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STRUCTURAL STUDIES OF TRANSCRIPTIONAL REGULATION BY LysR-TYPE TRANSCRIPTIONAL REGULATORS IN BACTERIA

by Maharani Koentjoro

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REVIEWS OPEN ACCESS

STRUCTURAL STUDIES OF TRANSCRIPTIONAL REGULATION BY LysR-TYPE TRANSCRIPTIONAL REGULATORS IN BACTERIA

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ABSTRACT

LysR-type transcriptional regulators (LTTRs) comprise one of the largest families of transcriptional regulators in bacteria and control gene expression of various types of metabolic, virulence and physiological functions. LTTRs typically form homotetramers and require an inducer molecule(s) to activate the transcription of target genes. The N-terminal region of LTTRs contains a DNA binding domain (DBD) with the winged helix-turn-helix motif that specifically binds the promoter region of target genes. The C-terminal region of LTTRs is connected to the DBD by a linker helix and forms the regulatory domain (RD) that contains a binding pocket for inducer molecules. Crystal structures of several LTTR family members together with their biochemical analyses have provided a potential mechanism for the initial process of transcription activation by LTTRs. First, helix α3 of the winged helix-turn-helix motif in DBD is supposed to distinguish the recognition binding site (RBS) in the promoter region, resulting in complex formation through interactions between two DBDs in the tetrameric LTTR and RBS. Formation of this complex seems to enable interactions between the other two DBDs in the LTTR tetramer and the activation binding site (ABS) in the promoter region. The binding of the tetrameric LTTR to both the RBS and ABS causes the promoter DNA to adopt a bent structure because the four DBDs in the tetrameric LTTR are arranged in a V-shaped manner at the bottom of the LTTR. Interaction of an inducer molecule(s) with the RD seems to cause a quaternary structural change of the LTTR that relaxes the bending angle of the promoter DNA with a concomitant shift of the bound DBDs at the ABS. These events facilitate recruitment of RNA polymerase to its binding site in the promoter region, which overlaps with the ABS for LTTR.

Keywords: Bacteria, chlorocatechol, LysR–type transcriptional regulator, transcription

1. Introduction

LysR-type transcriptional regulators (LTTRs) represent one of the largest families of prokaryotic transcriptional regulators (Henikoff *et al*., 1988), and functional orthologues are also found in archaea (Sun and Klein, 2004) and in chloroplast of a red alga (Minoda *et al*., 2010). LTTRs regulate transcription of genes that code for proteins that have diverse functions, including degradation of aromatic compounds, biosynthesis of amino acids, synthesis of virulence factors, CO_2-fixation, N_2-fixation, antibiotic resistance, cell division, quorum sensing and oxidative stress responses (reviewed in Maddocks and Oyston, 2008 and Schell, 1993). Table 1 shows several examples of LTTRs to show the variety of the function of the regulated genes.

LTTRs were initially defined in 1988 by Henikoff *et al*. They found primary structure similarities in bacterial transcription proteins, AmpR, LeuO, LysR, IlvY, CysB, NodD, MetR and TfdO, and designated these proteins as LysR family members. LTTRs typically consist of ~300 amino acids and bind their target promoters as homotetramers (Akakura and Winans, 2002b; Feng *et al*., 2003). An LTTR located on the promoter must bind to an inducer molecule(s) to activate transcription. Some LTTRs are known to be present as a dimer or octamer (Parsek *et al*., 1994; Sainsbury *et al*., 2009); however, these examples are relatively rare. Primary sequence analysis and biochemical studies suggest

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Table 1. Examples of LysR-type transcriptional regulator

