounding	*PAL* (+), *CHS* (+)	ND	Common bean	Lawton and Lamb 1987
Xanthomonas campestris pv. *campestris*	Cinnamoyl-CoA reductase (+)	Induction of HR during incompatible interaction	*Arabidopsis*	Lauvergeat *et al.* 2001
Trehalose	*Glutathione S-transferase* (+)	Alternation of disaccharide levels and induction of stress response proteins	*Arabidopsis*	Bae *et al.* 2005
Soluble sugars	*PR-Q* (+), *PAR-1* (+)	Repression of *RbcS* and *CAB*	Tobacco	Herbers *et al*. 1996a
Suc	*PR-2* (+), *PR-5* (+)	SA- but not NPR1-dependent sugar sensing	*Arabidopsis*	Thibaud *et al*. 2004
Glc	*CHS* (+)	Upregulation of stress genes and down regulation of light-mediated signaling genes		Li *et al.* 2006
Repression of photosynthesis				
Glc, Acetate	*RbcS* (-)	Repression of Maize C_4 pyruvate phosphodikinase by Glu and acetate	Maize	Sheen 1990
Chitosan, Benzoic acid, Endothall	*RbcS* (-)	ND	*Chenopodium*	Ehness *et al*. 1997
Okadaic acid[8], Calyculin[9]	*RbcS* (-)	Inhibition of greening of etiolated seedling by okadaic acid	Maize	Sheen 1993
Sclerotinia sclerotiorum	*RbcS* (-)	ND	Sunflower	Mouly and Roby 1988
Tobacco mosaic virus	*OEC* (-)	Increase of viral replication in the OEC silenced plants	Tobacco	Abbink *et al*. 2002
Pseudomonas syringae	*CAB* (-)	Localized decrease of photosynthesis by bacterial infection	*Arabidopsis*	Bonfig *et al*. 2006
Suc	*CAB (-)*	Induction of stress response genes and depression of light mediated signaling genes	*Arabidopsis*	Osuna *et al*. 2007

[1] Updated from the data in Ehness *et al.* (1997)*
[2] genes involved in carbon metabolism or stress-related signals
[3] (+), up-regulation/increase; (-), down-regulation/decrease
[4] ND, not described
[5] 6-deoxyGlu, sugar analog
[6] Chitosan, fungal elicitor
[7] Endothall, phosphatase inhibitor
[8] Okadaic acid, phosphatase inhibitor
[9] Calyculin, phosphatase inhibitor
Abbreviations: CHS, Chalcone synthase; CW-INV, cell wall invertase; Fru, fructose; Glc, glucose; Mal, maltose; Man, mannitol; OEC, oxygen-evolving complex in photosystem II; PAL, phenylalanine ammonia-lyase; PI, proteinase inhibitor; Suc, sucrose; SUSY, sucrose synthase

The corollary of this is that in order to successfully initiate disease in plants, pathogens will need to suppress the defense response of the host and acquire host nutrients. In order to effectively exploit host-driven hexose sources, fungal pathogens often utilize a haustorium to increase the area of surface contact with the plant host and maximize nutrient flow to favor pathogen growth. In order to facilitate hexose accumulation, some pathogens also make full use of host enzymes and transporters, in addition to their own apparatus. In this context during plant-pathogen interactions, elevated CW-INV activity hydrolyzes sucrose into glucose and fructose in the apoplast, which then allows the invading pathogen to access these sugar molecules for its nutritional requirements (Herbers *et al*. 2000; Roitsch *et al*. 2003). Fungal pathogens not only depend upon host CW-INV but also utilize their own invertases to satisfy their nutritional demand (Voegele *et al*. 2006). This is of course consistent with the fact that pathogen infection causes a rapid removal of extracellular carbohydrates. It has further been reported that some pathogens absorb nutrients by a facilitated HXT activity that resides in the haustorium, a specialized feeding structure (Voegele *et al*. 2001).

Barley leaves exhibiting *mlo*- or *Mla12*-based resistance to powdery mildew have been found to show a small accumulation of hexoses within 48 hours (Swarbrick *et al*. 2006). In these localization studies, hexoses are observed to accumulate in areas of the leaf that actively exhibit resistance responses. A rapid accumulation of sugars at an early stage of resistance defense response in plants is consistent with their active utilization in fueling host defense reactions

and/or their activity as signals that induce the expression of defense genes. In contrast, a progressive build up of hexoses and sucrose becomes apparent during a susceptible interaction, suggesting that high levels of sugars throughout the susceptible interaction are needed for pathogen growth. Nonetheless, the competition for sugars between pathogenic microbes and their host plants at the site of infection may play an important role in determining the outcome of the plant defense response. Hence, sugar accumulation at the early stage of pathogen infection may lead to a successful plant defense, whereas its accumulation during late stages is likely to favor the nutrient demands of the invading organisms, resulting in disease.

