

## Homologs of old yellow enzyme in plants

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### Abstract

Old Yellow Enzyme (OYE) is a flavin mononucleotide-dependent oxidoreductase. 12-oxophytodienoic acid reductases (OPRs) are OYE homologs and are represented by multigene families in plants. OPRs catalyze the reduction of double bonds in  $\alpha,\beta$ -unsaturated aldehydes or ketones. They belong to the octadecanoid pathway, which converts linolenic acid to jasmonic acid (JA). Individual OPR family members may have distinct functions due to their different substrate specificity, subcellular localization, tissue distribution, and differential regulation of their expression in response to specific environmental cues. Based on their differential preferences for 12-oxophytodienoate (OPDA) stereoisomers, these enzymes are classified into two subgroups: OPRI and OPRII. OPRI enzymes preferentially catalyze the reduction of cis-(-)OPDA over the JA precursor cis-(+)OPDA, and therefore, they are not involved in JA biosynthesis. Although a significant progress has been made to understand the exact physiological roles of OPR enzymes, the function of OPRI subgroup members in plants remains largely unknown. Enzymes belonging to this subgroup are possibly involved in defense responses and signaling. The members of the OPRII subgroup are required for JA biosynthesis because they catalyze the reduction of the JA precursor cis-(+)OPDA. This review will highlight some characteristics of this family in *Arabidopsis* and other species and discuss the physiological role of OPR family members in plants.

**Keywords:** Old Yellow Enzyme; 12-oxophytodienoic acid reductase; 12-oxophytodienoate; jasmonic acid;  $\alpha,\beta$ -unsaturated compound; defense response.

**Abbreviations:** JA\_jasmonic acid; OPDA\_oxophytodienoate; OPR\_oxophytodienoic acid reductase; OYE\_old yellow enzyme.

### Introduction

Old Yellow Enzyme (OYE) is a flavin mononucleotide-dependent oxidoreductase (Raine et al., 1994) and was initially isolated from brewer's bottom yeast (Warburg and Christian, 1932). Oxophytodienoate reductases (OPRs) are a small group of flavin-dependent oxidoreductases in plants and belong to a class of enzymes closely related to the yeast OYE (Williams and Bruce, 2002). Plant OPRs are usually encoded by a multigene family. To date, several OPR isozymes have been identified in various plant species (Strassner et al., 1999; Sanders et al., 2000; Schaller et al., 2000; Stintzi and Browse, 2000; Strassner et al., 2002; Agrawal et al., 2003; Matsui et al., 2004; Zhang et al., 2005). Early biochemical studies of the enzymatic activity of OPRs in *Arabidopsis* and tomato have led to their classification into two subgroups (OPRI and OPRII), based on their differential preferences for 12-oxophytodienoate (OPDA) stereoisomers (Schaller et al., 1998; Strassner et al., 1999; Schaller et al., 2000). Members of the OPRI subgroup have a rather broad substrate specificity and catalyze the reduction of double bonds in  $\alpha,\beta$ -unsaturated aldehydes or ketones (Uchida, 2003). Moreover, OPRI enzymes preferentially catalyze the reduction of cis-(-)OPDA over cis-(+)OPDA, and therefore, they are not involved in jasmonic acid (JA) biosynthesis. The members of the OPRII subgroup are required for JA biosynthesis because they catalyze the reduction of the JA precursor cis-(+)OPDA (Schaller et al., 1998). Biochemical and genetic studies in *Arabidopsis* and other plant species have significantly advanced the understanding of the OPR

