Escherichia coli CreBC Is a Global Regulator of Gene Expression That Responds to Growth in Minimal Media*

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We have identified nine genes, the expression of which are regulated by the CreBC two-component system: the first members of the cre regulon. They are divided into eight transcriptional units, each having a promoter-proximal TTCACnnnnnTTCAC “cre-tag” motif. The cre regulon genes are: the ackA/D operon, the products of which collectively catalyze the conversion of acetyl-CoA into acetate and ATP; talA, which encodes an enzyme involved in the mobilization of glyceraldehyde-3-phosphate into the pentose phosphate pathway; radC, which encodes a RecG-like DNA recombination/repair function; malE, which is the first gene in the malEFG maltose transporter operon; trgB, which encodes an ADP-ribosyl pyrophosphorylase; and three other genes, creD, yidS and yieI, the products of which have not been assigned a function. Expression of each of these cre regulon genes is induced via CreBC during growth in minimal media, with the exception of malE, which is more tightly repressed. The diverse functions encoded by the cre regulon suggest that CreBC is a global regulator that sits right at the heart of metabolic control in Escherichia coli.

Bacteria respond rapidly to physical and nutritional changes in their environment and regulate the expression of sets of genes in response to specific environmental and metabolic signals. One control paradigm is the two-component regulator (TCR) where the tasks of detecting the signal and responding to it are undertaken by separate proteins (1). One component, the signal sensor, belongs to an extended family of histidine kinases that autophosphorylate when activated by an appropriate signal. The second element, a member of the response regulator family of transcription factors, is activated by the phosphorylation of an aspartate residue, with the phosphate donor being the phospho-histidine of its partner signal sensor (1).

A recently described TCR, BlrAB, regulates the production of multiple β-lactamases in several Aeromonas spp. in response to β-lactam exposure (2–4). BlrAB is most homologous (60–70%) at the amino acid level to CreBC, an Escherichia coli TCR for which no specific function has been assigned (5). The CreC signal sensor, originally designated PhoM, was discovered because it can act as a phosphate donor for PhoB, a response regulator that controls expression of the pho regulon. This regulon encodes functions (e.g. alkaline phosphatase, PhoA) that are involved in cytoplasmic inorganic phosphate homeostasis, and its usual control system is the PhoBR TCR (5). Autophosphorylation of the PhoR signal sensor is triggered when the concentration of inorganic phosphate falls below a critical threshold. This results in the phosphorylation of PhoB via pho-relay, causing an increase in its affinity for the “pho box,” a specific DNA binding motif, that is promoter-proximal in all pho regulon genes. Binding of PhoB to the pho box stimulates (or in some cases represses) transcription of the downstream gene (5–7).

In phoR null mutants, activation of the pho regulon depends on CreC (8, 9), which is not responsive to phosphate concentration but rather to the carbon source in the growth medium. For example, PhoA expression is induced in phoR− mutants during growth in minimal salts medium with glucose, acetate, or pyruvate as carbon and an energy source (10). On the basis of this finding, it was suggested that the normal function of CreC is to monitor changes in carbon supply and that cross-talk with PhoB reflects similarities between CreC and PhoR such that both serve as phosphate donors for PhoB. Because cross-talk only occurs in mutants lacking the phospho-PhoB phosphatase activity residing in PhoR, it may not have any physiological relevance in wild-type cells (5). The creC gene is part of a four-gene cluster, creABCD (11); the functions of CreA and CreD are unknown, but CreB is a putative response regulator and is homologous to PhoB. CreB is a target for pho-relay from phospho-CreC and is believed to be the cognate CreC response regulator (12), although its target genes have never been defined (5, 10–12).

When the β-lactamase genes of Aeromonas jandaei were first cloned into E. coli, their expression was observed to be low level (13). Mutants were obtained in which expression of the β-lactamases was increased, and the mutations mapped to the cre gene cluster (13). The subsequent identification of BlrAB (a close homologue of CreBC) as a TCR that regulates β-lactamase expression in A. jandaei and other aeromonads (2–4), led to the suggestion that CreB specifically regulates the expression of cloned Aeromonas spp. β-lactamase genes, a hypothesis for which there is some direct evidence (13, 14). In this study, we have extended these findings to locate a consensus sequence, the “cre tag,” which is found close to the promoters of all CreBC-regulated Aeromonas spp. β-lactamase genes. This information was used to find E. coli cre-tag genes, which all have their expression regulated by CreBC. Thus we have defined, at least in part, the cre regulon.