UNIVERSAL FEATURES OF THE CARBON METABOLIC FLUX DURING THE DEFENSE RESPONSE IN PLANTS

To resist an attack by microbial pathogens, plants have evolved an effective defense system (Chisholm *et al*. 2006) which is primarily dependent upon pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI). Plants have also acquired a more specialized mechanism to trigger a strong defense response, often including a PCD phenoltype hypersensitive response (HR), once the host recognizes the presence of pathogen effector proteins. This effector-triggered immunity (ETI) has been explained by a genetic interaction model between resistance (*R*) and avirulence (*Avr*) genes (Hammond-Kosack and Jones 1997; Martin *et al*. 2003; Chisholm *et al*. 2006). Subsequently, successful plant rejection of invading pathogens is accomplished by a timely activation of defense responses such as the generation of reactive oxygen species (ROS) and the synthesis of pathogen-related proteins (Lamb *et al*. 1989; Bowles 1990; Conrath *et al*. 2002; Martin *et al*. 2003; Nimchuk *et al*. 2003; Glazebrook 2005). Global gene expression patterns that arise during plant-pathogen interactions have also been investigated (Scheideler *et al*. 2002; Craigon *et al*. 2004; Zipfel *et al*. 2004). In these analyses, a shift from a housekeeping to a defense response of the primary carbon metabolic flux in plants is commonly observed, which is favorable to fending off a pathogen attack. In this review, we focus on carbon metabolic pathways, including sucrose to hexose conversion and hexose utilization, as hexoses are considered to be key regulators of several cellular pathways in plants, including development and defense responses.

The alteration in the carbon flux in response to pathogen invasion appears to be centralized to increase the production and utilization of hexoses. Many studies using bacterial, fungal or viral systems have found that the expression of the apoplast-localized invertase, *CW-INV*, is highly elevated during pathogen infection (Sturm and Chrispeels 1990; Benhamou *et al*. 1991; Sturm and Tang 1999; Chou *et al*. 2000; Hall and Williams 2000; Herbers *et al*. 2000; Roitsch *et al*. 2003; Cho *et al*. 2005), suggesting that this sucrose-cleaving enzyme plays a crucial role in plant-pathogen interactions. The results of earlier reports have also shown that *CW-INV* expression is up-regulated following sugar treatment. Considering the fact that a higher CW-INV activity increases the sugar levels, pathogen infection and up-regulation of the *CW-INV* gene results in a positive sugar feedback circuit (Roitsch 1999). There is compelling evidence that type III effector molecules from the virulent strain of *Xanthomonas campestris* pv. *vesicatoria* (*Xcv*) suppress *CW-INV* expression in pepper leaves during the early stages of infection. This might assist successful bacterial colonization of the host plant (Biemelt and Sonnewald 2006). Conversely, a TTSS-deficient mutant that is unable to establish disease in plants causes strong induction of *CW-INV* gene expression following infection of pepper leaves. This suggests that the translocation of type III effectors into host cells is required to achieve transcriptional regulation of *CW-INV*. It remains to be determined how these bacterial effectors regulate *CW-INV* gene expression. Consistently, in the *mlo*- and *Mla12*-mediated resistance responses in barley leaves to powdery mildew, CW-INV activity increases more rapidly and to a much greater extent compared with infected susceptible leaves (Swarbrick *et al*. 2006). There are a few contradictory findings, which are not in agreement with the proposed role of CW-INV during plant-pathogen interactions. For example, inactivation of the *Arabidopsis CW-INV1* gene, which is responsible for all induced CW-INV activity in mechanically wounded leaves, did not affect localized alterations in source-to-sink transition status of wounded leaves or wound-regulated gene expression (Quilliam *et al*. 2006). This may imply that a number of enzymes associated with carbohydrate metabolism including sucrose synthase play a similar role with CW-INV in wounded leaves.

