# Chapter 6
# Polyamine Catabolism in Plants

**Tomonobu Kusano, Dong Wook Kim, Taibo Liu, and Thomas Berberich**

**Abstract** The copper-dependent amine oxidases (CuAOs) and flavin-containing polyamine oxidases (PAOs) are involved in polyamine (PA) catabolic processes. Studies on plant CuAOs are still incomplete, whereas research on plant PAOs has advanced significantly in the past decade. The maize PAO, the best studied plant PAO, and the barley PAOs were shown to catalyze PAs in a terminal catabolic pathway. Therefore, plant PAOs were assumed to have terminal catabolic activity, which differs from the back-conversion activity of mammalian PAOs. However, plant PAOs that have back-conversion activity are now reported. Here, studies on PAOs from the two model species *Arabidopsis thaliana* and *Oryza sativa* are compiled, and research on CuAOs is updated. Our current understanding of the roles of PAOs and CuAOs in plant development and defense responses is described.

**Keywords** *Arabidopsis thaliana*, back-conversion pathway • Copper-dependent amine oxidase • *Oryza sativa*, plant, polyamine oxidase • Terminal catabolism pathway

## 6.1 Introduction

Polyamines (PAs) are involved in growth, development, and adaptation against various environmental changes in plants (Kusano et al. 2008; Alcázar et al. 2010; Bassard et al. 2010; Handa and Mattoo 2010; Mattoo et al. 2010; Takano et al. 2012). Major plant PAs are the diamines putrescine (Put) and cadaverine (Cad, abundant in legumes), the triamine spermidine (Spd), and the tetraamines spermine (Spm) and thermospermine (T-Spm). Cellular PA levels are regulated with a

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dynamic equilibrium between biosynthesis and catabolism. PA catabolism is catalyzed by two classes of amine oxidases: the copper-containing amine oxidases (CuAOs) and the polyamine oxidases (PAOs). CuAOs (EC 1.4.3.6) are dimers of identical 70- to 90-kDa subunits, and each subunit contains a single copper ion and a 2,4,5-trihydroxyphenylalanine quinone (TPQ) cofactor (Medda et al. 1995b; Dawkes and Phillips 2001). Crystal structures have been solved for amine oxidases from *Escherichia coli* and pea seedlings (Møller and McPherson 1998). By contrast, PAOs (EC 1.5.3.11) are monomeric enzymes and contain a noncovalently bound flavin adenine dinucleotide (FAD) as a cofactor. The first characterized apoplastic maize PAO and barley PAOs oxidize PAs in a terminal catabolic pathway. The recently characterized *Arabidopsis* and rice PAOs oxidize PAs in an alternative pathway, the back-conversion pathway. The most updated information on plant CuAOs and PAOs is provided in this chapter. Specific reviews on plant PAOs are available (Cona et al. 2006; Angelini et al. 2010; Wimalasekera et al. 2011a; Moschou et al. 2012).

## 6.2 PAOs

### *6.2.1 Terminal Catabolic Pathway and Back-Conversion Pathway*

The PA catabolic pathway has been well studied in mammals. Spd/Spm $N^1$-acetyltransferase (SSAT; EC 2.3.1.57; Casero and Pegg 1993) modifies Spd and Spm before PAO action. This acetylation process is a rate-limiting step in the catabolic pathway (Wallace et al. 2003). A mammalian PAO oxidizes $N^1$-acetyl Spm and $N^1$-acetyl Spd at the carbon on the *exo*-side of the $N^4$-nitrogen to produce Spd and Put, respectively (Vujcic et al. 2002; Wu et al. 2003; Cona et al. 2006). Mammalian Spm oxidases (SMOs) and the yeast orthologue (encoded by *Fms1*) oxidize Spm at the carbon on the *exo*-side of the $N^4$-nitrogen to produce Spd, 3-aminopropanal, and $H_2O_2$ without acetyl modification (Wang et al. 2001; Vujcic et al. 2002; Cervelli et al. 2003); thus, mammalian PAOs and SMOs catalyze back-conversion reactions. The molecular evolution of the *PAO* and *SMO* genes has been discussed recently (Polticelli et al. 2012).

