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Herbicide-related signaling in plants reveals novel insights for herbicide use strategies, environmental risk assessment and global change assessment challenges

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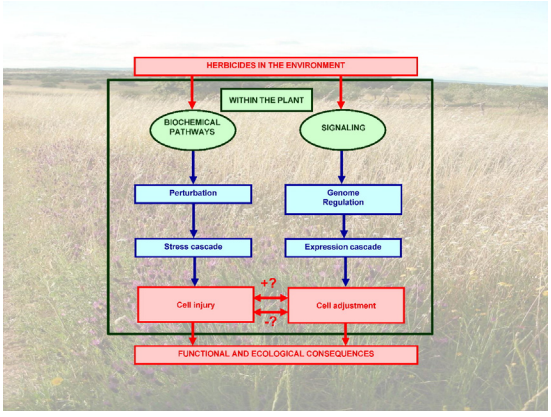
HIGHLIGHTS

- The standard view of herbicide mode-of-action is target-centered and unilinear.
- This view does not reflect the complex mechanisms of plant-herbicide interactions.
- Plasticity of herbicide-related signaling leads to positive or negative outcomes.
- These novel mechanisms could be useful to improve herbicide use strategies.
- They should also be taken into account for environmental risk assessment.

GRAPHICAL ABSTRACT



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ABSTRACT

Herbicide impact is usually assessed as the result of a unilinear mode of action on a specific biochemical target with a typical dose-response dynamics. Recent developments in plant molecular signaling and crosstalk between nutritional, hormonal and environmental stress cues are however revealing a more complex picture of inclusive toxicity. Herbicides induce large-scale metabolic and gene-expression effects that go far beyond the expected consequences of unilinear herbicide-target-damage mechanisms. Moreover, groundbreaking studies have revealed that herbicide action and responses strongly interact with hormone signaling pathways, with numerous regulatory protein-kinases and -phosphatases, with metabolic and circadian clock regulators and with oxidative stress signaling pathways. These interactions are likely to result in mechanisms of adjustment that can determine the level of sensitivity or tolerance to a given herbicide or to a mixture of herbicides depending on the environmental and developmental status of the plant. Such regulations can be described as rheostatic and their importance is discussed in relation with herbicide use strategies, environmental risk assessment and global change assessment challenges.

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1. The classical ecotoxicological view of herbicide action overlooks the complexity of plant-herbicide interactions

Herbicides are part of the range of chemicals that enable crop protection, maintenance of crop yields and economic viability of agriculture (Arias-Estévez et al., 2008; Zhou et al., 2015). The impact of herbicides on plant communities in the field or in the environment at large is often considered in classical toxicological or ecotoxicological terms of a single mode of action on a particular biochemical target with a straightforward dose-response dynamics (Délye, 2013; Délye et al., 2013; Saika et al., 2014). However, it is also well established that weed resistance to herbicides can involve non-target-site mechanisms (Délye, 2013; Rong Tan et al., 2015; Saika et al., 2014; Vivancos et al., 2011), as occurs in the case of multiple-herbicide-resistant *Echinochloa phyllopogon* biotypes that are able to carry out active herbicide detoxification (Iwakami et al., 2014). These non-target-site mechanisms are usually considered to be related to the dynamics of the herbicide molecule (reduced herbicide penetration, reduced herbicide translocation, enhanced herbicide degradation) or to enhanced defence against collateral stresses (increased stress protection, increased stress repairs).

Transcriptomics and metabolomics studies (Han et al., 2014; Qian et al., 2011, 2012; Ramel et al., 2007, 2012; Serra et al., 2013, 2015a, 2015b; Vivancos et al., 2011; Zhang et al., 2016) demonstrate that herbicide action is integrated within a larger cellular and molecular context involving expression regulation of hundreds of genes covering fundamental structural and physiological functions: transcription, translation, cellular communication and signaling, central metabolism, energy metabolism, biogenesis, stress responses, programmed cell death, cell homeostasis, senescence. However, as pointed out by Zhou et al. (2015), sensing and signal transduction mechanisms that underlie xenobiotic-related gene regulation remain elusive in plants, in contrast with mammalian cells and yeast where xenobiotic sensors have been characterized. Moreover, even herbicide metabolites that are considered to be inactive cause major metabolomic and molecular modifications under conditions of no observable adverse effects (Serra et al., 2013, 2015a, 2015b) and non-herbicidal synthetic compounds used as herbicide safeners in some monocotyledonous crops (Riechers et al., 2010) provide protection through induction of plant defence and detoxification gene expression (Ramel et al., 2012; Riechers et al., 2010). On the other hand, field studies and empirical evidence have shown that environmental physicochemical factors (cold, heat, drought) and growth and development parameters significantly influence plant sensitivity to herbicide treatment (Klingaman et al., 1992; Vila-Aiub et al., 2013), thus emphasising potential involvement of complex physiological mechanisms in the outcomes of herbicide treatments.

The importance of these interferences with herbicide effects strongly indicates that major questions concerning the precise mechanisms through which herbicides affect and kill plants remain to be addressed (Qian et al., 2015b; Vivancos et al., 2011). Recent developments using mutation approaches have revealed unexpected links between herbicide tolerance and plant regulatory genes that are unrelated to herbicide targets or herbicide metabolisms (Faus et al., 2015; Fukudome et al., 2014; Kurepa et al., 1998; Ramel et al., 2012; Sanchez-Villarreal et al., 2013; Sharkhuu et al., 2014; Smeets et al., 2013). It is therefore timely to reassess the novel mechanisms that are involved in plant-herbicide interactions (Section 2), to re-consider whether the unilinear herbicide-target-disruption-death string of events is still relevant or should be replaced with an inclusive-toxicity regulatory model (Section 3), and to evaluate how novel models of plant-herbicide interactions are important to deal with pressing agro-environmental issues such as herbicide use strategies, environmental risk assessment and global change assessment challenges (Section 4).

