Identification of the Subunit of cAMP Receptor Protein (CRP) That Functionally Interacts with CytR in CRP-CytR-mediated Transcriptional Repression*

(Received for publication, November 12, 1999, and in revised form, January 27, 2000)

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At promoters of the Escherichia coli CytR regulon, the cAMP receptor protein (CRP) interacts with the repressor CytR to form transcriptionally inactive CRP-CytR-promoter or (CRP)$_2$-CytR-promoter complexes. Here, using “oriented heterodimer” analysis, we show that only one subunit of the CRP dimer, the subunit proximal to CytR, functionally interacts with CytR in CRP-CytR-promoter and (CRP)$_2$-CytR-promoter complexes. Our results provide information about the architecture of CRP-CytR-promoter and (CRP)$_2$-CytR-promoter complexes and rule out the proposal that masking of activating region 2 of CRP is responsible for the transcriptional inactivity of the complexes.

The Escherichia coli cAMP receptor protein (CRP; also referred to as catabolite gene activator protein, or CAP) is a global transcriptional regulator. CRP serves as a transcriptional activator at numerous promoters and also can serve as a transcriptional co-activator, repressor, or co-repressor (reviewed in Ref. 1). CRP binds to a 22-bp 2-fold-symmetric DNA site located in or near each CRP-regulated promoter. CRP is a dimer of two identical subunits, each consisting of 209 amino acids. The crystallographic structure of the CRP-DNA complex shows that one subunit of CRP interacts with one half of the DNA site, and the other subunit of CRP interacts with the other half of the DNA site, in an approximately 2-fold-symmetric fashion (2, 3).

Activation of transcription at simple CRP-dependent promoters (i.e. promoters that require only CRP for activation) involves direct protein-protein contact between CRP and RNA polymerase (RNAP). At promoters that have a DNA site for CRP located upstream of the DNA site for RNAP (class I CRP-dependent promoters), a determinant consisting of amino acids 156–164 of CRP (“activating region 1” (AR1)) makes direct contact with the RNAP α-subunit C-terminal domain (αCTD) (1, 4, 5). At CRP-dependent promoters that have the DNA site for CRP centered near position –42 (class II CRP-dependent promoters), AR1 interacts with the αCTD, and a second determinant, consisting of amino acids 19, 21, and 101 of CRP (“activating region 2” (AR2)), interacts with the RNAP α-subunit N-terminal domain (αNTD) (1, 6, 7).

“Oriented heterodimer” analysis (in which CRP heterodimers having one subunit with a mutant activating region and one subunit with a wild-type activating region are constructed, oriented on promoter DNA, and analyzed) has defined, for each class of CRP-dependent promoter, which subunit of the CRP dimer functionally presents each activating region (7–10). At class I CRP-dependent promoters, AR1 is functionally presented by the promoter-proximal subunit of the CRP dimer (9, 10). At class II CRP-dependent promoters, AR1 is functionally presented by the promoter-distal subunit, and AR2 is functionally presented by the promoter-proximal subunit (7, 8, 10).

Promoters of the CytR regulon contain DNA sites for both CRP and the repressor CytR (11). At these promoters, CRP interacts alternatively, and mutually exclusively, with RNAP or with CytR (12). Under conditions in which CytR is inactive (in the presence of cytidine), CRP interacts with RNAP to form transcriptionally active CRP-RNAP-promoter complexes, making the same interactions as at the above-described class I and class II CRP-dependent promoters. Under conditions in which CytR is active (in the absence of cytidine), CRP interacts with CytR to form transcriptionally inactive CRP-CytR-promoter complexes.

The simplest promoter of the CytR regulon (cytRP) contains a DNA site for CRP centered at position –63.5 and a DNA site for CytR centered at position –41.5; this promoter forms 1:1 CRP-CytR-promoter complexes (13, 14). Most promoters of the CytR regulon contain two DNA sites for CRP (typically centered at or near positions –93.5 and –41.5) that flank the DNA site for CytR (e.g. deoP2, cdd-P, udp-P, and nupG-P); these promoters form 2:1:1 (CRP)$_2$-CytR-promoter complexes, with one CytR dimer sandwiched between two CRP dimers (11, 15).

