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RESEARCH ARTICLE

Arabidopsis AtMPV17, a homolog of mice MPV17, enhances osmotic stress tolerance

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Abstract Mutation in the human *MPV17* gene or the functional yeast orthologue *SYM1* result in mitochondrial DNA depletion. *MPV17* homologs are also found in plants including *Arabidopsis*, but the function of these genes remain unclear. *Arabidopsis* genome contains 10 *MPV17* homologs. Among these, the AtMPV17 protein was localized in mitochondria as MPV17 and SYM1. The yeast *sym1* knock out mutant cannot grow on ethanol-containing medium at 37 °C. *AtMPV17* complements the ethanol growth defection of *sym1* yeast *MPV17* ortholog cells at 37 °C, suggesting that *AtMPV17* is a functional ortholog of *SYM1*. *AtMPV17* knock out mutant, *atmpv17* show similar growth and seed development to those of the wild-type plant on normal growth condition. However, *atmpv17* mutant is more sensitive to ABA and mannitol during germination and seedling growth than wild type plants. Growth retardation of the *atmpv17* knock out mutant on medium containing ABA and mannitol is complemented by *AtMPV17* overexpression. These results suggest that the *AtMPV17* contributes to osmotic stress tolerance in plants.

Keywords At3g24570 · *AtMPV17* · Osmotic stress · Mitochondrial protein

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Introduction

Drought is a severe environmental stress and limits the growth and yield of plants. In order to cope with water deficit, plants have developed strategies involving a number of physiological and morphological modifications that are reflected at the gene expression level. The plant hormone, abscisic acid (ABA) plays a major role in the plant response to water stress (Raghavendra et al. 2010). Reactive oxygen species (ROS) function as signal transduction molecules to regulate different pathways during plant acclimation to abiotic stress, but are also toxic byproducts of stress metabolism (Choudhury et al. 2017). Microarray and RNA sequencing techniques provide insights into the expression of abiotic stress-inducible genes (Seki et al. 2001; Im et al. 2017). Stress response genes include proteins involved in stress signaling, enzymes for compatible solutes, late embryo abundant (LEA) proteins, heat shock proteins (HSPs), and scavengers of reactive oxygen species (ROS) produced by oxidative stress (Hoekstra et al. 2001; Shinozaki and Yamaguchi-Shinozaki 2007; Nakashima et al. 2014; Shinozaki et al. 2015). These stress-induced genes play a role in protecting macromolecules and membranes against water deficit or in regulating gene expression and signal transduction (Shinozaki and Yamaguchi-Shinozaki 2007; Nakashima et al. 2014; Shinozaki et al. 2015). However, a lot of abiotic stress-inducible genes require further study for their molecular and physiological function to be understood.

Previously, we identified and reported on *PyMPV17*, a desiccation response gene detected based on comparison of the transcriptomes of the gametophytic thalli of *Pyropia* under control and desiccation condition (Wi et al. 2020). *PyMPV17* encodes a homolog of MPV17, which is associated with mitochondrial DNA depletion syndromes in

humans and mice (Spinazzola et al. 2006; Lollgene and Weiher 2015). MPV17 homologs have also been studied in zebrafish (*Tra*) and yeast (*SYM1*), in which mutants of these homologs cause different phenotypes, respectively (Weiher et al. 1990; Karasawa et al. 1993; Trott and Morano 2004; Krauss et al. 2013). In yeast, the *MPV17* ortholog *SYM1* is required for growth on an ethanol-containing medium at 37 °C (Trott and Morano 2004). The expression of human *MPV17* in *sym1* mutant yeast cells complements the 37 °C ethanol growth defect, suggesting that these proteins are functional orthologs (Trott and Morano 2004). Genetic data suggest that SYM1 exhibits channel-like properties to transport small molecules, such as oxaloacetate and alpha-ketoglutarate, across the inner mitochondrial membrane (Dallabona et al. 2010; Reinhold et al. 2012). Mutation of *MPV17* gene leads to an increased ROS production ability in mice (Binder et al. 1999; Antonenkov et al. 2015). Recent research has shown that in mice, *mpv17* deficient mutants show a marked increase in rGMPs in mitochondrial DNA (Moss et al. 2017). MPV17 serves to transport nucleotides, such as dGTP, dTTP, or dTMP, from the cytosol to the mitochondria (Rosa et al. 2016; Moss et al. 2017; Alonzo et al. 2018).