LTTR	Function of regulated gene(s)	Inducing agent or condition	Origin	Reference
AmpR	β-Lactamase synthesis	1,6-anhydroMurNAc-peptides (changes in peptidoglycan metabolite levels)	*Citrobacter freundii*, *Enterobacter cloacae*	Lindberg *et al*., 1985
AphB	Virulence factor production control	environmental stimuli	*Vibrio cholerae*	Kovacikova and Skorupski, 1999
ArgP (IciA)	L-Arginine exporter, amino acid metabolism	arginine	*Escherichia coli*	Nandineni and Gowrishankar, 2004
AtzR	Cyanuric acid catabolism	cyanuric acid and nitrogen limitation	*Pseudomonas* sp.	García-González *et al*., 2005
BenM	Benzoate catabolism	*cis*, *cis*-muconate, benzoate	*Acinetobacter baylyi*	Collier *et al*., 1998
CatR	Catechol catabolism	*cis*, *cis*-muconate	*Pseudomonas putida*	Rothmel *et al*., 1991
CbbR	Carbon dioxide fixing	ribulose 1,5-bisphosphate	*Rhodobacter sphaeroides* *Xanthobacter flavus*	Gibson and Tabita, 1993
CbnR	Chlorocatechol catabolism	(2-chloro-) *cis*, *cis*-muconate	*Cupriavidus necator*	Ogawa *et al*.,1999
ClcR	Chlorocatechol catabolism	2-chloro-*cis*, *cis*-muconate	*Pseudomonas putida*	Coco *et al*., 1993
CrgA	Biosynthesis of pili and capsule	α-methylene-γ-butyrolactone	*Neisseria meningitidis*	Deghmane *et al*., 2000
CysB	L-Cysteine synthesis	*N*-acetylserine	*Salmonella typhimurium*	Kredlich, 1971
DntR	2,4-Dinitrotoluene	2,4-dinitrotoluene, salicylate	*Burkholderia* sp.	Smirnova *et al*., 2004
FinR	Ferredoxin-$NADP^+$ reductase	oxidative and osmotic stresses	*Pseudomonas putida*	Lee *et al*., 2006
HrsM	Expression of selenoproteins involved in energy metabolism and methanogenesis	Unknown	*Methanococcus maripaludis*	Quitzke *et al*., 2018
IlvY	Synthesis of isoleucine and valine	α-acetohydroxybutyrate, α-acetolactate	*Escherichia coli*	Wek and Hatfield, 1988
LdhR	Cellular aggregates and biofilm formation	Unknown	*Bukholderia multivorans*	Silva *et al*., 2018
LeuO	Leucine synthesis, environmental adaptation and virulence	Unknown	*Salmonella typhimurium*, *Escherichia coli*	Hertzberg *et al*., 1980
LysR	Lysine synthesis	diaminopimelate	*Escherichia coli*	Stragier *et al*., 1983
MetR	Synthesis and transport of methionine and cysteine	homocysteine	*Escherichia coli*, *Salmonella typhimurium*	Urbanowski *et al*., 1987
NahR	Catabolism of naphthalene and salicylate	salicylate	*Pseudomonas putida*	Yen and Gunsalus 1985
NhaR	Na^+/H^+ antiporter	Na^+	*Escherichia coli*	Rahav-Manor *et al*., 1992
NodD	Nitrogen fixation and symbiosis	flavonoids	*Rhizobium meliloti*, *Rhizobium leguminosarum*	Mulligan and Long, 1985 Rossen *et al*., 1985
OccR	Octopine catabolism	octopine	*Agrobacterium tumefaciens*	Habeeb *et al*., 1991
OxyR	Oxidative stress response	H_2O_2, redox changes	*Escherichia coli*, *Salmonella typhimurium*	Christmann *et al*., 1989
PcaQ	Protocatechuate catabolism	β-carboxy-*cis*, *cis*-muconate	*Agrobacterium tumefaciens*	Parke, 1993
PrhO	Type III secretion system	Unknown	*Ralstonia solanacearum*	Zhang *et al*., 2018
RovM	Cell invasion, virulence, and flagellar motility	Unknown	*Yersinia pseudotuberculosis*	Heroven and Dersch, 2006
TfdT	Chlorocatechol catabolism	2- and 3-chlorobenzoates, 3- and 4-chlorocatechol	*Burkholderia* sp.	Liu *et al*., 2001
TsaR	*p*-Toluenesulfonate catabolism	*p*-toluenesulfonate	*Comamonas testosteroni*	Tralau *et al*., 2007
ToxR	Toxoflavin biosynthesis and export	toxoflavin	*Burkholderia glumae*	Kim *et al*., 2004
VirR	Virulence	oxidative stress, high temperatures, low pHs	*Rhodococcus equi*	Russel *et al*., 2004
YofA	Cell division	Unknown	*Bacillus subtilis*	Lu *et al*., 2007

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that LTTRs are composed of two domains: a DNA binding domain (DBD) and a regulatory domain (RD) (Schell, 1993).

DNase I footprinting analyses have revealed that LTTRs bind to an approximately 60 bp region of the promoter DNA corresponding to *ca.* –80 to –20 upstream of the transcriptional start site in the absence of the inducer (Fig. 1) (Wek and Hatfield, 1988; Fisher and Long, 1989; Ogawa *et al.*, 1999). The binding region of the promoter can be divided into two parts: the recognition binding site (RBS) and activation binding site (ABS). The RBS has an inverted repeat structure and two inverted repeat sequences are interrupted by several nucleotides (Huang and Schell, 1991; Toledano *et al.*, 1994; Porrúa *et al.*, 2010, MacLean *et al.*, 2011). DNA sequence comparison of various promoters for LTTRs revealed a consensus sequence of RBS, the T–N_{11}–A motif (Figs. 1 and 2). The region of ~ 60 bp covered by LTTRs in the promoter containing presumably the RBS and ABS has been confirmed for the following examples: IlvY (Wek and Hatfield, 1988), NodD (Fisher and Long, 1989), OxyR (Storz *et al.*, 1990; Toledano *et al.*, 1994; Kullik *et al.*, 1995a), NahR (Huang and Schell, 1991), OccR (Wang *et al.*, 1992; Akakura and Winans, 2002b), CatR (Parsek *et al.*, 1994), ClcR (McFall *et al.*, 1997b), GcvA (Jourdan and Stauffer, 1998), CbnR (Ogawa *et al.*, 1999), AphB (Kovacikova and Skorupski, 2001), CysB (Lochowska *et al.*, 2004), YtxR (Axler-DiPerte *et al.*, 2006), ArgP (Laishram and Gowrishankar, 2007; Minh *et al.*, 2018), AtzR (Porrúa *et al.*, 2007), PcaQ (MacLean *et al.*, 2008), ToxR (Kim *et al.*, 2009), NAC (Rosario *et al.*, 2010) and ThnR (Rivas–Marín *et al.*, 2016). Gel mobility shift and DNase I footprinting results indicate that LTTRs form stronger interactions with the RBS than with the ABS (MacLean *et al.*, 2008; Porrúa *et al.*, 2010). Although LTTRs interact weakly with the ABS, this site is essential for transcriptional activation (Tover *et al.*, 2000; Porrúa *et al.*, 2010). In the ABS, the binding site of an LTTR shifts from site-1 to site-2 upon inducer binding (or upon receiving an environmental signal) (Bundy *et al.*, 2002; McFall, *et al.*, 1997b; Devesse *et al.*, 2011; Porrúa *et al.*, 2013). Binding of an LTTR to promoter DNA causes DNA bending, whose angle is generally relaxed when an inducer molecule(s) binds to the LTTR. After relaxation of this DNA bending, RNA polymerase seems to be recruited to the promoter site to activate transcription.

