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MicroReview

The galactose regulon of *Escherichia coli*

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Summary

Galactose transport and metabolism in *Escherichia coli* involves a multicomponent amphibolic pathway. Galactose transport is accomplished by two different galactose-specific transport systems. At least four of the genes and operons involved in galactose transport and metabolism have promoters containing similar regulatory sequences. These sequences are recognized by at least three regulators, Gal repressor (GalR), Gal isorepressor (GalS) and cAMP receptor protein (CRP), which modulate transcription from these promoters. The negative regulators, GalR and GalS, discriminate between utilization of the high-affinity (regulated by GalS) and low-affinity (regulated by GalR) transport systems, and modulate the expression of genes for galactose metabolism in an overlapping fashion. GalS is itself autogenously regulated and CRP dependent, while the gene for GalR is constitutive. The *gal* operon encoding the enzymes for galactose metabolism has two promoters regulated by CRP in opposite ways; one (P_1) is stimulated and the other (P_2) inhibited by CRP. Both promoters are strongly repressed by GalR but weakly by GalS. All but one of the constituent promoters of the *gal* regulon have two operators. The *gal* regulon has the potential to coordinate galactose metabolism and transport in a highly efficient manner, under a wide variety of conditions of galactose availability.

Introduction

The sugar D-galactose is of importance to *Escherichia coli*, not only as an energy source, but as a building block in complex polysaccharide formation. First, energy is produced by catabolism of galactose to the glycolytic intermediate, glucose-1-phosphate. Second, two of the intermediates of the galactose metabolic pathway, UDP-galactose and UDPglucose are required for biosynthetic glycosylation reactions. This makes the galactose pathway, also known as the Leloir pathway, an amphibolic one. Many of the genes involved in the transport and metabolism of galactose have been identified and characterized. Since the last review of the regulation of transcription of the *gal* operon, which was known to encode the first three enzymes of galactose metabolism (Adhya, 1987) new regulatory and structural genes of galactose transport and metabolism have been identified and sequenced. In addition, it has been shown that most of these genes, including the *gal* operon, are modulated by common regulatory mechanisms and form a regulon. In this review, we will summarize more recent information about the galactose genes and their products, examine how these genes are regulated, and discuss possible mechanisms for co-ordination of transcription of these genes and their implications. The map positions of the galactose genes on the *E. coli* chromosome are shown in Fig. 1.

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Galactose-transport genes

D-galactose is primarily transported by two specific transport systems, one with high-affinity (K_m = 1 μM) and the other with low-affinity (K_m = 50–450 μM) for the sugar. The high-affinity galactose transport is accomplished by the action of the three proteins of the methyl-D-galactoside permease system encoded by the *mgl* operon (Robbins *et al.*, 1976), while low-affinity galactose transport is facilitated by galactose permease, the *galP* gene product (Riordan and Kornberg, 1977). Both are discussed in greater detail below. Galactose is also transported with much less efficiency by four other transport systems (see Silhavy *et al.*, 1978 for a review of *E. coli* sugar transport). These additional systems, which transport galactose because of their broad specificity, can be divided into two groups — the proton-linked transport systems and the sugar-binding protein transport complexes. The proton-linked transport proteins belong to a large family of transport proteins that generally have 12 putative transmembrane domains and similar structural motifs (Henderson, 1991; Henderson *et al.*, 1992; Griffith *et al.*, 1992). Three members of this family of proteins can transport

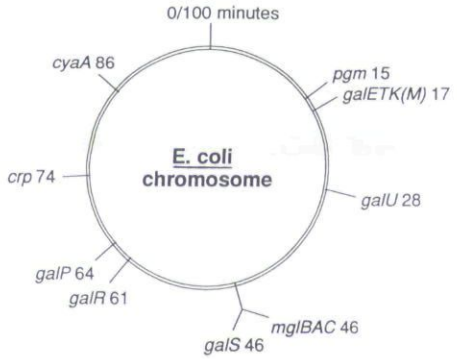

Fig. 1. The map positions of the structural and regulatory genes for galactose transport and metabolism on the *E. coli* chromosome and described in the review. *M* is a putative fourth cistron of the *gal* operon discussed in the text.

galactose non-specifically: LacY permease; MelB permease: and AraE, the low-affinity L-arabinose transport protein. Arabinose and galactose transports are also accomplished by a sugar-binding high-affinity transport complex, encoded by the genes of the *araFGH* operon (Silhavy *et al.*, 1978). There are several similarities between arabinose transport and galactose transport that may account for the low-efficiency galactose transport by the arabinose transport system as discussed below.

