Chloroplast cyclophilin has been identified as a potential candidate of enzymes in chloroplasts that are regulated by thioredoxin (Motohashi, K., Konno, A., Stumpf, M. T., and Hisabori, T. (2001) Proc. Natl. Acad. Sci. U. S. A. 98, 11224–11229). In the present study we found that the peptidyl-prolyl cis-trans isomerase activity of cyclophilin is fully inactivated in the oxidized form. Reduction of cyclophilin by thioredoxin-m recovered the isomerase activity. Two crucial disulfide bonds were determined by disulfide-linked peptide mapping. The relevance of these cysteines for isomerase activity was confirmed by the mutagenesis studies. Because four cysteines residues in *Arabidopsis thaliana* cyclophilin were conserved in the isoforms from several organisms, it appears that this redox regulation must be one of the common regulation systems of cyclophilin.

Cyclophilin (CyP) is a member of immunophilin superfamily and a target of the immunosuppressive drug cyclosporin A (1). CyP shows peptidyl-prolyl cis-trans isomerase (PPIase) activity and functions as a catalyst in protein folding, facilitating the slow isomerization around Xaa-Pro peptide bonds, which is a general rate-limiting step of protein folding (2, 3). The second major role of CyP is its function as a component in cellular signaling. CyP is essential for the regulation of immunosuppression in mammalian T-cells (4, 5). In plants CyP was first reported by Gasser et al. (6). Breiman et al. (7) found cyclosporin A-sensitive PPIase in chloroplasts. The corresponding gene for this enzyme was cloned in the nuclear genome of *Arabidopsis thaliana* as a single gene targeted to chloroplast (8). Members of the CyP family were identified in various organelles of plants (8–12), and the *A. thaliana* genome project identified at least 10 isoforms of typical cyclophilins (13). However, the physiological significance of CyP in plant cytoplasm and in chloroplasts has been obscure thus far (9, 14, 15). The important function of CyP in the process of T-cell activation for the regulation of immunosuppression in mammalian cells suggests that CyP also has an important physiological role in the plant cell, e.g. in signal transduction. Although CyPs of some eukaryotic organisms have several conserved cysteines, there is still no information available on the role of these cysteines. However, we found that CyP is the potential target protein of chloroplast thioredoxin (Trx) (16).

Trx is a small, ubiquitous, disulfide oxidoreductase with two redox active cysteines at the active center (17–19). The active site sequence (-Trp-Cys-Gly-Pro-Cys-) of Trx is well conserved regardless of the lower overall sequence homology. Trx induces a conformational change in the target protein via exchange of the disulfide bond and thereby modulates the activity of these enzymes. The mechanism for reduction of target proteins by Trx has been studied in vitro (20, 21). The first Cys in the active site sequence of Trx probably forms a mixed disulfide intermediate with the target protein. Then the established disulfide bond between the two redox partners is attacked by another cysteine of Trx. Consequently the reduced form of the target protein is released from Trx, and Trx itself is oxidized.

In the chloroplasts of higher plants two Trx isoforms, designated *f*-type (Trx-*f*) and *m*-type (Trx-*m*) based on their first identified target proteins, are well known (18, 22, 23). The various chloroplast enzymes are regulated by reduction of their internal disulfide or reoxidation of thiols. Calvin cycle enzymes, glyceraldehyde-3-phosphate dehydrogenase, fructose-1,6-bisphosphatase, sedoheptulose-1,7-bisphosphatase, and phosphoribulokinase, are regulated by their redox states, and their activities are enhanced in the reduced enzymes (24). Recently several approaches to identify the target proteins of Trx have been challenged (16, 25, 26). Within the captured candidate proteins, we identified CyP as an unreported Trx target in chloroplasts (16).

In the present study, we revealed that CyP in chloroplasts is an actual target protein of Trx and that the PPIase activity of CyP is regulated by the reduction of the internal disulfide bond by Trx-*m*. In addition, cysteine residues involved in this redox regulation were identified.

