H₂O₂-sensitive Fur-like Repressor CatR Regulating the Major Catalase Gene in *Streptomyces coelicolor*

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**Streptomyces coelicolor** produces three distinct catalases to cope with oxidative and osmotic stresses and allow proper growth and differentiation. The major vegetative catalase A (CatA) is induced by H₂O₂ and is required for efficient aerobic growth. In order to investigate the H₂O₂-dependent regulatory mechanism, an H₂O₂-resistant mutant (HR40) overproducing CatA was isolated from *S. coelicolor* A3(2). Based on the genetic map location of the mutated locus in HR40, the wild type *catR* gene was isolated from the ordered cosmid library of *S. coelicolor* by screening for its ability to suppress the HR40 phenotype. *catR* encodes a protein of 138 amino acids (15319 Da), with sequence homology to ferric uptake regulator (Fur)-like proteins. Disruption of *catA* caused CatA overproduction as observed in the HR40 mutant, confirming the role of CatR as a negative regulator of *catA* expression. The levels of *catA* and *catR* transcripts were higher in HR40 than in the wild type, implying that CatR represses transcription of these genes. Transcripts from the *catA* and *catR* genes were induced within 10 min of H₂O₂ treatment, suggesting that the repressor activity of CatR may be directly modulated by H₂O₂. A putative CatR-binding site containing an inverted repeat of 23 base pairs was localized upstream of the *catA* and *catR* gene, on the basis of sequence comparison and deletion analysis. CatR protein purified in the presence of dithiothreitol bound to this region, whereas oxidized CatR, treated with H₂O₂ or diamide, did not. The redox shift of CatR involved thiol-disulfide exchange as judged by modification of free thiols with 4-acetamido-4'-maleimidylstilbene-2,2'-disulfonate. From these results we propose that CatR regulates its downstream target genes as a repressor whose DNA binding ability is directly modulated by redox changes in the cell.

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All aerobically growing organisms come into contact with reactive oxygen species, generated as a by product of normal respiratory processes or from encounter with exogenous oxi-

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1 The abbreviations used are: Fur, ferric uptake regulator; Ahp, alkylhydroperoxide reductase; AMS, 4-acetamido-4'-maleimidylstilbene-2,2'-disulfonate; CatA, catalase A; RerA, a regulator of SigR; DTT, dithiothreitol; PCR, polymerase chain reaction; PAGE, polyacrylamide gel electrophoresis; kb, kilobase(s).
revealed yet (12). In addition to these, it has been reported that S. coelicolor possesses two kinds of superoxide dismutases (Ni-SOD and FeZn-SOD encoded by sodN and sodF, respectively), an alkyl hydroperoxide reductase system (encoded by aphCD), and a thioredoxin system (encoded by trxBA) as oxidative defense proteins (13–16). Three transcriptional regulation systems controlling the expression of a subset of these oxidative defense proteins have been found: an anti-σ factor RsrA which binds a cognate σ factor, σR, in a redox-dependent manner and thus regulates σR-dependent transcription of the trxBA and sigR genes (16, 17); OxyR which activates the aphCD gene but not the catA genes (15); and FurA which regulates catalase peroxidase gene (catC; Ref. 12). A soxR-like gene has been predicted from the sequence information (S. coelicolor Genome Project, The Sanger Center).

The redox-dependent activity modulation is best described for RsrA. It binds and sequesters σR from transcribing trxBA and its own gene under reducing conditions. Upon oxidation by H₂O₂ or a thiol-oxidizer diamide, it loses its binding activity, releasing σR to transcribe its target genes. The redox-dependent modulation of RsrA activity is mediated via thiol-disulfide exchange. The induced thioredoxin, in turn, reduces RsrA, forming a negative feedback loop. This allows the homeostatic control of intracellular redox conditions by RsrA. Not much is yet known about the activity modulation of OxyR in S. coelicolor nor the mechanism of H₂O₂-dependent induction of the major catalase. In this study, we report on the isolation and characterization of another novel redox-sensitive regulator CatR, which serves as a transcriptional repressor regulating the catA gene.

**EXPERIMENTAL PROCEDURES**

**Bacterial Strains and Culture Conditions—**S. coelicolor A3(2)/J1501 was mutagenized with UV to isolate H₂O₂-resistant mutants (18). J1915, a gkhA derivative of M145 (19), was used to disrupt the catR gene. Streptomycetes cells were grown in YEME medium for liquid culture, and on R2YE, nutrient agar (NA), or minimal medium plates for surface culture (20). E. coli ET12567, a non-methylation strain, was used to prepare DNA to transform S. coelicolor (21).

