Dynamics of Glucose Transport in *Escherichia coli*

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Contributor: Ofelia E. Carreón-Rodríguez, Guillermo Gosset, Adelfo Escalante, Francisco Bolívar

Escherichia coli is the best-known model for the biotechnological production of many biotechnological products, including housekeeping and heterologous primary and secondary metabolites and recombinant proteins, and is an efficient biofactory model to produce biofuels to nanomaterials. Glucose is the primary substrate used as the carbon source for laboratory and industrial cultivation of *E. coli* for production purposes. Efficient growth and associated production and yield of desired products depend on the efficient sugar transport capabilities, sugar catabolism through the central carbon catabolism, and the efficient carbon flux through specific biosynthetic pathways. The genome of *E. coli* MG1655 is 4,641,642 bp, corresponding to 4702 genes encoding 4328 proteins. The EcoCyc database describes 532 transport reactions, 480 transporters, and 97 proteins involved in sugar transport. Nevertheless, due to the high number of sugar transporters, *E. coli* uses preferentially few systems to grow in glucose as the sole carbon source. *E. coli* nonspecifically transports glucose from the extracellular medium into the periplasmic space through the outer membrane porins. Once in periplasmic space, glucose is transported into the cytoplasm by several systems, including the phosphoenolpyruvate-dependent phosphotransferase system (PTS), the ATP-dependent cassette (ABC) transporters, and the major facilitator (MFS) superfamily proton symporters.

Keywords: carbohydrate transport ; PTS ; ABC transporter ; glucose transport ; *Escherichia coli*

1. Introduction

Glucose is the essential carbon source for growing and cultivating heterotrophic bacteria, such as *Escherichia coli*, for laboratory and production purposes. This sugar is the primary carbon and energy source for large-scale biotechnological processes and provides faster and optimum growth compared with other carbon sources. *E. coli* preferentially uses glucose in the presence of sugar mixtures, preventing using other carbon sources. Several transcriptional and post-transcriptional regulatory mechanisms control the preferential use of glucose over other sugars. The transcriptional control mechanism known as carbon catabolite repression (CCR) prevents the expression of more than 180 genes (including transport and catabolic genes) and the inducer exclusion mechanism, where the uptake or synthesis of an inducer molecule of a sugar catabolic operon is prevented [1][2][3][4][5][6][7][8][9][10].

The genome size of *E. coli* strain K-12 MG1655 is 4,641,652 bp, corresponding to 4702 genes encoding 4328 proteins, 228 RNA genes, and 146 pseudogenes. Transport comprises 532 reactions, including 480 transporters (EcoCyc database https://biocyc.org/ECOLI/organism-summary, accessed on 1 May 2023) [11]. Among them, 97 proteins are involved in sugar transport (**Table 1**). Additionally, numerous transporters with overlapping sugar specificities for monosaccharides increase the potential capability to transport glucose [6], indicating the extraordinary capability and plasticity of transporting and growing glucose as a carbon source. In contrast to the higher sugar transport systems included in *E. coli* K12, according to the BioCyc database [12], other organisms such as *Salmonella enterica* serovar Typhimurium str LT2 possess just three glucose transmembrane transporters, *Listeria monocytogenes* 10403S do not report any hexose transporter, and *Pseudomonas aeruginosa* PA01 reports only two hexose importers [11].

Table 1. Carbohydrate transport systems in *Escherichia coli* K12 substr. MG1655.

