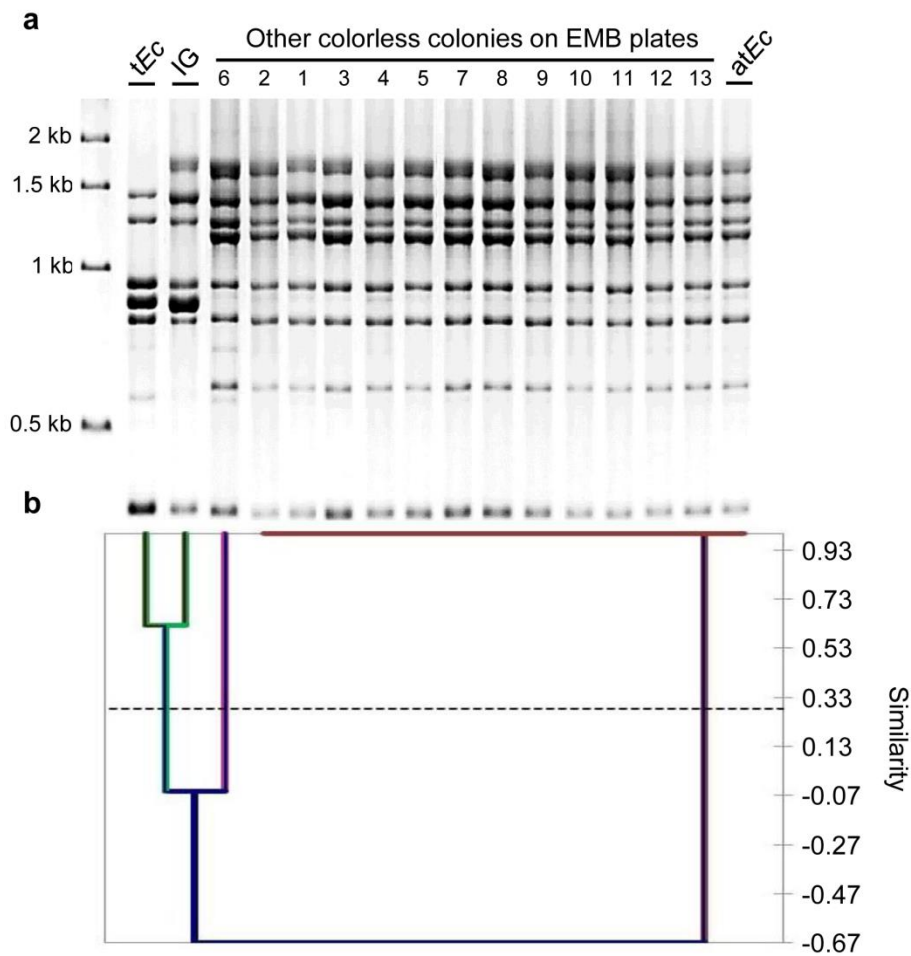
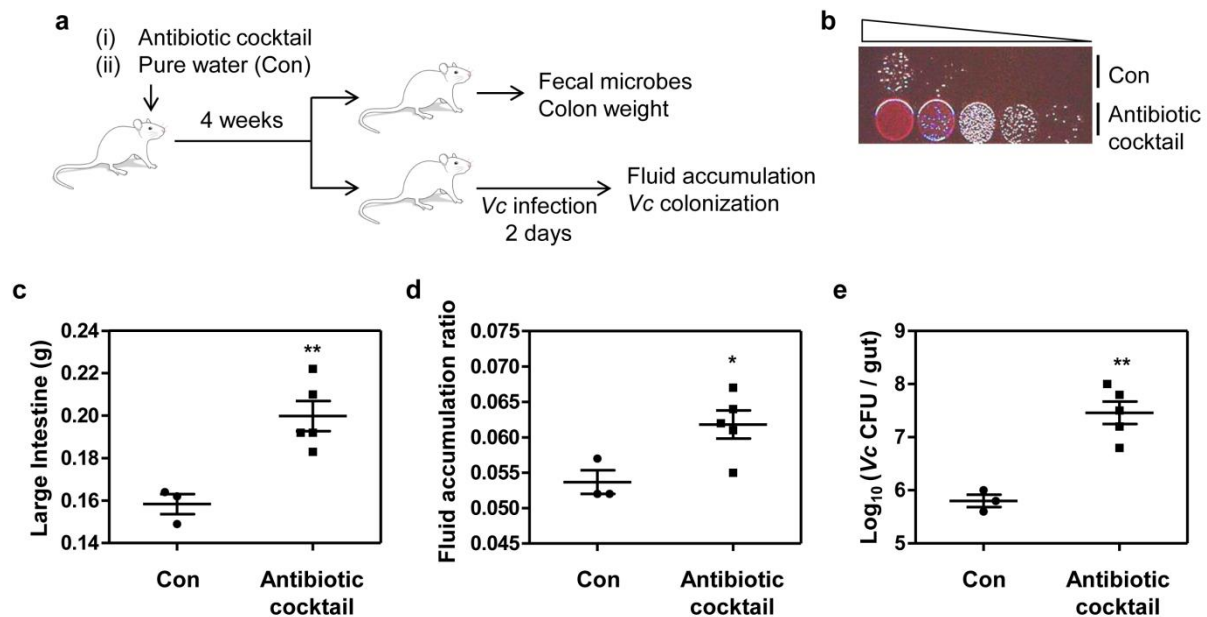


Supplementary Figure 1. Relative quantities of the indicated groups of bacteria in SI tissue homogenates. Adult mice (n=5) were treated with SM or VAN as described in Fig. 1A. Untreated mice were used as controls. The copy numbers of the 16S rRNA gene of γ -proteobacteria (a), Enterobacteriaceae (b), *E. coli* (c), *Bifidobacterium* (d), *Lactobacillus* (e) and *Bacteroides* (f) were determined by real-time PCR and normalized to that of host *gapdh*. Values are expressed as means \pm SEMs and are displayed on a log scale. * $P < 0.05$, ** $P < 0.005$, *** $P < 0.001$ vs. the relative quantities of the control group for each panel. *NS, not significantly different between the groups as determined by ANOVA.



