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11. cDNAs encoding wild-type and nonphosphorylatable (T35A) human I-1 were subcloned into the pT7-7 and pT7-5 vectors, respectively. The vectors were transformed into *Escherichia coli* BL21 (DE3). The recombinant proteins were expressed and purified by sequential trichloracetic acid (TCA) precipitation with I-1 purified from rabbit skeletal muscle as a marker. Homogeneously purified I-1 was obtained with preparative SDS–polyacrylamide gel electrophoresis (PAGE), and the purified proteins were phosphorylated with PKA and adenosine triphosphate (ATP)–γ-S [S. Endo, X. Zhou, J. Connor, B. Wang, S. Shenolikar, *Biochemistry* **35**, 5220 (1996)].
12. Field potentials were monitored and HFS delivered as described (*7*); 2 to 3 min after, the final train slices were removed from the recording chamber and placed on a cold plate. The CA1 region was rapidly dissected out and frozen at −70°C. Individual CA1 samples were lysed in 100 μl of lysis buffer [50 mM tris, 4 mM EGTA, 10 mM EDTA, 15 mM Na phosphate, 100 mM β-glycerophosphate, 10 mM NaF, 0.1 mM pepstatin, 1 mM phenylmethylsulfonyl fluoride (PMSF), and 2 mM benzamidine (pH 7.5)] and ground three times for 30 s with a pellet pestle (Kontes glassware, Vineland, NJ). The resulting lysate was spun down at 15,000*g* at 4°C for 10 min, and the supernatant was then assayed for total protein concentration. Twenty micrograms of protein from each sample was run on a 15% SDS-PAGE gel. The samples were transferred onto a polyvinylidene difluoride membrane overnight (25-mA constant current) and then blotted with an antibody to either phosphorylated DARPP-32/I-1 or recombinant human I-1. The monoclonal antibody (mAb) to phosphorylated DARPP-32/I-1 (provided by G. L. Snyder and P. Greengard) (*29*) was blotted at 1/1000 dilution into tris-buffered saline (TBS) + 0.3% Tween 20. It was probed with a horseradish peroxidase (HRP)–conjugated antibody to mouse, diluted 1/2500 in TBS + 0.3% Tween. The polyclonal antibody to human I-1 was blotted at 1/2500 dilution in TBS and probed with 1/2500 dilution of antibody to rabbit. Both blots were developed with enhanced chemiluminescence (ECL), revealing bands at 28 kD, which correspond to native I-1 in these gels.
13. Hippocampal slices were treated and dissected as described above (*7*, *12*). Individual CA1 regions were homogenized in 50 mM tris (pH 7.5), 0.2 mM EDTA, 0.2 mM EGTA, leupeptin (2 μg/ml), aprotinin (2 μg/ml), and 10 nM okadaic acid. Phosphatase activity of 20 ng of protein of CA1 homogenate was measured with the Protein Phosphatase Assay System (GIBCO BRL) in a final concentration of 3.3 nM okadaic acid. With this method, inclusion of 100 nM thiophosphorylated I-1 inhibited >90% of phosphatase activity, confirming the selectivity of the system for PP1.
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19. Hippocampal slices were stimulated and field potentials measured, and the CA1 region was dissected out as described (*7*, *12*). CA1 (2.5 μg) extract from a single CA1 sample was run on a 10% SDS-PAGE, transferred to nitrocellulose, and then blotted with a mAb to Thr[286]-phosphorylated CaMKII α subunit (Affinity Bioreagents, Golden, CO) [B. L. Patton, S. S. Molloy, M. B. Kennedy, *Mol. Biol. Cell* **4**, 159 (1993)] or a polyclonal antibody to CaMKII (Upstate Biotechnology, Lake Placid, NY). The mAb to autophosphorylated CaMKII was blotted at 1/2000 dilution into 5% nonfat dried milk, 0.1% Tween, and 1 μM microcystin-LR in phosphate-buffered saline (PBS). It was probed with an HRP-conjugated antibody to mouse at 1/3000 dilution into 5% nonfat dried milk and 0.1% Tween in PBS. The polyclonal antibody to CaMKII was blotted at 1 μg/ml in 3% nonfat dried milk in PBS and probed with a 1/3000 dilution of antibody to rabbit. Both blots were developed with ECL, revealing a band at ~50 kD (corresponding to the α subunit of CaMKII).
20. Homogenates from individual CA1 regions were assayed for CaMKII activity essentially as described [M. Mayford, J. Wang, E. R. Kandel, T. J. O'Dell, *Cell* **81**, 891 (1995)]. Tissue was homogenized in a buffer containing 50 mM Hepes (pH 7.5), 0.5 mM EDTA, 0.5 mM EGTA, 100 mM sodium pyrophosphate, 25 mM NaF, 10 mM sodium-β-glycerophosphate, 1 μM okadaic acid, leupeptin (60 μg/ml), aprotinin (60 μg/ml), 0.4 mM dithiothreitol (DTT), and 0.1 mM PMSF. Protein concentrations were assayed by Bradford assay (Bio-Rad) with bovine serum albumin (BSA) as the standard. The enzyme reaction mix consisted of 50 mM Hepes (pH 7.5), 10 mM $MgCl_2$, BSA (100 μg/ml), leupeptin (200 μg/ml), 0.4 mM DTT, 0.6 mM EGTA, 0.2 mM EDTA, 2 μM Wiptide (PKA inhibitor; American Peptide), 2 μM protein kinase C (PKC) (19-36) peptide (PKC inhibitor; American Peptide, Sunnyvale, CA), 200 μM ATP, [γ-^{32}P]ATP (100 μCi/ml), and 20 μM autocamtide-2 (CalBiochem), with either 1 mM $CaCl_2$ and calmodulin (5 μg/ml) (total activity) or 2 mM EGTA (Ca^{2+}-independent activity). Enzyme reactions were carried out at 30°C for 1 min in a final volume of 50 μl. Assays were run in quadruplicate. The reaction was initiated by the addition of 2 μg of CA1 homogenate and terminated by the addition of an equal volume of 10% ice-cold TCA. The protein was pelleted, and the supernatant was spotted onto Whatman P81 filter paper and washed three times for 10 min with water. The amount of ^{32}P incorporated into substrate peptide was determined by liquid scintillation counting.
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A Calcium Sensor Homolog Required for Plant Salt Tolerance