**EXPERIMENTAL PROCEDURES**

**Preparation of Trx-m**—The recombinant Trx-*m* was expressed in *Escherichia coli* (27) and was purified as follows. The *E. coli* cells were suspended in 25 mM Tris-HCl (pH 7.5) containing 0.5 mM dithiothreitol (DTT), disrupted by a French pressure cell (5501-M, Ohtake Works, Tokyo) and centrifuged at 100,000 × *g* for 40 min at 4 °C. The supernatant was applied to a DEAE-Toyopearl 650 M column (Toyo, Tokyo) and then eluted with a 0–150 mM linear gradient of NaCl in 25 mM Tris-HCl (pH 7.5) and 0.5 mM DTT. The peak fraction containing Trx-*m* was collected, and solid ammonium sulfate was added to be the final form. Reduction of cyclophilin by thioredoxin-m was confirmed by the mutagenesis studies. Because four cysteines residues in *Arabidopsis thaliana* cyclophilin were conserved in the isoforms from several organisms, it appears that this redox regulation must be one of the common regulation systems of cyclophilin.
calculate the rate constants under various conditions. CyP (3.0 M) oxidized CyP was used; none, the change was measured without CyP. B, $K_m$ values at the various concentration of ammonium sulfate. The protein was incubated with or without Trx-m (3 μM) and DTT (50 μM), red, CyPox; ox, CyPox; M, Trx-m.

Preparation of CyP—E. coli BL21(DE3) cell carrying CyP-pET23c, the plasmid for the wild-type CyP (CyP WT), was cultured at 37°C, and the desired protein expression was induced by the addition of isopropyl-β-D-thiogalactopyranoside (0.5 mM) at 25°C. CyP WT was obtained as soluble protein and purified as described previously (16).

Preparation of the Mutant CyP—To prepare the mutant CyPs, CyP C128S/C175S, CyP C53S/C128S/C170S/C175S (CyPNoCys), the plasmid for the wild-type CyP (CyP WT), was cultured at 37°C for 30 h at 11,000 g. The quantification of Sulfhydryl Groups

The Quantitative Analysis of Sulphhydril Groups—The number of free sulphhydril groups in CyP molecule was determined using 5,5'-dithio-bis(2-nitrobenzoic acid) (34). 5,5'-Dithio-bis(2-nitrobenzoic acid) (final concentration of 1.6 M) was applied to a butyl-Toyopearl 650 M column, and eluted with a 1.6 to 0 M inverse gradient of ammonium sulfate. The peak fraction containing CyP was collected and stored at −80°C. The protein concentration of CyP was determined by the method described previously (30).

To determine the internal disulfide partner cysteines, CyP WT was digested with sequencing grade trypsin (catalog no. V5111, Promega) for 20 h at 37°C. The mixtures of proteolytic peptides were separated by reversed-phase HPLC column (Cosmosil 5C18 AR-300, 4.6 × 150 mm, Nacalai tesque, Kyoto, Japan) at a flow rate of 0.5 ml/min with solvent A (0.1% (v/v) trifluoroacetic acid) and solvent B (90% (v/v) acetonitrile and 1% (v/v) trifluoroacetic acid) using the gradient elution (2% solvent B at 0–5 min, 2–50% solvent B at 5–50 min, 50–80% solvent B at 50–60 min, 80% solvent B at 60–70 min). The peptide fragments were monitored at 220 nm. N-terminal amino acid residues, was used. AMS labeling was carried out as described previously (16), and CyPox and reduced CyP (CyPred) were separated by 15% (w/v) SDS-PAGE.

**Peptide Mapping and Analysis**—To determine the first-order rate constant for spontaneous isomerization (31). The oxidized or reduced form of CyP (3 μM) was incubated with or without Trx-m (3 μM) and DTT (50 μM), and the mobility of the proteins was visualized after SDS-PAGE.

