Minireview

Molecular evolution of the modulator of chloroplast ATP synthase: origin of the conformational change dependent regulation

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Abstract Chloroplast ATP synthase synthesizes ATP by utilizing a proton gradient as an energy supply, which is generated by photosynthetic electron transport. The activity of the chloroplast ATP synthase is regulated in several specific ways to avoid futile hydrolysis of ATP under various physiological conditions. Several regulatory signals such as $\Delta\mu H^+$, tight binding of ADP and its release, thiol modulation, and inhibition by the intrinsic inhibitory subunit ε are sensed by this complex. In this review, we describe the function of two regulatory subunits, γ and ε, of ATP synthase based on their possible conformational changes and discuss the evolutionary origin of these regulation systems.

Key words: Chloroplast ATP synthase; Gamma subunit; Redox regulation; Epsilon subunit

1. Introduction

ATP synthase occurs ubiquitously on energy transducing membranes such as chloroplast thylakoid membranes, mitochondrial inner membranes, and bacterial plasma membranes. ATP synthase synthesizes ATP from ADP and phosphate by utilization of a proton gradient across the membranes, which is formed by the photosynthetic or respiratory electron transfer chain [1]. The water-soluble, membrane peripheral sector of ATP synthase is called F_1. F_1 consists of five subunits with a stoichiometry of $\alpha_3\beta_3\gamma_1\delta_1\varepsilon_1$ [2]. F_o is the hydrophobic membrane-spanning sector and is composed of $a_1b_2c_{10-14}$ [3–6].

Three catalytic sites for ATP synthesis and hydrolysis are located on the β subunits at the interface with the α subunits and three non-catalytic sites on the α subunits at the interface with the β subunits [7]. Based on the amino acid sequences and their molecular structures, the α and β subunits are related proteins. Fig. 1 shows the phylogenetic trees for α and β subunits. Obviously, most of the selected sequences which are adopted for the calculation of the tree showed similar genetic distances from the virtual origin. For each subunit, we could not observe groups with marked differences to the majority, while organisms with a similar origin seem to be very close (bacteria with Na^+-ATP synthase, cyanobacteria and chloroplasts, and mitochondria, respectively) and were categorized in the same group. In addition, the number of conserved amino acid residues within the intended sequences, which are identical in the homologous regions of all of the exemplified organisms in the figure, was more than 20% for both α and β subunits. These values were extremely high compared with those for the γ (4.3%) and ε (3.7%) subunits of F_oF_1.

The γ subunit, the central axis located in the $\alpha_3\beta_3$ hexagon, is functionally important to confer catalytic cooperativity within the three catalytic sites [8]. Relative rotation between the $\alpha_3\beta_3$ hexagon and the γ subunit was first postulated by P.D. Boyer based on the analysis of catalytic site cooperativity [9]. In 1997, H. Noji et al. succeeded in video-recording the unidirectional rotation of an actin filament attached to the γ subunit of the $\alpha_3\beta_3\gamma$ complex [10]. In this experiment, they immobilized a partial complex of F_1 from the thermophilic bacterium *Bacillus* PS3 on a glass surface and observed the rotation of γ during ATP hydrolysis. Rotation of the γ subunit in *Escherichia coli* F_1 (EF_1) [11,12] and chloroplast F_1 (CF_1) [13] were also demonstrated using the same method. In this way the relative rotation of the γ subunit against the $\alpha_3\beta_3$ hexagon was confirmed in all major F_1-ATPases.

In contrast to other F_oF_1, CF_oCF_1 is a latent enzyme, which in vivo is activated by $\Delta\mu H^+$ across the thylakoid membrane [14]. In addition, the activity of CF_oCF_1 is modulated by the redox state of two cysteines in the γ subunit. The enzyme becomes more active when the disulfide bond is reduced by thioredoxin, which is reduced by the photosynthetic electron transport system [15,16]. Another physical regulator of CF_oCF_1 is the ε subunit, which is an intrinsic inhibitor subunit. From crystal structure analysis it was suggested that the ε subunit may have at least two different conformations within the complex [17–19]. In addition, it is reported that when the ε subunit of EF_1 takes the conformation that allows the carboxy-terminal α-helix region to reach the β subunit in the complex, the ε subunit inhibits ATP hydrolysis activity but not ATP synthesis activity [20]. The accumulated information on the γ and ε subunits obtained from the structural and biochemical aspects allows a more detailed understanding of the molecular mechanism of the regulation based on the conformational change of these subunits in the complex.

