Defining the *Pseudomonas aeruginosa* SOS Response and Its Role in the Global Response to the Antibiotic Ciprofloxacin

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Pseudomonas aeruginosa infections can be virtually impossible to eradicate, and the evolution of resistance during antibiotic therapy is a significant concern. In this study, we use DNA microarrays to characterize the global transcriptional response of *P. aeruginosa* to clinical-like doses of the antibiotic ciprofloxacin and also to determine the component that is regulated by LexA cleavage and the SOS response. We find that genes involved in virtually every facet of metabolism are down-regulated in response to ciprofloxacin. The LexA-controlled SOS regulon identified by microarray analysis includes only 15 genes but does include several genes that encode proteins involved in recombination and replication, including two inducible polymerases known to play a role in mutation and the evolution of antibiotic resistance in other organisms. The data suggest that the inhibition of LexA cleavage during therapy might help combat this pathogen by decreasing its ability to adapt and evolve resistance.

Pseudomonas aeruginosa is a common opportunistic human pathogen which is particularly infamous for the high rates of illness and death it causes in patients with cystic fibrosis (18). Once established, *P. aeruginosa* infections can be controlled with some antibiotics, for example, the fluoroquinolones, but are virtually impossible to eradicate, at least in part due to the pathogen's ability to progress through a series of physiological changes that facilitate infection and persistence (18). Its ability to adapt to environmental stress, such as antibiotic therapy, may be related to the large size of its genome (6.3 Mb) and the large number of genes that encode transcriptional regulators.

One of the most important transcriptional responses to environmental stress in bacteria is the SOS response. In *Escherichia coli* (9) and *Bacillus subtilis* (2), it involves the controlled derepression of 43 and 33 genes, respectively, whose protein products facilitate the repair and/or tolerance of DNA damage. Transcription of these genes is induced by the single-stranded DNA (ssDNA) that results from stalled replication forks or direct damage to DNA (15). RecA forms filaments on the ssDNA that mediate recombinational repair and also bind and induce autocleavage of the SOS gene repressor, LexA, resulting in the transcription of the repressed genes. Interestingly, ciprofloxacin, the prototypical fluoroquinolone and an important antibiotic for treating *P. aeruginosa* infections, induces LexA cleavage and the SOS response in *E. coli* (11, 33).

In this study, we determined the global and SOS-mediated transcriptional response of *P. aeruginosa* PAO1 to clinical-like levels of ciprofloxacin. Experiments and controls were repeated in triplicate, which allowed us to identify changes in transcription with a confidence level of $P \le 0.001$. The data reveal a complex and coordinated LexA-independent response to ciprofloxacin that involves the down-regulation of metabo-

lism, motility, and permeability. The LexA-mediated response is limited to the induction of 15 genes that appear to provide specialized DNA recombination and replication functions.

In addition to furthering our understanding of how the transcriptional response of P. aeruginosa contributes to its pathogenicity, we are interested in understanding the potential utility of LexA autoproteolysis inhibitors. For many bacteria, LexA is known to repress genes that regulate processes such as phage mobilization (17, 21, 34), resistance element transfer (3), toxin production (17, 21, 34, 38), mutation (14, 15, 26, 32), and the evolution of resistance (7, 8). For example, we recently demonstrated both in vivo and in vitro that the acquisition of the chromosomal mutations required for the evolution of ciprofloxacin resistance in E. coli requires the autoproteolysis activity of LexA and the subsequent induction of the error-prone SOS polymerases in both wild-type (7) and hypermutator strains (8). Thus, suitably designed inhibitors of LexA could be administered with different antibiotics to prevent the emergence of resistance. Identification of the SOS regulon in P. aeruginosa is expected to help define the broader utility of such drugs.

MATERIALS AND METHODS

Bacterial strains and growth. *P. aeruginosa* PAO1 was obtained from G. Sundin. Unless specified, solid medium was Lennox LB (28) plus 1.6% agar (LBA); liquid medium was Miller LB (28) (LB). For selection, antibiotics were used for *E. coli* and *P. aeruginosa* PAO1, respectively, as follows: streptomycin (Sm), 30 µg/ml and 250 µg/ml; gentamicin (Gm), 15 µg/ml and 50 µg/ml. Ciprofloxacin was obtained from MP Biomedicals (Aurora, Ohio) and used at the concentrations indicated below. All bacteria were grown aerobically at 37° C.

Strain construction. Primer sequences were designed based on the *P. aeruginosa* genome database (http://v2.pseudomonas.com) (35, 39). A *lexA* allelic exchange cassette was assembled containing ~800 bp of homology surrounding *lexA*, the *lexA* open reading frame, and the Gm^r marker from vector pBBR1MCS-5 (22) using assembly PCR and the primers listed in Table S1 at the website http://www.scripps.edu/chem/romesberg/. The resulting cassette was cloned into vector pKNG101 (20) to create pRTC0021; the S125A mutation was then introduced using primers PA_lexA_S125A_QCF and PA_lexA_S125A_QCR and the QuikChange site-directed mutagenesis kit (Stratagene) to create vector pRTC0022.

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pRTC0022 was transformed into *E. coli* strain SY-17 and introduced into *P. aeruginosa* by conjugative transfer with selection on M9 plus 0.2% citrate and Gm to select clones that integrated the allelic exchange cassette into the chromosome by either a single- or double-crossover event. Replica plating onto M9 plus 0.2% citrate containing either Gm or Sm identified clones containing the allelic exchange cassette and lacking the vector sequences due to a double-crossover event. Colonies were verified as Gm^r and Sm^s, and the mutation was confirmed by sequencing.

Confirmation that the LexA(S125A) mutant is not cleaved in response to ciprofloxacin. For each strain, five clones were grown in LB for 18 h. Cultures were diluted 1:500 and grown to mid-log phase (optical density at 60 nm [OD₆₀₀], \sim 0.4 to 0.5), and then ciprofloxacin was added to a final concentration of 1 µg/ml. At 0, 30, and 120 min following ciprofloxacin addition, cell aliquots were removed and stored at -20°C. During the experiment, the OD₆₀₀ and viable CFU per ml were monitored for each of the cultures (see Fig. 1A and B, below). This protocol is identical to that used to prepare samples for the transcriptional studies (below). Whole-cell lysates were prepared by sonication in phosphatebuffered saline, and the soluble fraction was collected and normalized for total protein concentration (Bio-Rad protein assay). Samples were separated on a 15% sodium dodecyl sulfate-polyacrylamide gel electrophoresis gel and transferred to a 0.2-µm nitrocellulose membrane. Immunostaining was performed with a rabbit polyclonal antiserum to LexA (1:8,000; 2 h; kindly provided by J. Little) and horseradish peroxidase-linked anti-rabbit antibody (1:20,000; 1 h; Upstate Biotechnology), followed by detection with ECL Plus (GE Biosciences).

Growth rate measurement. For each strain, three cultures were inoculated into 2 ml tryptic soy broth (Difco) and grown for 16 h with shaking, followed by continued growth after a 100-fold dilution in tryptic soy broth. At the indicated time points, the OD_{600} was measured and the number of viable CFU per ml was determined by dilution plating.

Sensitivity to UV light and MMS. Three independent cultures of each strain were grown overnight in LB. Appropriate dilutions were plated onto LBA, and UVC irradiations were performed using a G8T5 germicidal tube (Ushio America, Cypress, CA). UV fluences were determined using a UVX radiometer with a UVX-25 sensor (UV Products). After irradiation, plates were protected from light and incubated for 2 days before colonies were counted. To determine the methyl methanesulfonate (MMS; Aldrich) sensitivity, three independent cultures were grown overnight in LB. Appropriate dilutions were plated onto LBA containing MMS at the indicated concentrations and incubated for 2 days before colonies were counted.

MIC determination. For each strain, three independent cultures were grown for 25 h in LB containing no antibiotic. From each culture, $\sim 10^5$ CFU were used to inoculate LB containing increasing concentrations of ciprofloxacin in 96-well plates. Inoculations were done in duplicate to yield a total of six data points per strain. After 18 h of incubation, growth was measured by reading the OD₆₅₀ in a $V_{\rm max}$ Kinetic microplate reader (Molecular Devices, California). The MIC was defined as the lowest concentration of ciprofloxacin that prevented any detectable growth.

Transcriptional analysis. *P. aeruginosa* genome arrays containing 25-mer probe sets for over 5,500 open reading frames from PAO1, 199 probe sets corresponding to 100 intergenic regions, and 117 probe sets from other *P. aeruginosa* strains were obtained from Affymetrix (Santa Clara, CA). A complete description and annotation for this *P. aeruginosa* genome array is available at http://www.affymetrix.com.

Sample preparation and data analysis. For each strain, five clones were inoculated in LB and grown for 18 h. Cultures were diluted 1:500 and grown to mid-log phase (OD_{600} , ~0.4 to 0.5), at which point ciprofloxacin was added to a final concentration of 1 µg/ml. At 0, 30, and 120 min following ciprofloxacin addition, appropriate volumes from each of the five cultures per strain were pooled and added to 2 volumes of RNAprotect reagent (QIA-GEN); cell pellets were stored at 4°C until RNA extraction. Total RNA was extracted using the RNeasy Mini kit (QIAGEN) at the end of the sample collection period. This procedure was repeated three independent times to generate three samples each just prior to and 120 min post-ciprofloxacin addition. Details of data analysis and reverse transcription-PCR validation have been provided along with our supplementary data sets via the internet (http://www.scripps.edu/chem/romesberg/).

Microarray accession numbers. Microarray data have been deposited at the National Center for Biotechnology Information's Gene Expression Omnibus database (http://www.ncbi.nlm.nih.gov/geo/) under the accession number GSE5443.



FIG. 1. Population kinetics of *P. aeruginosa* strains during microarray and whole-cell lysate sample preparation monitored by OD (A) and CFU/ml (B). Filled and open triangles represent PAO1 and the LexA(S125A) mutant, respectively. Time zero is defined as the point immediately following ciprofloxacin addition. As described in the text, samples for total RNA extraction and whole-cell lysates were collected at 0, 30, and 120 min post-ciprofloxacin addition. (C) Analysis of total full-length LexA measured by Western blotting with anti-LexA antibody.

RESULTS

General characterization of the *P. aeruginosa* SOS response. We constructed a *lexA*(S125A) mutant of *P. aeruginosa* PAO1, where the catalytic serine of LexA has been replaced with alanine. We monitored the levels of full-length LexA in response to added ciprofloxacin (1 μ g/ml ciprofloxacin) and showed that while the wild-type protein underwent cleavage, the mutant protein remained intact (Fig. 1).

No significant growth attenuation was observed with the *lexA*(S125A) strain relative to its isogenic parental strain (log phase doubling times of 45.0 ± 3.5 and 45.5 ± 4.5 min were observed for the LexA mutant and PAO1 strains, respectively [means \pm standard deviations]), as was previously observed with analogous mutants of *E. coli* (15). Relative to the wild-type strain, we found that the *lexA*(S125A) mutant was hypersensitive to UV irradiation (Fig. 2A) but not to MMS (Fig. 2B) or ciprofloxacin [the ciprofloxacin MIC for both wild-type PAO1 and the *lexA*(S125A) strain was 0.125 µg/ml]. This suggests that the *P. aeruginosa* SOS response is important for repairing DNA damage associated with UV irradiation but not with MMS or ciprofloxacin.



FIG. 2. Killing kinetics of *P. aeruginosa* strains, as shown by survival following UV (A) or MMS (B) treatment. PAO1 and the LexA (S125A) mutant are represented by filled and open triangles, respectively.

Characterization of the *P. aeruginosa* transcriptional response to ciprofloxacin. Using DNA microarrays, we transcriptionally profiled mid-log-phase PAO1 at 30 and 120 min after exposure to suprainhibitory concentrations of ciprofloxacin (1 μ g/ml; 8× MIC) (Fig. 1A and B). Only the magnitude of the observed changes was different, and so we focused the analysis on the 120-min data set. We observed that the levels of 196 transcripts increase at least twofold and the levels of 408 transcripts decrease at least twofold relative to levels immediately before the addition of the drug (Table 1; see also our supporting information at http://www.scripps.edu/chem/romesberg/).

Sixty-four of the genes that are up-regulated in response to ciprofloxacin are in regulons that are likely controlled by LexA-like repressors (Table 2). For example, the autoregulated LexA-like Ser-Lys dyad repressor PtrR (25) is up-regulated by 5-fold, and seven genes thought to be directly or indirectly under its control are up-regulated by up to 100-fold. One of these genes, *ptrB*, acts to repress the type III secretion system (40). Thus, via induced cleavage of PtrR, exposure to ciprofloxacin results in a down-regulation of the type III secretion system. In addition, 35 nearby cryptic prophage genes spanning from PA0614 to PA0648 are strongly up-regulated. Another putative phage repressor that shares similarities with LexA and is highly homologous to PtrR is PA0906. PA0906 is divergently transcribed from a putative operon that spans PA0907 to PA0911. PA0906 and the five genes of this operon are up-regulated 20- to 80-fold after exposure to the drug. Overall, the data suggest that at least one-third of the positive transcriptional response to ciprofloxacin is controlled by LexAlike repressors.