**TABLE I**

| Condition            | $k_{cat}/K_m$ (s⁻¹·μM⁻¹) |
|----------------------|--------------------------|
| CyPox                | 8.32                     |
| CyPox + Trx-m + DTT  | 4.57                     |
| CyPox + DTT          | 1.14                     |
| CyPox + Trx-m        | 0.04                     |
| CyPox                | 0.07                     |

**FIG. 2.** Determination of the CyP redox state by AMS labeling. The oxidized or reduced form of CyP (3 μM) was incubated with or without Trx-m (3 μM) and DTT (50 μM), and the PPIase activity of oxidized form of CyP (CyPox) was purified by the method for CyP WT. However, CyPox; ox, CyPox; M, Trx-m.

The PPIase activity of oxidized or reduced CyP was measured as described (31–33) with minor modifications. An assay mixture containing 35 mM HEPES-NaOH (pH 8.0), 50 μM N-succinyl-Ala-Ala-Pro-Phe-4-methylcoumaryl-7-amide (Peptide Institute) was incubated at 10°C. The chymotrypsin (final concentration 20 μM) was added to initiate the reaction. CyP was added after 15 s. Absorbance at 360 nm was monitored by UV spectrophotometry. First-order rate constants ($k_{cat}/K_m$) were derived by a curve fit to a first-order rate equation ($k_{cat}/K_m = \frac{(A_{ox} - A_{red})}{k_r}$, where $k_r$ is the rate constant). The $k_{cat}/K_m$ values were calculated according to the equation $k_{cat}/K_m = \frac{k_{cat}}{K_m}$ (32).
The PPIase activity of CyP is affected by reduction or oxidation. We measured the PPIase activity using the model substrate peptidylproline. Therefore we examined whether the PPIase activity was measured in the presence of various concentrations of CyPox or CyPred, and the amounts of reactive sulfhydryls were determined from $\epsilon_{412} = 13,380 \text{ M}^{-1}\text{cm}^{-1}$ (35).

**RESULTS**

The Oxidized CyP Is Inactive as PPIase—In the previous study, we reported that chloroplast CyP is a possible target protein for Trx-m and that CyPred could be reduced by Trx-m in vitro (16). CyP, known as a member of the immunophilin superfamily, promotes the isomerization from cis-form to trans-form in peptidylproline. Therefore we examined whether the PPIase activity of CyP is affected by reduction or oxidation. We measured the PPIase activity using the model substrate N-succinyl-Ala-Ala-Pro-The-4-methylcoumaryl-7-amide and monitored the change of the absorbance at 360 nm derived by the release of the methylcoumaryl moiety from the artificial model peptide when the trans-form peptide was digested by $\alpha$-chymotrypsin. A slow increase in absorbance was observed even in the absence of the catalyzing enzyme, indicating that the model substrate was gradually transferred from the cis-form to the trans-form irrespective of PPIase (Fig. 1A, none). The addition of CyPox did not change the rate of increase in absorbance at 360 nm (Fig. 1A, CyPox). Thus, PPIase activity of CyP must be suppressed when CyP is present in the oxidized form. In contrast, the model substrate was rapidly shifted to the trans-form and digested by $\alpha$-chymotrypsin when CyP$_{red}$ was added to the assay mixture (Fig. 1A, CyP$_{red}$). The $K_{\text{abs}}$ value of PPIase activity was measured in the presence of various concentrations of CyP$_{red}$ or CyP$_{ox}$ and the $K_{\text{cat}}/K_{\text{m}}$ values were calculated as described under “Experimental Procedures” (Fig. 1B and Table I). The activity of CyP$_{ox}$ was less than 1% of the CyP$_{red}$ activity, suggesting that CyP is inactive in the oxidized form.

