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# Plant peroxisomes at the crossroad of NO and $H_2O_2$ metabolism[FA]

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Invited Expert Review

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**Abstract** Plant peroxisomes are subcellular compartments involved in many biochemical pathways during the life cycle of a plant but also in the mechanism of response against adverse environmental conditions. These organelles have an active nitro-oxidative metabolism under physiological conditions but this could be exacerbated under stress situations. Furthermore, peroxisomes have the capacity to proliferateand also undergo biochemical adaptations depending on the surrounding cellular status. An important characteristic of peroxisomes is that they have a dynamic metabolism of reactive nitrogen and oxygen species (RNS and ROS) which generates two key molecules, nitric oxide (NO) and hydrogen peroxide ($H_2O_2$). These molecules can exert signaling functions by means of post-translational modifications that affect the functionality of target molecules like proteins, peptides or fatty acids. This review provides an overview of the endogenous metabolism of ROS and RNS in peroxisomes with special emphasis on polyamine and uric acid metabolism as well as the possibility that these organelles could be a source of signal molecules involved in the functional interconnection with other subcellular compartments.

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## INTRODUCTION

Plant peroxisomes are organelles with a single membrane and a spherical or oval morphology, and behind their simple appearance peroxisomes are highly dynamic compartments involved in different important physiological functions ( Baker and Paudyal 2014; Corpas 2015a; Goto-Yamada et al. 2015; Oikawa et al. 2015; del Río and López-Huertas 2016). A typical property of peroxisomes is their metabolic plasticity, since their enzymatic content can change depending on the organism, cell- and tissue-type, and environmental conditions (Desai and Hu 2008; Hu et al. 2012; del Río 2013). However, in all cases peroxisomes have been shown to have a basal metabolism of reactive oxygen species (ROS) and reactive nitrogen species (RNS) which points out that this nitro-oxidative activity could be an important function of peroxisomes (Corpas 2015b; Corpas et al. 2017). At the same time, this metabolic flexibility put the peroxisomes at the crossroad of different metabolic pathways, allowing the interrelationship of peroxisomes with other subcellular compartments, including oil bodies, plastids or mitochondria (Sunil et al. 2013; Sewelam et al. 2014; Demarquoy and Le Borgne 2015; van Wijk 2015; Palma et al. 2015; Kmiecik et al. 2016; Noctor and Foyer 2016). All these subcellular compartments are involved in many physiological processes, ranging from seed and pollen germination (Li et al. 2014), nitrogen metabolism, fatty acid β-oxidation, photorespiration, stomatal movement,

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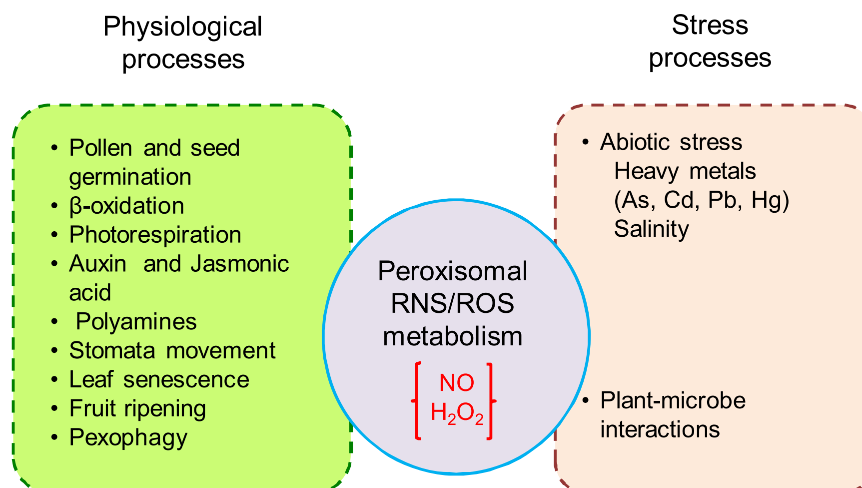


**Figure 1. Overview of the implication of peroxisomal reactive nitrogen species (RNS) / reactive oxygen species (ROS) metabolism in physiological and stress processes in higher plants**

Nitric oxide and $H_2O_2$ are generated in numerous physiological processes as signal molecules or as simple by-products of different pathways, such as β-oxidation or photorespiration. Under stress conditions, both nitric oxide (NO) and $H_2O_2$ can be overproduced and they can cause molecular damages (oxidation and/or nitration) or be involved in defense against pathogens.

senescence, fruit ripening, response to abiotic stresses (Smertenko 2017), to interactions among beneficial (Borucki 2007) and pathogenic micro-organisms (Kubo 2013; Sørhagen et al. 2013: Roos et al. 2014; Zhong et al. 2016) (Figure 1). In fact, there are data suggesting that some ROS/RNS could function as retrograde signals (Fransen and Lismont 2018; Su et al. 2018).

