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Structure and Expression of *OsMRE11* in Rice

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In yeast and human cells, the Mre11 complex, which consists of Mre11, Rad50, and Xrs2/Nbs1 proteins, participates in basic aspects of chromosome metabolism, such as the repair of meiotic DNA breaks and telomere maintenance. In this study, we isolated a full-length cDNA clone, pOsMre11, encoding a rice ortholog of the Mre11 protein. Its predicted protein sequence (M_r = 79.2 kDa and pI value = 5.91) contains a metallo-phosphoesterase domain at its N-terminal region, and a single putative DNA binding domain in the central region of the protein, with significant homology to corresponding motifs in human and yeast Mre11 proteins. The *OsMRE11* gene is constitutively expressed in all tissues examined here, including leaves, roots, tillers, and meristems, as well as in undifferentiated callus cells. When 10-d-old rice seedlings were treated with 0.025% methyl methanesulfonate (MMS) or 30 watts of UV-C light, they were apparently damaged by those genotoxic agents, with plants being more seriously injured by the latter. RNA gel blot analysis showed that the level of *OsMRE11* mRNA remained unchanged during the 1- to 4-d incubation period with MMS. In contrast, *OsMRE11* expression appeared to increase after 3 d of irradiation. In addition, treatments with salicylic acid and jasmonic acid, two important defense-related hormones, significantly activated the *OsMRE11* gene. Based on these results, we discuss the possible functions of the OsMre11 protein in a mechanism by which the stability of rice chromosomes is maintained.

Keywords: DNA repair, genome stability, genotoxic agents, Mre11, *Oryza sativa* L.

An organism's genome is often exposed to various DNA-damaging agents from the extra-cellular environment, e.g., ultraviolet (UV) light, ionizing radiation, and other genotoxic agents, as well as during intracellular processes such as oxygen metabolism. Because this damage is highly detrimental to the cell, its accurate and immediate repair is crucial for maintaining genetic stability (Ljungman and Lane, 2004). DNA double strand breaks (DSBs), i.e., breaks in both strands of a duplex DNA molecule, are particularly dangerous to that stability. In eukaryotic cells, two different repair mechanisms for DSBs have been identified (Christmann et al., 2003; Scharer, 2003). The nonhomologous end joining (NHEJ) pathway, which mediates the ligation of two broken DNA ends, is the major DNA repair method in most higher eukaryotes. Homologous recombination (HR) is predominantly found in single-celled organisms, such as yeast, and uses genetic information from homologous DNA sequences as a template for error-free DSB repair.

In the yeast *Saccharomyces cerevisiae*, the Mre11 protein complex, which consists of Mre11, Rad50, and Xrs2/Nbs1 proteins, has been shown to play an essential role in the initial stage of DSBs repair (Connelly and Leach, 2002; D'Amours and Jackson, 2002; Stracker et al., 2004). Yeast two-hybrid analysis and protein co-immunoprecipitation assays have revealed that these three proteins form a functional complex (Johzuka and Ogawa, 1995; Usui et al., 1998). In addition, a biochemical assay has shown that the Mre11 protein contains double-stranded and single-stranded nuclease activity, suggesting its role in repairing DSBs (Paull and Gellert, 2000; D'Amours and Jackson, 2002). Orthologs of Mre11 have been identified in all organisms investigated to date, including humans and *Arabidopsis*. As with yeast, those human and *Arabidopsis* Mre11 proteins interact with their respective Rad50 proteins (Dolganov et al., 1996; Daoudal-Cotterell et al., 2002). In human cells, Mre11 and Rad50 proteins form a complex at the linear DNA ends, implying a structural role during DSB

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repair (de Jager et al., 2001).

Compared with the extensive knowledge of yeast and human Mre11 proteins, an understanding of the structure and biological roles of the Mre11 protein in higher plants is still rudimentary. Bundock and Hooykaas (2002) have isolated two different *Arabidopsis* knock-out mutants of the *MRE11* gene (*AtMRE11*). Both mutant lines are hypersensitive to DNA-damaging treatment and exhibit lengthened telomeres, suggesting a critical cellular function for AtMre11. Furthermore, an Mre11 deficiency is closely associated with chromosomal instability in *Arabidopsis* somatic cells (Puizina et al., 2004). In the current study, we focused on elucidating the adaptive mechanism in rice, the most important and widely cultivated crop in Korea, against various sources of stress. Our particular aim was to isolate and characterize a broad spectrum of genes induced by genotoxic agents in that species. In addition, we analyzed the expression pattern of the *OsMre11* gene encoding a homolog of Mre11 protein in response to methyl methane sulfonate (MMS) and UV irradiation in rice plants.