The number of genes that are down-regulated in response to

ciprofloxacin is more than twice the number that are up-regulated. The down-regulated response appears to involve virtually every facet of cellular metabolism, including general metabolism, cell wall/capsule biosynthesis, DNA replication/ repair, cell division, motility, and quorum sensing (Table 1; see also our supporting information at http://www.scripps.edu/chem /romesberg/). Changes observed were similar for all genes in a given operon, supporting the physiological significance of their regulation.

We observed significant and consistent changes in the operons encoding the subunits of ATP synthase (PA5553 to PA5561), which all decrease between 4- and 13-fold, and the subunits of NADH dehydrogenase complex I (PA2637 to PA2649), which all decrease between 2- and 5-fold. Similar decreases were observed in the response to acute H_2O_2 damage (30). In addition, while *nrdA* and *nrdB*, which encode the ribonucleotide reductase complex, are both up-regulated in response to ciprofloxacin four- to eightfold, two genes in a separate operon (PA5496 and PA5497) that are predicted to encode an alternate ribonucleotide reductase are down-regulated three- to fourfold. In addition, genes encoding many other proteins involved in metabolism were down-regulated after exposure to the drug (Table 1; see also our supporting information at the website http://www.scripps.edu/chem/romesberg/).

In addition to the decreased transcription of genes involved in general metabolism, decreases are also observed with genes involved in DNA metabolism. An operon containing genes that encode components of the replication machinery, including dnaA, dnaN, recF, and gyrB, is down-regulated ~4-fold in response to ciprofloxacin. In addition, genes encoding DNA polymerase I, the HolB subunit of DNA polymerase III, and the DNA binding protein HU are all down-regulated two- to fivefold. The recG and ruvABC genes, all encoding proteins thought to be important for repairing ciprofloxacin-induced damage (7, 11), are down-regulated, albeit less than twofold. In contrast, recA, recX, and recN are up-regulated 7- to 17-fold. Interestingly, the three genes encoding damage-inducible DNA polymerases, PA0923, PA0670, and PA0669, are upregulated in response to ciprofloxacin. PA0923 encodes a dinBlike Y-family polymerase and is up-regulated fourfold in response to ciprofloxacin. PA0670 and PA0669 encode two polymerases recently shown to be involved in damage-induced mutagenesis in Caulobacter crescentus (16) and are up-regulated two- and sixfold, respectively. The overall pattern of expression in the DNA replication genes suggests a shift from the canonical DNA replication enzymes to the inducible polymerases in response to ciprofloxacin.

Nearly all of the major cell division and lipopolysaccharide genes are significantly down-regulated. Of particular note are the changes observed in the *wbp* region, which encodes the B-band lipopolysaccharide O antigen and spans from PA3141 to PA3160. Transcription of these genes decreased by two- to sixfold after exposure to ciprofloxacin. Another interesting trend is the down-regulation of 41 genes that encode proteins involved in motility. We also observe a two- to fourfold increase in transcription of two major efflux proteins (MexC and MexR) and a four- to fivefold decrease in transcription of three major membrane pore proteins (OprD, OprG, and OprI). These changes in mobility and permeability are consistent with

7104 CIRZ ET AL.

ORF function,	Corro	A	Fol	Fold change ^a	
regulation, and name	Gene	Annotation	PAO1	LexA(S125A)	
General metabolism					
Downregulated	_				
PA5553	atpC	ATP synthase ε chain	-6.9	-6.4	
PA5554	atpD	ATP synthase β chain	-12.7	-12.7	
PA5555	atpG	ATP synthase γ chain	-10.8	-12.5	
PA5556	atpA	ATP synthase α chain	-10.0	-10.1	
PA5557	atpH	ATP synthase δ chain	-7.5	-9.4	
PA5558	atpF	ATP synthase B chain	-8.5	-7.7	
PA5559	atpE	ATP synthase C chain	-7.3	-8.4	
PA5560	atpB	ATP synthase A chain	-8.2	-7.5	
PA5561	atpl	ATP synthase protein I	-4.3	-4.3	
PA2637	nuoA	NADH dehydrogenase I chain A	-2.5	-2.8	
PA2638	nuoB	NADH dehydrogenase I chain B	-3.4	-4.1	
PA2639	nuoD	NADH dehydrogenase I chain C, D	-2.4	-2.3	
PA2640	nuoE	NADH dehydrogenase I chain E	-2.9	-2.6	
PA2641	nuoF	NADH dehydrogenase I chain F	-2.9	-3.0	
PA2642	nuoG	NADH dehydrogenase I chain G	-2.9	-3.6	
PA2643	nuoH	NADH dehydrogenase I chain H	-3.2	-3.1	
PA2644	nuoI	NADH dehydrogenase I chain I	-3.0	-3.1	
PA2645	пиоЈ	NADH dehydrogenase I chain J	-5.0	-5.7	
PA2646	nuoK	NADH dehydrogenase I chain K	-4.6	-4.3	
PA2647	nuoL	NADH dehydrogenase I chain L	-5.0	-5.4	
PA2648	nuoM	NADH dehydrogenase I chain M	-4.0	-4.9	
PA2649	nuoN	NADH dehydrogenase I chain N	-4.7	-4.9	
DNA metabolism					
Downregulated					
PA5345	recG	Recombination/repair	-1.8	-2.4	
PA0966	ruvA	Branch migration	-1.7	-1.7	
PA0967	ruvB	Branch migration	-1.6	-1.5	
PA0965	ruvC	Holliday junction resolvase	-1.6	-1.3	
PA1804	hupB	DNA binding protein HU	-4.7	-5.4	
PA0004	gyrB	Gyrase subunit B	-3.4	-3.6	
PA0003	recF	Recombination	-4.0	-3.8	
PA0001	dnaA	Replication initiation factor	-3.3	-2.9	
PA0002	dnaN	Beta clamp	-3.9	-4.2	
PA2961	holB	DNA polymerase III δ' subunit	-2.9	-2.0	
PA5493	polA	DNA polymerase I	-1.6	-1.4	
Upregulated					
PA0923	dinB	Y-family polymerase	3.7	2.1	
PA0669	dnaE2	Damage-inducible polymerase	1.9	1.3	
PA0670	imuB	Damage-inducible polymerase	6.3	1.1	
PA3616	recX	RecA regulation	7.1	1.1	
PA3617	recA	Recombination/repair	7.4	1.0	
PA4763	recN	Recombination/repair	17.2	1.0	
Nucleotide metabolism					
Downregulated					
PA5496		Predicted ribonucleotide reductase	-4.1	-3.4	
PA5497		Predicted ribonucleotide reductase	-2.6	-2.7	
Upregulated					
PA1155	nrdB	Ribonucleotide reductase small chain	3.8	3.7	
PA1156	nrdA	Ribonucleotide reductase large chain	7.9	7.7	
Cell division					
Downregulated					
PA4407	ftsZ	Cell division protein FtsZ	-2.7	-2.3	
PA4408	ftsA	Cell division protein FtsA	-2.9	-2.7	
PA4409	ftsO	Cell division protein FtsO	-3.1	-2.7	
PA4413	ftsW	Cell division protein FtsW	-2.4	-1.9	
	J-~ / /	F			
Upregulated	<u> </u>				
PA0373	ftsY	Signal recognition particle receptor	1.5	1.4	

TABLE 1. TI	ranscriptional	response	to	1 μg/ml	ciprofloxacin
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Continued on following page