2. Herbicide action on plants occurs within the network of metabolic plasticity, stress acclimation and programmed cell death

2.1. Integration of herbicide responses with hormonal, nutritional and environmental responses

Numerous transcriptomics studies of plant-herbicide interactions have highlighted the major impacts of herbicide treatments on the expression of hormone-related genes (Doğramaci et al., 2015; Han et al., 2014; Köster et al., 2012; Li et al., 2015; Ramel et al., 2007; Serra et al., 2013; Stamm et al., 2014; Zhang et al., 2016). The dynamics of abscisic acid (ABA), auxins, brassinosteroids, cytokinins, gibberellins, ethylene, jasmonate, and salicylate are thus likely to be directly or indirectly involved in plant responses to herbicide treatments. Conversely, treatments with hormones such as auxins (Kerchev et al., 2015), brassinosteroids (Zhou et al., 2015), or salicylate (Cui et al., 2010) can interfere with the effects of herbicides or pesticides. Brassinosteroids (Zhou et al., 2015) and salicylate (Cui et al., 2010) directly regulate genes that are related to herbicide detoxification, and activation of auxin signaling (Kerchev et al., 2015) counteracts the cell death effects of photorespiration, which is involved in the responses to several herbicides (Serra et al., 2013, 2015a, 2015b; Vivancos et al., 2011). Analysis of transcriptomic, proteomic or metabolomic modifications also shows that herbicide treatments have major impacts on genes and proteins involved in stress and nutrition signaling pathways: ROS signaling, membrane stress signaling, photosystem and light stress signaling, endoplasmic reticulum stress signaling, drought and salinity signaling, nutritional starvation signaling, and cell death signaling (Duhoux et al., 2015; Faus et al., 2015; Gaines et al., 2014; Goossens et al., 2001; Horn et al., 2013; Li et al., 2015; Ozgur et al., 2014; Ramel et al., 2007, 2009a; Serra et al., 2013, 2015a, 2015b; Walley et al., 2015; Wang et al., 2012).

Herbicide treatments modify metabolic networks that include gene-regulating metabolic signals (Ramel et al., 2007, 2009a, 2013; Serra et al., 2013, 2015a, 2015b; Vivancos et al., 2011), such as sucrose, glucose, trehalose, serine, or leucine, which are major effectors of the sensing mechanisms that integrate metabolism, stress and development (Emanuelle et al., 2015; Tomé et al., 2014). Some of these effectors interact with master regulators of metabolism, such as the SNF1 (sucrose non-fermenting 1)-related kinase 1 (SnRK1) (Baena-González et al., 2007; Emanuelle et al., 2015; Tomé et al., 2014) and the target-of-rapamycin (TOR) kinase (Tomé et al., 2014; Xiong et al., 2013), which exert major controls on the regulation of genes involved in catabolic processes (proteolysis, amino acid catabolism, sugar degradation, lipid catabolism) that can compensate low carbohydrate and low energy situations. In *Arabidopsis*, SnRK1 acts through the activation of bZIP transcription factors on asparagine biosynthesis and branched-chain amino acid metabolism (Dietrich et al., 2011), and the dynamics of these important amino acids is affected by chemically- and functionally-diverse herbicides, such as acetolactate synthase inhibitors (Duhoux et al., 2015), glyphosate (Serra et al., 2013, 2015a, 2015b; Vivancos et al., 2011), or atrazine (Ramel et al., 2013), by the atrazine derivative hydroxyatrazine (Serra et al., 2013, 2015a), and by the glyphosate derivative aminomethylphosphonic acid (AMPA) (Serra et al., 2013, 2015a).

Even though its main target is Photosystem II (PSII) (Qian et al., 2014b), atrazine also regulates branched-chain amino acid metabolism genes in *Arabidopsis*, whether under normal nutritional conditions or under conditions of sucrose feeding (Ramel et al., 2013). Under conditions of sucrose feeding, atrazine increases the expression of the *At5g49450* gene (Ramel et al., 2007), which encodes the bZIP1 transcription factor that is involved in the reprogramming of amino acid metabolism (Dietrich et al., 2011). Baena-González et al. (2007) demonstrated that, in *Arabidopsis*, the transcriptional effects of diuron [(3,4-dichlorophenyl)-1,1-dimethylurea], another PSII inhibiting herbicide, directly depended on the carbohydrate and energy sensor SnRK1.

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Interestingly, the animal AMP-activated kinase (AMPK) energy sensor, which belongs to the same eukaryotic protein kinase family as SnRK1, responds to any cellular stress that threatens to lower ATP levels in order to reduce energy consuming pathways and induce catabolism (Hardie et al., 2012). This sensing of metabolic threats in the presence of drugs or xenobiotics (Hardie et al., 2012) is mediated in animal cells by AMPK-dependent responses to xenobiotic stresses resulting from the action of reactive oxygen species (ROS) and activation of upstream regulatory protein kinases (Blättler et al., 2007; Zmijewski et al., 2010). The occurrence of similar effects in plant cells in the presence of exogenous sucrose, which entails the absence of sugar starvation signaling, may therefore tentatively be ascribed to endogenous ROS-mediated signaling (Ramel et al., 2013).

2.2. Characterization of regulatory-protein mutations that interfere with herbicide responses

Initial characterization of most of these relationships between plant-herbicide interactions and signaling processes (Section 2.1) originated from correlation or co-expression patterns between physiological responses, transcript levels and metabolite levels. However, in a number of cases, causal relationships have also been established by mutation analysis of key signaling components resulting in important modifications of plant responses to herbicide treatment and in enhanced sensitivity or tolerance to herbicides (Table 1). Initial identification of such a causal relationship between signaling components and herbicide responses resulted from the discovery of paraquat-induced oxidative stress tolerance in the *Arabidopsis* late-flowering *gigantea* mutant (Kurepa et al., 1998). Subsequent characterization of GIGANTEA as a circadian oscillator and a transcriptional regulator involved in numerous signaling interactions (Dalchau et al., 2011; Fowler et al., 1999) and confirmation of enhanced paraquat tolerance in other *gigantea* mutants (Sanchez-Villarreal et al., 2013) established that regulatory and signaling processes previously unrelated to herbicide action had a significant impact on herbicide responses. Moreover, involvement of circadian clock modules was independently confirmed by the effects of the chemically-distinct herbicide imazethapyr on flowering (Qian et al., 2014a).

Table 1 shows that mutant analysis studies have now uncovered more signaling components and more signaling pathways that are linked to herbicide responses and whose impairment modulates herbicide action: a stress-responsive transcriptional regulator (Rama Devi et al., 2006), the ethylene signaling CTR1 kinase (Sulmon et al., 2007), the protein kinase of eukaryotic translation initiation factor-2α (eIF2α) (Faus et al., 2015; Zhang et al., 2008), GRAS-family transcription factors (Fode et al., 2008), the ClpR4 subunit of the chloroplast-localized Clp protease complex (Saini et al., 2011), the cytokinin response factor 6 (CRF6) transcription factor (Ramel et al., 2012), the jasmonate signaling COI1 component of ubiquitin-ligase complexes (Köster et al., 2012), the circadian clock regulator TIME FOR COFFEE (Sanchez-Villarreal et al., 2013), the TOR kinase carbon and energy sensor (Xiong et al., 2013), the protein phosphatase of C-terminal domain RNA polymerase II (Fukudome et al., 2014), and the red/far-red photoreceptor phytochrome B (Sharkhuu et al., 2014). All of these herbicide-signaling interactions differ from the direct interactions that necessarily occur between hormone-analogue herbicides, such as auxinic analogues, and corresponding hormone-binding proteins, such as auxin receptors or transporters (Gleason et al., 2011).