In *Arabidopsis*, a sink-specific hexose transporter *AtSTP4* is induced in conjunction with the increased activity of CW-INV after infection with the fungal pathogen *Erysiphe cichoracearum* (Fotopoulos *et al*. 2003; Scharte *et al*. 2005). Analysis of the expression profile of sugar transporters in *Botrytis cinerea*-challenged *Arabidopsis* points to the induction of pathogen-specific sugar transporter genes (Craigon *et al*. 2004). A recent finding also indicates that the non-host pathogen *B. cinerea* enhances glucose transport in *Pinus pinaster* suspension-cultured cells through *de novo* transcription and protein synthesis of sugar transporters (Azevedo *et al*. 2006). In addition, transcripts of an *Arabidopsis* sucrose transporter (SUT) *AtSUC3* that is mainly expressed in sink organs appear to be strongly enhanced by wounding, suggesting that *AtSUC3* is possibly involved in importing carbohydrates from the apoplast after infection or wounding to cover the enhanced metabolic demand of adjacent cells, and to remove any extracellular carbohydrates which may be exploited by pathogens (Meyer *et al*. 2004).

The concept of an alteration in carbon flux in response to pathogen infection in plants is also supported by a number of previous studies. Hexokinase (HXK), a key enzyme involved in this carbon shift, was found to be up-regulated immediately after pathogen challenge or sugar treatment (Scheideler *et al*. 2002; Price *et al*. 2004; Cho *et al*. 2006a; our unpublished data). In *Arabidopsis*, HXK, which catalyzes the ATP-dependent conversion of hexose to hexose-phosphate, is known to act as a sensor of the levels and phosphorylation status of sugars, and to transmit this information to the nucleus through a signal transduction pathway (Moore *et al*. 2003; Rolland and Sheen 2005; Cho *et al*. 2006b). Transgenic plants expressing catalytically inactive *AtHXK1* alleles in the *Arabidopsis* HXK mutant *glucose insensitive2* (*gin2*) support various signaling processes, including gene expression, cell proliferation, root and inflorescence growth, and leaf expansion and senescence (Moore *et al*. 2003), suggesting that the catalytic and sensory functions of AtHXK1 can be uncoupled in the *Arabidopsis* plant.

The fact that the carbon flow is concentrated toward the production of hexose-phosphate infers an important function of HXK-mediated metabolism during the plant defense response. In this context, the expression of the *Arabidopsis PR1* and *PR5* genes has been found to depend upon the HXK-catalyzed glycolysis pathway (Xiao *et al*. 2000). Recently, several studies have suggested that mitochondria-associated HXK that is coupled to ATP production during cellular metabolism plays a pivotal role in the regulation of apoptosis in animal cells (Pastorino *et al*. 2002; Majewski *et al*. 2004). In mammalian cells, the binding of mitochondria-associated HXK II and voltage-dependent anion channel (VDAC) located in outer membrane inhibits cytochrome c release and prevents the proapoptotic protein Bax from inducing mitochondrial disruption and PCD (Pastorino *et al*. 2002). Virus-induced gene silencing (VIGS) of a tobacco mitochondria-localized HXK, *Hxk1*, causes the spontaneous formation of necrotic lesions in leaves, indicating that the silencing of tobacco *Hxk1* activates PCD (Kim *et al*. 2006). Similarly, *Arabidopsis* plants overexpressing *AtHXK1* and *AtHXK2*, mitochondria-localized HXKs, are prevented from initiating PCD as a result of oxidative stresses caused by