MPV17 homologs are found in plants, including *Arabidopsis thanliana*, in which the genome contains 10 *MPV17* homologs. Among them, PMP22 and PMP22-like are located in the peroxisome, four MPV17 homologs are located in the plastid, while other four MPV17 homologs are mitochondrial (Tugal et al. 1999; Murphy et al. 2003; Wiese 2014). Among the four mitochondrial *MPV17* homologs in *Arabidopsis*, *At3g24570* encodes a polypeptide showing the highest amino acid sequence homology with mouse MPV17, but the function of this gene remains unclear. Here, we report that *Arabidopsis At3g24570* encodes a *MPV17* homolog and have, therefore, named it as *AtMPV17*. Genetic analysis demonstrated that *AtMPV17* enhances osmotic stress tolerance in plants.

Materials and methods

Plant materials

Arabidopsis thaliana L. ecotype Colombia-0 (Col-0) was used in this study. Seeds were surface sterilized and germinated on solid Murashige and Skoog (MS) medium, containing 3% sucrose and 1 × SH vitamins (Sigma, St. Louis, MO, USA). The pH of the MS medium was adjusted to 5.7, and 1% phyto agar was added to solidify the mixture. Seeds were sown in plastic pots containing a 3:1 mixture of potting soil and vermiculite. The plants were grown under white light of approximately 2500 lx at 23 °C, with a day/night cycle of 16 h/8 h.

The *AtMPV17* knockout *Arabidopsis* mutant seed, SAIL_747_D10, which has a T-DNA at 145 bp upstream from the *AtMPV17* gene initiation codon (Supplementary Fig. 1A) was obtained from the Syngenta Arabidopsis Insertion Library (SAIL) collection and germinated on MS medium plates containing 25 ug/ml of Basta (phosphinotricin, Duchefa, Netherland). T-DNA insertion in the *AtMPV17* gene of knockout plants was verified by PCR using the gene-specific primers 5′-GCCCAATGATATTGCAACAGC-3′ and 5′-TCGCTGGTACCATCTCCAAAG-3′ for *AtMPV17* and 5′-AAATGGATAAATAGCCTTGCTTCC-3′ and 5′-ATTAGGCACCCCAGGCTTTAC-3′ for the left and right borders of the T-DNA, respectively (Supplementary Fig. 1B and 1C). Expression of *AtMPV17* in *Arabidopsis* plants was verified by RT-PCR using the *AtMPV17* specific primers described above (Supplementary Fig. 1D). The homozygous line of *atmpv17* gene was selected using the Mendelian test on MS agar plates containing Basta and confirmed by PCR analysis (Supplementary Fig. 1B and 1C).

Identification and analysis of *AtMPV17*

The *Arabidopsis* genome contains 10 MPV/PMP22 homologs (Wiese 2014). Among them, the four MPV17 homologs located in the mitochondria were used for sequence comparison and phylogenetic analysis. *At3g24570* encodes a polypeptide showing the highest amino acid sequence homology with mouse MPV17 and is located in the same branch as mouse MPV17. It was, therefore, named as *AtMPV17* and selected for further analysis. Multiple sequence alignments of amino acid sequences and motifs were performed using the ClustalX software. A phylogenic analysis was conducted according to the neighbor-joining method in the MEGA7 program.

The cDNA covering the full ORF of *AtMPV17* was PCR-amplified from total RNA of *Arabidopsis* using the primers 5′-ATGTTGAAGCTTTGGAGATGGTA-3′ and 5′-TACTCCGCCTTGGCCACC-3′. PCR product was cloned into a pGEM T-easy vector (Promega, USA) and sequenced. The putative molecular weights and isoelectric point (pI) values of *AtMPV17* were analyzed using the Geneious R8 (Biomatters Limited, New Zealand) software. Transmembrane domains were predicted using the TMpred program (https://embnet.vital-it.ch/software/TMPRED_form.html).

Cellular localization of AtMPV17

The *AtMPV17* coding region was amplified by PCR to identify the cellular location of the encoded AtMPV17 protein. The full open reading frame (ORF) sequence of the

AtMPV17 cDNA was fused upstream of a reporter gene encoding the green fluorescent protein (GFP) in the p326-CaMV35S-*GFP* plant expression vector (p326-*GFP*) (Lee et al. 2001). This p326-35S-*AtMPV17-GFP* recombinant vector (p326-*AtMPV17-GFP*) was introduced into tobacco (*Nicotiana benthamiana*) protoplasts as described by Yoo et al. (2007). MitoTracker Red (Invitrogen, USA) was used to visualize the mitochondria in tobacco protoplasts according to the manufacturer's instructions. Protoplasts were examined under a laser scanning confocal microscope (Leica TCS SP5, Germany). GFP was excited using a 488 nm laser beam and the emitted signal was detected with a spectral hybrid detector at 500–550 nm.