For instance, in line with the interactions between plant metabolism and herbicide responses, the *tor* mutation of carbon and energy signaling Glucose-TOR kinase affects the expression of genes involved in xenobiotic degradation (Xiong et al., 2013). Moreover, some of these mutations (Table 1) result in higher tolerance or higher sensitivity to herbicides, thus indicating that multiple independent signaling pathways can control or modulate the nature and extent of herbicide responses, that signaling and regulation processes may enhance

Table 1
Regulatory-protein mutations that interfere with herbicide responses in *Arabidopsis thaliana*. CPL: C-terminal domain phosphatase-like; COI: coronatine insensitive; CRF: cytokinin response factor; CTR: constitutive triple response; 2,4-D: 2,4-dichlorophenoxyacetic acid; Ds: Dissociation transposon; GCN: general control non-repressible; GRAS: gibberellic acid insensitive-repressor of GA1-SCARECROW; PHYB: phytochrome B; SCL: SCARECROW-like; SIB: sigma factor-binding protein; TIBA: 2,4,6-triiodobenzoate; TIC: time for coffee; TOR: target of rapamycin.

Gene identity	Gene product	Signaling pathway	Type of mutation	Mutant	Effects on herbicide responses	Reference
At1g22770	GIGANTEA	Circadian clock	Ethyl methanesulfonate	*gi-3*	Higher tolerance to paraquat	Kurepa et al. (1998)
At4g24275	Unknown	Control of transcription	T-DNA insertion, RNAi	Δ8L4, 8L4-RNAi	Decrease of 2,4-D-activated as-1 promoter activity	Rama Devi et al. (2006)
At5g03730	CTR1	Ethylene signaling	Ethyl methanesulfonate	*ctr1-12*	Higher tolerance to atrazine	Sulmon et al. (2007)
At5g06950 *At5g06960* *At3g12250*	TGA2 TGA5 TGA6	Class II TGA factors	Triple deletion	*tga2 tga5 tga6* triple mutant	Decreased expression of TIBA- or 2,4-D-inducible genes	Fode et al. (2008)
At1g07530	SCL14	GRAS regulatory proteins	T-DNA insertion	*scl14*	Decreased expression of TIBA- or 2,4-D-inducible genes	Fode et al. (2008)
At3g59410	GCN2	Amino acid starvation response	Ds insertion	*gcn2*	Enhanced sensitivity to glyphosate	Zhang et al. (2008)
At4g17040	HON5	CLP PROTEASE R SUBUNIT 4	Ethyl methanesulfonate	*hon5*	Higher tolerance to norflurazon	Saini et al. (2011)
At2g39940	COI1	Jasmonate signaling	T-DNA insertion	*coi1-t*	Decreased expression of TIBA-inducible genes	Köster et al. (2012)
At3g61630	AP2/CRF6	Cytokinin signaling	T-DNA insertion	*ap2-2d*	Higher tolerance to atrazine	Ramel et al. (2012)
At3g56710	SIB1	Plastidial transcription	T-DNA insertion	*sib1-1*	Higher tolerance to atrazine	Ramel et al. (2012)
At3g22380	TIC	Circadian clock	T-DNA insertion	*tic-2*	Higher sensitivity to paraquat	Sanchez-Villarreal et al. (2013)
At1g22770	GIGANTEA	Circadian clock	T-DNA insertion	*gi-2*	Higher tolerance to paraquat	Sanchez-Villarreal et al. (2013)
At1g50030	TOR KINASE	Nutrient sensing	Estradiol-inducible RNAi	*tor-es*	Overexpression of xenobiotic-degradation genes	Xiong et al. (2013)
At5g58003	CPL4	RNA polymerase II regulation	RNAi	*cpl4*	Enhanced tolerance to chlorosulfuron	Fukudome et al. (2014)
At2g18790	PHYB	Photoreceptor	T-DNA insertion	*gre1*	Enhanced tolerance to glyphosate	Sharkhuu et al. (2014)
At3g59410	GCN2	Amino acid starvation response	Ds insertion	*gcn2*	Enhanced tolerance to glyphosate	Faus et al. (2015)

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herbicide toxicity, and that plant responses to herbicides can be regulated by signaling pathways that are also involved in the responses to environmental, hormonal and nutritional cues.

Nevertheless, the exact mechanisms that link these signaling components and herbicide responses have not yet been characterized. The involvement of signaling processes in plant-herbicide interactions may be ascribed to cascading effects of herbicide action, such as ROS (Ramel et al., 2009a) or membrane (Teixeira et al., 2007) perturbations, or to homeostatic correlations, such as the consequences of carbon or nitrogen perturbations (Faus et al., 2015; Serra et al., 2013). It can also be speculated that herbicide-related signaling processes could be related not only to endogenous sensing and signaling of cellular perturbations (Smeets et al., 2013), but also to environmental sensing and signaling of herbicide-interfering environmental cues (Ramel et al., 2012), or to chemical sensing and signaling of herbicide or xenobiotic structures interacting with the plant cell. Mechanisms of primary sensing of xenobiotic structures, which have been characterized in animal cells, have however remained elusive in the case of plant cells (Ramel et al., 2012), even if various situations of plant-xenobiotic interactions suggest that such primary sensing may also exist in plant cells (Ramel et al., 2012).

Qian et al. (2015a, 2015b) have shown that low levels of imazethapyr induced major metabolic and molecular changes in flowers or in roots. However, these imazethapyr treatments were carried out at IC50 concentrations yielding some level of toxicity. In contrast, Serra et al. (2013) have found that environmentally-observed residual levels (760 nM) of the atrazine metabolite hydroxyatrazine, which is considered to be inactive (Cherifi et al., 2001), caused significant modifications of metabolite and transcript levels (Fig. 1) in the absence of negative growth or physiological effects. Some of these molecular effects, such as the induction of ABA-related *CYP707A3* (Kitahata et al., 2005) and auxin-related *RVE1* (Rawat et al., 2009), could reflect processes of interference with endogenous signaling and changes in hormone dynamics. However, the induction of such significant effects by low levels of inactive herbicide derivative in the absence of physiological or developmental toxicity is likely to require some kind of xenobiotic-sensing mechanism that remains to be characterized (Ramel et al., 2012). Similarly, herbicide-protection effects of safeners are ascribed to safener-mediated sensing and signaling processes (Ramel et al., 2012; Riechers et al., 2010). This is why the integration of signaling processes in plant-herbicide interactions (Table 1, Fig. 1) must take into account not only endogenous processes, but also environmental processes (Fig. 2).