High-affinity galactose transport

High-affinity galactose transport is accomplished by a galactose-binding protein (GBP) and two membrane-associated transport proteins (Robbins *et al.*, 1976). The complex is called MeGal or the P-MG transport system. The genes for these three proteins are organized, as mentioned before, into the *mgl* operon, named for the ability of this complex to also facilitate the transport of methyl-β-D-galactopyranosides. The operon, which encodes GBP (*mglB*), and the two membrane-associated proteins (*mglA* and *mglC*), is similar to the *araFGH* high-affinity arabinose transport operon in function, organization and structure of its gene products (Hogg *et al.*, 1991; Scripture *et al.*, 1987; Vyas *et al.*, 1991). In addition to high-affinity galactose transport, GBP is required for galactose chemotaxis (Ordal and Adler, 1974). After binding to galactose, GBP interacts with the chemotactic signal protein Trg to mediate chemotaxis against a galactose concentration gradient (Kondoh *et al.*, 1979; Hazelbauer *et al.*, 1981).

Low-affinity galactose transport

When present at high extracellular concentrations, galactose is transported into *E. coli* preferentially by a galactose-specific proton-linked transport protein, galactose permease, (GalP). The *galP* gene (Riordan and Kornberg, 1977) has recently been sequenced and the deduced GalP amino acid sequence is 64% identical to AraE, the L-arabinose proton-linked transport protein (Roberts, 1992; Henderson *et al.*, 1992). There are four known members — AraE, LacY, MelB and GalP — of the proton-symporter family. AraE is the only member of the family, other than GalP, that transports galactose, though with much less affinity than GalP. Like most proton-linked sugar transport proteins, sequence comparison of GalP indicates that it contains 12 putative membrane-spanning α-helices in two groups of six, with a large hydrophilic loop between helices 6 and 7 (Roberts, 1992; Henderson *et al.*, 1992). The similarities between corresponding helices in the two groups of six suggest a duplication event in the evolution of the *galP* gene (Roberts, 1992; Griffith *et al.*, 1992).

Galactose metabolism genes

Up to six genes are involved in the initial steps of D-galactose metabolism; *galK* (galactokinase), *galT* (galactose-1-phosphate uridylyltransferase), *galE* (uridine-diphosphogalactose-4-epimerase), *galU* (UTP: α-D-glucose-1-phosphate uridylyltransferase), and *pgm* (phosphoglucomutase). They have been reviewed previously by Adhya (1987). A mutarotase function, encoded by a *galM* gene, may be involved in the intracellular interconversion of D-α- and D-β-galactose (G. Bouffard, K. Rudd and S. Adhya, in preparation; Maskell, 1992). The complete sequence of *galM* has been determined. The deduced amino acid sequence of mutarotase is similar to the ones of *Streptococcus thermophilus*, *Lactobacillus helveticus*, and *Acinetobacter calcoaceticus* (Poolman *et al.*, 1990; Mollet and Pilloud, 1991; Gatz and Hillen, 1986). *galM* turns out to be a fourth gene of the *gal* operon, composed of *galE*, *T*, *K* and *M*, in that order.

The sequence of the *galU* gene has also recently been determined by Ueguchi and Ito (1992) and by A. C. Weissborn, M. K. Rumley and E. P. Kennedy (personal communication). The *galU* gene product is similar to glucose-1-phosphate uridylyltransferase, called CelA, from *Acetobacter xylinum* in amino acid sequence and is over 54% identical to a hypothetical second glucose-1-phosphate uridylyltransferase, most likely the *galF* gene product, in *Salmonella typhimurium* LT2 (A. C. Weissborn *et al.*, personal communication). The *pgm* gene is yet to be cloned and sequenced.