TABLE 1-Continued

Test information Center Automotic PAOI LearAS125A LTS biogrammed in the provided sugar epimerase/delydratase -2.2 -2.1 -2.3 -2.3 -2.8 -2.9 -2.8 -2.9 -2.8 -2.9 -2.8	ORF function,	0	A	Fold change ^a	
LIN biospathesisDevence patientDevence patientPA3141whpMKuckoride sugar epimerase/dehydratase -2.2 PA3145whpMGlycosyltransferase -3.8 PA3146whpMProbable NAD-dependent epimerase/dehydratase -3.8 PA3147whpMProbable Sylcosyltransferase -3.8 PA3148whpMProbable Sylcosyltransferase -3.4 PA3149whpMProbable Sylcosyltransferase -5.4 PA3149whpMProbable CuDPA-acetylgitocoanine 2-epimerase -3.4 PA3153wfmOnanigen transferase -4.3 PA3155wfpMProbable acetyltransferase -2.7 PA3155wfpMProbable acetyltransferase -2.7 PA3158whpMProbable cotyltransferase -2.7 PA3160wczO-antigen chain length regulator -2.5 PA3161wczO-antigen chain length regulator -2.2 DownregulatedProbable cutorecitoperion -1.8 PA3160wczO-antigen chain length regulator -2.2 Downregulated -2.2 -1.7 PA3155fimUType 4 finbrial biogenesis protein FimU -2.6 PA3161fildHypothetical protein -3.7 PA3152fildHypothetical protein -3.7 PA3153fildHypothetical protein -3.7 PA3164fildThrietinbiogenesis -7.7 PA3155fildHypothetical protein -1.7 PA3167fild	regulation, and name	Gene	Annotation	PAO1	LexA(S125A)
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	LPS biosynthesis				
PA111workworkworkwork -2.4 -2.1 -2.1 PA1146workGrossing reprint matching epinerase/delydicatase -2.4 -2.5 -2.5 PA1148workworkProbable glycosyl transferase -3.8 -4.2 PA1148workProbable glycosyl transferase -3.8 -4.2 PA1130wbpfProbable glycosyltransferase -5.4 -6.4 PA1151workProbable glycosyltransferase -4.3 -3.2 PA1152workProbable aniotransferase -4.3 -3.2 PA1153workProbable activitransferase -2.3 -2.5 PA1151workProbable activitransferase -2.3 -2.5 PA1151workProbable UDP-glucose(IDP mannose dehydrogenase -2.5 -2.5 PA1151workProbable UDP-glucose(IDP mannose dehydrogenase -2.5 -3.3 PA1152filMHyootheical protein -1.4 -1.7 PA153moltType 4 fimbrial biogenesis protein FimU -2.6 -2.5 PA1151filMHyootheical protein -1.6 -1.7 PA1522filMHyootheical protein -3.0 -3.0 PA1532filMHyootheical protein -2.5 -3.0 PA1525pilZType 4 fimbrial biogenesis -2.6 -3.5 PA153pil/FType 4 fimbrial biogenesis -2.6 -3.5 PA152pil/KMethytransferase -2.2 -2.5 P	Downregulated	1.14		2.2	2.1
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	PA3141 DA 2145	wbpM wbpI	Nucleotide sugar epimerase/denydratase	-2.2	-2.1
PA184uppProbable glocost fransforme -3.8 -3.2 PA1184upplProbable UDPX-acceptigencomine 2-epimerase -3.4 -3.9 PA1319upplProbable glocost fransformes -6.1 -5.2 PA150upplProbable glocost fransformes -6.1 -5.2 PA1513upplProbable aninotransformes -4.3 -3.2 PA153upplProbable accept fransformes -2.3 -2.5 PA153upplProbable accept fransformes -2.3 -2.8 PA153upplProbable accept fransformes -2.3 -2.8 PA150upplProbable accept fransformes -2.3 -2.5 PA150upplProbable accept fransformes -2.5 -2.5 PA160upplType 4 finibrial biogenesis protein Finul -2.6 -2.5 PA150finulType 4 finibrial biogenesis protein Finul -2.6 -2.5 PA1512filMHoothing moting -2.2 -1.3 Downcegalated -2.2 -1.3 -1.7 -1.5 PA152filMHoothing moting -2.6 -1.7 PA152pilMMotility protein -2.6 -2.5 PA151pilMMotility motin -2.6 -1.7 PA152pilMType 4 finibrial biogenesis -1.6 -1.7 PA355pilMType 4 finibrial biogenesis -2.6 -5.9 PA4520finUType 4 finibrial biogenesis -2.6 -2.5	PA3145 PA3146	wbpL wbpK	Probable NAD dependent enimerase/debudratase	-3.8	-2.8
	PA3147	whnI	Probable alveosyl transferase	-3.8	-4.2
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	PA3148	whnI	Probable UDP-N-acetylølucosamine 2-enimerase	-3.4	-3.9
PA150 $w_0^{h}G$ LPS biosynthesis protein-6.1-5.2PA153 wx O-antigen translocase-4.3-3.2PA355 $wbpE$ Probable accipitransferase-4.5-4.1PA156 $wbpE$ Probable accipitransferase-3.3-3.8PA3153 $wbpE$ Probable accipitransferase-3.3-3.9PA3159 $wbpA$ Probable colepitransferase-2.5-3.1PA3160 wzz O-antigen chain length regulator-2.5-3.1Downregulated mU Type 4 finibrial biogenesis protein FimU-2.6-2.5PA3150fm/UType 4 finibrial biogenesis-1.8-1.7PA350fm/UType 4 finibrial biogenesis-3.0-3.0PA4500fm/UTwiching molitip rotein-2.6-2.5PA3111fm/UTwiching molitip rotein-3.0-3.0PA4512p/I/LType 4 finibrial biogenesis-1.6-1.7PA3260p/I/ZType 4 finibrial biogenesis-2.6-2.5PA4525p/I/LType 4 finibrial biogenesis-6.6-5.9PA4525p/I/LType 4 finibrial biogenesis-2.0-2.1PA4525p/I/LType 4 finibrial biogenesis-2.0-2.4PA4525p/I/LType 4 finibrial biogenesis-2.2-2.1PA4525p/I/LType 4 finibrial biogenesis-2.2-2.1PA4525p/I/LType 4 finibrial biogenesis-2.0-2.4PA4525p/I/L <t< td=""><td>PA3149</td><td>wbpH</td><td>Probable glycosyltransferase</td><td>-5.4</td><td>-6.4</td></t<>	PA3149	wbpH	Probable glycosyltransferase	-5.4	-6.4
PA3153 $wcix$ O-antigen translokase -4.3 -3.2 PA3155 $wlpD$ Probable anotythransferase -4.3 -4.3 PA3157Probable accitytransferase -2.7 -3.0 PA3159 $wlpD$ Probable accitytransferase -2.7 -3.0 PA3159 $wlpD$ Probable cotytransferase -2.9 -2.8 PA3159 $wlpD$ Probable UDP-gucose/GDP-mannose dehydrogenase -2.9 -2.8 PA3150 wzz O-antigen chain length regulator -2.5 -3.1 Motility Provergulated -3.7 -3.3 -3.9 PA3151 jmV Motility protein -3.0 -3.0 PA3152 jmV Motility protein -3.0 -3.0 PA4510 mV -1.8 -1.7 -3.0 PA311 $pull$ Twitching motility protein -2.2 -2.1 PA4510 mV -1.8 -1.7 -3.0 PA4521 jmV Motility protein -3.0 -3.0 PA4523 $pulL$ Type 4 finbrial biogensis -1.6 -1.7 PA4525 $pulK$ Methytransferase -2.1 -1.7 PA4526 $pulB$ Type 4 finbrial biogensis -6.4 -5.0 PA4528 $pulD$ Type 4 finbrial biogensis -2.6 -2.5 PA4531 jmU Type 4 finbrial biogensis -2.6 -2.5 PA4532 pU Type 4 finbrial biogensis -2.6 -2.5 PA4533 pU Type 4 finbrial biogensis	PA3150	wbpG	LPS biosynthesis protein	-6.1	-5.2
PA3155whpEProbable actificantsferase-4.5-4.1PA3156whpDProbable actificantsferase-3.3-2.8PA3157Probable colderatificantsferase-3.3-3.9PA3158whpAProbable colderatificantsferase-2.5-3.8PA3160wzzO-antigen chain length regulator-2.5-3.8MotilityDownregulated-2.6-2.5-3.1DownregulatedfmrlType 4 finbrial biogenesis protein FimU-2.6-2.5PA350fmrlMotility protein fmV-3.8-3.1PA352fmrlTwiching molity protein-3.6-3.1PA353pl/HTwiching molity protein-3.6-3.0PA45412pl/KMethytrunsferase-2.1-1.17PA3050pl/ZType 4 finbrial biogenesis proteors-2.7-7.3PA4112pl/KMethytrunsferase-3.1-1.17PA32060pl/ZType 4 finbrial biogenesis proteors-2.7-3.6PA4525pl/BType 4 finbrial biogenesis proteors-2.7-6.4PA4525pl/BType 4 finbrial biogenesis-2.6-2.5PA4525pl/DType 4 finbrial biogenesis-2.0-2.4PA4525pl/DType 4 finbrial biogenesis-2.1-1.7PA4525pl/DType 4 finbrial biogenesis-2.5-2.4PA4551pl/DType 4 finbrial biogenesis-2.6-2.5PA4552pl/DType 4 finbrial biogenesis <td< td=""><td>PA3153</td><td>wzx</td><td>O-antigen translocase</td><td>-4.3</td><td>-3.2</td></td<>	PA3153	wzx	O-antigen translocase	-4.3	-3.2
PA3156whpDProbable accyltransforase-3.3-2.8PA3157Probable accyltransforase-2.7-3.0PA3158whpBProbable CUP-glucose/GDP-mannose dehydrogenase-2.9-2.8PA3160wzzO-antigen chain length regulator-2.5-3.1MotilityDowaregulated-2.6-2.5PA3159thm/pAProbable CUP-glucose/GDP-mannose dehydrogenase-2.6-2.5PA3151fimUType 4 fimbrial biogenesis protein FimU-2.6-2.5PA3151fimVMotility protein FimV-3.7-3.3PA1822filMHypothetical protein-1.8-1.7PA4035ptl/TTvitching motility protein-3.0-3.0PA4111ptlTvitching motility protein-3.0-3.0PA4120ptl/AMtyltransforase-1.1-1.7PA4452ptl/AType 4 finbrial biogenesis-6.8-6.8PA4525ptl/AType 4 finbrial biogenesis-6.8-6.8PA4525ptl/AType 4 finbrial biogenesis-2.2-2.1PA4525ptl/DType 4 finbrial biogenesis-2.2-2.1PA4526ptl/DType 4 finbrial biogenesis-2.6-2.5PA4527ptl/DType 4 finbrial biogenesis-2.2-2.1PA4528ptl/DType 4 finbrial biogenesis-2.2-2.1PA4529ptl/DType 4 finbrial biogenesis-2.6-2.5PA4529ptl/DType 4 finbrial biogenesis<	PA3155	wbpE	Probable aminotransferase	-4.5	-4.1
PA3157Probable acciptransferase -2.7 -3.0 PA3159whpAProbable oxioordeuctuse -3.3 -3.9 PA3150wtpAProbable oxioordeuctuse -2.5 -3.1 PA3150wtpAProbable oxioordeuctuse -2.5 -3.1 MotilityDownregulated -2.6 -2.5 -3.1 PA4500fimUType 4 finbrial biogenesis protein FimU -2.6 -2.5 PA3151fimVMotility protein FimV -3.7 -3.3 PA4520pilTTvitching motility protein -3.0 -3.0 PA4501pilTTvitching motility protein -2.2 -2.1 PA4502pilAMypothetical protein -2.6 -2.5 PA4503pilTTvitching motility protein -3.0 -3.0 PA4504pilZType 4 finbrial biogenesis -1.6 -1.7 PA4525pilAType 4 finbrial biogenesis -6.8 -8.0 PA4525pilAType 4 finbrial biogenesis -2.2 -2.1 PA4525pilDType 4 finbrial biogenesis -2.2 -2.5 PA4528pilDType 4 finbrial biogenesis -2.2 -2.5 PA4531pilVType 4 finbrial biogenesis -2.2 -2.5 PA4531pilVType 4 finbrial biogenesis -2.2 -2.5 PA4531pilVType 4 finbrial biogenesis -2.2 -2.5 PA4541pilVType 4 finbrial biogenesis -2.5 -2.5 PA4551pilV	PA3156	wbpD	Probable acetyltransferase	-3.3	-2.8
PA3158whpBProbable ODP-glucose(GDP-mannose dehydrogenase -3.3 -3.9 PA3150wszO-antigen chain length regulator -2.5 -3.1 MotilityDowrnegulated -2.5 -3.1 PA450fimUType 4 fimbrial biogenesis protein FimU -2.6 -2.5 PA3115fimVMotility protein FinV -3.7 -3.3 PA1822filMHypothetical protein -1.8 -1.7 PA0051pulTTwitching motility protein -2.2 -2.1 PA4152pulKHypothetical protein -1.8 -1.7 PA4525pulKType 4 finbrial biogenesis procursor -1.6 -1.7 PA4525pulKType 4 finbrial biogenesis -6.8 -8.0 PA4525pulKType 4 finbrial biogenesis -6.8 -8.0 PA4525pulKType 4 finbrial biogenesis -2.2 -2.2 PA4525pulKType 4 finbrial biogenesis -2.2 -2.4 PA4525pulKType 4 finbrial biogenesis -2.2 -2.4 PA4525pulKType 4 finbrial biogenesis -2.2 -2.5 PA4526pulKType 4 finbrial biogenesis -2.2 -2.5 PA4528pilVType 4 finbrial biogenesis -2.2 -2.5 PA4551pilVType 4 finbrial biogenesis -2.2 -2.2 PA4552pilKType 4 finbrial biogenesis -2.5 -2.4 PA554pilVType 4 finbrial biogenesis -3.7 -6.1 </td <td>PA3157</td> <td></td> <td>Probable acetyltransferase</td> <td>-2.7</td> <td>-3.0</td>	PA3157		Probable acetyltransferase	-2.7	-3.0
PA3150wbpAProbable UDP-glucose/GDP-mannese dehydrogenase -2.5 -2.5 -3.1 Motility Downregulated-2.5 -3.1 PA3150 ywz O-antigen chain length regulator -2.5 -3.1 PA350 $fimU$ Type 4 fimbrial biogenesis protein FimU -2.6 -2.5 PA3152 $fimV$ Motility protein -1.8 -1.7 PA0305 $pull$ Twitching motility protein -3.0 -3.0 PA0411 $pull$ Twitching motility protein -2.2 -2.1 PA350 $pilT$ Type 4 fimbrial biogenesis -1.6 -1.7 PA352 $pilA$ Methyltransferase -2.1 -1.7 PA4525 $pilA$ Type 4 fimbrial biogenesis -6.8 -8.0 PA4525 $pilA$ Type 4 fimbrial biogenesis -6.8 -8.0 PA4525 $pilA$ Type 4 fimbrial biogenesis -2.0 -2.5 PA4525 $pilA$ Type 4 fimbrial biogenesis -2.2 -2.1 PA4526 $pilB$ Type 4 fimbrial biogenesis -2.2 -2.5 PA4528 $pilD$ Type 4 fimbrial biogenesis -2.2 -2.5 PA4529 $pilD$ Type 4 fimbrial biogenesis -2.2 -2.5 PA4529 $pilD$ Type 4 fimbrial biogenesis -2.6 -2.5 PA4529 $pilD$ Type 4 fimbrial biogenesis -2.6 -2.5 PA4529 $pilD$ Type 4 fimbrial biogenesis -2.6 -2.5 PA4539 $pilD$ Type 4 fimbrial biogenesis	PA3158	wbpB	Probable oxidoreductase	-3.3	-3.9