Supplementary Figure 2. Genome typing of *E. coli* cells growing as colorless colonies. (a) RAPD amplification products. The RAPD reaction was performed as described in Methods with the primers listed in Supplementary Table 1. Reaction products were analyzed on agarose gels. A total of 14 colorless colonies (including “atEc” in the far right lane; the genome of this strain was fully sequenced) were included in the assay. In addition, one colony exhibiting the typical *E. coli* growth phenotype on EMB plates (“tEc”) and one intermediate green colony isolated from the feces of VAN-treated mice (“IG”) were analyzed. (b) Dendrogram based on RAPD analysis. Thirteen of the colorless strains, including atEc, shared 100% genomic similarity. However, strain 6 was an exception.

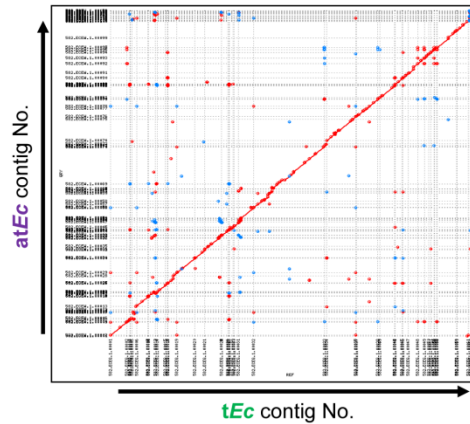


Supplementary Figure 3. Atypical *E. coli* cells proliferate in mice treated with a mixture of 4 antibiotics. (a) Schematic diagram of the experimental procedure. Four-week-old female Balb/c mice were treated with an antibiotic cocktail (ampicillin, 100 µg/mL; vancomycin, 10 µg/mL; metronidazole, 50 µg/mL; and neomycin, 30 µg/mL) for 4 weeks. Antibiotics were administered in the drinking water. (b) Representative EMB plate showing substantial proliferation of colorless atypical *E. coli* strains after antibiotic treatment. Aliquots of mouse fecal suspensions were serially diluted and spotted onto EMB plates. (c) The large intestine was removed from each control (n=3) or antibiotic-treated mouse (n=5) and weighed. Values are expressed as means ± SEMs and are displayed on a linear scale. ** $P < 0.01$ vs. control mice. (d) Antibiotic-treated (n=5) and control (n=3) mice were challenged with Vc. On day 2 post-infection, the fluid accumulation (FA) ratio of each group was measured and is plotted on a linear scale. * $P < 0.05$ vs. the FA ratio of the Vc-infected control group. (e) Vc colonization in each group. The number of Vc CFUs was determined by plating serial dilutions of intestinal homogenates onto LB plates supplemented with 200 µg/mL SM. Values are expressed as means ± SEMs and are displayed on a log scale. * $P < 0.005$ vs. Vc CFUs from the control group.

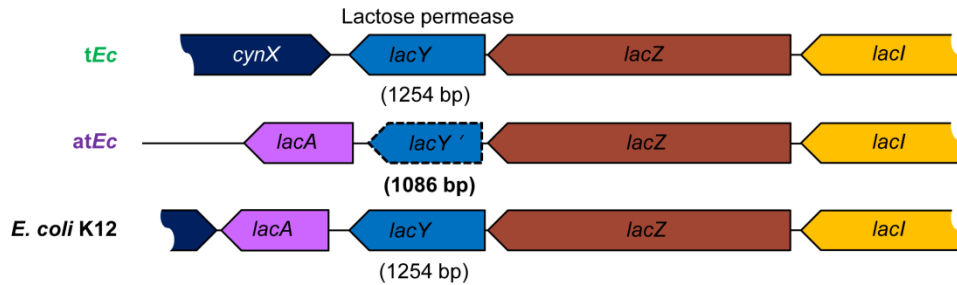
a. Genome information

	size	GC contents	CDS
<i>tEc</i>	4.72 Mb	50.65 %	4,403
<i>atEc</i>	5.24 Mb	50.56 %	5,019
<i>E. coli</i> K12	4.64 Mb	50.79 %	4,299

