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DNA Microarray Analysis of the Expression Profile of *Escherichia coli* in Response to Treatment with 4,5-Dihydroxy-2-Cyclopenten-1-One

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We carried out DNA microarray-based global transcript profiling of *Escherichia coli* in response to 4,5-dihydroxy-2-cyclopenten-1-one to explore the manifestation of its antibacterial activity. We show that it has widespread effects in *E. coli* affecting genes encoding proteins involved in cell metabolism and membrane synthesis and functions. Genes belonging to the regulon involved in synthesis of Cys are upregulated. In addition, *rpoS* and RpoS-regulated genes responding to various stresses and a number of genes responding to oxidative stress are upregulated.

A number of antibiotics are available against a variety of bacteria; however, in recent years, the emergence of multiple-drug-resistant bacteria has been a primary concern. This has provided an incentive to search for newer and more effective antibacterial compounds. Previously we described one such compound, 4,5-dihydroxy-2-cyclopenten-1-one (DHCP), having antibacterial activity against a variety of gram-negative and -positive bacteria, such as *Escherichia coli* and *Salmonella*, *Bacillus*, and *Staphylococcus* spp., etc. DHCP is prepared by the heat treatment of uronic acid or its derivatives (12). It is also produced from roasted or parched vegetables, fruits, cereals, mushrooms, sea algae, cortex, or cartilage. It has been shown elsewhere to have potential applications as a therapeutic or preventive agent against cancer and also as an antibacterial agent in antiseptics, dentifrices, cosmetics, and bathing agents (12). We isolated a multicopy suppressor of DHCP toxicity from an *E. coli* genomic library. The gene encoding this suppressor was designated *dep*, and the putative protein encoded by this gene was designated Dep. The Dep protein showed high homology to known efflux proteins conferring resistance to a number of antibiotics including chloramphenicol, bicyclomycin, and tetracycline. However, it did not confer cross-resistance to any of the antibiotics tested (15). The exact mechanism of action of DHCP is not known.

In the present study, we analyzed the global transcriptional pattern of *E. coli* in response to DHCP by DNA microarray-based technology to explore the manifestation of the antibacterial activity of DHCP. We show that DHCP has widespread effects in *E. coli* affecting genes encoding proteins involved in cell metabolism and membrane synthesis and functions.

DNA microarray-based global transcription profiling of *E. coli* in response to DHCP treatment. Previously we showed that the growth of *E. coli* strain JM83 [F^- *ara*Δ(*lac-proAB*) *rpsL*(Str^r)] (22) was impaired in the presence of DHCP (250 μM) after 3 h of incubation and that cells stopped growing after 5 h (15). Our main objective in the present study was to identify all of the *E. coli* open reading frames that exhibited a significant increase or decrease in mRNA abundance caused by the DHCP treatment. The cells were grown in the presence of 250 μM DHCP as described previously (15). In brief, cells grown overnight in Luria-Bertani medium were diluted into fresh Luria-Bertani medium. After the growth reached 50 Klett units, DHCP was added at 250 μM and growth was further monitored. After growth reached 90 to 100 Klett units, the culture was diluted 10-fold into medium containing the same concentration of DHCP. The cells were harvested after a total of 8 h of incubation with DHCP. Control cells were grown in a similar manner without DHCP and harvested at an optical density at 600 nm comparable to the final optical density at 600 nm of the DHCP-treated cells. The total RNA was extracted by the hot phenol method described previously (16). It was further purified with an RNeasy Minikit (Qiagen) and was then treated with DNase I followed by phenol-chloroform treatment and ethanol precipitation. It was quantified by measuring absorbance at 260 nm. The purity of RNA was confirmed by agarose gel electrophoresis. The mRNAs were converted to cDNAs with coincident labeling with Cy3-dUTP or Cy5-dUTP (Amersham Pharmacia). Random hexamer $pd(N)_6$ (Amersham Pharmacia) was used as a primer. We used the IntelliGene *E. coli* chip, version 1 (Takara Shuzo Co., Ltd., Shiga, Japan). This represents the entire set of *E. coli* K-12 W3110 open reading frames. The analysis of the density of each spot and calculation of the expression ratio for each spot were carried out by using the analysis software Imagine, version 4 (Takara catalog no. BD001). For adjustment of signals between Cy3 and Cy5, the DNA chip includes internal controls. We carried out the DNA microarray experiment three times and with label swaps to ensure consistency. Calculation of the expression ratios of the corresponding spots allowed pairwise comparisons of the relative transcript levels for each *E. coli* gene under the two growth conditions. The cell density of the control (untreated) and DHCP-treated cells used was the same; thus, the changes seen in the microarray were not substantially influenced by the difference in cell densities. Only those genes whose expression levels differed by a ratio of at least 4 were evaluated. In some cases, genes belonging to the same operon or category were evaluated even if the ratios

