Supplementary Material

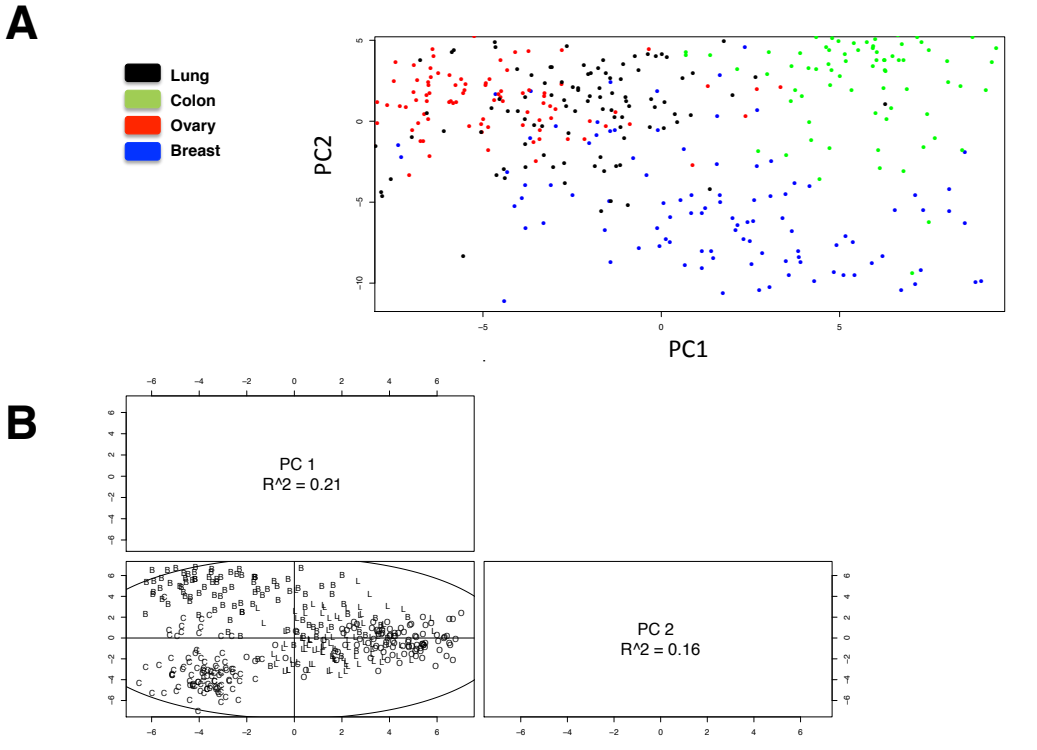
Supplementary Methods.

Contingency table comparing mitochondrial vs. cytosolic isoforms in the context of tumor/normal over-expression (combined across all cancer types in study). This test was done only on enzymes that have both mitochondrial and cytosolic isoforms included in the SGOC network (6 mitochondrial and 5 cytosolic enzymes , 4 cancer types). Fisher's exact p-value = 0.02

	Over-expressed in tumor	Not over-expressed in tumor
Mitochondrial isoforms	12	12
Cytosolic isoforms	3	17

Supplementary Figure 1 related to Figure 1.

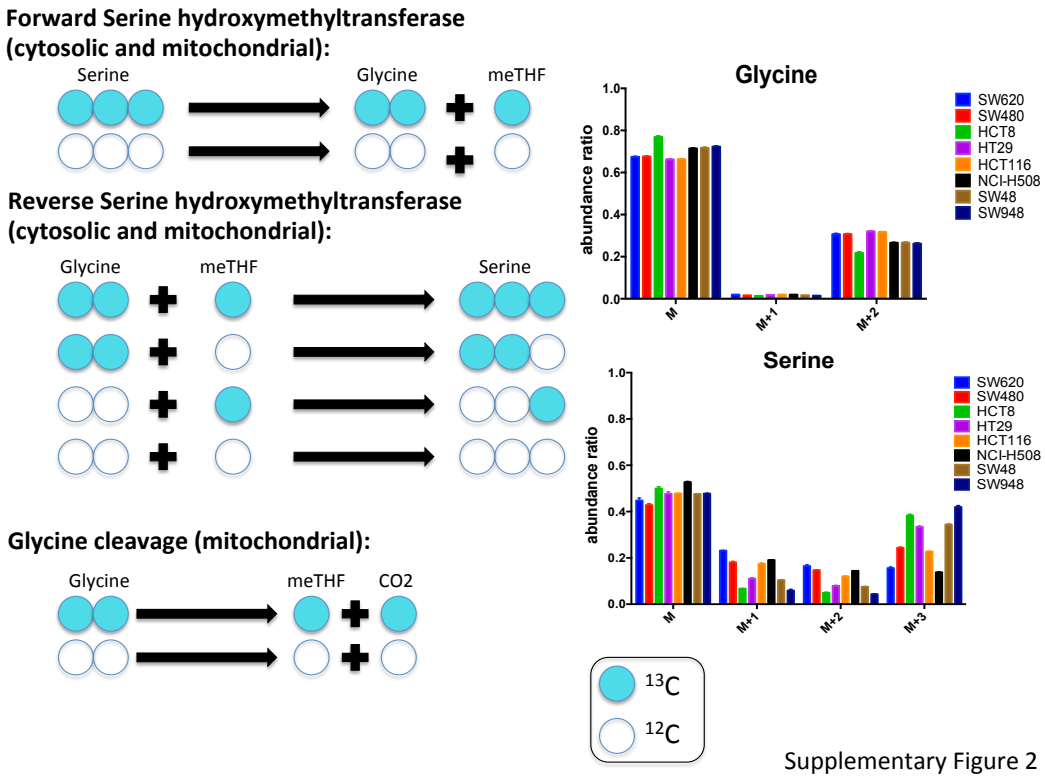
A.)Principal component analysis on 100 randomly picked samples from each cancer type (400 samples total). The second principal component (PC2) is plotted against the first principal component (PC1). B.) Principal component analysis on 100 randomly picked samples from each cancer type (400 samples total). Different cancer types are shown by letters (B:Breast, O:Ovary, C:Colon, L:Lung). The second principal component (PC2) is plotted against the first principal component (PC1). Fraction of variation explained by each PC is shown as R^.