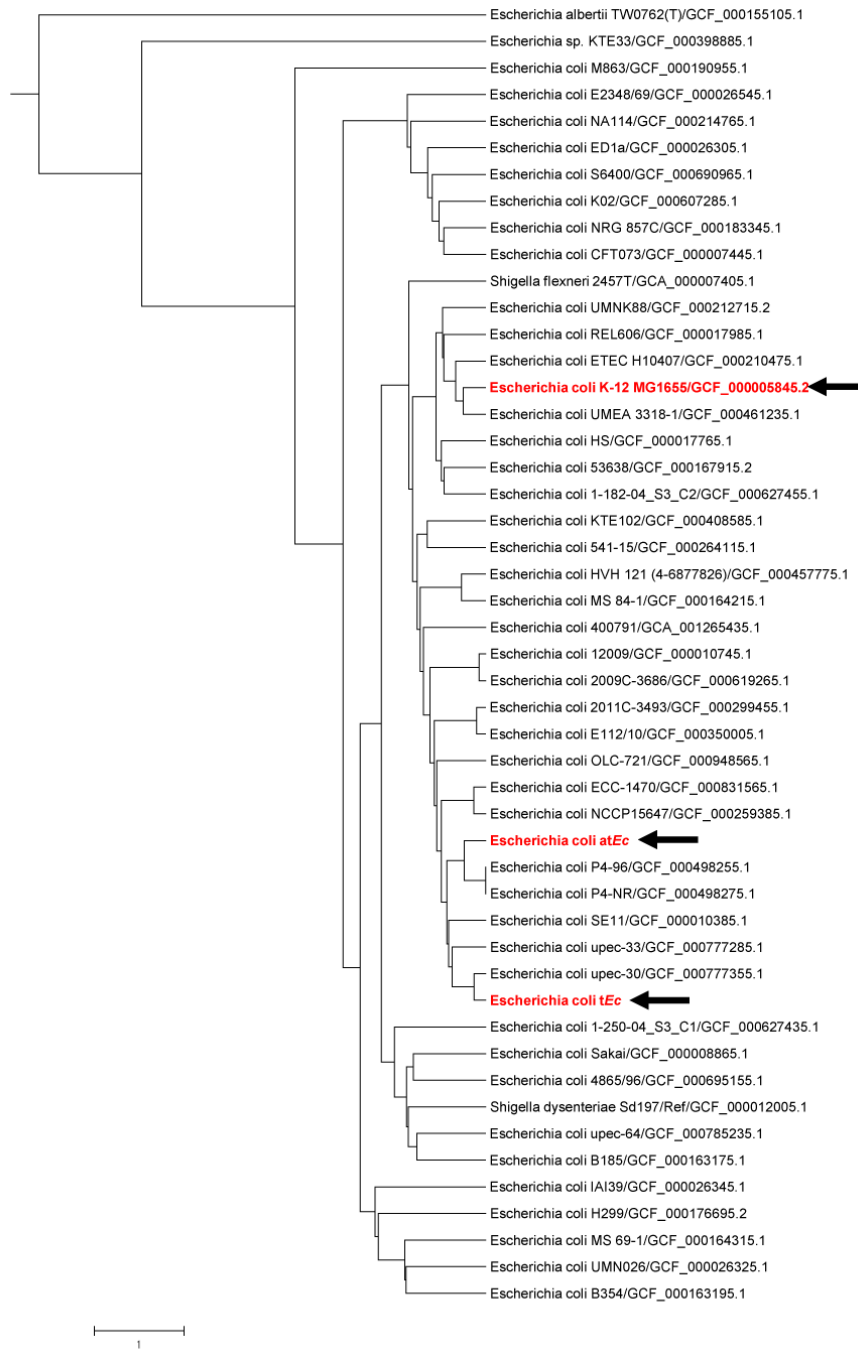
b. MUMmer dot plot



c. Genetic structure of *lac* operon



Supplementary Figure 4. Whole genome sequencing provides an explanation for why the *atEc* strain forms colorless colonies on EMB plates. (a) Comparison of the genome sequences of the *atEc*, *tEc*, and K12 strains. (b) Alignment of the *atEc* and *tEc* genomes using the Maximal Unique Match (MUM) system, which extracts the longest possible nucleotide matches of both genomes. Each dot represents a match between the two genomes. Red and blue dots indicate matches in the forward and reverse direction, respectively. (c) Comparison of the genetic structures of the *lac* operons of the different strains. The *lacY* gene of the *atEc* strain was truncated (dotted line), while the *tEc* strain harbored an intact *lacY* gene. The length and direction of each arrow indicate the relative size and transcriptional direction of each gene.

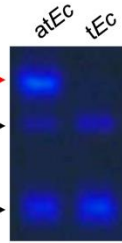


Supplementary Figure 5. Genome-based phylogenetic relationship of atEc, tEc strains with other representative *E. coli* and *Shigella* strains. Three *E. coli* strains, whose genomes were compared in Fig. S4A, were indicated with black arrows. The dendrogram was constructed based on average nucleotide identity (ANI) values.

a. Catalase genes

	KatE	KatG	extra KatE (eKatE)
<i>tEc</i>	753 aa (750/753)	726 aa (725/726)	
<i>atEc</i>	753 aa (749/753)	726 aa (725/726)	750 aa
<i>E. coli</i> K12	753 aa	726 aa	