EXPERIMENTAL PROCEDURES

Bacterial Strains and Culture Conditions—The strains of E. coli used in the study were DH5α ΔlacU169 (Δ80lacZΔM15), supE44, rfbD1,
The cre-c DNA Tag Associated with Aeromonas spp. β-Lactamase Genes—In two previous studies using creBC mutants, the E. coli CreBC TCR was implicated in controlling the expression of cloned Aeromonas spp. β-lactamase genes (13, 14). To investigate whether the wild-type CreBC TCR can regulate the expression of Aeromonas spp. β-lactamases in a medium-dependent manner, the three Aeromonas hydrophila (ampH, cepH, and imiH) and three Aeromonas veronii bv. Sobria (ampS, cepS, and imiS) β-lactamase genes were introduced into E. coli DH5α (cre−) separately on multicopy plasmids, and β-lactamase activities in the cell extracts were measured after growth of the recombinants to mid-log phase in nutrient broth or in minimal medium with either glucose, glyceral, or pyruvate as carbon source (Fig. 1). In all cases, there was a significant increase in β-lactamase expression after a switch from complex to minimal medium, with the actual carbon source used only contributing a small amount to the overall increase. These effects were not seen when UB5254, a creC::Kn derivative of DH5α, was used, confirming that the activation of β-lactamase expression in minimal medium is a CreBC-dependent event (Fig. 1).

These findings argued for the presence of a specific transcription factor binding sequence near the promoter of each β-lactamase gene, mediating CreBC-dependent control. To find whether this was the case, sequences upstream of the ATG initiation codon for all six β-lactamase genes were aligned and searched for common motifs. To facilitate analysis, transcriptional start points for each β-lactamase gene in DH5α grown in glucose minimal medium were determined via reverse transcription of total RNA. Primer sequences were designed from the E. coli MG1655 genome sequence (23) and were: acaAlfa forward (5′-CTACACGTGCTGATGAGATG-3′) and reverse (5′-CGATCTCTGGTCAGACCTGC-3′) (these primers span the intergenic region of ackA and pta and report the expression of the operon); talTa forward (5′-CGATTCACCTGCTGTCG-3′) and reverse (5′-CAGCGAGCTGAGTGGTGCA-3′) and reverse (5′-CAGCGAGCTGAGTGGTGCA-3′) and reverse (5′-GAAACATACTCTCCACGC-3′) and reverse (5′-GAAACATACTCTCCACGC-3′); and ampC forward (5′-CGCGTACGACACCAG-3′) and reverse (5′-CGATGACCGACGCTGCGT-3′).

RT-PCR products were purified and sequenced as described previously (23) to confirm that the target message had been amplified.

RESULTS

Identification of a cre Gene Tag Associated with Aeromonas spp. β-Lactamase Genes—In two previous studies using creBC mutants, the E. coli CreBC TCR was implicated in controlling the expression of cloned Aeromonas spp. β-lactamase genes (13, 14). To investigate whether the wild-type CreBC TCR can regulate the expression of Aeromonas spp. β-lactamases in a medium-dependent manner, the three Aeromonas hydrophila (ampH, cepH, and imiH) and three Aeromonas veronii bv. Sobria (ampS, cepS, and imiS) β-lactamase genes were introduced into E. coli DH5α (cre−) separately on multicopy plasmids, and β-lactamase activities in the cell extracts were measured after growth of the recombinants to mid-log phase in nutrient broth or in minimal medium with either glucose, glyceral, or pyruvate as carbon source (Fig. 1). In all cases, there was a significant increase in β-lactamase expression after a switch from complex to minimal medium, with the actual carbon source used only contributing a small amount to the overall increase. These effects were not seen when UB5254, a creC::Kn derivative of DH5α, was used, confirming that the activation of β-lactamase expression in minimal medium is a CreBC-dependent event (Fig. 1).