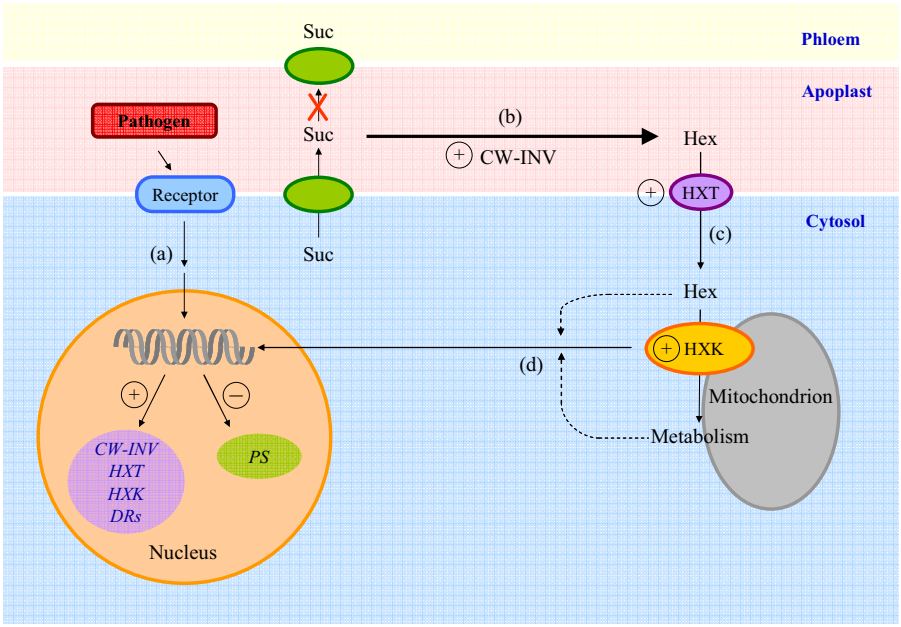

Fig. 1 Model for the universal primary carbon flow leading to a local sugar-enhanced defense response during a plant-pathogen interaction. (**a**) Pathogen infection up-regulates *CW-INV*, *HXT*, *HXK*, and *Defense-related* (*DR*) genes by PAMP- or effector-triggered immune response. (**b**) Increased CW-INV activity reduces phloem loading of sucrose and accumulates hexose in the apoplast. Sugar accumulation at the early stage of pathogen infection is crucial for successful plant defense. (**c**) Hexoses in the apoplast are imported to the cytosol via the increased activity of HXT. (**d**) Upon the accumulation of hexose sugars, hexokinase-dependent or independent and glycolysis-dependent pathways positively regulate the expression of *CW-INV*, *HXT*, *HXK*, and *DR* genes and down-regulate *photosynthesis-related* (*PS*) genes. '+' and '-', respectively, indicate the up- and down-regulation of mRNA, protein, or enzyme activity. Hex, hexose; Suc, sucrose.

H_2O_2 and α-picolinic acid (Kim *et al*. 2006). Examination of the *gin2* mutant harboring pathogen infection may help to further investigate the roles of HXK as a sugar sensor and glycolysis-catalyzing enzyme during the plant defense response.

In summary, increased CW-INV activity caused by invading biotrophic pathogens reduces the phloem loading of sucrose and leads to the accumulation of hexoses in the apoplast. Hexose accumulation results in a switch of photoassimilates from a source to a sink status in infected tissues. Subsequently, apoplastic hexose uptake into host cells is accelerated by increased activity of plasma membrane located HXTs which might stimulate activation of intracellular defense responses. During these processes, HXK-mediated sugar sensing and/or metabolism might be involved in the regulation of defense responses in plants (**Fig. 1**).

USE OF AN IMBALANCE IN CARBON PARTITIONING AS A SYSTEMIC DEFENSE SIGNAL

The induction of the defense response in plants requires both energy and the activation of sink metabolism. A carbon flow from the phloem parenchyma to the neighboring sieve elements in many plants is achieved largely via sucrose through either plasmodesmata (PD)-mediated symplastic movement or apoplastic transport (Lalonde *et al*. 2004; Lim *et al*. 2006). In pathogen-infected leaves, a remarkable accumulation of hexose is assumed to occur in the intracellular space owing to reduced export and increased import of sugars, because a dramatic change in the steady state levels of hexose phosphates is not detectable (Herbers *et al*. 2000), and a decline in sucrose efflux from the infected tissues is observed (Scharte *et al*. 2005). This notion is supported by other findings that the activities of insoluble invertase CW-INV and HXT are highly increased in pathogen-infected tissue (Roitsch *et al*. 2003; Azevedo *et al*. 2006).

Transgenic tobacco plants expressing a yeast invertase in the subcellular compartment apoplast or vacuole appeared to develop spontaneous necrotic lesions similar to HR in source leaves (Sonnewald *et al*. 1991). The development of necrotic sectors in transgenic plants with the apoplastic or vacuolar invertase was found to be linked to the source state of a leaf. Bleaching that is paralleled by the inhibition of photosynthesis follows the sink to source transition zones, starting at the rim of the leaf and moving to the base. A similar line of evidence has shown that the expression of yeast invertase in the apolast or vacuole induces *PR* gene expression and confers increased resistance against potato virus Y (Herbers *et al*. 1996b, 2000). In contrast, the transcript levels and enzymatic activity of cytosolic invertase (C-INV) are not significantly changed in response to invading pathogen (Chou *et al*. 2000; Herbers *et al*. 2000). These data suggest that a remarkable change in the source to sink status of nutrients, which is achieved through the increased hexose pool in either the apoplast or vacuole, is likely to be essential for mediating a successful systemic defense response in plants. Thus, it is noteworthy that only hexose accumulation in the cellular compartments belonging to the secretory pathway induces enhanced disease resistance (Herbers *et al*. 1996b). Consistently, transgenic plants expressing an antisense transcript of the *SUT* gene, *SUT1*, exhibit a massive accumulation of leaf carbohydrates and abnormalities that are similar to disease symptoms, such as curled and bleached leaves (Riesmeier *et al*. 1994).