b



c. Amino acid sequence alignment of eKatE and KatE

```

KatE      NSQHNKFNPHQSPHSDSSEAKPGMDSLAPEDGSHRPAEPTPPGAQPTAPGSLKAPDT
eKatE     M I KKNKADFTSNGSNKKA I STVEPHYEDTAPAKEY I KSLT S I SPPGVPEHMPGSDKTPKN
* : : : : : * : : : : * : : : : : : : : : : : : : : : : : : : : : : : : : : :

KatE      RNEKLSLEDVFKGSENYALT NQGVRI A DQNSLRA GNRGPTLLEDF I LREK I THFDHE
eKatE     RNEKLTQLDKFFAPQGESLRTNQGVI SDQNSLSKSGRSTLLEDF I LREK I THFDHE
*****:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....

KatE      RI PER I V HARGSA AHGV FQPYKLSDI TKADFL SDPNKI TPVVFVSTVGGAGSADTVR
eKatE     RI I PERVYHARGTGAHV FQVY ESLASYTTAEFLQDPSYKTPVVFVSTVGGSRGSADTVR
*****:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....

KatE      D I RGFAT KFYT EEGI FDLVGNNTPI FF I QDAHKFPDFVHAVKPEPHAI PQGQSAHDTF#
eKatE     D I RGFAT KFYT KEGT FDLVGNNTPVYFF I QDA I KFPDFVHAVKPEPHNEI PQGQSAHDTF#
*****:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....

KatE      DYVSLQPETLHWMIWMSDRGI PRSYRTMEGFG I HTFPL I NAEQKATVYFHWKPLAGKA
eKatE     DYVSLQPETLHWMIWMSDRGI PRSYRMMEGFG I HTVVM I NAEQGHFI FFWKPYVGVYS
*****:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....

KatE      SLVWDEAKLTDGRDPFHRRELVEA I EAGDFPEVELGFL I PEEDEFKDFDLDLPTKL I
eKatE     SL I WDEAQLTGDGDFHRRELVES I EAGDVPVELGLQ I I PEEDEHKDFDI LDPTKL I
*****:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....

KatE      PEELVYQRYGKMYLNINPQWFAENEQAFFPHGI V PGLDFTNDPLLOGRLFSY I DTQ I
eKatE     PESLVYPYHLVGNMYLNINPQWVSETEQWAFQGN I V PGI DFDSDPLLOGRLFSY I DTQ I
** : : * : : * : : * : : * : : * : : * : : * : : * : : * : : * : : * : :

KatE      SRLGGNPFHEI P I NRPT CPYHNFQRDGMHRMGI DTPANVFNPS I NDNWPRETPPQPKRG
eKatE     SRLGGNPFHEI P I NKPI CPFHNRQRDGMHRMGI SG-TANVFNPS I NDNWPREAPP---TEG
*****:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....

KatE      GFESYQERVEGKVIERSPSFGEVYSHRFLWLSQIPFEQRHI VDGFSFELSKVYHPY I R
eKatE     GF I TYQRPVNGVYKSRKRSSTF I DYSQPRFLWLSQITKVEQNH I VDGFSFELSKVYHPY I R
** : : * : : * : : * : : * : : * : : * : : * : : * : : * : : * : : * : :

KatE      ERVYDQLAHLDTLAQA VAKNLGI ELTDDQLNI TPPPVDVNSLKKDPSLSLYA I PDGQVKG
eKatE     ERVYNQLTY I DHQLAQSVADNLGI KLSQEQKHPGPI NGLSKDPSLSMVDGHHQ I LKS
*****:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....

KatE      RYVATLLNDEVRSADLLA I LKALKAGVHAKLLYSRMGEVTDGDTVLP I AATFAGAPSL
eKatE     RQVATLAADGVCGDA I DNI MKTLKQVGVHGI FAFPHGR I TSLQGNIEVNGT I EGNPSY
***** : : : : : * : : * : : * : : * : : * : : * : : * : : * : : * : : * : :

KatE      TVDQV I VPCG--N I ADI ADNGDANVYLMEAVKHLKPI ALAGDARFKKAT I KVAQDQEEGI
eKatE     MYDQV I I PDGEDS I DLSMKNGNAKHYY I QAFKHLKAI GLOKAKFLYDA LPLPKPDEGI V
***** * : : : * : : * : : * : : * : : * : : * : : * : : * : : * : : * : :

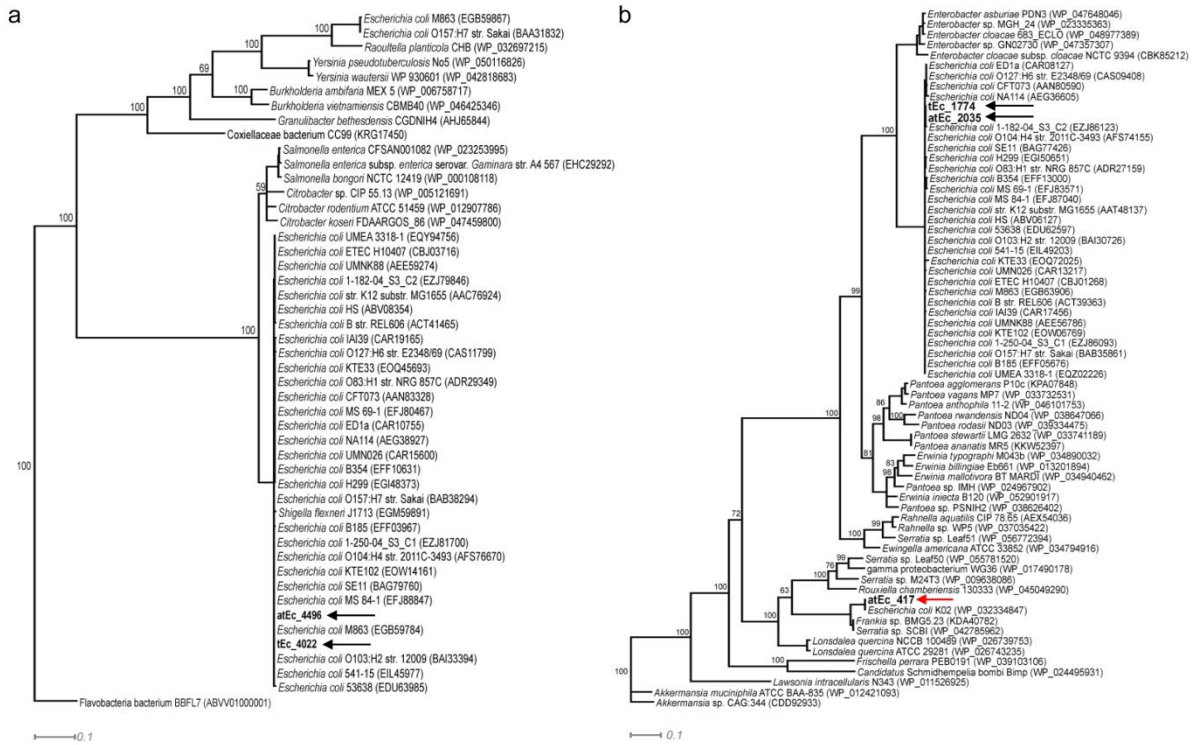
KatE      YEADSDQSFNDELLTLMAHRVWSRI PK I DKI PA
eKatE     VGDKAAD---LAEAFQWVRGHR I WSRESVAQE I AG
* : : * : : : : : * : : * : : : : :
    
```