Transcriptional regulators of the galactose genes

Of the genes of galactose uptake and metabolism discussed above, *galP*, *mglBCA* and *galETKM* are part of the *gal* regulon. The *galU* and *pgm* genes do not appear to be subject to galactose regulation (M. J. Weickert and S. Adhya, unpublished results). The known regulators of the

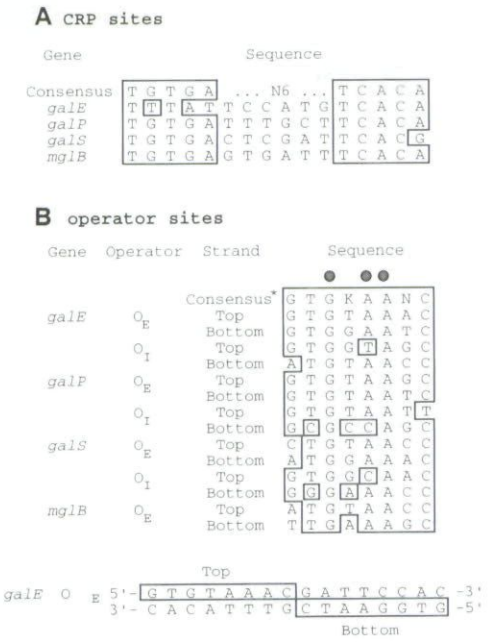

Fig. 2. DNA sequences involved in or potentially involved in regulation of transcription at *gal* regulon promoters.
A. CRP–cAMP binding sites in *gal* regulon promoters. Nucleotides enclosed within boxed region are homologous to the CRP–cAMP binding site consensus sequence (Ebright *et al.*, 1984; Barber and Zhurkin, 1990).
B. Comparison of half sites for the symmetric operator sequences and potential operators. The 5′ antisense (left top half) sequence and the 3′ sense (right bottom half) sequence are aligned in a 5′ to 3′ orientation (see *galO*$_E$ example). Boxed nucleotides are identical to *, the consensus *gal* operator of Majumdar and Adhya (1987). The filled circles above the consensus sequence indicate bases believed to make direct contact with GalR.

regulon are *galR*, *galS* and *Crp*, which encode Gal repressor (GalR), Gal isorepressor (GalS) and cyclic AMP receptor protein (CRP), respectively.

The *gal* operon has two promoters; P_1 and P_2. They have served as a model system for examining both positive and negative regulation of transcription. All three regulators, CRP, GalR and GalS, which modulate *gal* regulon transcription, work at these two promoters. cAMP and CRP, acting as a complex, stimulate (positive control) transcription at P_1, whereas they inhibit transcription from P_2. Both GalR and GalS negatively regulate transcription of P_1 and P_2 (reviewed in Adhya, 1987; Tokeson *et al.*, 1991; Golding *et al.*, 1991; Weickert and Adhya, 1992a; Choy and Adhya, 1992).

GalR and GalS are over 53% identical and 85% similar and are members of a large family of related transcriptional regulatory proteins in bacteria, called the GalR–LacI family (Weickert and Adhya, 1992b). These regulators contain an amino-terminal domain through which they bind specific operators with dyad symmetry. When associated with DNA, these regulators are virtually symmetric dimers. Additional conserved domains are involved in substrate (inducer) binding, dimerization, and for some, like LacI, tetramerization. The most common functional feature of these regulators is that they act as transcriptional repressors, although some of them may also activate transcription at some promoters.

CRP, which is not a member of the GalR–LacI family of regulators, also functions as a symmetric dimer by binding to DNA sites with dyad symmetry located upstream of the RNA polymerase in the promoters. CRP can activate or repress transcription. CRP acts through one or both of the following mechanisms: by directly contacting RNA polymerase and by inducing structural change in the DNA (for reviews, see Adhya and Garges, 1990; Bell *et al.*, 1990; Eschenlauer and Reznikoff, 1991; Ishihama, 1993; Kolb *et al.*, 1993; Zhou *et al.*, 1993).