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Excessive sodium (Na^+) in salinized soils inhibits plant growth and development. A mutation in the *SOS3* gene renders *Arabidopsis thaliana* plants hypersensitive to Na^+-induced growth inhibition. *SOS3* encodes a protein that shares significant sequence similarity with the calcineurin B subunit from yeast and neuronal calcium sensors from animals. The results suggest that intracellular calcium signaling through a calcineurin-like pathway mediates the beneficial effect of calcium on plant salt tolerance.

Soil salinity stresses plant growth and agricultural productivity (*1*). For many salt-sensitive plants, glycophytes, which include most crop plants, a major part of the growth inhibition is caused by excess Na^+ (*2*). High Na^+ disrupts potassium (K^+) nutrition and, when accumulated in the cytoplasm, inhibits many enzymes (*3–5*). Adding calcium (Ca^{2+}) to root growth medium enhances salt tolerance in glycophytic plants (*6–8*). Ca^{2+} sustains K^+ transport and K^+-Na^+ selectivity in Na^+-challenged plants (*8*).

In *Arabidopsis thaliana*, the recessive *sos3* mutant is hypersensitive to Na^+ and another alkali ion, Li^+ (*9*). Under salt stress, *sos3* plants accumulate more Na^+ and retain less K^+ than the wild type. *sos3* mutant plants are also incapable of growing under low-K^+ conditions. Increased Ca^{2+} in the culture medium can partially suppress the Na^+ hypersensitivity of *sos3* plants and completely suppress the defect in K^+ nutrition (*9*). These phenotypes suggest that the *SOS3* gene product is part of a crucial pathway for mediating the beneficial effect of Ca^{2+} during salt stress (*9*).