Moreover, herbicide-related regulations cover a large range of genes and proteins corresponding to various functional categories, such as herbicide target proteins (Godar et al., 2015), ROS defence mechanisms (Ramel et al., 2007; Serra et al., 2013), xenobiotic detoxification (Das et al., 2010; Köster et al., 2012; Ramel et al., 2007; Serra et al., 2013), energy, carbon and nitrogen homeostasis (Das et al., 2010; Li et al., 2015; Serra et al., 2013, 2015a, 2015b; Vivancos et al., 2011), or development (Ramel et al., 2007; Stamm et al., 2014). The complexity of signaling interactions and the variety of functional categories that are affected (Fig. 2) imply that complex regulatory loops can integrate xenobiotic signaling, endogenous signaling, xenobiotic and environmental signaling interactions, xenobiotic and endogenous signaling interactions, and modulate herbicide action on their protein targets. For instance, herbicide-induced metabolic changes can affect endogenous signaling and lead to proteomic and metabolic modifications that can modulate the levels of herbicide molecules or of target proteins (Fig. 2). The existence of such regulatory loops emphasizes the potential importance of the time dependence of herbicide responses, with a race between defence and injury that can lead to alternative outcomes of tolerance-enhancement or injury-enhancement, of the developmental stage, and of the initial physiological state of exposure.

3. Molecular interactions between herbicide action and plant cell responses are complex, variable and rheostatic

3.1. Development- and environment-dependent variability of herbicide efficiency

The variability of plant-herbicide interactions has been thoroughly documented both empirically and experimentally, with important

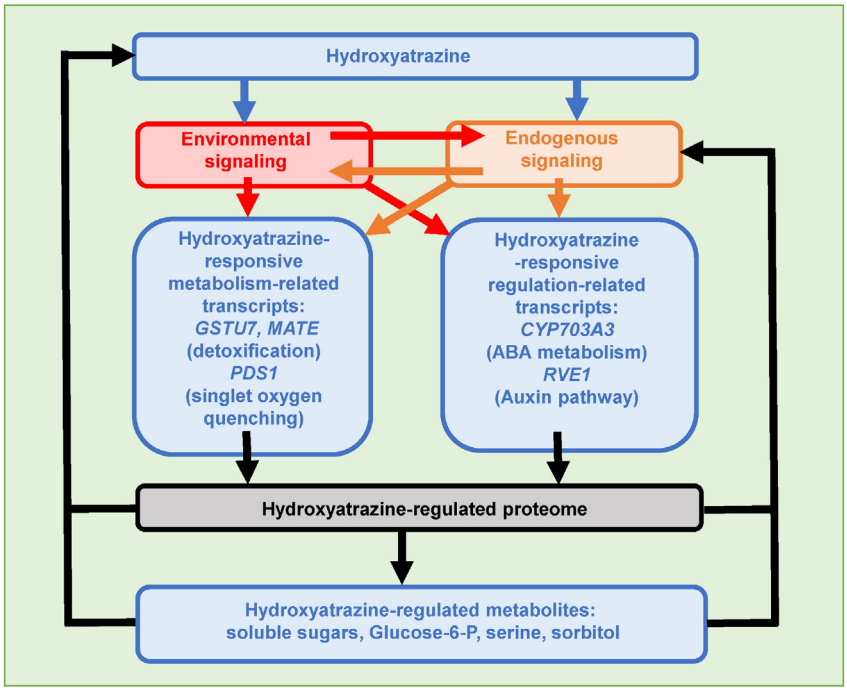

Fig. 1. Integration of the metabolic and gene expression modifications induced by the atrazine metabolite hydroxyatrazine in *Arabidopsis thaliana*. Blue arrows and boxes correspond to experimental treatments and actual metabolite and transcript measurements (Serra et al., 2013). Red and orange arrows and boxes respectively correspond to potential environmental and endogenous signaling processes. Black arrows represent processes that can integrate converging herbicide, environmental and endogenous signaling. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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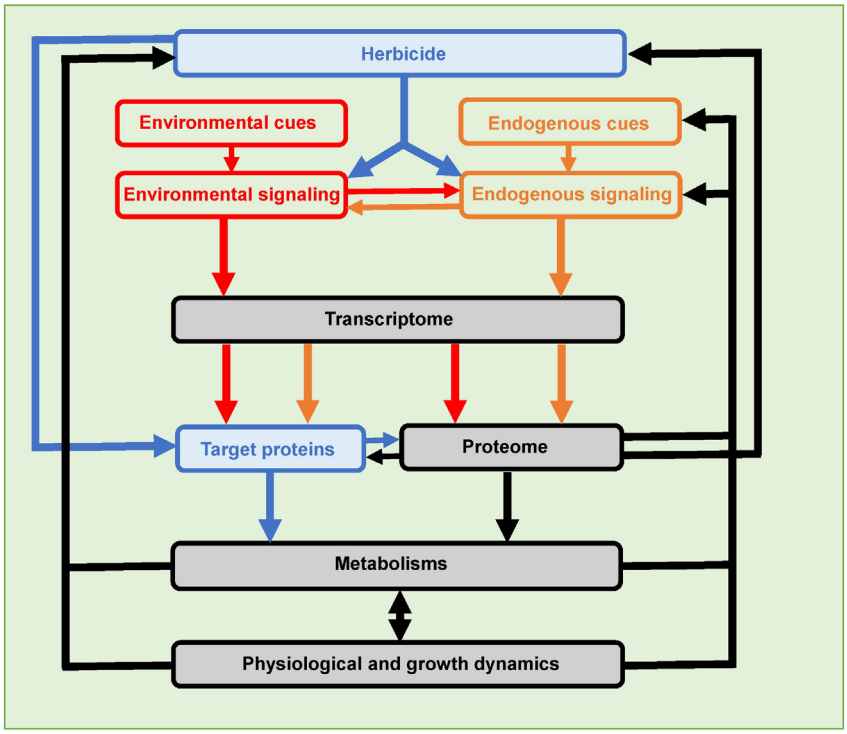