Supplementary Figure 1

Supplementary Figure 2 related to Figure 6.

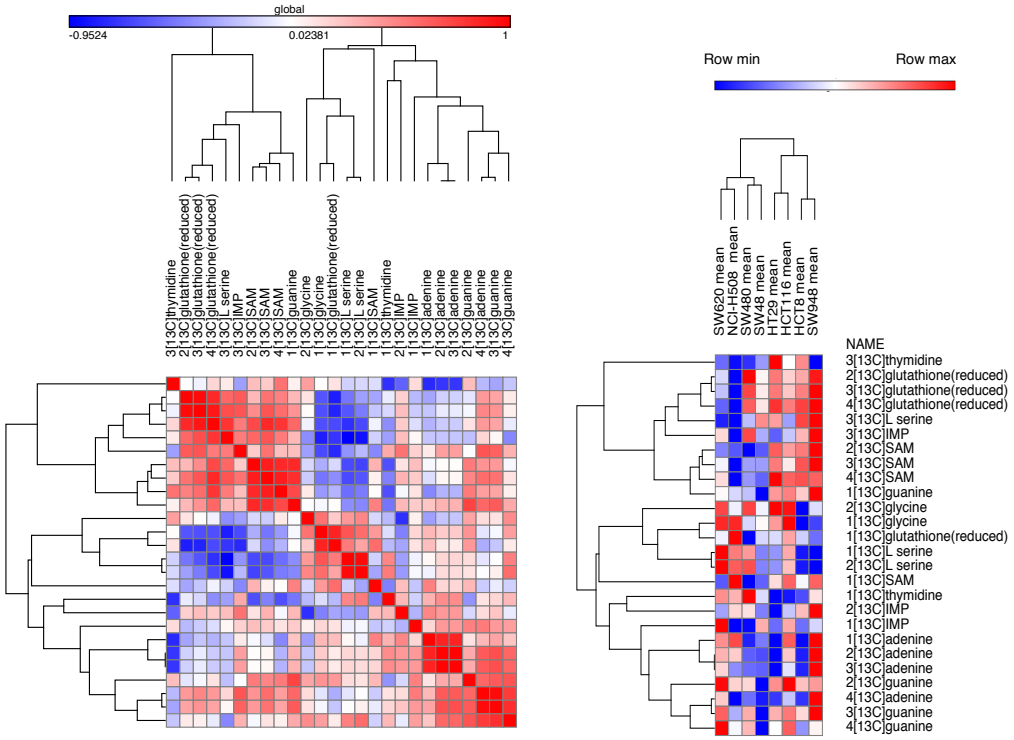
Schematic showing the mass isotopomer distribution (MID) patterns observed for serine and glycine in our 13C-serine tracing experiment (right) along with the chemical reactions explaining the patterns observed (left).



Supplementary Figure 2

Supplementary Figure 3 related to Figure 4.