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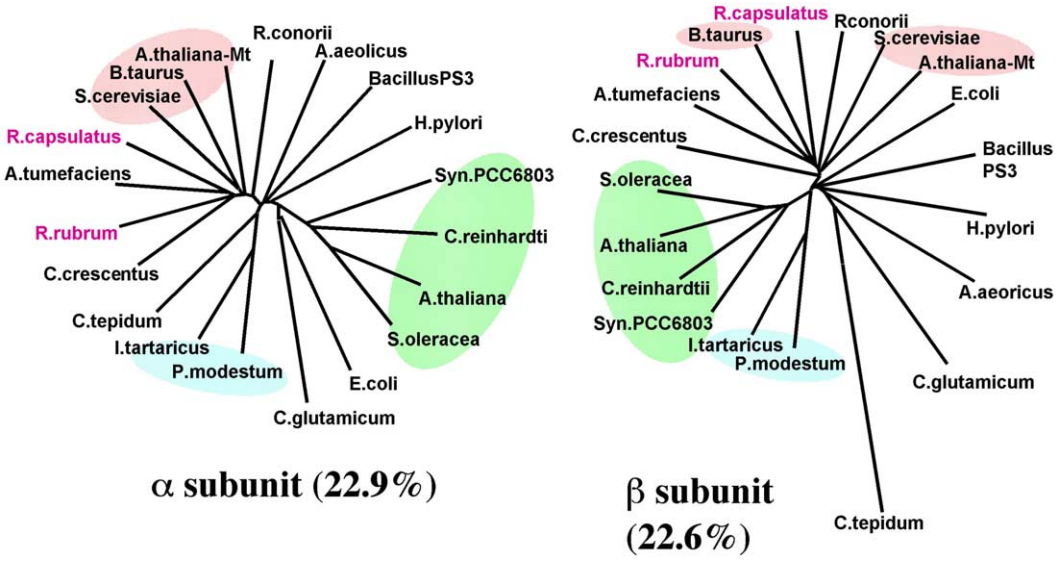

Fig. 1. Unrooted phylogenetic tree of the α and β subunits of ATP synthase. Phylogenetic relationships were analyzed with the DIAGLINE multiple sequence alignment algorithm [53]. The bacteria with Na^+-ATP synthase are marked in blue. The sequences related to chloroplast are marked in green, and those related to mitochondria are marked in red. Photosynthetic bacteria are purple-colored. The accession numbers for the proteins shown in the tree for the α subunit are: *Propionigenium modestum*, P29706; *Ilyobacter tartaricus*, AAM94911; *Chlorobium tepidum*, AAM73250; *Caulobacter crescentus* (caulobacter) G87676; *Rhodospirillum rubrum*, S08581; *Agrobacterium tumefaciens*, H97673; *Rhodobacter capsulatus*, P72245; *Saccharomyces cerevisiae*, S45401; *Bos taurus*, P19483; mitochondria of *Arabidopsis thaliana* (*A. thaliana*-Mt), P92549; *Rickettsia conorii*, Q92G86; *Aquifex aeolicus*, G70359; *Bacillus* PS3, S01401; *Helicobacter pylori*, P55987; *Synechocystis* sp. 6803, S17751; *Chlamydomonas reinhardtii*, 1913451A; *A. thaliana*, P56757; *Spinacia oleracea*, S00584; *Escherichia coli*, P00822; *Corynebacterium glutamicum*, BAB98603. For the β subunit: *P. modestum*, P29707; *I. tartaricus*, AAM94913; *Synechocystis* sp. 6803, P26527; *C. reinhardtii*, C24829; *A. thaliana*, P19366; *S. oleracea*, P00825; *C. crescentus*, E87676; *A. tumefaciens*, AE2898; *R. rubrum*, P05038; *B. taurus*, P00829; *R. capsulatus*, P72247; *R. conorii*, Q92G88; *S. cerevisiae*, S57144; *A. thaliana*-Mt, BAC43182; *E. coli*, B91213; *Bacillus* PS3, P07677; *H. pylori*, P55988; *A. aeolicus*, O67828; *C. glutamicum*, P42464; *C. tepidum*, AAM72266. The given percentages show the ratio of the completely conserved amino acids in the whole sequences used for the calculation of these phylogenetic trees (for detail, see text).

