Figure S1, Related to Figure 1. The impact of oncogenic mutations on cellular proliferation and metabolism.

A. Adherent cell proliferation rates of indicated YAMC cell derivatives prior to and following metabolite extraction and processing for LC-MS/MS. Proliferation rates indicated above graph are for time period +/- 4 hours from metabolite extraction. Data are means ± S.D.

B. Percentage of senescence associated and acidic β-gal activity depicted in representative images on right. Senescence associated (pH 6) and acidic (pH 4) β-gal activity were measured at time of metabolite extraction and processing for LC-MS/MS. Values are represented as average of two independent experiments. Representative scale bar, 20 μm.

C. PLS-DA model validation and classification with different number of components using the R caret package through Metaboanalyst. The red star indicates the optimum model.

D. Permutation testing of the PLS-DA model shown in Fig 1F. Testing was performed using the separation distance based on the ratio of the between group sum of squares and the within group sum of squares (B/W ratio). The test statistic distribution frequency is plotted.

E. Loadings plot for principal components 1 and 2 shown in Fig 1F, with indicated metabolites strongly correlated with the transformed state.
Figure S2, Related to Figures 1 and 4. The impact of oncogenic mutations on oxidative pentose phosphate pathway (PPP) and pyruvate carboxylation. A. Schematic of differential glucose carbon oxidation reactions and the downstream impact on lactate labeling. B. Parental murine colon crypt epithelial cells (Y), or cells retrovirally transduced with either vector controls (BN), DN-p53\textsuperscript{175H} (mp53), CA-Ras\textsuperscript{12V} (Ras), or both oncogenic alleles (mp53Ras) were pulsed with 1,2-\textsuperscript{13}C-glucose for 6h and then processed for LC-MS/MS. The ratio of labeled lactate containing one versus two \textsuperscript{13}C atoms is indicative of the PPP:glycolytic flux ratio; nonoxidative PPP flux yields lactate containing one \textsuperscript{13}C atom, whereas glycolytic flux yields two \textsuperscript{13}C atoms. C. Schematic of TCA cycle labeling upon pyruvate carboxylation versus dehydrogenation (by PDH). D. The cells in (B) were pulsed with 3-\textsuperscript{13}C-glucose for 24h and then processed for LC-MS/MS. The percentage of 1,\textsuperscript{13}C-labeled malate represents the percentage of malate produced from pyruvate carboxylation. In contrast, pyruvate oxidation mediated by the pyruvate dehydrogenase complex releases this carbon as CO\textsubscript{2}. 
Figure S3, Related to Figure 2. Oncogenic LDH isoform switching in human cancers.  
A-H. LDHB or LDHA RNA expression in human pancreas, prostate, or colon tissue.  
(A, D, G) LDHB or LDHA RNA expression in tumor vs normal tissue based on cDNA microarray data from the Gene Expression Omnibus (GEO) database.  
(B, E, H) LDHB or LDHA RNA expression in tumor vs normal tissue based on expression data from the TCGA database.  
(C, F, I) LDHB or LDHA RNA expression in tumors with both p53 and Ras mutations (Tumor: mp53+Ras), tumors with p53 but not Ras mutation (Tumor: mp53), tumors with Ras but not p53 mutation (Tumor: Ras), and tumors with neither p53 nor Ras mutation (Tumor: neither).  
(A-H) *p<0.05 versus non-tumor and **p<.01 versus non-tumor, by student’s t-test.  
#p<0.05 and ##p<.01, by ANOVA F-test and Tukey method.  
All y-axis values represent linear scale.
Figure S4, Related to Figure 2-4. Oncogenic LDH isoform switching is important for coupling of glycolysis to glutamine driven TCA anaplerosis.  A-B. (A) LDHB or (B) LDHA RNA expression measured in indicated mp53/Ras derivative cell populations prior to implantation into mice (Pre-inject) and in tumors (Tumor) that arose from these cells following xeno-implantation. Expression was measured by real time quantitative PCR. Data are means ± S.E. of the mean.  C. Relative intracellular metabolite levels of indicated derivatives of mp53/Ras cells, determined by LC-MS/MS. Measurements made following 24 hr cell culture in 1% oxygen. Data are means ± S.E. of the mean. *p<0.05 versus vector control, by student’s t-test.  D. Cells were labeled with 13C-glucose for 90 minutes at 1% oxygen and the relative abundance of 13C- and 12C-isoisomers was determined by LC-MS/MS. Bars represent total relative abundance of a given metabolite and shading indicates isotopologue composition. Isotopologue species are indicated by m+n, with m+0 representing the unlabeled fraction. **p<0.01 for total 13C-isotopologue abundance of indicated metabolite versus that metabolite’s total 13C-isotopologue abundance in vector control, by student’s t-test. Measurements were made following 8-10 hr cell culture in 1% oxygen.  