function. However, unequivocal biological functions have been demonstrated for only a few (OPRII) members of this family in a limited number of species (Schaller and Weiler, 1997b; Schaller et al., 1998; Biesgen and Weiler, 1999; Strassner et al., 1999; Schaller et al., 2000; Stintzi and Browse, 2000; Strassner et al., 2002). As mentioned above, the members of the OPRII subgroup are the only enzymes in the family that participate in the octadecanoid pathway yielding JA (Liechti and Farmer, 2006). The biosynthesis of JA was first elucidated by Vick and Zimmermann (1984). Jasmonates such as JA, methyl jasmonate, OPDA, and related cyclopentenones are ubiquitous, lipid-derived compounds with signaling functions in plant development. In addition, they are involved in responses to biotic and abiotic stresses (Wasternack, 2007; Wasternack et al., 2012). Although significant progress has been made towards the understanding of the physiological importance of OPR enzymes, the function of OPRI enzymes in plants remains unclear. Several studies have examined the expression levels of the OPR genes under different growth conditions and treatments. Some biotic and abiotic stress factors and signaling molecules have been shown to enhance the expression of OPRI genes (Biesgen and Weiler, 1999; Zhang et al., 2005; Li et al., 2011). Therefore, the enzymes of the OPRI subgroup are likely to be involved in defense responses and signaling (Biesgen and Weiler, 1999; Zhang et al., 2005; Li et al., 2011). OPRI subgroup members catalyze the reduction of  $\alpha,\beta$ -unsaturated compounds, which are mostly

formed as a result of oxidative damage to the cell (Strassner et al., 1999; Tani et al., 2008). Beynon et al. (2009) have suggested a role for *Arabidopsis AtOPR1* and *AtOPR2*, which are OPR enzymes, in xenobiotic detoxification toward trinitrotoluene (TNT). The enzymatic activity and expression patterns of these proteins clearly indicate a role of OPR1 subgroup in defense responses.

### OYE and its homologs

Flavoenzymes are oxidoreductases that form a diverse family of redox proteins that typically use either flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN) as cofactors (Spencer et al., 1976). Flavoenzymes catalyze a wide range of essential biochemical reactions, including electron transfer, dehydrogenation, and hydroxylation reactions, involving many different types of compounds (Williams and Bruce, 2002; Trotter et al., 2006). OYE (EC 1.6.99.1) was the first flavoenzyme to be identified (reviewed by Breithaupt et al., 2009). OYE is a flavin mononucleotide-dependent oxidoreductase (Raine et al., 1994) and was initially isolated from brewer's bottom yeast (Warburg and Christian, 1932). OYE is a dimer protein with a molecular weight of approximately 45 kDa and an overall structure of an  $\alpha/\beta$  barrel (Fox and Karplus, 1994).

A rapidly growing family of OYE homologs has been identified in organisms of both prokaryotic and eukaryotic origins (Buckman and Miller, 1998). OYE and its homologs from bacteria, yeast, and plants can reduce the olefinic bond of  $\alpha,\beta$ -unsaturated carbonyl compounds, which is an activity that is rather uncommon for flavoenzymes (Williams and Bruce, 2002; Stuermer et al., 2007). The reaction catalyzed by OYEs proceeds via a ping-pong bi-bi mechanism including NAD(P)H binding, reduction of FMN, release of NAD(P)<sup>+</sup>, substrate binding, and reduction (Massey and Schopfer, 1986). Previous reports have indicated the induction of OYE during oxidative stress in fungi (Trotter et al., 2006; Nizam et al., 2014). OYE homologs function in xenobiotic detoxification (Beynon et al., 2009). They detoxify the breakdown products of lipid peroxidation and other toxic electrophilic compounds (Williams and Bruce, 2002; Trotter et al., 2006).

Several OYE homologs have been identified in both monocotyledonous and dicotyledonous plant species (Schaller et al., 1998; Strassner et al., 1999; Sanders et al., 2000; Schaller et al., 2000; Stintzi and Browse, 2000; Strassner et al., 2002; Agrawal et al., 2003; Zhang et al., 2005). These plant homologs are referred to as OPRs.

