BarA is a membrane-associated protein that belongs to a subclass of tripartite sensors of the two-component signal transduction system family. In this study, we report that UvrY is the cognate response regulator for BarA of *Escherichia coli*. This conclusion is based upon homologies with analogous two-component systems and demonstrated by both biochemical and genetic means. We show that the purified BarA protein is able to auto-phosphorylate when incubated with \([\gamma-\text{32P}]\text{ATP}\) but not with \([\alpha-\text{32P}]\text{ATP}\) or \([\gamma-\text{32P}]\text{GTP}\). Phosphorylated BarA, in turn, acts as an efficient phosphoryl group donor to UvrY but not to the non-cognate response regulators ArcA, PhoB, or CpxR. The specificity of the transphosphorylation reaction is further supported by the fact that UvrY can receive the phosphoryl group from BarA-P but not from the non-cognate tripartite sensor ArcB-P or ATP. In addition, genetic evidence that BarA and UvrY mediate the same signal transduction pathway is provided by the finding that both *uvrY* and *barA* mutant strains exhibit the same hydrogen peroxide hypersensitive phenotype. These results provide the first biochemical evidence as well as genetic support for a link between BarA and UvrY, suggesting that the two proteins constitute a new two-component system for gene regulation in *Escherichia coli*.

Signal transduction by phosphorylation and dephosphorylation of cellular proteins plays pivotal roles in the regulation of numerous cellular processes in both prokaryotes and eukaryotes. In prokaryotes, these processes are accomplished partly by a family of two-component signal transducing systems that enable bacteria to adapt to changing environments (1–3). Typically, such a system comprises a membrane associated sensor kinase and its cognate response regulator. Signal reception by the sensor kinase stimulates an ATP-dependent autophosphorylation at a conserved histidine residue. The phosphorylated sensor kinase then catalyzes a transphosphorylation of the cognate response regulator at a conserved aspartate residue, thereby rendering it functional, typically as a transcriptional regulator. Upon cessation or subsidence of signaling, both the sensor kinase and the response regulator undergo dephosphorylation allowing signal decay and silencing of the system.

Data derived from genome sequencing projects indicate that an organism such as *Escherichia coli* possesses some 30 typical two-component systems (4). The majority of the sensor kinases consist of an N-terminal cytosolic segment, a canonical pair of transmembrane segments linked by a periplasmic bridge, and an orthodox transmitter domain with a conserved histidine residue. However, a few sensors are more complex; they possess an additional central receiver domain with a conserved aspartate residue and a C-terminal phosphotransfer domain with a conserved histidine residue, which is known as the Hpt-domain. Recent studies have shown that several tripartite sensors catalyze the phosphorylation of their cognate response regulators via an ATP→His→Asp→His→Asp phosphorelay (5–7) as well as the dephosphorylation of the phospho-response regulator by a reverse Asp→His→Asp→P phosphorelay (8). In addition, a SixA (signal inhibitory factor X) protein was suggested to be able to specifically catalyze the dephosphorylation of the histidine-P of the phosphotransfer domain of ArcB (9). Furthermore, intracellular metabolic intermediates have been reported to enhance the rate of autophosphorylation of the ArcB sensor kinase (10). This complex mode of action is believed to provide multiple levels of control that play important roles in the “fine tuning” of such a system.