Complementation assay in yeast

Yeast transformation and complementation assays were conducted as described by Wi et al. (2020). Briefly, the *AtMPV17* coding region was amplified using forward and reverse primers containing an upstream *Xho*I site and a downstream *Bam*HI site and then introduced into the *Xho*I and *Bam*HI sites of the pDR195 vector (Addgene, Plasmid #36028). Recombinant plasmid DNA was introduced into the yeast *Δsym1* cells using the electroporation method, as described by Manivasakam and Schiest (1993). The yeast cells were cultured in yeast extract peptone dextrose (YPD) medium till cultures reached an OD 660 nm of 0.4, after which they were diluted to 10^{-1}–10^{-4} in a yeast extract peptone ethanol (YPE) medium. In total, 10 µL of the diluted cells were plated onto YPE agar medium plates, and then they were cultured in a 38 °C chamber.

Generation of transgenic *Arabidopsis*

The *AtMPV17* coding region was amplified by PCR using gene-specific forward and reverse primers (5′-AGATTG-CAAACTTCAGATA-3′ and 5′-TACTCCGCCTTGGC-CACC-3′) containing the *Xba*I and *Sma*I recognition sequences and introduced into the pBI121 vector under the control of the 35S promoter (Supplementary Fig. 2A). The recombinant vector was introduced into *Agrobacterium tumefaciens* GV3101 cells. The *Arabidopsis atmpv17* mutant was transformed as described previously (Ha et al. 2007), and the transgenic plants were named *atmpv17*-OX. Seeds were surface-sterilized and germinated on MS agar plates containing Basta and kanamycin (50 µg/ml) to select for transgenic plants. Six homozygous transgenic lines were isolated using Mendelian test on MS agar plates containing Basta and kanamycin. *Arabidopsis* genomic DNA was isolated from green leaves using a DNeasy Plant Mini Kit (Qiagen) and used as a PCR template to check for the insertion of the *AtMPV17* gene (Supplementary Fig. 2B). The seeds of homozygous transgenic plants were used for abiotic stress assay.

Abiotic stress tolerance test

In order to assay osmotic stress tolerance, *Arabidopsis* seeds, col_0, *atmpv17*, and *atmpv17*-OX were surface-sterilized and sown on MS agar plates containing 150–300 mM mannitol. To assay the response to ABA, *Arabidopsis* seeds were sown on MS agar medium containing 0.5–1 µM ABA. Seeds were germinated and cultured at 23 °C for 3–5 days under 16 h/8 h light/dark conditions. Seed germination and seedling growth on medium containing ABA or mannitol were reduced compared to those under control conditions. Seedlings sensitive to ABA or mannitol in the culture medium had unopen yellow cotyledons. The ratio of cotyledon greening was obtained from three biological replicates.

Results and discussion

Identification and characterization of *AtMPV17*

Previously, we reported that *PyMPV17,* a desiccation response gene, from the marine red alga *Pyropia yezoensis,* encodes a mouse *MPV17* homolog and plays a role in osmotic stress tolerance (Im et al. 2017; Wi et al. 2020). *MPV17* homologs are found in all eukaryotes, including plants. The *Arabidopsis* genome contains 10 *MPV17* homologs, among them, four homologs encode mitochondrial proteins (Wiese 2014). Comparison of amino acid sequences and phylogenetic analysis of the four *Arabidopsis* mitochondrial MPV17 homologs, mouse and human MPV17, and yeast SYM1, a yeast ortholog of MPV17, showed that *At3g24570* is distinct from other three *Arabidospsis* mitochondrial MPV17 homologs and it was, thus, assigned to the group of animal MPV17 (Fig. 1a). *At3g24570* encodes a polypeptide showing significant amino acid sequence homology with mouse MPV17 (Fig. 1b) and thus named as *AtMPV17*.