**Cloning catR from the Ordered Cosmid Library—**Based on genetic mapping of the mutated locus in the H₂O₂-resistant mutant HR40, ordered cosmids from K13 to 2E1 (kindly provided by H. Kieser), encompassing the mthB locus (22), were tested to isolate catR. Cosmid DNAs were prepared from E. coli ET12567, and introduced into HR40 protoplasts following denaturation (23). Cosmid-integrated clones were selected on R2YE medium containing 200 μg/ml kanamycin, and the spores were plated on MM containing 200 mM deoxyglucose plus 150 μg/ml hygromycin. The surviving colonies, expected to have lost the vector including the counterselectable gkhA by second crossover, were confirmed for apramycin sensitivity by replica plating. The catR disruption was then confirmed by Southern hybridization.

**Overproduction and Purification of CatR from E. coli—**The catR coding region was amplified by PCR with mutagenic primers CR1 (5’-AGGCTGATGATATAGTGAC-A3’-Ndel site underlined) and CROB (5’-CAGGATATGATCTGCAGCCT-3’-BamHI site underlined). The PCR product was cut with Ndel and BamHI and cloned into pET21c (Novagen) to generate pH7. E. coli BL21(DE3)pLysS cells transformed with pH7 were grown in LB medium to A₆₀₀ of 0.5 and then induced with 1 mM isopropyl-1-thio-β-D-galactopyranoside (10 minutes). After harvest, cells were resuspended in lysis buffer (20 mM Tris-HCl, pH 7.9, 0.15 mM NaCl, 5 mM EDTA, 2 mM dithiothreitol (DTT)), 10 mM MgCl₂, 1 mM phenylmethylsulfonyl fluoride, and 10% glycerol) and disrupted by sonication. The lysate was centrifuged at 16,000 × g for 10 min, and the supernatant was precipitated with 60% ammonium sulfate. The pellet was dissolved in and dialyzed against TGED buffer (10 mM Tris-HCl, pH 7.9, 0.1 mM EDTA, 2 mM DTT, and 10% glycerol). The dialysate was subjected to chromatography on heparin-Sepharose CL-6B, Q-Sepharose, Superdex-75, and Mono-Q columns. The final eluate from Mono-Q, eluted at 0.2–0.3 M NaCl in TGED buffer, contained CatR protein at more than 90% homogeneity. Purified CatR was stored at −70 °C in 50% glycerol before use.

**Mobility Shift Assay—**The catR promoter region from −111 to +71 nucleotides from the start codon was generated by PCR with primers CR1 (5’-CTCTTGCGACT CGCGCCG-3’) and CRS1 (5’-TCGGCAGACGACCGCCGCGTCCG-3’). The catA promoter region from −84 to +254 nucleotides from the start codon was generated by PCR with primers CAD84 (5’-AGCA GGTCTGCAGCGACCGAGC-3’) and CAC (5’-TCGGGAGATGCGCTCGTGC-3’). The PCR product was end-labeled with [32P]ATP using T4 polynucleotide kinase. Unincorporated isotopes were removed by centrifugation through a Sephadex G-50 spin column. The end-labeled probe (about 30,000 cpm for less than 0.1 pmol per each reaction) was incubated with 200 ng (13 pmol) of purified CatR in 20 μl of binding buffer (10 mM Tris-HCl, pH 7.5, 1 mM MgCl₂, 40 mM KCl, 100 μg of poly(dI-dC) per ml, and 5% glycerol) at 30 °C for 10 min. The DNA/protein mixture was electrophoresed on a 5% native PAGE in 20 mM Tris borate buffer, and analyzed by autoradiography.

**Western Blot Analysis—**Polyclonal antibody against purified CatR was raised in mice. The reacting signal was detected by goat anti-mouse immunoglobulin G conjugated with horseradish peroxidase using the Western ECL detection system (Amersham Pharmacia Biotech).