The BarA (also known as AirS) sensor kinase (Fig. 1) of *E. coli* is a member of the subclass of tripartite sensor kinases. The *barA* gene was first identified by its ability, when expressed from a high copy number plasmid, to phenotypically suppress a deletion mutant of the EnvZ sensor kinase and to control the OmpR regulator protein. The cross-talk between BarA and OmpR, however, could not be demonstrated in vitro, and the cognate response regulator for BarA was not identified (11). Thus, the suppression phenomenon may be an artifact resulting from cross-talk of an orphan response regulator in the absence of its cognate sensor kinase. The *barA* gene has been reported to be transcriptionally activated in uropathogenic *E. coli* strain DS17 upon pyelonephritis-pili attachment to its carbohydrate receptor on eukaryotic host cells and to be required for activation of the siderophore system. Therefore, it was suggested that BarA may direct the coordinate regulation of the iron acquisition machinery in uropathogenic *E. coli*, and play a key role in colonization during urinary tract infections (12). Recently, BarA was shown to be involved in the bacterial adaptive responses against hydrogen peroxide-mediated stress by activating transcription of the sigma factor RpoS, which in turn controls the expression of KatE, the major catalase of *E. coli* (13). Here, we present the results of experiments directed to identify the cognate response regulator for the BarA sensor kinase of *E. coli*.
**UvrY Is the Cognate Response Regulator of BarA in *E. coli***

**EXPERIMENTAL PROCEDURES**

**Bacterial Strains and Plasmids**—To delineate the function of the *E. coli* MC4100 BarA protein, we disrupted the gene with a kanamycin cassette and created a chromosomal null mutant by allelic gene replacement. The barA gene from MC4100 was amplified by polymerase chain reaction (PCR)\(^1\) using primers 5'-GCTGG-3' and 5'-GAAACCCGCTCATAAAAAGCC-3' (MWG Biotech) and Pfu polymerase. The 3119-nucleotide fragment was cloned between the SpeI and EcoRV sites in vector pBR322. A kanamycin resistance cassette was excised from pUC4K (Amersham Pharmacia Biotech) with BamHI and ligated between the two BglII sites in the BarA open reading frame (ORF), creating pBR322BarA::kan. This construct was digested with EcoRI, blunted with Klenow, and then digested with SpeI to release the 3705-nucleotide barA::kan fragment, which subsequently was subcloned into pCDV442 (14) using the Smal and SpeI sites. The resultant construct was conjugated from strain S17Apr to MC4100 (naldixic acid-resistant), and bacteria were selected with naldixic acid (20 μg/ml) and kanamycin (50 μg/ml). Co-integrates were further selected on LB plates containing 5% sucrose and kanamycin (100 μg/ml). Resolution products were subsequently selected for growth on plates containing kanamycin and inability to grow on plates containing ampicillin. Western blot was used to confirm the absence of the BarA protein. Strain CS4923 (barA::kan) was kindly provided by Dr. G. Moolenaar. Both barA and uvrY mutants were reintroduced into MC4100 using P1-vir lysates to create AKP014 and AKP023, respectively, and confirmed genotypically by Southern blotting and PCR. Strain CS4923 (barA::kan) was kindly provided by M. Prahalad and C. T. Walsh (Harvard Medical School), was prepared as described (18).

**Purification of His6-tagged Proteins**—*E. coli* M15 cells co-transformed with pREP4 and the appropriate pQE30 derivative were grown in 1 liter of medium (16 g of tryptone, 10 g of yeast extract, and 5 g of NaCl/liter) supplemented with 100 μg ampicillin/ml and 25 μg kanamycin/ml. Expression of the His6-tagged proteins was induced at mid-exponential phase (A\(_{600}\) 0.5–0.6) by the addition of 2 μl isopropyl-β-D-thiogalactopyranoside. Cultures were harvested after 5 h of induction. Protein purification was performed at 4 °C under non-denaturing conditions, as described in protocol 5 for native purification of cytoplasmic proteins in the QIAexpressionist manual (Qiagen). Purification was based on affinity chromatography using the chelate absorbent Ni-NTA-nitrilotriacetic acid resin that interacts with the 6xHis tag. The proteins were eluted by imidazole, which was subsequently removed by dialysis (16). Following dialysis, the proteins were concentrated in Centricon 10 units (Amicon) and stored at −20 °C. The Coomassie Blue protein assay reagent (Pierce) was employed to estimate protein concentrations, using bovine serum albumin as a standard. SDS-PAGE of the purified proteins revealed that each had the expected molecular weight and that the preparations were essentially homogeneous (data not shown). PhoB, a kind gift of M. Prahalad and C. T. Walsh (Harvard Medical School), was prepared as described (18).

