Table S1. An overview of genes involved in DNA methylation, DNA demethylation, and one-carbon metabolism pathway that were analyzed in this study

Gene	Full Name	Role	Detailed Role	Reference[a]
DNMT1	DNA methyltransferase 1	Maintenance DNA methylation	Maintenance DNA methyltransferase	[1]
DNMT3A	DNA methyltransferase 3A	*De novo* DNA methylation	*De novo* DNA methylation	[1]
DNMT3B	DNA methyltransferase 3B	*De novo* DNA methylation	*De novo* DNA methylation	[1]
DNMT3L	DNA methyltransferase 3-like protein	Stimulates enzymatic activity of DNMT3A	Stimulation of enzymatic activity of DNMT3A	[1]
TET3	Tet methylcytosine dioxygenase 3 (ten-eleven translocation-3)	DNA demethylation	Conversion of 5-mC to 5-hmC, 5-fC and 5-caC	[1, 2]
AICDA (AID)	Activation-induced cytidine deaminase	DNA demethylation	DNA demethylation via deamination of 5-mC or 5-hmC	[2-4]
APOBEC1	Apolipoprotein B mRNA editing activity DNA deaminase 1	DNA demethylation	DNA demethylation via deamination of 5-mC or 5-hmC	[2-4]
APOBEC2	Apolipoprotein B mRNA editing activity DNA deaminase 2	DNA demethylation	DNA demethylation	[2-4]
APOBEC3A	Apolipoprotein B mRNA editing activity DNA deaminase 3A	DNA demethylation	DNA demethylation, possibly via deamination of 5-mC or 5-hmC	[2-4]
APOBEC3C	Apolipoprotein B mRNA editing activity DNA deaminase 3C	DNA demethylation	DNA demethylation, possibly via deamination of 5-mC or 5-hmC	[2-4]
TDG	Thymine-DNA glycosylase	DNA demethylation	Excision of target bases including 5-fC and 5-caC to initiate BER pathway	[2-4]
GADD45A	Growth arrest and DNA damage 45 protein A	DNA demethylation, DNA repair	DNA repair-mediated DNA demethylating factor that can reactivate genes which had been silenced by methylation; also involved in apoptosis	[5-8]
IDH1	Isocitrate dehydrogenase 1	Produces metabolites that interfere with TET-mediated DNA demethylation	IDH1 mutations lead to accumulation of 2-HG, TET inhibition and DNA hypermethylation	[2, 9-13]
IDH2	Isocitrate dehydrogenase 2	Produces metabolites that interfere with TET-mediated DNA demethylation	IDH2 mutations lead to accumulation of 2-HG, TET inhibition and DNA hypermethylation	[2, 9-13]
MGMT	O(6)-methylguanine-DNA methyltransferase	DNA repair via demethylation of O^6-meG	Demethylates O^6-methylguanine lesions. MGMT also removes larger O^6-alkyl	[14]

