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RES transformation for biosynthesis and detoxification

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The reactive electrophilic species (RES), typically the molecules bearing α,β-unsaturated carbonyl group, are widespread in living organisms and notoriously known for their damaging effects. Many of the mycotoxins released from phytopathogenic fungi are RES and their contamination to cereals threatens food safety worldwide. However, due to their high reactivity, RES are also used by host organisms to synthesize specific metabolites. The evolutionary conserved glyoxalase (GLX) system scavenges the cytotoxic α-oxoaldehydes that bear RES groups, which cause host disorders and diseases. In cotton, a specialized enzyme derived from glyoxalase I (GLXI) through gene duplications and named as specialized GLXI (SPG), acts as a distinct type of aromatase in the gossypol pathway to transform the RES intermediates into the phenolic products. In this review, we briefly introduce the research progress in understanding the RES, especially the RES-type mycotoxins, the GLX system and SPG, and discuss their application potential in detoxification and synthetic biology.

reactive electrophilic species, glyoxalase, gossypol, mycotoxin, detoxification, aromatase

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Introduction

Plants are frequently exposed to endogenous and exogenous toxins such as the by-products of primary metabolism, the specialized metabolites derived from the surrounding organisms, and the chemicals of industrial or other origins. The sedentary and autotrophic plants rely heavily on biochemical mechanisms of defense and, consequently, have evolved diverse and elaborate detoxification systems for survival under adverse environmental conditions (Riechers et al., 2010). Detoxification pathways often involve transformation of the active groups present in the toxins for coping with their detrimental impacts on cells, a feature that is particularly evident in the case of metabolic removal of reactive electrophilic species (RES).

Plants are able to detoxify RES by complex processes that exhibit myriad diversities among species. On the other hand, plants also utilize the highly reactive RES to synthesize

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various types of specialized metabolites (Huang et al., 2020; Luo et al., 2016; Zhou et al., 2016). Furthermore, the defensive compounds produced by plants (phytoalexins) are frequently RES (Figure 1), such as cucurbitacins produced by plants of the Cucurbitaceae family (Shang et al., 2014) and cinerins synthesized in *Tanacetum cinerariifolium* (Li et al., 2019). Much attention has been paid to cleaning up RES toxins from the environments through various approaches, yet less has been achieved in applying plant enzymes to transform RES toxins, despite that the great complexity in plant specialized metabolic pathways offers a variety of unusual catalytic functions (Weng et al., 2012). Here, we introduce the GLX system and a distinct aromatase specialized from a conserved RES scavenging enzyme in cotton plants. The detoxification enzymes are a treasure of further investigation and hold great application potential.

RES and the glyoxalase system

Compounds containing α,β-unsaturated carbonyl, referred to as RES (Figure 1), are inevitably produced during cellular metabolism in all domains of life, ranging from archaea and bacteria to eukaryotes (Farmer and Davoine, 2007). The high reactivity of RES lies in the ability of the α,β-unsaturated bond which forms Michael adducts with thiol and amino groups in biomolecules. Several endogenous RES including certain signaling molecules are reported, among which glyoxal (GO) and methylglyoxal (MGO) are cytotoxic and generated as by-products of glycolysis (Lee and Park, 2017). These acyclic α-oxoaldehydes contain two adjacent carbonyl groups and are therefore exceptionally reactive in attacking proteins and nucleotides, resulting in the formation of a variety of adducts and crosslinks collectively named advanced glycation or lipoxidation end products (Aldini et al., 2013). Therefore, their levels must be timely controlled in healthy cells and the detoxification reactions are of vital importance.

The glyoxalase (GLX) system (Figure 2), discovered over 100 years ago, is a conserved preemption pathway for detoxification of the α-oxoaldehydes, particularly MGO, which involves two consecutive reactions catalyzed by glyoxalase I (GLXI) and glyoxalase II (GLXII), respectively (Racker, 1951; Thornalley, 1990). First, in the presence of glutathione (GSH), the MGO-GSH adduct hemithioacetal is formed spontaneously, and the GLXI catalyzes its isomerization to *S*-D-lactoylglutathione (Sankaranarayanan et al., 2017). Then the GLXII splits the thiolester into D-lactate and GSH for recycling. GLXI is a divalent metal ion-dependent isomerase and categorized into two classes: the Ni^{2+}-/Co^{2+}-dependent and the Zn^{2+} dependent, and the catalytic mechanism of GLXI has been elucidated in detail (Cameron et al., 1999; Thornalley, 2003). In animals, glyoxalases play a protective role against diabetes, cancer, anxiety, obesity and other age-related disorders (Hovatta et al., 2005; Kuhla et al., 2006; Lv et al., 2018; Rabbani and Thornalley, 2014; Scheckhuber et al., 2010). In plants, numerous studies have demonstrated the role of glyoxalases in conferring tolerance to multiple stresses and in fertility control through reducing the MGO level (Alvarez Viveros et al., 2013; Sankaranarayanan et al., 2017; Sankaranarayanan et al., 2015).