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erably more transcriptional activation during growth in minimal medium than when only a single motif was observed (Figs. 1 and 2). As such, the direct repeat sequence was denoted a cre tag (i.e. a label for genes, the transcription of which is regulated directly or indirectly by CreBC). We speculated that cre tags would be associated with those *E. coli* genes that are subject to CreBC-dependent transcriptional control. Searches of the entire *E. coli* MG1655 genome sequence (23) for the direct repeat sequence revealed 13 instances (Table I). For a direct repeat to be classed as a cre tag, the criteria used were that it should be oriented in the same direction as a 3′-proximal gene and within 450 base pairs of that gene’s ATG initiation codon. Eight of the 13 direct repeats fitted these criteria, leading to the identification of *ackA*, *talA*, *radC*, *malE*, *trgB*, *creD*, *yidS*, and *yieI* as cre-tag genes (Table I). *ackA* is known to be the lead gene of the *ackA/pta* operon (24), thus *pta* was also classified as a cre-tag gene.

Expression of cre-tag Genes During Growth in Complex and Glucose Minimal Media—The relative expression of cre-tag genes in *E. coli* growing in nutrient broth or minimal medium was determined by RT-PCR analysis (Fig. 3). Glucose was chosen as the minimal carbon source to retain catabolite repression and thus limit the possible complications of changing the medium. Both DH5α (*cre* ) and UB5254 (*creC*::KmR) were used for these studies to enable the determination of CreBC-specific effects. When DH5α was grown in glucose minimal medium, expression of all the cre-tag genes except *malE* was significantly higher than during growth in nutrient broth (Fig. 3). The genes did not all have the same level of transcriptional activation; the greatest was of *ackA/pta*, which increased about 50-fold. In most cases, differences in -fold transcriptional activation were caused by a variable level of transcription during growth in nutrient broth (Fig. 3). The change in *malE* expression was the reciprocal, with a considerable transcriptional repression during growth in glucose minimal medium. Differential expression of cre-tag genes in response to switching from complex to minimal medium was not seen in UB5254, a *creC* insertion mutant, where cre-tag mRNA levels were actually decreased (for *malE*, levels were slightly increased) from the *cre* + level in broth and did not change significantly...
The entire MG1655 genome sequence (23) was saved as a text file without line breaks or spaces in Microsoft Word 2000. Searches for the direct repeat TTCACnnnnnTGCAc or the complement GTGAAAtnnnnTGAA were performed using the "find" facility ("n" was substituted for "?" meaning "any character"). The closest 3′-proximal open reading frame is listed; open reading frames further away than 450 base pairs from the direct repeat were not considered.

| Sequence | Open reading frame |
|----------|--------------------|
| TTTCCTCACTTAC | ackA/pta |
| TTACGTAACTTAC | talA |
| TTACGGTCTTAC | Nothing |
| TTACAAAGGTTC | yidS |
| TTACCCTCTTC | yieI |
| TTACCTGATTAC | Nothing |
| TTACCGTTCTTAC | creD |
| TTACTTTTGTTC | Nothing |
| TTACGGTTATTC | Nothing |
| TTACCACCTTC | Nothing |
| TTACATTTTATC | trgB |
| TTACCTGATTTC | radC |
| TTACGAGCCCTC | maeE |

after the switch to minimal medium (Fig. 3). Furthermore, UB5254 grew slowly compared with DH5α (doubling time more than tripled) in glucose, maltose, glycerol, and pyruvate minimal media and not at all in acetate minimal medium, but its growth rate was the same as the cre + strain when grown in broth (Table II).