Gene(s)	Transporter Family	Transported Sugar	PROTEINS	Cellular Location
alsBAC	**ABC**	**D-allose**	**D-allose ABC transporter membrane**	**P, IM, C**
araFGH	**ABC**	**L-Arabinose**	**Arabinose ABC transporter**	**P, IM, C**
malEFG-malK	**ABC**	**Maltose/maltodextrine**	**Maltose ABC transporter**	**P, IM, C**

Gene(s)	Transporter Family	Transported Sugar	PROTEINS	Cellular Location
malK	ABC	Maltose/maltotetraose/ maltotriose	Maltose ABC transporter ATP binding subunit	IM
mglBAC	ABC	D-galactose/methyl-galactoside	D-galactose/methyl-galactoside ABC transporter	P, IM, C
rbsACB	ABC	Ribose/D-xylose	Ribose ABC transporter	P, IM
upgBAEC	ABC	*sn*-Glycerol 3-phosphate	*sn*-Glycerol 3-phosphate ABC transporter	P, IM, C
xylFHG	ABC	D-Xylose	Xylose ABC transporter	P, IM, C
yphFED	ABC	Sugar	Putative ABC transporter	P, IM
ytfQRT-yjfF	ABC	β-D-Galactofuranose α-D-Galactofuranose	Galactofuranose ABC transporter	P, IM
araE	MFS (SP)	Arabinose	Arabinose:H^+ symporter	IM
dgoT	MFS (ACS)	D-Galactonate	D-Galactonate:H^+ symporter	IM
fucP	MFS (FHS)	L-Fucose/D-arabinose/ L-galactose	L-fucose:H^+ symporter	IM
galP	MFS (SP)	D-Galactose	Galactose:H^+ symporter	IM
garP	MFS (ACS)	Galactarate/D-glucarate	Galactarate/D-glucarate transporter	IM
glpT	MFS (OPA)	Glycerol-3-phosphate	sn-glycerol 3-phophate:phosphate antiporter	IM
gudP	MFS (ACS)	Galactarate/D-glucarate	Galactarate/D-glucarate transporter	IM
lacY	MFS (OHS)	Lactose/melibiose	Lactose/melibiose:H^+ symporter	IM
lgoT	MFS (ACS)	L-Galactonate	L-Galactonate:H^+ symporter	IM
setA	MFS (SET)	Lactose	Sugar exporter SetA	IM
setB	MFS (SET)	Lactose	Sugar exporter SetB	IM
setC	MFS (SET)	Arabinose-like	Putative arabinose exporter	IM
uhpC	MFS (OPA)	Sugar phosphate	Inner membrane protein sensing glucose-6-phosphate	IM
uhpT	MFS (OPA)	Hexose-6-phosphate	Hexose-6-phosphate:phosphate antiporter	IM
xylE	MFS (SP)	Xylose	D-xylose:H^+ symporter	IM
ydeA	MFS (DHA1)	Arabinose	L-arabinose exporter	
agaBCD	PTS	Galactosamine	Galactosamine specific PTS system EIIBCD	IM, C
agaV	PTS	n-acetyl-D-galactosamine (galactose)	N-acetyl-D-galactosamine specific PTS system IIB	C
ascF	PTS	β-Glucoside (arbutin/cellobiose/salicin)	β-Glucoside specific PTS enzyme IIBC	IM
bglF	PTS	β-Glucoside (metil-β-D-glucoside, arbutine, salicin, β-D-glucose)	β-Glucoside specific PTS enzyme II/BglG kinase/BglG phosphatase	IM
chbAC	PTS	β-D-Cellobiose/chitobiose (starch, sucrose)	N, N'-diacetyl chitobiose-specific PTS enzyme IIAC	C
chbB	PTS	β-D-Cellobiose/chitobiose (starch, sucrose)	N, N'-diacetyl chitobiose-specific PTS enzyme IIB	IM
cmtA	PTS	Mannitol (fructose and mannose)	Mannitol-specific PTS enzyme IICB	IM
cmtB	PTS	Mannitol (fructose and mannose)	Mannitol-specific PTS enzyme IIA	C