The *SOS3* locus is on chromosome V between the molecular markers *nga139* and *CDPK9* (*9*). Mapping of yeast artificial chromosome (YAC) clones containing *nga139* or *CDPK9* (or both) (*10*) placed *SOS3* between the left end of YAC EG20H2 (20H2L) and the left end of YAC CIC12F2 (12F2L) (Fig. 1A). Bacterial artificial chromosome (BAC) clones hybridizing to 20H2L or 12F2L (or to both) were isolat-

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ed, and their end fragments were mapped genetically (Fig. 1A). A binary cosmid clone (COS21-1) hybridizing to the left end of BAC TAMU1E7 (1E7L) and the right end of BAC TAMU2D1 (2D1R) was identified that complements the *sos3* mutant (*11*). 1E7L and 2D1R were sequenced, and the sequences match the MOP9 p1 clone sequenced by the Japanese KAZUSA genome sequencing center (*12*). Genomic DNA fragments corresponding to putative open reading frames (ORFs) between 1E7L and 2D1R were amplified from *sos3* mutant plants and sequenced. The analysis revealed a 9–base pair (bp) deletion in the hypothetical *P3* gene. The deletion is consistent with the *sos3* mutation having been generated by fast neutron bombardment (*9*). Genomic DNA covering the predicted *P3* ORF was amplified from wild-type plants and cloned into the pBIN19 binary vector to complement the *sos3* mutant (*13*). Fifty independent transformants were tested, and all complemented the *sos3* phenotype (Fig. 2).

