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Review

Carbon catabolite repression in Gram-positive bacteria, including the recently developed insights

Ken-ichi Yoshida

Carbon catabolite repression (CCR) in Gram-positive bacteria is a sophisticated, evolutionarily tuned regulatory network that integrates carbon availability with global cellular physiology. This review traces the development from initial observations of CCR to the molecular elucidation of catabolite control protein A (CcpA)-mediated control, describing the roles of HPr, Crh, and HPrK/P in sensing glycolytic flux and transcriptional regulation. CCR ensures the preferential utilisation of the most efficient carbon source while simultaneously suppressing unnecessary catabolic pathways, thereby regulating a wide range of biological processes. Species-specific variations in CCR underscore the ecological and evolutionary diversity of this system. Besides metabolism, CCR influences pathogenicity in some pathogenic bacteria, linking nutrient sensing to host interaction strategies. Its multidimensional impacts extend to biotechnology, fermentation optimisation, probiotic performance, and potential antimicrobial strategies targeting nutrient prioritisation. As omics-based approaches reveal CCR as a global integrator of carbon, nitrogen, and stress pathways, future research must unravel species-specific architectures, regulatory nuances, and evolutionary implications to understand and harness the complex regulatory system.

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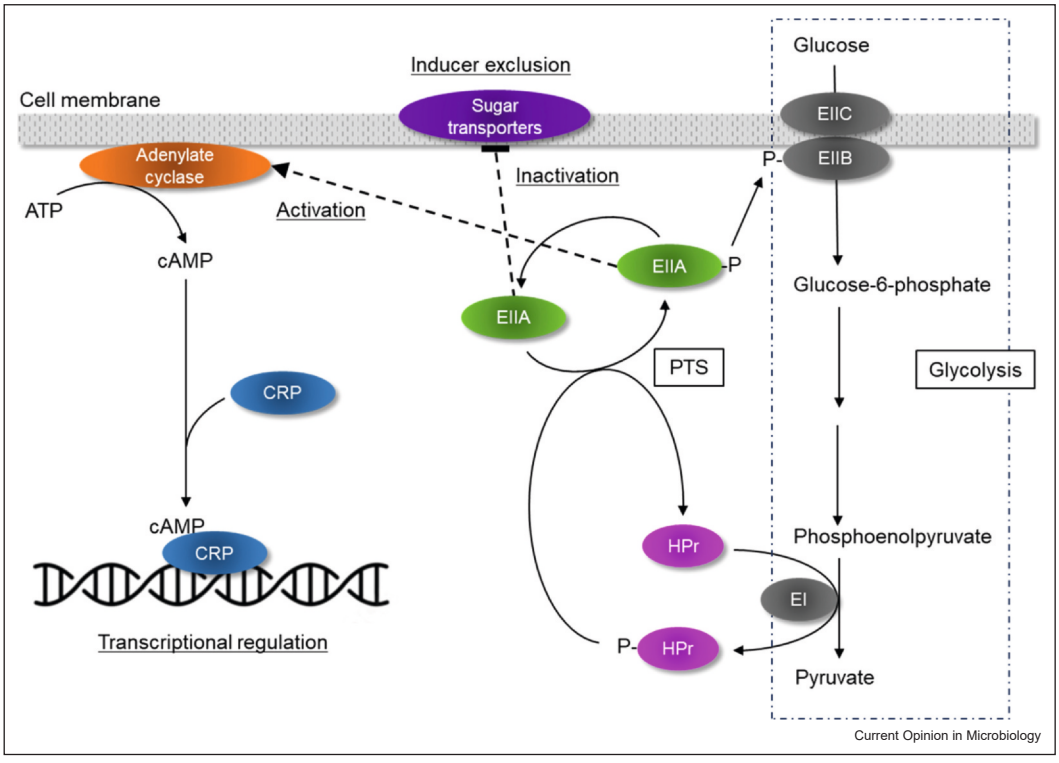
Introduction

Carbon catabolite repression (CCR), often referred to simply as catabolite repression, is a global regulatory mechanism that enables bacteria to prioritise the utilisation of preferred carbon sources, such as glucose, over less favourable alternatives. This phenomenon ensures metabolic efficiency and competitive survival in nutrient-variable environments. Historically, the concept of CCR was first described in Monod's monograph in 1942 [1], which provided evidence that preferred carbon substrates coordinate bacterial growth dynamics and enzyme formation. Subsequent studies by Monod and Triani expanded this framework by characterising the inducible enzyme system and its glucose inhibition [2]. Successively, Magasanic's integrative study clearly established CCR as a central regulatory principle in bacterial metabolism [3]. Collectively, these early studies established the conceptual and experimental foundation for understanding CCR as an overarching regulatory mechanism integrating nutrient availability and transcriptional control.