A specific aromatization pathway derived from GLX system

Although detoxification enzymes can be rather flexible in catalysis, to date little is known about the latent activities of GLXI beyond isomerization of the thiolesters. Recently, we discovered that, in cotton, a specialized GLXI variant (SPG) has evolved into a distinct aromatase in synthesizing phenolic compounds (Huang et al., 2020). Gossypol and related sesquiterpene phenolics in cotton plants function as phytoalexins in defense against diverse herbivores and pathogens, but their wide presence in cotton tissues diminishes or complicates the use of cottonseed products as feedstuff and edible oil (Tian et al., 2016a). Gossypol is a dimer of hemigossypol which harbors a naphthalene core (fused pair of benzene rings). In the gossypol biosynthetic pathway (Figure 3), several enzymatic oxidation steps act sequentially on the bicyclic sesquiterpene(+)-δ-cadinene to form the RES compounds, which serve as intermediates for further modifications (Tian et al., 2018). Although the levels of these RES in plants are low under normal physiological conditions, repression of specific downstream enzymes by virus induced gene silencing (VIGS) led to accumulation of the RES intermediates, among which 8-hydroxy7-keto-δ-cadinene was particularly toxic and severely distorted the plant response to pathogen infection (Tian et al., 2019).

Plants of the cotton lineage have evolved highly active enzymes to prevent the accumulation of cytotoxic RES during gossypol biosynthesis. SPG could efficiently transforms 8,11-dihydroxy7-keto-δ-cadinene and 3-hydroxy-furocalamen-2-one to furocalamen and deoxyhemigossypol, respectively, through aromatization (Figure 3). The two substrates bear reactive α-hydroxy carbonyls in B and A rings, respectively, and SPG is responsible for aromatization of both.

In the GLXI system MGO reacts with GSH non-enzymatically to form the α-hydroxy carbonyl before the GLXI-mediated isomerization. In contrast, in the gossypol pathway the reactive carbonyl groups are installed enzymatically by successive hydroxylation and dehydrogenation steps independent of GSH. In accordance, during specialization SPG has lost the GSH binding motif which, combined with other amino acid substitutions, reshaped the