In plants, the first characterized maize and barley PAOs catalyze terminal catabolic reactions (Fig. 6.1) (Federico et al. 1990, 1996; Tavladoraki et al. 1998; Radova et al. 2001; Cervelli et al. 2001, 2004, 2006). This type of PAO oxidizes the carbon at the *endo* side of the $N^4$-nitrogen of Spm and Spd, producing *N*-(3-aminopropyl)-4-aminobutanal and 4-aminobutanal, respectively, as well as 1,3-diaminopropane and $H_2O_2$ in both reactions (Cona et al. 2006; Angelini et al. 2010). In 2006, Tavladoraki et al. reported that plants have a back-conversion type of PAO (Fig. 6.1). They showed that *Arabidopsis* AtPAO1 produces Spd from Spm and norspermidine from norspermine (Norspm). AtPAO1 is the first plant PAO known to catalyze a PA back-conversion reaction. The current consensus indicates that plants have two types of PAOs: one catalyzes a terminal catabolic reaction whereas the other catalyzes a PA back-conversion reaction.

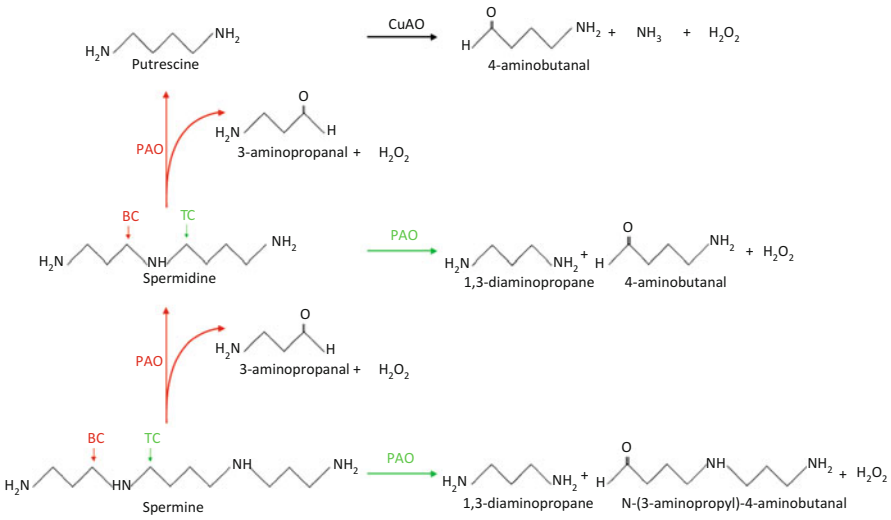


**Fig. 6.1** Schematic drawing of the polyamines (PA) catabolic pathways in plants. Diamine Put is converted to 4-aminobutanal along with ammonia and hydrogen peroxide ($H_2O_2$) by a reaction catalyzed by CuAO. On the other hand, triamine Spd and tetraamines, Spm and T-Spm, are catabolized by two alternative pathways: one is a terminal catabolism (*TC*) pathway (marked by *green arrows*) and the other is a back-conversion (*BC*) pathway (marked by *red arrows*). The positions of carbon oxidized by TC- and BC-type PAOs are also indicated with short *green* and *red arrows*, respectively

In the next sections, the characterization of PAOs in two model plants, *Arabidopsis thaliana* and *Oryza sativa*, is summarized.

### 6.2.2 *PAOs in* Arabidopsis thaliana

In *A. thaliana*, five *PAO* genes have been identified, which are named *AtPAO1* to *AtPAO5*. To date, four of the gene products, namely AtPAO1 to AtPAO4, have been biochemically characterized (Tavladoraki et al. 2006; Moschou et al. 2008, 2012; Kamada-Nobusada et al. 2008; Takahashi et al. 2010; Fincato et al. 2011, 2012). AtPAO1 localizes in the cytoplasm and oxidizes Spm, T-Spm, and Norspm, but not Spd, in a back-conversion reaction (Tavladoraki et al. 2006). AtPAO2, AtPAO3, and AtPAO4 localize in peroxisomes (Moschou et al. 2008; Kamada-Nobusada et al. 2008). All the peroxisomal PAOs show PA back-conversion activity, although they differ in PA specificity (Moschou et al. 2008; Kamada-Nobusada et al. 2008; Takahashi et al. 2010; Fincato et al. 2011). AtPAO2 and AtPAO3 convert Spm to Put via Spd, whereas AtPAO4 produces less Put from Spm, which is explained with the very low $k_{cat}$ value for Spd (Fincato et al. 2011). AtPAO5 localizes in the cytoplasm (Fincato et al. 2011; DWK unpublished data). In *Arabidopsis*, two PAOs are in the cytoplasm and the remaining three PAOs localize in the peroxisome, indicating that no PAOs exist in the apoplastic space (Table 6.1). AtPAO5 shows PA back-conversion