CCR in Gram-negative bacteria is best characterised in *Escherichia coli*, where the cyclic AMP (cAMP)–cAMP receptor protein (CRP) regulatory system governs it (Figure 1). This system lowers the expression levels of genes required for the utilisation of alternative carbon sources, thereby ensuring preferential glucose consumption [4,5]. The key components are cAMP and the CRP (also known as catabolite activator protein) [6]. When glucose is abundant, its uptake through the phosphotransferase system (PTS) results in dephosphorylation of $EIIA^{Glc}$, because the phosphate group is transferred to the glucose, yielding glucose-6-phosphate [7]. Conversely, when glucose is not available, the phosphorylated form of $EIIA^{Glc}$ increases, activating adenylate cyclase to elevate intracellular cAMP levels [7]. With sufficient cAMP, CRP becomes its active form, cAMP–CRP, which is required for transcriptional activation of operons involved in the metabolism of non-preferred carbon sources, such as lactose and arabinose [8]. On the other hand, dephosphorylated $EIIA^{Glc}$, which increases upon glucose uptake, inhibits transporters for non-preferred carbon sources (inducer exclusion), reinforcing glucose preference and contributing to diauxic growth [9]. The current understanding of CCR in Gram-negative bacteria is too complex to describe fully here, as the mechanism forms a multi-layered network to include sugar phosphate stress and the regulation of sugar transporters, involving various additional regulators and regulatory RNAs, as recently reviewed in detail [10].

Figure 1



CCR in Gram-negative bacteria. The 'classical' view of CCR of Gram-negative bacteria is illustrated. To take up glucose via PTS, HPr receives a phosphate group from phosphoenolpyruvate via EI. The phosphate group is successively transferred to $EIIA^{Glc}$ and to glucose, generating glucose-6-phosphate. When glucose is available, unphosphorylated $EIIA^{Glc}$ accumulates and inactivates transporters for other carbon sources (inducer exclusion). When glucose is unavailable, phosphorylated $EIIA^{Glc}$ accumulates and activates adenylate cyclase, increasing intracellular cAMP. cAMP then binds to CRP, forming a transcriptional activator that promotes the expression of genes for alternative carbon source utilisation (transcriptional regulation). As a result, glucose is preferentially used when available, while secondary carbon source metabolism is enhanced when glucose is absent. Although no details are provided here, the CCR in Gram-negative bacteria functions through a highly interconnected network that integrates the sugar phosphate stress response and the regulation of transporters modulated by multiple protein regulators and regulatory RNAs.