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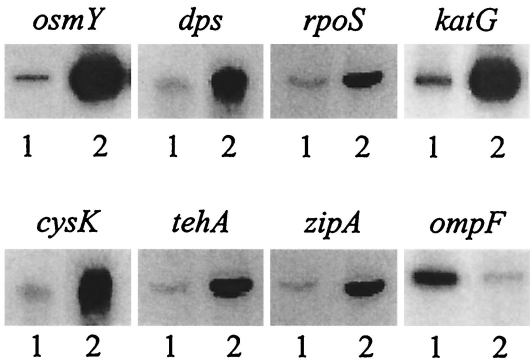

FIG. 1. Effect of DHCP on the levels of mRNAs. Total RNA was extracted by the hot phenol method as described in the text, and primer extension analysis was carried out with deoxyoligonucleotides corresponding to *osmY*, *dps*, *rpoS*, *katG*, *cysK*, *tehA*, *zipA*, and *ompF*. Lanes 1 and 2 in each case represent mRNAs isolated from control (untreated) and DHCP-treated cells, respectively.

differed by a factor of only 3 or a little less than 3. Ratios above 0 indicate induction and below 0 indicate repression by DHCP treatment. Selected results seen with DNA microarray analysis were confirmed by primer extension with deoxyoligonucleotides corresponding to some of the genes significantly affected. The primer extension and the deoxyoligonucleotides used for detection of *osmY*, *dps*, *rpoS*, *katG*, and *ompF* were described previously (14). The deoxyoligonucleotides used for detection of *cysK*, *tehA*, and *zipA* were primer 3969805 (5′-CAGGCGA ACCAGCGGCGTGTGACC-3′), which corresponds to the region from codons 20 to 13 of *cysK* (4); primer 3969806 (5′-GTAGCCTGCCGGCAAATTGAGCAC-3′), which corresponds to the region from codons 13 to 6 of *tehA* (21); and primer 3969807 (5′-GATTAATATCAGACGCAAATCCTG-3′), which corresponds to the region from codons 10 to 3 of *zipA* (10). The results are shown in Fig. 1 and summarized in Table 1. The results of the two methods are in agreement.

Genes encoding ribosomal proteins are affected by DHCP treatment. As the concentration of DHCP and time period of exposure chosen for the present experiment severely impaired growth, one would expect significant secondary effects due to growth inhibition, and these changes do not necessarily reflect the site of action of DHCP. One manifestation of lower growth rate is that the translational machinery of the cell is affected, as evidenced by lower levels of ribosomal proteins. Most of the genes encoding ribosomal L proteins showed reduced levels, although in most cases the effect was not severe (approximately two- to threefold).

TABLE 1. Comparison of data from DNA microarray and primer extension

Gene	Ratio by[a]:	
	Microarray	Primer extension
osmY	12.00	15.00
dps	13.00	12.00
rpoS	4.00	4.00
katG	9.00	9.00
cysK	20.00	18.00
tehA	5.00	5.00
zipA	5.00	5.00
ompF	0.06	0.06

[a] Ratios of the respective mRNA levels in the DHCP-treated and control (untreated) cells in each case are shown. Values shown are means of three independent experiments.

Effect of DHCP on membrane-associated functions. As seen from Tables 2 and 3, a number of genes encoding proteins related to cell membrane were significantly affected. Predominantly the cellular transport systems were affected, especially those involving transport of iron, spermidine, and putrescine. The most prominent difference (47-fold increase) was seen in the case of *creD*, encoding CreD. Since the exact function of CreD is not known (3), it is difficult to judge the physiological significance of this observation. One interesting point is that *creD* is regulated by CreBC, a member of the *cre* regulon and a presumed global regulator (3). Another gene regulated by CreBC is *talA* (3), whose expression was also increased eightfold in the present study (Table 2). *talA* encodes an enzyme involved in the mobilization of glyceraldehyde-3-phosphate into the pentose phosphate pathway. The expression of other CreBC-regulated genes such as *yidS* and *yieI*, the products of which have not been assigned any function yet, also increased fourfold. However, more genes known to be regulated by CreBC, such as *ackA*, *pta*, *radC*, *malE*, and *trgB*, were not induced by DHCP. In fact, *ackA* expression decreased fourfold (Table 3). Some additional factors may be involved in the regulation of expression of these genes.