Similarities among *gal* regulon promoters

The promoter regions of the *gal* and *mgl* operons, and of the *galP*, *galU*, *galR* and *galS* genes have been sequenced. The transcription start sites have been determined for the *gal* and *mgl* operons (Irani *et al.*, 1989; Hogg *et al.*, 1991; Weickert and Adhya, 1992a), and the *galR* and *galS* genes (Weickert and Adhya, 1993). Although the *mgl*, *galR* and *galS* genes, unlike the *gal* operon, contain only one promoter each, their promoter regions and that of *galP* contain sequences homologous to GalR- and GalS-binding sites (*gal* operators) and CRP–cAMP-binding sites (Fig. 2) present in the *gal* operon with more or less similar arrangements (Fig. 3): (i) all of them contain a CRP–cAMP-binding site (Fig. 2A) near −40 with respect to the start site of transcription (Fig. 3) and act as type II promoters (Ishihama, 1993). CRP binding to the −40 sites activates transcription from the P_1 promoter of the *gal* operon as well as from the *mgl*, *galS* and *galP* promoters. Transcription from these promoters is reduced three- to 20-fold upon disruption of the *crp* gene (*galP*$_1$: Irani *et al.*, 1989; *galS*: Weickert and Adhya, 1993; *galP* and *mgl*: M. J. Weickert and S. Adhya, unpublished results).

Like O_E in the *gal* operon, a *gal* operator is located at the −60 region in *mgl*, *galR* and *galS* (Figs 2B and 3). Similar also to the *gal* operon, *galR* and *galS* but not *mgl* have a second *gal* operator sequence (O_I) in the cognate protein-coding region. GalR has been shown to negatively regulate, like the *gal* operon promoters, the *galP* promoter (Wilson, 1974). GalS negatively regulates the promoter of its own gene, *galS* (Weickert and Adhya, 1993) and the *mgl* promoter (Weickert and Adhya, 1992a). It is not clear whether repression of *galP* and *galS* genes requires a DNA looping by the use of bipartite operators much like the mechanism implicated in the *gal* operon (Haber and Adhya, 1988; Mandal *et al.*, 1990; Choy and Adhya, 1992).

Interestingly, all of the *gal* regulon promoters, except the

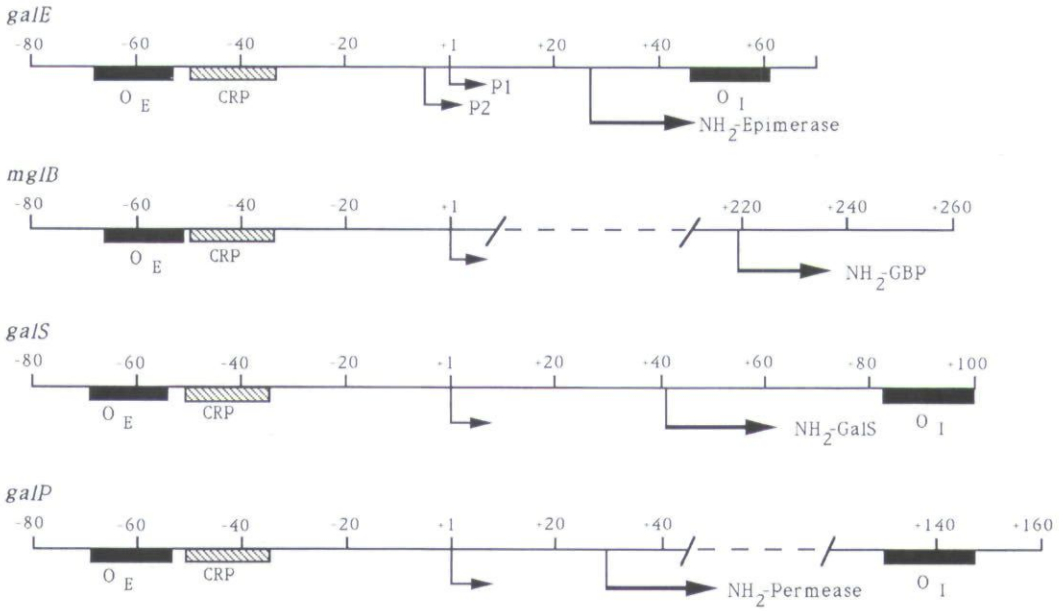

Fig. 3. A comparison of the *gal*, *mgl*, *galS* and *galP* regulatory regions. Transcription initiates at +1, indicated by the small arrow, and in *gal*, also initiates at −5 (P_2). The beginning of the protein coding region is indicated by the larger arrow. CRP and repressor binding sites (operators) are represented by crosshatching and black boxes, respectively. Operator sites are internal (O_I) or external (O_E) to the protein-coding region.