**Table 6.1** Characteristics of PAOs and CuAOs in *Arabidopsis thaliana* and *Oryza sativa*

| Gene name | Accession no. | Gene ID | Mode of reaction | Substrate Specificity | Subcellular localization | References |
|---|---|---|---|---|---|---|
| *A. thaliana* | | | | | | |
| *AtPAO1* | NM_121373 | At5g13700 | BC | T-Spm, Spm | Cytoplasm | Tavladoraki et al. (2006), Takahashi et al. (2010), Fincato et al. (2011, 2012) |
| *AtPAO2* | AF364952 | At2g43020 | BC | Spd, Spm, T-Spm | Peroxisome | Kamada-Nobusada et al. (2008), Takahashi et al. (2010), Fincato et al. (2011, 2012) |
| *AtPAO3* | AY143905 | At3g59050 | BC | Spd, Spm, T-Spm | Peroxisome | Moschou et al. (2008), Takahashi et al. (2010), Fincato et al. (2011, 2012) |
| *AtPAO4* | AF364953 | At1g65840 | BC | Spm, T-Spm | Peroxisome | Kamada-Nobusada et al. (2008), Takahashi et al. (2010), Fincato et al. (2011) |
| *AtPAO5* | AK118203 | At4g29720 | BC | Spm, T-Spm | Cytoplasm | Fincato et al. (2012), Kim et al. (in preparation) |
| *O. sativa* | | | | | | |
| *OsPAO1* | NM_001050573 | Os01g0710200 | BC | Spm, T-Spm | Cytoplasm | Liu et al. (2014a) |
| *OsPAO2* | NM_001055782 | Os03g0193400 | n.d. | | n.d. | |
| *OsPAO3* | NM_001060458 | Os04g0623300 | BC | Spd, Spm, T-Spm | Peroxisome | Ono et al. (2012) |
| *OsPAO4* | NM_001060753 | Os04g0671200 | BC | Spm, T-Spm | Peroxisome | Ono et al. (2012) |
| *OsPAO5* | NM_001060754 | Os04g0671300 | BC | Spm, T-Spm | Peroxisome | Ono et al. (2012) |
| *OsPAO6* | NM_001069545 | Os09g0368200 | TC (?) | | n.d. | |
| *OsPAO7* | NM_001069546 | Os09g0368500 | TC | Spm, Spd | Apoplast | Liu et al. (2014b) |
| *A. thaliana* | | | | | | |
| *ATAO1* | NM_117580 | At4g14940 | TC | Put | Apoplast | Møller and McPherson (1998) |
| *AtCuAO1* | NM_104959 | At1g62810 | TC | Put, Spd | Apoplast | Wimalasekera et al. (2011b), Planas-Portell et al. (2013) |
| *AtCuAO2* | NM_102906 | At1g31710 | TC | Put, Spd | Peroxisome | Planas-Portell et al. (2013) |
| *AtCuAO3* | AY120717 | At2g42490 | TC | Put, Spd | Peroxisome | Planas-Portell et al. (2013) |