**Phosphorylation and Transphosphorylation Assays**—Unless otherwise specified, phosphorylation assays were carried out at room temperature in the presence of 40 μM [γ-32P]ATP (specific activity 2 Ci/mmol, PerkinElmer Life Sciences), 33 mM HEPES (pH 7.5), 50 mM KCl, 5 mM MgCl\(_2\), 1 mM dithiothreitol, 0.1 mM EDTA, and 10% glycerol. The reactions were initiated by the addition of [γ-32P]ATP, terminated by the addition of an equal volume of 2X SDS sample buffer, and immediately subjected to SDS-PAGE on 15% gels. In time course experiments, the samples were mixed with the SDS sample buffer and kept on ice until the last portion was taken. The radioactivity of proteins resolved in the gels was determined qualitatively by autoradiography of the dried gels with X-Omat AR (Kodak). A PhosphorImager (Molecular Dynamics) was used for quantitative analyses.

**Hydrogen Peroxide Sensitivity Assays**—The agar diffusion assay was performed by dividing an LB-agar plate into three equal sectors, where \(^{10^6}\) cells of AKP023 (barA:kan), AKP014 (barA::kan), and MC4100 (the isogenic wild type strain) was spread. A filter paper disc impregnated with 0.1 mM H\(_2\)O\(_2\) was placed at the intersection, the plate was incubated overnight at 37 °C, and the zone of growth inhibition was measured.

The quantified survival of cultures exposed to hydrogen peroxide was determined as described previously (13). Briefly, AKP023, AKP014, and MC4100 were grown in LB, and at mid-exponential phase (A\(_{600}\) of 0.2) the three cultures were divided into two equal portions. One of the portions was challenged with 1.0 mM hydrogen peroxide, while the other served as a control. Aliquots of the cultures were removed at 10, 20, 40, and 60 min, diluted appropriately, plated out onto LB-agar.

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\(^1\) The abbreviations used are: PCR, polymerase chain reaction; ORF, open reading frame; PAGE, polyacrylamide gel electrophoresis.
plates, and incubated at 37 °C overnight. The relative survival of the culture was determined by comparing the viability of the treated cultures to that of the untreated ones.

RESULTS

Search for Analogous Two-component Systems—A homology search approach was undertaken to get insight into the Bar two-component system. We initially searched for ORFs that were homologous to the entire amino acid sequence of the BarA sensor kinase in data bases using the BLASTP 2.0.6 program (National Institutes of Health, Bethesda, MD). Proteins exhibiting the highest identity to BarA were the ExpS of *Erwinia carotovora* (58%) and the GacS (LemA) of *Pseudomonas syringae* (37%). ExpA and GacA have been identified by genetic means as the respective cognate regulators for these sensors (19, 20). However, supportive biochemical evidence for these links is lacking. A subsequent search for ORFs homologous to ExpA and GacA identified a group of typical bacterial response regulator proteins with high homology (Fig. 2), including UvrY of *E. coli* (14), SirA of *Salmonella typhimurium* (21), and VarA of *Vibrio cholerae* (22) as well as highly homologous ORFs in the genomes of *Klebsiella pneumoniae*, *Yersinia pestis*, and *Shewanella putrefaciens*. The *E. coli* uvrY gene derives its name from a close linkage to the uvrC gene on a bifunctional transcript (14), a genomic organization shared by all of the above response regulators. The uvrY gene is known to encode a subunit of the UvrABC enzyme, which is involved in DNA repair (23), but mutations in uvrY have no specific effect on this system (15). Nonetheless, UvrY is the only *E. coli* protein that exhibits a considerable homology to ExpA and GacA, suggesting that UvrY may be the cognate response regulator for BarA.