In potato tubers, reduced activity of the plastidic ATP/ADP transporter 1 (AATP1) causes a decrease in the starch and increase in the glucose content (Geigenberger *et al*. 2001). In transgenic tubers, the accumulation of transcripts encoding defense-related proteins and thus enhanced resistance to the soft rot-causing bacterial pathogen *Erwinia carotovora* or the fungus *Alternaria solani* (Linke *et al*. 2002; Conrath *et al*. 2003) have been observed. However, the expression of a cytoplasmic yeast invertase in potato tubers results in a drastic susceptibility to *E. carotovora*, although these plants possessed increased hexose levels (Conrath *et al*. 2003). Interestingly, grafting experiments between *AATP1* antisense and wild type plants indicate the presence of a systemic signal generated in *AATP1* antisense rootstocks, which potentiates the cellular defense responses in the leaves of wild type scions. This indicates that high sugar levels *per se* does not cause pathogen resistance, but rather that the alteration of primary carbon metabolism induced by decreased AATP1 activity generates a translocated signal that leads to various defense responses, eventually contributing to a robust level of plant resistance.

The *Arabidopsis* mutant *hys1* (*hypersenescence1*), exhibiting a hyper-responsive phenotype to exogenously applied sugar, was found to be allelic to the *cpr5* (*constitutive expressor of pathogenesis-related genes 5*) mutation (Yoshida *et al*. 2002). A *cpr5* mutant displayed spontaneous pathogen defense response, including the expression of *PR* genes and enhanced resistance to virulent pathogens (Bowling *et al*. 1997). Analysis of the *hys1/cpr5* mutation indicated that imbalanced sugar signaling in the mutant via either increased sensitivity of HXK to sugar or enhanced sugar signaling flow is related to spontaneous pathogen defense responses. Thus, the *hys1/ cpr5* mutation provides a clear link between imbalanced sugar signaling and the de-