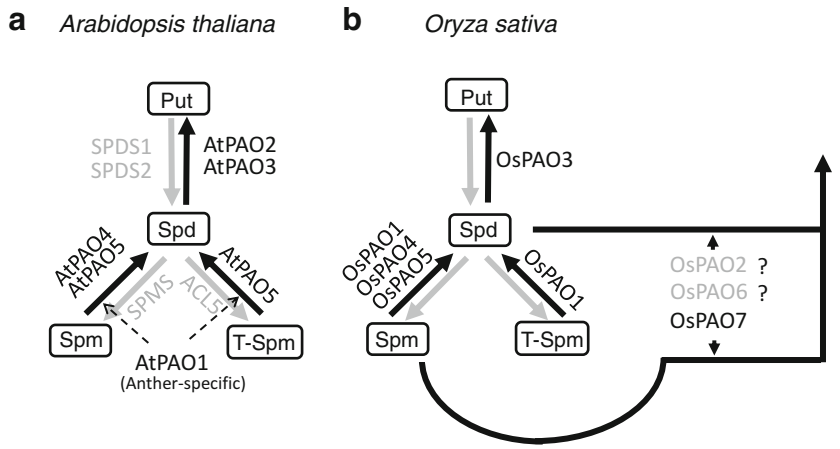


**Fig. 6.2** Main reactions catalyzed by PAOs in *Arabidopsis* and rice plants. **a** All five PAOs back-convert different PAs in *Arabidopsis thaliana*. **b** Four PAOs of seven back-convert different PAs, and two PAOs of the remaining three catabolize PAs by the terminal catabolic pathway

activity with a preference for Spm and T-Spm (DWK, unpublished data). Tavladoraki et al. (2006) reported that recombinant AtPAO1 produced very small amounts of 1,3-diaminopropane (DAP) during Spm oxidation, suggesting that this enzyme oxidizes Spm through a terminal catabolic pathway, although this activity is very low compared to that of its back-conversion activity. In summary, all *Arabidopsis* PAOs primarily catalyze back-conversion reactions (Table 6.1, Fig. 6.2a).

*Arabidopsis PAO*s exhibit distinct and organ-specific expression patterns. *AtPAO1* is expressed primarily in the root transition region between the apical meristem and the elongation zone, and it is also expressed in anthers. *AtPAO2* is expressed in the quiescent center, columella initials, and pollen, whereas *AtPAO3* is expressed in columella, guard cells, and pollen. *AtPAO4* is expressed in whole roots and all flower organs except petals, and *AtPAO5* is expressed in the vascular system of roots and hypocotyls (Takahashi et al. 2010; Fincato et al. 2012). Abscisic acid (ABA)-induced expression of *AtPAO1* in root tip and *AtPAO2* in guard cells has been reported (Fincato et al. 2012). These results suggest that each AtPAO has distinct physiological roles.

### *6.2.3 PAOs in* Oryza sativa

This monocotyledonous model plant harbors seven *PAO* genes, sequentially designated *OsPAO1* to *OsPAO7*. Three *PAO*s, namely, *OsPAO3*, *OsPAO4*, and *OsPAO5*, are expressed at higher levels both at the seedling stage and at the reproductive stage compared to those of the other four *OsPAO*s. The gene products contain peroxisomal-targeting signals in their carboxy-termini, and they localize in peroxisomes

(Table 6.1, Fig. 6.2b) (Ono et al. 2012). OsPAO3, OsPAO4, and OsPAO5 have PA back-conversion activity (Ono et al. 2012). Studies on *Arabidopsis* and rice PAOs suggest that, even in other plants, peroxisome-localized PAOs could be predicted to have back-conversion activity. *OsPAO1* lacks introns, similar to that of the *Arabidopsis AtPAO5*. *OsPAO1* expression is induced by treatment with tetraamine, Spm, or T-Spm. In *OsPAO1*-promoter *GFP*-transgenic rice plants, the initially observed GFP signal in the root transition region between the apical meristem and the elongation zone is expanded in the elongation zone by tetraamine treatment (Liu et al. 2014a). Consistent with the specific induction by tetraamines, recombinant OsPAO1 prefers tetraamines as substrate, and back-converts them to Spd, but not further to Put. This enzyme shows different pH optima, with pH 6.0 for T-Spm and pH 8.5 for Spm (Liu et al. 2014a). OsPAO1 localizes in the cytoplasm. The remaining three OsPAOs, namely, OsPAO2, OsPAO6, and OsPAO7, resemble each other, and show high identity to the maize ZmPAO and the barley HvPAO1 and HvPAO2, suggesting that they function in a terminal catabolic pathway. The recombinant OsPAO7 produces DAP from Spm and Spd, demonstrating that OsPAO7 is a terminal catabolic-type enzyme (Liu et al. 2014b). OsPAO7 is located in the peripheral boundary of the plant cell, possibly through its amino-terminal signal peptide and transmembrane sequence. *OsPAO7* is expressed in flower organs, especially anther walls and pollen, but not in pistils (Liu et al. 2014b). The peroxisomal *OsPAO* members *OsPAO3*, *OsPAO4*, and *OsPAO5* are also expressed in anthers (Liu et al. 2014b).