Gene(s)	Transporter Family	Transported Sugar	PROTEINS	Cellular Location
fruA	PTS	Fructose and mannose	Fructose-specific PTS multi-phosphoryl transfer protein FruA PTS system EIIBC	IM
frvA	PTS	Fructose-like	Putative PTS enzyme IIA	C
frvB	PTS	Fructose-like	Putative PTS enzyme IIBC	IM
frwB—frwD	PTS	Fructose-like	Fructose-like PTS system EIIB	C
frwC	PTS	Fructose-like	Fructose-like PTS system EIIC	IM
fryC	PTS	Fructose-like	Fructose-like PTS system EIIC	IM
fryB	PTS	Fructose-like	Fructose-like PTS system EIIB	C
gatA	PTS	Galactitol	Galactitol-specific PTS system EIIA	C
gatB	PTS	Galactitol	Galactitol-specific PTS system EIIB	C
glvBC	PTS	α-Glucoside	Alpha-glucoside PTS system EIICB	IM
malX	PTS	Maltose/glucose	PTS enzyme IIBC component MalX	IM
manYZ	PTS	Mannose	Mannose-specific PTS system EIICD	IM
manX	PTS	Mannose	Mannose-specific PTS system EIIAB	IM, C
mngA	PTS	2-O-α-mannosyl-D-glycerate	2-O-α-mannosyl-D-glycerate specific PTS enzyme IIABC	IM
mtlA	PTS	Mannitol (fructose, mannose)	Mannitol-specific PTS enzyme IICBA	IM
nagE	PTS	n-Acetylglucosamine	N-acetylglucosamine-specific PTS enzyme II	IM
ptsG	PTS	Glucose	Glucose-specific PTS enzyme IIBC component	IM
ptsHIcrr	PTS	Glucose	*ptsH*, phosphor carrier protein HPr *ptsI*, PTS enzyme I *crr*, Enzyme IIA^{Glc}	C
sgcA	PTS	Galactitol-like	Galactitol-specific PTS system EIIA	C
sgcB	PTS	Galactitol-like	Galactitol-specific PTS system EIIB	C
sgcC	PTS	Galactitol-like	Galactitol-specific PTS system EIIC	IM
srlA	PTS	Glucitol/Sorbitol	Sorbitol specific PTS system IIC_2	IM
srlB	PTS	Glucitol/Sorbitol	Sorbitol specific PTS system EIIA	C
srlE	PTS	Glucitol/Sorbitol	Sorbitol specific PTS system $IIBC_1$	IM
treB	PTS	Trehalose	Trehalose-specific PTS enzyme IIBC	IM
ulaABC	PTS	Ascorbate	L-ascorbate specific PTS system EIICBA	IM, C
bglH	OT (C/P)	β-Glycosides	Carbohydrate-specific outer membrane porin, cryptic	OM
glpF	OT (MIP)	Glycerol	Glycerol facilitator	IM
lamB	OT (C/P)	Maltose	Maltose outer membrane channel/phage lambda receptor protein	OM
melB	OT (EDP)	Melibiose	Melibiose:H^+/Na^+/Li^+ symporter	IM
ompF	OT (C/P)	Sugar	Outer membrane porin F	OM
ompC	OT (C/P)	Sugar	Outer membrane porin C	OM

Transport mechanisms: ABC, ABC transporter system; MFS, Major facilitator superfamily (SP, Sugar porter family; OHS, Oligosaccharide symporter family; FHS, Fucose symporter family; SET, sugar efflux transporter; DHA1, The drug

H^+Antiporter-1; OPA, Organophosphate.Pi antiporter; ACS, Anion/cation symporter); PTS, PTS transporter system; OT, Other transporters (MIP, The major intrinsic protein (aquaporin); C/P, Channels and pores; EPD, Electrochemical potential-driven transporters). Cellular location: OM, Outer membrane; P, Periplasm; IM, Inner membrane; C, Cytoplasm. Table elaborated from data available in the EcoCyc database (https://ecocyc.org, accessed on 1 May 2023) [11].

According to the high capability to transport glucose, wild-type strains of *E. coli* can grow efficiently in minimal broth, such as M9 broth supplemented with glucose as the sole carbon source, achieving higher specific growth rates (μ), e.g., *E. coli* K12 shows a μ = 0.57 h^{-1} [13], strain MG1655, μ = 0.92 h^{-1}, and the derivative strain JM101, μ = 0.7 h^{-1} [5]. The transport and breakdown of imported glucose through the glycolytic pathway supplies at least 12 biosynthetic precursors necessary for the biosynthesis of all the structural blocks of the cell from this carbon source [11].