CyP$_{ox}$ Can Be Reduced, and the PPIase Activity Is Reactivated by Trx-m—We examined whether CyP$_{ox}$ could be reduced and the PPIase activity reactivated by Trx-m. When CyP$_{ox}$ was incubated with Trx-m only, PPIase activity was not observed (Fig. 1B). Weak PPIase activity was detected when 50 $\mu$M DTT was used instead of Trx-m. In contrast, PPIase activity recovered to 55% of the rate observed in the reduced state when Trx-m was added together with 50 $\mu$M DTT (Fig. 1B and Table I). Inactivation and partial recovery of PPIase activity was dependent on the redox conditions following the redox state of CyP, which was visualized by AMS labeling (Fig. 2).

Identification of Cysteine Pairs Involved in Disulfide Bond Formation in CyP$_{ox}$—CyP from A. thaliana contains four cysteine residues allowing six different combinations of disulfide bonds. To specify the cysteine pairs involved in disulfide formation that are responsible for the regulation of the PPIase activity, CyP$_{ox}$ was digested by proteases, and the resultant peptide fragments were separated by reversed-phase HPLC after incubation under non-reduced or reduced conditions (Fig. 3). We identified a single redox-responsive peptide fragment in trypsin-digested and in chymotrypsin-digested fragments of CyP$_{ox}$—CyP$_{red}$, respectively (Fig. 3A, TO1, and Fig. 3C, CTO1). Under reduced conditions, TO1 emerged with two specific peaks (Fig. 3B, TR1 and TR2). In the case of the reduced fragments after chymotrypsin digestion, CTO1 disappeared and three specific peaks emerged (Fig. 3D, CTR1, CTR2, and CTR3). The elution profiles of the peptide fragments from CyP$_{red}$ were very similar to those of CyP$_{ox}$ proteolytic fragments after reduction (data not shown). These redox-specific peptide fragments were analyzed by N-terminal peptide sequencing and mass spectrometry (Table II). TO1 obtained by trypsin digestion of CyP$_{ox}$ was composed of two peptides, which were recovered as two peaks, TR1 and TR2, under reduced conditions. The TR1 peptide contains Cys$^{175}$, whereas TR2 contains Cys$^{176}$. Therefore these two cysteines should form the disulfide bond. In the case of chymotrypsin cleavage, CTO1 was composed of two peptides containing Cys$^{53}$ and Cys$^{179}$, respectively. The peptide containing Cys$^{53}$ of CyP was recovered as CTR1 in the reduced frag-
Redox Regulation of Chloroplast Cyclophilin

**Table II**

Peptide mapping analysis of oxidized CyP using N-terminal peptide sequencer and MALDI-TOF mass spectrometry

| Peptide fraction | Peptide fragment | Fragment mass (Calc.) | Fragment mass (Obs.) |
|------------------|------------------|-----------------------|----------------------|
| TO1<sup>4</sup>  | 10<sup>HTGPGILSMAN</sup>ICTVK<sup>131</sup> | Not detected<sup>4</sup> | 2762.3 |
| 11<sup>TYACGLPLDA</sup> | 1164.7 | 1164.8 |
| 12<sup>TYACGLPLDA</sup> | 1164.8 | 1164.8 |
| TR2<sup>4</sup>  | 10<sup>HTGPGILSMAN</sup>ICTVK<sup>131</sup> | Not detected<sup>4</sup> | 2762.9 |
| 11<sup>TGEGKEKY</sup> | 828.4 | 828.4 |
| 12<sup>DVKKKGYRI</sup> | 1178.8 | 1178.6 |
| CTO1<sup>4</sup>  | 51<sup>TGEGKEKY</sup> | Not detected<sup>4</sup> | 1218.8 |
| 52<sup>DGEVPVTENFR</sup> | Not detected<sup>4</sup> | 1558.9 |
| CTR1<sup>2</sup> | 51<sup>TGEGKEKY</sup> | Not determined | 2368.2 |
| 52<sup>DGEVPVTENFR</sup> | Not determined | 888.5 |
| CTR2<sup>2</sup> | 39<sup>GEVVPVTEN</sup>CTGEGKY<sup>59</sup> | Not determined | 888.4 |
| 49<sup>GEVVPVTEN</sup>CTGEGKY<sup>59</sup> | Not determined | 888.4 |
| CTR3<sup>2</sup> | 11<sup>ACEGLPLDA</sup> | 888.5 | 888.4 |

<sup>4</sup> Residue numbers denote the amino acid positions in the sequence of the mature protein. The underlines indicate the amino acid sequences determined by N-terminal peptide sequencer.