2. The characteristic redox regulation of the chloroplast ATP synthase

The chloroplast ATP synthase is a thiol enzyme and the activity is modulated by the redox state of two cysteines located on the γ subunit after membrane potential dependent activation [15,16]. Based on comparison of the amino acid sequence of CF_1-γ with that of MF_1-γ and the reported structure for MF_1 [17], the key region for the redox regulation (35 amino acid residues) must be inserted around the marked position shown in Fig. 2. Although the three-dimensional structure of CF_1-γ including this inserted region is not solved yet, the secondary structure prediction suggests that the inserted regulatory region is mainly composed of a long loop with a twice coiled short α-helix. According to this prediction, the inserted sequence must have enough length to reach the lower part of the α or β subunits. If this is the case, the possible interaction between a part of the regulatory region of the γ subunit and of the αβ hexagon must be important for regulation of the rotation of the γ subunit as suggested by observation of the regulation of rotation of the single molecule [21]. In that study, a frequent long pause during rotation under oxidizing conditions was observed, though the rate of counter-clockwise rotation of γ in the complex was almost the same under reducing and oxidizing conditions. Deletion of the three negatively charged residues (^{210}Glu-^{211}Asp-^{212}Glu) near the regulatory cysteines can reverse the redox regulation of ATP hydrolysis activity [22]. In the case of this mutant, the redox regulation of the rotation of γ was also reversed (Ueoka-Nakanishi and Hisabori, unpublished). In contrast, deletion of the other portion of the regulatory region did not induce this kind of inverse regulation [22].

When we observed the redox regulation of the rotation at the single molecule level, we recognized that some of the enzyme molecules can rotate smoothly even under oxidizing conditions and this rotation rate was similar to the revolution rate under reducing conditions (see [21], Fig. 2). The distinct difference of the rotation under these two states was observed from the length and the frequency of the pause during rotation. From this study, we proposed a new idea on the mechanism of the suppression of the enzyme activity when the γ subunit is in the oxidized state. Because we often observed the normal rate of rotation even under oxidizing conditions, we concluded that the γ subunit potentially is able to rotate similarly as under reducing conditions. However, we observed an increase of the long pauses under oxidizing conditions, suggesting that the regulatory region will induce the non-rotation state frequently when the regulatory cysteines form a disulfide bridge. The lower enzyme activity under oxidizing conditions must therefore be a consequence of the change of the equilibrium between the rotation and the pause.

To study the significance of this regulatory region in the F_oF_1 complex, we recently constructed a chimeric F_oF_1 complex in which the major part is the thermophilic F_oF_1 while the γ or ε subunits or both are substituted with the respective subunits from CF_1. Redox regulation of the activity of this chimeric F_oF_1 complex was only observed when both the γ and ε subunits were derived from CF_1, suggesting that the proper

combination of these two subunits and their interaction are especially important for the regulation (Konno and Hisabori, unpublished).

Hence, the redox regulatory sequence fragment inserted into the γ subunit has various interesting features and raises the question about the origin of this domain. Fig. 3 shows the phylogenetic tree of the γ subunits. The γ subunit shows a low degree of sequence conservation even at the conserved structural domains, the amino-terminal and carboxy-terminal α-helices and Rossman fold domains. Only 4% of the amino acid residues within the conserved structural domains are identical. In this tree, cyanobacteria and the chloroplasts of green algae and higher plants are obviously located in the same group, although F_1 from the thylakoid membranes of cyanobacteria is not a thiol enzyme [23]. Both γ subunits from higher plant CF_1 and cyanobacterial F_1 possess inserted amino acid residues compared to other bacterial or mitochondrial F_1-γ. The remarkable difference between the inserted region of cyanobacterial F_1-γ and that of the chloroplast F_1-γ is due to a further insertion of nine amino acid residues including two regulatory cysteines [24]. The difference in the inserted regions is small, and the introduction of nine amino acid residues from spinach CF_1-γ into the counter position on *Synechocystis* F_1-γ made the cyanobacterial enzyme redox sensitive [25,26].