P_2 promoter of the *gal* operon, contain an unusual spacing (21 bp) between the −35 and −10 sequences, which are defined by their homology to the consensus hexamers involved in RNA polymerase binding. In the promoters aligned in Fig. 3, the −35 hexamer overlaps the promoter-proximal half of the CRP–cAMP site. These similarities suggest that mechanisms involved in regulating these promoters are probably conserved among them. Since the *gal* operon promoters are the best studied of this group, we will review the mechanisms involved in regulation of the *gal* operon before extrapolating similar regulatory mechanisms for the other related promoters.

How *gal* operon transcription is regulated

The unusual spacing between the −10 and −35 hexamers of the $galP_1$ promoter (21 bp) and the relatively low homology of the −35 region with the consensus −35 hexamer, has a profound effect on RNA polymerase binding to the *gal* promoter. RNA polymerase binding at $galP_1$ does not require specific contacts in the −35 region (Chan and Busby, 1989; Chan *et al.*, 1990). Chemical and DNase footprinting of the *gal* promoter indicate that RNA polymerase fails to protect the −35 region while upstream sequences, up to −55, are protected. The DNA in the promoter region is probably distorted by these compensatory upstream contacts (Chan and Busby, 1990; A. Majumdar and S. Adhya, in preparation). In addition, the $galP_1$ promoter is partially dependent upon three phased poly-adenine stretches upstream of the CRP site, but on the same face of the DNA helix as the CRP site and −10 region (Lavigne *et al.*, 1992). These poly-adenine regions are naturally curved, and their presence increases the rate of RNA polymerase occupation and isomerization at P_1, especially in the presence of CRP–cAMP. Bent sequences alone can also activate P_1 transcription when they substitute for the CRP–cAMP site (Bracco *et al.*, 1989). Note that one of the predominant features of CRP–cAMP binding to DNA is the induction of a pronounced DNA bend (Wu and Crothers, 1984).

In the normal *gal* operon, CRP–cAMP binding switches transcription initiation between start sites from P_1 and P_2 entirely to P_1 (Irani *et al.*, 1989; Goodrich and McClure, 1992; Choy and Adhya, 1993). In the absence of CRP–cAMP, initiation occurs in approximately equal proportions from these two overlapping promoters while binding of CRP–cAMP switches initiation predominantly (>95%) to P_1. CRP–cAMP bound to the DNA promotes transcription initiation preferentially at P_1 by both increasing RNA polymerase binding to P_1 and elevating the rate of isomerization to open complex at P_1.

Negative regulation of the *gal* operon by GalR *in vivo* requires simultaneous DNA binding by dimers of GalR to palindromic operator sites (O_E and O_I) flanking the promoter region. In experiments where one of the *gal* operators was replaced with a *lac* operator, there was no repression (Haber and Adhya, 1988; Mandal *et al.*, 1990; Choy and Adhya, 1992; Brenowitz *et al.*, 1990). However, when both operators were replaced by *lac* operators, LacI repressor was able to fully repress the operon. This requirement for the binding of the same type of repressor to each operator suggests that an interaction between the