**UvrY Is the Cognate Response Regulator of BarA in E. coli**

**UvrY**

| UvrY (a) | SirA (b) | ExpA (c) | VarA (d) | GacA (e) | ORF (f) | ORF (g) | ORF (h) |
|----------|----------|----------|----------|----------|---------|---------|---------|
| *E. coli* | *S. typhimurium* | *E. carotovora* | *V. cholerae* | *P. aeruginosa* | *K. pneumoniae* | *Y. pestis* | *S. putrefaciens* |
| 100% | 96% | 82% | 75% | 60% | 89% | 82% | 70% |
| *S. typhimurium* | *E. carotovora* | 100% | 83% | 76% | 60% | 89% | 83% |
| *V. cholerae* | *P. aeruginosa* | 100% | 72% | 59% | 78% | 84% | 66% |
| *K. pneumoniae* | *Y. pestis* | 100% | 61% | 72% | 71% | 76% |
| *S. putrefaciens* | *F. uraoga* | 100% | 57% | 56% | 59% |

**Fig. 2. A,** sequence alignment of: *a,* *E. coli* UvrY; *b,* *S. typhimurium* SirA; *c,* *E. carotovora* ExpA; *d,* *V. cholerae* VarA; and *e,* *P. aeruginosa* GacA; regulator proteins and the homologous ORFs of: *f,* *K. pneumoniae* contig 1572 (incomplete sequence); *g,* *Y. pestis* contig 669; and *h,* *S. putrefaciens* contig 5557. The receiver domain, amino acids 1–99, contains the catalytic site (DD) and the site of phosphorylation (D). The helix-turn-helix motif suggested to mediate DNA binding is shown in **bold** at position 169–187. Asterisks indicate conserved residues. B, percentage of identity between the listed regulator proteins.

**RESULTS**

Search for Analogous Two-component Systems—A homology search approach was undertaken to get insight into the Bar two-component system. We initially searched for ORFs that were homologous to the entire amino acid sequence of the BarA sensor kinase in data bases using the BLASTP 2.0.6 program (National Institutes of Health, Bethesda, MD). Proteins exhibiting the highest identity to BarA were the ExpS of *Erwinia carotovora* (58%) and the GacS (LemA) of *Pseudomonas syringae* (37%). ExpA and GacA have been identified by genetic means as the respective cognate regulators for these sensors (19, 20). However, supportive biochemical evidence for these links is lacking. A subsequent search for ORFs homologous to ExpA and GacA identified a group of typical bacterial response regulator proteins with high homology (Fig. 2), including UvrY of *E. coli* (15), SirA of *Salmonella typhimurium* (21), and VarA of *Vibrio cholerae* (22) as well as highly homologous ORFs in the genomes of *Klebsiella pneumoniae*, *Yersinia pestis*, and *Shewanella putrefaciens*. The *E. coli* uvrY gene derives its name from a close linkage to the uvrC gene on a bifunctional transcript (14), a genomic organization shared by all of the above response regulators. The uvrY gene is known to encode a subunit of the UvrABC enzyme, which is involved in DNA repair (23), but mutations in uvrY have no specific effect on this system (15). Nonetheless, UvrY is the only *E. coli* protein that exhibits a considerable homology to ExpA and GacA, suggesting that UvrY may be the cognate response regulator for BarA.

**BarA Autophosphorylation and Transphosphorylation of UvrY**—To test whether UvrY is the cognate response regulator for BarA, we cloned, overexpressed, and purified UvrY and BarA as His6-tagged proteins. For the purposes of this study, and to facilitate the purification of the sensor protein, we used BarA-(199–918), deprived of amino acid residues 1–198 that constitute the transmembrane segments. Previous studies on several sensor kinases showed that removal of the transmembrane segments does not affect the processes of autophosphorylation and the subsequent transphosphorylation of the cognate regulator proteins (24–29). Purified His6-BarA-(199–918) (hereafter referred to as ‘BarA’) was incubated with [γ-32P]ATP, and the time course of the reaction was followed. The protein was rapidly phosphorylated (the phosphorylated...
Subsequently, the level of both UvrY-P and BarA-P rapidly became labeled, whereas BarA-P slowly during the course of the experiment. This result was unexpected, because excess \( \gamma^{-32}\text{P}\)ATP was not separated from the reaction mixture. However, at the end of the reaction, the level of BarA-P declined, an event indicative of autophosphatase activity harbored by many tripartite sensor kinases (8, 30).