The peroxisomal enzymatic machinery of plants also participates in the biosynthesis of key regulatory molecules such as jasmonic acid (JA) or the auxin indole-3-acetic acid (IAA) (Gfeller et al. 2010; León 2013; Spiess and Zolman 2013). This allows the interconnection of peroxisomes with other subcellular compartments because the JA precursor 12-oxophytodienoic acid (OPDA) is generated in the chloroplasts and then transported to the peroxisomes, where through several rounds of β-oxidation, JA is synthesized. It should be highlighted that NO can stimulate JA production by inducing the expression of the *OPR3* gene which codes for the peroxisomal oxophytodienoate reductase 3 (Mur et al. 2013). On the other hand, the auxin precursor indole-3-butyric acid (IBA) is converted into IAA through a battery of β-oxidation enzymes including the predicted short-chain dehydrogenase/reductase indole-3-butyric acid response1 (IBR1), the acyl–CoA dehydrogenase/oxidase-like IBR3 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3098716/ – bib70), the predicted enoyl–CoA hydratase IBR10, enoyl–CoA hydratase 2 (ECH2) and the 3-ketoacyl–CoA thiolase encoded by *PED1* (Strader et al. 2010; Strader and Bartel 2011). These pathways are also an important source of $H_2O_2$ and some enzymes involved in the generation of this important metabolite are modulated by NO (Huang et al. 2004; Mur et al. 2013) which supports the existence of interconnection networks among these phytohormones, $H_2O_2$, NO and peroxisomes. On the other hand, the photorespiratory pathway is an important source of $H_2O_2$ and this implies the coordination among peroxisomes and other organelles, like chloroplasts and mitochondria. Moreover, it is known that the activity of some peroxisomal enzymes is regulated by NO, like the $H_2O_2$-producing glycolate oxidase and the hydroxypyruvate reductase (HPR1), which are inhibited by *S*-nitrosation and nitration, respectively (Corpas et al. 2017).

During the last 20 years biochemical, cellular, proteomic, *in silico* and reverse genetic approaches, among others, have extended our knowledge about the complexity of plant peroxisomes. The identification of new components threw more light on the physiological functions of peroxisomes present in different plant tissues (leaves, seeds, roots, fruits) of diverse plant

species at different stages of development (Corpas et al. 1999; McCartney et al. 2005; Reumann et al. 2007, 2009, 2016; Eubel et al. 2008; Lingner et al. 2011; Bussell et al. 2013; Meng et al. 2014; Oikawa et al. 2015; Shai et al. 2016; Palma et al. 2009, 2018; Pan and Hu 2018; Pan et al. 2018). There are excellent reviews on the biogenesis and function of plant peroxisomes (Igamberdiev and Lea 2002; Mullen and Trelease 2006; Hu et al. 2012; Goto-Yamada et al. 2015; Cross et al. 2016; Kao et al. 2018). However, there are new data that extend our knowledge about peroxisomes. It is known that proteins with no peroxisomal targeting signals can "piggyback" into peroxisomes by interacting with peroxisomal targeting signal (PTS)-containing proteins (Kataya et al. 2015). It has been demonstrated that the peanut clump virus (PCV)-encoded P15 can be targeted into peroxisomes where it is deactivated (Incarbone et al. 2017, 2018) suggesting a new peroxisomal function for P15 as a regulator of the virus cycle. It has been found that the 33 kDa auxiliary replicase protein (p33) of cucumber necrosis virus (CNV), which is targeted into peroxisomes, induces necrosis because it alters the peroxisomal $H_2O_2$ scavenging function (Rochon et al. 2014). In another case, it has been reported that protein denominated TGBp1 (triple gene block protein 1) from the pepino mosaic virus can interact with catalase to increase its activity and trigger virus accumulation (Mathioudakis et al. 2013). Moreover, the peroxisomal import system has started to be used as a strategy model to generate designed peroxisomes with a protein composition on demand (Cross et al. 2017).