The outer and inner membrane in *E. coli* imposes two different processes for glucose transport from the extracellular medium into the cytoplasm (**Figure 1**). The outer membrane acts as a molecular sieve to pass diverse hydrophilic molecules such as glucose. Extracellular solutes enter by diffusion through the inner channel of the outer membrane porins (OMP) into the periplasmic space in a non-selective process, limited only by the cutoff size of the OMP inner channel and the physicochemical properties of the solutes. However, some specificity is observed in some OMPs, such as LamB [14][15]. Different transporters mediate the import of periplasmic glucose into the cytoplasm against a gradient concentration mechanism, comprising (i) the phosphoenolpyruvate (PEP)/glucose Phosphotransferase-driven Group Translocators (PTS) systems, (ii) the primary active glucose transporters of the ATP-Binding Cassette (ABC) superfamily, specifically, ATP-dependent transporters, and (iii) the secondary active solute (glucose)/cation symporters members of the Major Facilitator Superfamily (MFS), utilizing H^+ proton gradients maintained by the ATPases system (**Table 1**) [6][11][16][17]. In this research, researchers review the characteristics and mechanisms of the abovementioned glucose transporter systems in *E. coli*, the regulatory circuits recruiting the specific or concomitant use of these transport systems under specific growing conditions (e.g., switching from glucose-rich to glucose-limited conditions), and the cross-taking interactions between several transporters resulting in the unspecific glucose transport. Finally, researchers describe several examples of transporter engineering, including introducing heterologous and non-sugar transport systems to produce several valuable metabolites efficiently.