MATERIALS AND METHODS

Plant Materials and Experimental Treatments

Dry seeds of rice (*Oryza sativa* L. japonica cv. Dongjin) were surface-sterilized with 30% commercial bleach (0.5% NaOCl) for 10 min, then rinsed numerous times with tap and distilled water. Seeds were germinated in darkness at 30°C for 4 d, and the seedlings were then reared in a growth chamber at 28°C under continuous light. For the experiments with methyl methanesulfonate (MMS), the seedlings were transferred to a liquid MS medium, to which 0.025% MMS (Sigma, USA) was added. Our irradiation treatments involved exposing 10-d-old seedlings, in an MS medium on a clean bench, to 30 watts UV-C light for 1 to 4 d.

Rice plants were also subjected to abiotic stresses and hormones as described previously (Park et al., 2003; Lee et al., 2004), but with slight modifications. To induce salt stress, 10-d-old seedlings were soaked in solutions containing 150 mM NaCl for various time periods. Other leaf tissues were sprayed with 100 μM salicylic acid (SA) or 100 μM jasmonic acid (JA), or were wounded with a razor blade, and then harvested at different time points. For low-temperature stress, the plants were transferred to an incubator set at 4°C. Other seedlings were dehydrated, as described previously (Choi et al., 2002), by placing them under dim light on Whatman 3MM filter paper at room temperature and approximately 60% humidity under dim light. The degree of water stress was determined by their decrease in fresh weight (5 to 30%). At the end of each type of treatment, all tissues were immediately frozen in liquid nitrogen and stored at -80°C until used.

Polymerase Chain Reaction

PCR was conducted as described by Yang et al. (2002), but with modifications. First-strand cDNA was synthesized from 1 μg poly(A)RNA isolated from mature leaves of one-month-old rice plants. It was then PCR-amplified using oligonucleotide primers (5′-CGGGATCCATGCAGGGAGACGAA-3′ and 5′-CGG-GAT- CCTCATCTCCTCCTAACAGC-3′). These primer sequences corresponded to the DNA sequences at the 5′- and 3′-ends, respectively, of the pOsMRE11 cDNA. The *Bam*HI site was included at the 5′-ends of the sense and antisense primers to facilitate subcloning of PCR products. PCR was performed in a total volume of 50 μL containing 5 μL of the first-strand cDNA reaction products, 1 mM primers, 10 mM Tris (pH 8.0), 50 mM KCl, 1.5 mM $MgCl_2$, 0.01% gelatin, 200 mM deoxynucleotides, and 2.5 units of Taq polymerase (Promega, USA). Twenty cycles were carried out, each consisting of 1 min at 94°C, 2 min at 55°C, and 2 min at 72°C, in an automatic thermal cycler (Perkin-Elmer/Cetus, USA). PCR products were separated on an agarose gel, then eluted and re-amplified by PCR to increase the amount of DNA available for subsequent subcloning.

Isolation of Genomic DNA and Southern Blot Analysis

Rice leaf genomic DNA was isolated as described previously (Chae et al., 2000), with modifications. Each gram of leaf tissue was pulverized under liquid nitrogen and suspended in 3 mL extraction buffer [8.0 M urea, 50 mM Tris-Cl (pH 7.5), 20 mM EDTA, 250 mM NaCl, 2% (w/v) sarcosyl, 5% (v/v) phenol, and 20 mM 2-mercaptoethanol]. After successive extractions with phenol/chloroform/isoamylalcohol (25:24:1, v/v), the aqueous phase was concentrated by ethanol precipitation. The pellet was re-suspended in 10 mM Tris-Cl (pH 7.5) and 1 mM EDTA adjusted to a density of 1.5 g mL^{-1} by the addition of CsCl. Afterward, the DNA was centrifuged overnight at 200,000g. The DNA band was collected, extracted

with water-saturated 1-butanol, precipitated by ethanol, and re-suspended in 10 mM Tris-Cl (pH 7.5) and 1 mM EDTA. Rice genomic DNA (10 μg per lane) was digested with appropriate enzymes, separated by electrophoresis in a 0.7% agarose gel, and blotted onto a nylon membrane filter (Amersham,USA). The filter was hybridized to a ^{32}P-labeled pOsMre11 cDNA clone under high stringent conditions.