Formation of CRP-CytR-promoter and (CRP)$_2$-CytR-promoter complexes involves both CRP-CytR and CytR-DNA interactions (16–18). CRP-CytR interaction involves a determinant consisting of residues 12, 13, 17, 105, 108, and 110 of CRP (the “repression region” (RR); a determinant that is immediately adjacent to AR2 of CRP) and a chemically complementary determinant within the C-terminal domain of CytR (16, 19, 20). CytR-DNA interactions involve a helix-turn-helix DNA binding motif within the N-terminal domain of CytR (21, 22). CytR-DNA interactions are essential for complex formation at physiological levels of CytR but are not essential at high levels of CytR. Thus, CytRΔ9–49, a CytR derivative completely defec-
tive in CytR-DNA interaction, can form transcriptionally inactive (CRP)_2-CytR-promoter complexes at the deoP2 promoter when overproduced in vivo (23).

The mechanism by which formation of CRP-CytR-promoter and (CRP)_2-CytR-promoter complexes results in transcriptional repression remains to be established. Three (not mutually exclusive) models seem possible. (i) CytR may interfere with interaction between AR1 of CRP and αCTD of this DNA segment. (ii) CytR may interfere

| Strain | Genotype | Source |
|--------|----------|--------|
| Sa2929 | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10 | Ref. 16 |
| Sa2928 | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10 | Ref. 16 |
| Sa2929ΔcrpE181V | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, attλ:crpE181V | This work |
| Sa2929/pBHK491 | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, pBHK491 | This work |
| Sa2929/O-CC/CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, pOU-O-CC, pKLPC4 | This work |
| Sa2929/O-CC/Δ(a13)CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, pOU-O-CC, pKLPC4-13A | This work |
| Sa2929/O-CC/CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, pOU-O-CC, pKLPC4 | This work |
| Sa2929/O-CC/Δ(a13)CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, pOU-O-CC, pKLPC4-13A | This work |
| Sa2929/O-CC/pC19/CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, pOU-O-CC, pC19, pKLPC4 | This work |
| Sa2929/O-CC/pC19/Δ(a13)CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, pOU-O-CC, pC19, pKLPC4-13A | This work |
| Sa2929/O-CC/CytRΔ9–49/CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, pOU-O-CC, pC19-CytRΔ9–49, pKLPC4 | This work |
| Sa2929/O-CC/CytRΔ9–49/Δ(a13)CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, pOU-O-CC, pC19-CytRΔ9–49, 49, pKLPC4-13A | This work |
| Sa2929/O-CC-CR/CYTΔ9–49/Δ(a13)CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, pOU-O-CC, pC19-CytRΔ9–49, pKLPC4-13A | This work |
| Sa2929ΔcrpE181V/OX-OXC/pC19/CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, attλ:crpE181V, pOU-OX-OXC, pC19, pKLPC4 | This work |
| Sa2929ΔcrpE181V/OX-OXC/pC19/Δ(a13)CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, attλ:crpE181V, pOU-OX-OXC, pC19, pKLPC4-13A | This work |
| Sa2929ΔcrpE181V/OX-OXC/CytRΔ9–49/CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, attλ:crpE181V, pOU-OX-OXC, pC19-CytRΔ9–49, pKLPC4 | This work |
| Sa2929ΔcrpE181V/OX-OXC/CytRΔ9–49/Δ(a13)CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, attλ:crpE181V, pOU-OX-OXC, pC19-CytRΔ9–49, pKLPC4-13A | This work |
| Sa2929ΔcrpE181V/OX-OXC/DkΔ9–49/pC19/CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, attλ:crpE181V, pOU-OX-OXC, pC19, pKLPC4 | This work |
| Sa2929ΔcrpE181V/OX-OXC/DkΔ9–49/pC19/Δ(a13)CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, attλ:crpE181V, pOU-OX-OXC, pC19, pKLPC4-13A | This work |
| Sa2929ΔcrpE181V/OX-OXC/DkΔ9–49/Δ(a13)CRP | Δdeo, Δlac, cytR::scarf-96 zdh-732::Tn10, attλ:crpE181V, pOU-OX-OXC, pC19, pKLPC4-13A | This work |