Fig. 2. Hypothetical general scheme of the signaling integration of herbicide action in plants. Blue arrows and boxes reflect various potential impacts of herbicides (Qian et al., 2011, 2012; Qian et al., 2014b; Ramel et al., 2007, 2009a; Serra et al., 2013; Vivancos et al., 2011). Red and orange arrows and boxes respectively correspond to potential environmental (Köster et al., 2012; Ramel et al., 2012; Sharkhuu et al., 2014) and endogenous (Cui et al., 2010; Faus et al., 2015; Köster et al., 2012; Ramel et al., 2012; Zhou et al., 2015) signaling processes. Black arrows represent processes that can integrate converging herbicide, environmental and endogenous signaling (Cortleven et al., 2014; Cui et al., 2010; Rong Tan et al., 2015). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

agronomical and economical consequences in terms of weed control efficiency and costs (Klingaman et al., 1992; Mohr et al., 2007; Sharkhuu et al., 2014). The efficiency of herbicide application greatly depends on the growth stage of weeds (Klingaman et al., 1992). Low or high temperatures can significantly alter the sensitivity to herbicides (Godar et al., 2015; Vila-Aiub et al., 2013), and there are numerous reports linking herbicide efficiency to the time of day at which it is applied (Mohr et al., 2007; Sharkhuu et al., 2014). Conversely, it has been shown that suboptimal efficiency on primary targets, under conditions of low doses of herbicide treatment, can induce hormetic effects of enhanced plant growth (Belz and Duke, 2014; Velini et al., 2008).

There is a general lack of understanding of the mechanisms underlying this great variability of plant-herbicide interactions (Belz and Duke, 2014; Doğramaci et al., 2015; Godar et al., 2015; Sharkhuu et al., 2014), but the existence of signaling mechanisms interacting with herbicide action (Fig. 2) suggests that the status of these signaling mechanisms in the individual plant may play an important role in determining the outcome of the plant-herbicide interaction. Precise understanding of herbicide-related signaling processes may thus prove to be essential for explaining this development- and environment-dependent variability of herbicide efficiency.

3.2. Characterization of rheostatic mechanisms of herbicide sensitivity

Herbicides that inhibit amino acid biosynthesis, such as glyphosate, chlorsulfuron, or imazethapyr, are widely used on a global scale. Inhibition of amino acid biosynthesis pathways by these herbicides induces proteolytic processes and subsequent increases of free amino acids (Orcaray et al., 2010; Zulet et al., 2013) that can compensate for a certain period of time the depletion of amino acid synthesis. This compensation can play an adaptive role leading to the possibility of escape from herbicide stress. On the other hand, the persistence of this compensatory response can also lead to proteolytic and apoptotic processes that accelerate cell and plant death. In accordance with this metabolic and adaptive context, Zhang et al. (2008) and Faus et al. (2015) have shown that regulatory processes of amino acid utilization play a major role in modulating the effects of amino acid synthesis inhibitors in plants. Mutation of *AtGCN2*, homologue of yeast general control nonderepressible-2 protein in *Arabidopsis*, strongly modifies responses to glyphosate (Faus et al., 2015; Zhang et al., 2008), thus indicating that the amino acid starvation response, the regulation of protein synthesis through eIF2α phosphorylation, and the control of apoptotic processes are important to regulate the adaptive value of amino acid-generating proteolysis (Zulet et al., 2013).

Comparison of the results of Zhang et al. (2008) and Faus et al. (2015) also reveals that the GCN2 regulatory protein can mediate opposite effects of sensitivity or tolerance to glyphosate. The exact reason for these opposite effects has not been directly and experimentally elucidated. However, xenobiotic stress is generally related to significant perturbations of carbon and nitrogen metabolic integration, with major variations of soluble sugars (Serra et al., 2013, 2015a, 2015b), and is strongly affected by the carbon status (Ramel et al., 2007, 2009a, 2009b). The distinct nutritional conditions of high or low carbon:nitrogen ratios used respectively by Zhang et al. (2008) and Faus et al. (2015) reflect contrasting situations of carbohydrate availability or limitation (Tomé et al., 2014). The differential impact of the *gcn2* mutation on glyphosate responses may thus result from interactions between GCN2, or other components of the regulatory pathway, and the carbon and nitrogen status of the plant for the management of amino acid fluxes. Such interactions may in turn modulate how plant cells perceive dynamic changes of amino acid levels, thus facilitating either sensitivity or tolerance to herbicide treatment, in relation with proapoptotic or cytoprotective effects (Faus et al., 2015).

The effects of mutations affecting circadian clock and light regulations on responses to glyphosate and paraquat (Table 1) provide further evidence of the importance of metabolic homeostasis in the responses

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to a range of herbicides, and also provide a strong mechanistic basis to the observation that the timing of herbicide application plays an important role in treatment efficiency (Mohr et al., 2007). These effects of circadian clock and light regulations on herbicide responses have been ascribed to alterations in the oscillations of soluble carbohydrate levels (Sanchez-Villarreal et al., 2013) and of shikimate pathway transcripts (Sharkhuu et al., 2014). Indeed, circadian clock components, such as GIGANTEA, are in close interaction with sucrose and carbohydrate metabolism (Dalchau et al., 2011). Moreover, differences of carbon allocation and the levels of soluble carbohydrates influence the sensitivity to oxidative stress and to the herbicide atrazine (Couée et al., 2006; Ramel et al., 2009b; Sulmon et al., 2011). In other words, the circadian regulation of metabolism, the carbon status resulting from carbon assimilation and allocation, the metabolic status that results from growth and development, and the various factors (light, temperature, drought, hypoxia) that act on endogenous carbohydrate levels are likely to set the plant at a given level of potential tolerance to the impact of herbicide treatment.