The fivefold increase in the level of *tehA*, encoding a protein that confers resistance to tellurite, seems to be significant. Tellurite causes toxicity in a number of gram-negative bacteria. The exact mechanism of this toxicity is not known; however, it has been shown elsewhere to cause oxidative stress and may replace sulfur in various proteins, rendering them nonfunctional (9, 18). Overexpression of *tehA* also confers resistance to compounds such as tetraphenylarsonium Cl, ethidium bromide, crystal violet, and proflavin, similar to that inferred from multidrug resistance pumps (19).

DHCP induces RpoS and proteins regulated by RpoS. RpoS is a global stress response regulator and is also known to be involved in quorum sensing in *E. coli* (11, 17). Next we examined the effect of DHCP on *rpoS* levels and found that *rpoS* was induced fourfold after the treatment with DHCP. The RpoS level also increased four times (data not shown). The gene *dps* is regulated by RpoS and encodes Dps, a protein induced by oxidative and osmotic stress (2, 13). This gene was induced 13-fold (Table 2). Other genes such as *osmY* and *katG*, encoding RpoS-regulated stress proteins OsmY and KatG, respectively (11, 23), were also significantly induced. Interestingly, genes encoding some of the other RpoS-regulated proteins that are not involved in the stress response were also induced, probably as a manifestation of higher levels of RpoS itself or gene-to-gene inconsistencies in the data. Examples of these include *hdeB*, *otsA*, *poxB*, and *wrbA* (Table 2).

Effect of DHCP on the genes involved in the cell metabolism. Similarly to the effect on membrane genes, DHCP treatment affected a number of processes involved in metabolism of the cell, some of these probably being secondary effects of the treatment. The most prominent genes affected by the DHCP treatment were the ones encoding proteins involved in cysteine synthesis. A remarkable increase was observed in expression of the genes belonging to the regulon involved in synthesis of Cys,

TABLE 2. Genes induced by DHCP treatment

Gene	Gene product and/or function	Ratio (DHCP treated/ control)
Genes involved in membrane synthesis and function		
atzN	Zinc-transporting ATPase	11
cpxP	Periplasmic protein precursor	5
creD	Inner-membrane protein CreD	47
czcD	Cation efflux protein CzcD	4
fliY	FliY protein precursor	9
msyB	Membrane protein	4
tehA	Tellurite resistance protein TehA	5
rpoS and RpoS-regulated genes		
dps	DNA-binding protein Dps	13
hdeB	10k-1 protein precursor	6
katG	Catalase hydroperoxidase I	9
osmY	Hyperosmotically induced protein	12
otsA	Trehalose-6-phosphate synthase	11
poxB	Pyruvate oxidase	15
rpoS	RNP polymerase sigma factor RpoS	4
wrbA	Trp repressor binding protein	14
Genes involved in cell metabolism		
aldH	Aldehyde dehydrogenase homolog	7
cysA	Sulfate/thiosulfate transport protein	3
cysD	Sulfate adenylyltransferase	6
cysH	Adenylsulfate reductase	7
cysI	Sulfite reductase (NADPH) alpha subunit	7
cysJ	Sulfite reductase (NADPH) beta subunit	5
cysK	Cysteine synthase	20
cysM	*O*-Acetylserine (thiol)-lyase B	3
cysN	Sulfate adenylyltransferase	5
cysP	Thiosulfate-binding protein CysP precursor	4
cysQ	Ammonium transport protein CysQ	3
cysU	Sulfate transport system permease	5
cysW	Sulfate-thiosulfate transport protein CysW	15
fbp	Fructose-1,6-bisphosphatase	4
galE	UDP-glucose 4-epimerase	5
galM	Aldose 1-epimerase	4
galP	Galactose proton symport	5
galT	Galactose-1-phosphate uridylyl transferase	7
glnH	Glutamine-binding protein precursor	5
gltB	Glutamate synthase (NADPH) large chain	4
gsp	Glutathionylspermidine synthase-amidase	4
hmpA	Flavohemoprotein	4
hyfG	Hydrogenase-4 component G	10
ilvB	Acetolactate synthase	4
lysU	Lysine-tRNA ligase	4
moaA	Molybdenum cofactor biosynthesis protein	4
moaB	MoaB protein	4
moaC	MoaC protein	3
moaD	Molybdopterin (Mpt) converting factor	4
pfkB	6-Phosphofructokinase isoenzyme	5
Genes encoding proteins with diverse functions		
ahpF	Alkyl hydroperoxide reductase	4
bfr	Bacterioferritin	5
marA	Multiple antibiotic resistance protein MarA	5
mdaB	Modulator of drug activity	10
nemA	*N*-Ethylmaleimide reductase	8
nrdH	Glutaredoxin-like protein	21
nrdI	NrdI protein	10
soxS	SoxS protein	4
talA	Patatire transaldolase	8
tehB	Tellurite resistance protein TehB	5
zipA	Cell division protein	5