E. Extracellular serine levels in culture media of indicated derivatives of mp53/Ras cells, determined by LC-MS/MS. Measurements were made following 8-10 hr cell culture in 1% oxygen and data are means ± S.E. of the mean. *p<0.05 versus vector control, by student’s t-test.  F. Cells were labeled with 13C-glutamine for 90 minutes at 1% oxygen and the relative abundance of 13C- and 12C-isoisomers was determined by LC-MS/MS. Bars represent total relative abundance of a given metabolite and shading indicates isotopologue composition. Isotopologue species are indicated by m+n, with m+0 representing the unlabeled fraction. **p<0.01 for total 13C-isotopologue abundance of indicated metabolite versus that metabolite’s total 13C-isotopologue abundance in vector control, by student’s t-test. Measurements were made following 8-10 hr cell culture in 1% oxygen.  G. Adherent cell proliferation of indicated derivatives of mp53/Ras cells in 1% oxygen and in the presence of exogenously supplied alanine (+ala) when indicated. Data are means ± S.D.
Figure S5, Related to Figures 3-6. Kinetic labeling of central carbon metabolic pools. A-E. Indicated derivatives of (A-C) mp53/Ras cells, (D) HCT116, or (E) SW480 cells were pulsed with $^{13}$C-glucose or $^{13}$C-glutamine for indicated time and the relative abundance of $^{12}$C- and $^{13}$C-isoforms was determined by LC-MS/MS. Graphs represent percentage of indicated metabolite pools that turnover from $^{12}$C- to $^{13}$C-isoforms over time, with $^{13}$C representing the sum of all m+1 or greater species) Data are means ± S.E. of the mean. (A-B) Labeling after 8-10 hr cell culture in 1% oxygen.
Figure S6, Related to Figure 5. GPT2 couples glycolysis to glutamine driven TCA anaplerosis in mp53/Ras cells. A-B. Cells were labeled with $^{13}$C-glucose or $^{13}$C-glutamine for 90 minutes and the relative abundance of $^{13}$C- and $^{12}$C-isotopes was determined by LC-MS/MS. Bars represent total relative abundance of a given metabolite and shading indicates isotopologue composition. Isotopologue species are indicated by $m+n$, with $m+0$ representing the unlabeled fraction. *$p<0.01$ for total $^{13}$C-isotopologue abundance of indicated metabolite versus that metabolite’s total $^{13}$C-isotopologue abundance in all other cell lines, by student’s t-test. C. Cells were labeled with $\alpha-^{15}$N-glutamine and the relative abundance of $^{15}$N- and $^{14}$N-isotopes was determined by LC-MS/MS. Graph represents percentage of indicated metabolite pools that turnover from $m+0$ to $m+1$ over time. D-F. Adherent cell proliferation of indicated derivatives of mp53/Ras cells in the presence of exogenously supplied alanine (+ala) or pyruvate (+pyr) when indicated. Data are means + S.D. (F) proliferation assayed in 1% oxygen. G. Endogenous GPT2 RNA expression measured in indicated mp53/Ras derivative cell populations prior to implantation into mice (Pre-inject) and in tumors (Tumor) that arose from these cells following xeno-implantation. Expression was measured by real time quantitative PCR. Data are means + S.E. of the mean.
**Figure S7, Related to Figure 6. GPT2 dependency of human colon cancer cells.**

**A-B.** GPT2 RNA expression in human colon tissue. (A) GPT2 RNA expression in tumor vs normal tissue based on expression data from the TCGA database. (B) GPT2 RNA expression in colon tumors with both p53 and Ras mutations (Tumor: mp53+Ras), tumors with p53 but not Ras mutation (Tumor: mp53), tumors with Ras but not p53 mutation (Tumor: Ras), and tumors with neither p53 nor Ras mutation (Tumor: neither). (A-B) \*p<0.001 versus non-tumor, by student’s t-test. All y-axis values represent linear scale.

**C-E.** The indicated derivatives of HCT116 or SW480 human colon cancer cells were labeled with \(^{13}\)C-glucose or \(^{13}\)C-glutamine for 90 minutes and the relative abundance of \(^{13}\)C- and \(^{12}\)C-isofoms was determined by LC-MS/MS. Bars represent total relative abundance of a given metabolite and shading indicates isotopologue composition. Isotopologue species are indicated by m+n, with m=0 representing the unlabeled fraction. **p<0.01 for total \(^{13}\)C-isotopologue abundance of indicated metabolite versus that metabolite’s total \(^{13}\)C-isotopologue abundance in shGFP control, by student’s t-test.