Since the molecular mechanism of transcriptional activation remains a central issue in biology, many studies have been performed in the field of LTTRs. Although full details of the transcription activation mechanism by LTTRs remains elusive, crystal structures of LTTRs and biochemical studies on the basis of the crystal structures have revealed parts of the transcription activation mechanism by LTTRs. In this review, we have summarized studies of LTTRs on the basis of their tertiary structures.

2. CbnR: one of the representative models for LTTRs

CbnR is a member of the LTTR family (Ogawa and Miyashita, 1999; Ogawa *et al.*, 1999) and one of the best-characterized LTTRs. In 1999, Ogawa *et al.* identified CbnR as a positive regulator for *cbnABCD* genes (Ogawa *et al.*, 1999) in *Cupriavidus necator* NH9. *cbnABCD* genes encode a series of enzymes involved in the *ortho*-cleavage pathway of chlorocatechols. CbnR forms a tetramer in solution and interacts with the RBS and ABS in the *cbnA* promoter region. *cis*, *cis*-Muconate or 2-chloro-*cis*, *cis*-muconate serves as an inducer of CbnR. In the *cbnA* promoter region, the RBS spans the region –76 to –49 upstream of the transcription start site of the *cbnA* gene (Fig. 1). The RBS is presumed to be necessary for anchoring CbnR to the promoter region with its 5 bp inverted repeats (TTACG–N_5–CGTAA) (N: nucleotide). The inverted repeats of RBS in the *cbnA* promoter contain the consensus T–N_{11}–A motif for LTTRs (the conserved T and A are underlined in the above sentence). The ABS spans the region –44 to –19 upstream of the transcription start site of the *cbnA* gene and overlaps with the –35 and –10 elements, which are

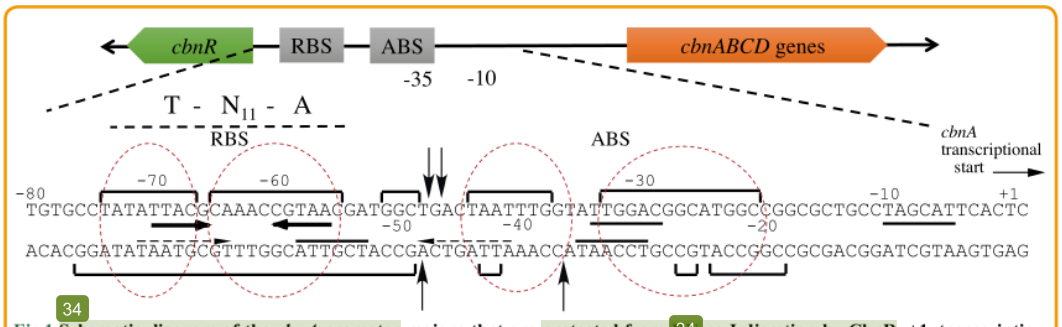

Fig.1 Schematic diagram of the *cbnA* promoter regions that are protected from DNase I digestion by CbnR. +1, transcription start site (dashed circles show locations that are masked by CbnR). The –35 and –10 regions of the *cbnA* promoter are shown (Ogawa *et al.*, 1999). Vertical arrows indicate hyper-sensitive DNase I digestion regions.

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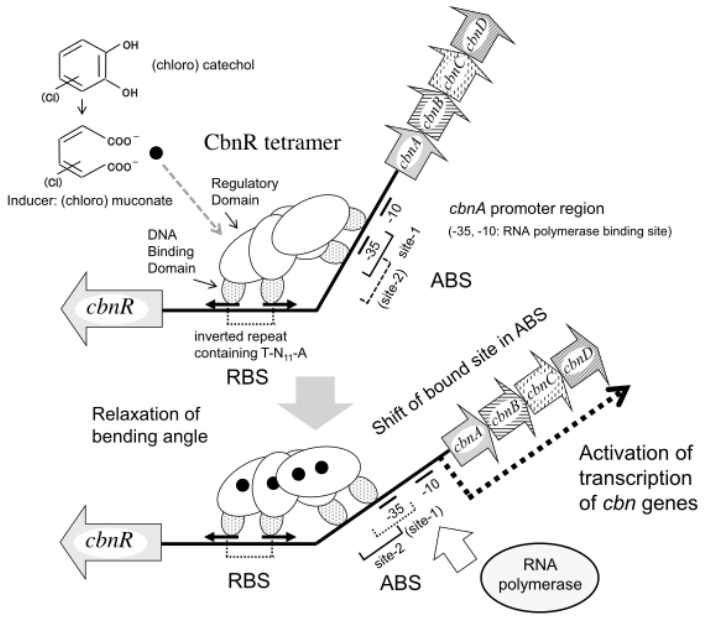

Fig.2 Model describing the transcriptional activation mechanism by CbnR. One dimer in the tetramer CbnR binds to the RBS and the other dimer in the CbnR tetramer binds to the ABS. This causes a bend in the DNA that prevents the RNA polymerase accessing the promoter because the –35 box is masked. Upon binding the inducer, the dimer bound to the ABS shifts from site-1 to site-2 in the ABS. This movement exposes the –35 box and allows RNA polymerase binding to the –35 box.