PA3100wzO-antigen chain length regulator -2.5 -3.1 Motility DownregulatedPA3115fmUType 4 fimbrial biogenesis protein FimU -2.6 -2.5 -2.6 PA3115fmVMotility protein FimV -3.7 -3.3 -3.3 PA1822filMHypothetical protein -1.8 -1.7 PA0395pilTTwitching motility protein -3.0 -3.0 PA04112pilKMethyltransferase -2.1 -1.7 PA3250pilZType 4 fimbrial biogenesis -1.6 -1.7 PA4525pilZType 4 fimbrial biogenesis -6.4 -5.9 PA4527pilCType 4 fimbrial biogenesis -2.2 -2.1 PA4528pilDType 4 fimbrial biogenesis -2.2 -2.2 PA4525pilWType 4 fimbrial biogenesis -2.2 -2.2 PA4525pilWType 4 fimbrial biogenesis -2.2 -2.2 PA4551pilWType 4 fimbrial biogenesis -2.2 -2.2 PA4552pilWType 4 fimbrial biogenesis -2.5 -4.5 PA555pilV2Type 4 fimbrial biogenesis -5.7 -6.1 PA5040pilQType 4 fimbrial biogenesis -3.7 -4.0 PA5051pilWType 4 fimbrial biogenesis -2.5 -2.5 PA5032pilOType 4 fimbrial biogenesis -2.5 -2.5 PA5041pilPType 4 fimbrial biogenesis -2.5 -2.4 PA1100filFFl	PA3159	wbpA	Probable UDP-glucose/GDP-mannose dehydrogenase	-2.9	-2.8
Motility Jowaregulated Dowaregulated intl Type 4 fimbrial biogenesis protein FimU -2.6 -2.5 PA3151 finl/ Motility protein FimV -3.7 -3.3 PA1822 fill/ Hypothetical protein -1.8 -1.7 PA3955 pill Twitching motility protein -2.2 -2.1 PA4011 pill Twitching motility protein -3.0 -3.0 PA4012 pilk Methyltransferase -2.1 -1.7 PA4525 pill Type 4 fimbrial biogenesis -6.4 -5.9 PA4525 pill Type 4 fimbrial biogenesis -2.6 -2.5 PA4525 pill Type 4 fimbrial biogenesis -2.2 -2.1 PA4525 pill Type 4 fimbrial biogenesis -2.2 -2.2 PA4525 pill Type 4 fimbrial biogenesis -2.2 -2.1 PA4551 pill Type 4 fimbrial biogenesis -2.2 -2.1 PA4551 pill Type 4 fimbrial biogenesis -2.2 <	PA3160	WZZ	O-antigen chain length regulator	-2.5	-3.1
Downregulated -2.6 -2.5 PA4550 fimU Type 4 fimbrial biogenesis protein FimU -3.7 -3.3 PA1852 filM Hypothetical protein -1.8 -1.7 PA0395 pilT Twiching motility protein -2.2 -2.1 PA0411 pil Twiching motility protein -3.0 -3.0 PA0420 pilK Methyltransferase -2.1 -1.7 PA3525 pilA Type 4 fimbrial biogenesis -1.6 -1.7 PA4525 pilA Type 4 fimbrial biogenesis -6.8 -8.0 PA4525 pilA Type 4 fimbrial biogenesis -6.4 -5.9 PA4527 pilO Type 4 fimbrial biogenesis -2.6 -2.5 PA4528 pilV Type 4 fimbrial biogenesis -2.6 -2.5 PA4531 pilV Type 4 fimbrial biogenesis -2.6 -2.5 PA4551 pilV Type 4 fimbrial biogenesis -2.7 -6.1 PA4552 pilV Type 4 fimbrial biogenesis -2.2 <td>Motility</td> <td></td> <td></td> <td></td> <td></td>	Motility				
PA350 fmV Vipe 4 mibrial biogenesis protein Finu -2.6 -2.5 -2.5 PA3115 film Hybridity protein -1.8 -1.7 PA3395 pill Twitching motility protein -2.6 -2.3 PA3395 pill Twitching motility protein -2.2 -2.1 PA3411 pill Twitching motility protein -2.2 -2.1 -1.7 PA350 pill Twitching motility protein -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -2.8 -1.6 -1.7 PA4525 pill Type 4 fimbrial biogenesis -2.6 -2.5 PA4525 pill Type 4 fimbrial biogenesis -2.6 -2.5 PA4525 pill Type 4 fimbrial biogenesis -2.2 -2.1 PA4535 pill Type 4 fimbrial biogenesis -2.2 -2.2 -2.2 -2.2 -2.2 -2.2 -2.2 -2.2 -2.1 PA4555 pill Type 4 fimbrial biogenesis -3.5 -3.5 PA4554	Downregulated	0 11		2.6	2.5
PA3132 fmV Moluly protein PrinV -3,1 -3,1 -3,1 PA3822 fil/ Twiching motility protein -1,2 -2,1 -1,7 PA0395 pil/ Twiching motility protein -3,0 -3,0 PA0411 pil/ Twiching motility protein -3,0 -3,0 PA0402 pil/ Type 4 fimbrial biogenesis -1,6 -1,7 PA3525 pil/ Type 4 fimbrial biogenesis -6,8 -8,0 PA4525 pil/ Type 4 fimbrial biogenesis -6,4 -5,9 PA4525 pil/ Type 4 fimbrial biogenesis -2,6 -2,5 PA4525 pil/ Type 4 fimbrial biogenesis -2,3 -2,0 PA4535 pil/ Type 4 fimbrial biogenesis -1,3 -1,5 PA4534 pil/ Type 4 fimbrial biogenesis -1,9 -1,5 PA4535 pil/ Type 4 fimbrial biogenesis -2,2 -2,1 -2,1 PA4534 pil/ Type 4 fimbrial biogenesis -1,5 -6,6 PA5043 -3,5 -7,5 -6,6 PA5041 pi	PA4550	fimU	Type 4 fimbrial biogenesis protein FimU	-2.6	-2.5
PA0395 pll7 Tivitching motility protein -1.8 -1.7 PA0395 pll7 Tivitching motility protein -3.0 -3.0 PA0412 pllK Methyltransferase -2.1 -1.7 PA2960 pllZ Type 4 fimbrial biogenesis preursor -2.7.8 -1.9.7 PA4525 pllB Type 4 fimbrial biogenesis preursor -2.7.8 -1.9.7 PA4525 pllD Type 4 fimbrial biogenesis -6.6 -8.0 PA4527 pllC Type 4 fimbrial biogenesis -6.2 -2.5 PA4528 pllD Type 4 fimbrial biogenesis -2.2 -2.1 PA4527 plW Type 4 fimbrial biogenesis -2.2 -2.3 -2.0 PA4535 plW Type 4 fimbrial biogenesis -2.2 -2.1 -1.5 PA4555 plW2 Type 4 fimbrial biogenesis -1.9 -1.5 PA5040 pl/Q Type 4 fimbrial biogenesis -1.9 -1.5 PA5041 pl/D Type 4 fimbrial biogenesis -3.1 -3.1 PA5042 pl/D Type 4 fimbrial biogenesis -5.1	PA3115	fimV	Motility protein FimV	-3./	-3.3
PA0411 plf Parting moting protein -2.2 -2.1 PA0412 plf Twitching motility protein -3.0 -3.0 PA0412 plf Methyltransferase -2.1 -1.7 PA2506 plf Type 4 fimbrial biogenesis -1.6 -1.7 PA4525 plf Type 4 fimbrial biogenesis -6.8 -8.0 PA4527 plf Type 4 fimbrial biogenesis -6.4 -5.9 PA4528 plf Type 4 fimbrial biogenesis -2.6 -2.5 PA4525 plf Type 4 fimbrial biogenesis -2.9 -2.4 PA4525 plf Type 4 fimbrial biogenesis -2.2 -2.1 PA4555 plf Type 4 fimbrial biogenesis -1.9 -1.5 PA5040 plf Type 4 fimbrial biogenesis -7.5 -6.6 PA5041 plf Type 4 fimbrial biogenesis -3.7 -6.16 PA5042 plf Type 4 fimbrial biogenesis -2.5 -2.4 PA5043 plf Type 4 fimbria	PA1822 DA0205	JUM nilT	Hypothetical protein	-1.8	-1./
PA0H12 plik Protein guident guident -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 -3.0 Pave	PA0595 DA0411	pu I pil I	Twitching motility protein	-2.2	-2.1
PA2960 pil2 Type 4 finbrial biogenesis 2.1 1.7 PA352 pilA Type 4 finbrial biogenesis -1.6 -1.7 PA4525 pilB Type 4 finbrial biogenesis -27.8 -19.7 PA4527 pilC Type 4 finbrial biogenesis -6.4 -5.9 PA4528 pilD Type 4 finbrial biogenesis -2.6 -2.5 PA4521 pilV Type 4 finbrial biogenesis -2.2 -2.1 PA4525 pilV Type 4 finbrial biogenesis -2.2 -2.1 PA4551 pilV Type 4 finbrial biogenesis -2.2 -2.1 PA4552 pilV Type 4 finbrial biogenesis -2.2 -2.1 PA4553 pilV Type 4 finbrial biogenesis -2.5 -7.5 -6.6 PA5040 pilQ Type 4 finbrial biogenesis -3.7 -6.1 PA5041 pilV Type 4 finbrial biogenesis -3.7 -4.0 PA5042 pilO Type 4 finbrial biogenesis -3.7 -4.0 PA100	PA0411 PA0412	pilk pilK	Methyltransferase	-3.0	-3.0
PA4525pildType 4Imbrail biogenesisproductPA4526pildType 4Imbrail biogenesis-6.8-8.0PA4527pilCType 4Imbrail biogenesis-6.4-5.9PA4528pilDType 4prepilin peptidase-7.7-6.4PA4525pilUType 4Imbrail biogenesis-2.6-2.5PA451pilVType 4Imbrail biogenesis-2.9-2.4PA4555pilVType 4Imbrail biogenesis-2.2-2.1PA4555pilV1Type 4Imbrail biogenesis-1.9-1.5PA4555pilV1Type 4Imbrail biogenesis-7.5-6.6PA5040pilQType 4Imbrail biogenesis-7.5-6.6PA5041pilDType 4Imbrail biogenesis-3.7-4.0PA5042pilOType 4Imbrail biogenesis-3.7-4.0PA1044filDFlagellar capping protein-2.6-1.9PA1100filEFlagellar nook-swail body complex-2.8-2.4PA1101filFFlagellar motor switch protein-1.6-1.7PA1103filHFlagellar motor switch protein-2.0-1.6PA1455filMFlagellar motor switch protein-2.0-1.6PA1403filMFlagellar synthesis-1.9-1.5PA1404filDFlagellar synthesis-1.9-1.5PA1455filMFlagellar synthesis-1.9-1.5<	PA 2960	piiK nilZ	Type 4 fimbrial biogenesis	-2.1	-1.7
PA4526pilBType 4 fimbrial biogenesis-6.8-80PA4527pilCType 4 fimbrial biogenesis-6.4-5.9PA4528pilDType 4 fimbrial biogenesis-7.7-6.4PA450fimUType 4 fimbrial biogenesis-2.6-2.5PA451pilVType 4 fimbrial biogenesis-2.3-2.0PA452pilWType 4 fimbrial biogenesis-2.2-2.1PA4551pilVIType 4 fimbrial biogenesis-2.2-2.2PA4553pilVIType 4 fimbrial biogenesis-1.9-1.5PA5040pilQType 4 fimbrial biogenesis-5.7-6.6PA5041pilQType 4 fimbrial biogenesis-7.5-6.6PA5042pilOType 4 fimbrial biogenesis-3.7-4.0PA1044pilMType 4 fimbrial biogenesis-3.7-4.0PA1045pilMType 4 fimbrial biogenesis-2.8-2.4PA5041pilMType 4 fimbrial biogenesis-2.6-1.9PA5042pilOType 4 fimbrial biogenesis-2.6-1.9PA5043pilMType 4 fimbrial biogenesis-2.6-2.5PA5043pilMType 4 fimbrial biogenesis-2.6-2.1PA104filDHagellar nock-basal body complex-2.8-2.4PA1101filFFlagellum M-ring outer membrane protein precursor-2.5-2.4PA1103filHFlagellar synthesis-1.6-1.7PA1105filDFlagellar synthesis <td>PA4525</td> <td>nilA</td> <td>Type 4 fimbrial biogenesis precursor</td> <td>-27.8</td> <td>-19.7</td>	PA4525	nilA	Type 4 fimbrial biogenesis precursor	-27.8	-19.7
PA4527pilCType 4 fimbrial biogenesis -6.4 -5.9 PA4528pilDType 4 fimbrial biogenesis -7.7 -6.4 PA4528pilDType 4 fimbrial biogenesis -2.6 -2.5 PA451pilVType 4 fimbrial biogenesis -2.9 -2.4 PA4522pilVType 4 fimbrial biogenesis -2.2 -2.1 PA453pilV1Type 4 fimbrial biogenesis -2.2 -2.1 PA4535pilV1Type 4 fimbrial biogenesis -1.5 -1.5 PA4541pilV2Type 4 fimbrial biogenesis -5.1 -5.1 PA5041pilQType 4 fimbrial biogenesis -5.1 -5.1 PA5042pilOType 4 fimbrial biogenesis -5.1 -5.1 PA5043pilNType 4 fimbrial biogenesis -5.1 -5.1 PA5044pilMType 4 fimbrial biogenesis -2.6 -1.9 PA1100filEFlagellar capping protein -2.6 -1.9 PA1101filEFlagellar motor switch protein -1.8 -1.6 PA1102filGFlagellar synthesis -2.0 -1.7 PA1103filHFlagellar synthesis -2.0 -1.7 PA1104filIFlagellar synthesis -1.6 -1.7 PA1105filIFlagellar synthesis -1.6 -1.7 PA1104filIFlagellar synthesis -1.6 -1.7 PA1445filOFlagellar synthesis -1.6 -1.7 PA1446filP <td< td=""><td>PA4526</td><td>nilR</td><td>Type 4 fimbrial biogenesis</td><td>-6.8</td><td>-8.0</td></td<>	PA4526	nilR	Type 4 fimbrial biogenesis	-6.8	-8.0
PA4528 $pilD$ Type 4 prepilin peridase -7.7 -6.4 PA4520 $fimU$ Type 4 fimbrial biogenesis -2.6 -2.5 PA4551 $pilV$ Type 4 fimbrial biogenesis -2.9 -2.4 PA4552 $pilW$ Type 4 fimbrial biogenesis -2.3 -2.0 PA4553 $pilV$ Type 4 fimbrial biogenesis -2.2 -2.1 PA4555 $pilV$ Type 4 fimbrial biogenesis -1.9 -1.5 PA5040 $pilQ$ Type 4 fimbrial biogenesis -7.5 -6.6 PA5041 $pilP$ Type 4 fimbrial biogenesis -5.1 -5.1 PA5041 $pilP$ Type 4 fimbrial biogenesis -4.5 -3.5 PA5043 $pilN$ Type 4 fimbrial biogenesis -4.5 -3.5 PA5044 $pilM$ Type 4 fimbrial biogenesis -2.6 -1.9 PA1100filEFlagellar capping protein -2.6 -1.9 PA1100filEFlagellar motor switch protein -1.8 -1.6 PA1101filfFlagellar motor switch protein -1.8 -1.6 PA1102fildFlagellar motor switch protein -2.0 -1.7 PA1104filiIFlagellar motor switch protein -2.6 -1.3 PA1445filOFlagellar synthesis -1.6 -1.3 PA1445filOFlagellar synthesis -1.6 -1.3 PA1445filOFlagellar synthesis -1.6 -1.3 PA1457cheZChemotaxis transducer -2.3 -1	PA4527	pilC	Type 4 fimbrial biogenesis	-6.4	-5.9
PA4550fmUType 4 fmbrial biogenesis -2.6 -2.5 PA4551 $pilV$ Type 4 fmbrial biogenesis -2.9 -2.4 PA4552 $pilW$ Type 4 fmbrial biogenesis -2.2 -2.0 PA4554 $pilV1$ Type 4 fmbrial biogenesis -2.2 -2.2 PA4555 $pilV2$ Type 4 fmbrial biogenesis -1.9 -1.5 PA5040 $pilQ$ Type 4 fmbrial biogenesis -5.7 -6.6 PA5041 $pilP$ Type 4 fmbrial biogenesis -7.5 -6.6 PA5042 $pilO$ Type 4 fmbrial biogenesis -5.1 -5.1 PA5043 $pilN$ Type 4 fmbrial biogenesis -4.5 -3.5 PA5044 $pilN$ Type 4 fmbrial biogenesis -4.5 -3.5 PA5044 $pilN$ Type 4 fmbrial biogenesis -2.6 -1.9 PA1004 $filD$ Flagellar capping protein -2.6 -1.9 PA1100 $filF$ Flagellar hook-basal body complex -2.8 -2.4 PA1101 $filF$ Flagellar synthesis -2.0 -1.7 PA1104 $filI$ Flagellar synthesis -2.0 -1.6 PA1105 $filI$ Flagellar motor switch protein -2.0 -1.6 PA1445 fiO Flagellar synthesis -1.6 -1.3 PA1445 fiO Flagellar synthesis -1.6 -1.3 PA1445 fiO Flagellar synthesis -1.6 -1.8 PA1445 fiO Flagellar synthesis -2.4 -2.20	PA4528	pilD	Type 4 prepilin peptidase	-7.7	-6.4