**RESULTS**

**Characterization of an H₂O₂-resistant Mutant of S. coelicolor—**An H₂O₂-resistant mutant HR40 was generated by UV mutagenesis of spores from S. coelicolor A3(2)/J1501 as described previously (18). It grows as rapidly as the wild type and differentiates normally, although it produces less of the blue antibiotic, actinorhodin, than the wild type. The protein profile of HR40 was compared with that of its parent (J1501) on SDS-PAGE (Fig. 1A). A prominent difference in HR40 was the overproduction of catalase A. No other significant changes in protein profile were observed. HR40 overproduced a 50-kD form of CatA as judged by Western blot analysis (Fig. 1B). Measurement of the catalase activity in cell extracts also produced similar results (data not shown).

Expression of other antioxidant enzymes such as catalase peroxidase (CatC) and alkyl hydroperoxide reductase system (AhpC) was lowered in HR40 (Fig. 1B). The level of catalase B...
A

Fig. 1. Overproduction of catalase A in H2O2-resistant mutant HR40. A, the profile of total proteins from HR40 (lanes 4–6) and its wild type parent J1501 (lanes 1–3). Extracts prepared from cells grown in YEME medium for 24, 48, and 72 h were subjected to SDS-PAGE followed by staining with Coomassie Brilliant Blue. The prominent band of catalase A is denoted (CatA). B, levels of various antioxidant enzymes. The amount of catalases (CatA, CatB, and CatC) and alkylhydroperoxide reductase system (AhpC and AhpD) was determined by Western blot analysis of the same cell extracts used in panel A. For each track, 20 μg of protein was analyzed except for CatA detection in the HR40 extract, where 2 μg of protein was analyzed.

(CatB), a stationary phase-specific catalase, did not change significantly (Fig. 1B). Although HR40 was more resistant to H2O2 than the wild type, it was slightly sensitive to cumene hydroperoxide, consistent with the reduced expression of AhpCD. Sensitivity of HR40 against superoxide generating agents such as paraquat, plumbagin, and menadione was similar to that of J1501 (data not shown).

Cloning of catR—The mutation (catR1) in HR40 had been previously mapped close to the mthB2 locus by genetic crosses (18). This locus is near the center of the chromosome, being separated by more than half a genome distance from catA, which has been physically mapped to the AseI fragment near one end of the linear chromosome (22). Therefore, catR may be likely to encode a regulator for catalase A production, the catR1 allele giving rise to either a repressor with lost function or an activator with gained function. It has been previously suggested that catA expression may be regulated by a repressor system on the grounds that the presence of catA promoter fragments on a multicopy plasmid increased the production of catalase A in Streptomyces lividans. Therefore, assuming that the catR1 allele may be a repressor of catalase A production, we attempted to clone the wild type catR by introducing into HR40 genomic DNAs from ordered cosmids spanning the mthB2 locus, screening for wild type levels of catalase production as follows: since HR40 overproduces catalase A, application of 30% H2O2 solution on top of its colonies generates the explosive evolution of O2 in contrast to mild bubbling on wild type colonies. Using this handy screening tool, we were able to select two overlapping cosmids (6F2 and 7E4) out of 23 cosmids (from K15 to 2E1) tested, as candidates harboring the catR gene. Cosmids 6F2 and 7E4 overlapped by about 21 kb. To localize catR more precisely, various restriction fragments of the overlapping region were subcloned into pSET152, a conjugation vector containing a phage integration site (att) (24). The recombinant plasmids were introduced into HR40 and tested for phenotype suppression. We found that a 1.2-kb HincII-BamHI fragment (in pJH3113) was able to repress catalase overproduction in HR40, whereas its subfragment (0.8-kb HincII-BglII fragment in pJH3115) was not (Fig. 2, A and B, lanes 3 and 4). This enabled us to narrow down the position of the catR gene.

Nucleotide sequence analysis revealed that the insert DNA in pJH3113 contained two open reading frames, one coding for a Fur homologue (Fig. 2C). The nucleotide sequence of Cosmid 6F2 and 7E4 overlaps by about 21 kb. To localize catR more precisely, various restriction fragments of the overlapping region were subcloned into pSET152, a conjugation vector containing a phage integration site (att) (24). The recombinant plasmids were introduced into HR40 and tested for phenotype suppression. We found that a 1.2-kb HincII-BamHI fragment (in pJH3113) was able to repress catalase overproduction in HR40, whereas its subfragment (0.8-kb HincII-BglII fragment in pJH3115) was not (Fig. 2, A and B, lanes 3 and 4). This enabled us to narrow down the position of the catR gene.