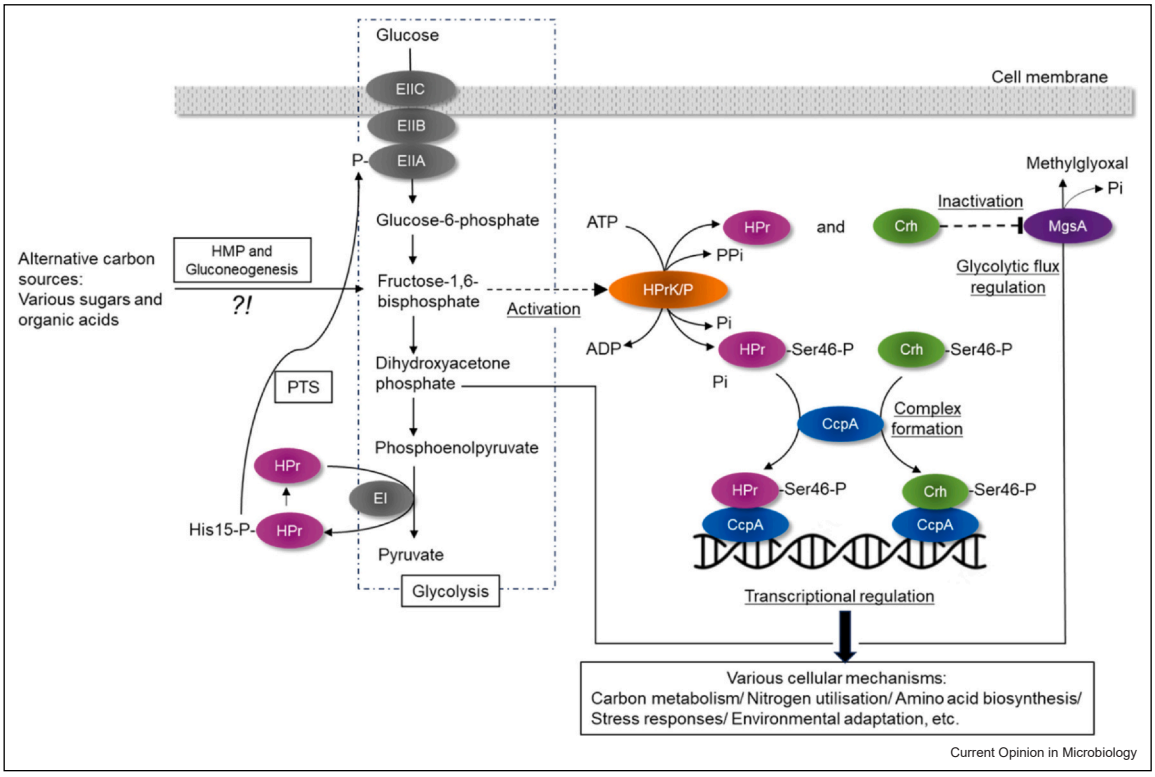
Gram-positive bacteria employ a distinct strategy. They depend on the catabolite control protein A (CcpA), which was identified as the principal transcriptional regulator for CCR in *Bacillus subtilis* [11–14]. This review describes the molecular mechanisms, physiological roles, evolutionary implications, and applied significance of CCR in Gram-positive bacteria.

Mechanisms of carbon catabolite repression in Gram-positive bacteria

CcpA belongs to the LacI/GalR family of transcriptional regulators and binds to specific DNA sequences called catabolite-responsive elements (*cre* sites) [11,12,15]. In *B. subtilis*, the *cre* sites are determined to be a 14-base pair sequence with partial dyad symmetry: TGWAAN-CGNTNWCA (where W represents A or T, and N represents any base), which is a highly degenerate pseudo-palindromic sequence conserved within the genome [13,15]. The location of *cre* sites with respect to promoters determines whether CcpA acts as a repressor or activator, for example, repression of alternative sugar operons and activation of glycolytic genes to enhance glucose metabolism [16]. In some cases, CcpA binds to the *cre* sites located considerably downstream of the transcription units, thereby preventing the continuation of subsequent transcription (transcription load block) [15–17].

HPr of Gram-positive bacteria is phosphorylated alternatively at two sites: His15 for sugar transport and Ser46 for regulatory purposes [18–21] (Figure 2). In the PTS, His15 receives a phosphate group from an intermediate of glycolysis, phosphoenolpyruvate. It transfers the phosphate group to $EIIA^{Glc}$ for the uptake of glucose into the cell in the form of glucose-6-phosphate [18,21]. When glucose is abundant, another intermediate of fructose-1,6-bisphosphate accumulates to activate the kinase function in HPr kinase/phosphorylase (HPrK/P), which phosphorylates HPr at Ser46 to generate HPr-Ser46-P [19–21]. HPr-Ser46-P forms a complex with CcpA, enhancing its DNA-binding efficiency [19,20,22]. Under lower glucose conditions, HPr-Ser46-P is