**F-I.** Adherent cell proliferation of indicated derivatives of HCT116 or SW480 human colon cancer cells in the presence of exogenously supplied alanine (+ala) or pyruvate (+pyr) when indicated. Data are means ± S.D. **J.** Glutaminase (GLS) protein expression by western blot in indicated derivatives of HCT116 or SW480 cells: shGFP control (shGFP), GLS knockdown-1 (shGLS-1), or GLS knockdown-2 (shGPT2-2). GAPDH serves as loading control.

**K-M.** The indicated derivatives of HCT116 or SW480 cells were labeled with \(\alpha\)-\(^{15}\)N-glutamine or \(^{13}\)C-glutamine for 90 minutes and the relative abundance of \(^{15}\)N- and \(^{14}\)N-isofoms and \(^{13}\)C- and \(^{12}\)C-isofoms was determined by LC-MS/MS. Bars represent total relative abundance of a given metabolite and shading indicates isotopologue composition. Isotopologue species are indicated by m+n, with m=0 representing the unlabeled fraction. **p<0.01 for total \(^{13}\)C-isotopologue abundance of indicated metabolite versus that metabolite’s total \(^{13}\)C-isotopologue abundance in shGFP control, by student’s t-test.

**N-O.** Tumor volumes four weeks after 8-12 subcutaneous implantations of the indicated cell lines in the flanks of nude mice. Median tumor volume is indicated by horizontal line. \*P<0.01 versus shGFP, by student’s t-test.
| Metabolic Process          | Mean p-value | Significant at 0.05 by post hoc Fisher’s LSD                                                                 |
|----------------------------|--------------|-------------------------------------------------------------------------------------------------------------|
| Lactate Production         | 2.79E-6      | mp53/Ras - YAMC; mp53/Ras - mp53; mp53/Ras - Ras; mp53/Ras - BN; mp53 - Ras; mp53 - BN                      |
| Glucose Consumption        | 5.11E-5      | mp53/Ras - YAMC; mp53/Ras - mp53; mp53/Ras - Ras; mp53/Ras - BN; mp53 - YAMC; mp53 - BN; Ras - BN            |
| Glutamine Consumption      | 7.58E-7      | mp53/Ras - YAMC; mp53/Ras - mp53; mp53/Ras - Ras; mp53/Ras - BN; mp53 - Ras; Ras - YAMC; Ras - BN             |
| Fatty Acid Biosynthesis    | 3.13E-10     | mp53/Ras - YAMC; mp53/Ras - mp53; mp53/Ras - Ras; mp53/Ras - BN; mp53 - Ras; mp53 - YAMC; mp53 - BN; Ras - BN |
| Metabolite                        | YAMC  | mp53/Ras | mp53  | Ras  | BN   |
|----------------------------------|-------|----------|-------|------|------|
| 1,3-diphosphoglycerate           | 3094 ± 1144 | 6460 ± 1406 | 4963 ± 1202 | 2890 ± 744 | 3447 ± 1527 |
| 2-dehydro-D-gluconate            | 4001 ± 702 | 6733 ± 631  | 5876 ± 4124 | 3759 ± 662  | 3876 ± *  |
| 3-hydroxy-3-methylglutaryl-CoA    | 3846 ± *   | 6644 ± 3356 | 4969 ± 2565 | 2849 ± *   | 4194 ± 1041 |
| 6-phospho-D-gluconate            | 4018 ± 357 | 8366 ± 1634 | 4746 ± 1694 | 6404 ± 2749 | 3525 ± 1011 |