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To confirm the role of CatR as a repressor of catA gene expression, the catR gene in strain J1915 was disrupted as described under “Experimental Procedures.” The ΔcatR mutant (JH11) showed no defect in growth or differentiation, except that it produced a reduced amount of actinorhodin on R2YE plates as observed for HR40. As expected, JH11 overproduced catalase A to an extent comparable to HR40 (Fig. 2B, lane 6).

The catR Gene Encodes a Fur-like Protein—The catR gene encodes a protein of 138 amino acids with a deduced molecular mass of 15,319 Da and close similarity to Fur-like proteins of


Following H2O2 treatment were monitored by S1 mapping (Fig. 3). The cysteine residues are marked in **bold**. The Arg51 (R51) residue of CatR within the putative helix-turn-helix motif, which is mutated to glutamine in HR40, are shaded in **bold**. Asterisks and dots indicate identical and similar matches, respectively.

**H2O2 Induction of the catA and catR Transcripts**—We analyzed the transcripts from the catA and catR genes in wild type and HR40 mutant by S1 mapping (Fig. 4). HR40 produced catA transcripts drastically more than the wild type, suggesting that catA transcription is under the negative control of CatR. HR40 also produced more catR transcripts than the wild type, especially the longer one (catRp2), whose 5' end lies at about 70 nucleotides upstream from the translation start site. The 5' ends of the shorter transcripts (catRp1) were located at multiple sites immediately downstream of the ATG codon. A putative promoter (TGGGGA-N18-TAGGCT) resembling the sequences recognized by the major 3' factor $\alpha^{helix}$ was identified upstream of the translation start codon, separated from ATG by 7 residues. Therefore, it is conceivable that the shorter transcripts were generated from degradation of transcripts initiated at the translation start site (catRp1). catRp2 start sites were located more precisely by high-resolution S1 mapping at 74 and 66 nucleotides upstream from the ATG codon (data not shown). A putative $\alpha^{helix}$-type promoter (TTG-GCC-N17-TACAAT) was found upstream of the 74 site. The observation that catRp2 transcript was highly expressed in HR40, like the catA transcript, suggests that transcription from both catRp2 and the catA promoter is negatively regulated by CatR. The catRp1 promoter may be partially regulated by CatR. The production of CatR protein was also elevated in HR40 as judged by Western analysis (data not shown).

**Kinetics of rapid induction by H2O2 of both genes** suggests that the transcriptional regulation is mediated by activity modulation of an already existing regulator, most likely CatR, by H2O2. The delay observed for catA transcript in reaching and decaying from the maximum level might reflect the higher stability of catA transcript than catR. The changes in the level of CatA and CatR proteins followed the changes in mRNAs as judged by Western analysis (Fig. 5). The CatR protein began to increase from 20 min, reaching a maximum value between 40 and 50 min following H2O2 treatment. The CatR protein also began to increase from 20 min reaching a maximum value at about 40 min.

**Identification of the Putative Binding Site of CatR**—On the basis of the assumption that CatR binds directly to the promoter region of catA and catR genes we examined the nucleotide sequences of these promoter regions. The nucleotide sequences of the two promoter regions were compared with the similar sequence region of the furV-bca genes from S. venezuelae (Fig. 6). furV is divergently transcribed from the neighboring bca gene, whereas the transcription units of the catR and catA gene in S. coelicolor are distantly located. We identified an inverted repeat of 23 base pairs in all these genes; between -32 and -54 nucleotides from the start codon for catR and furV, between -70 and -92 for catA, and between -73 and -95 for bca genes. Counting from the catA transcription start site (+1),

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**Fig. 3.** Comparison of the amino acid sequence of CatR with other Fur homologues. The predicted amino acid sequence of CatR from *S. coelicolor* (Sco; AF186372) was aligned with other bacterial Fur homologues: *S. venezuelae* (SveFurV (X14792)); *B. subtilis* (BsuFurR (Z99108)); *S. reticuli* (SreFurR (Y14317)); *S. coelicolor* FurR (AF126956); *M. tuberculosis* (MtFurA (Z97193)). The completely conserved residues are shaded. The cysteine residues are marked in **bold**. The Arg51 (R51) residue of CatR within the putative helix-turn-helix motif, which is mutated to glutamine in HR40, are shaded in **bold**. Asterisks and dots indicate identical and similar matches, respectively.