### Oxophytodienoate reductases (OPR)

OPRs are a small group of flavin-dependent oxidoreductases. They belong to a class of enzymes closely related to the yeast OYE (Williams and Bruce, 2002). The name "OPR" is derived from the only member with an established function, i.e., OPR3 (from *Arabidopsis thaliana*). OPR3 catalyzes the reduction of the cyclopentenone (9S,13S)-12-oxophytodienoate [(9S,13S)-OPDA] to the corresponding cyclopentanone in the JA biosynthetic pathway (Vick and Zimmerman, 1984; Schaller, 2001; Schaller et al., 2004; Liechti and Farmer, 2006). The OPR enzyme was first purified from cell cultures of *Corydalis sempervirens* (Schaller and Weiler, 1997a) and the homologous cDNA was later cloned from *A. thaliana* and named *AtOPR1* (Schaller and Weiler, 1997b). Two highly related, differentially expressed genes, *opr1* and *opr2*, have been found in the genome of *A. thaliana* (Biesgen and Weiler, 1999). Plant

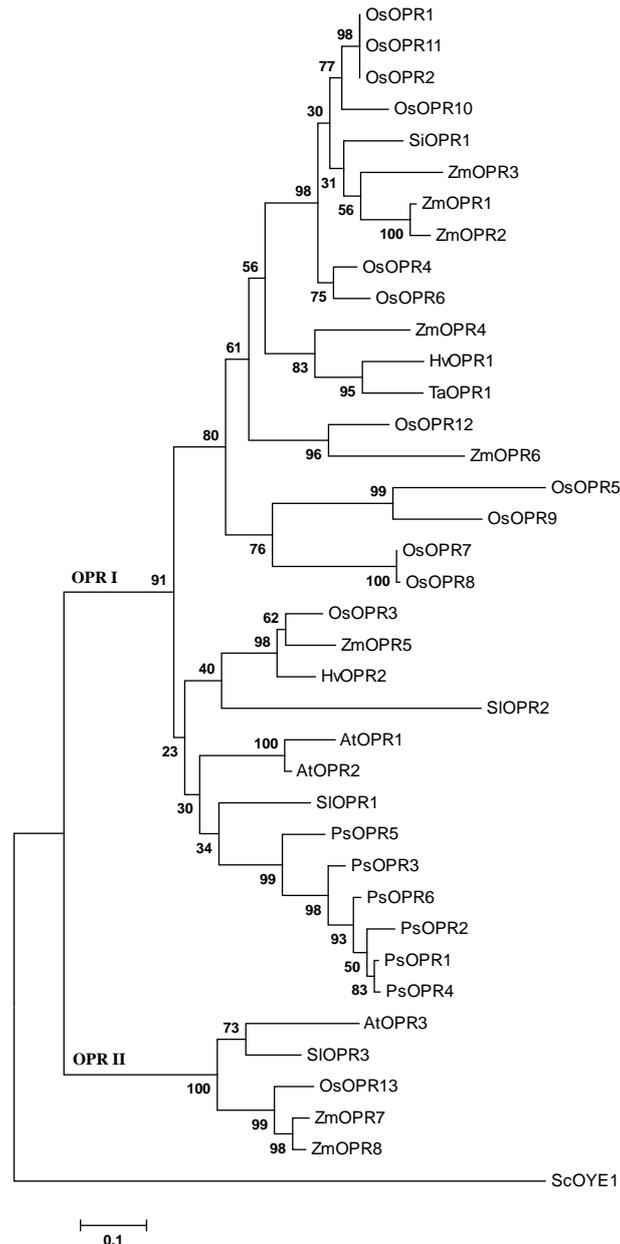
OPRs are usually encoded by a multigene family. Several OPR isozymes have been identified in various plant species; three isoforms exist in *Solanum lycopersicon* (tomato) (Strassner et al., 1999; Strassner et al., 2002) and six in *A. thaliana* (thale cress) (Sanders et al., 2000; Schaller et al., 2000; Stintzi and Browse, 2000). Among the cereal crops, 13 OPR genes were identified in rice (*Oryza sativa*) genome (Agrawal et al., 2003) and eight in the maize (*Zea mays*) genome (Zhang et al., 2005). Recently, two members of the OPR gene family (OPR subgroup I) have been cloned and characterized in barley (Abu-Romman, 2012; Al-Momany and Abu-Romman, 2014). In peas, six members of just one OPR gene subgroup (OPRI subgroup) have been cloned and biochemically characterized, suggesting that the pea genome encodes more than six OPR genes (Matsui et al., 2004) (Figure 1).