Independent studies have revealed that the *At3g61630* gene, which encodes the AP2/ERF family cytokinin-response factor 6 (CRF6) that is directly connected to the cytokinin signaling pathway (Cutcliffe et al., 2011), can be induced by the triazine atrazine (Ramel et al., 2007), by paraquat (methyl viologen) (Zwack et al., 2013) and by the sulfonylurea chlorsulfuron (Fukudome et al., 2014). Moreover, Ramel et al. (2012) have shown that mutation of *At3g61630* led to significant and complex modifications in the responses to atrazine with enhanced tolerance under conditions of carbohydrate limitation and decreased tolerance under conditions of sucrose feeding. It therefore seems likely that modifications of CRF6 levels lead to alterations in the general response to herbicides belonging to distinct chemistry/mode-of-action categories. The CRF6-encoding *At3g61630* gene is transcriptionally induced by exogenous sucrose (Ramel et al., 2007), by exogenous cytokinins (Zwack et al., 2013), by drought and osmotic stress (Mizoguchi et al., 2010; Winter et al., 2007) and by temperature variations (Pecinka et al., 2010; Winter et al., 2007). Moreover, the cytokinin signaling pathway is directly involved in light stress responses and in the maintenance of photosystem II (Cortleven et al., 2014), which is the biochemical target of atrazine (Sulmon et al., 2004; Ramel et al., 2007). The action of atrazine on plants seems therefore to involve not only the biochemical pathway of photosystem II inhibition (Ramel et al., 2009a; Qian et al., 2014b), but also a cytokinin-dependent signaling pathway leading to the repression of key stress response genes and the induction of apoptotic processes (Ramel et al., 2007, 2012; Couée et al., 2013). The efficiency of atrazine toxicity could therefore be envisaged as an inclusive toxicity resulting from the action on several processes. Moreover, in the case of chlorsulfuron, the mutation of CPL4 (Table 1) can increase the IC50 in *Arabidopsis* seedlings from less than 10 nM (Singh et al., 1992) to over 40 nM (Fukudome et al., 2014), thus suggesting that the CPL4 regulatory protein contributes to herbicide toxicity. It can thus be hypothesized that variable amounts or activity levels of regulatory proteins may act as adjustable cursors, *i.e.* as rheostats, whose setting integrates nutritional, hormonal and environmental cues and determines the variability and intensity of herbicide responses.

In any situation of abiotic stress, adaptive responses of plants are adjusted not only to the nature of the stress, but also to the stress intensity, to stress oscillations and to the dynamic consequences of the stress situation, including pre-injury "threats" on essential mechanisms (Claeys et al., 2014). The precision of these adjustments involves a myriad of endogenous signals (hormone levels, nutrient levels, storage levels, growth rates, structural components, stress-induced metabolites) not only in terms of absolute levels of individual factors, but also in terms of interactions, ratios, spatio-temporal dynamics, rhythms and signal shapes. Even the limited range of regulatory proteins currently identified to be involved in herbicide responses (Table 1) gives an idea of the complexity of the herbicide-related signaling network (circadian clock, light, phytohormones, nutrients, transcription, plastid biogenesis). It is therefore important to comprehend how this complexity of response mechanisms connects with the complex parameters of herbicide exposures *in natura*: variable levels of herbicides, from low residual levels to recommended dosages of application; variable modalities of exposure with different modalities of entry into the plant; variable dynamics of herbicide interaction, from chronic and residual impact to acute exposure; variable combinations of various herbicides or of various herbicide derivatives with other types of organic xenobiotics.

4. Consequences for herbicide use strategies, environmental risk assessment and global impact analysis

4.1. Implications of herbicide-related signaling for herbicide use and development

As described in Section 3, herbicide-related signaling studies have revealed that herbicides can affect plants through parallel biochemical and signaling pathways (Couée et al., 2013). This may be highly relevant for the development of novel herbicide molecules, which should be designed to target both biochemical processes and signaling processes in order to cause plant injury while dampening the induction of defence mechanisms, or for the development of chemical synergists designed to repress the induction of resistance-related enzymes (Yu and Powles, 2014). Herbicide-related signaling also provides a plant-centered mechanistic explanation for well documented cases of environmental variability of herbicide treatment efficiency, such as in the case of light- and temperature-dependent failures (Godar et al., 2015; Sharkhuu et al., 2014). Conversely, the molecular analysis of herbicide-related signaling interactions is useful to unravel unsuspected relationships between herbicide treatments and nutritional, hormonal or stress-response processes. For instance, several herbicide-related signaling pathways that are revealed by mutant analysis (Table 1) overlap with signaling pathways of responses to non-xenobiotic environmental stimuli such as biotic stress (Fode et al., 2008), nitrogen nutrition (Zhang et al., 2008), temperature stress (Köster et al., 2012), or light conditions (Sanchez-Villarreal et al., 2013).

Such knowledge could be directly useful to improve adjustment of herbicide treatments to fluctuating environmental conditions or to novel environmental conditions that are imposed by global change (Lobell and Field, 2007). Table 1 shows that many plant regulation pathways (ethylene, jasmonate, cytokinins, salicylate, brassinosteroids, auxins, sucrose, soluble sugars, pathogen-related signals) interact with herbicide action (Cui et al., 2010; Fode et al., 2008; Kerchev et al., 2015; Zhou et al., 2015). Herbicide treatments and plant regulator/elicitor treatments could therefore be combined to optimize the protocols of herbicide applications under varying environmental conditions (Yu and Powles, 2014). Serra et al. (2013, 2015a) have also shown that residual levels of herbicides, herbicide metabolites and fungicides could have significant impacts on plants, whether positive or negative, through root exposure and through cumulative or interactive effects that involve signaling and gene expression processes. Residual levels of hydroxyatrazine, the atrazine derivative that is found in soils as a persistent organic pollutant, can induce protective mechanisms against the deleterious effects of atrazine (Fig. 1). Residual levels of glyphosate also induce important metabolite and transcript changes (Serra et al., 2013, 2015a) at concentrations (1–2 μM) that are much lower than the 230 μM (Orcaray et al., 2010) or 55 mM (Vivancos et al., 2011) treatments that lead to growth (Orcaray et al., 2010) or photosynthesis (Vivancos et al., 2011) arrest. Pre-treatment with the auxin-like herbicide 2,4-D induces protection against diclofop in the major global weed *Lolium rigidum* (Gaines et al., 2014). Such interactions between herbicides, herbicide residues and other pesticides and the impact of pesticide carryover levels on plants (Cui et al., 2010; Ding et al., 2014; Rong Tan et al., 2015) suggest that soil residual pesticides could be additional risk factors for crop injury or for weed control failure. Thus, in

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the long term and at least in certain agricultural contexts, background contaminating organic pollutants could be monitored for potential interactions with further herbicide treatments and the choice of herbicide treatment could take into account this information.