| aconitate                        | 3441 ± 1385 | 2450 ± 525   | 4903 ± 1218 | 4136 ± 1206 | 6490 ± 767   |
| adenosine 5'-phosphosulfate      | 5287 ± 1515 | 3801 ± 842   | 4960 ± 1245 | 5095 ± 1345 | 6223 ± 997   |
| ADP                              | 5748 ± 1524 | 4884 ± 879   | 5588 ± 907  | 5316 ± 1202 | 7832 ± 656   |
| ADP-D-glucose                    | 6166 ± 2141 | 3928 ± 2156  | 2429 ± 915  | 3766 ± 1428 | 4576 ± 2079  |
| allantoate                       | 3625 ± 974  | 6348 ± 1212  | 5765 ± 1069 | 3758 ± 401  | 3338 ± 761   |
| AMP                              | 9243 ± 1023 | 4820 ± 890   | 5553 ± 789  | 7521 ± 644  | 10000 ± 681  |
| anthranilate                     | 5049 ± 1311 | 5872 ± 4128  | 2655 ± 1056 | 6103 ± 1764 | 5973 ± 590   |
| CDP                              | 2784 ± 493  | 6655 ± 1635  | 4490 ± 656  | 3308 ± 676  | 3795 ± 701   |
| coenzyme A                       | 2499 ± 790  | 5291 ± 2028  | 3489 ± 452  | 5814 ± 1645 | 3045 ± 1114  |
| CTP                              | 3474 ± 1175 | 7862 ± 965   | 6216 ± 867  | 4645 ± 996  | 4567 ± 606   |
| dATP                             | 4136 ± 2249 | 2726 ± 602   | 3203 ± 1570 | 2706 ± 1700 | 5204 ± 1745  |
| dCTP                             | 3375 ± 1017 | 7176 ± 1190  | 5738 ± 1189 | 3324 ± 995  | 2926 ± 479   |
| deoxyribose-phosphate            | 5625 ± 1898 | 7178 ± 1677  | 6340 ± 1019 | 7490 ± 1773 | 5052 ± 937   |
| D-gluconate                      | 3978 ± 891  | 4716 ± 758   | 4321 ± 727  | 6180 ± 1094 | 9067 ± 489   |
| D-glucono-lactone-6-phosphate    | 3256 ± 1280 | 4021 ± 802   | 4792 ± 1115 | 4593 ± 1889 | 4657 ± 1934  |
| dihydroxy-acetone phosphate      | 2137 ± 651  | 8101 ± 1899  | 6701 ± 1426 | 2404 ± 1344 | 1782 ± 304   |
| D-sedoheptulose-7-phosphate      | 5307 ± 914  | 4215 ± 670   | 4842 ± 788  | 6809 ± 741  | 6335 ± 1025  |
| dTTP                             | 1770 ± 428  | 7378 ± 1043  | 5619 ± 1043 | 2335 ± 508  | 2070 ± 410   |
| fructose-6-phosphate             | 5401 ± 1559 | 6010 ± 1582  | 4670 ± 787  | 4273 ± 701  | 3276 ± 229   |
| fumarate                         | 3836 ± 1999 | 3557 ± 1109  | 1815 ± 460  | 3806 ± 2089 | 4227 ± 2001  |
| GDP                              | 5151 ± 1288 | 4219 ± 783   | 5761 ± 1007 | 5200 ± 1014 | 7490 ± 832   |
| Compound                      | Value1   | Value2   | Value3   | Value4   | Value5   |
|-------------------------------|----------|----------|----------|----------|----------|
| glutathione                  | 4259 ± 1053 | 3344 ± 601 | 4360 ± 722 | 2571 ± 618 | 7961 ± 955 |
| glycerate                    | 6745 ± 1101 | 4256 ± 1051 | 3476 ± 1087 | 5717 ± 995 | 4669 ± 767 |
| hexose-phosphate             | 6623 ± 859 | 6543 ± 638 | 5541 ± 610 | 7071 ± 954 | 4554 ± 718 |
| IDP                          | 5234 ± 1538 | 4358 ± 742 | 5425 ± 1215 | 4861 ± 1178 | 7401 ± 798 |