The results of the electrophoresis of RT-PCR products formed upon amplification using the *AtMPV17* specific primer set covering the full ORF showed the presence of two transcripts (data not shown). The second band was much weaker and slightly smaller than that of the major transcript cDNA. The *Arabidopsis* information resource (TAIR) show that there are two transcripts for the locus *At3g24570*; *At3g24570.1* and *At3g24570.2* (https://www.arabidopsis.org/servlets/TairObject?type=locus&name=AT3G24570). *At3g24570.1* encodes a polypeptide consisting of 235 amino acid residues, with a molecular weight of 26.95 kDa and a pI of 9.63. In transcript *At3g24570.2*,

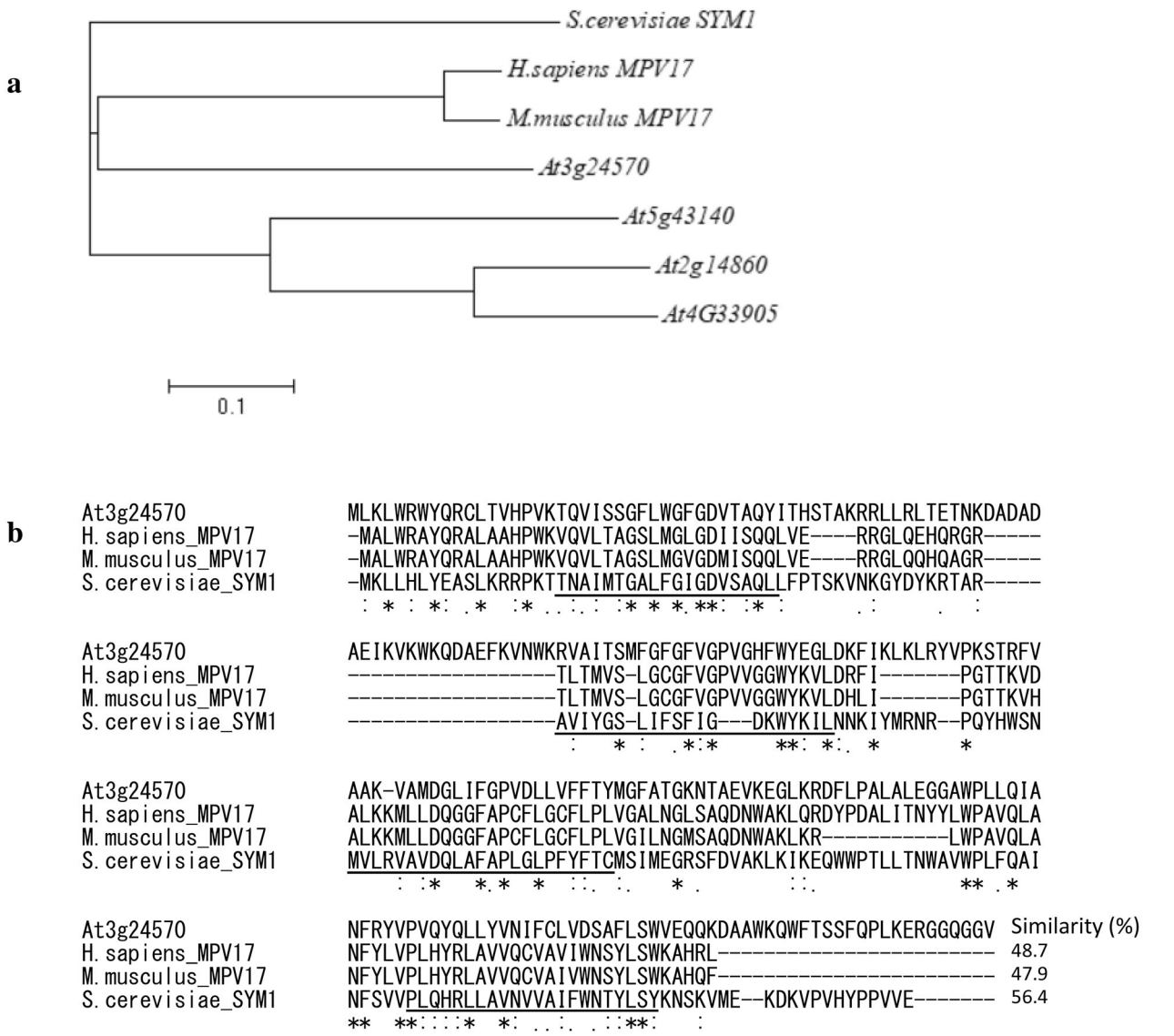

Fig. 1 Amino acid sequence alignment and phylogenic analysis of *AtMPV17*. **a** Phylogenic analysis of four mitochondrial *Arabidopsis AtMPV17* homologs, with its homologs in mouse (*M. musculus_MPV17*), human (*H. sapiens_MPV17*) and yeast (*S. cerevisiae_SYM1*). The *AtMPV17* homologs from *Arabidopsis* are marked with the *Arabidopsis* genome initiative (AGI) gene code. The phylogenic analysis was conducted with the neighbor-joining method using MEGA7 software. **b** Amino acid sequence alignment of *At3g24570* and its homologs in mice, humans and yeast. Four transmembrane domains identified in MPV17 homologs are underlined. Asterisks (*) and colons (:) indicate identical and similar amino acid residues, respectively. The alignment was performed using CLUSTALW

the 3′-splicing site of the first intron is extended by 39 nucleotides. As a result, the transcript *At3g24570.2* encodes a polypeptide of 222 amino acids, shortened by 13 amino acid residues in the second exon. We cloned *At3g24570.1* cDNA and used it for further analysis of *AtMPV17* in this study.