### OPR subgroup I and subgroup II

The early biochemical studies of the enzymatic activity of OPRs in *Arabidopsis* and tomato have shown that these enzymes could be classified into two subgroups: OPRI and OPRII. This classification is based on differential preferences of these enzymes for OPDA stereoisomers (Schaller et al., 1998; Strassner et al., 1999; Schaller et al., 2000). Members of the OPRI subgroup have broad substrate specificity. They catalyze the reduction of double bonds in  $\alpha,\beta$ -unsaturated aldehydes or ketones (Uchida, 2003). Moreover, OPRI subgroup enzymes preferentially catalyze the reduction of (9R,13R)-12-oxo-10, 15(Z)-octadecatrienoic acid (9R,13R-OPDA) *cis*-(-)OPDA over (9S,13S)-12-oxo-10,15(Z)-octadecatrienoic acid (9S,13S-OPDA) *cis*-(+)OPDA, the only natural precursor of JA. Therefore, they are not involved in JA biosynthesis. In contrast, the members of the OPRII subgroup take part in JA biosynthesis catalyzing the reduction of (9S,13S)-12-oxo-10,15(Z)-octadecatrienoic acid (9S,13S-OPDA) *cis*-(+)OPDA, the only natural precursor of A (Schaller et al., 1998). *AtOPR3* of *Arabidopsis* and *SIOPR3* of tomato (subgroup II) efficiently reduce the natural isomer 9S,13S-OPDA to 3-oxo-2(2'(Z)-pentenyl)-cyclopentane-1-octanoic acid (OPC 8:0), the precursor of JA (Schaller and Weiler, 1997b; Schaller et al., 1998; Biesgen and Weiler, 1999; Strassner et al., 1999; Schaller et al., 2000; Stintzi and Browse, 2000; Strassner et al., 2002). *AtOPR1*, *AtOPR2*, pea PsOPR enzymes PsOPR1 to PsOPR6, rice OsOPR1, and tomato *SIOPR1* and *SIOPR2* belong to subgroup I. These enzymes cannot catalyze this step and therefore, are not a part of the JA biosynthetic pathway (Schaller and Weiler, 1997b; Schaller et al., 1998; Biesgen and Weiler, 1999; Sobajima et al., 2003; Matsui et al., 2004).

### Physiological role of OPRs

The biochemical and genetic studies in *Arabidopsis* and other plant species have improved our understanding of the OPR function. However, the exact biological roles are known for only a few OPRII members of this family and in a limited number of species. The biological significance of many OPRs is still largely unknown (Strassner et al., 2002; Agrawal et al., 2003; Zhang et al., 2005). Moreover, the differences between family sizes in eukaryotes pose many questions about the evolution and functional divergence of the OPR gene family. Therefore, extensive comparative genome studies will be necessary to elucidate the evolution and function of this gene family in plants (Li et al., 2009). The individual OPR family members may have distinct functions due to their different substrate specificities,