| citrate/isocitrate           | 3423 ± 1221 | 2329 ± 543 | 3669 ± 972 | 4043 ± 1880 | 7331 ± 1645 |
| lactate                      | 5429 ± 969 | 8832 ± 880 | 5761 ± 931 | 5718 ± 658 | 1649 ± 441 |
| myo-inositol                 | 5519 ± 5172 | 1451 ± 7055 | 502 ± 7676 | 167 ± 6871 | 3129 ± 2976 |
| N-acetyl-glucosamine-1-phosphate | 7524 ± 737 | 7513 ± 971 | 7714 ± 783 | 7609 ± 1441 | 8379 ± 442 |
| NAD+                         | 6321 ± 1059 | 5651 ± 1419 | 4443 ± 646 | 6040 ± 1047 | 4022 ± 892 |
| NADH                         | 4511 ± 1282 | 5961 ± 1634 | 5615 ± 1238 | 4148 ± 1242 | 3694 ± 581 |
| NADP+                        | 3818 ± 1223 | 6057 ± 1103 | 4887 ± 780 | 6040 ± 1221 | 6906 ± 796 |
| NADPH                        | 2249 ± 924 | 5570 ± 1864 | 4097 ± 907 | 6358 ± 1496 | 3370 ± 995 |
| orotate                      | 3560 ± 793 | 2616 ± 642 | 3332 ± 1406 | 8123 ± 2966 | 599 ± 4081 |
| orotidine-5'-phosphate       | 1512 ± 1162 | 329 ± 134 | 1275 ± 1061 | 784 ± 282 | 5919 ± 4081 |
| oxaloacetate                 | 5645 ± 4355 | 3588 ± 707 | 3800 ± 1200 | 2658 ± 1368 | 8845 ± 370 |
| pantethenate                 | 7961 ± 1506 | 6971 ± 589 | 5730 ± 621 | 6155 ± 950 | 8403 ± 833 |
| phenylpyruvate               | 5815 ± 4185 | 3809 ± 3139 | 551 ± 2634 | 1247 ± 2247 | 911 ± 637 |
| p-hydroxybenzoate            | 3057 ± 1055 | 1911 ± 672 | 2160 ± 363 | 1379 ± 178 | 7349 ± 2651 |
| propionyl-CoA                | 6431 ± 1396 | 6441 ± 2138 | 8598 ± 1402 | 3940 ± 211 | 4127 ± 4081 |
| pyruvate                     | 4038 ± 969 | 5840 ± 1181 | 2867 ± 478 | 6096 ± 1071 | 4110 ± 595 |
| quinolinate                  | 4780 ± 1711 | 3186 ± 1017 | 324 ± 532 | 2627 ± 1277 | 3852 ± 1357 |
| ribose-phosphate             | 2826 ± 797 | 8611 ± 772 | 6861 ± 995 | 3122 ± 431 | 2135 ± 540 |
| glycerol-3-phosphate         | 6809 ± 715 | 7680 ± 656 | 8676 ± 404 | 3460 ± 636 | 2365 ± 451 |
| succinate                    | 5611 ± 1306 | 4671 ± 896 | 3729 ± 900 | 4164 ± 1208 | 5542 ± 892 |
| taurine                      | 1872 ± 392 | 442 ± 127 | 471 ± 534 | 126 ± 9008 | 322 ± 989 |
| UDP                          | 4805 ± 1013 | 4468 ± 1271 | 3486 ± 845 | 5496 ± 1230 | 3901 ± 989 |
| UDP-D-glucose                | 4837 ± 992 | 7574 ± 923 | 6750 ± 883 | 4789 ± 937 | 5721 ± 407 |
| Metabolite                    | Average ± SEM 1 | Average ± SEM 2 | Average ± SEM 3 | Average ± SEM 4 | Average ± SEM 5 |
|-----------------------------|----------------|----------------|----------------|----------------|----------------|
| UDP-D-glucuronate           | 5330 ± 1464    | 6589 ± 912     | 6480 ± 948     | 5566 ± 1091    | 5468 ± 490     |
| UDP-N-acetyl-glucosamine    | 6380 ± 1146    | 7127 ± 948     | 7519 ± 994     | 5181 ± 909     | 6550 ± 604     |
| Xanthine                    | 3490 ± 2175    | 1141 ± 157     | 1199 ± 110     | 1387 ± 267     | 4682 ± 2076    |