SYM1 and MPV17 are mitochondrial proteins (Spinazzola et al. 2006). When the C-terminus of AtMPV17 was masked by EYFP fusion, AtMPV17 signals were displayed as like a mitochondrial fluorescence pattern (Wiese 2014). To examine the intracellular localization of AtMPV17, we constructed recombinant *AtMPV17-GFP* DNA construct and introduced it into tobacco (*Nicotiana bethamiana*) protoplasts. Tobacco protoplasts were stained with a MitoTracker to visualize the location of mitochondria in the cells. Fluorescence of the AtMPV17-GFP fusion protein overlapped with the MitoTracker signal (Fig. 2). These results demonstrated that AtMPV17 is located in mitochondria, similarly to SYM1 and MPV17. Both MPV17 and SYM1 have four predicted transmembrane domains (Spinazzola et al. 2006; Lollgen and Weiher 2015). Transmembrane domains found in MPV17 were

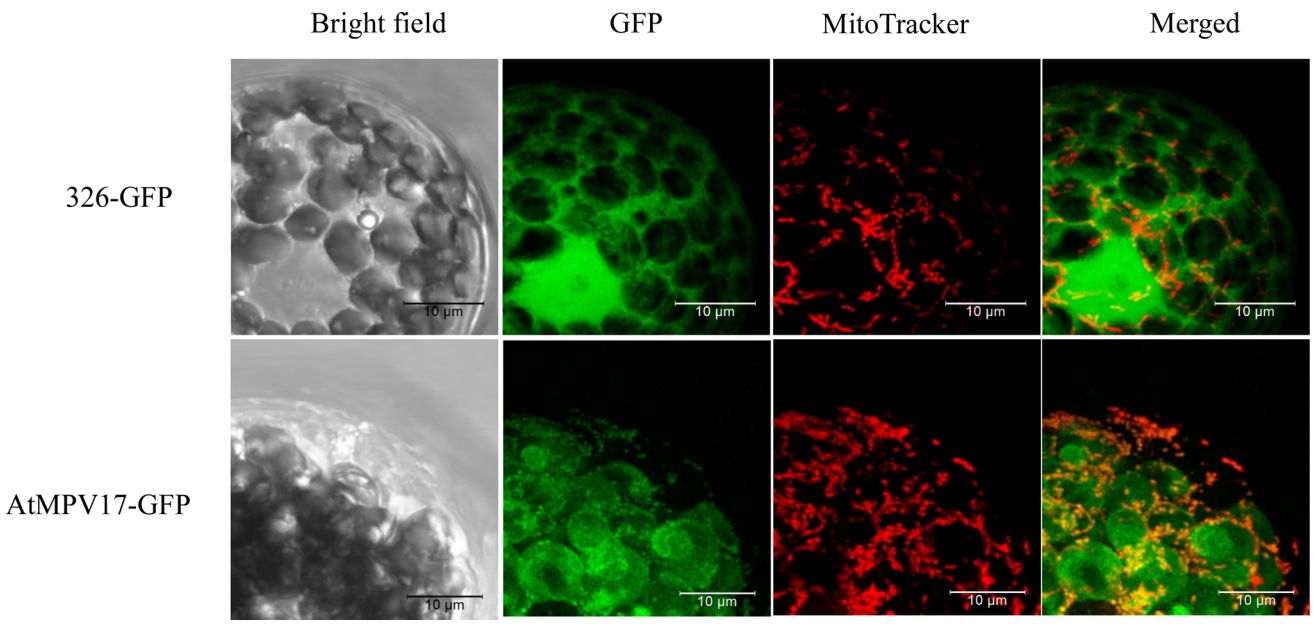

Fig. 2 Subcellular localizations of AtMPV17. A reporter gene encoding green fluorescent protein (GFP) was fused to *AtMPV17* under the control of a CaMV 35S promoter in the 326-*GFP* vector and introduced into tobacco protoplasts. The tobacco protoplasts were examined to evaluate GFP expression using a laser confocal scanning microscope. MitoTracker Red was used to track the mitochondria in the tobacco protoplasts. GFP; cell images taken AtMPV17-GFP location after GFP fluorescence; MitoTracker; cell images with a MitoTracker show the location of mitochondria, Merged; merged image of the GFP and the MitoTracker images. The scale bar represents 10 μm