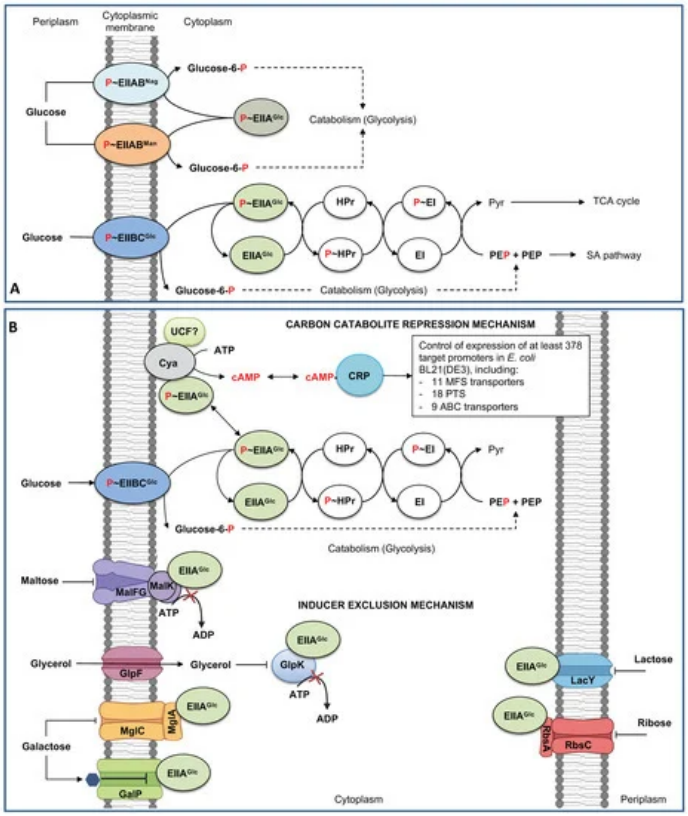

Figure 1. The PTS glucose in *Escherichia coli*, the carbon catabolite repression, and inducer exclusion mechanisms. (**A**). Components and function of PTS glucose. Alternative glucose transport and phosphorylation by $EIIAB^{Man}$ and $EIICBA^{Nag}$. (**B**). Carbon catabolite repression and inducer exclusion mechanisms. cAMP, cyclic-AMP DNA-binding transcriptional dual regulator; CRP, DNA-binding transcriptional dual regulator; Cya, adenylate cyclase; GalP, galactose permease; GlpF, glycerol facilitator; GlpK, glycerol kinase; LacY, lactose permease, MalFG, maltose ABC transporter membrane subunits F and G; MalK (dimeric), maltose ABC transporter ATP binding subunit; PEP, phosphoenolpyruvate; Pyr, pyruvate, RbsA, ribose ABC transporter ATP binding subunit; RbsC, ribose ABC transporter membrane subunit; TCA, the tricarboxylic acid

cycle. The hexagon in GalP indicated a galactose; red-labeled P indicates a phosphate group in the phosphotransference mechanism. P~ indicates phosphorylated forms of PTS proteins. SA, shikimic acid. The dotted lines indicated several enzymatic reactions. ⊥ shows interrupted mechanisms or reactions. Figure composed from [6][11][17][18][19][20][21][22][23].

2. Dynamics of Glucose Transport in *E. coli* under Sugar-Limiting Conditions

Despite the essential role of the PTS glucose system in glucose transport and phosphorylation in *E. coli*, as well as in controlling the preferential consumption of glucose over other non-PTS sugars, the cultivation of *E. coli* under nutritional stress conditions results in a differential expression and synthesis of other transport systems nor PTS Glc for glucose transport. Nutritional stress conditions under glucose-limited cultivation (1–300 µM, defined as a hunger condition) or under glucose starvation conditions (<0.1 µM) (growing under glucose-limited chemostat) result in lower specific growth rates (0.1–0.9 h^{-1}) [24][25]. Under these scavenging conditions, *E. coli* activates the transcription and translation of alternative, high-affinity transporters for glucose such as several ABC transporters [24]. This process starts with the synthesis of the endogenous inducers galactose and maltotriose [24], which induces, respectively, the expression of the operon *mglBAC* (member of the *gal* regulon), the operons *malEFG (*maltose ABC transporter), the *malKlamBmalM* operon encoding for the maltose ABC transporter ATP binding subunit (MalK), the maltose outer membrane channel/phage lambda receptor protein (LamB), and the maltose regulon periplasmic protein (MalM), both part of the *mal* regulon [11][24]. Additionally, the glucose limitation condition results in elevated levels of cAMP compared to the concentration when growing in high glucose concentration, activating the expression of the above operons [24][25][26] (**Figure 2**).