RNA polymerase binding sites (Fig. 1). Notably, binding of CbnR to both the ABS and RBS of the *cbnA* promoter is likely to cause a bending of the promoter DNA by 78°. The binding angle was estimated by circular permutation gel shift analysis. Upon inducer binding, the bend angle is relaxed to 54°. While similar degrees of bend angles and relaxation upon inducer binding have been reported for other LTTR-binding promoter regions (McFall *et al*., 1997a; van Keulen *et al*., 1998; Minh *et al*., 2018), analysis of the tetrameric DntR by small angle X-ray scattering (SAXS) suggests that the bend angles obtained by circular permutation gel shift results could be underestimates (Lerche *et al*., 2016). Considering biochemical analyses of other LTTRs, the relaxation of the bend angle in the CbnR-DNA complex might be accompanied with a shift of CbnR binding in the ABS (Fig. 2) (Ogawa *et al*., 1999). Although such a shift of the binding site in ABS was not observed in the CbnR system, we presume this shift takes place because it has been observed in other LTTRs (Ogawa *et al*., 1999).

CbnR is the first example for which the crystal structure of a full-length LTTR was determined (Muraoka *et al*., 2003). Therefore, CbnR has been a representative model to study the molecular mechanism of transcription activation by LTTRs. Mutational analyses of CbnR was performed on the basis of its crystal structure (Moriuchi *et al*. 2017). Furthermore, the crystal structure of the DBD of CbnR (hereafter CbnR(DBD)) complex with promoter DNA has been determined (Koentjoro *et al*., 2018). The crystal structure of the CbnR(DBD)-DNA complex revealed the molecular mechanism of the sequence specificity of CbnR (Koentjoro *et al*., 2018). In this report, we frequently use the crystal structure of CbnR as a representative model of LTTRs.

3. Overall and subunit structures of CbnR and other LTTRs

The first tertiary structure describing structural features of an LTTR was the crystal structure of the RD of CysB (hereafter CysB(RD)) (Tyrrell *et al*., 1997). The CysB(RD) structure is a homodimer and each domain is composed of two subdomains. The crystal structure of CysB(RD) provides information about the inducer binding site. Although the crystal structure of CysB(RD) provided a valuable structural base for biochemical analysis of LTTRs,

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several questions remained unanswered: (1) the arrangement of the four subunits in the tetrameric LTTRs; (2) the mechanism of DNA bending by an LTTR upon interaction with the promoter DNA; (3) the mechanism of specific interactions between an LTTR and the RBS/ABS; (4) the mechanism of the conformational change of the RD upon inducer binding; and (5) the quaternary structural changes of the LTTR upon inducer binding. These are critical questions for understanding the functional mechanism(s) of LTTRs. Some of these questions have been answered using structural information of LTTRs obtained after the CbnR structure was solved, whereas some of these questions remain elusive.

The first crystal structure of a full-length LTTR was determined for CbnR (Muraoka *et al*., 2003). Full-length CbnR forms a tetramer in the crystalline state (Fig. 3(A)). Since several biochemical studies have revealed that LTTRs are typically homotetramers in solution (Bundy *et al*., 2002; Jovanovic *et al*., 2003; Jang *et al*., 2018), the tetrameric structure of CbnR represents a model quaternary structure of various LTTRs. The quaternary structure of tetrameric CbnR is unique among tetrameric proteins; the tetramer of CbnR does not have the *222* point group symmetry, which is a typical point group found in tetrameric proteins. In CbnR, the four subunits in the tetramer do not have the same conformation but adopt two distinct conformations, compact and extended forms (Fig. 3(B)). The CbnR tetramer can be described as a dimer of dimers that assembles *via* two distinct dimerization interfaces (Muraoka *et al*., 2003; Ezezika *et al*., 2007b; Monferrer *et al*., 2010; Devesse *et al*., 2011; Jo *et al*., 2015). The first dimer interface is located between two linker helices (residues 59–89; see below). This interaction forms a DBD dimer, in which two DBDs are related by a local two-fold axis. In the DBD dimer, one subunit adopts the compact conformation, whereas the other dimer adopts the extended conformation. The second interface is located between RDs (Fig. 3(A)). The interaction between two RDs makes a dimer of RDs, resulting in the formation of a dimer of the DBD dimers (tetrameric CbnR). This unique architecture of CbnR is shared among other tetrameric LTTRs. BenM, TsaR, DntR and OxyR were found to form essentially the same tetramer in the crystalline state (Ruangprasert *et al*., 2010; Monferrer *et al*., 2010; Devesse *et al*., 2011; Jo *et al*., 2015). Four DBDs in the tetrameric CbnR arrange in a V-shape at the bottom of the CbnR tetramer (Fig. 3(A)). This likely explains the DNA bending observed in the CbnR-promoter DNA complex. Interestingly, CrgA adopts a homo-octamer (Sainsbury *et al*., 2009) with the RDs forming a dimer interface of the dimeric CrgA. MetR, CatR, IlvY and NodD3 have also been identified as dimers in solution by biochemical analysis (Maxon *et al*., 1990; Parsek *et al*., 1994; Fisher and Long, 1993; Bender, 1991).

The crystal structure of CbnR revealed that the subunits of CbnR are composed of two domains and one linker helix (Fig. 4). Residues 1–58 of CbnR forms the DBD, which has a winged helix–turn–helix (wHTH) motif. The linker helix (residues 59–89) connects the DBD to the RD and RD is composed of residues 90–291 (Fig. 4). RD is responsible for interactions between subunits demonstrated in the crystal structure of CysB(RD) and is likely to be involved in the recognition of the inducer (Muraoka *et al*., 2003; Dangeard *et al*., 2015; Ruangprasert *et al*., 2010).