Our knowledge on the metabolism of ROS and more recently RNS in plant peroxisomes has also been significantly augmented. In previous works, we have described the main enzymatic and non-enzymatic components implicated in the generation of ROS and RNS in plant peroxisomes, and how these species can be controlled under physiological and stress conditions (del Río 2015; Corpas et al. 2017). In the present review some peroxisomal pathways which affect other subcellular compartments are highlighted with special emphasis on the function of two key molecules, NO and $H_2O_2$. Research in forthcoming years will very likely reveal more functions for plant peroxisomes associated with these important signaling molecules (Koffler et al. 2014; Tripathi and Walker 2016; Mignolet-Spruyt et al. 2016; Singh et al. 2017).

## NITRIC OXIDE (NO) IS A KEY PIECE IN THE PUZZLE OF THE PEROXISOMAL METABOLISM

Our knowledge on the sources and functions of NO in plant metabolism has experienced significant advances in recent years (Astier et al. 2018; Begara-Morales et al. 2018), although there are still important and significant gaps. We still await the unequivocal identification of the enzymatic source of NO generation in different subcellular compartments, like chloroplasts, mitochondria and peroxisomes, among others (Jeandroz et al. 2016; Chamizo-Ampudia et al. 2017).

Plant peroxisomes were the first cell organelles where a L-arginine-dependent NO synthase activity (NOS-like activity) was identified. This activity had similar biochemical requirements to animal NOS isozymes, with nicotinamide adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), calcium and calmodulin as cofactors (Barroso et al. 1999; Corpas et al. 2004). Some years later the presence of an inducible NOS activity in animal peroxisomes was also discovered (Stolz et al. 2002). By complementary technological approaches it was possible to advance in the characterization of this peroxisomal NOS-like activity as well as the detection of NO in peroxisomes by three different methods: (i) electron paramagnetic resonance (EPR) spectroscopy with the spin trap $Fe(MGD)_2$; (ii) ozone chemiluminiscence; and (iii) fluorometric analysis with 4,5-diaminofluorescein diacetate which allowed corroboration of the presence of NO in peroxisomes (Corpas et al. 2009, 2004) (Figure 2). Additionally, further reports have shed light on the peroxisomal protein responsible for the NO generation. The import of this NOS-like protein into peroxisomes is dependent on peroxins PEX12 and PEX13 (Corpas et al. 2009) and it seems to have a PTS type 2 (PTS2) (Corpas and Barroso 2014), like that of peroxisomal NOS from animal origins (Loughran et al. 2013). More recently, it has been corroborated that the NO generation in peroxisomes is strictly dependent on calmodulin and calcium (Corpas and Barroso 2018). All these data have allowed us to get a more complete picture of the puzzle that represents the peroxisomal NO in plants.

Further research has emphasized the relevance of NO in peroxisomal metabolism with the discovery that different key peroxisomal enzymes, like catalase, hydroxypyruvate reductase and glycolate oxidase,