also present in AtMPV17 (Fig. 1b). Previous studies reported that MPV17 and SYM1 are membrane proteins with four hydrophobic regions, leaving the C- and N-terminus at the same side of the membrane (Spinazzola et al. 2006; Lollgen and Weiher 2015). It has been suggested that SYM1 forms a channel in the lipid membrane and exhibits channel-like properties to transport small molecules, such as oxaloacetate and alpha-ketoglutarate (Dallabona et al. 2010; Reinhold et al. 2012). Recent research showed that MPV17 serves as a transporter that transfers nucleotides, such as dGTP, dTTP, and dTMP, from the cytosol to the mitochondria (Rosa et al. 2016; Moss et al. 2017; Alonzo et al. 2018). However, the physiological and molecular functions of *Arabidopsis MPV17* homologs, including *AtMPV17,* remain unclear.

AtMPV17 complements the phenotype of the yeast *sym1* mutant

The AtMPV17 shares amino acid sequence homology with SYM1, a yeast ortholog of mouse MPV17. The yeast *sym1* KO mutant cannot grow on ethanol-containing medium at 37 °C (Trott and Morano 2004). In order to examine if *AtMPV17* complements the function of *SYM1*, *AtMPV17* cDNA was first introduced into an *sym1* yeast mutant and, then, cell growth in a medium containing ethanol (YPE) at 30 °C and 38 °C was assayed (Fig. 3). The yeast *sym1*

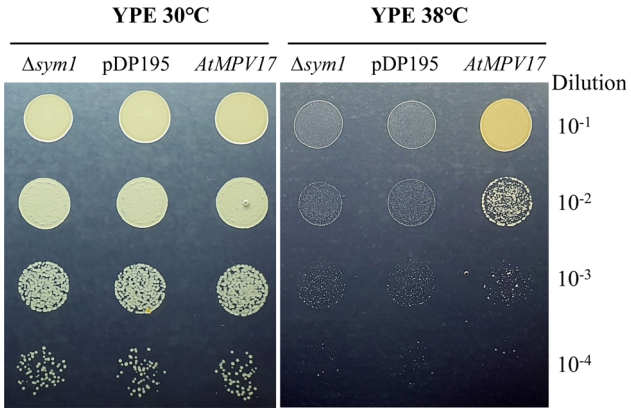

Fig. 3 *AtMPV17* complements the 38 °C ethanol growth defect of the yeast *sym1* mutant. The *AtMPV17* gene was introduced into yeast *sym1* mutant cells (*Δsym1*). The empty vector (pDP195) was also introduced into *sym1* mutant cells and used as control. The yeast cells were diluted to 10^{-1}–10^{-4} in fresh medium, and 10 μL of diluted cells were inoculated onto agar plates to assay the cells' growth in a medium containing ethanol (YPE) at 30 °C or 38 °C. The yeast cells also grew on YPE medium containing ethanol at 30 °C, but not at 38 °C. However, yeast cells that over-expressed *AtMPV17* can grow on the YPE medium at 38 °C. These results demonstrated that *AtMPV17* complemented *SYM1* gene functions in yeast

mutant (*Δsym1*) and *sym1* mutant containing an empty pDP195 vector (pDP195) are used as controls. The *sym1* mutant and *sym1* cells containing pDP195 did not grow on YPE medium at 38 °C, but grew well at 30 °C (Fig. 3). However, *sym1* yeast cells over-expressing *AtMPV17* were

able to grow on YPE medium at 38 °C as well as at 30 °C. These results show that expression of *AtMPV17* in *sym1* mutant yeast cells complements the 38 °C ethanol growth defect of the *sym1* cells. This result demonstrates that *PyMPV17* plays the same role as *SYM1* in yeast cells and that it is a functional ortholog of *SYM1*, indicating that *MPV17* homologs are functionally conserved and evolutionarily important.

AtMPV17 is associated with osmotic stress tolerance in *Arabidopsis*

In order to study *AtMPV17* function in plants, we obtained and analyzed *Arabidopsis* KO mutant, *atmpv17*. Previously, we reported that *PyMPV17* isolated from the marine red algae, *Pyropia yezoensis,* enhances osmotic stress tolerance in the single cell green alga, *Chlamydomons* (Wi et al. 2020). Therefore, we checked if *AtMPV17* was involved in osmotic stress tolerance in *Arabidopsis*. Seeds of the *Arabidopsis* wild-type (Col-0) and *atmpv17* were germinated on MS agar plates with or without mannitol (Fig. 4). No significant differences in phenotype were found between Col-0 and *atmpv17* grown on MS agar plates without mannitol, but the germination and seedling growth of *atmpv17* were significantly delayed compared to those of the control when grown on MS agar plates containing 150 mM mannitol (Fig. 4).