such as *cysA*, *cysD*, *cysH*, *cysI*, *cysJ*, *cysK*, *cysM*, *cysN*, *cysP*, *cysQ*, *cysU*, and *cysW* (3- to 20-fold [Table 2]). Among these, *cysK* expression showed the maximum increase of 20-fold. Interestingly, *cysG* and *cysS*, which do not belong to this regulon, were not affected by the DHCP treatment. Genes belonging to other operons induced by the DHCP treatment were those belonging to the *gal* operon and the *moa* operon, involved in galactose and molybdenum metabolism, respectively (Table 2). On the other hand, the expression of genes belonging to the *ent* operon decreased. The *fru* (*fruB* and *fruK*) system was also severely inhibited (8- and 33-fold, respectively) (Table 3).

DHCP affects a number of proteins with diverse functions. Interestingly, *tehB*, encoding TehB, involved in tellurite resistance, was induced fivefold, similarly to *tehA* (Table 2). *ahpF*, *bfr*, and *soxS*, encoding alkyl hydroperoxide reductase, bacterioferritin, and SoxS protein, respectively, which respond to oxidative stress (1, 5, 7), were also induced about fourfold. A gene (*mdaB*) encoding MdaB (modulator of drug activity) was also induced 10-fold. Overproduction of MdaB imparts resistance to two topoisomerase inhibitors, adriamycin and etoposide, and presumably acts by modulating topoisomerase IV activity (6). However, in the present study, levels of *parC* and *parE*, the genes encoding two subunits of topoisomerase IV, did not change upon DHCP treatment. The gene *marA*, encoding multiple antibiotic resistance protein MarA, was also induced fivefold. The genes *nrdH* and *nrdI*, encoding glutaredoxin proteins, were also significantly induced by DHCP. Interestingly, genes involved in virulence such as the *sap* (sensitivity to antimicrobial peptides) operon genes were repressed by the DHCP treatment (Table 3).

In addition, the expression of a number of genes such as *yafB*, *ybgS*, *ydiC*, *yeeU*, *yedD*, *yggG*, *yhbW*, *yhcN*, *yhhQ*, *yhjX*, *yidS*, *yieI*, *yjbJ*, *ymgA*, *ynhA*, *ynhC*, *ynhD*, and *ynhE*, the products of which have not been assigned any functions yet, increased significantly.

Antibacterial activity of DHCP. The present study shows that DHCP has global effects in *E. coli*, affecting many genes encoding proteins that are involved in general metabolism and membrane synthesis and function. Interestingly, a number of genes responding to oxidative and osmotic stress were upregulated. In addition, *tehA*, *tehB*, and *cysK*, which confer resistance to tellurite, were upregulated significantly. The modes of resistance to tellurite and the mechanism of its toxicity have been of great interest to researchers and have not been fully understood. It has been shown elsewhere that *cysK* mediates tellurite resistance in *E. coli* and TehA and TehB confer resistance to tellurite; Cys residues in these proteins are involved in binding to tellurite, and TehB needs *S*-adenosylmethionine to bind tellurite. It is a dimer that can bind both of these compounds in mediating resistance to tellurite. Tellurite generates oxidative stress and may replace sulfur in various proteins, rendering them nonfunctional (8, 9, 18, 20). In the present study, in addition to *cysK*, *tehA*, and *tehB*, the genes encoding proteins such as AhpF, Dps, KatG, SoxS, and Bfr, which respond to oxidative stress, were upregulated. This suggests that DHCP may be generating stress inside the cell, and its manifestations are apparent in a number of secondary effects observed in the present study. Since genes belonging to the regulon involved in synthesis of Cys were significantly upregulated by the DHCP