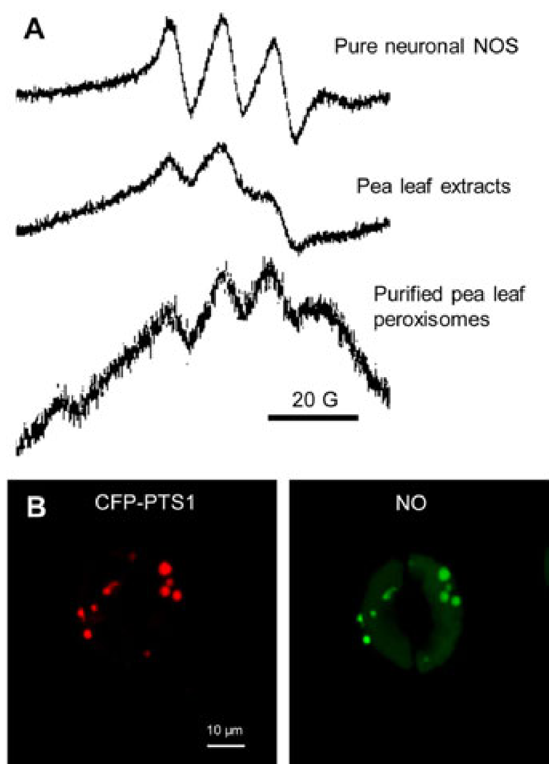


**Figure 2. Detection of nitric oxide (NO) in peroxisomes by electron paramagnetic resonance (EPR) spectroscopy and confocal laser scanning microscopy (CLSM)**
**(A)** EPR spectra of the NO-spin adduct of the Fe(MGD)$_2$ complex in different samples (purified neuronal NOS as control, pea leaf extracts and purified pea leaf peroxisomes). Reproduced with permission from Corpas et al. (2004) Plant Physiol 136: 2722–2733. Copyright American Society of Plant Biologists. **(B)** Images illustrating CLSM *in vivo* detection of peroxisomes (red) (left panel) and nitric oxide (green) (right panel) in guard cells of transgenic *Arabidopsis* seedlings expressing CFP-PTS1. Reproduced with permission from Corpas et al. (2017) Redox Biol 11: 535-542. Copyright Springer.

can undergo post-translational modifications (PTMs) mediated by NO, such as *S*-nitrosylation (or *S*-nitrosation) and/or nitration (Corpas et al. 2017).

## CATALASE IS THE MAIN PEROXISOMAL $H_2O_2$-SCAVENGING ENZYME WHICH IS A TARGET OF NO

Catalase (EC 1.11.1.6.) is recognized as one of the most important antioxidant enzymes, that catalyzes the decomposition of $H_2O_2$ to water and oxygen and is predominantly localized in peroxisomes. Consequently, it is considered as a reliable marker enzyme of these organelles in both animal and plant cells. In higher plants, catalase is encoded by a multigene family and the number of catalase isozymes could change depending on the plant species, organ, developmental stage or environmental conditions (Ni et al. 1990; Frugoli et al. 1996, 1998; McClung 1997; Polidoros and Scandalios 1997; Hite et al. 1999; Corpas et al. 1999; Talarczyk et al. 2002; Mhamdi et al. 2012). Catalase is usually a homotetrametic protein with subunits of around 55 kDa and it has been demonstrated that it is regulated at post-transcriptional and post-translational levels (Schmidt et al. 2002, 2006).

The identification of the presence of NO in plant peroxisomes (Corpas et al. 2004, 2009) plus some additional evidence from *in vitro* and proteomic analyses has shown that catalase activity can be modulated by NO. The main modifications mediated by NO, including *S*-nitrosation or *S*-nitrosylation (addition of NO to the thiol groups of Cys residues) and nitration (addition of $-NO_2$ groups mainly to Tyr residues) provoke the inhibition of catalase activity (Clark et al. 2000; Chaki et al. 2015; Corpas et al. 2017). This indicates that NO may indirectly regulate the level of peroxisomal $H_2O_2$.

## PEROXISOMAL AMINE OXIDASE (AO) AND POLYAMINE OXIDASE (PAO): SOURCES OF $H_2O_2$

The most relevant polyamines (PAs) in plant cells are putrescine (Put), spermidine (Spd) and spermine (Spm). They are involved in cell division, organ development, leaf senescence, abiotic stresses, fruit development and ripening (Tiburcio et al. 2014). PAs are synthesized from arginine and ornithine by arginine decarboxylase (ADC) and ornithine decarboxylase (ODC) but some peroxisomal enzymes have also been identified to be involved in PAs catabolism as well as its back-conversion. These enzymes are copper-containing amine oxidases (CuAOs) and FAD-dependent polyamine oxidases (PAOs), both generators of $H_2O_2$ as a product of their catalytic activity (Figure 3). There are different isozymes present in several cellular localizations including cytoplasm, apoplast and peroxisomes. Table 1 summarizes the identified isozymes of PAOs and