PA4551 plV $Type 4$ fimbrial biogenesis -2.9 -2.4 PA4552 $pilW$ Type 4 fimbrial biogenesis -2.3 -2.0 PA4553 $plVT$ Type 4 fimbrial biogenesis -2.2 -2.1 PA4555 $plVT$ Type 4 fimbrial biogenesis -1.9 -1.5 PA5040 plQ Type 4 fimbrial biogenesis our membrane protein -5.7 -6.1 PA5041 $pilD$ Type 4 fimbrial biogenesis -5.1 -5.1 -5.1 PA5042 $pilO$ Type 4 fimbrial biogenesis -4.5 -3.5 PA5043 $pilM$ Type 4 fimbrial biogenesis -4.5 -3.5 PA5044 $pilM$ Type 4 fimbrial biogenesis -2.6 -1.9 PA1004filDFlagellar capping protein -2.6 -1.9 PA1101filFFlagellar hook-basal body complex -2.8 -2.4 PA1102filGFlagellar motor switch protein -1.8 -1.6 PA1103filHFlagellar motor switch protein -1.6 -1.7 PA1105filIFlagellar synthesis -2.0 -1.6 PA1445filOFlagellar synthesis -1.6 -1.7 PA1445filOFlagellar synthesis -2.4 -2.4 PA1445filOFlagellar synthesis -1.6 -1.7 PA1445filOFlagellar synthesis -1.6 -1.7 PA1446filPFlagellar synthesis -1.6 -1.3 PA1446filPFlagellar synthesis -1.6 <td>PA4550</td> <td>fimU</td> <td>Type 4 fimbrial biogenesis</td> <td>-2.6</td> <td>-2.5</td>	PA4550	fimU	Type 4 fimbrial biogenesis	-2.6	-2.5
PA4552 $pilW$ Type 4 fimbrial biogenesis -2.3 -2.0 PA4554 $pilY1$ Type 4 fimbrial biogenesis -2.2 -2.1 PA4555 $pilY2$ Type 4 fimbrial biogenesis -1.9 -1.5 PA5040 $pilQ$ Type 4 fimbrial biogenesis -7.5 -6.6 PA5041 $pilQ$ Type 4 fimbrial biogenesis -7.5 -6.6 PA5042 $pilO$ Type 4 fimbrial biogenesis -5.1 -5.1 PA5043 $pilN$ Type 4 fimbrial biogenesis -4.5 -3.5 PA5044 $pilM$ Type 4 fimbrial biogenesis -3.7 -4.0 PA1094 $filD$ Flagellar capping protein -2.6 -1.9 PA1100 $filE$ Flagellar hox/-basal body complex -2.8 -2.4 PA1101 $filF$ Flagellar motor switch protein -1.8 -1.6 PA1102 $filG$ Flagellar synthesis -2.0 -1.7 PA1103 $filH$ Flagellar synthesis -2.0 -1.8 PA1445 $filO$ Flagellar synthesis -1.6 -1.7 PA1445 $filO$ Flagellar synthesis -1.6 -1.3 PA1445 $filO$ Flagellar synthesis -1.8 -1.6 PA1445 $filO$ Flagellar synthesis -1.8 -1.3 PA1445 $filO$ Flagellar synthesis -1.7 -2.4 PA1446 $filP$ Flagellar synthesis -1.7 -1.8 PA1445 $filO$ Flagellar synthesis -1.7 -1.8	PA4551	pilV	Type 4 fimbrial biogenesis	-2.9	-2.4
PA4554 $pilY1$ Type 4 fimbrial biogenesis -2.2 -2.1 PA4555 $pilY2$ Type 4 fimbrial biogenesis -1.9 -1.5 PA5040 $pilQ$ Type 4 fimbrial biogenesis -7.5 -6.6 PA5041 $pilP$ Type 4 fimbrial biogenesis -7.5 -6.6 PA5042 $pilO$ Type 4 fimbrial biogenesis -5.1 -5.1 PA5043 $pilN$ Type 4 fimbrial biogenesis -4.5 -3.5 PA5044 $pilM$ Type 4 fimbrial biogenesis -4.5 -3.5 PA5044 $pilM$ Type 4 fimbrial biogenesis -2.6 -1.9 PA1004filiDFlagellar capping protein -2.6 -1.9 PA1100filiEFlagellar capping protein -2.6 -1.9 PA1101filiFFlagellar motor switch protein -1.8 -1.6 PA1102filiGFlagellar synthesis -2.0 -1.7 PA1103filiHFlagellar synthesis -2.0 -1.7 PA1104filiFlagellar synthesis -2.0 -1.6 PA1445filiOFlagellar synthesis -1.6 -1.3 PA1445filiOFlagellar synthesis -1.6 -1.3 PA1445filiOFlagellar synthesis -1.6 -1.3 PA1446filiPFlagellar synthesis -1.6 -1.3 PA1445filiOFlagellar synthesis -1.6 -1.3 PA1445filiOFlagellar synthesis -1.8 -1.5 PA1446filiP<	PA4552	pilW	Type 4 fimbrial biogenesis	-2.3	-2.0
PA4555 $pil/2$ Type 4 fimbrial biogenesis -1.9 -1.5 PA5040 $pil/2$ Type 4 fimbrial biogenesis -5.7 -6.1 PA5042 $pil/2$ Type 4 fimbrial biogenesis -7.5 -6.6 PA5043 $pil/1$ Type 4 fimbrial biogenesis -5.1 -5.1 PA5043 $pil/1$ Type 4 fimbrial biogenesis -4.5 -3.5 PA5044 $pil/1$ Type 4 fimbrial biogenesis -4.5 -3.5 PA5044 $pil/1$ Type 4 fimbrial biogenesis -2.6 -1.9 PA1100filEFlagellar cophicab scale body complex -2.8 -2.4 PA1101filFFlagellar motor basal body complex -2.8 -2.4 PA1102filGFlagellar motor switch protein -1.8 -1.6 PA1103filHFlagellar synthesis -2.0 -1.7 PA1104fil/Flagellar synthesis -2.0 -1.6 PA1445fil/0Flagellar synthesis -1.6 -1.3 PA1445fil/0Flagellar synthesis -1.6 -1.3 PA1447fil/0Flagellar synthesis -1.6 -1.3 PA1457che2Chemotaxis response regulator -2.8 -2.4 PA1458Probable chemotaxis signal transduction kinase -2.0 -1.8 PA1457che2Chemotaxis signal transduction kinase -2.0 -1.8 PA1458Probable chemotaxis signal transduction methyltransferase -1.7 -1.7 PA1461motDFlagellar mo	PA4554	pilY1	Type 4 fimbrial biogenesis	-2.2	-2.1
PA5040 $pilQ$ Type 4 fimbrial biogenesis outer membrane protein -5.7 -6.1 PA5041 $pilP$ Type 4 fimbrial biogenesis -7.5 -6.6 PA5042 $pilO$ Type 4 fimbrial biogenesis -5.1 -5.1 PA5043 $pilN$ Type 4 fimbrial biogenesis -4.5 -3.5 PA5044 $pilM$ Type 4 fimbrial biogenesis -4.5 -3.5 PA100fliEFlagellar capping protein -2.6 -1.9 PA1100fliEFlagellar hock-basal body complex -2.8 -2.4 PA1101fliFFlagellar motor switch protein -1.8 -1.6 PA1102fliGFlagellar motor switch protein -1.6 -1.7 PA1104fliIFlagellar synthesis -2.0 -1.6 PA1445fliOFlagellar synthesis -2.0 -1.6 PA1445fliOFlagellar synthesis -1.6 -1.3 PA1446fliPFlagellar synthesis -1.6 -1.3 PA1445fliOFlagellar synthesis -1.6 -1.3 PA1445fliOFlagellar synthesis -1.6 -1.3 PA1445fliOFlagellar synthesis -1.6 -1.3 PA1445fliOFlagellar synthesis -1.6 -1.3 PA1446fliPFlagellar synthesis -2.0 -1.8 PA1455cheYChemotaxis response regulator -2.8 -2.6 PA1456cheYChemotaxis signal transduction kinase -2.0 -1.7	PA4555	pilY2	Type 4 fimbrial biogenesis	-1.9	-1.5
PA5041 $pilP$ Type 4 fimbrial biogenesis -7.5 -6.6 PA5042 $pilO$ Type 4 fimbrial biogenesis -5.1 -5.1 PA5043 $pilN$ Type 4 fimbrial biogenesis -4.5 -3.5 PA5044 $pilM$ Type 4 fimbrial biogenesis -3.7 -4.0 PA1094 $filD$ Flagellar capping protein -2.6 -1.9 PA1100 $filE$ Flagellar capping protein -2.8 -2.4 PA1101 $filF$ Flagellar mok-basal body complex -2.8 -2.4 PA1102 $filG$ Flagellar mok-basal body complex -2.6 -1.9 PA1103 $filH$ Flagellar synthesis -2.0 -1.7 PA1104 $filI$ Flagellar synthesis -2.0 -1.6 PA1433 $filM$ Flagellar synthesis -2.0 -1.6 PA1445 $filO$ Flagellar synthesis -1.6 -1.3 PA1446 $filP$ Flagellar synthesis -1.6 -1.3 PA1446 $filO$ Flagellar synthesis -1.6 -1.3 PA1457 $cheZ$ Chemotaxis response regulator -2.8 -2.6 PA1458Probable chemotaxis signal transduction kinase -2.0 -1.8 PA1459Probable chemotaxis signal transduction methyltransferase -1.7 -1.8 PA1450 $filO$ Flagellar motor protein -2.1 -1.8 PA1459Probable chemotaxis signal transduction kinase -2.0 -1.8 PA1450 $filO$ Flagellar motor protein<	PA5040	pilQ	Type 4 fimbrial biogenesis outer membrane protein	-5.7	-6.1
PA5042 <i>pilO</i> Type 4 fimbrial biogenesis-5.1-5.1PA5043 <i>pilN</i> Type 4 fimbrial biogenesis-4.5-3.5PA5044 <i>pilM</i> Type 4 fimbrial biogenesis-3.7-4.0PA1094 <i>fliD</i> Flagellar capping protein-2.6-1.9PA1100 <i>fliF</i> Flagellar hook-basal body complex-2.8-2.4PA1101 <i>fliF</i> Flagellar motor switch protein-1.8-1.6PA1102 <i>fliG</i> Flagellar synthesis-2.0-1.7PA1103 <i>fliH</i> Flagellar synthesis-2.0-1.6PA1104 <i>fliI</i> Flagellar synthesis-2.0-1.6PA1435 <i>fliO</i> Flagellar synthesis-2.0-1.6PA1445 <i>fliI</i> Flagellar synthesis-1.6-1.7PA1445 <i>fliIO</i> Flagellar synthesis-1.6-1.3PA1445 <i>fliIO</i> Flagellar synthesis-1.6-1.8PA1445 <i>fliIO</i> Flagellar synthesis-1.6-1.3PA1446 <i>fliP</i> Flagellar synthesis-1.6-1.3PA1445 <i>fliO</i> Flagellar synthesis-1.8-1.3PA1446 <i>fliP</i> Flagellar synthesis-1.8-1.3PA1456 <i>cheY</i> Chemotaxis signal transduction kinase-2.0-1.8PA1459Probable chemotaxis signal transduction methyltransferase-1.7-1.4PA1459Probable chemotaxis signal transduction methyltransferase-1.7-1.4PA1461 <i>motD</i> Flagellar motor prote	PA5041	pilP	Type 4 fimbrial biogenesis	-7.5	-6.6
PA5043pilNType 4 fimbrial biogenesis-4.5-3.5PA5044pilMType 4 fimbrial biogenesis-3.7-4.0PA1094filDFlagellar capping protein-2.6-1.9PA1100filEFlagellar capping protein-2.8-2.4PA1101filFFlagellar motor switch protein-1.8-1.6PA1103filHFlagellar motor switch protein-1.8-1.6PA1104filIFlagellar synthesis-2.0-1.7PA1105filJFlagellar synthesis-2.0-1.6PA1443filMFlagellar synthesis-2.0-1.6PA1445filOFlagellar synthesis-2.0-1.6PA1445filOFlagellar synthesis-1.6-1.3PA1446filPFlagellar synthesis-1.6-1.3PA1445fliQFlagellar synthesis-1.6-1.3PA1445fliQFlagellar synthesis-1.6-1.3PA1446fliPFlagellar synthesis-1.6-1.3PA1445fliQFlagellar synthesis-1.8-1.5PA1447fliQFlagellar synthesis-2.4-2.5PA1456cheYChemotaxis response regulator-2.8-2.6PA1457cheZChemotaxis signal transduction kinase-2.0-1.7PA1458Probable chemotaxis signal transduction kinase-2.0-1.8PA1459Probable chemotaxis transductor-2.1-1.8PA1461motDFl	PA5042	pilO	Type 4 fimbrial biogenesis	-5.1	-5.1
PA5044 plM Type 4 fmbrral biogenesis -3.7 -4.0 PA100fliDFlagellar capping protein -2.6 -1.9 PA1100fliEFlagellar hook-basal body complex -2.8 -2.4 PA1101fliFFlagellar hook-basal body complex -2.5 -2.4 PA1102fliGFlagellar motor switch protein -1.8 -1.6 PA1103fliHFlagellar synthesis -2.0 -1.7 PA1104fliIFlagellar synthesis -2.0 -1.6 PA1443fliMFlagellar synthesis -2.0 -1.6 PA1445fliOFlagellar synthesis -2.0 -1.8 PA1445fliOFlagellar synthesis -1.6 -1.3 PA1445fliOFlagellar synthesis -1.6 -1.3 PA1445fliQFlagellar synthesis -1.6 -1.3 PA1446fliQFlagellar synthesis -1.6 -1.3 PA1456cheYChemotaxis response regulator -2.8 -2.0 PA1457cheZChemotaxis signal transduction kinase -2.0 -1.8 PA1458Probable chemotaxis signal transduc	PA5043	pilN	Type 4 fimbrial biogenesis	-4.5	-3.5
PA1094 <i>ftiD</i> Flagellar capping protein -2.6 -1.9 PA1100 <i>ftiE</i> Flagellar hook-basal body complex -2.8 -2.4 PA1101 <i>ftiF</i> Flagellum M-ring outer membrane protein precursor -2.5 -2.4 PA1102 <i>ftiG</i> Flagellar motor switch protein -1.8 -1.6 PA1103 <i>ftiH</i> Flagellar synthesis -2.0 -1.7 PA1104 <i>ftiI</i> Flagellar synthesis -2.0 -1.6 PA1435 <i>ftiU</i> Flagellar synthesis -2.0 -1.6 PA1446 <i>ftiP</i> Flagellar synthesis -1.6 -1.3 PA1446 <i>ftiP</i> Flagellar synthesis -1.6 -1.3 PA1446 <i>ftiP</i> Flagellar synthesis -1.8 -1.3 PA1447 <i>ftiQ</i> Flagellar synthesis -1.8 -1.3 PA1456 <i>cheY</i> Chemotaxis response regulator -2.8 -2.0 PA1457 <i>cheZ</i> Chemotaxis signal transduction kinase -2.0 -1.8 PA1458Probable chemotaxis signal transduction methyltransferase -1.7 -1.4 PA2654Probable chemotaxis transducer -2.3 -1.7 -1.8 PA1401 <i>motD</i> Flagellar motor protein -1.7 -1.8 -1.6 PA1461 <i>motD</i> Flagellar motor protein -1.7 -1.8 -1.6 PA1464 <i>probable purine binding chemotaxis protein</i> -2.0 -1.7 -1.8 PA1097 <i>fteQ</i> Transcriptional regulator RhlR -2.0 -1.7 <t< td=""><td>PA5044</td><td>pilM</td><td>Type 4 fimbrial biogenesis</td><td>-3.7</td><td>-4.0</td></t<>	PA5044	pilM	Type 4 fimbrial biogenesis	-3.7	-4.0