RNA Isolation and Northern Blot Analysis

Total RNAs of rice plants were obtained through a method adapted from the protocols of Chae et al. (2000). They were first precipitated overnight at 4°C by the addition of 0.3 vol. of 10 M LiCl, then precipitated in ethanol. Afterward, 40 μg of RNA was fractioned by electrophoresis in a 1.0% formaldehyde-agarose gel and blotted onto a nylon membrane filter. Equal loading of RNA was confirmed by visualizing the ethidium bromide-stained ribosomal RNA content under UV light at the end of electrophoresis. The filter was hybridized to various ^{32}P-labeled cDNA probes for rice *OsMRE11* and the actin gene. The blot was then washed and visualized by autoradiography at -80°C. Hybridization signals were quantified with a PhosphorImager (Fuji, Japan).

Subcellular Localization of OsMre11

The soluble-modified green fluorescent protein (smGFP) cDNA was fused in frame to the 3′-end of the full-length pOsMre11 coding region. Transient expression of these smGFP fusion constructs was then examined by introducing the DNAs into onion (*Allium cepa*) epidermal cells via particle bombardment, according to the manufacturer's protocol (Bio-Rad, USA). Fluorescence photographs of those cells were taken by a Axiophot fluorescence microscope (Zeiss, Germany) fitted with fluorescein isothiocyanate filters (excitation filter, 450 to 490 nm; emission filter, 520 nm; dichroic mirror, 510 nm) and Fuji 400 color film. The optimal exposure time was 1 s.

RESULTS AND DISCUSSION

Recent sequencing of the rice genome has allowed us to identify a rice *MRE11* ortholog (*OsMRE11*) (http://kropbase.snu.ac.kr). The *OsMRE11* gene consists of 21 exons interrupted by 20 introns, whose junctions are in agreement with the consensus intron/exon borders of plant genes (Fig. 1A). We have now isolated a full-length cDNA clone encoding OsMre11 from developing rice plants. Poly(A)RNA was obtained from one-month-old leaves. After the first strand cDNA was synthesized from 1 μg of poly(A)RNA, PCR was carried out with oligonucleotides 5′-CGGGATTCATGCAGGGAGACGAA-3′ as the upstream primer, 5′-CGGGATCCTCATCTCCTCCTAACAGC-3′ as the downstream primer, and the first-strand cDNA as template. These primer sequences were generated based on the genomic DNA sequence, and corresponded to the N-terminal (MQGDE) and C-terminal (AVRRT) amino acid sequences, respectively, of the predicted OsMre11 protein. The coding region of *OsMRE11* (Fig. 1B) comprises 2118 b encoding a protein of 706 amino acid residues, with a predicted molecular mass of 79.2 kDa and a pI value of 5.91.

Complete sequencing for pOsMre11 enabled us to assess its structural relationship with other Mre11 proteins. The rice Mre11 protein shares 72% identity with the *Arabidopsis* AtMre11, but has lower sequence identity with other Mre11 proteins, such as yeast XlMre11 (41%) and human HsMre11 (38%) (Fig. 1B). As with other Mre11 homologs, the OsMre11 protein possesses a metallo-phosphoesterase domain at its N-terminal region. Sequence identity among different Mre11 proteins is highest in this phosphoesterase domain, but is less pronounced in the C-terminus (Fig. 1B). In addition, a putative single DNA binding domain is located in the central region. Overall, these architectural conservations suggest that the OsMre11 protein is functionally relevant in rice plants. In the course of an extensive search in the rice genome database, we identified an additional putative Mre11-like protein. This polypeptide is 61% and 56% identical to the OsMre11 at the nucleotide and amino acid levels, respectively (Fig. 1B). The Mre11-like gene (GenBank accession number XP_480352) is localized on Chromosome 8, whereas *OsMRE11* is localized on Chromosome 4 (data not shown).