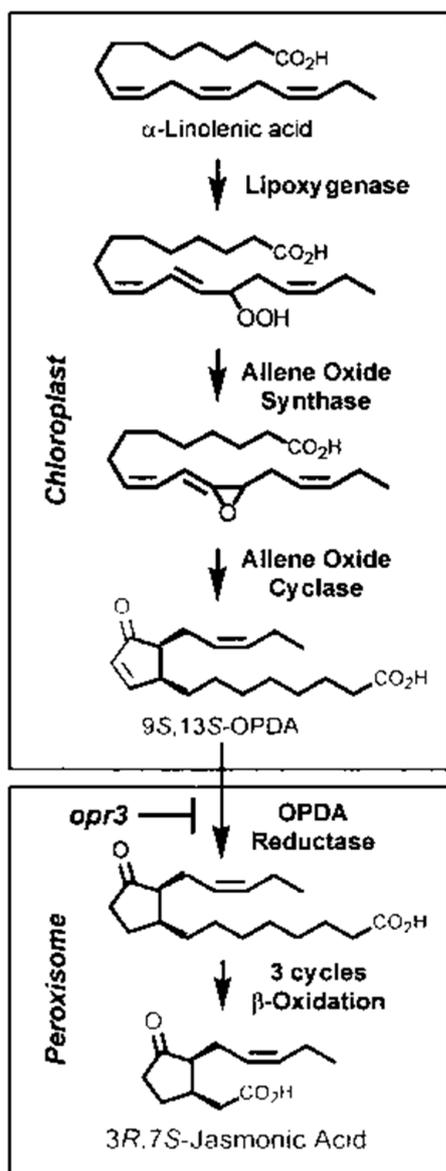
**Fig 1.** Maximum-likelihood phylogenetic tree of deduced amino acid sequences of plant OPRs generated with MEGA 5 software. The OPRs in the phylogenetic tree include *Arabidopsis* (At), barley (Hv), foxtail millet (Si), maize (Zm), pea (Ps), rice (Os), wheat (Ta), and tomato (Sl). The percentage of 1000 bootstrap replicates is given above each branch. The bar represents an evolutionary distance. The OYE 1 of *Saccharomyces cerevisiae* (ScOYE1) was included as the outgroup.

subcellular localization, tissue distribution, and differ in the regulation of their expression upon specific environmental cues (Strassner et al., 2002; Zhang et al., 2005).

### Jasmonic acid biosynthesis

The OPRII subgroup enzymes are the only members of the family that participate in the octadecanoid pathway yielding JA (Liechti and Farmer, 2006). The involvement of OPRII members in JA biosynthesis has been further proven using reverse genetic analysis. Knockout mutants in genes encoding OPRII enzymes are deficient in JA biosynthesis and show impaired jasmonate-dependent gene expression (Sanders et al., 2000; Stintzi and Browse, 2000). *Arabidopsis AtOPR3* mutant was shown to be impaired in JA biosynthesis

and is male-sterile. This phenotype can be complemented biochemically by exogenous JA (Stintzi and Browse, 2000) or genetically by overexpression of an OPRII gene in the mutant background (Tani et al., 2008). The biosynthesis of JA was first described by Vick and Zimmermann (1984). The JA biosynthetic pathway (Figure 2) starts with the release of  $\alpha$ -linolenic acid ( $\alpha$ -LeA) from chloroplast membranes by specific lipases, a process that can be triggered by wounding (Conconi et al., 1996) or local and systemic signals (Narváes-Vásquez et al., 1999).  $\alpha$ -LeA is then converted to a fatty acid hydroperoxide (9Z,11E, 13S, 15Z)-13-hydroxy-9,11,15 -octadecatrienoic acid (13-HPOT) in a reaction catalyzed by 13-lipoxygenase (13-LOX) (Feussner and Wasternack, 2002). 13-HPOT is dehydrated to the unstable allene oxide 12, 13(S)-epoxy-9(Z), 11, 15, (Z)- octadecatrienoic