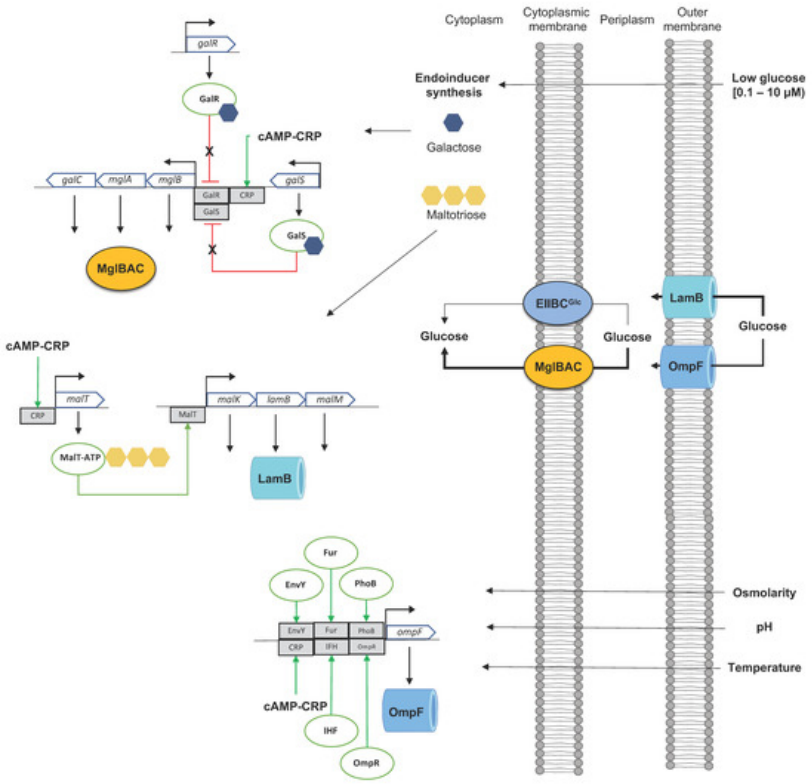

Figure 2. Induction of high-affinity glucose transporter growing in glucose-limiting conditions. Growing *E. coli* under glucose-limiting chemostat conditions induces the expression of the high-affinity glucose transporters MglBAC and OMP LamB by the coordinate action of cAMP–CRP and the autoinducers galactose or maltotriose. Induction of the *mglBAC* operon: autoinducer galactose (blue hexagon) binds to negative transcriptional repressors of the *gal* regulon GalR and GalS, inactivating them. cAMP–CRP binds to the DNA-binding transcriptional region of the *mglBAC* operon (gray rectangle), inducing its transcription and translation. Induction of the *malKlamBmalM* operon: autoinducer maltotriose (yellow triple hexagons) binds to the DNA-binding transcriptional activator MalT, inhibiting the repression of the operon, resulting in a higher transcription and the synthesis of encoding proteins, including LamB. Bold lines in transporters indicate increased glucose transport resulting from higher protein concentration. LamB increases glucose permeability to the periplasm, and MglBA acts as a high-affinity glucose transporter from the periplasm to the cytoplasm. EnvY, DNA-binding transcriptional activator EnvY; Fur, DNA-binding transcriptional dual regulator Fur; IHF, integration host factor; OmR, OmpR dimer; PhoB, DNA-binding transcriptional dual regulator PhoB. Red lines show repression mechanisms. Green arrows induction mechanisms. Gray rectangles show specific DNA-binding transcriptional regions. Figure composed from references [11][15][24][25][27][28][29].

When growing at limiting micromolar glucose concentrations (hunger response), outer membrane porins in *E. coli* (mainly OmpF/OmpC) can permeate glucose. However, the affinity of LamB for carbohydrates selects this OMP as the primary way to introduce extracellular glucose to the periplasm [24][25]. Induction of the *malKlamBmalM* operon by maltotriose-MalT (DNA-binding transcriptional activator MalT-maltotriose-ATP) induced under glucose limitation increases expression of *lamB*. This condition suggests an increased concentration of LamB in the outer membrane and an increased concentration of periplasmic glucose, which is then transported into the cytoplasm by MglBAC and MalEFG transporters. The availability of the inducer D-galactose inactivates both the GalR repressor and the DNA-binding transcriptional dual regulator GalS (**Figure 2**), allowing the expression of *mglBAC* by cAMP–CRP [11][30][31], and the *malEFG* operon is induced by the presence of maltotriose-MalT and the cAMP–CRP complex [11]. Overexpression of the highly sensitive glucose transportation system comprising the *malKlamBmalM* and *mglBAC* operons showed a higher expression level during the hunger response (LamB 60X, MglBAC 20X, and OmpF 20X). However, the expression level of these operons was lower in starvation conditions (LamB 5X, MglBAC 1X, and OmpF 7X) compared to the expression level growing in glucose-rich conditions [25][27][28]. Increased expression and translation of *ompF* were observed under glucose limitation at D = 0.3 h^{-1} in glucose- or nitrogen-limited chemostat cultures [29].

Inactivation of PTS glucose in *E. coli* for the selection of mutants avoiding PEP consumption for aromatic compounds production purposes [32][33] imposes a severe nutritional stress condition when PTS^- mutants are grown in glucose as the sole carbon source, resulting in a severe decrement the specific growth rate of PTS^- mutants (**Table 2**).

Table 2. Nutritional stress conditions imposed in several *E. coli* strains resulting from the inactivation of PTS.