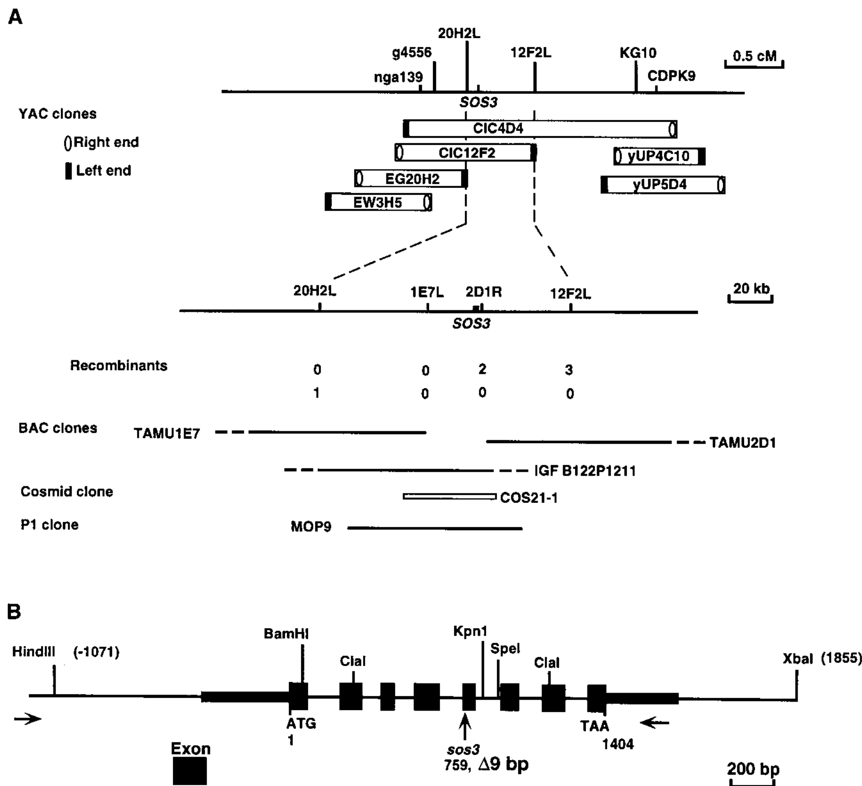

Fig. 1. Cloning and sequence analysis of the *SOS3* gene. (**A**) Summary of positional cloning. Molecular markers nga139 and CDPK9 were used as the starting points for identifying the overlapping YAC clones (*10*). RFLP analysis delimited the *SOS3* locus to a 120–kilobase (kb) region between the left ends of EG20H2 and CIC12F2 (*10*). A BAC contig was assembled within this region (*10*). The left end of TAMU1E7 was used as a probe to isolate cosmid clones for transformation into *sos3* mutant plants. The cosmid COS21-1 rescued *sos3* mutant phenotypes (*11*). Facilitated by the release of the genomic sequence of the entire MOP9 P1 clone (*12*), the *SOS3* gene within the complementing cosmid was identified through sequencing candidate genes from the *sos3* mutant plants; cM, centimorgans. (**B**) Gene structure of *SOS3* and position of the *sos3* mutation. Positions are relative to the initiation codon. Horizontal arrows indicate the left and right borders of the genomic fragment that complemented *sos3* mutant phenotypes.

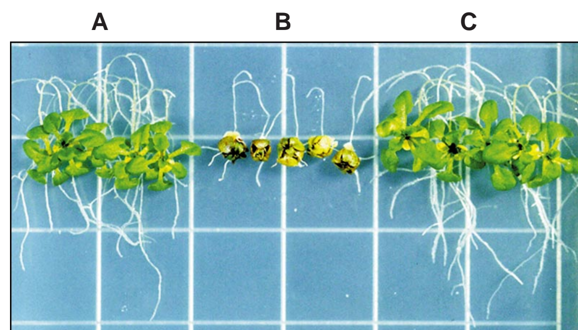

Fig. 2. Complementation of *sos3* by the wild-type *SOS3* gene. (**A**) Wild type. (**B**) *sos3*. (**C**) Transgenic *sos3* containing the wild-type *SOS3* gene. Four-day-old seedlings grown on MS nutrient medium were transferred to a Murashige-Skoog medium supplemented with 100 mM NaCl. The picture was taken 10 days after the transfer to 100 mM NaCl. The plants were grown upside down for observation of root growth after the root-bending assay (*5*). The wild-type, *sos3*, and complemented *sos3* plants did not show any difference when grown on MS medium without supplementation of NaCl (*27*).

The transcribed sequence of the *SOS3* gene was determined by sequencing several overlapping cDNAs obtained by library screening and by reverse transcriptase polymerase chain reaction (RT-PCR) (*14*). The deduced amino acid sequence of the *SOS3* gene is similar to that of a large number of EF hand calcium-binding proteins (*15*). The protein SOS3 is predicted to contain three potential Ca^{2+}-binding sites (*15*) (Fig. 3). The deletion in the *sos3* mutant occurred in a highly conserved region and likely disables Ca^{2+} binding of the second putative EF hand (Fig. 3).

The proteins most similar to the *SOS3* gene product are the B subunit of calcineurin (CnB) (*16*) and animal neuronal calcium sensors (NCS) (*17–19*). Like CnB (*16*) and NCS (*18*), SOS3 also contains a putative myristoylation motif [MGXXXS/T(K)] (*20*, *21*) at the NH_2-terminus. The deduced amino acid sequence of *SOS3* shows 27 to 31% identity and 49 to 51% similarity with CnB from various organisms. Although a calcineurin-like protein has been implicated to be involved in several plant processes (*22*), its biochemical or molecular identity has been elusive. In animal cells, calcineurin plays a key role in diverse cellular functions, including T cell activation, neurotransmission, neutrophil migration, and Na^+ homeostasis (*23*). In the yeast *Saccharomyces cerevisiae*, calcineurin is required to switch K^+ transport from low- to high-affinity mode for improved K^+-Na^+ selectivity during Na^+ stress (*24*). It is also essential for the transcriptional induction of the *ENA1* gene encoding a Na^+–adenosine triphosphatase that pumps Na^+ out of the cell (*24*). Loss-of-function mutations in CnB confer increased sensitivity of yeast cells to Na^+ inhibition (*24*). The functional and sequence similarities between SOS3 and yeast CnB indicate that SOS3 may be part of a plant calcineurin.