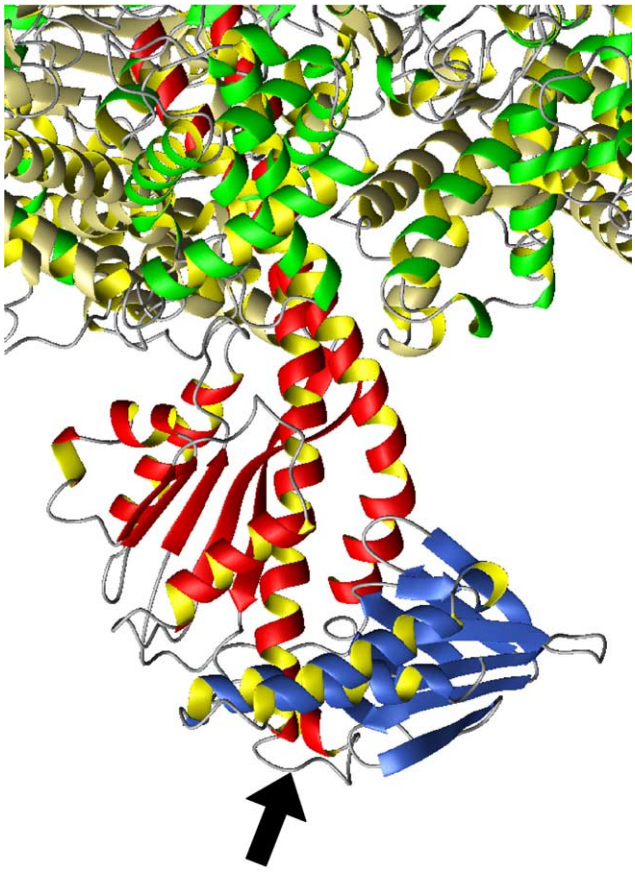

Fig. 2. Three-dimensional structure of the γ and ε subunits in the F_1 complex. The structure was drawn with the protein molecule visualizing software, Molmol, using the coordinates of the mitochondrial F_1-ATPase provided by Gibbons et al. [17]. The γ subunit is shown in red and the ε subunit (mitochondrial δ subunit) in blue. The original mitochondrial ε subunit is omitted. The position of the specific insertion on the chloroplast γ subunit is shown by the arrow.

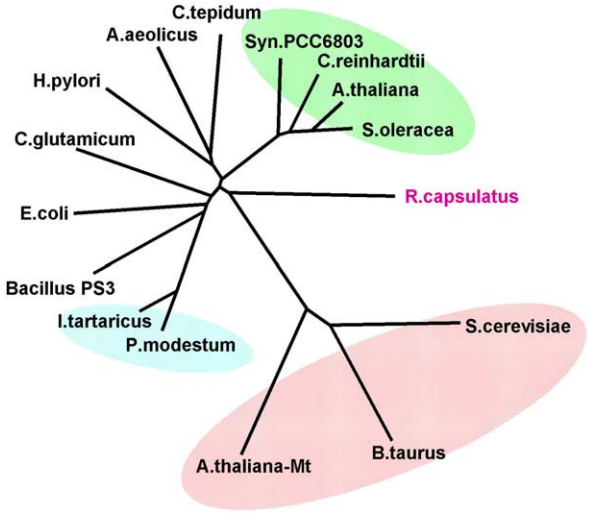

Fig. 3. Phylogenetic tree of the γ subunit. Phylogenetic relationships were analyzed as in Fig. 1. The use of color is as in Fig. 1. The accession numbers for the proteins shown in the tree are: *P. modestum*, S29040; *I. tartaricus*, AAM94912; *Bacillus* PS3, P09222; *E. coli*, P00837; *C. glutamicum*, BAB98604; *H. pylori*, P56082; *A. aeolicus*, AAC07791; *C. tepidum*, AAM73249; *Synechocystis* sp. 6803, S08257; *C. reinhardtii*, P12113; *A. thaliana*, Q01908; *S. oleracea*, P05435; *R. capsulatus*, P72246; *S. cerevisiae*, P38077; *B. taurus*, P05631; *A. thaliana*-Mt, Q96250.

However, neither this inserted regulatory region nor these specific nine amino acid residues show similarity to other sequences that are registered in the protein databases. This suggests that the sequence for the regulatory region developed independently in the cyanobacteria first, then continued in the chloroplasts, finally resulting in a thiol regulated CF_1.