In *Oryza sativa*, four OsPAOs, namely, OsPAO1, OsPAO3, OsPAO4, and OsPAO5, function in a back-conversion pathway, whereas two OsPAOs, OsPAO7 and possibly OsPAO6, function in a terminal catabolic pathway. Because of the rather long truncation at its amino-terminal region, OsPAO2 may not be a functional enzyme. Even in *O. sativa*, the PA back-conversion pathway is a dominant route of PA catabolism. The terminal catabolic pathway may function in specific tissues and/or during specific developmental stages (Table 6.1, Fig. 6.2b) (Liu et al. 2014b). To explore the distinct roles of OsPAOs in various physiological processes, genetic approaches such as gene silencing by RNAi are required.

## 6.3 CuAOs

### *6.3.1 General Information on Plant CuAOs*

Molecular features, substrate specificities, inhibitors, stoichiometry of the catalyzed reaction, spectroscopic features, prosthetic groups, and reaction mechanisms of plant CuAOs have been reviewed previously (Medda et al. 1995a). CuAOs are homodimers in which each subunit, consisting of approximately 670–780 amino acids, contains a copper ion and a redox cofactor TPQ, generated by posttranslational autocatalytic modification from an active-site tyrosine residue (Møller and McPherson 1998; Dawkes and Phillips 2001). CuAOs have rather diverse sequences, and only approximately 30 amino acid residues are fully conserved (Tipping and

McPherson 1995; Møller and McPherson 1998; Planas-Portell et al. 2013). Of those residues, 3 conserved histidine residues may be the ligands for copper binding, and tyrosine at the 406 position is modified to TPQ in pea CuAO. Plant CuAOs generally catalyze the oxidation of the diamines Put and Cad at the primary amino group to give 4-aminobutylaldehyde and 5-aminopentylaldehyde, which spontaneously cyclize to $\Delta^1$-pyrroline and $\Delta^1$-piperideine, respectively, along with ammonia and $H_2O_2$ (Federico and Angelini 1991; Medda et al. 1995a).

### 6.3.2 *CuAOs in* Arabidopsis thaliana

Although *Arabidopsis* contains at least ten CuAO-like genes, only four genes have been biochemically characterized, including *AtAO1* (At4g14940), *AtCuAO1* (At1g62810), *AtCuAO2* (At1g31710), and *AtCuAO3* (At2g42490) (Table 6.1) (Møller and McPherson 1998; Planas-Portell et al. 2013). AtAO1 produced in insect Sf9 cells oxidizes Put but not Spd. *AtAO1* expression is observed in vascular tissue and root-cap cells, both of which are destined to undergo programmed cell death (Møller and McPherson 1998). AtCuAO1, AtCuAO2, and AtCuAO3 oxidize Put and Spd but not Spm (Planas-Portell et al. 2013). AtCuAO1 is an extracellular protein such as AtAO1, whereas AtCuAO2 and AtCuAO3 are localized in peroxisomes. Temporal expression and hormonal responses of *AtCuAO1* to *AtCuAO3* have been reported. *AtCuAO1* is responsive to ABA and salicylic acid (SA), *AtCuAO2* is responsive to methyl jasmonate (MeJA) and wounding, and *AtCuAO3* responds to several stimuli such as ABA, SA, flagellin, and MeJA, but not to wounding or the ethylene precursor ACC (Planas-Portell et al. 2013). Tun et al. (2006) showed that exogenously applied PAs rapidly produced nitric oxide (NO) in *Arabidopsis*. The group further demonstrated that *Arabidopsis AtCuAO1* was involved in PA-induced NO production (Wimalasekera et al. 2011b).

## 6.4 CuAO and PAO Are Involved in Crucial Biological Processes

### 6.4.1 *Root Development and Xylem Differentiation*

Treatment with a specific PAO inhibitor attenuates both Spd-induced root cell growth inhibition and Spd-induced cell-cycle arrest. The PAO inhibitor also disrupts differentiation of the secondary wall of meta-xylem elements and xylem parenchymal cells. Overexpression of maize *PAO* in tobacco plants induces programmed cell death (PCD) in root-cap cells (Tisi et al. 2011). The results suggest that $H_2O_2$ produced by Spd oxidation triggers secondary wall deposition and induces PCD. A link between PAs and PCD has been reviewed recently by Moschou and Roubelakis-Angelakis (2014).