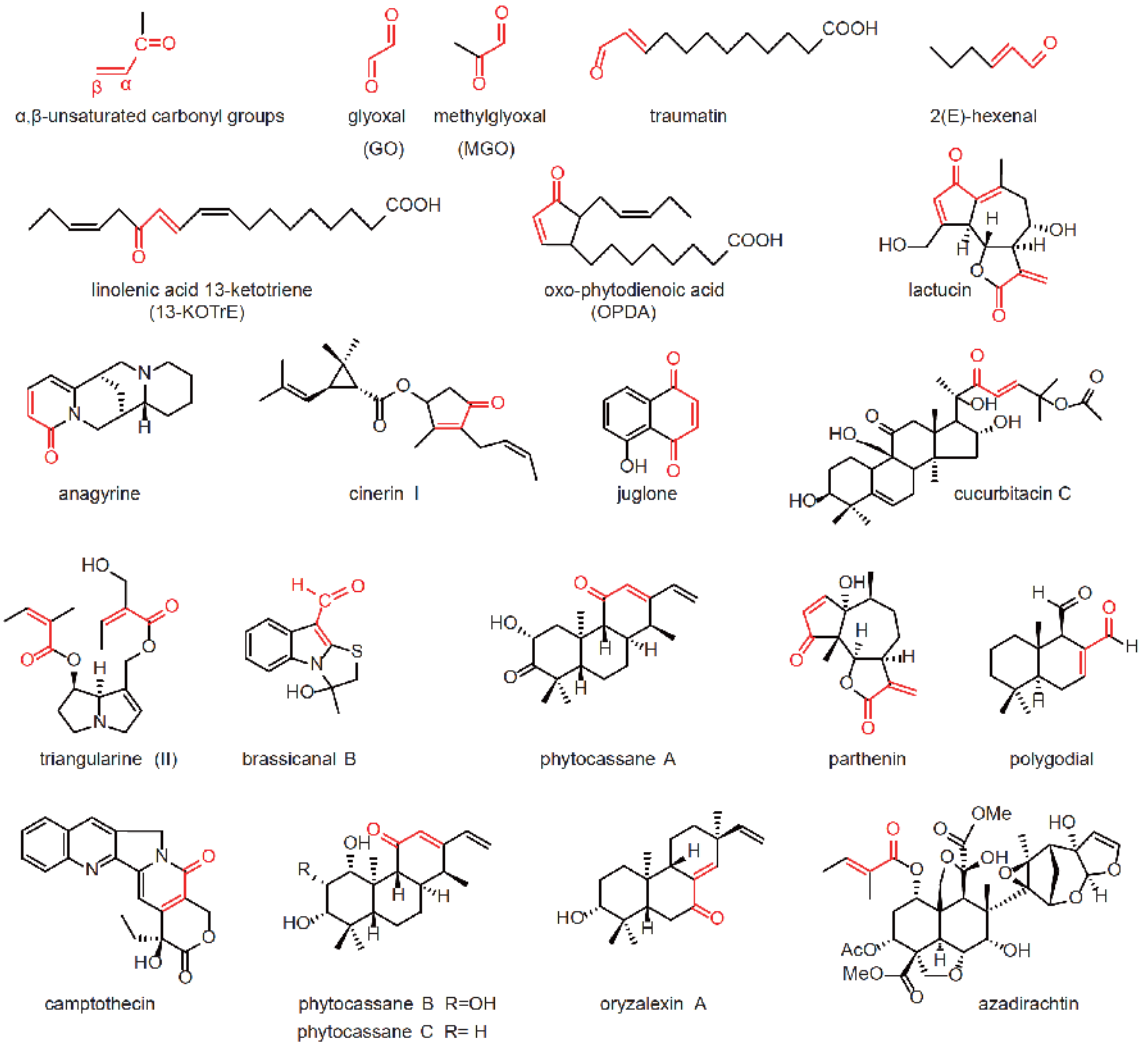

Figure 1 (Color online) Examples of naturally occurring RES. Electrophilic regions comprising α,β-unsaturated carbonyl groups are indicated in red.

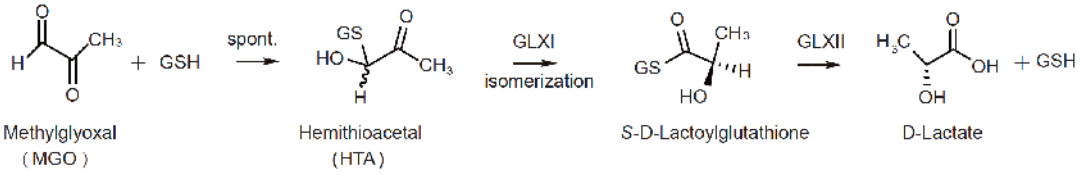

Figure 2 Detoxification of MGO by the glyoxalase system. GLXI catalyzes the isomerization of the MGO-GSH adduct hemithioacetal (HTA) to *S*-D-lactoylglutathione, followed by conversion to non-toxic acid catalyzed by GLXII.

catalytic pocket for recognizing cyclic substrates (Huang et al., 2020).

Application potentials in toxin transformation

Toxins present in the environments and particularly in crops cause serious health concerns worldwide (Xia et al., 2019). Fungi living on plants may release metabolites during infection and growth, including mycotoxins that are toxic to humans and animals. It was estimated that around 300 to 400 fungal metabolites are recorded as mycotoxins (Hussein and Brasel, 2001), many of which are chemically stable and their residuals survive product processing. Based on the surveys over an 8-year period (January 2004 to December 2011), contaminants of the major types of mycotoxins could be found in over 70% of the samples tested (Streit et al., 2013). Clearly, fungal diseases not only reduce crop yield but also undermine the product quality and food safety. Chemical and physical treatments have been widely used to degrade or remove hazardous chemicals and toxins; however, biotransformation approaches are generally more target-specific