Averages and SEM from four independent experiments performed in duplicate (n=8).

* indicates that metabolite was not found in enough replicates to yield an SEM

*Measurement of oxidized glutathione is representative of total glutathione pool due to oxidation during sample preparation
| Metabolite                        | YAMC  | mp53/Ras | mp53 | Ras  | BN   |
|----------------------------------|-------|----------|------|------|------|
| 3-Phosphoglycerate               | 678 ± 104 | 1200 ± 194 | 802 ± 131 | 633 ± 144 | 734 ± 133 |
| 5-phosphoribosyl 1-pyrophosphate| 151 ± 58  | 856 ± 125 | 351 ± 59  | 129 ± 49  | 168 ± 27  |
| acetyl-CoA                       | 216 ± 59  | 388 ± 84  | 421 ± 160 | 150 ± 36  | 523 ± 150 |
| α-ketoglutarate                  | 29725 ± 10848 | 38189 ± 9995 | 22510 ± 3511 | 19948 ± 4854 | 26147 ± 4802 |
| ATP                              | 81543 ± 23836 | 98726 ± 18503 | 102482 ± 16591 | 94429 ± 20555 | 119458 ± 9398 |
| citrate/isocitrate               | 11769 ± 4309 | 6081 ± 1482 | 10779 ± 2795 | 8378 ± 2968 | 15196 ± 2865 |
| CTP                              | 4035 ± 1364 | 9130 ± 1121 | 7218 ± 1007 | 5394 ± 1157 | 5304 ± 704 |
| glyceraldehyde-3-phosphate/ DHAP| 181 ± 55   | 686 ± 161  | 14554 ± 852 | 2354 ± 615  | 1693 ± 97  |
| fructose bisphosphate            | 3458 ± 756  | 6267 ± 744  | 204 ± 114  | 204 ± 114  | 151 ± 26   |
| GTP                              | 12020 ± 3203 | 11221 ± 1991 | 10883 ± 1696 | 10320 ± 2632 | 12148 ± 2422 |
| malate                           | 11821 ± 3478 | 14748 ± 1770 | 12445 ± 2636 | 12282 ± 3128 | 21515 ± 2023 |
| malonyl-CoA                      | 41 ± 12    | 100 ± 23   | 70 ± 25    | 39 ± 8     | 39 ± 11    |
| phosphoenolpyruvate              | 292 ± 27   | 1383 ± 228 | 761 ± 134  | 430 ± 61   | 433 ± 100  |
| UTP                              | 11777 ± 3887 | 24475 ± 3476 | 18895 ± 3603 | 12683 ± 4163 | 15262 ± 2425 |

Averages and SEM from ≥ 3 independent experiments performed in duplicate.
| Compound                  | p.value    | -LOG10(p) | FDR       | Fisher's LSD                                                                 |
|--------------------------|------------|-----------|-----------|-------------------------------------------------------------------------------|
| taurine                  | 4.01E-22   | 21.397    | 2.97E-20  | BN - mp53; BN - mp53/Ras; BN - Ras; BN - YAMC; YAMC - mp53; YAMC - mp53/Ras; YAMC - Ras |
| sn-glycerol-3-phosphate  | 1.62E-10   | 9.7914    | 5.98E-09  | mp53 - BN; mp53/Ras - BN; YAMC - BN; mp53 - Ras; mp53 - YAMC; mp53/Ras - Ras; mp53 - YAMC; mp53/Ras - mp53; mp53 - Ras; mp53 - YAMC; mp53/Ras - YAMC |
| 5-phosphoribosyl 1-pyrophosphate | 1.17E-08 | 7.9326    | 2.88E-07  | mp53/Ras - BN; mp53/Ras - mp53; mp53 - Ras; mp53 - YAMC; mp53/Ras - Ras; mp53/Ras - YAMC; mp53/Ras - YAMC |
| phosphoenolpyruvate      | 4.55E-07   | 6.3423    | 8.41E-06  | mp53/Ras - BN; mp53/Ras - mp53; mp53 - Ras; mp53 - YAMC; mp53/Ras - Ras; mp53/Ras - YAMC; mp53/Ras - YAMC |
| D-gluconate              | 8.94E-07   | 6.0488    | 1.32E-05  | BN - mp53; BN - mp53/Ras; BN - Ras; BN - YAMC; Ras - mp53; Ras - YAMC |
| ribose-phosphate         | 3.23E-06   | 5.4907    | 3.98E-05  | mp53 - BN; mp53/Ras - BN; mp53 - Ras; mp53 - YAMC; mp53/Ras - Ras; mp53/Ras - YAMC; mp53/Ras - YAMC |
| dTTP                     | 4.03E-06   | 5.3951    | 4.26E-05  | mp53/Ras - BN; mp53/Ras - mp53; mp53 - Ras; mp53 - YAMC; mp53/Ras - Ras; mp53/Ras - YAMC; mp53/Ras - YAMC |
| lactate                  | 3.99E-05   | 4.3993    | 0.000369  | mp53/Ras - mp53; mp53/Ras - Ras; mp53/Ras - YAMC |
| glutathione disulfide     | 6.62E-05   | 4.1789    | 0.000545  | BN - mp53; BN - mp53/Ras; BN - Ras; BN - YAMC |
| fructose-1,6-bisphosphate| 0.000146   | 3.8344    | 0.001084  | mp53 - BN; mp53/Ras - BN; mp53 - Ras; mp53/Ras - Ras; mp53/Ras - YAMC |
| D-glyceraldehyde-3-phosphate | 0.002539 | 2.5954    | 0.017077  | mp53/Ras - BN; mp53/Ras - mp53; mp53/Ras - Ras; mp53/Ras - YAMC |
| 3-phosphoglycerate       | 0.007416   | 2.1298    | 0.045734  | mp53/Ras - BN; mp53/Ras - mp53; mp53/Ras - Ras; mp53/Ras - YAMC |
| dCTP                     | 0.011465   | 1.9406    | 0.06526   | mp53/Ras - BN; mp53/Ras - Ras; mp53/Ras - YAMC |
| CTP                      | 0.014036   | 1.8528    | 0.07419   | mp53/Ras - BN; mp53 - YAMC; mp53/Ras - Ras; mp53/Ras - YAMC |
| pyruvate                 | 0.032798   | 1.4842    | 0.15813   | mp53/Ras - mp53; Ras - mp53 |
| malonyl-CoA               | 0.03419    | 1.4661    | 0.15813   | mp53/Ras - BN; mp53/Ras - Ras; mp53/Ras - YAMC |
| UDP-D-glucose            | 0.043639   | 1.3601    | 0.18996   | mp53/Ras - Ras; mp53/Ras - YAMC |
Table S5, Related to Figures 3-5: isotopologue labeling in mp53/Ras cells