			adducts, and is thereby involved in resistance to nitrosourea-based anticancer drugs	
MBD1	Methyl-CpG-binding domain protein 1	Binding to methylated DNA, transcriptional modulation	Transcriptional repression, DNA repair	[1, 15-17]
MBD2	Methyl-CpG-binding domain protein 2	Transcriptional modulation, possible DNA demethylation, binding to methylated DNA	Possible roles in transcriptional activation or repression, possible DNA demethylation	[1, 15, 18]
MBD3	Methyl-CpG-binding domain protein 3	Binding to 5-hmC	Transcriptional repression	[1, 15]
MBD4 (MED1)	Methyl-CpG-binding domain protein 4	DNA repair	DNA repair, possible roles in demethylation and maintenance DNA methylation	[4, 16, 17]
MeCP2	Methyl-CpG-binding protein 2	Binding to methylated DNA, transcriptional modulation, forms a complex with TET1	Transcriptional repression, participation in TET1 complexes that lead to DNA demethylation	[1, 15]
PCNA	Proliferating cell nuclear antigen	DNA repair and replication; interactions with DNMT1 and TET1	Participates in DNA repair and replication. It may affect both DNA methylation via interaction with DNMT1 and DNA demethylation by forming a complex with TET1	[11, 19]
USP7 (HAUSP)	Herpes virus–associated ubiquitin specific protease	Promotes DNA methylation via control of DNMT1	Regulates DNMT1 abundance, stability and activity	[19, 20]
SMUG1	Single-strand-selective monofunctional uracil-DNA glycosylase	DNA demethylation, DNA repair	A member of the uracil-DNA glycosylase superfamily which is involved in DNA repair and DNA demethylation via the base excision repair (BER) pathway by participating in degradation of 5-hydroxymethyluracil (5-hmU) to unmethylated cytosine	[1, 2, 4]
MTHFR	5, 10-methylenetetrahydrafolate reductase	OCM: regulation of folate metabolism	Catalyzes one of the central OCM reactions: the NADPH-dependent reduction of 5,10-methylenetetrahydrafolate (5,10-methyleneTHF) to 5-methylTHF	[21, 22]
MTHFD1	Methylenetetrahydrafolate dehydrogenase 1	OCM: Cytoplasmic roles as FTHF synthetase, CH^{+}-THF cyclohydrolase, and CH_2-THF dehydrogenase	Combines the functions of 10-formyl-THF synthetase, 5,10-methenyl-THF cyclohydrolase, and 5,10-methylene-THF	[21, 23, 24]

			dehydrogenase that catalyze the reversible interconversion in the cytoplasm of THF into 5,10-methyleneTHF, via 10-formylTHF and 5,10-methenylTHF. These reactions produce 5,10-methyleneTHF, a cofactor required for thymidylate biosynthesis.	
MTR	Methionine synthase	OCM: remethylation of Hcy to methionine	Remethylates Hcy to methionine	[23]
MTRR	5-methyltetrahydrafolate-homocysteine methyltransferase reductase	OCM: generates functional methionine synthase	Produces active methionine synthase, MTR	[25, 26]
CBS	Cystathionine β-synthase	OCM: catalyzes the condensation of Hcy and Ser to cystathionine	Participates in the reactions that lead to the conversion of Hcy to cysteine, removing Hcy from the methylation cycle	[25]
TCN2	Transcobalamin II	OCM: vitamin B12 transport	Transport protein for cobalamin	[27]
SHMT1	Serine hydroxymethyl transferase 1	OCM: catalyzes the reversible conversion of Ser and THF to glycine and CH_2-THF	Catalyzes the synthesis of 5-formylTHF from 5,10-methenylTHF in the cytoplasm and limits the availability of 5-methylTHF for Hcy remethylation and SAM biosynthesis; some reports also noted its possible activity in the nucleus	[21]
TYMS (TS)	Thymidylate synthase	OCM: catalyzes the conversion of dUMP to dTMP	Catalyzes the 5,10-methyleneTHF-dependent conversion of deoxyuridinemonophosphate (dUMP) into deoxythymidine monophosphate (dTMP), which serves as a precursor for DNA synthesis and is used DNA repair	[21, 23]
DHFR	Dihydrofolate reductase	OCM: conversion of dihydrofolate to THF	Catalyzed the reduction of dihydrofolate (DHF) to THF	[21, 23]
BHMT	Betaine-homocysteine methyltransferase	OCM: remethylation of Hcy to methionine	Participates in remethylation of Hcy to methionine via a reaction that is an alternative to the reactions regulated by MTR and MTRR	[23, 28]
CTH	Cystathionase (cystathionine γ-lyase)	OCM: conversion of cystathione to cysteine	Irreversible degradation of cystathionine, which is derived from Hcy, to cysteine, which contributes to removal of Hcy from	[25, 29, 30]