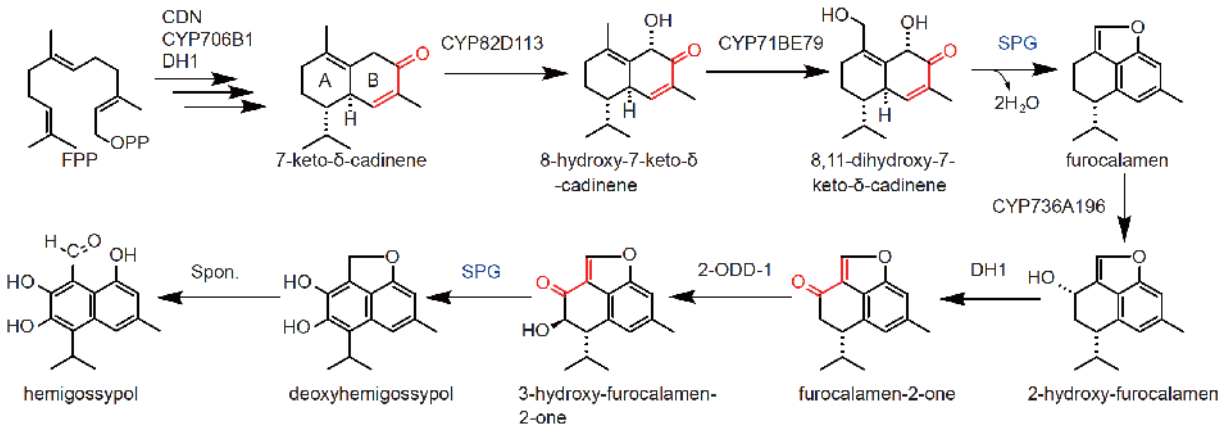

Figure 3 (Color online) SPG catalyzes the aromatization of both A and B rings in the gossypol biosynthetic pathway (Huang et al., 2020; Tian et al., 2018). Electrophilic α,β-unsaturated carbonyl groups are indicated in red.

and eco-friendly.

Plants contain a plethora of enzymes that metabolize RES to alleviate or eliminate their toxicity. Besides the GLX system, various RES-detoxifying enzymes have been identified, including cytochrome P450s, aldo-keto reductases (AKRs), alkenal/alkenone reductases (AORs), and small chain dehydrogenases/reductases (SDRs) (Dick et al., 2001; Kolb et al., 1994; Mano et al., 2005; Simpson et al., 2009; Yamauchi et al., 2011). Compared to the primary metabolic enzymes which usually have a high level of substrate stringency, detoxification enzymes generally show relaxed substrate recognition thus offer a rich repertoire for exploring new catalytic activities (Huang et al., 2020).

The toxicity of RES mainly derives from their ability to react with the nucleophilic atoms in proteins or DNA, and a large portion of toxins produced by fungi and bacteria are RES. Type B trichothecenes, which have a characteristic keto group at C-8 in their chemical structures, are the frequently detected mycotoxins contaminating cereal grains (Arunachalam and Doohan, 2013). Deoxynivalenol (DON), 3-acetyldeoxynivalenol (3A-DON) and 15-acetyldeoxynivalenol (15A-DON) are the most common and devastating type B trichothecenes produced by the phytopathogenic *Fusarium graminearum* and *F. culmorum* (McCormick et al., 2011; Richard, 2007; Tian et al., 2016b). The *Fusarium* species infect crops in the field, including the staple food crops of wheat, maize and rice, reducing the yield of cereal grains and causing destructive loses to farmers. Worse still, the DON toxin contamination in cereals poses an important threat to the global food safety. Because SPG exhibits certain promiscuity towards substrates as it efficiently catalyzes the aromatization of both 8,11-dihydroxy-7-keto-δ-cadinene and 3-hydroxy-furocalamen-2-one, we wondered that it may recognize other cyclic RES compounds. Indeed, *in vitro* SPG could transform 3A-DON into a less active metabolite, plus an unstable compound. Thus, as a standalone enzyme catalyzing complex reactions on RES, SPG provides a promising active site for mycotoxin bio-detoxification (Huang et al., 2020).

In addition to DON, fungi synthesize a tremendous number of RES-type compounds, as shown in Figure 4, which have a multitude of functions and are produced mainly by three genera: *Aspergillus*, *Penicillium* and *Fusarium* (Ben Taheur et al., 2019; Kang et al., 2017; Li et al., 2020). Of these specialized metabolites penicillic acid, moniliformin, DON and their structurally related compounds also bear a hydroxy group next to the reactive carbonyl moiety, as the two gossypol pathway intermediates do. It would be of great interest to see if SPG and the GLX system can be developed into molecular tools to degrade these fungal toxins.

Perspectives

Very recently the World Economic Forum proposed a plan to develop synthetic biology approach for bioproduction, remediation and pollution control, aiming at transformation of waste into value-added molecules or energy (de Lorenzo et al., 2018). Our finding tells that plants had invented this strategy long before human intelligence: modification of a scavenger to synthesize powerful defense compounds. The specialization process of SPG presents a textbook example of enzyme evolution: following the whole genome or large fragment duplication and subsequent local amplifications, the newborn copies undergo functional innovation starting from the catalytic promiscuity of the parental protein, along with trimming off the unnecessary domains (Huang et al., 2020; Peng et al., 2020; Wang et al., 2016).