|                  | 13C-glucose labeling | 13C-glutamine labeling |
|------------------|----------------------|------------------------|
|                  | glycine | serine | alanine | aKG | malate | citrate | glycine | serine | alanine | aKG | malate | citrate |
|                  | 1.5hrs  | 2hrs   | 1.5hrs  | 2hrs | 1.5hrs  | 2hrs   | 1.5hrs  | 2hrs   | 1.5hrs  | 2hrs | 1.5hrs  | 2hrs   |
| Vector (LDH-rev) | m+0: 90% | m+0: 88% | m+0: 91% | m+0: 91% | m+0: 25% | m+0: 23% | m+0: 41% | m+0: 43% | m+0: 59% | m+0: 59% | m+0: 54% | m+0: 54% |
|                  | m+3: 10% | m+3: 12% | m+3: 9% | m+3: 9% | m+3: 75% | m+3: 77% | m+5: 59% | m+5: 57% | m+2: 3% | m+3: 28% | m+3: 31% | m+3: 10% |
| LDH-rev           | m+0: 92% | m+0: 92% | m+0: 94% | m+0: 93% | m+0: 29% | m+0: 33% | m+0: 42% | m+0: 41% | m+0: 56% | m+0: 50% | m+0: 50% | m+0: 57% |
|                  | m+3: 8% | m+3: 8% | m+3: 6% | m+3: 6% | m+3: 67% | m+3: 67% | m+5: 59% | m+5: 59% | m+2: 4% | m+3: 31% | m+3: 35% | m+4: 8% |
| Vector (shGPT2)  | m+0: 21% | m+0: 19% | m+0: 21% | m+0: 19% | m+0: 62% | m+0: 50% | m+0: 34% | m+0: 29% | m+0: 50% | m+0: 39% | m+0: 39% | m+0: 66% |
|                  | m+3: 79% | m+3: 81% | m+3: 79% | m+3: 81% | m+3: 72% | m+3: 72% | m+3: 2% | m+3: 2% | m+3: 16% | m+3: 10% | m+3: 10% | m+2: 2% |
| shGPT2           | m+0: 37% | m+0: 33% | m+0: 37% | m+0: 33% | m+0: 37% | m+0: 37% | m+0: 41% | m+0: 35% | m+0: 52% | m+0: 45% | m+0: 45% | m+0: 70% |
|                  | m+3: 63% | m+3: 67% | m+3: 63% | m+3: 67% | m+3: 54% | m+3: 54% | m+4: 2% | m+4: 2% | m+4: 12% | m+4: 10% | m+4: 10% | m+3: 4% |

Indicated derivatives of mp53/Ras cells were pulsed with 13C-glucose or 13C-glutamine for indicated time and the relative abundance of 12C- and 13C-isotopologues was determined by LC-MS/MS. Values represent percentage of indicated metabolite pools for all detectable isotopologues (m+n), with m+0 representing the unlabeled fraction.
Table S6, Related to Figure 6: isotopologue labeling in HCT116 cells