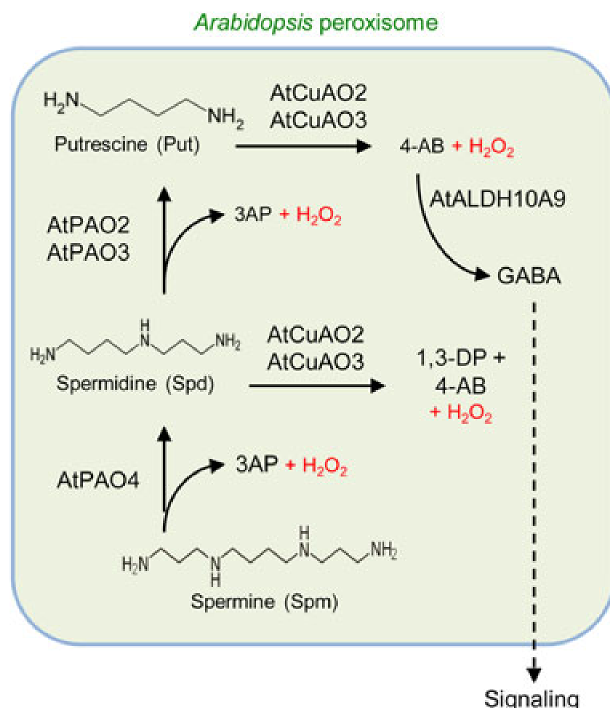


**Figure 3. Peroxisomal polyamine (PA) metabolism in *Arabidopsis thaliana***
In peroxisomes there are some isoenzymes of polyamine oxidase (PAO) and copper-dependent amino oxidase (CuAO) which are involved in PA catabolism as well as its back-conversion. In this pathway the signaling molecule γ-aminobutyric acid (GABA) can be generated, and in all steps $H_2O_2$ is produced. 3AP, 3-aminopropanal; AtALDH10A9, peroxisomal aldehyde dehydrogenase; 4-AB, 4-aminobutanal; 1,3-DP, 1,3-diaminopropane.

CuAOs in *Arabidopsis thaliana* whose presence in peroxisomes has been experimentally confirmed (Takahashi et al. 2010; Planas-Portell et al. 2013; Kusano et al. 2015).

The existence of PAO in animal peroxisomes has been known for many years (Schrader and Fahimi 2004) but in plant peroxisomes its presence and potential function have been more recently reported (Moschou et al. 2008). In plants, PAOs are not only involved in the terminal catabolism of polyamines but they can also catalyze the polyamine back-conversion pathway. Among the five *PAO* genes present in *Arabidopsis* (*AtPAO1-AtPAO5*), the gene that encodes AtPAO3 contains the tripeptide (SRM) at the C terminus which

**Table 1. Hydrogen peroxide-generating peroxisomal isoenzymes of copper-containing amine oxidases (CuAOs) and FAD-dependent polyamine oxidases (PAOs) identified in *Arabidopsis thaliana***

| Enzymes | Gene locus | PTS1 | Substrate /mode of reaction | Location or conditions of gene expression |
|---|---|---|---|---|
| AtCuAO2 | *At1g31710* | Without PTS1 | Put, Spd/ Terminal catabolism | MeJA, Wounding |
| AtCuAO3 | *At2g42490* | SKL | Put, Spd/ Terminal catabolism | ABA, SA, flagelin, MeJA |
| AtPAO2 | *At2g43020* | SRL | Spd, Spm/ Terminal catabolism and Back-conversion pathway | Roots (Quiescent center, Columella), pollen |
| AtPAO3 | *At3g59050* | SRM | Spd, Spm/ Terminal catabolism and Back-conversion pathway | Guard cells, pollen |
| AtPAO4 | *At1g65840* | SRM | Spm/ Terminal catabolism and Back-conversion pathway | Roots and flowers |

PTS1, peroxisomal targeting signal 1; Put, putrescine; Spm, spermine; Spd, spermidine.

is a peroxisomal targeting signal type I (PTS1) and its presence in peroxisomes has been experimentally demonstrated (Moschou et al. 2008). AtPAO3 catalyzes the sequential conversion/oxidation of Spm to Spd, and Spd to Put, and JA, salicylic acid, wounding and flagellin strongly induce the *AtPAO3* expression. This suggests a role for the peroxisomal $H_2O_2$-producing AtPAO3 in stress defense responses (Moschou et al. 2008). Moreover, the peroxisomal AtPAO3 is critical for the elongation of pollen tube by modulating a plasma membrane $H_2O_2$-dependent $Ca^{2+}$-influx channel (Wu et al. 2010), a process where peroxisomal NO is also involved (Prado et al. 2004). Even more, it has been reported that the *Arabidopsis* mutant of peroxisomal *Atpao3* had an enhanced superoxide ($O_2^{\cdot -}$) production by a NADPH-oxidase with a concomitant activation of the mitochondrial alternative oxidase pathway affecting the electron transfer chain (Andronis et al. 2014). This suggests that the peroxisomal AtPAO3 is involved in the cellular ROS homeostasis affecting both peroxisomal and mitochondrial metabolism (Andronis et al. 2014). Complementary data have also shown the peroxisomal localization of AtPAO2 and AtPAO4, the latter being involved in polyamine catabolism in root peroxisomes (Andronis et al. 2014). Gene expression analyses also connected *AtPAO4* with the response to drought stress and flavonoid biosynthesis (Kamada-Nobusada et al. 2008). Similarly, rice (*Oryza sativa*) genome also contains genes of seven OsPAO isoforms that are termed *OsPAO1–OsPAO7*, and the proteins OsPAO3, OsPAO4, and OsPAO5 are localized in peroxisomes (Ono et al. 2012). In tomato (*Solanum lycopersicum*) there are also seven PAO genes (*SlPAO1–SlPAO7*), and isoforms SlPAO2, SlPAO3, SlPAO4 and SlPAO5 each contain a C-terminal PTS1, SRM, suggesting their peroxisomal localization (Hao et al. 2018). Gene expression analyses showed that *SlPAO2*, *SlPAO3*, *SlPAO4* and *SlPAO5* are specially induced under low temperature (4 °C) and heat, but *SlPAO4* is also overexpressed under drought stress (Hao et al. 2018).