			the methylation cycle	
AHCY (SAHH)	S-adenosyl-L-homocysteine hydrolase	OCM: hydrolysis of SAH to adenosine and Hcy	Catalyzes reversible hydrolysis of *S*-adenosyl-*L*-homocysteine to Hcy and adenosine	[30, 31]
ALDH1L1	10-formyl tetrahydrofolate dehydrogenase (aldehyde dehydrogenase 1 family, member L1), cytosolic	OCM: irreversible oxidation of FTHF to THF and CO_2	Encodes 10-formyltetrahydrofolate dehydrogenase (FDH), a major regulator of folate metabolism in the cytoplasm via $NADP^+$ -dependent irreversible oxidation of 10-formylTHF to THF. This process controls the availability of folate-bound carbon groups for biosynthetic processes, cell growth, and remethylation of Hcy, and it affects the availability of methyl groups for cellular methylation reactions	[32, 33]
ATIC	5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase	OCM: purine biosynthesis	Purine biosynthesis	[34]
GART	Phosphoribosylglycinamide formyltransferase	OCM: purine biosynthesis	Purine biosynthesis	[34]
MTHFS	Methylenetetrahydrofolate synthase	OCM: purine biosynthesis	Encodes 5,10-methenylTHF synthetase which catalyzes the irreversible conversion of 5-formylTHF to 5,10-methenylTHF	[21]
FTCD	Glutamate formiminotransferase	OCM: histidine catabolism	Provides one-carbon units resulting from histidine catabolism to the folate pool	[21]
MAT1A	L-methionine S-adenosyltransferase I, alpha	OCM: catalyzes SAM biosynthesis from methionine and ATP	Catalyzes biosynthesis of SAM, the major source of methyl groups for methylation reactions	[35]
MAT2A	L-methionine S-adenosyltransferase II, alpha	OCM: catalyzes SAM biosynthesis from methionine and ATP	Catalyzes biosynthesis of SAM	[35]
MAT2B	L-methionine S-adenosyltransferase II, beta	OCM: catalyzes SAM biosynthesis from methionine and ATP	Catalyzes biosynthesis of SAM	[35]
NNMT	Nicotinamide N-methyltransferase	OCM: N-methylation of nicotinamide and other pyridines using SAM as methyl donor	Generates 1-methylnicotinamide in a reaction that consumes methyl units from SAM and reduces the ratio of SAM to Hcy	[36, 37]
PON1	Paraoxonase 1	OCM: generates Hcy from homocysteine thiolactone	Generates Hcy from homocysteine thiolactone	[38]
SLC19A1	Reduced folate carrier	OCM: transport of folate and drugs	Major transporter of folate and of antifolate	[22, 25,

(RFC1)		across cell membrane	cancer drugs across cell membrane	39-42]
FOLR1 (FRα)	Folate receptor 1	OCM: folate endocytosis	Folate endocytosis	[40]
FOLR2 (FRβ)	Folate receptor 2	OCM: folate endocytosis	Folate endocytosis	[40]
FOLR3 (FRγ)	Folate receptor 3	OCM: folate endocytosis	Folate endocytosis	[40]
SHMT2	Serine hydroxymethyl transferase 2	OCM: mitochondrial folate metabolism for glycine synthesis	Encodes the mitochondrial isozyme of serine hydroxymethyltransferase	[43]
AMT	Aminomethyltransferase	OCM: glycine cleavage system in mitochondria	Involved in the glycine cleavage system in mitochondria that generates 5,10-methylene-THF	[21]
MTHFD2	Methylenetetrahydrofolate dehydrogenase 2	OCM: mitochondrial NAD^+-dependent CH_2-THF dehydrogenase and CH^+-THF cyclohydrolase	Bifunctional mitochondrial NAD^+-dependent 5,10-methylene-THF dehydrogenase /5,10-methenyl-THF cyclohydrolase	[43]
MTHFD2L	Methylenetetrahydrofolate dehydrogenase 2-like	OCM: Mitochondrial dual redox cofactor-specific CH_2-THF dehydrogenase and CH^+-THF cyclohydrolase	5,10-methyleneTHF dehydrogenase and 5,10-methenyl-THF cyclohydrolase in the mitochondrial OCM pathway	[18]
PEMT	Phosphatidylethanolamine-N-methyltransferase	OCM: biosynthesis of phosphatidyl choline via interaction with SAM	Catalyzes the *de novo* synthesis of phosphatidylcholine using SAM as methyl donor	[30]
FOLH1 (GCPII, PSMA)	Folate hydrolase (glutamate carboxypeptidase II)	Conversion of dietary folate to folate and its intestinal absorption	Intestinal absorption of dietary folate and its conversion to folate	[24]
ALDH2	Aldehyde dehydrogenase 2 (mitochondrial)	Metabolizes acetaldehyde, which may affect folate levels and inhibit DNA methylation	Affects folate levels *in vivo* by producing high levels of acetaldehyde in alcohol metabolism and reducing the cleavage of folate	[44]