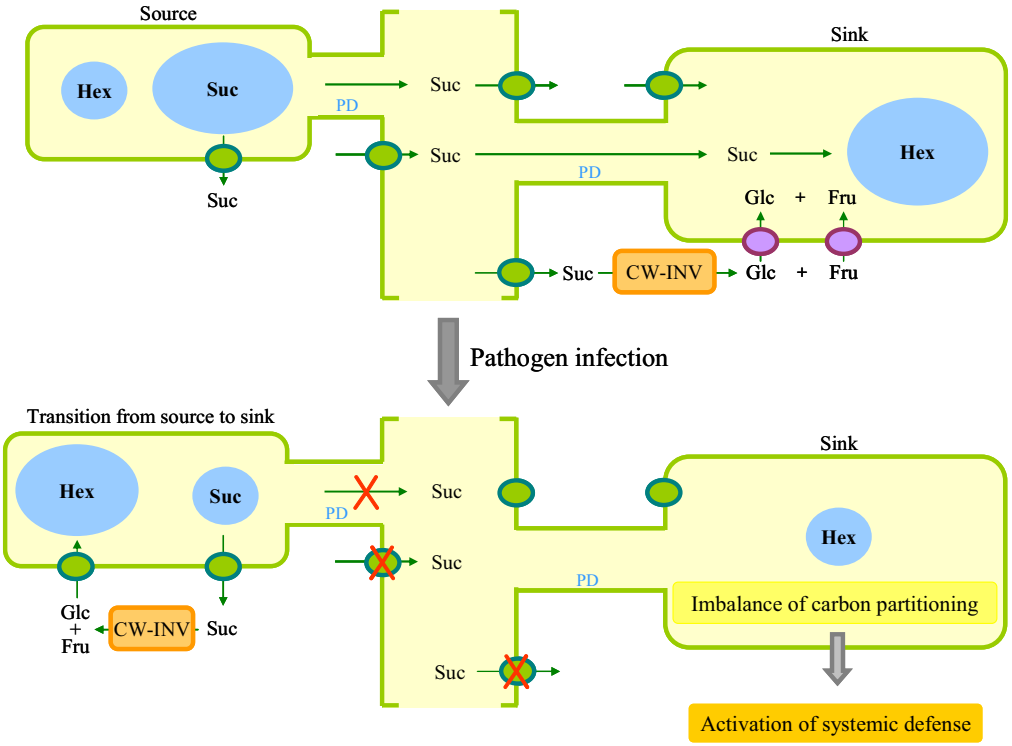

Fig. 2 Model of sugar-induced systemic plant defense response. (Top) Sucrose is mobilized to sink organs as a supply of nutrients for plant growth and development. (Bottom) Upon pathogen infection, a reprogramming of the carbon fluxes from sucrose to hexose, mainly involved in the activity of CW-INV, causes a blockage of sucrose uploading via SUT or PD. Subsequently, this leads to sugar starvation in the physiological sink organs. Thus, an imbalance of carbon partitioning functions as a defense signal that functions towards a systemic disease resistance response. Fru, fructose; Glc, glucose; Hex, hexose; Suc, sucrose.

fense response of plants.

Transcription profiling using the ATH1 GeneChip array was examined in *Arabidopsis* cells cultured under conditions of sucrose starvation (Contento *et al*. 2004). These conditions are commonly assumed to be similar to those of the sink tissues on the basis of observations that the sucrose efflux dramatically declines in pathogen-infected source tissues. Interestingly, transcription levels of both *SUTs* and *HXTs* appeared to be highly increased by sucrose starvation. This is consistent with the data obtained from the global expression analysis of the plant-pathogen interactions that show an effective response to the invading organisms. It is evident that the physiological sink organs compete with new sinks generated by pathogen infection. Because new sinks generated by pathogen infection sequester a high amount of soluble sugars, the physiological sink regions of the entire host plant would be expected to encounter sugar starvation, and thereby functions as a transmittable systemic signal of pathogen infection. In the barley *albostrians* mutant having white and green leaves due to different plastid differentiation, the white leaves show enhanced resistance to powdery mildew and stronger constitutive or pathogen-induced transcript accumulation, compared with the green leaves (Jain *et al*. 2004). Recent examinations of the maize *tie-dyed1* mutant, which develops variegated yellow and green leaf sectors, have revealed that the yellow sectors have reduced photosynthesis rates and accumulate high levels of sugars (Braun *et al*. 2006). Thus, it is probable that the yellow sectors retain their sink identity and continue to import carbon from neighboring green source tissues, causing an imbalance of the carbon partitioning in the mutant plant. In this context, it will be interesting to determine whether *tie-dyed1* displays an enhanced defense response, and to investigate the changes in the sugar levels and in the expressions of some carbon metabolic enzyme genes such as *CW-INV* and *HXK* in white and green leaves of the *albostrians* mutant, in response to pathogen invasion.

In summary, the remarkable decline in the carbon efflux from infected leaf tissues and the facilitated influx into local pathogen-infected host cells might support the competetive strength of the host cells. Thus, during the early phase of pathogen infection, a locally increased hexose concentration in infected tissue could mediate enhanced defense responses. Nonetheless, the disturbance of sugar partitioning caused by a rapid reallocation of soluble sugars may bring about the activation of a local tissue infected with pathogen and ultimately of a systemic defense response in remote sites of the host plant (**Fig. 2**).

CONCLUDING REMARKS

Several lines of evidence now suggest that plants elevate their hexose levels immediately in response to invading biotrophic pathogens, which in turn might trigger the host defense responses, although sugars are themselves the main nutrient source for pathogens. In particular, the reprogramming of the carbon flow from sucrose to hexose in pathogen-infected tissues supports the crucial role of hexose in the plant defense response. Thus, increases in the size of the hexose pool during the early phase of pathogen infection might be important for successful plant defense. The accumulation of hexose at the sites of pathogen-invasion initiates the local imbalance of carbon distribution, which then turns on a local defense response. Subsequently, the starvation of sink nutrients caused by a decline in sucrose efflux may generate a systemic defense response signal. This notion is supported by the fact that the induction of both the *PR* genes and SAR correlates with the accumulation of sugars. HXK is also possibly involved as a sugar sensor in mediating plant defense responses. However, it remains to be elucidated how elevated hexose turns on different activators (e.g., transcription factors) to reinforce plant defense responses.

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