**Plasmids**

| Plasmid | Characteristics | Source |
|---------|----------------|--------|
| pOU254  | Ap<sup>+</sup>; ori-pR1; lacZYA | Ref. 15 |
| pO-CC   | Tc<sup>+</sup>; ori-pR2; P<sub>O-CC-lacZYA</sub> | This work |
| pO-CX   | Tc<sup>+</sup>; ori-pR2; P<sub>O-CX-lacZYA</sub> | This work |
| pO-XC   | Tc<sup>+</sup>; P<sub>O-XC-lacZYA</sub> | This work |
| pOU-O-CC| Ap<sup>+</sup>; ori-pR1; P<sub>O-CC-lacZYA</sub> | This work |
| pOU-O-CX| Ap<sup>+</sup>; ori-pR1; P<sub>O-CX-lacZYA</sub> | This work |
| pKLPC4  | Spec<sup>+</sup>; Tc<sup>+</sup>; P<sub>KLPC4</sub> | Ref. 19 |
| pKLPC4-13A | Spec<sup>+</sup>; Tc<sup>+</sup>; P<sub>KLPC4-13A</sub> | Ref. 19 |
| pKLPC4-181V | Spec<sup>+</sup>; P<sub>KLPC4-181V</sub> | This work |
| pYZCRP  | Ap<sup>+</sup>; ori-pBR322; ori-fl <sup>+</sup>; crp<sup>+</sup> | Ref. 33 |
| pPC181V | Ap<sup>+</sup>; ori-pBR322; crp<sup>+</sup> | Ref. 31 |
| pC19    | Cm<sup>+</sup>; ori-pBRR322 | Ref. 23 |
| pC19-CytRΔ9–49 | Cm<sup>+</sup>; ori-pBRR322; P<sub>cytR-Δ9–49</sub> | Ref. 23 |
| pBHK491 | Ap<sup>+</sup>; ori-pSC101<sup>‡</sup>; att<sub>λ</sub> | B. H. K., unpublished |
| pTAC3590| Ap<sup>+</sup>; Km<sup>+</sup>; ori-pBR322; att<sub>λ</sub> | Ref. 24 |
| pREII-NHα| Ap<sup>+</sup>; ori-pBR322; P<sub>SV40-express</sub> | Ref. 7 |
with interaction between AR2 of CRP and αNTD of RNAP (by interacting with a determinant on CRP immediately adjacent to AR2, preventing access of αNTD to AR2). (iii) CytR may interfere with interaction between RNAP and the core promoter.

As a first step to distinguish among these models, we have used oriented heterodimer analysis (9) to determine which subunit of the CRP dimer functionally interacts with CytR in CRP-CytR-mediated transcriptional repression and to relate the identity of this subunit to the identities of the subunits that functionally present AR1 and AR2 in CRP-mediated transcriptional activation.

**EXPERIMENTAL PROCEDURES**

**Strains—** E. coli strains used are listed in Table I. Strain SØ9299 (crpE181V) was constructed by replacing the SoI–EcoRI bla segment of plasmid pTAC3590 (24) with the SoI–EcoRI crpE181V segment of plasmid pKPLC–E181V (constructed as in Ref. 19), introducing the resulting minicircles into strain SØ9299/pBH491, and isolating Km<sup>+</sup> Ap<sup>+</sup> transformants at 42 °C (method of Refs. 24 and 25).