In order to determine if the *AtMPV17* gene rescues delayed germination and seedling growth of *atmpv17* on medium containing mannitol, we generated the transgenic plants overexpressing the *AtMPV17* gene (*atmpv17*-OX). Figure 4 shows the effect of mannitol on seedling growth in the wild-type (Col-0), *atmpv17*, and *atmpv17*-OX lines. No significant differences in phenotype were found between Col-0, *atmpv17*, and *atmpv17*-OX on MS agar plates without mannitol. However, delayed germination and seedling growth of *atmpv17* upon induction of osmotic stress by mannitol treatment was complemented by overexpression of the *AtMPV17* gene (Fig. 4c). The *atmpv17*-OX transgenic plant, overexpressing the *AtMPV17* gene, germinated and grew better than both the wild type and the *atmpv17* plants (Fig. 4a, b). These results demonstrate that *AtMPV17* is associated with tolerance to osmotic stress induced by mannitol in *Arabidopsis*.

The *atmpv17* plants were also much more sensitive to ABA, a plant stress hormone (Fig. 5). When *Arabidopsis* seeds were germinated and cultured on MS medium containing 0.5 μM ABA, *atmpv17* show delayed germination and seedling growth. The sensitivity of *atmpv17* to ABA was also rescued by introducing and expressing the *AtMPV17* gene (*atmpv17*-OX), similarly to the induction of osmotic stress by mannitol treatment (Figs. 4, 5). ABA is accumulated under osmotic stress conditions and plays an important role in the stress response and tolerance of plants (Raghavendra et al. 2010; Nakashima and Yamaguchi-Shinozaki 2013). Under various abiotic stress conditions, as well as dehydration, ABA regulates many genes that may play a role in the abiotic stress tolerance of plants