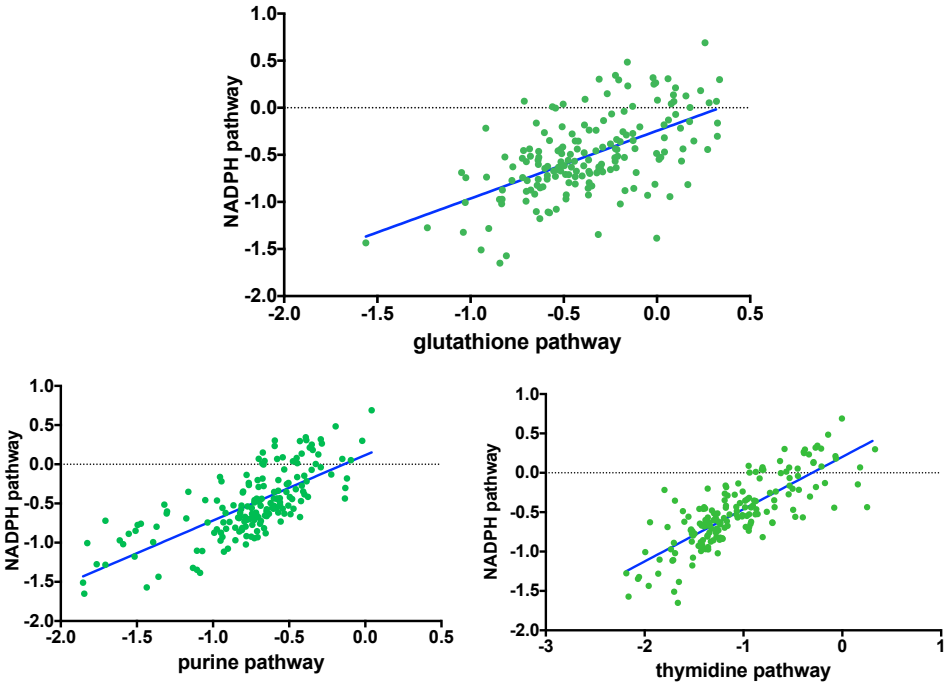
Heatmaps of abundance ratios of some of the labeled isotopomers from the 13C experiment. On the right, hierarchical clustering is shown for the 8 colon cancer cell lines in the columns and the labeled metabolites in rows. The left heatmap shows the similarity matrix of pairwise Spearman correlations across labeled isotopomers.



Supplementary Figure 3

Supplementary Figure 4 related to Figure 5.

Scatterplots of average pathway expressions in TCGA colon cancer samples. A significantly positive association (regression p-value<0.0001) is seen in all three cases between NADPH pathway and glutathione, purine, or thymidine pathways.



Supplementary Figure 4

Table S1 related to Table 1. Results of the statistical analysis on the SGOC expression levels.

The SGOC genes are listed in the first column with mitochondrial enzymes highlighted in yellow. Mean and CV for LOWESS normalized gene expression values are shown across each cancer type. The "T-T highest" column shows the cancer type

with the highest average expression for each gene across the 4 cancer types. Mann-Whitney-Wilcoxon p-values and effect sizes are reported for each test in the following two columns. “N-N” columns summarize similar analysis across the 4 normal tissue types. The following “T-N” columns show the results of tumor vs. normal overexpression tests, with Mann-Whitney-Wilcoxon p-values and effect sizes reported for each gene in each tissue type. Finally, “T-N Var” columns show results of comparing absolute values of difference from mean in tumors vs. corresponding normal tissues, again reporting Mann-Whitney-Wilcoxon p-values and effect sizes for each gene in each tissue type (“-“ denotes missing data).

Table S2 related to Figure 1A. List of genes excluded from our network.

All genes manually excluded from the analysis in the second step of the network reconstruction are listed. These genes were excluded from further analysis due to non-specificity of the reactions that they are involved in.

Table S3 related to Figure 6. Estimated fluxes.

Estimated fluxes and associated fitting errors are listed. All fluxes are fitted or calculated based on flux balance (exceptions are gcs, shmt2-, x_methf- and dil_methf that were fixed). Results from a Monte-Carlo simulation using parameters that reflect HCT116 cells are also shown (MC-ave: average flux from 500 iterations; MC-sd: standard deviation; MC-cv: coefficient of variation).

	SW620	SW480	HCT8	HT29	HCT116	NCI-H508	SW48	SW948	MC-ave	MC-sd	MC-cv
Fshmt1+	7.79	3.44	1.41	1.61	2.96	6.56	1.64	1.21	2.99	0.26	0.09
Fshmt1-	7.19	2.37	0.32	0.70	2.07	5.35	0.59	0.25	2.18	0.21	0.10
Ftr_gly	0.48	0.26	0.58	0.34	0.32	0.28	0.48	0.66	0.33	0.06	0.18
Fx_ser+	0.55	0.10	0.00	0.21	0.31	0.28	0.03	0.09	0.33	0.11	0.33
Fphgdh	0.06	0.12	0.09	0.08	0.15	0.44	0.07	0.01	0.13	0.04	0.35
Fshmt2+	0.46	0.06	0.00	0.17	0.27	0.24	0.04	0.05	0.34	0.11	0.32
Fshmt2-	0.01	0.01	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.00
Fgcs	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.00	0.00
Fx_methf+	0.46	0.06	0.01	0.17	0.26	0.23	0.04	0.04	0.33	0.11	0.32
Fx_methf-	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.00
Fdilmethf	1.00	5.00	5.00	1.00	1.00	1.00	1.00	10.00	1.00	0.00	0.00
Fthddn	0.54	0.99	0.36	0.10	0.18	0.91	0.57	0.70	0.28	0.03	0.11
Fadedn	0.76	0.59	0.54	0.57	0.75	0.81	0.58	0.75	0.91	0.02	0.02
Fx-gly	0.51	0.12	0.05	0.27	0.35	0.28	0.07	0.05	0.38	0.11	0.28