To assess the exact copy number of *OsMRE11* in the genome, we performed Southern blot analysis. Genomic DNA isolated from mature leaves was digested with *Eco*RI, *Hin*dIII, *Spe*I, or *Xba*I, then hybridized with a ^{32}P-labeled OsMre11 cDNA clone under high stringent conditions. These hybridizations detected only one major band by those enzyme digestions (Fig. 2A), thereby implying that the *OsMRE11* gene is present in a single copy per haploid rice genome.

To investigate the spatial and temporal expression pattern of the *OsMRE11* gene, we used RNA gel blot analysis to monitor the level of corresponding mRNA

in different tissues at various developmental stages. Total RNAs isolated from the leaves, roots, tillers, and meristems of ten-day-old, one-month-old and two-month-old plants were hybridized with ^{32}P-labeled cDNA probes. Transcript levels (~2.4 kb) for *OsMRE11* were substantial in every tissue examined, and at all three stages (Fig. 2B). In addition, the *OsMRE11* gene was expressed in undifferentiated callus cells. These

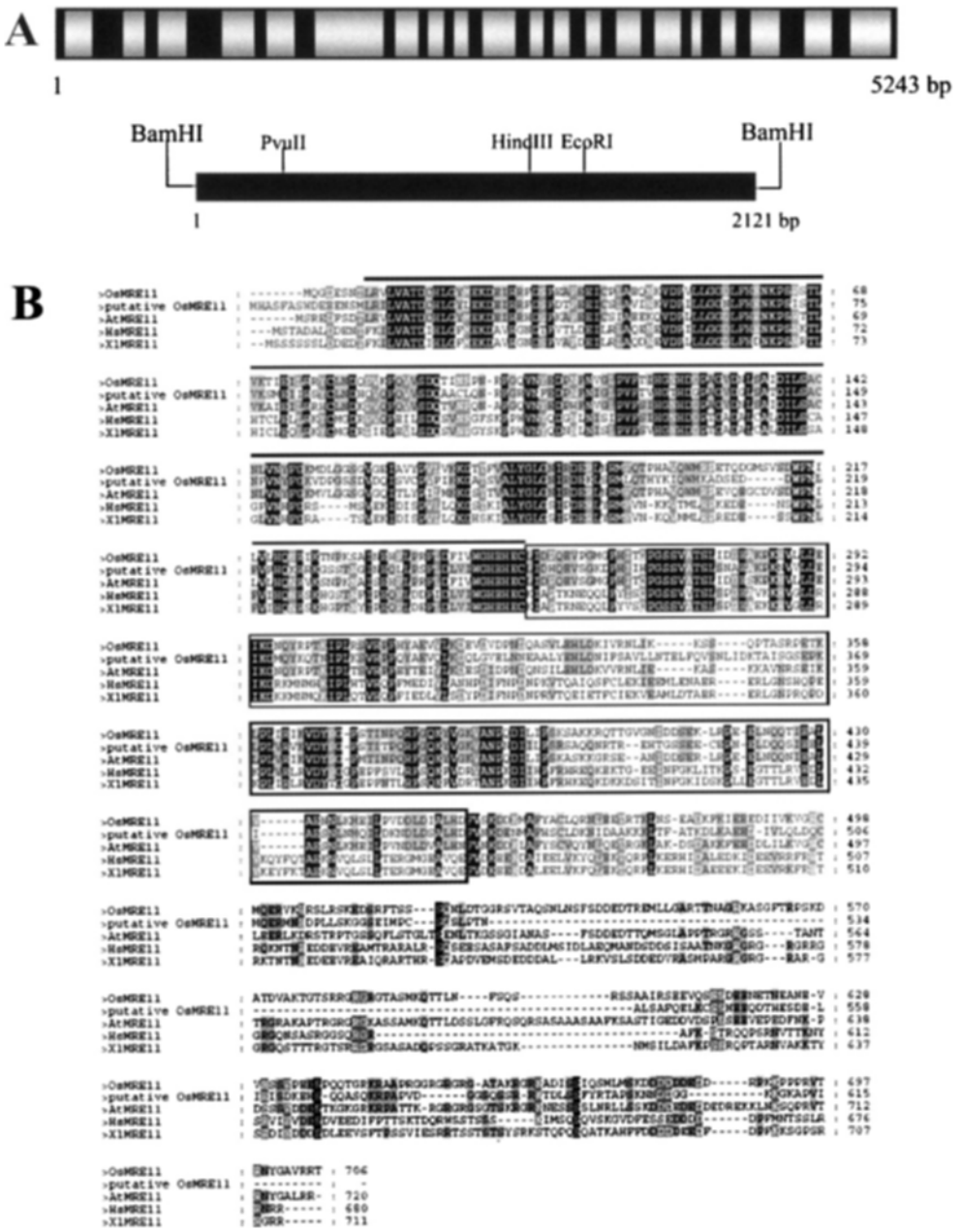

Figure 1. Organization and translation product of rice *OsMRE11* gene. **(A)** Depiction of overall structure of *OsMRE11* and its corresponding cDNA clone, pOsMre11. Exons are shown as filled-in boxes and introns are open boxes. Solid bar represents coding region, while solid lines designate 5′- and 3′-untranslated regions. Sequence of pOsMre11 has been deposited in