With animal NCS, SOS3 shares 30 to 31% identity and 49 to 50% similarity in amino acid sequence. NCS belongs to the recoverin subfamily of EF hand calcium-binding proteins that are expressed mainly in the brain or in photoreceptor cells (*17–19*). Proteins in this subfamily may function either by stimulating protein phosphatases (*17*) or by inhibiting protein kinases (*25*).

Salt stress, like drought, elicits a rapid rise in the cytosolic Ca^{2+} concentration (*7*, *26*). This rise in Ca^{2+} presumably initiates a signaling cascade, resulting in plant adaptive responses. The sequence similarity between SOS3 and CnB and NCS suggests

Fig. 3. Sequence comparison of SOS3 (GenBank accession number AF060553) with yeast CnB subunit (*16*) and frog NCS (*19*). Dots indicate gaps introduced to maximize the sequence alignment. Residues identical or similar in at least two of the three sequences are shaded dark or light, respectively. The three predicted EF hands (*15*) of SOS3 are underlined. Asterisks indicate the basic residues in the Ca^{2+}-binding sites of SOS3 where conserved acidic residues are found in other EF hand proteins (*15*). The double line marks residues deleted in the *sos3-1* allele (*21*).

that SOS3 responds to the Ca^{2+} signal by activating a protein phosphatase or inhibiting a protein kinase (or by doing both) that then regulates K^+ and Na^+ transport systems. Although there do not appear to be conspicuous differences between the cytosolic Ca^{2+} signals elicited by drought and salinity (*26*), subtle differences in their kinetics and subcellular spatial arrangement could result in drought- or salinity-specific responses. The specific role of SOS3 in the tolerance of the ionic but not the osmotic component of salt stress (*9*) strongly supports the existence of ionic stress–specific calcium signaling.

For plants, the amount and interactions of three abundant soil cations, Ca^{2+}, K^+, and Na^+, are essential determinants of potassium nutrition and salt tolerance and therefore greatly affect plant productivity. Our evidence suggests that SOS3 mediates the interaction of K^+, Na^+, and Ca^{2+}.

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Stabilization of Interleukin-2 mRNA by the c-Jun NH_2-Terminal Kinase Pathway

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Signaling pathways that stabilize interleukin-2 (IL-2) messenger RNA (mRNA) in activated T cells were examined. IL-2 mRNA contains at least two cis elements that mediated its stabilization in response to different signals, including activation of c-Jun amino-terminal kinase (JNK). This response was mediated through a cis element encompassing the 5′ untranslated region (UTR) and the beginning of the coding region. IL-2 transcripts lacking this 5′ element no longer responded to JNK activation but were still responsive to other signals generated during T cell activation, which were probably sensed through the 3′ UTR. Thus, multiple elements within IL-2 mRNA modulate its stability in a combinatorial manner, and the JNK pathway controls turnover as well as synthesis of IL-2 mRNA.

Gene expression is controlled at the transcriptional and posttranscriptional levels. Posttranscriptional regulation of gene expression in eukaryotic cells includes mRNA processing, turnover, and translation. Although control of gene transcription by extracellular stimuli through DNA-binding proteins has been widely studied (*1*), relatively little is known about regulation of mRNA turnover (*2*). Stability of mRNA is determined by cis-acting elements within the mRNA molecule, believed to be recognized by regulatory proteins (*2*). Such cis elements positively or negatively modulate mRNA stability and are present throughout the mRNA, including the coding region

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