The Transphosphorylation of UvrY by BarA Is Specific—The specificity of the UvrY transphosphorylation by BarA was then determined. As expected, UvrY failed to undergo autophosphorylation with \( \gamma^{-32}\text{P}\)ATP as the phosphoryl group donor (Fig. 5A). However, in the presence of BarA and \( \gamma^{-32}\text{P}\)ATP, UvrY became clearly labeled, indicating that its transphosphorylation is catalyzed by BarA. The possibility of BarA acting as a phosphoryl group donor for non-cognate response regulators, a concept documented as cross-talk (31), was then tested. Equimolar amounts of purified ArcA, PhoB, and CpxR were each incubated with BarA in the presence of \( \gamma^{-32}\text{P}\)ATP. BarA was heavily labeled but failed to transphosphorylate any of the tested non-cognate response regulators (Fig. 5A).

Finally, we tested if UvrY was able to accept the phosphoryl group from ArcB, the tripartite sensor kinase of the Arc two-component system of E. coli. As shown in Fig. 5B, ArcB was an efficient kinase for its cognate response regulator, ArcA, but failed to transphosphorylate UvrY at a detectable level. It should also be noted that, even though ArcB failed to transphosphorylate UvrY, a reduction in ArcB-P was observed. Thus, it seems reasonable to conclude that BarA specifically transphosphorylates UvrY and that the two proteins constitute a new two-component system.

Inactivation of Either BarA or UvrY Leads to Hydrogen Peroxide Hypersensitivity—It has previously been reported that mutations in the barA gene lead to poor growth in iron-limiting media (12) and to hypersensitivity when challenged with exogenous hydrogen peroxide (13). Based on our biochemical data, we predicted that a uvrY mutant strain would exhibit similar phenotypes as the barA mutant.

The iron limitation effect on the growth of a uvrY and a barA mutant strain was tested first. AKP023 (uvrY::cm), AKP014 (barA::kan), and MC4100 (wild type) were cultured in either minimal media or LB supplemented with either the iron chelators desferrioxamine or a,a’-dipyridyl at 0.2 mM, and the bacterial growth rate was monitored. Neither AKP023 nor the AKP014 mutant strain showed any significant growth defect as compared with the wild type strain (data not shown).

The hydrogen peroxide sensitivity was next assayed by the agar diffusion method. An LB-agar plate was divided into three equal sectors, where \( 10^8 \) cells of each strain (AKP023, AKP014, and MC4100) were spread. A filter paper disc impregnated with 0.1 mM \( \text{H}_2\text{O}_2 \) was placed at the intersection, and the plate was incubated overnight at 37 °C. As seen in Fig. 6A, the uvrY and the barA mutant strains were more sensitive to hydrogen peroxide than the wild type strain. The radius of the zone of growth inhibition of AKP023 and AKP014, respectively, was 1.9 and 1.6 times larger than that of the wild type strain (Fig. 6A). The hydrogen peroxide sensitivity of the barA and
was divided into three equal sectors, where peroxide hypersensitivity. A filter paper disc impregnated with 0.1 mM H₂O₂ was placed at the type), AKP014, and MC4100 were cultured in LB, and at mid-exponential growth (A₆₀₀ = 0.2) the three cultures were challenged with 1 mM H₂O₂, as described under “Experimental Procedures.” Fig. 6B shows that both uvrY and barA mutant strains were much more sensitive to hydrogen peroxide than the wild type strain (Fig. 6B). It is worth noting that the uvrY mutant showed a more severe survival defect than the barA mutant strain, in accordance with the agar diffusion assay. Thus, both the BarA and the UvrY gene products are needed for full protection against hydrogen peroxide-mediated stress, consistent with the conclusion that the two proteins belong to the same two-component system.