d. Nucleotide sequence identity of *atEc* *eKatE* gene

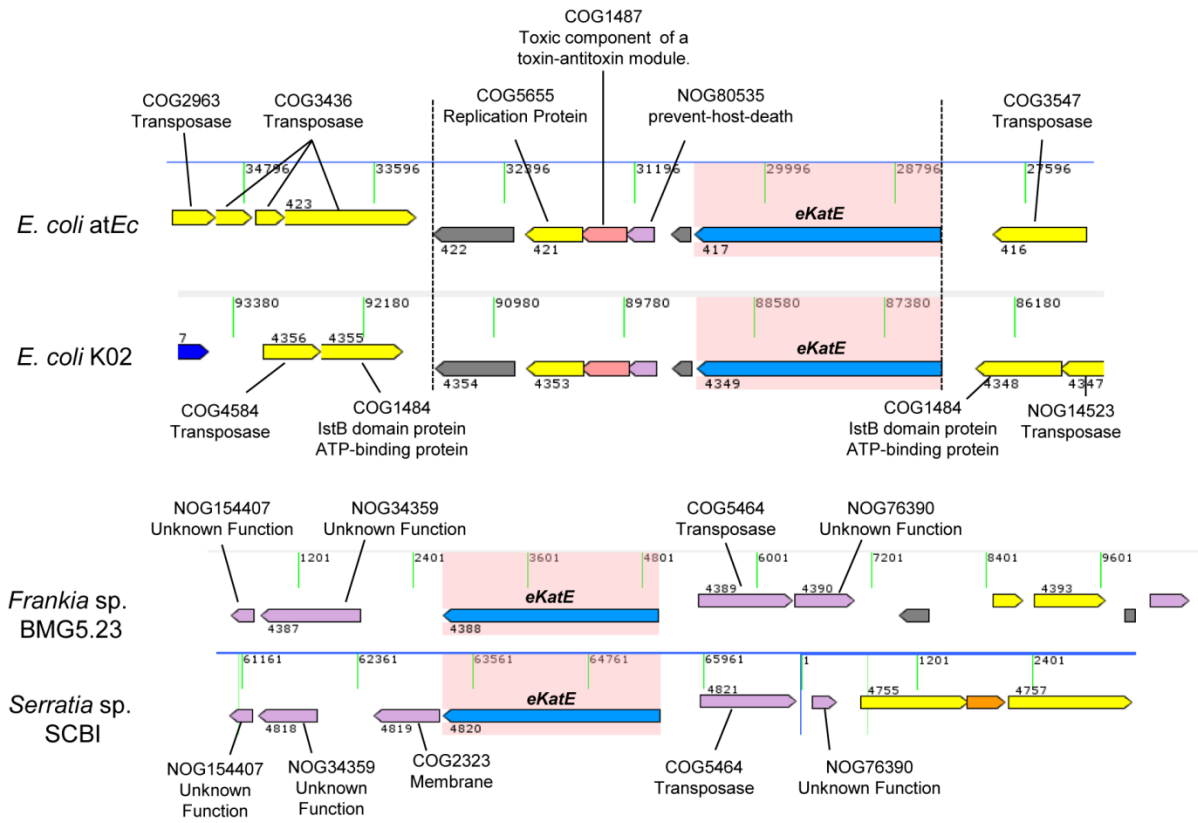
	<i>E. coli</i> <i>atEc</i>	<i>E. coli</i> K02	<i>Serratia</i> sp. SCBI	<i>Frankia</i> sp. BMG5.23
<i>E. coli</i> <i>atEc</i>		0/2253*	160/2250	160/2250
<i>E. coli</i> K02	100%		160/2250	160/2250
<i>Serratia</i> sp. SCBI	92.89%	92.89%		0/2250
<i>Frankia</i> sp. BMG5.23	92.89%	92.89%	100%	

* No. of different nucleotides/No. of nucleotides compared

Supplementary Figure 6. The *atEc* strain harbors an extra catalase-encoding gene. (a) The *atEc* strain possesses three catalase genes, while the *tEc* and K12 strains have two. The amino acid (aa) length of each catalase is indicated and the number of identical residues compared to the corresponding K12 protein is shown in parentheses. **(b)** In-gel catalase activity assay. Proteins in bacterial extracts were separated by native gel electrophoresis and catalase-specific bands were stained as described in the Methods section. Three distinct bands are shown in the left lane of the gel (*atEc* cell lysate). **(c)** Amino acid sequence alignment of KatE and eKatE. **(d)** The top 3 genes exhibiting the highest sequence identities to the *eKatE* gene. To identify similar genes, the NCBI database was searched using the BLASTn algorithm.