Parental Strain	PTS Mutation	Growth and Relevant Changes in the Expression of Several Genes Involved in Transport Respect the Parental Strain		References
MG1655	**Δ*ptsG***	**Aerobic conditions**	**Anaerobic conditions**	**[20]**
		Decrement in μ of 73%. Increased expression of *galS* and down-regulation of *galP* (0.2 X) and *manX* (0.5 X). Overexpression of the *mgl* operon in 10 X. Downregulation of *cyaA* and increased levels of cAMP: 552.5 X.	**Decrement in μ of 70.2%. Increased expression of *galS* and downregulation of *galP.* Increased expression of *malE* (48 X). Overexpression of the *mgl* operon in 48 X. Down-regulation of *cyaA* with increased levels of cAMP: 390.9 X.**	
JM101	**Δ*ptsHIcrr***	**Reduction in μ~85% to 57%. Overexpression of *mglB* 13.4 X and *lamB* 17.6 X. Overexpression of some genes of the *gal* regulon: *galP* 12.4 X, *galR* 3.2X, *galS* 4.9X.**		**[34][35]**
MG1655	***ptsHIcrr* KO**	**Reduction in μ~79%.**		**[36]**

The use of adaptive laboratory evolution (ALE) experiments for the selection of fast-growing derivatives in glucose from PTS^- mutants resulted in derivative mutants that increased the specific growth compared to the parental PTS^- mutants, developing several mutations, resulting in the selection of alternative glucose transporter systems to PTS glucose [32][35][36][37][38]. The characterization of evolved mutants derived from *E. coli* JM101, W3110, and MG1655 selected GalP as the primary glucose transporter for the phosphorylation of incoming glucose by Glk (glucokinase) from ATP [35][36][39][40]. The selection of GalP as the glucose transporter in evolved PTS^- derivatives resulted in the inactivation of the transcriptional repressor of the *gal* regulon GalR by the complete or partial deletion of *galR* or the selection of mutations resulting in the inactivation of the function of the repressor [5] (**Figure 3**). The selection of GalP for glucose transport in PTS^- evolved mutants results during the ALE experiment. In the ALE experiment of the PTS derivative from JM101, the evolving population grew exponentially after 75 h of cultivation. The transcriptional analysis of the evolved derivative mutant selected after 120 h of cultivation showed elevated transcription values for *galP* (13.1X), but a decrement in the transcript of *galR* (1.2) and *galS* (3.2X), suggesting the derepressing of *galP* and the synthesis of the transporter GalP [34][35]. The appearance of a mutated version of *galR* (deletion of the 72-bp region) was reported between 48–72 h of cultivation during an ALE experiment [41]. The proteomic analysis of the PTS mutant from JM101 and the evolved derivative PB12 mutant showed an increased concentration of LamB, ManX, and MglB in the parental PTS^- mutant (μ = 0.13 h^{-1}) compared to the observed protein concentration in the evolved derivative PB12 (μ = 0.44 h^{-1}). The concentration of LamB and MglB decreased in the evolved mutant, suggesting that MglBAC was selected as the glucose transporter in the Δ*ptsHIcrr* mutant and during the first 50–75 h of the ALE experiment [38], which was replaced by GalP during the evolution experiment [34][36][38][41] (**Figure 3**).