**DISCUSSION**

The experiments presented in this study identify the UvrY protein as the cognate response regulator for the BarA sensor kinase in *E. coli*, based on the following biochemical findings. First, purified BarA protein autophosphorylates when incubated with [γ-32P]ATP but not with [α-32P]ATP or [γ-32P]GTP, and BarA-P acts as a phosphoryl group donor to UvrY. Second, UvrY can receive the phosphoryl group from BarA-P but not from the non-cognate sensor ArcB-P or ATP. Third, BarA catalyzes the phosphorylation of UvrY but not the phosphorylation of the non-cognate response regulators ArcA, PhoB, or CpxR. The ability to demonstrate phosphotransfer with purified components also suggests that there are no intermediate proteins involved in the signal transduction. Genetic evidence that BarA and UvrY mediate the same signal transduction pathway is provided by the finding that both the uvrY and the barA mutant strains exhibit a hydrogen peroxide hypersensitive phenotype.

These results have a bearing on a whole family of analogous two-component systems, including the ExpS/ExpA of *E. carotovora* and the GacS/GacA of *Pseudomonas* sp. (Table I), as the links between the sensor and regulator components in these cases have only been defined genetically. Other members of this group of highly conserved proteins are the response regulators SirA of *S. typhimurium* and VarA of *V. cholerae* (Fig. 2). All response regulators of this family share not only considerable sequence homology (Fig. 2) but also genomic organization; first, the regulator genes are not linked with the sensor gene on the chromosome, and second, the regulator genes are directly followed by the uvrC ORF on a bicistronic transcript such that the two ORFs overlap for a short stretch. UvrC encodes a subunit of the UvrABC enzyme complex, which is involved in DNA repair (23). However, mutations in expA and uvrY have no specific effect on UV-induced DNA repair (15, 19). Nonetheless, most of those regulators, with the exception of UvrY the function of which has not yet been discovered, are known to be involved in the virulent life style of the respective bacteria (Table I). ExpA and GacA of *E. carotovora* and *Pseudomonas* sp., respectively, are key regulators for secreted proteases, toxins, and other extracellular compounds that are required for the pathogenic nature of these bacteria. The relationship between the regulators is also underlined by the fact that an expA mutation in *E. carotovora* can be complemented with the *E. coli* uvrY gene (19). Interestingly, it was recently reported that GacA regulates some of the genes under its control at the translational level; this was demonstrated by drastic changes in GacA-dependent expression upon changes of the ribosomal binding site of these mRNAs (32). The involvement of GacA in the process of translation, however, is most likely to be exerted indirectly by controlling the expression of a transcriptional regulator. The varA gene product of *V. cholerae* regulates transcription of the major subunit of the toxin-coregulated pilus and the production of cholera toxin. Mutations in varA lead to a lack of autoagglutination and a decreased virulence in an infant mouse model (22). The SirA gene product of *S. typhimurium*, which shows a 96% identity to UvrY of *E. coli*, regulates the expression of hiiA, which in turn controls virulence
genes on pathogenicity islands (Table I). It is noteworthy that a \textit{S. typhimurium} \textit{SirA} mutant has been shown to be avirulent in a bovine intestinal infection model (33). The recently released \textit{Salmonella} genome sequence revealed a close homologue to the \textit{E. coli} \textit{barA} gene. Intriguingly, a recent report also demonstrated that a mutation in the \textit{barA} homologue of \textit{Salmonella} decreases expression of the \textit{hilA}-controlled \textit{invF-lacZ} and \textit{prgH-lacZ} fusions, thus supporting a conclusion that \textit{Salmonella} \textit{BarA} and \textit{SirA} proteins are involved in the same signal transduction pathway (34).