Figure 2



CCR in Gram-positive bacteria. The CCR of Gram-positive bacteria is illustrated. To take up glucose via PTS, HPr receives a phosphate group from phosphoenolpyruvate to be HPr-His15-P. The phosphate group is successively transferred to the EIIA^{Glc} domain and to glucose, generating glucose-6-phosphate. Glucose-6-phosphate is converted into fructose-1,6-bisphosphate in glycolysis, and its intracellular levels are elevated to activate HPrK/P. The activated HPrK/P phosphorylates HPr to HPr-Ser46-P. HPr-Ser46-P and CcpA form a complex whose sequence-specific DNA-binding represses genes for the metabolism of secondary carbon sources (transcriptional regulation), leading to changes in various cellular mechanisms. Similarly, Crh is also phosphorylated to be Crh-Ser46-P to participate in the transcriptional regulation. When glucose is not available, fructose-1,6-bisphosphate levels are lowered, and HPrK/P dephosphorylates Crh-Ser46-P. The unphosphorylated Crh suppresses MgsA, which converts dihydroxyacetone phosphate to methylglyoxal, to allocate the proper metabolic flow (glycolytic flux regulation). It has been demonstrated that various carbon sources other than glucose can also induce CCR. Although details remain unclear, it is hypothesised that fructose-1,6-bisphosphate, which is generated via the hexose monophosphate pathway (HMP) and gluconeogenesis, may trigger activation of HPrK/P.

dephosphorylated by HPrK/P [23]. HPr-Ser46-P does not accept the phosphorylation at His15 and vice versa [12,24]. When phosphorylation occurs at a specific site on HPr (His15 or Ser46), HPr becomes less susceptible to phosphorylation at a second site [25].

Crh (carbon flux regulator HPr-like protein) is a paralogue of HPr [26,27]. It does not act in the PTS but performs a dual regulatory function (Figure 2). Crh also undergoes phosphorylation at Ser46 by HPrK/P when CCR functions, forming a complex with CcpA and participating in transcriptional regulation [26]. Additionally, Crh interacts with MgsA, the enzyme converting dihydroxyacetone phosphate to methylglyoxal [27]. This interaction serves as a safety mechanism preventing excessive production of methylglyoxal, a toxic byproduct of glycolysis. Methylglyoxal is highly reactive and damages proteins, DNA, and lipids; hence, MgsA activity is strictly regulated [28]. Structural analysis demonstrates that Crh binds directly to MgsA, modulating its enzymatic activity [29]. Phosphorylation of Crh at Ser46 abolishes its inhibitory function on MgsA activity [27]. By inhibiting MgsA, Crh controls methylglyoxal synthesis and acts as a metabolic safety valve to maintain glycolytic equilibrium [27,29]. Increased glycolytic intermediates thus enhance Crh phosphorylation, coordinating the carbon flux appropriately [27,29]. This dual role positions Crh at the crossroads of central metabolism and stress defence.

Another important mechanism involved in the CCR of Gram-positive bacteria is inducer expulsion. This mechanism is a physiological response in some species, including *Streptococcus pyogenes*, *Streptococcus bovis*, and *Lactobacillus lactis*, in which cells actively remove accumulated non-metabolisable inducers. It proceeds through a tightly coordinated two-step mechanism: intracellular dephosphorylation of the inducer-phosphate

followed by rapid ATP-activated efflux of the free inducer [30].

Physiological roles of carbon catabolite repression in Gram-positive bacteria

CcpA regulates hundreds of genes, including those for glycolysis, gluconeogenesis, and alternative sugar metabolism [15–17,22]. Mutants lacking CcpA show derepression of secondary sugar operons, reduced growth efficiency, and altered stress responses [13,31]. Physiological roles of glucose-dependent CCR are diverse and pleiotropic. It enables nutrient prioritisation, as it ensures glucose is metabolised first [13,31]. Energy efficiency is also supported, as it prevents wasteful expression of unnecessary catabolic enzymes [20]. It is involved in stress adaptation, which links carbon metabolism with stress responses [14,31]. Carbon overflow metabolism in *B. subtilis* refers to the redirection of excess carbon, typically under high glucose or nutrient-imbalanced conditions, into overflow metabolites such as acetate, acetoin, and 2,3-butanediol. This occurs when glycolytic flux exceeds the capacity of the tricarboxylic acid cycle and respiratory chain, forcing the cell to maintain redox balance and ATP generation through alternative pathways [32].

In some cases, CCR is related to virulence regulation. In *S. pyogenes*, glucose-dependent CCR affects toxin gene expression, linking metabolism with pathogenicity [33,34]. In pathogenic *Streptococci*, particularly in *Streptococcus pneumoniae*, glucose-dependent CCR influences the expression of virulence factors [35], and CcpA modulates capsule production and adherence [36]. Glucose-dependent CCR also has significant industrial relevance. For example, glucose-dependent CCR affects efficiency in lactate fermentation [20], as in a lactic acid bacterium, *Lactobacillus plantarum*, the genes for fructooligosaccharide (FOS) metabolism are tightly regulated, and CcpA-dependent repression ensures glucose is consumed before FOSs, impacting probiotic function and food fermentation [20,37].