**Plasmids—** Plasmids used are listed in Table II. Plasmid pO-CC was constructed by replacing the EcoRI–BamHI CC (−41.5) segment of plasmid pWR2CCC (−41.5) (28) by a synthetic DNA fragment prepared by annealing oligodeoxyribonucleotides 5′-AATTCGTTGCATTCGTTACA-3′ and 5′-GATATCCGAAACTCAATCTCCATC-3′ using 5′-phosphate 5′-endlabeled primers and plasmids pO-CC, pO-CX, and pO-XC as templates, followed by digestion with EcoRI and XhoI.

Plasmids pOUO-CC, pOUO-CX, and pOUO-XC were constructed by replacing the EcoRI–BglII Flp FI spacer segment of the low copy number plasmid pOU254 (15) with polymerase chain reaction-generated DNA fragments (prepared using 5′-CCGATTATCCGAAACTCAATCTCCATC-3′ and 5′-ATTCGTTGCATTCGTTACA-3′) as primers and plasmids pO-CC, pO-CX, and pO-XC as templates, followed by digestion with EcoRI and EcoRV.

**Proteins—** CRP and CytR derivatives were prepared using αMP affinity chromatography (27). CRP proteins were prepared as described (17, 23). RNAP was purified by metal ion affinity chromatography followed by ion exchange chromatography (7).

**RESULTS**

**Construction of Promoter Derivatives**

To analyze CRP-CytR-promoter complex formation, we constructed a set of three promoter derivatives, starting from the well characterized class II CRP-dependent promoter CC (−41.5) (1, 6, 26) (Fig. 1a). Each of the three promoter derivatives has a DNA site for CRP with two consensus half-sites (O-CC); a DNA site for CytR (29, 30) centered at position 26.35. The first DNA site for CRP and a consensus DNA site for CytR (29, 30) centered at position −63.5. The first has a DNA site for CRP and two consensus half-sites (O-CC); a consensus DNA site for CRP and a DNA site for CytR. Sequences from +118 to +49 are derived from the CC (−41.5) promoter (26). The sequence from +70 to −22 is from the deoF2 isolate C15–32 (30). The CytR operator is underlined, and the DNA half-sites for CRP are in boldface letters. b, promoters with two DNA sites for CRP and one DNA site for CytR. Sequences from +118 to +72 are as in a. A consensus DNA site for CRP is centered at position −94.5 to enable (CRP)<sub>2</sub>-CytR-promoter complex formation.

**TABLE III**

| CRP derivative | Repression |
|----------------|-----------|
|               | O-CC | CC-O-CC |
| CRP           |       |        |
|               | Cytr  | CytrΔ9–49 | Cytr | CytrΔ9–49 |
|                | %    | %       | %    | %        |
| CRP           | 76   | 0       | 98   | 93       |
| [Ala<sup>13</sup>]CRP | 0    | 0       | 63   | 9        |

**RESULTS**

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CRP-CytR-mediated Transcriptional Repression

The results of in vitro transcription experiments with the oriented heterodimers are presented in Fig. 2b. The [Val181]CRP/[Ala13]CRP heterodimer was functional in CRP-CytR-mediated transcriptional repression at O-XC (with the functional RR in the CytR-proximal subunit) but was not functional in CRP-CytR-mediated transcriptional repression at O-CX (with the nonfunctional RR in the CytR-proximal subunit). In contrast, the [Val181]CRP/CRP heterodimer, which served as a control with a functional RR in each subunit, was functional in CRP-CytR-mediated transcriptional repression at both O-XC and O-CX (as also was the control [Val181]CRP/[Val181]CRP homodimer, which served as a further control with a functional RR in each subunit; data not shown). We conclude that the CytR-proximal subunit of CRP functionally presents RR in CRP-CytR-promoter complex formation.

FIG. 3. (CRP)2-CytR-mediated transcriptional repression by oriented heterodimers. a, expected orientations of heterodimers at the XC-O-CX and CX-O-XC promoters. Shaded boxes, [Val181]CRP subunits; open boxes, CRP subunits. b, results of in vitro transcription experiments with oriented heterodimers. c, results of in vivo transcription experiments with oriented heterodimers.