Several crystal structures of full-length LTTRs have also been reported, namely AphB (PDB ID: 3T1B), ArgP (PDB ID: 3ISP), BenM (PDB ID: 3K1N), CrgA (PDB ID: 3HHG), DntR (PDB ID: 5AE5), MetR (PDB ID: 4AB6), OxyR (PDB ID: 4X6C) and TsaR (PDB ID: 3FXQ). These structures confirmed that the crystal structure of CbnR is a representative of the tetrameric LTTRs.

3.1 *Structure of the DNA binding domain* (*DBD*)

The DBD shares high amino acid sequence similarity for proteins that are members of the LTTR family (Fig. 5) (Schell 1993). Functional roles of amino acids involved in DNA binding have been analyzed by mutations of NahR (Schell and Sukhodhane, 1989), OxyR (Kullik *et al*., 1995b; Zaim and Kierzek, 2003), GcvA (Jourdan and Stauffer, 1998), CysB (Lochowska *et al*., 2001), CrgA (Deghmane and Taha, 2003), OxyS (Li and He, 2012) and MetR (Moriuchi *et al*, 2017). The DBD of LTTRs contains three helices (α1, α2 and α3) and two β-strands and adopts the so-called wHTH motif (Muraoka *et al*., 2003; Sainsbury *et al*., 2010; Monferrer *et al*., 2010; Zhou *et al*., 2010; Lerche *et al*., 2016). The α3 helix is referred to as the recognition helix because it recognizes specific DNA sequences by inserting into the major groove of the DNA. A deep cleft forms between the α1 and α3 helices, which is a favored structural feature to facilitate packing into DNA via hydrophobic interactions (Alanazi *et al*., 2013; Koentjoro *et al*., 2018). Two wHTH motifs from the DBD dimer bind to pseudo two-fold symmetric DNA operator sequences such that each monomer recognizes a half site (Laishram and Gowrishankar, 2007; Alanazi *et al*., 2013; Koentjoro *et al*., 2018).

3.2 *Interaction between LTTR(DBD) and promoter DNA*

Details of the DBD-DNA interaction have been analyzed using crystal structures of LTTR DBD complex with their target DNA. High sequence similarities of the amino acid sequences of the DBDs of LTTRs and the promoter DNA sequences suggest a conserved mechanism of promoter DNA recognition by the DBDs of LTTRs. Nonetheless, variation in the amino acid sequences of the DBDs of LTTRs appears to be required for recognition of distinct DNA promoter sequences (MacLean *et al*., 2008; Lönneborg and Brzezinski, 2011). Currently, crystal structures of BenM(DBD)-DNA and CbnR(DBD)-DNA complexes have been determined (Fig. 6). Comparative analysis of these crystal structures revealed several differences between CbnR(DBD) and

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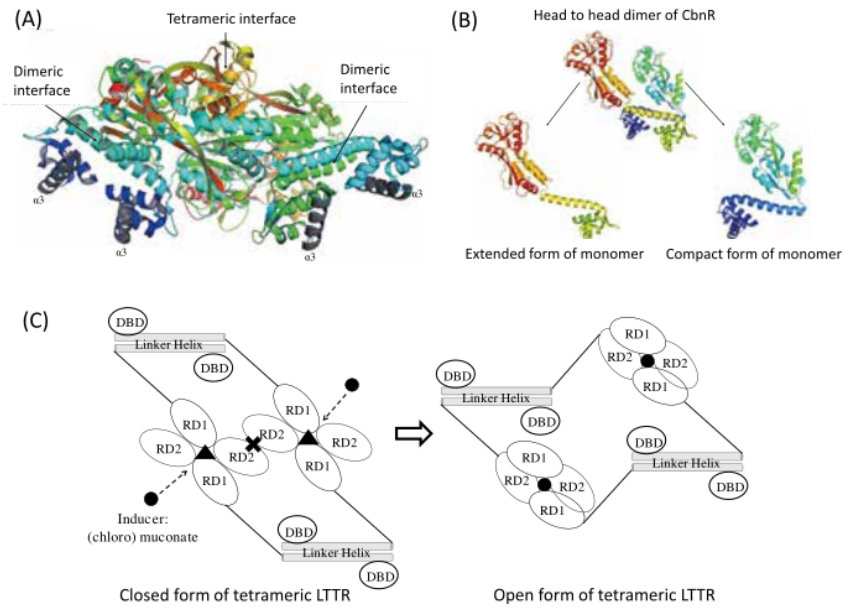

Fig.3 (A) Crystal structure of the tetrameric CbnR (PDB ID: 1IZ1); a representative LTTR homotetramer in a closed conformation. Helix α3 is the recognition helix (gray) (B). Structure of the DBD dimer. DBDs in the dimers are related by a two-fold rotational axis. The linker helix forms a dimer interface. In the DBD dimer, one subunit has a compact conformation and the other adopts an extended conformation. Dimerization of the DBD dimer to form a tetramer occurs through interactions of the RD. (C) Hypothetical model of the quaternary structural change. Left: the close conformation of the tetrameric LTTR. In the closed form, α-helices in the RD interact with each other (left). A conformational change to the RD occurs upon inducer binding. The small conformational change around the inducer binding cleft (IBC) transmitted in the RD seems to result in the loss of the helix-helix interaction found in the closed conformation. The loss of the helix-helix interaction is supposed to induce a relatively large quaternary structural change and the formation of an open conformation. In the open conformation of LTTR, the distance between the two α3 recognition helices at both edges of the tetrameric CbnR is closer than that in the closed form. Fig. 3(C) was reproduced from Monferrer *et al.*, (2010) Mol. Microbiol. 75: 1199-1214 with minor modification of omitting intermediate state.