GenBank database, accession number AY935255. **(B)** Alignment of derived polypeptide sequence of rice OsMre11, a rice Mre11-like protein (GenBank accession number XP_480352)), *Arabidopsis* AtMre11 (Bundock and Hooykaas, 2002), Yeast XlMre11 (GenBank accession number Q9W6K1), and human HsMre11 (Petrini et al., 1995). Amino acid residues that are conserved in at least three of five sequences are shaded, while amino acids identical in all five proteins are shown in black. Amino-terminal metallo phosphoesterase domain is indicated by solid line. Putative DNA binding domain is boxed. Dashes show gaps in amino acid sequences introduced to optimize alignment.

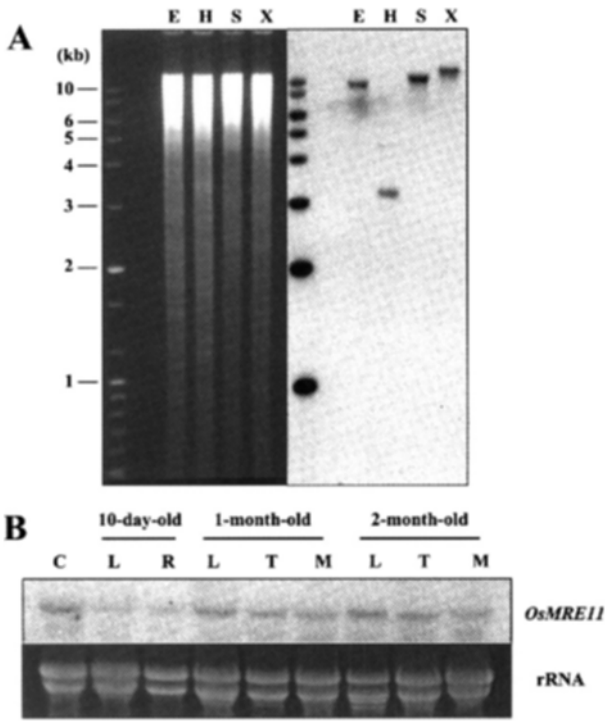

Figure 2. Hybridization analysis of *OsMRE11* genomic DNA and mRNA. **(A)** Southern blot analysis of *OsMRE11* in rice genomic DNA (10 µg per lane), which was digested with *Eco*RI (E), *Hin*dIII (H), *Spe*I (S), or *Xba*I (X), blotted onto nylon membranes, and hybridized with ^{32}P-labeled pOsMre11 cDNA clone. Blot was visualized by autoradiography. **(B)** RNA gel blot analysis of *OsMRE11* gene. Total RNAs (40 µg) isolated from various plant tissues were resolved on a 1.0% agarose-formaldehyde gel, which was then blotted onto a membrane filter. Blot was hybridized to ^{32}P-labeled probe for pOsMre11. Equivalence of RNA loading among lanes was demonstrated by ethidium bromide staining of RNA on gel. C, callus; L, leaf; T, tiller; R, root; M, meristem.