**Fig 2.** The jasmonic acid biosynthesis pathway (Howe, 2001). Copyright (2011) National Academy of Science, U.S.A.

acid (12,13-EOT) by the action of allene oxide synthase. Allene oxide cyclase hydrolyzes 12,13-EOT giving rise to OPDA, the final product of the plastid-located part of JA biosynthesis (Howe, 2001). The subsequent steps in the pathway occur in the peroxisomes (Strassner et al., 2002). They involve the reduction of the cyclopentenone ring of OPDA by a peroxisomal NADPH-dependent OPDA reductase (OPR3; Schaller et al., 2000; Stintzi and Browse, 2000; Strassner et al., 2002) to yield 3-oxo-2-(2<sup>'</sup>)-pentenyl-cyclopentane-1-octanoid (OPC 8:0), which in turn undergoes three rounds of  $\beta$ -oxidation to form JA (Delker et al., 2007). Jasmonates such as JA, methyl jasmonate, OPDA, and related cyclopentenones (oxylipins) are ubiquitous, lipid-derived compounds with signaling functions during plant responses to biotic and abiotic stresses (Breithaupt et al., 2006; Wasternack, 2014; Dar et al., 2015). JA levels increase dramatically upon wounding. This increase contributes to the resistance against insect herbivore damage by activating indirect (release of volatile organic compounds) or direct (production of defense proteins) defense responses (Farmer and Ryan, 1990; Creelman et al., 1992; Menke et al., 1999;

Howe, 2004). Studies of *Arabidopsis* mutants defective in either JA accumulation or perception have demonstrated that these mutants are highly susceptible to insect predators (McConn et al., 1997). Numerous experiments have supported the role of JA as a major signaling molecule in defense responses to necrotrophic pathogens (reviewed in Farmer et al., 2003) and biotrophic fungi (Thaler et al., 2004). Exogenous application of methyl jasmonate alleviates the adverse effect of drought stress in cauliflower (Wu et al., 2012) and salt stress in barley and soybean (Walia et al., 2007; Yoon et al., 2009). This response might be facilitated by the enhanced transcript levels and activities of antioxidant enzymes (e.g., ascorbate peroxidases and glutathione peroxidases) (Soares et al., 2010).

Besides its role in plant stress responses, JA acts as a plant-growth regulator. It affects a variety of developmental processes such as fruit ripening (Creelman and Mullet, 1997), root growth (Staswick et al., 1992), tendril coiling (Stelmach et al., 1999), tuber formation (Yoshihara et al., 1989), flower development, pollen maturation (Sanders et al., 2000; Stintzi and Browse, 2000), seed development (Wasternack et al., 2012), and senescence (Parthier, 1990). OPDA is the precursor of JA and belongs to an important class of jasmonates. Until recently, no tools have been available to permit the genetic separation of OPDA and JA effects *in vivo*. However, the studies of *Arabidopsis* plants lacking a functional *opr3* gene (Stintzi and Browse, 2000) have demonstrated that OPDA could be a biologically active substance. JA-deficient *opr3* plants are still capable of resistance to both the dipteran insect *Bradysia impatiens* and the fungal pathogen *Alternaria brassicicola*. This observation suggests that in the absence of JA, OPDA can regulate the plant defense response (Stintzi et al., 2001). Furthermore, the *Arabidopsis opr3* mutant accumulates OPDA after wounding in the absence of JA. These results demonstrate that OPDA is a potent gene regulator during the wound response in the absence of JA (Stintzi et al., 2001).

OPDA induces expression of a subset of genes that are not induced by JA (Farmer and Ryan, 1992; Stintzi et al., 2001; Taki et al., 2005; Ribot et al., 2008). Using a mini-array system consisting of 150 defense genes, Stintzi et al. (2001) have shown that OPDA not only upregulates the genes induced by JA, but also several genes that do not respond to JA. The authors have suggested that OPDA cooperates with JAs to regulate the expression of defense response genes (Stintzi et al., 2001). More recently, using an oligonucleotide array containing 21,500 *Arabidopsis* genes, Taki et al. (2005) have shown that a set of approximately 150 genes is induced by exogenous OPDA, but not by exogenous JA or Me-JA. They have found that approximately half of these OPDA-specific response genes are induced by wounding. These results have supplied another clue to the role of OPDA in the plant defense system. Moreover, OPDA is involved in the regulation of embryo development (Goetz et al., 2012), seed germination (Dave and Graham, 2012), and stomatal opening (Ohashi et al., 2005).