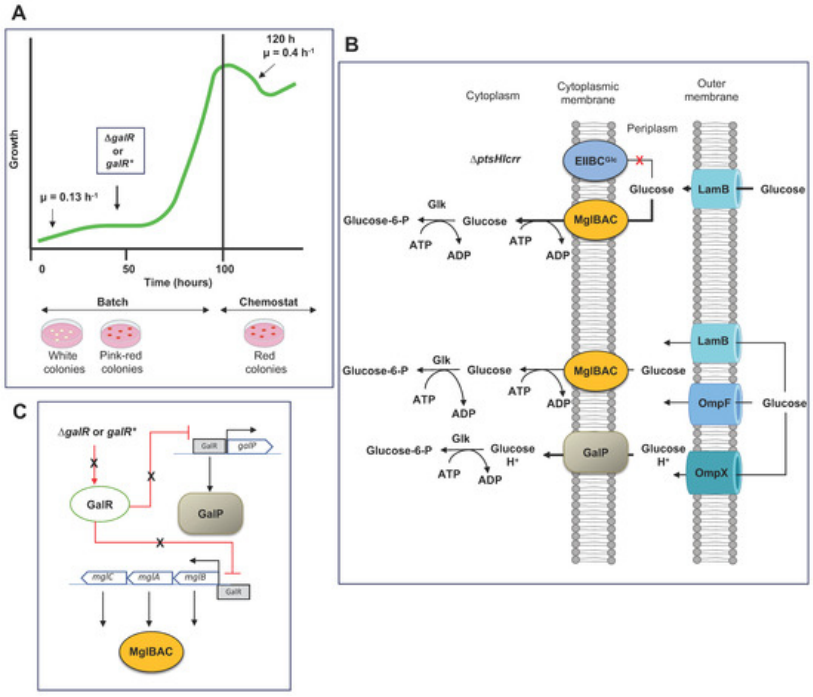

Figure 3. Selection of alternative glucose transporters during adaptive laboratory (ALE) experiments of a Δ*ptsHIcrr mut*ant (PTS⁻) of *E. coli* JM101. (**A**). ALE experiment with two-stage batch-chemostat stages in M9 minimal medium supplemented with glucose. The bold green line shows the overall growth profile starting with a μ = 0.1–0.13 h^{-1}. PTS mutants in the early stage of the ALE experiment showed a white-color phenotype in MacConkey agar supplemented with glucose selecting LamB to diffuse extracellular glucose from the extracellular medium into the periplasm and MglBAC to transport glucose from the periplasm into the cytoplasm. (**B**). Analysis of several intermediate mutants indicated that in the absence of PTS (Δ*ptsHIcrr*) mutants in the early stages of the ALE experiment selected, MglBAC for glucose transport (**upper** section). After 100 h of cultivation, the ALE experiment switched on a chemostat stage, isolating red colonies with increased μ values. Fast-growing mutants showed a μ = 0.4 h^{-1}, and further analysis showed that mutants selected GalP as the primary glucose transporter (**bottom** section). Bold arrows show a higher glucose transport. (**C**) shows the regulatory mechanisms resulting in the selection of MglBAC and GalP as alternative glucose transporters without the activity of PTS glucose. Proposed induction and synthesis mechanisms for LamB are illustrated in **Figure 2**. *galR**, mutated *galR*. Glk, glucokinase. OmpF, outer membrane porin; F OmpX, outer membrane porin X or OmpP. Red lines show repression mechanisms. Gray rectangles show specific DNA-binding transcriptional regions. This figure was composed of references [11][20][34][35][38][41].

The resultant, evolved, fast-growing derivative mutants from the ALE experiments recovered their specific growth rate to μ values ranging from 0.2 to 0.92 h^{-1} [5][35][36][39][40][41]. Nevertheless, the μ values in these fast-growing PTS^- mutants were consistently lower than those observed μ in the parental PTS^+ strains. The selection of alternative glucose transporters in the absence of PTS glucose involved the dependence of ATP to move one molecule of glucose across the inner membrane by the ABC transporters such as MglBAC, and the further phosphorylation of incoming glucose by Glk also from ATP, to yield glucose-6-P (total ATP cost = 2). The cotransportation of one molecule of glucose and one H^+ by GalP and the phosphorylation of imported glucose by Glk from ATP had an additional energetic cost because ATP synthase needed to hydrolyze ATP to maintain the proton gradient, resulting in a total ATP cost ≥ 1.25 [35][36][42]. In these mutants, the dependence of ATP for glucose transport and phosphorylation entailed a reduction in ATP and an increment of AMP levels with a decrement in energy availability, resulting in reduced growth rates [36].

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