Supplementary Figure 7. Maximum likelihood trees of *E. coli* and related taxa constructed using the amino acid alignments of KatG (a) and KatE (b) proteins. Numbers above branches show maximum-likelihood bootstrap supports from 1,000 non-parametric replicates (shown only if they were > 50). The trees were rooted by outgroups *Flavobacterium bacterium* BBFL7 (a) and *Akkermansia* sp. CAG:344 (b). Accession numbers of protein sequences are indicated between parentheses. The scale represents the number of substitutions per site. KatG and KatE proteins from atEc and tEc strains are shown with black arrows. The eKatE protein from atEc strain is shown with red arrow.

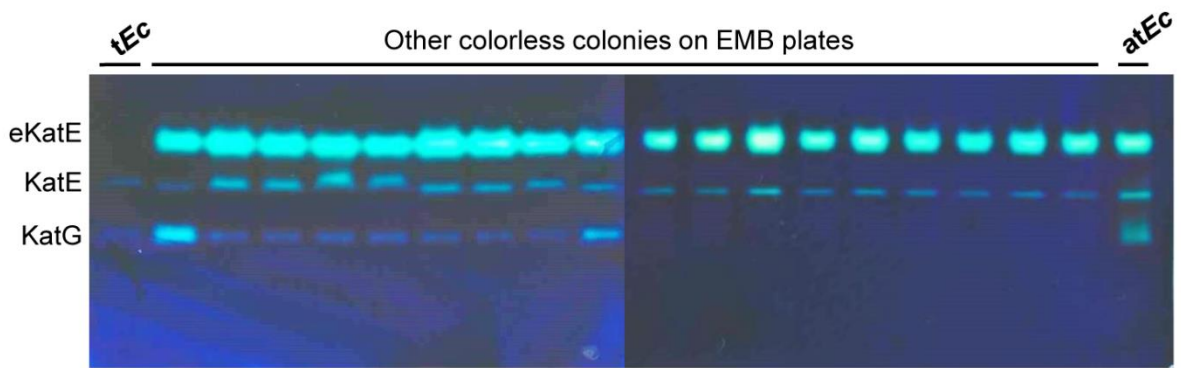


Supplementary Figure 8. Synteny comparison of *eKatE* genetic loci among *atEc*, *K02*, *Frankia sp. BMG5.23* and *Serratia sp. SCBI*. The *eKatE* genes (marked in blue arrows) and neighboring genes with annotation are displayed in each genome. Regions shown between two vertical dotted lines are identical in *atEc* and *K02* strains.

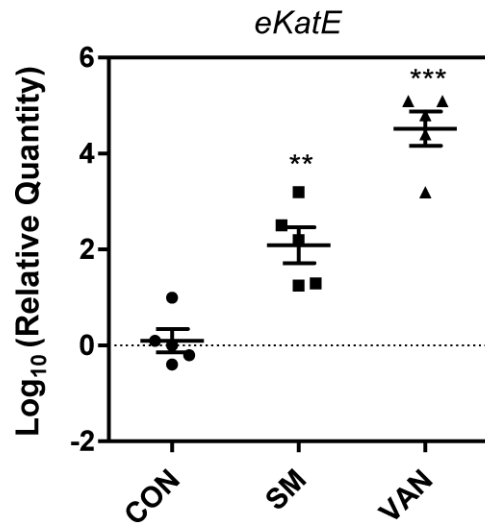


Gene	Size (bp)	Function
atEc 410	807	resolvase, site-specific recombinase XerD
atEc 411	306	CcdB
atEc 412	219	plasmid maintenance protein CcdA
atEc 413	258	hypothetical protein
atEc 414	591	hypothetical protein
atEc 415	348	hypothetical protein
atEc 416	855	transposase
atEc 417	2,253	eKatE
atEc 418	162	hypothetical protein
atEc 419	255	prevent-host-death
atEc 420	423	toxic component of a toxin-antitoxin (TA) module
atEc 421	513	replication Protein
atEc 422	729	hypothetical protein
atEc 423	1,260	transposase
atEc 424	249	transposase
atEc 425	348	transposase
atEc 426	381	transposase

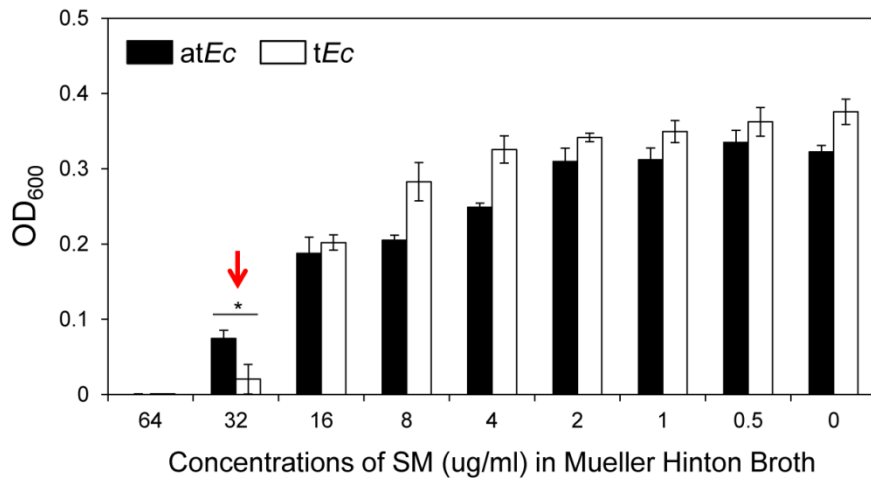
Supplementary Figure 9. A high-resolution physical map of the *eKatE* gene locus in the *atEc* chromosome. In the table, gene numbers, gene sizes (in bp) and putative functions are presented. Genes involved in transposition are shown with gray highlights, while those involved in plasmid maintenance are shown with orange highlights.