two repressor dimers, bound to their cognate sites, is required for full repression, and occurs by forming a loop of intervening DNA. Tetramerization by GalR dimers bound to operators to form a DNA loop, unlike that of LacI, has not yet been demonstrated *in vitro* and may reflect the requirement of an additional factor for the association to occur. Unlike LacI, GalR does not contain a mini-leucine zipper at the carboxyl terminus of the protein, which facilitates LacI tetramerization (Alberti *et al.*, 1991). GalR binds non-co-operatively to the two operator sites (Brenowitz *et al.*, 1990) and alters the DNA conformation (Wartell and Adhya, 1988; Majumdar and Adhya, 1989) at least in part by inducing a DNA bend (Kuhnke *et al.*, 1989; Zwieb *et al.*, 1989). RNA polymerase, CRP–cAMP, and GalR can all simultaneously occupy their respective binding sites demonstrating that steric hindrance cannot account for the regulation seen at the *gal* operon promoter (Adhya and Majumdar, 1987; Adhya, 1989; Goodrich and McClure, 1992). GalR and CRP bind independently to the *gal* operon (Dalma-Weiszhausz and Brenowitz, 1992). The DNA bending induced by CRP–cAMP binding does not apparently facilitate the formation of a DNA loop with GalR. However, the simultaneous occupancy of specific DNA sites by RNA polymerase, CRP–cAMP, and GalR, along with the phased bending of the DNA by each of the bound proteins, and by naturally occurring sequences, does indicate that a complex nucleoprotein structure exists at the *gal* operon promoters under repressed conditions. It is believed that the repressor keeps the RNA polymerase ineffective in such a complex (Adhya, 1989; Choy and Adhya, 1992).

The *gal* operon is induced by D-galactose or the non-metabolizable analogue, D-fucose. Induction of the *gal* operon requires inducer binding to GalR; in the presence of a high concentration of inducer, the repressor loses its affinity for DNA (Majumdar and Adhya, 1984; Majumdar *et al.*, 1987). In mutants lacking Gal repressor, the addition of galactose or fucose stimulates two- to fourfold greater *gal* expression (Tokeson *et al.*, 1991). This phenomenon, termed ultrainduction, is another negative-control mechanism that operates at the level of transcription, and is mediated by the GalS (Golding *et al.*, 1991; Weickert and Adhya, 1992a). GalS, like GalR, can be titrated specifically by multicopy *gal* operators to which the Gal repressor itself binds (Tokeson *et al.*, 1991). GalS is believed to repress transcription, although not efficiently, in a manner analogous to GalR (Weickert and Adhya, 1992a). The cause of the weak repression of the *gal* operon by GalS is unknown.

Implications for *gal* regulon promoters

The striking similarities between the *gal* regulon promoters suggest that many of the mechanisms involved in regulating the *gal* operon promoter P_1 by CRP–cAMP that are discussed above are likely to operate in the other promoters. The other *gal* regulon promoters may be somewhat less complicated than the *gal* operon promoter segment because there is no evidence for the presence of a second promoter. The promoter switching that occurs between *galP*$_1$ and P_2 by CRP–cAMP is probably necessary to maintain a minimal level of the *galE* and *galT* gene products under different growth conditions because of their importance in glycosylation reactions. There is no indication that the other genes in the *gal* regulon are similarly required in the absence of the CRP–cAMP complex.

It is possible that the internal *gal* operator, O_I, is coincidental in all other *gal* regulon promoters. The *mgl* promoter lacks an internal operator entirely, yet it is regulated at least four- to fivefold (Weickert and Adhya, 1992a). It has been shown that occupation of both O_E and O_I and DNA looping brings about complete repression of P_2 and P_1 by the Lac repressor (Choy and Adhya, 1992). Occupation of O_E alone by a repressor brings about 75% repression of P_1 but none of P_2. The cause of this repression without DNA looping needs to be investigated. It may parallel the repression of the *mgl* promoter by only one operator located at the region of O_E.

Co-ordination of *gal* regulon transcription by a two-repressor system

Understanding the co-ordination of *gal* regulon promoters is complicated by the unusual presence of an isorepressor, GalS. In addition to apparent cross-talk at the *gal* operators, the isorepressor is the primary negative regulator of two other *gal* regulon promoters (Weickert and Adhya, 1992a; 1993). With the identification of the isorepressor, it is clear that the repressor and isorepressor recognize the same or nearly the same operator sequence yet regulate different sets of promoters differently. This greatly complicates the potential mechanisms for control of transcription. The level at which such differential regulation occurs remains to be worked out. Figure 4 summarizes the spectrum of various protein–DNA interactions that contribute to modulation of transcription of *gal* regulon genes.