2-HG, 2-hydroxyglutarate**; 5-hmU**, 5-hydroxymethyluracil; **5-caC**, 5-carboxylcytosine; **5-fC,** 5-formylcytosine; **5-hmC,** 5-hydroxymethylcytosine; **5-mC,** 5-methylcytosine; **BER,** base excision repair; **CH^+-THF**, 5,10-methenyl-tetrahydrofolate; **CH_2-THF**, 5,10-methylene-tetrahydrofolate; **FDH**, 10-formyltetrahydrofolate dehydrogenase; **FTHF**, 10-formyl-tetrahydrafolate; **Hcy**, homocysteine; **OCM**, folate-mediated one-carbon metabolism pathway; **SAH**, *S*-adenosylhomocysteine; **SAM,** *S*-adenosylmethionine; **Ser**, serine; **THF**, tetrahydrafolate

[a] The list of references for Table S1 is provided after Table S2.

Table S2. Numbers of genes with concerted expression and their empirical *p*-values for each treatment condition

Drug	Concentration	Time (hours)	Number of genes with concerted expression	*P*-value
5-Azacytidine	High	2	3	0.6237
5-Azacytidine	High	6	15	0.1694
5-Azacytidine	High	24	36	0.3517
5-Azacytidine	Low	2	2	0.4805
5-Azacytidine	Low	6	8	0.0245**
5-Azacytidine	Low	24	24	0.1042
Doxorubicin	High	2	5	0.9307
Doxorubicin	High	6	20	0.1309
Doxorubicin	High	24	28	0.4328
Doxorubicin	Low	2	1	0.6757
Doxorubicin	Low	6	7	0.0205**
Doxorubicin	Low	24	19	0.0034**
Vorinostat	High	2	11	0.2011
Vorinostat	High	6	24	0.5076
Vorinostat	High	24	33	0.0076**
Vorinostat	Low	2	9	0.3379
Vorinostat	Low	6	23	0.3160
Vorinostat	Low	24	24	0.0463**
Paclitaxel	High	2	0	1.0000
Paclitaxel	High	6	0	1.0000
Paclitaxel	High	24	16	0.0001*
Paclitaxel	Low	2	0	1.0000
Paclitaxel	Low	6	1	0.4355
Paclitaxel	Low	24	16	0.0000*
Cisplatin	High	2	0	1.0000
Cisplatin	High	6	10	0.1481
Cisplatin	High	24	17	0.4196
Cisplatin	Low	2	1	0.2785
Cisplatin	Low	6	0	1.0000
Cisplatin	Low	24	5	0.1270

Empirical *p*-values were computed using 10,000 replications of random sampling of 56 genes from the 12,704 genes for which expression data were available in the TP Workbench. Genes were determined to have concerted expression when nearly all cell lines had a change in the same direction, with ≤ 15 cell lines showing a change in the opposite direction.

* $P < 0.00167$ (Bonferroni-adjusted *p*-value threshold for 5 agents, 2 concentrations, and 3 time points)

** $P < 0.05$

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