BenM(DBD) in the interaction with their specific DNA sequences. The overall structures of the two complexes were, however, found to be quite similar. In addition, three nucleotides out of four in each of the inverted repeat sequences are conserved between RBSs for CbnR and BenM; the nucleotide sequence of the inverted repeats of the RBS for CbnR is **T**T**A**C–N_7–GT**A**A and that for BenM is **A**T**A**C–N_7–GT**A**T (the conserved T and A for most LTTR-regulated promoters are underlined, and differences in the two inverted repeats are shown in bold type). Despite these similarities in the DBD and RBS, CbnR could not bind to the RBS recognized by BenM. Surprisingly, a single amino acid difference at residue 33, Thr33 in CbnR and Ser33 in BenM, explains their promoter sequence selectivity on the basis of the crystal structures of the complexes of DBD and DNA (Koentjoro *et al.*, 2018).

Interaction between the DBD and DNA was analyzed by mutations of the DBD and the promoter sequence. Interestingly, the length of the spacer sequence between the RBS and ABS affect the DNA binding activity of the LTTR in the absence of an inducer. Normally, the spacer length between the RBS and ABS is 3–6 bp (Sainsbury *et al.*, 2009; Li and He, 2012). Analysis by deletion and insertion of nucleotides in the spacer region revealed that the distance between the RBS and ABS is critical to the strength of the interaction with tetrameric LTTRs (Tover *et al.*, 2000; Minh *et al.*, 2018). ArgP is a LTTR protein that regulates arginine transport in *Escherichia coli* and is essential for transcriptional activation of the *argO* promoter (Zhou *et al.*, 2010). Increasing the length of the spacer sequence between the RBS and ABS of the *argO* promoter region resulted in a deficiency of transcription of *argO* (Minh *et al.*,

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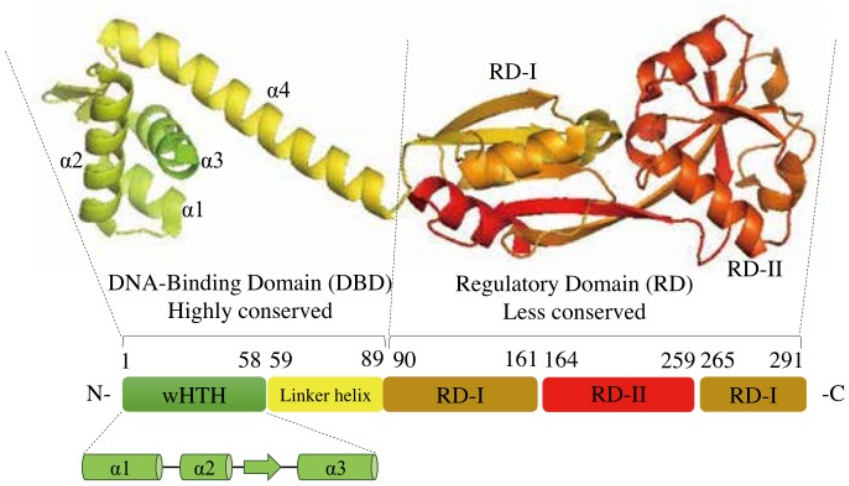

Fig.4 Structure of the CbnR subunit (PDB ID: 1IZ1). A cartoon model (top) and schematic drawing presenting the domain composition (bottom) are shown. The CbnR subunit is composed of the DNA binding domain (DBD) with the winged helix-turn-helix motif, the linker helix that is involved in dimerization, and the regulatory domain (RD) that has an inducer binding site

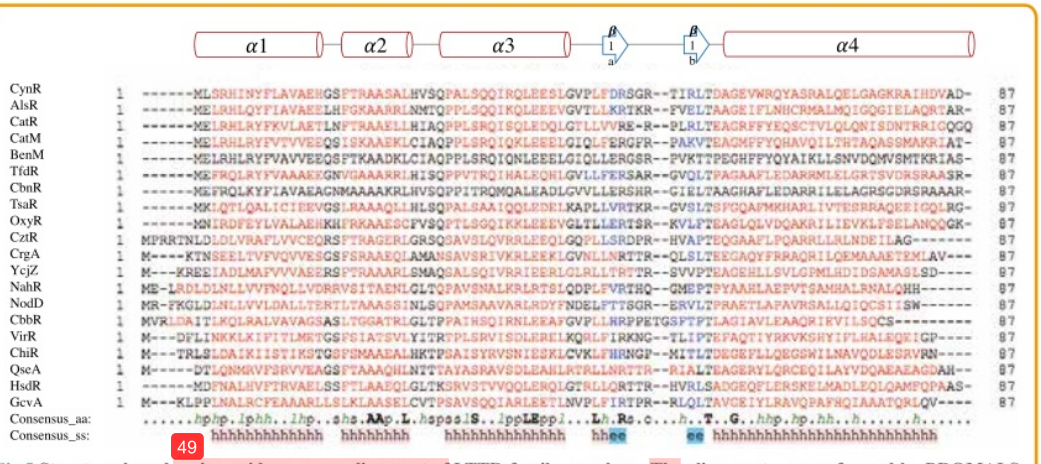

Fig.5 Structure-based amino acid sequence alignment of LTTR family members. The alignment was performed by PROMALS. Amino acids are colored according to PSIPRED secondary structure predictions. The sequences of BenM and CbnR are shown in black. For the other protein sequences, amino acids located in α-helices and β-strands are colored red and blue, respectively, and indicated as "h" and "e" on the bottom line of the figure, respectively.