The *Arabidopsis* peroxisomal localized CuAO2 and CuAO3 are also sources of $H_2O_2$ (Table 1). Considering that the polyamine back-conversion pathway (Spm to Put) takes place in peroxisomes, one of the physiological functions of both peroxisomal CuAOs should be to avoid the accumulation of Put which seems to inhibit the PAs back-conversion pathway (Planas-Portell et al. 2013). Nevertheless, these two CuAOs catalyze the conversion of Put to 4-aminobutanal (4-AB) which is then transformed into γ-aminobutyric acid (GABA) by an aldehyde dehydrogenase (ALDH) (Figure 3). These reactions connect peroxisomes with the accumulation of this non-proteinogenic amino acid which is usually accumulated as a mechanism of response to biotic and abiotic stresses (Ramesh et al. 2015). In *Arabidopsis* ten ALDHs have been identified, and AtALDH10A9 has been demonstrated to be present in peroxisomes (Zarei et al. 2016) which again evidences the relationship of peroxisomes with signaling molecules, such as GABA, and the response to stress conditions (Shelp and Zarei 2017). Moreover, *Arabidopsis thaliana* contains another peroxisomal copper amine oxidase ζ (CuAOζ) and the $H_2O_2$ generated by this enzyme is essential for lateral root development since it affects the auxin distribution in the plant tissue (Qu et al. 2017).

In recent years it has been reported that polyamine catabolism induces the synthesis of NO in different plant organs (Tun et al. 2006; Wimalasekera et al. 2011a; Yang et al. 2014; Diao et al. 2016; Agurla et al. 2018). In the catabolism of polyamines, polyamine oxidases and Cu-containing amine oxidases are involved, and in *Arabidopsis thaliana* isoform CuAO1 contributes to polyamine-induced NO biosynthesis, although the mechanism of this process is unknown (Wimalasekera et al. 2011b). The presence of PAOs and CuAOs in plant peroxisomes has suggested that these enzymes perhaps could be additional sources of NO generation in peroxisomes (Kaur et al. 2013), although this still has to be demonstrated.

## PEROXISOMAL URIC ACID METABOLISM WITH DUAL FUNCTIONS: GENERATION OF ROS AND PEROXYNITRITE SCAVENGING

Purines are part of nitrogen metabolism and include molecules such as adenine, guanine, hypoxanthine, xanthine and uric acid, among others. The purine pathway allows the recycling of the end products (glyoxylate and ammonia) to synthesize new organic compounds necessary to plant growth (Theimer and Beevers 1971; Nguyen 1980; Werner and Witte 2011; Hafez et al. 2017). Moreover, purine metabolism has also been associated with the mechanism of response to environmental stresses such as drought tolerance

(Stasolla et al. 2003; Watanabe et al. 2010; Irani and Todd 2016). The pathway is compartmentalized among cytosol, peroxisomes and endoplasmic reticulum but some of the key enzymes, such as the ROS-generating xanthine oxidoreductase and urate oxidase, as well as the metabolites xanthine, uric acid and allantoin, have been demonstrated to be present in peroxisomes (Corpas et al. 1997) (Figure 4).