In the chloroplasts of higher plants, nine enzymes are now biochemically confirmed as thiol regulated enzymes: glyceraldehyde-3-phosphate dehydrogenase [27], fructose 1,6-bisphosphatase (FBPase) [28], sedoheptulose 1,7-bisphosphatase [28], phosphoribulokinase (PRK) [28], CF_1 [15,16,24], NADPH dependent malate dehydrogenase (MDH) [29], glucose 6-phosphate dehydrogenase [29], Rubisco activase [30], and acetyl CoA carboxylase [31]. Among these enzymes, FBPase, PRK, MDH, and CF_1 obviously contain the additional inserted sequences including regulatory cysteines. However, these regions do not show any similarity to each other and there is no evidence on the origin of these regulatory sequences. Furthermore, ATP synthase is the only enzyme that was investigated with the single molecule observation technique [21]. Still the origin of the thiol regulation system of CF_1 is very enigmatic.

3. The intrinsic inhibitor subunit ε: inhibition and the relevance of its conformational change

Up to now, three different structures of the ε subunit have been reported. The δ subunit of MF_1 (the analogous subunit of the bacterial or chloroplast F_1-ε subunit) is located at the bottom of the F_1 complex and the carboxy-terminal α-helix portion is folded in close to the amino-terminal β-barrel domain [17]. The monomer structure of the ε subunit of EF_1 solved by X-ray analysis showed a similar structure as the δ subunit of MF_1 [32]. In contrast, the structure of the ε subunit in the partially deleted γ and ε co-complex of EF_1

[18] and that in EF_1 [19] was very different from the monomer structure or the structure of the mitochondrial δ subunit. The carboxy-terminal α-helix part of the ε subunit rose to the upper position of the γ subunit in EF_1.

Thus the ε subunit has two distinct domains: an amino-terminal β-barrel domain and a carboxy-terminal α-helix domain. The latter domain must be mobile in the complex depending on the environment. Indeed the adenine nucleotide dependent up and down motion of the carboxy-terminal α-helix part of the ε subunit in the F_1 or F_oF_1 complex has been suggested by cross-linking experiments in the case of *E. coli* F_1 [33] and thermophilic F_1 [34]. When the carboxy-terminal α-helix part was fixed in the down position, ε did not show inhibitory properties [34]. In addition, when the conformation of the ε subunit was fixed in an upper position by cross-linking, the ε subunit inhibited ATP hydrolysis activity but not ATP synthesis activity [20]. Thus a strong relation between the conformation of this carboxy-terminal α-helix part and the function of the subunit is suggested. In the case of the chloroplast ATP synthase, similar motion of the α-helices is suggested by chemical modification [35] and the accessibility of an antibody against this region [36].

What is the physiological role of the inhibitory effects of the ε subunit in the F_oF_1 complex? Up to now, based on the analysis of the whole genome sequences, it is known that the ε subunits of F_1 from three anaerobic bacteria, *Chlorobium tepidum* [37], *Rickettsia conorii* [38], and *Caulobacter crescentus* [39], lack the carboxy-terminal α-helix region. However, other organisms including both aerobic and anaerobic bacteria have full-length ε subunits. The deficient ε subunits are not specifically categorized in the phylogenetic tree (Fig. 4, blue letters). Several deletion mutants on this carboxy-terminal region of the ε subunit have been prepared and their features reported [40–42]. In the case of *E. coli* ATP synthase, deletion of only the carboxy-terminal α-helices did not affect cell growth on succinate medium [41]. The cells were unable to grow on succinate medium when the β-barrel region of the ε subunit was partially deleted. The ε subunit did not inhibit the ATPase activity of the ε-deficient complex when the carboxy-terminal α-helices were completely deleted [42]. As mentioned, the cross-link between the carboxy-terminal α-helix region and the β-barrel region by the introduction of two cysteines abolished the inhibitory function of ε [34]. Substitution of the positively charged residues, Lys and Arg, on the carboxy-terminal α-helix region into Ala, which potentially can interact with the negatively charged region, DELSDED, of the β subunit, strongly attenuates the inhibitory effect of the ε subunit [43]. From these studies, we concluded that the carboxy-terminal α-helix region of the ε subunit is important for both the interaction with the β subunit and its inhibitory features. Thus the physiological significance of this subunit including the physiological significance of the carboxy-terminal α-helix region is not yet clear.