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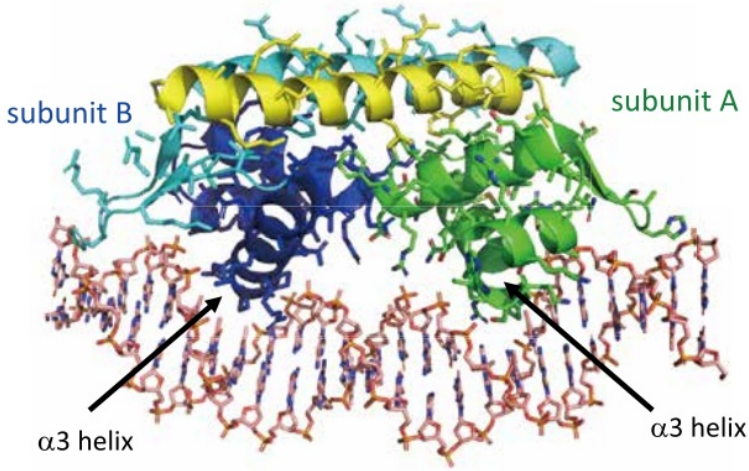

Fig.6 Crystal structure of the complex of CbnR(DBD) and RBS DNA (25 bp) (PDB ID: 5XXP). CbnR(DBD) binds to RBS DNA as a dimer. The DBDs of subunits A and B in the dimer are colored in green and blue, respectively, and linker helices of subunits A and B are colored in yellow and cyan, respectively. The arrows indicate α3 helices inserted into the major grooves of DNA.

2018). Thus, the distance between the RBS and ABS is likely to be critical for transcription activity.

3.3 *Regulatory domain (RD)*

The RD of LTTRs has an inducer binding cavity (IBC) and is presumed to play a critical role in the conformational change of the LTTR tetramer upon inducer binding (Choi *et al*., 2001; Maddocks and Oyston, 2008; Quade *et al*., 2011; Park *et al*., 2017). The RD from CysB was the first crystal structure solved of a RD (Tyrell *et al*., 1997). Subsequently, crystal structures of RDs of LTTR family members with inducer molecules bound (or adopting an inducing state conformation) have been reported. These include OxyR (Choi *et al*., 2001; Jo *et al*., 2015), DntR (Smirnova *et al*., 2004; Lerche *et al*., 2016), BenM and CatM (Ezezika *et al*., 2007a; Cra *et al*., 2009) and TsaR (Monferrer 2010). The RD is composed of two subdomains, RD-I and RD-II. The two subdomains are connected by two crossovers that form the IBC. RD-I consists of a five-stranded β-sheet with three α-helices surrounding this β-sheet structure. RD-II contains a five-stranded β-sheet that is strongly twisted and four α-helices (Fig. 4) (Tyrell *et al*., 1997; Muraoka *et al*., 2003; Monferrer *et al*., 2010; Quade *et al*., 2011; Park *et al*., 2017). Structural studies of BenM, OxyR, PcaQ, RovM, AphB and DntR have led us to hypothesize that inducer binding (or environmental change) to the RD of LTTR causes a conformational change in the RD that is propagated throughout the tetrameric LTTR and changes the bend angle of the promoter DNA (Kovacikova and Skorupski, 2001; Bundy *et al*., 2002; Smirnova *et al*., 2004; Quade *et al*., 2011; *et al*., 2012; Jo *et al*., 2015) However, while crystal structures of OxyR (Choi *et al*., 2001; Jo *et al*., 2015), BenM (Ezezika *et al*., 2007a) and DntR (Devesse *et al*., 2011) have revealed conformational changes of the RD upon inducer binding, conformational changes of tetrameric full-length LTTR upon inducer binding have not been observed in the crystal.

The functional significance of the RD was also analyzed by mutation analysis (Kullik *et al*., 1995a; Cebolla *et al*., 199 Lochowska *et al*., 2001; Akakura and Winans, 2002a; Dangel *et al*., 2005; Craven *et al*., 2009; Lang and Ogawa, 2009; Taylor *et al*., 2012). For example, our group performed a mutational study using CbnR (Moriuchi *et al*., 2017). Of the eight mutations to CbnR(RD), three mutations (Phe98Ala, Lys129Ala and Phe202Ala) appear to directly affect inducer binding, and this observation is corroborated by a study of BenM, in which the corresponding residues are known to interact with the cognate inducer molecule (Ezezika *et al*., 2007a). Interestingly, we obtained two constitutive active mutants, Arg199Ala and Val246Ala, which activated transcription without the inducer. The amino acid exchanges in these mutants appear to induce a structural change that mimics the change caused by inducer binding. These results indicate that conformational changes in the RD are important in activating transcription.

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3.4 *Transition from closed to open form of tetrameric LTTRs*

Protein–protein interactions are important for the assembly of tetrameric LTTRs (Bundy *et al*., 2002; Ezezika *et al*., 2007b; Sainsbury *et al*., 2009; Knapp and Hu, 2010; Ruangprasert *et al*., 2010; Devesse *et al*., 2011). Residues located at the interface regions of RDs (Fig. 3(A)) are responsible for the formation of tetramers. In particular, interactions between two DBD dimers are critical for formation of the tetramer (Muraoka *et al*., 2003; Ezezika *et al*., 2007b; Ruangprasert *et al*., 2010).