Xanthine oxidoreductase (XOR) converts xanthine into uric acid. This enzyme is an FAD-, molybdenum-, iron- and sulfur-containing hydroxylase enzyme which exists in two inter-convertible forms. They are designated as NAD-dependent xanthine dehydrogenase (XDH) and oxygen-dependent xanthine oxidase (XOD). Consequently, in this reaction either NADH or superoxide radicals ($O_2^{\cdot -}$) could be generated. It was first believed that XDH, the non-producer of $O_2^{\cdot -}$, was the only form present in plant cells and was exclusively localized in the cytosol. However, further experimental evidence showed that this enzyme was present in peroxisomes of several plant species such as watermelon cotyledons (Sandalio et al. 1988), pea leaves (del Río et al. 1989; Corpas et al. 2008) and pepper fruits (Mateos et al. 2003), and had the capacity of generating $O_2^{\cdot -}$ radicals (Sandalio et al. 1988; Yesbergenova et al. 2005; Corpas et al. 2008; Zarepour et al. 2010; Ma et al. 2016), being associated with a defense function.

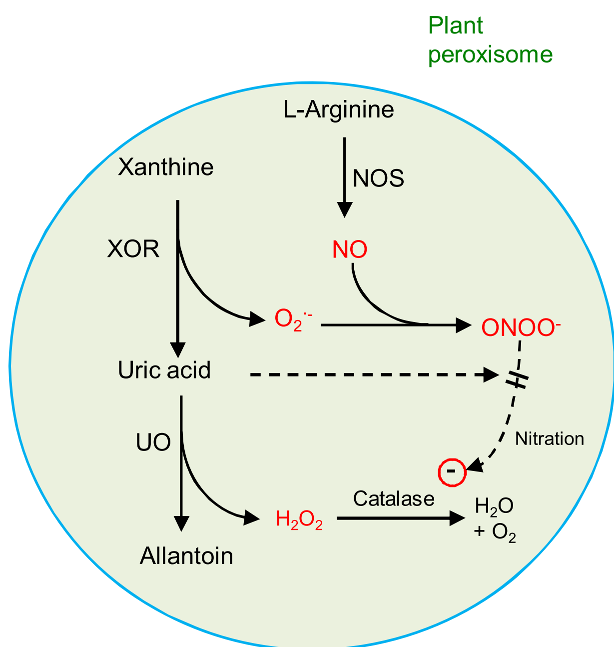


**Figure 4. Interrelationship between uric acid metabolism and reactive oxygen species (ROS) and reactive nitrogen species (RNS) produced in plant peroxisomes**
Xanthine oxidoreductase (XOR) activity generates uric acid with the concomitant generation of superoxide radical ($O_2^{\cdot -}$). Then urate oxidase (UO) activity produces allantoin and $H_2O_2$, which is decomposed by catalase. On the other hand, the larginine-dependent NOS-like activity generates nitric oxide (NO) that can react with superoxide ($O_2^{\cdot -}$) to generate peroxynitrite ($ONOO^-$) which is a powerful oxidant that can mediate post-translational modifications (such as tyrosine nitration) in some enzymes like catalase with inhibition of its activity. At the same time, uric acid has a recognized capacity to scavenge $ONOO^-$ and consequently allows prevention of its nitrating effects.

Mammalian xanthine oxidase (XOD) is a complex enzyme which is regulated by NO and peroxynitrite (Lee et al. 2000). However, it is important to remark that in animal cells and under anaerobic conditions, this enzyme can catalyze nitrite reduction with the concomitant generation of NO (Li et al. 2003, 2005), but this reaction has been erroneously extended to NO metabolism in plant peroxisomes. To our knowledge, in plant cells there are no experimental data that support the existence of this reaction, and particularly in peroxisomes that are characterized by an intense oxidative metabolism.

Urate oxidase (UO, EC 1.7.3.3), also called uricase, is a copper-containing enzyme that catalyzes the oxidation of uric acid to allantoin and $H_2O_2$ (Figure 4). This enzyme has been purified and characterized in different plant species (Tajima et al. 1991; Montalbini et al. 1997, 1999). The presence of urate oxidase in plant peroxisomes has been known for many years (Parish 1971; Theimer and Beevers 1971), and in peroxisomes isolated from pea leaves the content of xanthine, uric acid and allantoin has also been determined by high-performance liquid chromatography (Corpas et al. 1997). The relevance of this enzyme has been demonstrated in an *Arabidopsis* urate oxidase (*uox*) mutant which lacked the capacity of seedling establishment due to the accumulation of uric acid in all the plant tissues (Hauck et al. 2014).