Expression of cre-tag Genes in E. coli cre Mutants—A mutation denoted phoM-510 is widespread in Hfr-derived strains. This allele yields a form of CreC that is constitutively active (25). In HfrH growing in nutrient broth, levels of cre-tag gene expression were elevated markedly compared with those in DH5α, with increases of 2–15-fold, depending on the gene in question (Fig. 4). The effect on maeE was again the reciprocal. E. coli strain RB208 (cet2) has been shown previously to overproduce CreD (17), encoded by a cre-tag gene. Levels of cre-tag gene expression in RB208 growing in broth were between 2- and 4-fold higher than in HfrH, the RB208 parent (17), giving an increase in expression compared with DH5α of 4–55-fold (Figs. 3 and 4). Again, maeE expression was affected in quite the opposite way. The cet2 mutation does not dramatically affect the growth rate of RB208 compared with DH5α (cre +) in glucose, glycerol, pyruvate, and acetate minimal media, but growth is significantly slower in maltose minimal medium (Table II).

To define the specific creBC alleles carried by DH5α, HfrH, and RB208, PCR was used to recover these genes, and the amplification products were sequenced. All three strains were found to carry copies of wild-type creB. That HfrH has a mutation in creC (creC2), which results in an R77P amino acid substitution (5), was confirmed; in contrast and as expected, DH5α carries a copy of wild-type creC (23). The creC allele in RB208 (creC3) has two mutations, one generating an R77P amino acid substitution and a second generating a T264S substitution.

DISCUSSION
Expression of E. coli Genes at Eight Genetic Loci Is Subject to CreBC Control—The E. coli CreBC TCR was discovered fortuitously because its signal sensor, CreC, can act as phosphate donors for the pho regulon response regulator, PhoB, to activate transcription of phoA in mutants that lack the normal pho regulon signal sensor, PhoR (5, 8–10). One consequence of this is that expression of phoA no longer responds to phosphate levels but rather to carbon source (10), reflecting the change in signal sensor. Until now, however, no members of the cre regulon (the targets of CreBC) have been identified. Our study has revealed eight transcriptional units, ackA/pta, talA, radC, maeE, trgB, creD, yidS, and yieI, that can be assigned with confidence to the cre regulon. ackA and pta form an operon, although pta may also have its own promoter (24), creD is linked to genes encoding the CreBC TCR (11), but is expressed from its own promoter (17), and the other genes are spread around the genome. The evidence for assigning these genes to the cre regulon is as follows: (i) with respect to the cre + strain grown in broth, expression of the genes is increased (maeE is repressed) during growth in glucose minimal medium, but the disruption of creC prevents this activation/repression (Fig. 3), and (ii) certain point mutations in creC lead to increased expression of the genes (again, maeE is repressed) (Fig. 4).

Identification of a cre Tag—It was predicted that CreBC would regulate the expression of these eight transcriptional units because of the presence of a hyphenated tandem repeat, TTCACnnnnnTGCAc, within 450 base pairs of their ATG initiation codons. This prediction proved correct, so there is considerable circumstantial evidence that the cre tag is a transcription factor binding site. The overall arrangement of the cre tag is very similar to that of the PhoB binding site, the pho box (6, 7, 26), although the exact sequence is different. Thus, the simplest explanation of the observed effects is that CreB binds to the cre tag directly, and that the activation of CreC after a switch from complex to minimal medium leads to increased phosphorylation of CreB via phospho-relay, resulting in CreB binding to the cre tag more tightly and stimulating (repressing in the case of maeE) transcription of the cre tag gene. This would mirror the known mode of action of PhoBR, in which phosphate starvation leads to autophosphorylation of PhoR and phospho-relay to PhoB, which then binds to the pho box and activates or represses transcription of pho-regulon genes (5, 7, 8, 26). Of course it is possible that the regulation of cre tag gene expression by CreBC is indirect and mediated by the activation of a transcription factor other than CreB. In this scenario, transcription factor activation would be CreBC-dependent and would alter its affinity for the cre tag or some as yet undefined sequence, leading to alterations in cre regulon gene expression. These possibilities need to be addressed with further experimental work.

Of those media tested, the maximal expression of cloned Aeromonas spp. ß-lactamases in DH5α was during growth in pyruvate minimal medium (Fig. 1). The addition of 1% (v/v) nutrient broth reduces ß-lactamase expression to the levels seen during growth in nutrient broth alone.2 In contrast, the addition of 20 mM pyruvate to nutrient broth does not induce ß-lactamase expression (2). It is tempting to speculate, therefore, that autophosphorylation of CreC is repressed by some component of nutrient broth and that repression is relieved in minimal medium. High levels of phosphate repress autophosphorylation of the CreC homologue, PhoB, and this repression is relieved when phosphate levels fall (5). The true signal for CreC remains to be determined.