No phenotype has, so far, been associated with the \textit{E. coli} UvrY protein, whereas \textit{BarA} has recently been reported to protect \textit{E. coli} against hydrogen peroxide-mediated stress. In this work (13), it was shown that \textit{BarA} is involved in the induction of the sigma factor RpoS, which, in turn, activates expression of both \textit{HPI} and \textit{HPII} (Ref. 35 and references therein). Our present finding that inactivation of the \textit{uvrY} gene results in the same hydrogen peroxide hypersensitive phenotype (Fig. 6) provides genetic evidence for a functional link between the \textit{BarA} and \textit{UvrY} proteins. Together with the phylogenetic and biochemical data presented, we can also conclude that the two proteins constitute a two-component system.

\textit{BarA} has also been suggested to be important for the acquisition of iron via siderophores in the uropathogenic \textit{E. coli} strain DS17 (12). However, our results demonstrate that a \textit{barA} mutant of \textit{E. coli} strain MC4100 grew equally well as the wild type strain in iron-limiting media, suggesting that the previously demonstrated growth defect of a \textit{barA} mutant of \textit{E. coli} strain DS17 (12) is strain-specific. It is noteworthy that GacA, the response regulator of the homologue two-component system of \textit{Pseudomonas} \textit{sp.}, positively regulates the formation of siderophores in the phytopathogens \textit{Pseudomonas viridiflava} (36) and \textit{Pseudomonas marginalis} (36).

Physical attachment of bacteria to host cells via P-pili has been suggested to induce expression of \textit{BarA} (12), but as not all \textit{E. coli} strains express pyelonephritis-pili, other stimuli are also likely to act on \textit{BarA}. The fact that genes involved in invasion and type III secretion in \textit{S. typhimurium} are under the control of the \textit{SirA} response regulator (33) agrees well with a model in which a cognate sensor is stimulated by contact with the host cell. Although, several attempts to identify the environmental signals that activate the GacA-GacC and ExpS-ExpA two-component were without success (37), it seems reasonable to presume that similar contact-dependent stimulation of the sensor kinase may apply generally to all kinases of this family. Studies directed toward identifying specific genes under the control of the \textit{BarA}/UvrY two-component system in different \textit{E. coli}

\textbf{TABLE I}
\begin{tabular}{|l|l|l|}
\hline
Organism & Sensor/Regulator & Genes or phenotypes regulated \\
\hline
\textit{Escherichia coli} & \textit{BarA}/UvrY & Inactivation of either \textit{BarA} (13) or UvrY leads to hydrogen peroxide hypersensitivity (this study). \\
\textit{Salmonella typhimurium} & \textit{BarA}/\textit{SirA} & H\textit{ilA} expression from SPI 1 (21). H\textit{ilA}, in turn, directly or indirectly, regulates genes on the pathogenicity islands: SPI1 (21, 33), SPI4 and SPI5 (33); a \textit{SirA} mutant exhibits reduced virulence in a bovine gastroenteritis model (35). \\
\textit{Erwinia carotovora} & ExpS/ExpA & Genes encoding cellulase (19, 38), pectate lyase, and polygalacturonase (38); an \textit{ExpA} mutant exhibits reduced virulence in phytopathogenicity models (19). \\
\textit{Vibrio cholerae} & unknown/VarA & Genes encoding cholera toxin and TcpA (22); a \textit{VarA} mutant exhibits reduced virulence in infant mouse model (22). \\
\textit{Pseudomonas} & GacS/GacA & Genes encoding or involved in the production of: tryptophan side chain oxidase (39); 2,4-diacyctylephloroglucinol (40); hydrogen cyanide (40, 41); extracellular protease (42–44); phospholipase C (42); sigma factor \textit{\sigma} (45); homoserine lactone (36, 41, 46); pyocyanin (41); pyoluteorin (40, 41); swimming (46); fluorescent siderophores; alginate and pectate lyase (47); phenazine, fluorescent pyoverdin, and levan (36). Mutants in gacA exhibit reduced virulence in phytopathogenicity models. \\
\hline
\end{tabular}

\textsuperscript{a} See “Discussion.” The studies with \textit{Pseudomonas} involve the following strains: \textit{P. fluorescens}, \textit{P. aeruginosa}, \textit{P. syringae}, \textit{P. viridiflava}, \textit{P. aureofaciens}.
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