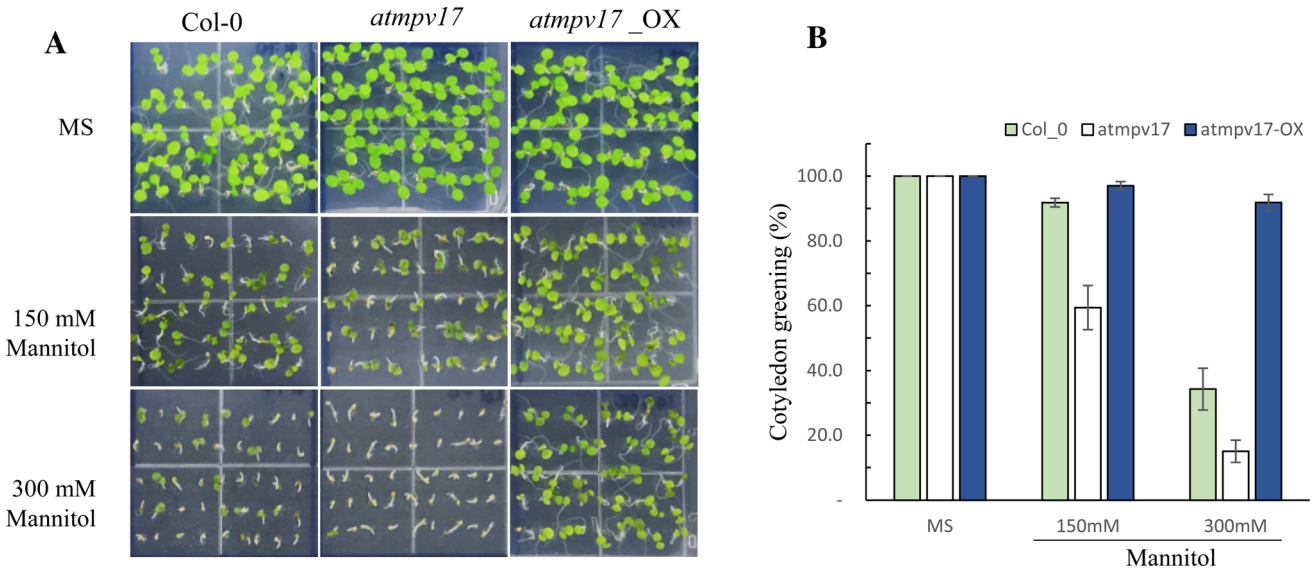

Fig. 4 The *AtMPV17* enhance tolerance for osmotic stress induced by mannitol. The *AtMPV17* gene was cloned into the pBI121 vector under control of the 35S promoter (Supplementary Fig. 2A) and introduced into *atmpv17* knockout mutants to generate transgenic plants (*atmpv17*-OX) that complemented and overexpressed the AtMPV17 gene. A, To analyze the role of the *AtMPV17* gene on mannitol-induced osmotic stress tolerance, *Arabidopsis* seeds, Col-0, *atmpv17* and *atmpv17*-OX were sown on the MS agar plates containing 150 mM or 300 mM mannitol and cultured for 3 days. B, Cotyledon greening indicates the ratio of seedlings with open green cotyledon to total seedlings. The ratio of cotyledon greening was obtained from three biological replicates. n = 45

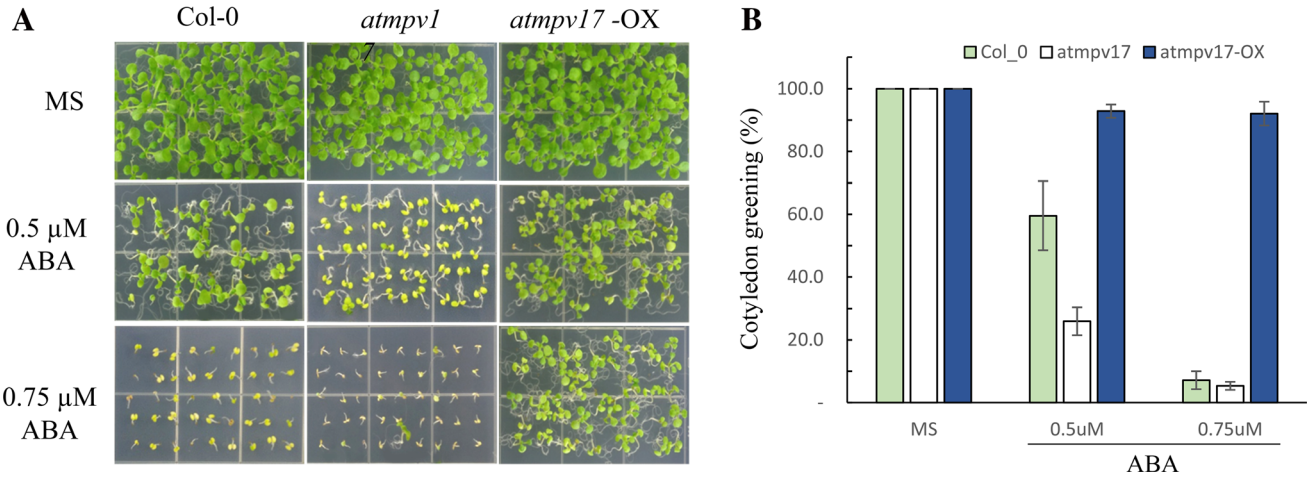

Fig. 5 *AtMPV17* plays a role in abiotic stress conditions. A, To analyze the role of the *AtMPV17* gene in abiotic stress tolerance, *Arabidopsis* seeds, Col-0, *atmpv17* and *atmpv17*-OX were sown on MS agar plates containing 0.5 µM or 0.75 µM ABA, and cultured for 5 days. B, Cotyledon greening indicates the ratio of seedlings with open green cotyledons to total seedlings. The ratio of cotyledon greening was obtained from three biological replicates. n = 45

(Shinozaki and Yamaguchi-Shinozaki 2007; Nakashima et al. 2014).

The molecular functions of *AtMPV17* are unclear, although our genetic analysis showed it to be associated with osmotic stress tolerance. Reactive oxygen species (ROS) are accumulated and involved in the regulation of different pathways under abiotic stress conditions in plants (Choudhury et al. 2017). Recently, we reported that *PyMPV17* identified from marine red algae is also associated with the reduction of malondialdehyde (MDA) increased by osmotic stress (Wi et al. 2020). Binder et al. (1999) showed that enhanced ROS levels were accompanied by the increased formation of lipid peroxidation adducts. It was reported that ROS formation was elevated in *MPV17* gene-deficient mice (Binder al et. 1999; Antonenkov et al. 2015). ROS are one of the most common groups of toxic intermediates produced by abiotic stress and oxidize a wide variety of cellular constituents (Choudhury et al. 2017). These results suggested that *AtMPV17* plays a role in osmotic stress tolerance in plants, including *Arabidopsis*.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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