**Fig. 4.** S1 mapping analysis of *catR* and *catA* transcripts in J1501 and HR40. RNAs were prepared from J1501 (lanes 1–3) and HR40 cells (lanes 4–6) grown in YEME for 12, 22, and 40 h. The 5' ends of *catR* and *catA* mRNAs were mapped by S1 nuclelease protection assay as described under “Experimental Procedures.” The transcripts from *catRp1*, *catRp2*, and *catA* promoters produce protected bands as designated.
CatR migrated as a 17-kDa band in SDS-PAGE, in close agreement with its predicted size (lane 1). AMS-treated CatR in the presence of 1 mM DTT migrated as a retarded band of 24 kDa (lane 2). Considering the molecular mass of AMS (500 Da), the extent of mobility retardation far exceeds that predicted from alkylation of all four available cysteines in CatR. This could have resulted from the conversion of CatR protein into a more relaxed conformation by AMS attachment. CatR oxidized by H$_2$O$_2$ or diamide did not exhibit any retardation upon AMS treatment, implying that all the cysteine residues were oxidized and formed disulfide bonds under the conditions employed (lanes 4 and 6). In the diamide-treated sample, a small amount of dimer-sized band appeared, as predicted from the formation of intermolecular disulfide bonds.

**DISCUSSION**

A number of bacteria contain multiple Fur homologues, whose role is specified in metal assimilation or oxidative stress response. Among three Fur-like proteins found in *B. subtilis*, Fur and Zur regulate the uptake of iron and zinc, respectively (29, 30), whereas PerR acts as a repressor for peroxide regulon (8). *Campylobacter jejuni* also contains PerR responsible for iron-dependent repression of catalase and alkyl hydroperoxide reductase, in addition to Fur which represses iron uptake genes (31).

*S. coelicolor* contains at least four Fur homologues; FurA which controls catalase peroxidase (encoded by catC) in a metal-dependent manner (12), CatR which controls catalase A production in response to H$_2$O$_2$, and two Fur-like proteins of unknown function predicted from the genome sequencing data base (*S. coelicolor* Genome Project, The Sanger Center). *Mycobacterium tuberculosis*, a close relative of *S. coelicolor* in being a Gram-positive bacterium of high G + C content, contains two fur-like genes, furA and furB. The furA gene is located upstream of the katG gene encoding catalase peroxidase (32, 33), similar to the equivalent gene organization in *Streptomyces reticuli* (furS-cpeB) (34) and *S. coelicolor* (furA-catC) (12). This group of Fur homologues seems to regulate the catalase peroxidase gene in a manner sensitive to metals but insensitive to H$_2$O$_2$, as observed in the regulation of mycobacterial katG or *S. coelicolor* catC (33, 12). On the other hand, CatR seems closely related with *B. subtilis* PerR in H$_2$O$_2$-dependent regulation of downstream target genes. Closer sequence match among CatR, PerR, and FurV of *S. venezuelae* suggests that these regulators may share similar characteristics of peroxide sensing (Fig. 3).

We postulate a model for the rapid adaptation response against H$_2$O$_2$ in *S. coelicolor* as demonstrated in Fig. 9. Under a normal reducing intracellular environment, CatR is bound to the catA and catR genes and represses their transcription. Upon exposure to H$_2$O$_2$, the free cysteine thiols of CatR are oxidized to form disulfide bonds, causing loss of DNA binding activity and thus derepression of catR and catA genes. The induced catalase A efficiently removes H$_2$O$_2$, whereas the overproduced CatR represses both genes as soon as peroxide is removed, thus forming an efficient negative feedback loop.

In contrast to *B. subtilis* PerR which is a global regulator of peroxide regulon involving several anti-oxidant genes, CatR in *S. coelicolor* seems to regulate only CatA production among the known peroxide-degrading enzymes including CatB, CatC, and AhpCD (15). Therefore, the induction of antioxidant enzymes in *S. coelicolor* seems to require more specific regulators for individual enzymes. In addition, unlike *B. subtilis* PerR regulon, whose induction at post-exponential phase is inhibited by Mn(II) or Fe(II) (7), catA expression in *S. coelicolor* is not induced at post-exponential phase and is relatively insensitive to the amount of metals used in our experiments. Addition of excess metal salts or the iron chelator dipyridyl to minimal...
media elicited little change in CatA levels (data not shown). Only a high concentration of Ni(II) (1 mM) in Nutrient agar plate medium repressed CatA expression (data not shown). However, in DNA binding assays, deprivation of metals by EDTA inhibited CatR binding, whereas addition of extra metals did not enhance the DNA binding. This indicates that not only reduced thiols of cysteine residues but also appropriate metals are required for CatR to bind to its specific target DNA. Further investigation is needed to reveal the specific cysteine residues and the type of metals, if any, involved in the redox modulation of CatR binding activity.