The amino-terminal β-barrel region is important for the interaction between the central stalk region and the subunit III (subunit c in the case of MF_oF_1 and bacterial F_oF_1) ring [44]. Partial deletion of the β-barrel region critically reduces the assembly efficiency of the ATP synthase complex [45,46]. The ε subunit was indispensable for the reconstitution of the F_oF_1 complex from the individual subunits [47]. Thus the β-barrel region of the ε subunit should be the important connector between F_1 and F_o.

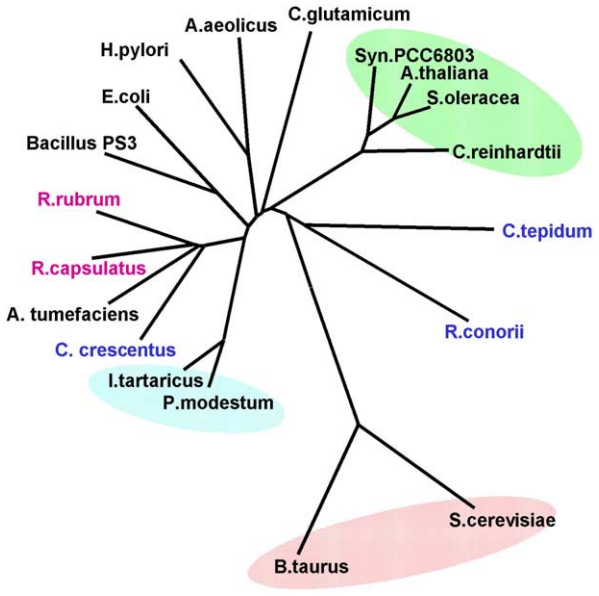

Fig. 4. Phylogenetic tree of the ε subunit. Phylogenetic relationships were analyzed as in Fig. 1. The use of color is as in Fig. 1. The organisms of which the ε subunit lacks the carboxy-terminal α-helix part are shown in blue letters. The accession numbers for the proteins shown in the tree are: *P. modestum*, S29042; *I. tartaricus*, AAM94914; *C. crescentus*, Q9A2W1; *A. tumefaciens*, Q8UC77; *R. capsulatus*, P72248; *R. rubrum*, P05442; *Bacillus* PS3, BAA96810; *E. coli*, B90106; *H. pylori*, C64661; *A. aeolicus*, O66903; *C. glutamicum*, Q9ETA7; *Synechocystis* sp. 6803, S75527; *A. thaliana*, BAA84391; *S. oleracea*, P00833; *C. reinhardtii*, S11898; *C. tepidum*, Q8KAC8; *R. conorii*, Q92G89; *S. cerevisiae*, Q12165; *B. taurus*, 1109216A.

4. Interaction between the γ and ε subunits

In the reported structures of F_1 or F_oF_1, the ε subunit interacts with the γ subunit at the amino-terminal β-barrel domain and the carboxy-terminal α-helix region of ε [17,18]. As shown by the single molecule experiments, the ε subunit is functionally a part of the rotor in the complex [48]. Furthermore, the redox state of the γ subunit directly affects the affinity of the ε subunit to the complex in CF_1 or CF_oCF_1 [49–51]. Recently we found that the proper combination of the ε subunit and the γ subunit is important to confer redox sensitivity to the chimeric complex F_oF_1 as mentioned. Since $\Delta\mu H^+$ across the thylakoid membranes formed by illumination can assist reduction of the disulfide bridge on γ by thioredoxin [52], the conformational change of the ε subunit promoted by $\Delta\mu H^+$ may directly influence the redox sensitivity of the γ subunit, although the molecular basis for these phenomena is not known very well.

5. Concluding remarks

So far, there is no direct evidence that could show the interaction of the regulatory region of the CF_1 γ subunit and the part of the ε subunit in CF_1 in the process of redox regulation. Although observations of the regulation of the rotation of γ at the single molecule level provided us with a new idea on the regulatory mechanism based on the equilibrium of the two different structures of the regulatory region [21], we of course need further information on these mechanisms based on the three-dimensional structure. When we ob-

tain structural data on the change of the conformation of the regulatory region dependent on the redox conditions, we will be able to describe the redox regulation mechanism of this enzyme at the molecular level.

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