Several observations are critical to an understanding of the *gal* regulon co-ordination. (i) The *gal* transport systems are negatively regulated by different repressors. The different affinities of each transport system for galactose suggests that induction should occur at different galactose concentrations for each. If so, we would expect that GalS will be induced at lower galactose concentrations than GalR, since the *mgl* operon is the more efficient transport system at low galactose concentrations. (ii) The *galS* gene is autoregulated and its expression is CRP–

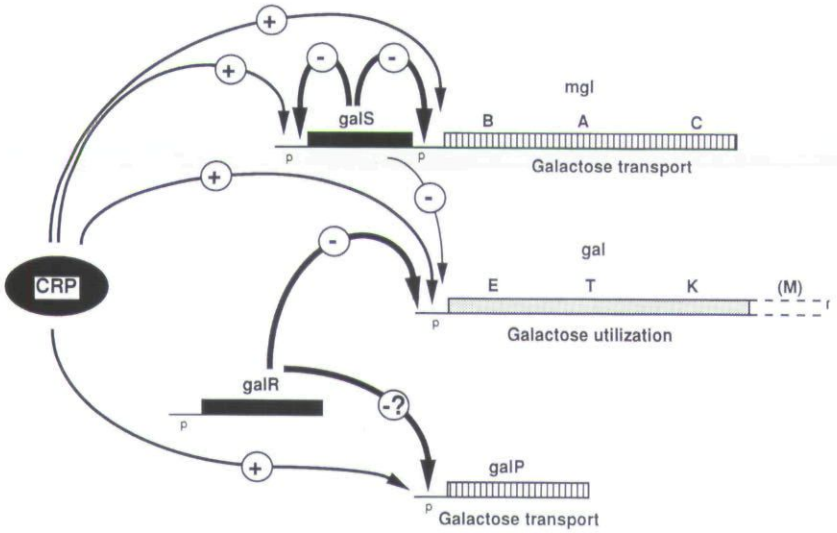

Fig. 4. Regulation of galactose transport and utilization by CRP, GalS and GalR. Heavy arrows with a minus encircled represent primary repression. The lighter arrow with an encircled minus equals ultrainduction. Medium arrows with an encircled plus represent positive regulation by CRP–cAMP. Promoters are (p) and coding regions are boxed. *M* is a putative fourth cistron of the *gal* operon as mentioned in the text.

cAMP dependent, while *galR* expression appears to be constitutive (Weickert and Adhya, 1993). Autoregulation of gene expression (reviewed in Maloy and Stewart, 1993) creates a condition-dependent concentration of the regulator. We do not know why the *galR* gene expression is constitutive, although it carries two operators, one external and one internal.

These two observations lead to the following suggestions. In the absence of galactose, GalS concentration is low, and may facilitate induction of the *mgl* operon at lower galactose concentrations simply by its own scarcity or by a greater sensitivity to galactose than GalR. The constitutivity of GalR synthesis coupled with the inducibility of GalS synthesis could result in a varying proportion of GalR to GalS during changes in galactose concentration and metabolism (through CRP–cAMP). If these highly related proteins can form heterodimers in the same fashion as eukaryotic transcription factors (Turner and Tjian, 1989; Gentz *et al.*, 1989) additional DNA and inducer binding specificities could be created. The proportion of heterodimers would be profoundly influenced by the relative proportions of the available repressor species. In experiments using purified GalR, the free energies of dimerization and DNA binding were nearly identical (Brenowitz *et al.*, 1990). Since dimerization is essential for DNA binding, it was suggested that an additional level of regulation might operate at the dimerization interface of GalR. The potential existence of an additional protein that may influence the dimerization increases the potential for regulation at this level.

A heterodimeric species is likely to have different induction kinetics and DNA binding specificities. If each protein has subtly different DNA-binding specificities, heterodimeric species allow for the orientation of the subunits depending upon the sequence of the binding site. This is especially important if protein–protein contacts between the repressor species and other components of the nucleoprotein complex contribute to regulation.

Though the promoters of the *gal* regulon are likely to have similar regulatory mechanisms, the two-repressor system creates the potential for uncoordinated control of these genes, although they involve related functions and sequences. This would allow a more precise and physiological control over genes whose expression must be carefully modulated to ensure efficient cell growth under conditions that vary considerably. If heterodimeric repressor species can be identified for the *gal* regulon, it seems likely that heterodimers of other repressor species will also be found playing a role in modulating transcription.

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