Among the diverse causes for weed control failure, there is an increasing worry concerning a worldwide trend towards emergence of single- or multiple-herbicide resistant weeds (Heap, 2016), thus jeopardising crop yields and global food security, and there are outstanding examples of rapid resistance evolution associated with cross resistance evolution, such as the case of the grass weed *Lolium rigidum* in Australia (Yu and Powles, 2014). Multiple herbicide resistance can evolve from accumulation of mutations that affect not only target-site, but also non-target-site genes (Délye et al., 2013; Liu et al., 2013). A great threat is specifically posed by the evolution of genes related to xenobiotic detoxification and stress tolerance responses, as increased detoxification directly affects herbicide levels in the cell (Délye, 2013; Yu and Powles, 2014), and as increased tolerance to common cell stress consequences, such as oxidative or membrane stress (Ozgur et al., 2014; Ramel et al., 2009a; Teixeira et al., 2007), can alleviate the impact of diverse classes of herbicides (Duhoux et al., 2015; Gaines et al., 2014). The involvement of master regulatory or signaling proteins that control the coordinated gene expression of cell stress, xenobiotic stress and xenobiotic detoxification responses (Ramel et al., 2012; Xiong et al., 2013) enhances the importance of such a threat. Independent studies (Fukudome et al., 2014; Ramel et al., 2012; Zwack et al., 2013) show that common regulatory proteins can be involved in the responses to herbicides (atrazine, chlorsulfuron, paraquat) of different classes and modes of action. Since adaptive evolution of weed populations is due to processes of selection pressure (Délye et al., 2013) and to situations that reduce plant mortality (Neve and Powles, 2005; Yu and Powles, 2014), it can be speculated that genes involved in cell stress and xenobiotic stress cross-tolerance can be under the selection pressure not only of recurrent applications of a given herbicide, but also of carry-over and accumulation of persistent herbicides, herbicide residues and other pesticides in agricultural soils (Cui et al., 2010; Zhang et al., 2016) or in field margins (Serra et al., 2013). Recurrent application of reduced herbicide rates and stress hardening of plants are known to enhance the risks of resistance evolution (Busi and Powles, 2009; Neve and Powles, 2005; Yu and Powles, 2014). Better knowledge of the cross interactions of herbicides and stress stimuli on plant defence and detoxification regulatory networks should be useful to obtain a better assessment of the risk of resistance emergence in a given agricultural context on the basis of its contamination by diverse classes of herbicides and xenobiotics and of its exposure to environmental change.

4.2. Involvement of herbicide-related signaling in the environmental impacts of herbicides

Extensive use of pesticides, with more than 500 different formulations (Arias-Estévez et al., 2008) and with a worldwide consumption in the range of 2.5 Tg per year (Wilson and Tisdell, 2001; Zhang et al., 2011), has resulted in widespread contamination with potential impact on environmental quality, human well-being and planetary sustainability (Arias-Estévez et al., 2008; Persson et al., 2013). Numerous studies, including exposure to radiolabelled compounds, have shown that residual levels of herbicides, which are widely found in plant tissues, in soils or in waters, can be readily transferred by uptake or consumption to a wide range of non-target organisms (Cui et al., 2010; Grundmann et al., 2011; Knapp et al., 2013; Simonich and Hites, 1995; Zhou et al., 2015). Moreover, food poisoning due to pesticide residues in crop products is a real threat to human health, especially in developing countries where rules and regulations of pesticide usage can be less stringent (Zhou et al., 2015).

The mechanisms of herbicide signaling that have been described in Sections 2 and 3 play major roles in the capacity of plants to tolerate herbicide stress (Kerchev et al., 2015; Ramel et al., 2007; Sulmon et al., 2004; Zhou et al., 2015). They also play major roles in the developmental and physiological effects that low levels of herbicides can exert on plants in the absence of significant or validated direct effects on the enzyme target and in the absence of toxic effects on growth and development (Li et al., 2015; Qian et al., 2014a; Serra et al., 2013, 2015a, 2015b). The exact nutrient conditions, especially those related to sucrose, that are used for internationally recognized protocols of toxicant testing (Organization for Economic Cooperation and Development, 2016) on eukaryotic photosynthetic organisms, whether algae or angiosperms, and the related results that have been used for environmental risk assessment, should therefore be reassessed in the light of the strong protective effects of sucrose against oxidative and xenobiotic stress (Couée et al., 2006; Ramel et al., 2007). Moreover, metabolic and molecular studies demonstrate that, even in the absence of conspicuous developmental or physiological effects, and therefore at much lower concentrations than those required for toxicity, herbicides or herbicide derivatives can cause significant modifications affecting key metabolites or key proteins that are involved in growth, cell homeostasis, stress defence, or biotic interactions (Li et al., 2015; Serra et al., 2013, 2015a, 2015b). For example, environmentally-observed soil residual levels of glyphosate (1.8 μM), AMPA (2.7 μM) or hydroxyatrazine (760 nM) activate the transcription of the gene encoding ABA degrading enzyme ABA 8′-hydroxylase (Serra et al., 2013), whose activity controls ABA levels and tolerance to drought and salinity stress (Horn et al., 2013). Finally, the effects of safener and chemical primer treatments (Borges et al., 2014; Riechers et al., 2010; Savvides et al., 2015) demonstrate that xenobiotic signaling effects can be effective in the field and in the environment.

This entails that risk assessment of the impact of residual herbicide levels on non-target plants should take into account not only actual injury or damage, but also the potential consequences of variations of central metabolic, developmental and functional markers, such as ABA, ascorbate or soluble sugars, which are important for abiotic and biotic stress defence (Couée et al., 2006). Finally, the demonstration that the transduction systems of plants can integrate several herbicide-related signals (Serra et al., 2013) highlights the necessity to consider global impacts of complex herbicide and xenobiotic mixtures that exist *in natura*, rather than chemical-by-chemical approaches that cannot detect cumulative or interactive effects. The separate effects of residual levels of AMPA and hydroxyatrazine on ABA degradation regulation could thus be related to the impact of combined hydroxyatrazine and AMPA on root growth (Serra et al., 2013).

Better insight into the signaling processes associated with herbicides should improve mathematical models predicting the joint effect of interacting mixtures of herbicide contaminants. The frequently-used concentration addition model, or toxic units approach, adds the toxicities of individual and similar molecules acting through the same mode of action (Loewe and Muischnek, 1926), whereas the independent action model (Bliss, 1939) takes into account the toxicities of molecules acting on independent targets. These models, which focus on "no-interaction" scenarios, overlook interactive effects where the toxicity of mixtures is not equal to the sum of single toxicities. There may be synergism or antagonism, especially in relation with signaling interactions (Serra et al., 2013, 2015a, 2015b). In order to take into account complex interactions, computational toxicology develops novel approaches taking into account molecular descriptors and computational techniques (Kim et al., 2013). However, these approaches do not readily estimate the specific involvement of all possible parameters in the resulting risk assessment. Moreover as described by Isensee et al. (1998), variation of pollutant combination influences the availability of toxic molecules and interactions with the plant compartment. Toxicant mixtures in natural environments are complex, and the quality and quantity of toxicants greatly vary under fluctuating physico-chemical conditions. The evaluation of all the necessary parameters to predict the toxicity of residual pollutions in natural environments is thus a real challenge. Detailed knowledge of biological mechanisms, under single or multiple pollution conditions, is therefore necessary to improve

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assessment and predicting tools in order to estimate environmental risks associated with residual contaminations.