The four cysteines of CatR in Cys\textsuperscript{382}-X\textsubscript{132}-Cys\textsuperscript{135} and Cys\textsuperscript{132}-X\textsubscript{135} are conserved in most Fur-like proteins (Fig. 3). If we assume that Fur homologues share basically similar tertiary structures, the cysteine pair Cys\textsuperscript{382} and Cys\textsuperscript{135} in CatR may be involved in structural zinc binding like its equivalent cysteine pairs in Fur proteins from E. coli and B. subtilis (29, 35, 36). Disulfide bond formation between these two cysteines may cause release of the coordinating zinc, and loss of DNA binding activity as a result. A similar mechanism has been postulated in the activation mechanism of E. coli heat shock protein Hsp33 (37). Hsp33 is a member of a newly discovered family of heat shock proteins, whose chaperone activity is induced by disulfide bond formation with concomitant release of coordinating zinc (37). Zinc transfer from eukaryotic zinc metallothionein to zinc-depleted protein is also affected by the oxidation state of the thiolate ligands. Oxidation of the thiolate ligands to form irreversible disulfide bond formation with concomitant release of coordinating zinc (37). Zinc transfer from eukaryotic zinc metallothionein to zinc-depleted protein is also affected by the oxidation state of the thiolate ligands. Oxidation of the thiolate ligands to form irreversible disulfide bond formation with concomitant release of coordinating zinc (37). Zinc transfer from eukaryotic zinc metallothionein to zinc-depleted protein is also affected by the oxidation state of the thiolate ligands. Oxidation of the thiolate ligands to form irreversible disulfide bond formation with concomitant release of coordinating zinc (37). Zinc transfer from eukaryotic zinc metallothionein to zinc-depleted protein is also affected by the oxidation state of the thiolate ligands. Oxidation of the thiolate ligands to form irreversible disulfide bond formation with concomitant release of coordinating zinc (37).
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FIG. 9. A model for the rapid H2O2-sensitive regulation by CatR. Reduced CatR binds to the catA and catR genes and represses their transcription (path A). Upon exposure to H2O2, the free cysteine thiols of CatR are oxidized to form disulfide bonds (B), causing loss of DNA binding activity and thus derepression of catA (C). The induced catalase removes H2O2 (D), whereas the induced CatR (coupled with an increase in the proportion of the reduced form as peroxide is removed) represses both genes (E), forming a negative feedback loop.

Activity of CatR.
The location of the CatR-binding site in catR and catA promoters suggests that CatR repress transcription of these genes via different modes. The transcription from the catRp2 promoter is likely to be blocked at the elongation stage whereas the catA transcription could be blocked at the initiation stage (see Fig. 6). The transcription from the catRp1 promoter, which is partially repressed by CatR, may be blocked at the initiation stage. The binding of CatR near the −35 promoter element may be effective for repression as observed in catA promoter, whereas binding at closer proximity as observed in catRp1 may be less effective. The similarity between CatR and FurV (from S. venezuelae) in the coding region as well as in the nucleotide sequences of the regulatory region suggests that FurV may act similarly to CatR in H2O2-dependent regulation of downstream target genes.

In addition to the previously described OxyR and sR/RsR systems, we have here identified another redox-sensitive transcriptional regulator controlling oxidative defense genes in S. coelicolor. Although not much is known about the detailed mechanism of activity modulation, all three regulators seem to involve thiol-disulfide exchange. The rich reservoir of potential transcriptional regulators predicted from the sequence data base (S. coelicolor Genome Project, The Sanger Center) leads us to expect a multitude of regulators responding to myriads of environmental cues. Along with detailed specificity, we expect to discover some unity in regulatory mechanisms in further investigations of the action mechanism of these regulators.

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H$_2$O$_2$-sensitive Fur-like Repressor CatR Regulating the Major Catalase Gene in
Streptomyces coelicolor

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