Although no quaternary structural changes of LTTRs upon binding an inducer have been observed in crystal structures, some crystal structures of LTTRs suggest a transition of the quaternary structure of tetrameric LTTR from a closed to open form upon binding an inducer (Monferrer *et al*., 2010; Lerche *et al*., 2016). In the closed form, there are interactions between two α helices from two RD-II subdomains (two αV helices from two distinct RD-II) that are related by a two-fold axis. Upon inducer binding, local conformational changes in the RD (Ezezika *et al*., 2007a; Devesse *et al*., 2011; Park *et al*., 2017) seem to disrupt helix-helix interactions leading to a structural change to the open form (Fig. 3(C)) (Choi *et al*., 2001; Monferrer *et al*., 2010; Devesse *et al*., 2011). This conformational change could possibly be mediated by the flexibility of the RD. These changes appear to occur in TsaR (Monferrer *et al*., 2010), ArgP (Zhou *et al*., 2010) and DntR (Devesse *et al*., 2011). These conformational changes are supposed to cause a shift of the binding site in ABS, resulting in productive contact of LTTR with the α C-terminal domain (α-CTD) of RNA polymerase on the promoter (Chugani *et al*., 1997; Fritsch *et al*., 2000; Lochowska *et al*., 2004).

Since there are helix-helix interactions (αV-αV interactions) between two RD-II subdomains in the tetrameric CbnR (Fig. 3(C), left panel), the crystal structure of CbnR can be considered to be a closed form. In contrast, as there are no corresponding helix-helix interactions in tetrameric TsaR, the structure of TsaR is an open form. Thus, the tetrameric CbnR is assumed to represent an inducer-free non-activating state, whereas tetrameric TsaR is an active state (Monferrer *et al*., 2010). Notably, a SAXS experiment successfully observed a corresponding change of the quaternary structure of DntR between the inducer-free and inducer-bound states (Lerche *et al*., 2016).

4. Sliding dimer model for transcriptional activation of LTTR

The sliding dimer model has been proposed to explain the scheme of transcriptional activation by LTTR (van Keulen *et al*., 2003; Porrúa *et al*., 2007; Monferrer *et al*., 2010; Lerche *et al*., 2016). Transcriptional activation by LTTR should begin with interactions with the RBS using two α3 helices in a DBD dimer of the tetrameric LTTR. After the LTTR-RBS interaction, the other DBD dimer in LTTR should bind the ABS (Sainsbury *et al*., 2009; Ruangprasert *et al*., 2010; Zhou *et al*., 2010; Alanazi *et al*., 2013; Rivas–Marín *et al*., 2016) to form the tetrameric LTTR-DNA complex. The order of binding, from RBS to ABS, is reasonable because the affinity between the DBD and RBS is significantly stronger than that between the DBD and ABS. Since the four DBDs in the LTTR tetramer arrange in a V-shape manner, it is reasonable to postulate that the interaction between tetrameric LTTR and promoter DNA causes bending of the DNA in accordance with the arrangement of the four DBDs. This LTTR-DNA complex without inducer is considered to be a resting state and seem to adopt the closed form of the tetrameric LTTR.

Inducer molecule binding to the IBC in the RD seem to trigger a quaternary structural change of the LTTR tetramer (Fig. 3(C)), resulting in the open form of the tetrameric LTTR on the promoter. The change in the quaternary structure of tetrameric LTTR is proposed to result in the rearrangement of the DBDs, leading to a relaxation of DNA bending. In this process, DBDs interacting with the ABS shift on the promoter and change the interaction site from site-1 to site-2 of the ABS (Fig. 2). Since site-1 of the ABS overlaps with the –35 box of the promoter, the shift of the binding site exposes the –35 box to enable RNA polymerase binding (Monferrer *et al*., 2010; Ruangprasert *et al*., 2010; Devesse *et al*., 2011). The change of the ABS recognition site has been demonstrated in studies of OxyR (Toledano *et al*., 1994), OccR (Wang *et al*., 1992), ClcR (McFall *et al*., 1997b) AtzR (Porrúa *et al*., 2010) and DntR (Lerche *et al*., 2016). In the sliding dimer mechanism, the change of the angle of bent DNA accompanied with a quaternary structural change of the tetrameric LTTR would be a critical step. After release of the –35 box for RNA polymerase binding, a complex involving LTTR, sigma factor and RNA polymerase would form on the promoter to initiate transcription.

5. Conclusions

In this review, we discussed how tertiary structures of LTTRs have provided valuable insight into the interaction of LTTRs with promoter DNA and aided our understanding of the mechanism of the initial step of transcriptional activation by LTTRs. Initiation of transcriptional activation is a multistep process that consists of a series of conformational changes of LTTRs, promoter DNA and their complexes. Although structural and biochemical analyses have revealed that relaxation of DNA bending and shift of the binding site on the ABS are critical steps for recruiting RNA polymerase to the promoter DNA, other important features of initiation of transcriptional activation remain poorly understood. Details of the quaternary structural changes of LTTRs upon inducer binding and structural details describing relaxation of the DNA bending angle can be analyzed with high-resolution tertiary structures. Furthermore, the molecular

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mechanism of transcriptional initiation is a critical question that could be answered based on the tertiary structure of the initiation complex. For future tertiary structure analysis, not only X-ray crystallography but also cryo-electron microscopy will play an important role. These are challenging structural problems that will be tackled in the near future.

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