The cre Regulon Encodes Diverse but Related Functions—Pta catalyzes the conversion of acetyl-CoA to acetyl-phosphate, whereas AckA converts this into acetate with the production of ATP. Both reactions are reversible, and the pathway is used as the first step in acetate catabolism (24). That these reactions are important to E. coli is attested to by the fact that pta mutants grow poorly in glucose, and not at all in acetate minimal medium, although growth is normal in nutrient broth (10, 24, 27). Our data are consistent with this in that a creC insertion mutant, in which ackA/pta expression is very low (Fig. 3), grows normally in broth but poorly in glucose and not at all in acetate minimal medium (Table II). Metabolic flux analysis has revealed that the reason for impaired growth of pta
mutants in glucose minimal medium is that disruption of Pta-AckA results in excessive pyruvate levels (27). This inhibits the production of phosphoenol pyruvate, which is essential for the import of various sugars including glucose via the phosphotransferase system (27). Hence, Pta-AckA are important for the maintenance of carbon flux for efficient growth on phosphotransferase system sugars but are not required during growth in nutrient broth, in which the major source of energy comes from amino acids, which are not phosphotransferase system substrates (28).

There are no reports that the import of pyruvate, glycerol, or maltose is phosphotransferase system-dependent, and yet inactivation of creC (E. coli UB5254) leads to poor growth when these compounds are the sole carbon source (Table II). It is therefore likely that the repression of some other important function results in the poor growth of UB5254. One possible candidate for this function is TalA, which reversibly converts glyceraldehyde-3-phosphate and sedoheptulose-7-phosphate into fructose-6-phosphate and erythrose-4-phosphate in the nonoxidative branch of the pentose-phosphate pathway (28). Erythrose-4-phosphate is an essential starting point for the production of aromatic amino acids and some vitamins, and during growth in minimal media, the majority of erythrose-4-phosphate is produced in this way (28). As such, TalA is an extremely important enzyme during growth in minimal media in which amino acids and vitamins have to be synthesized de novo, but is not required during growth in nutrient broth, in which these compounds are in plentiful supply (28).

The E. coli radC102(recG) mutation results in mild x-ray sensitivity but only in cells grown in complex medium; there is no effect during growth in minimal medium (29, 30). The radC gene was cloned because it complements the radC102(recG) mutation when present on a high copy number vector during growth in complex medium (31). It is possible that the effects of the radC102(recG) mutation are not apparent in minimal medium because of the overexpression of RadC in a cre-dependent manner (Fig. 3). The true function of RadC remains to be determined, although it is believed to be an ancillary factor in RecA-dependent repair of DNA damage and unblocking stalled replication forks (32).

TABLE II
Doubling time of E. coli cre mutants in different media

| Strain   | NB  | Glucose MM | Maltose MM | Glycerol MM | Acetate MM | Pyruvate MM |
|----------|-----|------------|------------|-------------|------------|-------------|
| DH5α     | 39.1| 61.4       | 110.5      | 66.7        | 178.4      | 258.3       |
| UB5254   | 42.8| 233.3      | 347.0      | 222.6       | >1000      | 794.9       |
| RB208    | 55.7| 87.6       | 352.6      | 90.4        | 193.6      | 275.6       |