**Discussion**

Only One Subunit of CRP Functionally Interacts with CytR—Our results establish that only one subunit of CRP, the CytR-
proximal subunit, functionally interacts with CytR in CRP-CytR-promoter complex formation at the O-CC promoter (Fig. 2). Our results further establish that only one subunit of each CRP dimer, the CytR-proximal subunit of each CRP dimer, functionally interacts with CytR in (CRP)₂-CytR-promoter complex formation at the CC-O-CC promoter (Fig. 3). Our results support the schematic models in Fig. 4 and structural models in Fig. 5.

Spatial Relationship between Determinants for Transcription Activation and the Determinant for CRP-CytR Interaction—In the absence of CytR, the O-CC promoter is a simple class II CRP-dependent promoter (Fig. 4a). At such a promoter, CRP activates transcription through two sets of interactions: (i) protein-protein interaction between AR1 of the upstream subunit of the CRP dimer and RNAP α-CTD, which interacts with the DNA segment immediately upstream of the CRP dimer; and (ii) protein-protein interaction between AR2 of the downstream subunit of the CRP dimer and RNAP α-NTD (Fig. 4a; Refs. 1, 6, and 7). Our results indicate that, at such a promoter, CytR interacts with the subunit of CRP that functionally presents AR1 but does not interact with the subunit of CRP that functionally presents AR2 (compare locations of blue, red, and yellow determinants in Figs. 4a and 5a).

In the absence of CytR, the CC-O-CC promoter is a compound class I/class II CRP-dependent promoter (Fig. 4c). At such a promoter, CRP activates transcription through three sets of interactions: (i) protein-protein interaction between AR1 of the downstream subunit of the CRP dimer and RNAP α-CTD, which interacts with the DNA segment immediately downstream of this CRP dimer; (ii) protein-protein interaction between AR1 of the upstream subunit of the CRP dimer in the −94 region and one copy of RNAP α-CTD, which interacts with the DNA segment immediately upstream of this CRP dimer; and (iii) protein-protein interaction between AR2 of the downstream subunit of the CRP dimer and RNAP α-NTD, which interacts with the DNA segment immediately downstream of this CRP dimer.
in the −42 region and RNAP αNTD (1). Our results indicate that, at such a promoter, CytR interacts with the subunit of CRP that functionally presents AR1 in each CRP dimer but does not interact with the subunit of CRP that functionally presents AR2 (compare locations of blue, red, and yellow determinants in Figs. 4, c and d, and 5b).

**Implications for Mechanism of Repression by CytR**—Our results indicate that, at both O-CC and CC-O-CC, CytR interacts with the CRP subunit that functionally presents AR1 (Figs. 4, b and d, and 5). Molecular modeling indicates that interaction between CytR and the CRP subunit that functionally presents AR1 is likely to interfere with interaction between AR1 and RNAP αCTD, both by obstructing access to AR1 and by obstructing access to the DNA segment adjacent to AR1 (Fig. 5). We propose that CytR inhibits transcription, at least in part, by interfering with interaction between AR1 and RNAP αCTD.

In contrast, our results indicate that CytR does not interact with the CRP subunit that functionally presents AR2 (Figs. 4, b and d, and 5). We propose that CytR does not inhibit transcription by interfering with interactions between AR2 and RNAP αNTD.

**Prospect**—Our results provide new information about the architecture of CRP-CytR-promoter and (CRP)$_2$-CytR-promoter complexes and constrain possible mechanisms for transcription repression by CytR. Important objectives for further work include determination of the subunit of CytR that functionally interacts with CRP and determination whether repression by CytR is solely due to interference with interaction between CRP and RNAP ("anti-activation") or also involves interference, directly or indirectly, with interactions between RNAP and the core promoter ("direct repression").

**Acknowledgments**—We thank Y. Kim for preparing CytR and RNAP. We thank Mads Nørregaard-Madsen for preparing Fig. 5.

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J. Biol. Chem. 2000, 275:11951-11956.
doi: 10.1074/jbc.275.16.11951

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