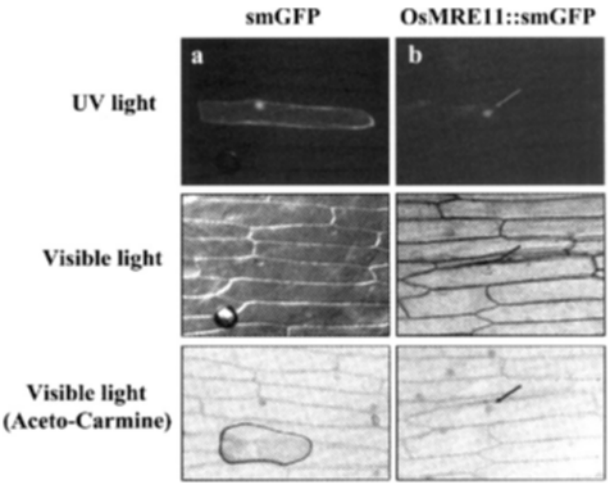

Figure 3. Nuclear localization of *OsMRE11* gene product. The *smGFP* coding region was fused in frame to 3′ end of full-length pOsMre11 coding region. Construct was introduced into onion epidermal cells via particle bombardment, then expressed under control of CaMV 35S promoter. Expression of introduced gene was viewed after 16 h by fluorescence microscopy under UV or visible light.

results are consistent with the view that OsMre11 is essential to normal plant development.

Because Mre11 proteins function in the DNA repair mechanism, we expected them to localize to the nucleus. To confirm this, we carried out an *in vivo* targeting experiment that employed an OsMre11-fused soluble-modified green fluorescent protein (smGFP) as a fluorescent marker in a transient transfection assay. The *smGFP* gene was fused to the 3′ end of the pOsMre11 coding region in frame under the control of the cauliflower mosaic virus (CaMV) 35S promoter, and the resulting construct was introduced into onion epidermal cells. Localization of the fusion protein was then determined by visualization. Here, the control smGFP was uniformly distributed throughout the cell (Fig. 3, panel a), whereas the OsMre11-smGFP fusion protein was exclusively localized to the nucleus (Fig. 3, panel b).

Previous reports have suggested that the Mre11 proteins function in diverse mechanisms of DNA repair and metabolism. Therefore, we next examined whether expression of *OsMRE11* changed in response to DNA-damaging treatments, i.e., 0.025% MMS or 30 watts UV-C irradiation. Our light-grown, 10-d-old seedlings were apparently damaged by these genotoxic agents, although not to the same extent (Fig. 4A). Under our experimental conditions, plants were more heavily injured by UV light than by MMS. For example, after 3 d of exposure to irradiation, it was easy to observe clear discoloration in root and leaf tissues, indicating serious damage to their cellular metabolism (Fig. 4A). In contrast, seedlings survived 3 d of MMS treatment, with apparent browning of the tissues being detected after 4 d of incubation. We then isolated total RNAs from these control and treated plants, and analyzed them by RNA gel blot analysis to monitor possible alterations. Although the level of *OsMRE11* mRNA remained unchanged during 1 to 4 d of MMS treatment (Fig. 4B), its expression increased after 3 d of exposure to UV light. We included the actin gene here as a negative control, and found that its mRNA level remained constant during the entire course of genotoxic treatments. Thus, we demonstrated here that the degree