This kind of risk assessment taking into account signaling processes and potential consequences of molecular modifications should be particularly important for assessing plant community dynamics under the constraints of global change and its associated conditions of abiotic and biotic stresses. It thus seems that, under certain types of conditions, low subtoxic or non-toxic levels of herbicides, of herbicide metabolites, or of other pesticides can also promote mechanisms of growth (Belz and Duke, 2014; Serra et al., 2015a; Velini et al., 2008) or stress defence (Serra et al., 2013, 2015a; Stamm et al., 2014) that could be adaptive for additional conditions of stress, such as drought or oxidative stress, and provide a mechanism of chemical priming against abiotic stress (Savvides et al., 2015). Conversely, Zhou et al. (2015) have suggested that knowledge on interactions between herbicide and endogenous signaling pathways in plants (as described in Fig. 2) could be important to develop novel methods of crop or crop product treatments, for instance with phytohormones, that would induce detoxification of toxic herbicide residues in plant tissues prior to harvest or during postharvest conservation.

4.3. Importance of herbicide-related signaling in the framework of planetary boundary threats

Global chemical pollution has been included in the conceptual framework of planetary boundaries which arguably aims to define the safe operating space for human societies to develop and thrive within a changing environment (Steffen et al., 2015). In this framework, introduction of novel chemical entities is considered of concern at the global level whenever these chemicals show persistence, mobility across scales, and potential impacts on Earth system processes (Steffen et al., 2015). This could potentially be the case for herbicides and their derivatives, which can be persistent in environmental compartments and the cause of widespread diffuse pollution (Arias-Estévez et al., 2008; Destandau et al., 2013). However, identification of chemicals or mixtures of chemicals that pose a real threat to a vital Earth system process is hampered by the possibility of cryptic effects where disruption may not be discovered until it occurs on a planetary scale (MacLeod et al., 2014; Persson et al., 2013). The biochemical, physiological, and developmental impacts of low levels of herbicides and their derivatives, the interactive effects of low levels of mixtures of herbicides and their derivatives, and the involvement of signaling processes that can convert signaling levels of a given chemical into a physiological or developmental reorientation of the plant suggest that diffuse levels of herbicide pollution could cause complex cascading effects on ecosystem functioning that are difficult to predict. This difficulty is compounded by the impact of other contaminating xenobiotics, especially other agriculture-related xenobiotics, on plant communities (Bártíková et al., 2016; Carter et al., 2015; Ford et al., 2010) and by interactions between the effects of herbicides with those of other pollutants (Serra et al., 2013, 2015a).

Signaling effects of herbicides or their derivatives can affect biochemical traits (carbon and nitrogen metabolites, sulfur metabolites, stress defence metabolites, secondary metabolites) and growth traits (root growth rate, lateral root formation, leaf elongation) that can have considerable impact on plant-rhizosphere-soil interactions (Philippot and Hallin, 2011), plant-phyllosphere-atmosphere interactions (Bringel and Couée, 2015) or plant-herbivory interactions (Hervé et al., 2014; Savary-Auzeloux et al., 2003). These effects can occur on plant species of outstanding ecosystemic importance, such as perennial ryegrass (Serra et al., 2015a), a major component of grazed pastures and grasslands that cover over 40% of Earth's land surface area (Barbehenn et al., 2004), or rice (Zhou et al., 2015), with a global harvested area of 14% of Earth's arable land (Philippot and Hallin, 2011). The effects of residual levels of herbicides and herbicide derivatives on soluble sugars, starch, carbon metabolism and root functioning (Ding et al., 2014; Serra et al., 2013, 2015a) suggest potential perturbations of carbon allocation in the plant, and could lead, at the global scale of grasslands, to potential perturbations of carbon sequestration and of plant-rhizosphere relationships. Effects on the balance between soluble sugars and N-rich (asparagine) or S-rich (methionine) amino acids (Serra et al., 2013, 2015a) could have cascading effects leading to enhanced plant-associated production of CH_4 and N_2O greenhouse gases and hamper processes of climate change mitigation (Lenhart et al., 2015; Philippot and Hallin, 2011). Moreover, the quantitative importance of the changes affecting N-rich asparagine and photorespiratory amino acids induced by low levels of herbicides and herbicide derivatives (Serra et al., 2015a) could reflect perturbations of N nutrition (Bloom, 2015) and of the N sink role of the plant (Homyak et al., 2016), which in turn could affect NO and N_2O emissions (Homyak et al., 2016). Increase of asparagine levels (up to 6-fold) as occurs under conditions of subtoxic herbicide contamination (Serra et al., 2015a) could also contribute to enhanced susceptibility to plant viruses in relation with infection-related ammonium toxicity (Fernández-Calvino et al., 2016). Finally, herbicide-induced changes in phagostimulating metabolites (sucrose, serine, alanine) and in essential branched-chain amino acids (Qian et al., 2015b; Serra et al., 2013, 2015a, 2015b) could affect feeding stimulation of insects (Hervé et al., 2014) or nitrogen quality of forage for livestock and wild animals (Savary-Auzeloux et al., 2003).

Herbicide signaling effects could thus contribute to global change and perturbations of community and ecosystem dynamics, but further work is required to investigate thoroughly these community- and ecosystem-level relationships. Moreover, signaling or physiological relationships between herbicide responses, abiotic stresses and biotic stresses (Baena-González et al., 2007; Cortleven et al., 2014; Goossens et al., 2010; Ramel et al., 2007) indicate that impact of global change stressors on plant communities under conditions of diffuse herbicide contamination is difficult to predict and requires dedicated studies (Laliberté and Tylianakis, 2012). Paradoxically, signaling pathways involved in chemical priming against multiple abiotic stresses (Borges et al., 2014; Savvides et al., 2015) largely overlap with signaling pathways activated by low levels of herbicides or herbicide derivatives. Priming with chemical donors of reactive oxygen or nitrogen species (Savvides et al., 2015) activates oxidative stress response pathways as also occurs with hydroxyatrazine or low levels of glyphosate (Serra et al., 2013, 2015b), and diverse cases of abiotic stress hardening after pre-treatment with low subtoxic levels of herbicides or pesticides have been described (Ford et al., 2010; Stamm et al., 2014). Further studies are therefore needed to determine whether the effects of global herbicide-related pollution on plants contribute to global change acceleration (MacLeod et al., 2014), hamper processes of global change mitigation (Philippot and Hallin, 2011), or paradoxically constitute a bulwark against some deleterious effects of global change-related stresses on plant communities (Savvides et al., 2015).

Conflict of interest

The authors do not have any commercial or financial conflict of interest regarding the present article.

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