The α,β-unsaturated carbonyl moiety is frequently encountered in intermediates of certain biosynthetic pathways, likely due to its high reactivity. Meanwhile, some of the endogenous signaling molecules are RES, such as the jasmonate biosynthesis intermediate 12-oxo-phytodienoic acid (OPDA) which itself functions in adjusting plant defense

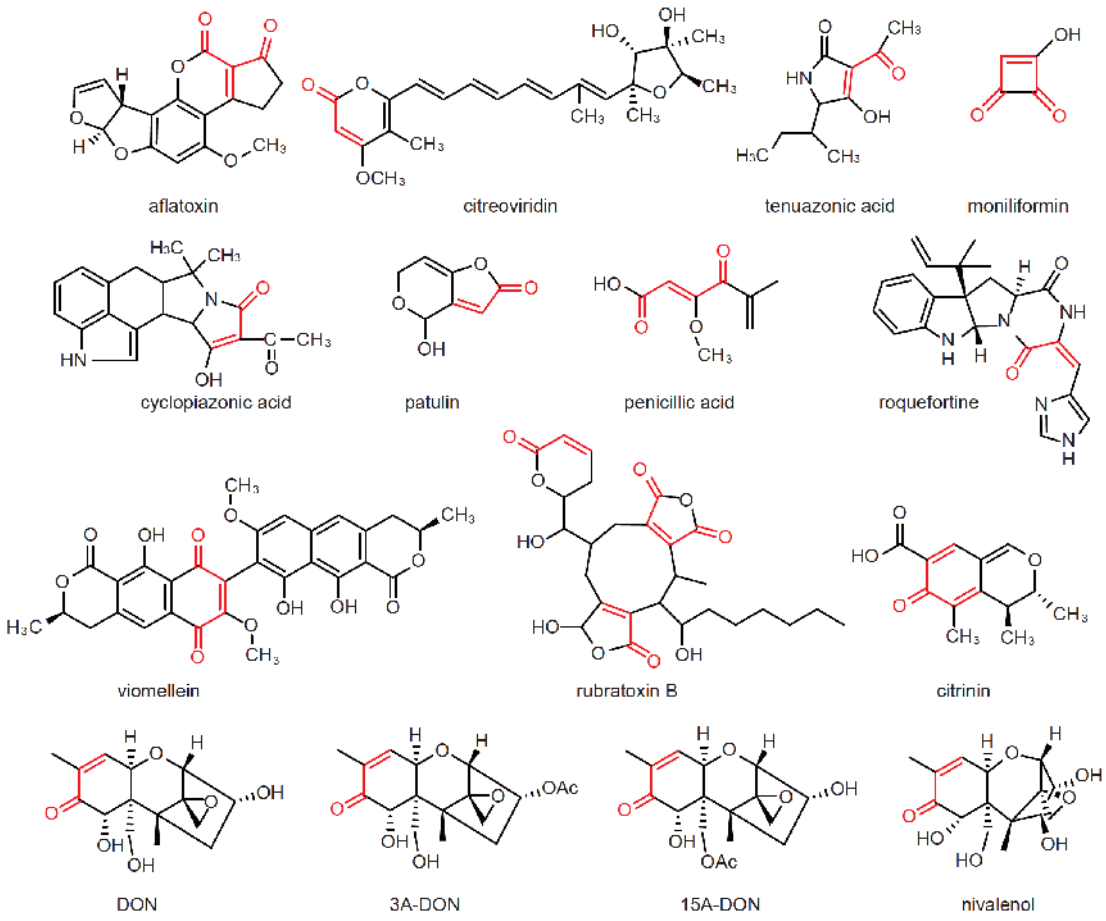

Figure 4 (Color online) Chemical structures of common mycotoxins harboring the α,β-unsaturated carbonyl groups. The mycotoxins are found in but not necessarily restricted to the following fungal genera: aflatoxin and cyclopiazonic acid in *Aspergillus*, tenuazonic acid in *Alternaria*, citreoviridin, citrinin, patulin, penicillic acid, roquefortine, rubratoxin B and viomellein in *Penicillium*, deoxynivalenol (DON), 3A-DON, 15A-DON, nivalenol and moniliformin in *Fusarium*.

(Dave and Graham, 2012; Taki et al., 2005). Given the enormous diversity in chemical space, we expect that more enzymes acting on RES will be identified in the future. Further investigations, including the exhaustive mutagenesis of the active sites and utilization of multi-reaction processes, will help develop green approaches to remove the troublesome RES or transform them into valuable products.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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