TABLE 3. Genes repressed by DHCP treatment

Gene	Gene product and/or function	Ratio (DHCP treated/control)
Genes involved in membrane synthesis and function		
ansP	L-Asparagine permease	0.29
atoE	Short-chain fatty acids	0.17
cheA	Chemotaxis protein CheA	0.25
fadL	Long-chain fatty acid transport protein	0.10
fecA	Iron(III) dicitrate transport protein FecA	0.16
fecB	Iron(III) dicitrate-binding protein	0.15
fecC	FecC protein	0.21
fecD	Iron(III) dicitrate transport system protein	0.15
fecE	Iron(III) dicitrate transport protein	0.11
fepA	Ferrienterochelin receptor precursor	0.25
fepC	Ferric enterobactin transport protein FepC	0.40
flhC	Flagellar transcriptional activator FlhC	0.29
flhD	Flagellar transcriptional activator FlhD	0.11
fliC	Flagellin	0.30
glf	UDP-galactopyranose mutase	0.20
lysP	Lysin-specific permease	0.16
motA	Chemotaxis protein MotA	0.18
motB	Chemotaxis protein MotB	0.40
nmpC	Outer membrane porin protein precursor	0.01
ompA	Outer membrane protein A precursor	0.23
ompC	Outer membrane protein C precursor	0.20
ompF	Outer membrane protein F precursor	0.06
ompT	Proteinase VII	0.11
pheP	Phenylalanine transport protein PheP	0.13
plsX	PlsX protein	0.28
potA	Spermidine and putrescine transport protein A	0.13
potB	Spermidine and putrescine transport system	0.13
potC	Spermidine and putrescine transport system	0.20
potD	Spermidine and putrescine transport protein D	0.19
rfc	Probably O-antigen polymerase	0.23
sdaC	Probable serine transport protein	0.25
secF	Secretion protein SecF	0.26
secG	P12 cytoplasmic membrane protein	0.30
secY	SecY protein	0.40
tsr	Methyl-accepting chemotaxis protein 1 (MCP-1)	0.22
tsx	Nucleoside-specific channel-forming protein	0.22
znu	High-affinity zinc uptake system protein	0.13
Genes involved in cell metabolism		
ackA	Acetate kinase	0.28
entA	2,3-Dihydro-2,3-dihydroxybenzoate	0.44
entB	Isochorismatase	0.23
entC	Isochorismate synthase	0.45
entE	Enterochelin synthetase	0.32
fruB	Phosphotransferase system	0.12
fruK	I-Phosphofructokinase	0.03
ndk	Nucleoside-diphosphate kinase	0.20
pheS	Phenylalanyl-tRNA synthetase α subunit	0.25
pheT	Phenylalanyl-tRNA synthetase β subunit	0.25
ptfB	Phosphotransferase system enzyme II	0.08
pyrD	Dihydroorotate oxidase	0.22
rfbC	dTDP-6-deoxy-D-glucose-3,5 epimerase	0.21
rfbD	dTDP-6-deoxy-L-mannose-dehydrogenase	0.27
Genes encoding proteins with diverse functions		
cirA	Colicin I receptor precursor	0.16
cspA	Cold shock protein	0.38
cspB	Cold shock protein	0.38
cspF	Cold shock protein	0.14
cspL	Cold shock protein	0.19
dnaJ	DnaJ protein	0.28
hns	DNA-binding protein H-NS	0.30
hsdS	Type I restriction enzyme	0.21
mcrB	5-Methylcytosine-specific restriction enzyme B	0.10
mcrC	McrC protein	0.11
mrdA	Penicillin binding protein	0.25
mrdB	Rod-shaped determining protein MrdB	0.24
sapA	Peptide transport periplasmic protein SapA	0.28
sapC	Peptide transport system permease protein	0.28
sapD	Peptide transport-ATP-binding protein	0.17
sapF	Peptide transport-ATP-binding protein	0.24
sfa	Sfa protein	0.24
speD	Adenosylmethionine decarboxylase	0.23
spoT	SpoT protein	0.22
suhB	Extragenic suppressor protein SuhB	0.23

treatment, it will also be interesting to see if DHCP is involved in Cys biosynthesis.

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