Supplementary Figure 10. Native gel-based catalase assay. All other *E. coli* strains (n=18) that formed colorless colonies on EMB plates produced eKatE. The native gel-based catalase activity assay was performed as described in Fig. 5A.



Supplementary Figure 11. Relative quantities of the *eKatE* gene present in SI tissue homogenates (n=5) as determined by real-time PCR. The level of mouse *gapdh* in each sample was used for normalization. The ratios of *eKatE* to host *gapdh* are displayed on a log scale (means ± SEMs). ** $P < 0.005$, *** $P < 0.001$ vs. the control group.



Supplementary Figure 12. Bacterial growth of *atEc* and *tEc* strains in the presence of increasing amounts of SM. Strains were grown in Mueller Hinton Broth, which has been commonly used for antibiotic sensitivity assay. * $P < 0.05$ between two growths.

Supplementary Table 1. Primers used in this study

1. Cloning		
Deletion of <i>eKatE</i> gene in <i>atEc</i> (5' to 3')*		
left-flanking region		F: ATATAGAGCTCGATGATATGAACGGCTCACCGG
		R: TAAATGGATCCCTTTTCGGCAGGTGCAGTATC
right-flanking region		F: CCCTTGGATCCATGATGCGTTGCCGTTGCCCAA
		R: ACACGAGCTCGACTTGTGTAGTAACGTTACTACG
Construction of P _{ctxAB} :: <i>luxCDABE</i> transcriptional fusion (5' to 3')		
P _{ctxAB}		F: CACATGAATTCACTATCGAGTCAGAGCAATCCG
		R: ATTGGTCTAGATTGTTAACAGAAAAATAATTGATCAAAC
<i>luxCDABE</i>		F: ATTCGTCGACACTAAAAAATTTTCATTATT
		R: GATATGAGCTCTACTCAGGAGAGCGTTCAC
Construction of Vc N16961 strain containing chromosomally encoded <i>ekatE</i> gene		
<i>atEc ekatE</i>		F: CATATGAATTCGGCAAGCCCACTTATCGTCAA
		R: CAATTAAGCTTTTAGCCAGCAATTTCTGTGCT
VC0512 600bp		F: AATTCGAATTCCTGAGGGAGCACTCCTGATAAG
		R: GATATGAGCTCCTGAGGCATCCATATCGGAAC
Construction of t <i>Ec</i> strain that express the <i>ekatE</i> gene		
pBAD24:: <i>ekatE</i>		F: AATTCGAGCTCGGCAAGCCCACTTATCGTCAA
		R: ATATCGAGCTCTGTCTTACAGGTGGATGGCCT
2. Quantitative real-time PCR		
Organisms	Target Genes	Sequences (5' to 3')
Mus musculus	<i>gapdh</i>	F: GTGTTCTACCCCAATGTGT
		R: ATTGTCATACCAGGAAATGAGCTT
γ-Proteobacteria	16S <i>rRNA</i>	F: CM ATGCCGCGTGTGTGAA**
		R: ACTCCCCAGGCGGT CD ACTTA***
Enterobacteriaceae	16S <i>rRNA</i>	F: GTTAATACCTTTGCTCATTGA
		R: ACCAGGGTATCTAATCCTGTT
<i>E. coli</i>	16S <i>rRNA</i>	F: CAGCCACACTGGAAGTGAAGA
		R: GTTAGCCGGTGCTTCTTCTG
<i>Bacteroides</i>	16S <i>rRNA</i>	F: AACGCTAGCTACAGGCTT
		R: CAATCGGAGTTCTTCGTG
<i>Lactobacillus</i>	16S <i>rRNA</i>	F: AGCAGTAGGGAATCTTCCA
		R: CACCGCTACACATGGAG
<i>Bifidobacterium</i>	16S <i>rRNA</i>	F: TCGCGTCYGGTGTGAAAG
		R: CCACATCCAGCRTCCAC
<i>Vibrio cholerae</i>	16S <i>rRNA</i>	F: CTGGAAGTGAACACCGGTCC
		R: CATGCGCTTTACGCCAGTA
<i>atEc</i>	<i>eKatE</i>	F: GAGTCTTTGGTCCCGTTCA
		R: ACTCCTCCCAAACGGCTAAT
3. RAPD		
M13 primer		5'- GAGGGTGGCGTCT

F, forward; R, reverse.

* Restriction enzyme recognition sequences are underlined.

**M is either A or C.

***D is either G, A or T.

Supplementary Table 3. Codon adaptation index (CAI) and GC contents of catalase genes in *atEc* strain.

Genes	Size (bp)	CAI	%G+C
<i>katE</i>	2,262	0.751	51.5
<i>katG</i>	2,181	0.812	55.8
<i>eKatE</i>	2,253	0.671	43.6