<sup>5</sup> Obs., observed mass (m/z) estimated by matrix-assisted laser desorption ionization/time-of-flight (MALDI-TOF) mass spectrometry.

<sup>6</sup> Calc., calculated monoisotopic mass of a single-charged molecule ([M + H]<sup>+</sup>) based on the assigned peptide sequence.

<sup>7</sup> These fractions were analyzed by MALDI-TOF mass spectrometry after reduction with DTT.

<sup>8</sup> Because of signal suppression by matrix molecules in matrix-assisted laser desorption ionization, the signals corresponding to the peptides were not detected.

<sup>9</sup> Peptide sequencing of this fraction indicated that this fragment was digested by chymotrypsin just after Tyr<sup>59</sup>.

![Fig. 4. The suggested disulfide bonds in CyP and the redox state of Cys mutants. A, the identified disulfide bonds in CyP are presented schematically. B, the oxidized (ox) or reduced (red) form of CyP mutants (3 µM) was incubated with Trx-m (3 µM) or DTT (50 µM) or both. The redox states of CyP were monitored by the AMS labeling method. In lane "red," original CyPs were AMS-labeled; lane "ox," CyPs were oxidized before AMS-labeling; lane "ox + DTT + M," oxidized CyPs were incubated with Trx-m and DTT. WT, wild type.](http://www.jbc.org/)

DISCUSSION

CyP Is a Trx-Regulated Enzyme—In the present study, we observed that the PPIase activity of CyP is modulated by the redox state of the molecule and revealed that CyP<sub>ox</sub> is an inactive PPIase, whereas CyP<sub>red</sub> is an active one (Fig. 1). A disulfide bond in CyP<sub>ox</sub> was definitively reduced by Trx<sub>m</sub>, and the PPIase activity of CyP was recovered by the reduction of disulfide bonds in CyP. We identified two critical disulfide bonds involved in the thiol modulation of PPIase activity, Cys<sup>53</sup>–Cys<sup>170</sup> and Cys<sup>128</sup>–Cys<sup>175</sup>.
Cyclophilin 3 from *Caenorhabditis elegans* has four cysteine residues, which correspond to the residues in *A. thaliana*. Their amino acid sequence homology is very high; the identity of the amino acids was 65%. The crystal structure of cyclophilin 3 has been reported (36), and the distance between Cα-Cα in each disulfide bond pair of CyP<sub>A</sub> in *A. thaliana* could be estimated based on the coordinates of the three-dimensional structure of cyclophilin 3. The distances between Cα-Cα in Cys<sup>63</sup>-Cys<sup>170</sup> and Cys<sup>125</sup>-Cys<sup>175</sup> was estimated as 16.49 and 18.91 Å, respectively. When Dorman et al. (36) reported the structure, they suggested the possible disulfide bond formation in cyclophilin 3 because the distance between the sulfur atoms of Cys<sup>40</sup> and Cys<sup>128</sup> was close enough (5.38 Å). Therefore, disulfide bond formation between Cys<sup>53</sup> and Cys<sup>175</sup> has not been found in our case (Table II and Fig. 4). As the calculation network involving CyP in chloroplasts. Further studies are necessary to clarify the physiological significance of redox regulation of CyP together with structure analysis to understand the redox regulation of PPIase activity.

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Chloroplast Cyclophilin Is a Target Protein of Thioredoxin: THIOL MODULATION OF THE PEPTIDYL-PROLYL CIS-TRANS ISOMERASE ACTIVITY

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