FIG. 3. Regulation of cre-tag gene expression in different growth media. DH5α (bars A and B) or UB5254 (bars C and D) were grown in nutrient broth (bars A and C) or in minimal medium containing glucose as sole carbon source (bars B and D) until an absorbance (600 nm) of 0.8 had been reached. Total cell RNA was extracted and purified according to that described under “Experimental Procedures.” RT-PCR was performed for the cre-tag genes, bands were separated by electrophoresis, and their intensities were quantified and normalized as set out under “Experimental Procedures.” Band intensities are reported as arbitrary units; all values are means of at least three separate RNA preparations, and errors (S.E.) are denoted as error bars.
The position of a transcription factor binding site relative to the transcriptional start site of a gene is usually critical for the precise effect of transcription factor binding. The only cre regulon gene in which a transcriptional start site has been determined is malE (33), and the start is actually 5'-proximal to the cre tag, i.e. the putative transcription factor binding site is in the malE transcript. This may well explain why the activation of CreBC causes repression of malE transcription while activating expression of the other genes. MalE is a component of the maltose transporter, and the promoter upstream of malE is known to drive transcription of the malEFG operon (33). Complex mechanisms regulate the expression of this operon; expression is activated by MalT, which binds to the malEFG promoter in its maltotriose-bound form and by the cAMP receptor protein, which binds in its cAMP bound form. In glucose minimal medium, there is neither activation of the promoter by MalT because of a lack of maltotriose nor activation by cAMP receptor protein because of a lack of cAMP (33). It is clear from our results that CreBC acts as an additional negative regulator of malE expression during growth in minimal medium, because the disruption of creC leads to increased malE expression (Fig. 3). Clearly, the repression of malE expression by CreBC is dominant to activation by MalT, because constitutive activation of CreBC (i.e. the creC3 allele) leads to a reduction of malE expression during growth in nutrient broth. E. coli RB208 (creC3) is able to grow in maltose minimal medium, so the reduction in malE expression caused by constitutive activation of CreBC is not sufficient to produce a true mal phenotype. However, growth in maltose minimal medium is impaired (doubling time is more than tripled) compared with DH5α (cre -), so there is a clear phenotypic effect (Table II).

The function of the trgB gene product (formally known as YqiE) has been assigned recently (34). TrgB is a member of the ADP-ribose pyrophosphorylase subfamily of the nudix hydrolases. ADP-ribose is toxic to E. coli, and the modulation of its concentration is particularly important during periods of metabolic stress, which is when it accumulates. TrgB converts ADP-ribose into AMP and ribose-5-phosphate (34). Ribose-5-phosphate, the terminal product of the oxidative branch of the pentose-phosphate pathway, is a precursor for histidine, tryptophan, and nucleic acid biosynthesis, thus its production is not required to the same extent during growth in complex as in minimal medium (29). Hence, TrgB may well fulfill two roles during minimal medium growth, the removal of ADP-ribose, and the production of ribose-5-phosphate.

Mutants such as RB208 that overproduce CreD were identified because they show tolerance to the protein antibiotic colicin E2 (35). The mechanism for tolerance is uncertain, but CreD, an inner membrane protein with no known function, is essential (17). The fact that three open reading frames encoding proteins with no known function (CreD, YidS, and YieI) have been shown to be part of the cre regulon may lead to a more targeted analysis of their functions.

Conclusions—It is clear from the functions encoded by the nine genes assigned to the cre regulon that CreBC is a regulator of considerable importance. The study of genes with less constrained cre tags (e.g. those with 9/10 identities or less) may lead to an expansion of the cre regulon and thus the elevation of CreBC into a true “global regulator.” The fact that creC mutants have been distributed so widely among laboratory E.
coli strains and are commonly used (25) means it is possible that many areas of E. coli research, particularly in the metabolic control of gene expression, will have to be re-examined in a cre+ background to confirm that the results obtained in a creC background were valid.

One final point that should be addressed is the reason why CreBC regulates the expression of Aeromonas spp. β-lactamase when cloned into E. coli (Fig. 1). There is increasing evidence that the regulation of β-lactamases in Aeromonas spp. is via the BlrAB TCR, which responds to β-lactam challenge of cells (2–4). BlrAB is highly homologous to E. coli functionally unrelated genes in (50x533)to do this by their partner signal sensor in response to different bind to the same DNA binding motif but that they are activated homology between the DNA binding domains of BlrA and CreB (2) but poor homology between the signal recognition domains of BlrB and CreC (3, 4). Thus it is probable that CreB and BlrA bind to the same DNA binding motif but that they are activated to do this by their partner signal sensor in response to different signals and that their binding sites control the expression of functionally unrelated genes in E. coli and Aeromonas spp., respectively. It may be that BlrAB regulates the expression of a blr regulon including genes other than the three β-lactamases, but this remains to be tested.

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