PA1100fillFlagellar nook-basal body complex -2.8 -2.4 PA1101fillFlagellar motor switch protein -1.8 -1.6 PA1102fildFlagellar synthesis -2.0 -1.7 PA1103fillFlagellar synthesis -2.0 -1.7 PA1105fillFlagellar synthesis -2.0 -1.6 PA1443fillFlagellar synthesis -2.0 -1.6 PA1445fillFlagellar synthesis -2.0 -1.6 PA1445fillFlagellar synthesis -1.6 -1.3 PA1446fillFlagellar synthesis -1.6 -1.3 PA1447filQFlagellar synthesis -1.8 -1.5 PA1447filQFlagellar synthesis -1.8 -1.3 PA1456cheYChemotaxis response regulator -2.8 -2.6 PA1457cheZChemotaxis signal transduction kinase -2.0 -1.8 PA1458Probable chemotaxis signal transduction methyltransferase -1.7 -1.4 PA2654Probable chemotaxis transducer -2.3 -1.7 PA1461motDFlagellar motor protein -2.1 -1.8 -1.6 PA1098fleSTwo-component sensor -1.8 -1.6 Quorum sensing Downregulated PA3477rhlRTranscriptional regulator RhlR -1.7 -1.7 PA1430lasRTranscriptional regulator Rhs -1.7 -1.7	PA1094	fliD	Flagellar capping protein	-2.6	-1.9
PA1101 <i>jttr</i> Flagellum M-ring outer memorane protein precursor -2.5 -2.6 PA1102 <i>ftiG</i> Flagellar motor switch protein -1.8 -1.6 PA1103 <i>ftiH</i> Flagellar synthesis -2.0 -1.7 PA1104 <i>ftiI</i> Flagellar synthesis -2.0 -1.6 PA1105 <i>ftiJ</i> Flagellar motor switch protein -2.0 -1.6 PA1443 <i>ftiM</i> Flagellar motor switch protein -2.0 -1.6 PA1445 <i>ftiO</i> Flagellar synthesis -1.6 -1.3 PA1446 <i>ftiP</i> Flagellar synthesis -1.6 -1.3 PA1447 <i>ftiQ</i> Flagellar synthesis -1.6 -1.3 PA1456 <i>cheY</i> Chemotaxis response regulator -2.8 -2.6 PA1457 <i>cheZ</i> Chemotaxis signal transduction kinase -2.0 -1.8 PA1458Probable chemotaxis signal transduction methyltransferase -1.7 -1.4 PA2654Probable chemotaxis transducer -2.0 -1.7 PA1461 <i>motD</i> Flagellar motor protein -1.7 -1.3 PA1464Probable purine binding chemotaxis protein -2.1 -1.8 PA1097 <i>fleQ</i> Transcriptional regulator RhlR -2.0 -1.7 PA1430 <i>lasR</i> Transcriptional regulator RhlR -1.7 -1.7 PA1430 <i>lasR</i> Transcriptional regulator LasR -1.7 -1.7	PA1100	fliE	Flagellar hook-basal body complex	-2.8	-2.4
PA1102 <i>Jub</i> Flagellar infoor switch protein -1.3 -1.6 -1.7 PA1103 <i>fliH</i> Flagellar synthesis -2.0 -1.6 -1.7 PA1104 <i>fliJ</i> Flagellar synthesis -2.0 -1.6 PA1443 <i>fliM</i> Flagellar synthesis -2.0 -1.6 PA1445 <i>fliO</i> Flagellar synthesis -1.6 -1.3 PA1445 <i>fliO</i> Flagellar synthesis -1.6 -1.3 PA1446 <i>fliP</i> Flagellar synthesis -1.6 -1.3 PA1447 <i>fliQ</i> Flagellar synthesis -1.6 -1.3 PA1456 <i>cheY</i> Chemotaxis response regulator -2.8 -2.6 PA1457 <i>cheZ</i> Chemotaxis signal transduction kinase -2.4 -2.5 PA1458Probable chemotaxis signal transduction methyltransferase -1.7 -1.4 PA2654Probable chemotaxis transducer -2.0 -1.7 PA1461 <i>motD</i> Flagellar motor protein -1.7 -1.7 PA1097 <i>fleQ</i> Transcriptional regulator -2.0 -1.7 PA1098 <i>fleS</i> Two-component sensor -1.8 -1.6 Quorum sensing Downregulated -1.8 -1.6 -1.6 -1.7 PA1430 <i>lasR</i> Transcriptional regulator RhlR -1.7 -1.7 PA1430 <i>lasR</i> Transcriptional regulator LasR -1.7 -1.7	PA1101 DA1102	JUF H:C	Flagellum M-ring outer memorane protein precursor	-2.5	-2.4
PA1103JunHagelian synthesis2.01.7PA1104flilFlagellum-specific ATP synthase-1.6-1.7PA1105flilFlagellar synthesis-2.0-1.6PA1443fliMFlagellar synthesis-2.0-1.8PA1445fliOFlagellar synthesis-1.6-1.3PA1446fliPFlagellar synthesis-1.8-1.3PA1447fliQFlagellar synthesis-1.8-1.3PA1456cheYChemotaxis response regulator-2.8-2.6PA1457cheZChemotaxis signal transduction kinase-2.0-1.4PA1459Probable chemotaxis signal transduction methyltransferase-1.7-1.4PA2654Probable chemotaxis transducer-2.0-1.7PA1461motDFlagellar motor protein-1.7-1.3PA1464Probable purine binding chemotaxis protein-2.1-1.8PA1097fleQTranscriptional regulator-2.0-1.7PA1430lasRTranscriptional regulator RhlR-1.7-1.7PA1430lasRTranscriptional regulator LasR-1.7-1.7	PA1102 PA1103	JuG AiH	Flagellar synthesis	-1.8 -2.0	-1.0
PA1107JiiFlagellar synthesis1.01.7PA1105fliJFlagellar synthesis-2.0-1.6PA1443fliMFlagellar motor switch protein-2.0-1.8PA1445fliOFlagellar synthesis-1.6-1.3PA1446fliPFlagellar synthesis-1.9-1.5PA1447fliQFlagellar synthesis-1.8-1.3PA1456cheYChemotaxis response regulator-2.8-2.6PA1457cheZChemotaxis-2.4-2.5PA1458Probable chemotaxis signal transduction kinase-2.0-1.8PA1459Probable chemotaxis signal transduction methyltransferase-1.7-1.4PA2654Probable chemotaxis transducer-2.3-1.7PA1461motDFlagellar motor protein-1.7-1.8PA1097fleQTranscriptional regulator-2.0-1.8PA1098fleSTwo-component sensor-1.8-1.6Quorum sensingDownregulated-1.8Transcriptional regulator RhlR-1.8-2.0PA1430lasRTranscriptional regulator RhlR-1.7-1.7-1.7	PA1103	jull fil	Flagellum-specific ATP synthese	-2.0	-1.7
PA1443fildFlagellar synthesis-2.0-1.8PA1445fliOFlagellar synthesis-1.6-1.3PA1446fliPFlagellar synthesis-1.9-1.5PA1446fliQFlagellar synthesis-1.8-1.3PA1447fliQFlagellar synthesis-1.8-1.3PA1456cheYChemotaxis response regulator-2.8-2.6PA1457cheZChemotaxis response regulator-2.4-2.5PA1458Probable chemotaxis signal transduction kinase-2.0-1.8PA1459Probable chemotaxis signal transduction methyltransferase-1.7-1.4PA2654Probable chemotaxis transducer-2.0-1.7PA1461motDFlagellar motor protein-1.7-1.3PA1097fleQTranscriptional regulator-2.0-1.7PA1098fleSTwo-component sensor-1.8-1.6Quorum sensing Downregulated PA3477rhlRTranscriptional regulator RhlR-1.8-2.0PA1430lasRTranscriptional regulator LasR-1.7-1.7-1.7	PA1105	fiI	Flagellar synthesis	-2.0	-1.6
PA1445fildFlagellar synthesis-1.6-1.3PA1446fliPFlagellar synthesis-1.9-1.5PA1447fliQFlagellar synthesis-1.8-1.3PA1456cheYChemotaxis response regulator-2.8-2.6PA1457cheZChemotaxis signal transduction kinase-2.4-2.5PA1458Probable chemotaxis signal transduction methyltransferase-1.7-1.4PA2654Probable chemotaxis signal transducer-2.3-1.7PA1461motDFlagellar motor protein-1.7-1.3PA1464Probable purine binding chemotaxis protein-2.1-1.8PA1097fleQTranscriptional regulator-2.0-1.7PA1098fleSTwo-component sensor-1.8-1.6Quorum sensing Downregulated PA3477rhlRTranscriptional regulator RhlR-1.8-2.0PA1430lasRTranscriptional regulator LasR-1.7-1.7-1.7	PA1443	fiM	Flagellar motor switch protein	-2.0	-1.8
PA1446fliPFlagellar synthesis-1.9-1.5PA1447fliQFlagellar synthesis-1.8-1.3PA1456cheYChemotaxis response regulator-2.8-2.6PA1457cheZChemotaxis isgnal transduction kinase-2.4-2.5PA1458Probable chemotaxis signal transduction methyltransferase-1.7-1.4PA2654Probable chemotaxis transducer-2.3-1.7PA1461motDFlagellar motor protein-1.7-1.3PA1464Probable purine binding chemotaxis protein-2.0-1.7PA1097fleQTranscriptional regulator-2.0-1.7PA1430lasRTranscriptional regulator RhlR-1.8-2.0PA1430lasRTranscriptional regulator LasR-1.7-1.7	PA1445	fliO	Flagellar synthesis	-1.6	-1.3
PA1447fliQFlagellar synthesis-1.8-1.3PA1457cheYChemotaxis response regulator-2.8-2.6PA1457cheZChemotaxis signal transduction kinase-2.4-2.5PA1458Probable chemotaxis signal transduction methyltransferase-1.7-1.4PA2654Probable chemotaxis transducer-2.3-1.7PA1461motDFlagellar motor protein-1.7-1.3PA1464Probable purine binding chemotaxis protein-2.1-1.8PA1097fleQTranscriptional regulator-2.0-1.7PA1430lasRTranscriptional regulator RhIR-1.8-2.0PA1430lasRTranscriptional regulator LasR-1.7-1.7	PA1446	fliP	Flagellar synthesis	-1.9	-1.5
PA1456cheYChemotaxis response regulator-2.8-2.6PA1457cheZChemotaxis-2.4-2.5PA1458Probable chemotaxis signal transduction kinase-2.0-1.8PA1459Probable chemotaxis signal transduction methyltransferase-1.7-1.4PA2654Probable chemotaxis transducer-2.3-1.7PA1461motDFlagellar motor protein-1.7-1.3PA1464Probable purine binding chemotaxis protein-2.0-1.7PA1097fleQTranscriptional regulator-2.0-1.7PA1098fleSTwo-component sensor-1.8-1.6Quorum sensing Downregulated PA3477rhlRTranscriptional regulator RhlR-1.8-2.0PA1430lasRTranscriptional regulator LasR-1.7-1.7-1.7	PA1447	fliO	Flagellar synthesis	-1.8	-1.3
PA1457cheZChemotaxis-2.4-2.5PA1458Probable chemotaxis signal transduction kinase-2.0-1.8PA1459Probable chemotaxis signal transduction methyltransferase-1.7-1.4PA2654Probable chemotaxis transducer-2.3-1.7PA1461motDFlagellar motor protein-1.7-1.3PA1464Probable purine binding chemotaxis protein-2.1-1.8PA1097fleQTranscriptional regulator-2.0-1.7PA1098fleSTwo-component sensor-1.8-1.6Quorum sensing Downregulated PA3477rhlRTranscriptional regulator RhlR-1.8-2.0PA1430lasRTranscriptional regulator LasR-1.7-1.7	PA1456	cheY	Chemotaxis response regulator	-2.8	-2.6
PA1458Probable chemotaxis signal transduction kinase-2.0-1.8PA1459Probable chemotaxis signal transduction methyltransferase-1.7-1.4PA2654Probable chemotaxis transducer-2.3-1.7PA1461motDFlagellar motor protein-1.7-1.3PA1464Probable purine binding chemotaxis protein-2.1-1.8PA1097fleQTranscriptional regulator-2.0-1.7PA1098fleSTwo-component sensor-1.8-1.6Quorum sensing Downregulated PA3477rhlRTranscriptional regulator RhlR-1.8-2.0PA1430lasRTranscriptional regulator LasR-1.7-1.7-1.7	PA1457	cheZ	Chemotaxis	-2.4	-2.5
PA1459Probable chemotaxis signal transduction methyltransferase-1.7-1.4PA2654Probable chemotaxis transducer-2.3-1.7PA1461motDFlagellar motor protein-1.7-1.3PA1464Probable purine binding chemotaxis protein-2.1-1.8PA1097fleQTranscriptional regulator-2.0-1.7PA1098fleSTwo-component sensor-1.8-1.6Quorum sensing Downregulated PA3477rhlRTranscriptional regulator RhlR-1.8-2.0PA1430lasRTranscriptional regulator LasR-1.7-1.7-1.7	PA1458		Probable chemotaxis signal transduction kinase	-2.0	-1.8
PA2654Probable chemotaxis transducer-2.3-1.7PA1461motDFlagellar motor protein-1.7-1.3PA1464Probable purine binding chemotaxis protein-2.1-1.8PA1097fleQTranscriptional regulator-2.0-1.7PA1098fleSTwo-component sensor-1.8-1.6Quorum sensing Downregulated PA3477rhlRTranscriptional regulator RhlR-1.8-2.0PA1430lasRTranscriptional regulator LasR-1.7-1.7	PA1459		Probable chemotaxis signal transduction methyltransferase	-1.7	-1.4
PA1461motDFlagellar motor protein-1.7-1.3PA1464Probable purine binding chemotaxis protein-2.1-1.8PA1097fleQTranscriptional regulator-2.0-1.7PA1098fleSTwo-component sensor-1.8-1.6Quorum sensing Downregulated PA3477rhlRTranscriptional regulator RhlR-1.8-2.0PA1430lasRTranscriptional regulator LasR-1.7-1.7	PA2654		Probable chemotaxis transducer	-2.3	-1.7
PA1464Probable purine binding chemotaxis protein-2.1-1.8PA1097fleQTranscriptional regulator-2.0-1.7PA1098fleSTwo-component sensor-1.8-1.6Quorum sensing Downregulated PA3477rhlRTranscriptional regulator RhlR-1.8-2.0PA1430lasRTranscriptional regulator LasR-1.7-1.7	PA1461	motD	Flagellar motor protein	-1.7	-1.3
PA109/ PA1098fleQ fleSTranscriptional regulator regulator-2.0 -1.7 -1.8-1.6Quorum sensing Downregulated PA3477rhlR lasRTranscriptional regulator RhlR-1.8 -1.7-2.0 -1.7	PA1464	a -	Probable purine binding chemotaxis protein	-2.1	-1.8
PA1098fleSTwo-component sensor-1.8-1.6Quorum sensing Downregulated PA3477rhlRTranscriptional regulator RhlR-1.8-2.0PA1430lasRTranscriptional regulator LasR-1.7-1.7	PA1097	fleQ	Transcriptional regulator	-2.0	-1.7
Quorum sensing Downregulated-1.8-2.0PA3477rhlRTranscriptional regulator RhlR-1.7-2.0PA1430lasRTranscriptional regulator LasR-1.7-1.7	PA1098	fleS	Two-component sensor	-1.8	-1.6
PA3477 <i>rhlR</i> Transcriptional regulator RhlR-1.8-2.0PA1430 <i>lasR</i> Transcriptional regulator LasR-1.7-1.7	Quorum sensing Downregulated				
PA1430 lasR Transcriptional regulator LasR -1.7 -1.7	PA3477	rhlR	Transcriptional regulator RhlR	-1.8	-2.0
	PA1430	lasR	Transcriptional regulator LasR	-1.7	-1.7