Supplementary Table 4. Genes involved in oxidative stress responses

Genes in atEc	Genes in tEc	Function	eggNOG ID
atEc_0008	tEc_4463	Aerobic respiration control protein arcA	COG0745
atEc_0025	tEc_0012	Hydrogen peroxide-inducible genes activator	COG0583
atEc_0189	tEc_0177	Lactoylglutathione lyase (EC 4.4.1.5)	COG0346
atEc_0212	tEc_0199	Hydroxyacylglutathione hydrolase (EC 3.1.2.6)	COG0491
atEc_0213	tEc_0200	FIG005121: SAM-dependent methyltransferase (EC 2.1.1.-)	COG0500
atEc_0417	-	eKatE, Catalase	COG0753
atEc_0676	tEc_0582	Glutamate--cysteine ligase archaeal (EC 6.3.2.2)	COG2170
atEc_0777	tEc_0682	Ferric uptake regulation protein FUR	COG0735
atEc_0983	tEc_0810	Non-specific DNA-binding protein Dps	COG0783
atEc_1009	tEc_0836	Uncharacterized glutathione S-transferase-like protein	COG0625
atEc_1020	tEc_0847	Glutaredoxin 1	COG0695
atEc_1098	tEc_0925	Hydroxyacylglutathione hydrolase (EC 3.1.2.6)	COG0491
atEc_1102	tEc_0929	Nicotinate phosphoribosyltransferase (EC 2.4.2.11)	COG1488
atEc_1121	tEc_0948	Paraquat-inducible protein A	COG2995
atEc_1122	tEc_0949	Paraquat-inducible protein B	COG3008
atEc_1123	tEc_0950	Paraquat-inducible protein B	COG3009
atEc_1231	tEc_1056	Glutaredoxin 2	COG2999
atEc_1286	tEc_1111	NAD-dependent protein deacetylase of SIR2 family	COG0846
atEc_1499	tEc_1316	Fumarate and nitrate reduction regulatory protein	COG0664
atEc_1624	tEc_1424	NAD-dependent glyceraldehyde-3-phosphate dehydrogenase (EC 1.2.1.12)	COG0057
atEc_1663	tEc_1461	Uncharacterized GST-like protein yncG	COG0625
atEc_1690	tEc_1494	Organic hydroperoxide resistance protein	COG1764
atEc_1936	tEc_1676	Glutathione S-transferase (EC 2.5.1.18)	COG0625
atEc_1947	tEc_1687	Superoxide dismutase [Cu-Zn] precursor (EC 1.15.1.1)	COG2032
atEc_1952	tEc_1692	Lactoylglutathione lyase (EC 4.4.1.5)	COG0346
atEc_1955	tEc_1695	Probable monothiol glutaredoxin GrIA	COG0278
atEc_1957	tEc_1697	Superoxide dismutase [Fe] (EC 1.15.1.1)	COG0605
atEc_2012	tEc_1753	Glutathione peroxidase (EC 1.11.1.9)	COG0386
atEc_2035	tEc_1774	KatE, Catalase (EC 1.11.1.6)	COG0753
atEc_2072	tEc_1811	Nicotinamidase (EC 3.5.1.19)	COG1335
atEc_2075	tEc_1814	NAD-dependent glyceraldehyde-3-phosphate dehydrogenase (EC 1.2.1.12)	COG0057
atEc_2129	tEc_1869	Paraquat-inducible protein A	COG2995
atEc_2130	tEc_1870	Paraquat-inducible protein B	COG3008
atEc_2724	tEc_2386	Probable glutathione S-transferase (EC 2.5.1.18), YfcF homolog	COG0625
atEc_2725	tEc_2387	Probable glutathione S-transferase (EC 2.5.1.18), YfcG homolog	COG0625
atEc_3117	tEc_2706	Glutaredoxin-like protein NrdH	COG0695
atEc_3131	tEc_2720	Glutamate--cysteine ligase (EC 6.3.2.2)	COG2918
-	tEc_2780	Organic hydroperoxide resistance transcriptional regulator	ENOG4111Y81
atEc_3470	tEc_3055	Glutathionylspermidine synthase (EC 6.3.1.8)	COG0754
atEc_3471	tEc_3056	Uncharacterized GST-like protein yghU	COG0625
atEc_3474	tEc_3060	Rubredoxin	ENOG4111JT6
atEc_3512	tEc_3106	Similarity with glutathionylspermidine synthase (EC 6.3.1.8), group 1	COG0754
atEc_3577	tEc_3172	Glutathione S-transferase, omega (EC 2.5.1.18)	COG0435
atEc_3682	tEc_3277	Aerobic respiration control sensor protein arcB (EC 2.7.3.-)	COG2198
atEc_3859	tEc_3456	Competence protein F homolog, phosphoribosyltransferase domain	COG1040
atEc_3893	tEc_3490	Gamma-glutamyltranspeptidase (EC 2.3.2.2)	COG0405
atEc_3944	tEc_3541	Glutathione reductase (EC 1.8.1.7)	COG1249
atEc_3985	tEc_3574	Cytochrome c551 peroxidase (EC 1.11.1.5)	COG1858
atEc_4069	tEc_3658	Uncharacterized GST-like protein yibF	COG0625
atEc_4092	tEc_3676	Glutaredoxin 3 (Grx3)	COG0695
atEc_4458	tEc_3984	Manganese superoxide dismutase (EC 1.15.1.1)	COG0605
atEc_4496	tEc_4022	KatG, Peroxidase (EC 1.11.1.7)	COG0376
atEc_4514	tEc_4042	OxyR, Hydrogen peroxide-inducible genes activator	ENOG410XNR2
atEc_4604	tEc_4132	Zinc uptake regulation protein ZUR	COG0735
atEc_4620	tEc_4149	Regulatory protein SoxS	ENOG4111IXA
atEc_4621	tEc_4150	Redox-sensitive transcriptional activator SoxR	COG0789
atEc_4750	tEc_4262	Nitrite-sensitive transcriptional repressor NsrR	COG1959
atEc_4758	tEc_4270	Similarity with glutathionylspermidine synthase (EC 6.3.1.8), group 1	COG0754

Genes involved in oxidative stress responses were searched against the whole genes in atEc and tEc strains with a key phrase “oxidative stress” using the CLgenomics software. An orthologous group that each protein belongs to is shown with its eggNOG ID (<http://eggnogdb.embl.de/>).