CCR in Gram-positive bacteria is not restricted to glucose but can be triggered by a variety of alternative carbon sources [5,20]. These often feed directly into central carbon metabolism and thereby enhance the function of CcpA, resulting in repression of genes required for the utilisation of less-favoured substrates [14,20,38]. In *B. subtilis*, organic acids produced in the tricarboxylic acid cycle, such as malate, citrate, fumarate, and succinate, serve as repressing carbon sources [38,39]. These organic acids may stimulate HPr-Ser46 phosphorylation and promote CcpA-dependent repression of the catabolism of gluconate, glycerol, inositol, and other substrates [31,39]. A similar hierarchy is observed in *Bacillus megaterium*, where fructose and malate repress the synthesis of xylanase and other polysaccharide-degrading enzymes through mechanisms similar to *B. subtilis* [40]. In *Staphylococcus aureus*, acetate, an abundant overflow metabolite during aerobic growth, acts as a preferred carbon source and contributes to CcpA-mediated repression of alternative metabolic pathways [41]. This regulatory linkage integrates carbon flux with expression of virulent factors, illustrating the broader physiological consequences. *Listeria monocytogenes* provides another example in which non-glucose sugars exert dominant regulatory control: cellobiose and related β-glucosides strongly repress the PrfA virulence regulon, demonstrating that CCR directly modulates pathogenicity [42]. In *Streptococci*, including *S. pyogenes* and *Streptococcus mutans*, lactose, galactose, and fructose are preferred carbon sources that activate CcpA-dependent repression [43,44]. Metabolites derived from fructose, including fructose-1–phosphate and fructose-1,6–bisphosphate, play roles as intracellular effectors that couple carbohydrate availability to global transcriptional control [44]. In *Clostridium acetobutylicum*, arabinose represses the expression of the xylose metabolism genes [45]. Very recently, it was demonstrated that thermophilic *Geobacillus kaustophilus* employs an atypical CCR of inositol catabolism genes driven by ribose and not by glucose at all [46]. Collectively, these examples demonstrate that CCR in Gram-positive bacteria is governed not only by glucose but also by other carbon sources. Preferred substrates can all serve as dominant repressing signals, enabling these organisms to optimise resource utilisation across diverse ecological niches [19,22,40].

Multidimensional impacts of carbon catabolite repression

To cite findings from genetics and molecular biology concerning CCR, we need to focus on the flexible binding site architecture of CcpA [31]. Recent studies revealed that CcpA can bind to diverse *cre* site arrangements, allowing fine-tuned regulation [47,48]. Some operons are controlled by additional repressors, adding further complexity to transcriptional control [47]. Transcriptomic studies revealed that CCR affects not only carbon metabolism but also nitrogen utilisation, amino acid biosynthesis, and stress responses [13,14,16,31]. These findings also give implications for the applications. Manipulating CCR can improve yields of desired metabolites for fermentation optimisation [48]. CCR influences the utilisation of carbohydrates by gut bacteria, thereby determining the health benefits of probiotics in terms of colonisation and growth [35]. As metabolic pathways can be precisely controlled by modifying CcpA or the *cre* site, applications in synthetic biology are also anticipated [48]. For possible medical applications, inhibiting CCR may weaken pathogens by disrupting their nutrient prioritisation, potentially contributing to the identification of novel antimicrobial targets [41]. Furthermore, elucidating

CCR links metabolism to pathogenicity, offering new therapeutic strategies for controlling virulence [35,36].