However, urate is recognized to be an effective peroxynitrite ($ONOO^-$) scavenger in animals and plants (Alamillo and García-Olmedo 2001; Koch and De Keyser 2006; Signorelli et al. 2016). It is noteworthy that $ONOO^-$, which is the product of the reaction between NO and $O_2^{\cdot -}$, has been proposed to regulate the conversion of XDH into the superoxide-generating form XOD (Sakuma et al. 1997). In addition, $ONOO^-$ also

mediates the process of protein tyrosine nitration (Bartesaghi and Radi 2018). The presence of $ONOO^-$ in peroxisomes has also been demonstrated (Corpas and Barroso 2014). Furthermore, some peroxisomal enzymes, including catalase, hydroxypyruvate reductase and monodehydroascorbate reductase (MDAR) have been shown to undergo post-translational modifications (PTMs) mediated by $ONOO^-$ that inhibit their activity (Corpas et al. 2017).

Accordingly, this purine pathway is necessary to generate superoxide radicals and consequently $ONOO^-$ which could inhibit catalase activity and provoke $H_2O_2$ accumulation, but at the same time it also generates urate which is an additional mechanism of control of the $ONOO^-$ level in peroxisomes (Figure 4). Thus, the equilibrium between these molecules could be very relevant under stress conditions.

## PEXOPHAGY AND ROS

Etymologically "phagy" is the process of "eating" and in the cell context is referred to as a mechanism to remove specific damaged components, from macromolecules to subcellular compartments. Consequently, the term pexophagy refers to a major pathway that removes damaged peroxisomes. This process seems to be especially important when peroxisomes undergo metabolic transitions, like for example glyoxysomes to leaf peroxisomes (Avin-Wittenberg and Fernie 2014; Kim et al. 2014; Lee et al. 2014; Fahy et al. 2017). In this sense, experimental data support the involvement of ROS metabolism in the mechanism of pexophagy since *Arabidopsis* peroxisomes with highly oxidized proteins are selectively degraded via autophagy (Shibata et al. 2013, 2014; Young and Bartel 2016). Very recently, using the animal cell line HepG2 as a model where catalase was inhibited by small interfering (si)RNA with the consequent accumulation of $H_2O_2$, the induction of pexophagy was observed (Lee et al. 2018). All these data suggest that the status of ROS metabolism could be a sensor of peroxisomal homeostasis which could serve as a regulator of pexophagy.

To our knowledge there is no information on the specific involvement of NO in pexophagy. However, recent data indicate that NO can mediate the autophagy of certain proteins. Thus, in the enzyme *S*-nitrosoglutathione reductase (GSNOR), which regulates the level of *S*-nitrosoglutathione (GSNO), it has been found that *S*-nitrosylation inhibits its activity (Guerra et al. 2016). And in *Arabidopsis* plants under stress by hypoxia, this NO-mediated PTM triggered the specific degradation of GSNOR via autophagy (Zhan et al. 2018). Considering the active NO metabolism existing in peroxisomes, it seems plausible that some peroxisomal enzymes, such as catalase or hydroxypyruvate reductase, that undergo NO-derived PTMs (Corpas et al. 2017) could also reveal a similar process, particularly under stress conditions.

## PERSPECTIVES

Plant peroxisomes have a very active nitro-oxidative metabolism where NO and $H_2O_2$ have a relevant function under physiological and stress conditions. Some components of the pathways mentioned in this work, such as polyamines or purines metabolism, have been known for a long time but the presence in plant peroxisomes of NO and other enzymatic components has raised new questions about the mechanisms of regulation of these pathways by new post-translational modifications, like *S*-nitrosylation (or *S*-nitrosation) and nitration. All these data point out the complexity of plant peroxisomal metabolism which seems to be much more intricate than expected, as well as new functions for peroxisomes in the connection with different subcellular compartments. In this sense, very recent data obtained in our laboratory indicated that plant peroxisomes also contain the gasotransmitter hydrogen sulfide ($H_2S$) which is a catalase inhibitor (Corpas et al. 2019), and raised new questions on the potential physiological function of $H_2S$ in the metabolism of plant peroxisomes.

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## AUTHOR CONTRIBUTIONS

F.J.C. wrote the manuscript. L.A.R. and J.M.P. discussed and revised the manuscript, and all authors read and approved the manuscript.

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