#### Other possible functions

As we mentioned in the previous section, the OPRII subgroup members are involved in the JA biosynthetic pathway. However, the function of OPR I enzymes in plants remains obscure. Several studies have examined the expression levels of the *OPRI* genes under different growth conditions and treatments. The members of this subgroup exhibit organ-specific expression and are differentially expressed during development. Biesgen and Weiler (1999)

have reported that *Arabidopsis AtOPR1* and *AtOPR2* (both OPR1) are transcribed in the roots and leaves but not in the flowers. The rice *OsOPR11* transcript is abundant in callus, leaf, and panicle tissues, while *OsOPR10* transcript is more common in the callus and stem than in the leaves and panicle. *OsOPR6* expression is weak in almost all rice tissues except for the leaves. *OsOPR8* gene is expressed in most rice tissues but not in the stems or panicles (Li et al., 2011). Zhang et al. (2005) have reported that the maize *ZmOPR1* transcript levels in roots, kernels, and ovaries are lower than the levels of the *ZmOPR2* transcript.

Several biotic and abiotic stress factors and signaling molecules enhance the expression of OPR1 genes. It is likely that the enzymes of the OPR1 subgroup are involved in defense responses and signaling. *Arabidopsis AtOPR1* and *AtOPR2* genes are upregulated in response to wounding and ultraviolet irradiation (Biesgen and Weiler, 1999). Weber et al. (2004) have reported that *AtOPR1* is upregulated in response to malondialdehyde, one of the best-known products of lipid oxidation. Zhang et al. (2005) have demonstrated that maize *ZmOPR1* and *ZmOPR2* are induced following inoculation with *Fusarium verticillioides* spores and after treatment with SA. The rice *OsOPR10* gene expression is upregulated in roots after JA and ABA treatment, while *OsOPR8* is strongly expressed under drought conditions, JA treatment, and wounding in shoot tissues (Li et al., 2011). Polyethylene glycol-induced drought stress upregulates the expression of foxtail millet gene *SiOPR1* in the roots only. Its expression level increases with the increasing water loss (Zhang et al., 2007). More recently, Dong et al. (2013) have reported that the overexpression of *TaOPR1* significantly enhances the salinity tolerance in wheat. The heterologous expression of this gene in *Arabidopsis* alleviates root growth restriction in the presence of NaCl and hydrogen peroxide and raises the sensitivity to ABA. These results suggest that OPR1 genes could be used in genetic engineering to enhance the plant stress tolerance. OPRs also participate in the detoxification of exogenous xenobiotic compounds (Mezzari et al., 2005; Skipsey et al., 2011). Beynon et al. (2009) have suggested that *Arabidopsis AtOPR1* and *AtOPR2* play a role in the xenobiotic detoxification process. Recombinant *AtOPR1* and *AtOPR2* proteins react with TNT *in vitro*, transforming it into nitro-reduced TNT derivatives. Furthermore, *Arabidopsis* plants overexpressing OPR1 remove TNT from the liquid culture faster and produce more TNT transformation products than the wild-type plants. It has been reported that OPR1 members catalyze the reduction of several  $\alpha,\beta$ -unsaturated compounds (Hall et al., 2007), which are mostly formed as a result of oxidative damages to the cell (Strassner et al., 1999; Tani et al., 2008). This enzymatic activity and the expression patterns of OPR1 indicate that this subgroup might be involved in the defense responses.

### Conclusions and future perspectives

The OPR gene family is important in the biosynthesis of JA and in the responses to both biotic and abiotic stress factors. The functions of OPR subgroup II have been analyzed in depth in the available publications. However, the functions of the members of OPR1 subgroup remain largely unexplored. Most of the studies investigating these enzymes deal with gene cloning and expression changes in response to hormones and environmental stimuli. Future research should explore the function of OPR1 subgroup members in detail, taking advantage of the available tools for reverse genetics, bioinformatics, and various omics technologies.

### Acknowledgments

Saeid Abu-Romman received support from the Scientific Research Deanship of Al-Balqa' Applied University (Grant No. 109013) for the project "Genomic and Bioinformatics Analysis of Oxo-Phytodienoate Reductases Gene Family in Barley." The authors apologize to colleagues whose work could not be directly cited because of space limitations.

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