Continued on following page

TABLE 1-Continued

ORF function,	Cana	Appotation	Fold change ^a	
regulation, and name	Gene	Annotation	PAO1	LexA(S125A)
Efflux				
Upregulated				
PA4599	mexC	RND multidrug efflux membrane fusion protein MexC precursor	4.4	3.1
PA0424	mexR	Multidrug resistance operon	2.2	1.6
Permeability				
Downregulated				
PA4067	oprG	Outer membrane protein OprG precursor	-4.8	-6.6
PA2853	oprI	Outer membrane lipoprotein OprI precursor	-1.7	-1.8
PA0958	oprD	Membrane porin OprD precursor	-4.7	-6.3
Pyocin synthesis				
Upregulated				
PA0611	ptrR	Repressor of ptrN/ptrB (ser-lys dyad)	5.0	4.3
PA0610	ptrN	Transcriptional activator of pyocin synthesis	55.6	48.7
PA0985		Pyocin S5	111.1	50.4
PA1150	pys2	Pyocin S2	66.7	41.7
PA1151	ımm2	Pyocin S2 immunity protein	17.5	12.6
PA3800		Pyocin protein	32.0	30.8
Phage region				
Upregulated			5 4 4	52.4
PA0614		Hypothetical/phage related	71.4	52.4
PA0615		Hypothetical/phage related	83.3	70.8
PA0616		Hypothetical/phage related	55.0	43.8
PA0017 PA0618		Hypothetical/phage related	83.3 82.2	00.3 57.5
PA0610		Hypothetical/phage related	00.0	50.1
PA0620		Hypothetical/phage related	90.9 71.4	56.1
PA0621		Hypothetical/phage related	50.0	38.5
PA0622		Hypothetical/phage related	58.8	52.1
PA0623		Hypothetical/phage related	50.0	38.8
PA0624		Hypothetical/phage related	55.6	40.0
PA0625		Hypothetical/phage related	66.7	55.1
PA0626		Hypothetical/phage related	125.0	75.7
PA0627		Hypothetical/phage related	83.3	57.5
PA0628		Hypothetical/phage related	90.9	64.3
PA0629		Hypothetical/phage related	100.0	84.8
PA0630		Hypothetical/phage related	83.3	54.9
PA0631		Hypothetical/phage related	111.1	76.5
PA0632		Hypothetical/phage related	111.1	84.4
PA0633		Hypothetical/phage related	76.9 71.4	62.9
PA0034 PA0635		Hypothetical/phage related	/1.4	54.8 71.8
PA0636		Hypothetical/phage related	55.6	/1.0
PA0637		Hypothetical/phage related	111.1	70.3
PA0638		Hypothetical/phage related	90.9	70.0
PA0639		Hypothetical/phage related	100.0	74.0
PA0640		Hypothetical/phage related	71.4	46.2
PA0641		Hypothetical/phage related	71.4	51.3
PA0642		Hypothetical/phage related	43.5	25.0
PA0643		Hypothetical/phage related	100.0	52.6
PA0644		Hypothetical/phage related	90.9	53.9
PA0645		Hypothetical/phage related	58.8	37.2
PA0646		Hypothetical/phage related	58.8	32.3
PA0647 PA0648		Hypothetical/phage related Hypothetical/phage related	50.0 58.8	32.7 46.0
		,, , , , , , , , , , , , , , , , , , ,		
Virulence/toxin				
Downregulated	T	Clobal regulator of virulance/metility	4.0	E A
ΓΑ4313 ΡΛ1718	mva 1	Type III export protein	-4.0 _7.2	-5.4
PA1710	pscE pscF	Type III export protein	_27	-0.0
PA1722	pscl	Type III export protein	-35	-37
PA1716	pscC	TTSS outer membrane protein precursor	-1.9	-1.3
	1			

Continued on following page

ORF function,	Gene	A	Fo	Fold change ^a	
regulation, and name		Annotation	PAO1	LexA(S125A)	
PA1713	exsA	Regulator of exoenzyme synthesis	-1.9	-1.5	
PA1710	exsC	Exoenzyme S synthesis protein C precursor	-3.5	-2.6	
PA1711	(exsE)		-3.5	-2.5	
PA1712	exsB	Exoenyzme S synthesis protein B	-4.6	-3.1	
Upregulated					
PA0612	ptrB	Suppressor of TTSS	166.7	178.1	
PA0613		In operon with PA0612	62.5	56.0	

TABLE 1-Continued

^a Difference in expression of PAO1 or the LexA(S125A) mutant 120 min after ciprofloxacin exposure compared to immediately prior to exposure.

the general trend toward reduced metabolic activity in response to antibiotic exposure.