When considering future challenges, it is necessary to deepen our understanding of the complexity of CCR regulation. This is because the CCR is not a simple on/off switch but rather integrates multiple signals. Furthermore, sufficient consideration of species-specific differences is essential. Whilst CcpA is conserved, its regulatory network differs amongst Gram-positive bacterial species. The example of *G. kaustopholus* starkly illustrates this issue [46]. In this bacterium, ribose rather than glucose is the preferred carbon source that triggers CCR, and it is suggested that not HPr but Crh functions as the primary partner for CcpA in this mechanism. Furthermore, glucose does not cause CCR at all [46]. Glucose, as the primary product of photosynthesis, constitutes the most abundant carbon source on Earth. Consequently, glucose is the most readily available carbon source and occupies a central position in carbon metabolism not only in bacteria but in most other biological systems [49]. The typical intracellular carbon metabolism network is based on glucose metabolism, and CCR has evolved to metabolise glucose as the most efficient carbon source first. However, the discovery of thermophilic bacteria possessing an atypical CCR that prioritises a carbon source other than glucose may necessitate a reconsideration of the traditional glucose-centric view. Nutritional and physical differences in the environments where species grow may be the driving force in this evolutionary selection. CCR is still considered profoundly complex, and quite recently, a novel motif linking carbon metabolism and pathogenicity expression, common to proteins contributing to CCR, was discovered in two Gram-positive pathogens, making future research highly anticipated [50]. Through detailed integrative systems biology approaches, including transcriptomics, proteomics, and metabolomics, insights may be gained that offer clues to accurately understanding the multidimensional impact of CCR and the necessity of its development [51]. Moreover, an evolutionary perspective is crucial. CCR should be reconsidered, reflecting survival adaptation strategies within nutrient-fluctuating environments.

Conclusion

CCR in Gram-positive bacteria is a highly integrated regulatory system that aligns nutrient availability with global physiology. Rather than a simple glucose-responsive switch, it functions as a multilayered network where metabolic signals, transcriptional regulators, and environmental cues converge. Central to this system is the interplay among CcpA, HPr, Crh, and glycolytic intermediates, whose phosphorylation-dependent interactions couple metabolic flux to transcriptional control and ensure prioritised use of preferred carbon sources. CCR also contributes to broader metabolic homoeostasis. Its physiological influence is extensive: in *B. subtilis*, CCR governs glycolysis, gluconeogenesis, stress responses, and sporulation, while in pathogens such as *S. pyogenes*, *S. aureus*, and *L. monocytogenes*, it modulates virulence. Species-specific preferences highlight CCR's ecological and evolutionary diversification, including the recent discovery of atypical CCR in *G. kaustophilus* prioritising ribose over glucose. CCR has implications for biotechnology and medicine, enabling metabolic engineering, fermentation improvement, and potential attenuation of pathogen virulence. Emerging omics approaches reveal CCR as a global integrator of carbon, nitrogen, and stress pathways. Future work must clarify atypical CCR architectures, evolutionary drivers, and the mechanistic nuances of CcpA–*cre* regulation, positioning CCR as a refined adaptive system central to microbial physiology and innovation.

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Ethical approval

There are no ethical issues in this research.

CRediT authorship contribution statement

Ken-ichi Yoshida: Conceptualization, Funding acquisition, Investigation, Writing – original draft, Writing – review & editing.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The author declares no conflicts of interest.

Declaration of Generative AI and AI-assisted technologies in the writing process

The author declares that no generative AI was used in the preparation of the manuscript.

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This publication highlights current strategies for integrating transcriptomic, proteomic, and metabolomic datasets, emphasising how machine-learning frameworks enhance biological interpretation and biomarker discovery.

Glossary

Catabolite control protein A (CcpA): A LacI/GalR-family transcription regulator that mediates CCR in Gram-positive bacteria by binding to *cre* sites and modulating gene expression in response to metabolic signals.

Catabolite-responsive element (cre site): A 14-bp pseudo-palindromic DNA sequence recognised by CcpA. Its position relative to the promoter determines whether CcpA activates or represses transcription.

Crh (HPr-like protein): A paralogue of HPr that is phosphorylated at Ser46 and participates in CCR. It also regulates methylglyoxal synthesis by interacting with MgsA.

Enzyme IIA^{Glc} (EIIA^{Glc}): A component of the PTS. Its phosphorylation state regulates adenylate cyclase activity and inducer exclusion in Gram-negative bacteria.

HPr (histidine-containing protein): A central phosphocarrier of the PTS that can be phosphorylated at His15 (for sugar transport) or Ser46 (for CCR) in Gram-positive bacteria.

HPr kinase/phosphatase (HPrK/P): A bifunctional enzyme that phosphorylates HPr or Crh at Ser46 in response to glycolytic intermediates and dephosphorylates them when glucose is not available.