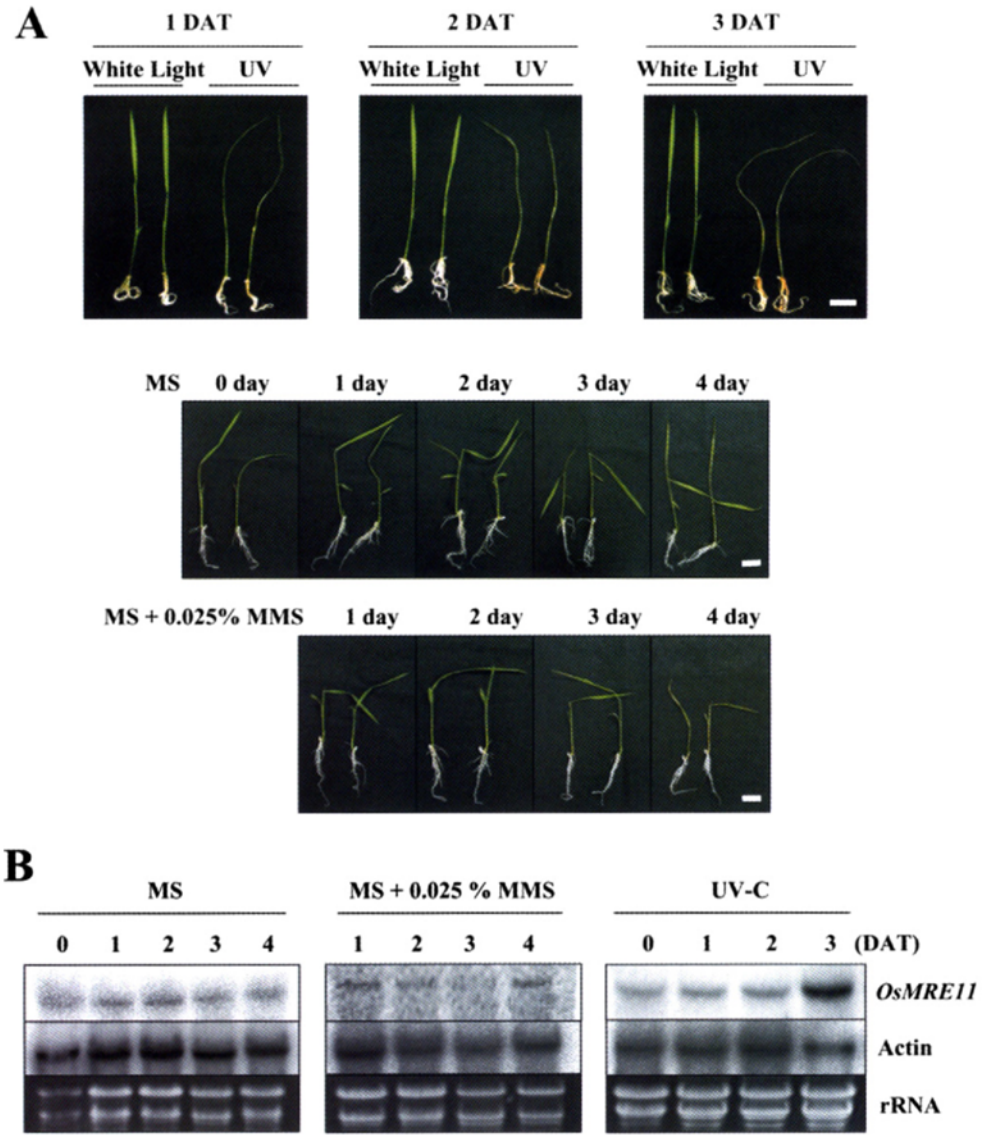

Figure 4. Treatments with genotoxic agents. **(A)** Response of 10-d-old light-grown rice seedlings to DNA damaging treatments, including UV-C irradiation (30 watts) or MMS (0.025%). Time periods are indicated above top row. White bars = 1 cm. **(B)** Expression of *OsMRE11* in response to MMS and UV exposure. Treated plants were harvested at indicated time points, and total RNAs (40 μg) were separated by electrophoresis on 1% formaldehyde-agarose gel, then blotted to Hybond-N nylon membrane. To ensure equal loading of RNA, gel was stained with ethidium bromide after electrophoresis. To confirm complete transfer of RNA to membrane filter, both gel and membrane were viewed under UV light at end of transferring. Filter was hybridized to ^{32}P-labeled pOsMre11 probe, washed and visualized by autoradiography at -70°C with intensifying screen. Actin gene was included in RNA expression experiments as negative control for genotoxic treatments.

of sensitivity in rice seedlings to such potentially damaging genotoxic agents seemed to be correlated with the expression pattern of *OsMRE11* mRNA.