Contribution of the *P. aeruginosa* **SOS genes to the ciprofloxacin-induced transcriptional response.** We next characterized the transcriptional response to ciprofloxacin in a *lexA*(S125A) PAO1 mutant under the same conditions as those used to characterize the wild-type strain. As expected, *lexA*, *recA*, *recX*, and *recN* are induced by ciprofloxacin in a LexA cleavage-dependent manner (Table 3). In addition, PA3413 and PA1045 are regulated by LexA. PA3413 is a probable homolog of *E. coli yebG*, which is LexA regulated in *E. coli* (29), but its biological function is not known. PA1045 appears to encode a DinG helicase (37), which is related to the mammalian XPD family of helicases, and it may play a role in transcription-coupled repair.

The induction of several hypothetical genes was found to depend on LexA cleavage: PA2288, PA3414, PA1044, PA0069, and PA0922. PA3414 is predicted to encode a protein of unknown function, but its location next to *yebG* (see above) suggests that these genes may be coordinatively transcribed. PA2288 encodes a hypothetical protein of no known function. However, it has recently been shown that mutation of *wspF*, which disrupts a signal cascade involved in biofilm formation,

TABLE 2. Other damage-inducible Ser-Lys dyads and downstream targets

ORF	Gene	Description	Fold change ^a
PA0906		Predicted transcriptional regulator (Ser-Lys dyad)	5.2
PA0907		Hypothetical, divergent to PA0906	30.3
PA0908		Hypothetical	17.5
PA0909		Hypothetical, related to phage	32.3
PA0910		Hypothetical	83.3
PA0911		Hypothetical	71.4
PA0611	ptrR	Transcriptional regulator (Ser-Lys dyad) of pyocin synthesis	5.0
PA0610	ptrN	Transcriptional activator of pyocin synthesis (regulated by ptrR)	55.6
PA0612	ptrB	Suppressor of TTSS	166.7
PA0613	1	In operon with PA0612	62.5
PA0985		Pyocin S5	111.1
PA1150	pys2	Pyocin S2	66.7
PA1151	imm2	Pyocin S2 immunity protein	17.5
PA3866		Probable pyocin protein	52.6

^a Difference in expression of PAO1 120 min after ciprofloxacin exposure compared to immediately prior to exposure.

causes a mild induction of *lexA* and *recA* (each 1.6-fold) and a 4.0- and 2.8-fold increase in PA3414 and PA2288 expression, respectively, supporting the association of these genes with the SOS response (19). PA1044 encodes a hypothetical protein with no known function that is divergently transcribed from PA1045 (see above). PA0922 and PA0069 are predicted to encode a hypothetical protein and a photolyase-like protein, respectively.

In E. coli there are three nonessential polymerases, each of which is LexA regulated: Pol II (encoded by polB), Pol IV (encoded by *dinB*), and Pol V (encoded by *umuC* and *umuD*). The P. aeruginosa genome encodes three nonessential polymerases, PA0923, PA0669, and PA0670. As mentioned above, transcription of PA0923, which encodes a polymerase that is highly homologous to E. coli dinB, is induced by ciprofloxacin; however, its induction is not LexA regulated. This agrees with recent findings in other organisms (6, 36) and suggests that a LexA-regulated *dinB* polymerase may be more the exception than the rule. In contrast, PA0669 and PA0670, which appear to be encoded in the same operon, are induced by ciprofloxacin in a LexA cleavage-dependent manner. PA0669 is predicted to encode an alternate alpha-subunit, and PA0670 is predicted to encode a Y-family polymerase. This operon resembles one that was recently found to play a role in damage-induced mutagenesis in the α -Proteobacteria Caulobacter crescentus (16), although a PAO1 mutant lacking this operon shows no signs of increased sensitivity to UV, MMS, or ciprofloxacin-mediated damage (R. T. Cirz and F. E. Romesberg, unpublished results). While we were able to detect sufficient levels of PA0670 in the microarray studies, the level of PA0669 was too low to observe a rigorous statistical difference between PAO1 and the LexA mutant directly (supporting information can be found at http: //www.scripps.edu/chem/romesberg/). However, using realtime PCR we were able to detect PA0669 mRNA after ciprofloxacin treatment, but not in the LexA mutant, confirming that this gene is LexA regulated (see Table S2 in our supporting information at http://www.scripps.edu/chem/romesberg/).

Analysis of the *P. aeruginosa* LexA box and other potential SOS genes. By identifying the SOS regulon empirically, we were also able to identify a consensus binding sequence for LexA, CTG-TATAA-ATATA-CAG (bold residues are 100% conserved) (Table 3). The consensus is essentially the same as that in *E. coli* with the exception of position eight, where it is most frequently a dA in *P. aeruginosa* and a dT in *E. coli*.

We searched the Pseudomonas genome (35, 39) for other

ORF	Gene	LexA box	Distance (bp) to start codon	Mismatches (bp) from consensus	Fold change PA01 vs LexA(S125A)
Consensus		CTG TATAA ATATA CAG ^a			
PA3008	sulA	Shared with PA3007			33.1
PA3007	lexA	CTG GATAA AAACA CAG	9	3	22.7
PA3413	yebG	CTG TATGG ATAAC CAG	40	4	13.9
PA4763	recN	CTG TATAA ATAAC CAG	24	2	10.4
PA2288		CTG TATGA ATGTA CAG	41	2	8.4
PA3414		Shared with PA3413			6.5
PA3617	recA	CTG TCTAC TTATA CAG	43	3	3.4
PA3616	recX	Shared with PA3617			3.5
PA1044		CTG GATAA ATTTT CAG	60	3	2.0
PA1045	dinG	CTG GATAA ATTTT CAG	54	3	1.7
PA0069	phl	CTG TATCC ATATA CAG	20	2	3.4
PA0922	1	CTG TATAT TCGTA CAG	52	4	5.7
PA0669	dnaE2	Shared with PA0671			
PA0670	imuB	Shared with PA0671			5.0
PA0671	sulA2	CTG TATTT ACATA CAG	137	3	6.3

TABLE 3. LexA-regulated genes identified in the microarray-based whole-genome transcription assay

^a The bold residues are 100% conserved.

potential LexA binding sites using the sequence $CTGN_2TN_7CAG$ with up to four mismatches in the central 10-bp region. In addition to the sites that regulate the 15 genes identified in our microarray studies, eight potential LexA binding sites were identified (see Table S4 in our supporting information at http: //www.scripps.edu/chem/romesberg/). Four are positioned between 128 and 154 bp from a gene, and four are intragenic. The microarray data suggest that either these sites do not bind LexA in vivo or that they do not effectively regulate expression. Thus, the data suggest that the 15 genes identified experimentally represent the entire LexA regulon.

DISCUSSION

The global transcriptional response to ciprofloxacin was previously examined in P. aeruginosa PAO1 grown for 2.5 h in the presence of sub-MIC and MIC levels of the drug (5). Ciprofloxacin was found to induce changes in the transcription of >900 and >1,200 genes at sub-MIC and MIC levels, respectively ($P \le 0.05$). While this study identified the increased transcription of the cryptic prophage genes spanning from PA0614 to PA0648 (5), which we also observed with supra-MIC levels of the drug, it did not identify any consistent and significant changes in genes involved in metabolism or proliferation (see Table S3 in our supporting information at http: //www.scripps.edu/chem/romesberg/). In fact, the present study reveals that the largest part of the response involves the downregulation of genes that encode proteins involved in general metabolism and DNA replication/repair, as well as the downregulation of genes involved in cell division, motility, quorum sensing, and cell permeability. These changes appear to be specific for higher, clinical-like levels of the drug and may contribute to the pathogen's survival during therapy, as has already been suggested for both planktonic and biofilm cells (1, 24). Indeed, this response is a reasonable survival strategy, considering that ciprofloxacin is more lethal to actively dividing cells than resting cells (11), and it may facilitate survival until a more specific response is orchestrated.

The SOS response is thought to be a major component of the bacterial response to stress and has been characterized thoroughly in *E. coli*, where it includes the derepression of 43 genes that orchestrate virtually the entire positive transcriptional response to UV irradiation (9). The only other globally characterized SOS response is that of *B. subtilis*, where 33 genes have LexA binding sites and are induced by UV irradiation and mitomycin C in a RecA-dependent manner. While the number of LexA-regulated genes in *E. coli* and *B. subtilis* is similar, only seven genes are common to both organisms.

By directly comparing the response to ciprofloxacin of LexAcleavable and uncleavable strains, we identified 15 P. aeruginosa genes that are induced by ciprofloxacin in a LexA cleavage-dependent manner. These genes appear to be controlled from nine LexA binding sites, with five of the sites controlling expression of divergent or polycistronic operons. The consensus binding site is the 16-nucleotide imperfect palindrome CTG-TATAA-ATATA-CAG (where the bold indicates absolutely conserved nucleotides). As expected, the SOS regulon includes lexA and recA. It also includes recN, recX, and probable yebG, dinG, and phl homologs, which are all commonly part of the SOS regulon in other bacteria. Also included is the polycistronic operon containing imuA/sulA, imuB, and dnaE2, as observed in several other SOS operons (12). The data suggests that, like other y-Proteobacteria, both DNA repair and induced mutation are central components of the LexA-regulated SOS response in P. aeruginosa. However, P. aeruginosa LexA appears to regulate only the recombinational repair proteins RecX and RecN and not the nucleotide excision repair proteins UvrA, UvrB, and UvrD, nor the recombinational repair proteins RuvA and RuvB, all of which are LexA regulated in both E. coli (9) and B. subtilis (2) and are also predicted to be LexA regulated in other γ -Proteobacteria (13). RecX is thought to associate with RecA and cap filament extension (10), while RecN is thought to cooperate in some forms of recombination (31). Why these recombination proteins are regulated by LexA in P. aeruginosa, while ones common to other SOS regulons are not, is unclear but likely reflects the environment in which the pathogen has adapted to survive.

Induced mutation in *E. coli* is controlled by LexA cleavagemediated derepression of *polB*, which encodes Pol II, *dinB*, which encodes Pol IV, and umuDC, which encodes the Pol V preprotein. P. aeruginosa does not have a umuDC homolog, and our data show that *polB* is not induced in response to ciprofloxacin and that dinB, while induced, is not repressed by LexA. Instead, P. aeruginosa appears to control induced mutation from the LexA-repressed imuA/sulA-imuB-dnaE2 operon. imuB and dnaE2 encode inducible polymerases, and their homologs are required for the majority of UV- and mitomycin C-induced mutations in the highly related organism Caulobacter crescentus (16). In addition, a dnaE2 homolog in Mycobacterium tuberculosis has been shown to be required for UV-induced mutation (4). The operon also appears in many other species and is predicted computationally to be universally LexA regulated (12). Interestingly, the presence of this operon has been correlated with the absence of a umuDC operon (12), suggesting that it may perform a similar function.

The SOS system may play an underappreciated role in the response to several commonly used antibiotics. In *E. coli*, the SOS response is induced by ciprofloxacin (11, 33), rifampin (7), β -lactams (27), and trimethoprim (23). While the LexA regulon of *P. aeruginosa* is significantly smaller than that of *E. coli*, or *B. subtilis*, it appears to have retained control over induced mutation. Thus, it seems likely that the initial reduction in metabolism observed in *P. aeruginosa* provides the SOS response time to induce mutations that allow it to persist and eventually to evolve resistance, as has been observed in *E. coli* (7, 8) and *M. tuberculosis* (4). These results suggest that an inhibitor of LexA cleavage might have a profound and favorable effect on *P. aeruginosa* therapy.

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