### 6.4.2 Pollen Tube Growth

Pollen contains high levels of PAs, which may be explained by high activities of PA biosynthetic enzymes (Song et al. 2002). PAs are proposed to play a role in pollen tube growth (Bagni et al. 1981; Song et al. 2002; Antognoni and Bagni 2008). Recently, a link between pollen tube growth and PAO was reported. Spd oxidase-derived $H_2O_2$ triggered the opening of hyperpolarization-activated $Ca^{2+}$-permeable channels in the pollen plasma membrane and enhanced pollen tube growth (Wu et al. 2010). Those authors showed that two allelic *Atpao3* loss-of-function mutants exhibited reduced pollen tube growth and seed number (Wu et al. 2010).

### 6.4.3 Salinity Stress

Su et al. (2007) show that γ-aminobutyric acid (GABA) produced by CuAO-mediated PA degradation plays a critical role in salinity stress. The involvement of AtCuAO1 in ABA-induced NO production suggests that CuAO is involved in the intermediate signaling pathway of ABA-mediated environmental stress responses, in which *rd29A* and *ADH1* expression is induced (Wimalasekera et al. 2011b). The involvement of PAO in abiotic and biotic adaptation is suggested. Under high salinity, reactive oxygen species produced by PAO activity in the apoplast sustain maize leaf growth (Rodriguez et al. 2009).

### 6.4.4 Pathogen Response

Walters (2003) indicated that CuAO activity was higher in incompatible interactions between plants and pathogens. For example, CuAO activity is high during the interaction of barley and powdery mildew fungus or that of chickpea and *Asochyta rabiei* (Angelini et al. 1993; Walters et al. 2002). PAO-derived $H_2O_2$ triggers the hypersensitive response (HR) in tobacco plants following infection with tobacco mosaic virus (TMV), and after treatment with cryptogein, a protein elicitor secreted by the oomycete *Phytophthora cryptogea* (Yoda et al. 2003, 2006). In tobacco plants carrying the *N* gene and the TMV system, the accumulation of apoplastic Spm is reported in response to TMV infection (Yamakawa et al. 1998). Takahashi et al. (2003, 2004) showed that this apoplastic Spm induces a subset of HR genes through mitochondrial dysfunction, and the resulting activation of two mitogen-activated protein kinases. In *Arabidopsis* and the cucumber mosaic virus (CMV) system, Spm-triggered defense gene induction was described. Treatment with the PAO inhibitor suppressed defense gene activation and compromised the defense response against CMV (Mitsuya et al. 2009). Marina et al. (2008) reported that tobacco plants infected by either the necrotrophic fungus *Sclerotinia sclerotiorum* or

by the biotrophic bacterium *Pseudomonas viridiflava* had higher PA levels and greater necrosis, which functioned to minimize growth of the nectrophic fungus, although it was beneficial for the biotrophic bacterium. Exogenously applied T-Spm and ectopic expression of *ACL5* (T-Spm synthase gene) increased *Arabidopsis* resistance to the biotrophic bacterium. The phenomenon was blocked by a PAO inhibitor, suggesting a role for T-Spm oxidation (Marina et al. 2013). Exogenously applied T-Spm restricted CMV multiplication via induced expression of a subset of pathogen-responsive *Arabidopsis* genes (Sagor et al. 2012). In all these cases, PAO is a crucial protein, and its reaction products ($H_2O_2$ and/or the aldehyde) play important roles in plant–pathogen interactions in the apoplastic space (Moschou et al. 2009).

## 6.5 Perspectives

The understanding of CuAOs and PAOs in *Arabidopsis* and PAOs in *Oryza sativa* has progressed significantly in recent years. Information on cellular localization, reaction chemistry, substrate specificity, and spatiotemporal expression patterns of CuAO and PAO family members is available. The involvement of CuAO and PAO in several physiological processes has been documented. However, most reports of physiological roles of CuAO and PAO are based on data using specific inhibitors. Knockout lines of specific CuAO or PAO genes and future research with advanced technologies will provide useful new data. New knowledge of the reaction mechanisms and physiological roles of CuAOs and PAOs can yield new strategies to produce higher-biomass plants and generate abiotic stress-tolerant plants by manipulating PA catabolic genes and PA levels.

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