As a next step, we considered the possibility that *OsMRE11* may be induced by abiotic stresses. To assess this possibility, ten-day-old seedlings were subjected to treatment with salt (150 mM NaCl), cold (4°C), drought (5 to 30% loss of fresh weight), or mechanical wounding. RNA gel blot analysis revealed that the expression of *OsMRE11* mRNA was unchanged by those adverse growing conditions (data not shown). We also examined the expression profile of *OsMRE11* in response to 100 μM salicylic acid (SA) and 100 μM jasmonic acid (JA), both of which are important defense-related hormones. There, levels of *OsMRE11* transcript were significantly up-regulated after 24 h of treatment with those stress hormones (Fig. 5). We also included the *OsPHGPX* gene, encod-

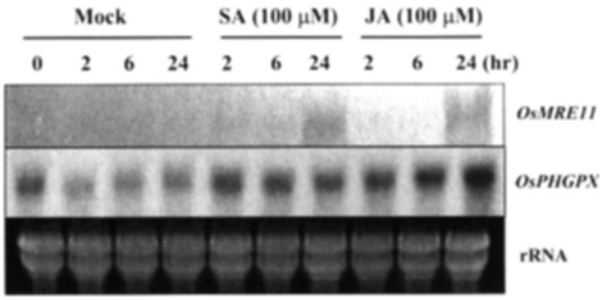

Figure 5. Expression pattern of *OsMRE11* gene after 10-d-old seedlings were subjected to 100 μM SA or 100 μM JA. Treated tissues were harvested at indicated time points and total RNAs (40 μg) were analyzed as described for Figure 4. Filter was hybridized to either ^{32}P-labeled pOsMre11 or pOsPHGPX, then washed and visualized by autoradiography at -70°C with intensifying screen. *OsPHGPX* gene (Agrawal et al., 2002) was included in RNA expression experiments as positive control for SA and JA treatments.

ing a rice glutathione peroxidase, as a positive control (Agrawal et al., 2002), and found that its transcript also was rapidly induced by SA and JA, although with different activation kinetics compared with that of *OsMRE11* mRNA. These results suggested that induction of *OsMRE11* was not an experimental artifact, but was specific to our SA and JA treatments (Fig. 5).

Several lines of evidence in yeast and human cells have shown that the Mre11 complex, a multi-subunit nuclease composed of Mre11, Rad50, and Xrs2/Nbs1, plays an important role in diverse mechanisms for DNA repair. Mutations in the genes that encode each component of this complex cause DNA-damage sensitivity, genome stability, telomere shortening, and defects during meiosis (D'Amours and Jackson, 2002; Stracker et al., 2004). This Mre11 complex has also been implicated in checkpoint signaling and DNA replication. In *Arabidopsis* plants, Mre11 is involved in fundamental aspects of chromosome stability, including the repair of meiotic DNA breaks and telomere maintenance (Bundock and Hooykaas, 2002; Puizina et al., 2004).

Here, we isolated a full-length cDNA clone that encodes rice Mre11 ortholog (Fig. 1) and found that the *OsMRE11* gene was activated by UV irradiation, resulting in apparent tissue damage of rice plants (Fig. 4). Our subcellular localization experiment demonstrated that OsMre11 is predominantly present in the nucleus (Fig. 3). Thus, we interpret these data to suggest that the OsMre11 protein might participate in the mechanism by which the stability of rice chromosomes is maintained. Our results further raise the possibility that OsMre11 may be involved in the process of DNA repair in response to UV irradiation. In addition, the *OsMRE11* gene is up-regulated by both SA and JA in rice seedlings (Fig. 5).

Regardless of these current findings, the functional significance of *OsMRE11* induction in response to stress hormones remains to be determined. It is worth noting that JA levels increase in response to UV light in *Arabidopsis*, and JA appears to be essential for the expression of a subset of UV-responsive genes (Stratmann, 2003). Furthermore, JA production is induced by O_3, one of the typical reactive oxygen species (ROS), which can damage nuclear DNA (Overmyer et al., 2003). On the other hand, SA and ROS have also been proposed as part of a positive feedback loop that amplifies signals leading to defense responses (Overmyer et al., 2003). Therefore, it is tempting to propose that JA- and SA-induced OsMre11 plays a role in the defense mechanism in response to ROS. Recently, we obtained a rice line that contains a mutated *OsMRE11* gene in which a T-DNA copy is integrated. We are now attempting to characterize the phenotype of this mutant plant. This study would bring us one step closer to understanding the mode of action by the Mre11 complex in higher plants.

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