|                | 13C-glucose labeling | 15N-glutamine labeling | 13C-glutamine labeling |
|----------------|----------------------|------------------------|------------------------|
|                | alanine              | glutamate              | aKG                    | malate              | citrate              |
| 1.5hrs         |                      |                        |                        |                     |                      |
| shGFP          | m+0: 38%             | m+0: 34%               | m+0: 38%               | m+0: 36%            | m+0: 23%             | m+0: 31%             | m+0: 30%             | m+0: 52%             | m+0: 46%             |
|                | m+3: 62%             | m+3: 66%               | m+3: 62%               | m+1: 64%            | m+3: 3%              | m+3: 3%              | m+2: 10%             | m+2: 14%             | m+3: 4%              |
| 2hrs           |                      |                        |                        |                     | m+4: 3%              | m+4: 2%              | m+3: 12%             | m+3: 10%             | m+4: 29%             |
|                |                      |                        |                        |                     | m+4: 72%             | m+5: 71%             | m+4: 47%             | m+4: 46%             | m+5: 8%              |
| shGPT2-1       | m+0: 96%             | m+0: 97%               | --                     | --                  | m+0: 23%             | m+0: 38%             | m+0: 48%             | m+0: 53%             | m+6: 9%              |
|                | m+3: 4%              | m+3: 3%                |                        |                      | m+3: 2%              | m+3: 3%              | m+2: 9%              | m+2: 7%              | m+3: 5%              |
|                |                      |                        |                        |                     | m+4: 2%              | m+4: 2%              | m+3: 7%              | m+3: 6%              | m+4: 19%             |
|                |                      |                        |                        |                     | m+5: 60%             | m+5: 58%             | m+4: 36%             | m+4: 34%             | m+5: 5%              |
| 2hrs           |                      |                        |                        |                     |                        |                      |                        |                      | m+6: 1%              |
| shGPT2-2       | m+0: 88%             | m+0: 87%               | --                     | --                  | m+0: 31%             | m+0: 27%             | m+0: 43%             | m+0: 49%             | m+6: 66%             |
|                | m+3: 11%             | m+3: 13%               |                        |                      | m+3: 3%              | m+3: 4%              | m+2: 10%             | m+2: 10%             | m+3: 3%              |
|                |                      |                        |                        |                     | m+4: 2%              | m+4: 4%              | m+3: 7%              | m+3: 8%              | m+4: 21%             |
|                |                      |                        |                        |                     | m+5: 65%             | m+5: 65%             | m+4: 40%             | m+4: 33%             | m+5: 5%              |
| shGLS-1        | --                   | --                     | m+0: 49%               | m+0: 51%            | m+0: 3%              | m+0: 30%             | m+0: 40%             | m+0: 38%             | m+6: 61%             |
|                |                      |                        | m+1: 51%               | m+1: 49%            | m+3: 0%              | m+3: 0%              | m+2: 11%             | m+2: 13%             | m+6: 1%              |
|                |                      |                        |                        |                     | m+4: 0%              | m+4: 0%              | m+3: 8%              | m+3: 7%              | m+4: 22%             |
|                |                      |                        |                        |                     | m+5: 69%             | m+5: 70%             | m+4: 41%             | m+4: 42%             | m+5: 14%             |
| shGLS-2        | --                   | --                     | m+0: 56%               | m+0: 52%            | m+0: 34%             | m+0: 37%             | m+0: 48%             | m+0: 43%             | m+6: 61%             |
|                |                      |                        | m+1: 44%               | m+1: 48%            | m+3: 0%              | m+3: 0%              | m+2: 10%             | m+2: 14%             | m+3: 3%              |
|                |                      |                        |                        |                     | m+4: 0%              | m+4: 0%              | m+3: 6%              | m+3: 8%              | m+4: 22%             |
|                |                      |                        |                        |                     | m+5: 66%             | m+5: 63%             | m+4: 36%             | m+4: 35%             | m+5: 10%             |
|                |                      |                        |                        |                     |                        |                      |                        |                      | m+6: 7%              |

Indicated derivatives of HCT116 cells were pulsed with 13C-glucose, 13C-glutamine, or 15N-glutamine for indicated time and the relative abundance of 12C- and 13C-isotopes was determined by LC-MS/MS. Values represent percentage of indicated metabolite pools for all detectable isotopologues (m+n), with m+0 representing the unlabeled fraction.
### Table S7, Related to Figure 6: Isotopologue Labeling in SW480 Cells

| Metabolite  | Alanine | Glutamate | αKG | Malate  | Citrate |
|-------------|---------|-----------|-----|---------|---------|
|             | 1.5hrs  | 2hrs      | 1.5hrs | 2hrs   | 1.5hrs  | 2hrs   |
| shGFP       | m+0: 32%| m+0: 33% | m+0: 32%| m+0: 29%| m+0: 20%| m+0: 18%|
|             | m+3: 66%| m+3: 67% | m+1: 68%| m+1: 71%| m+3: 12%| m+3: 12%|
|             |         |           |       |         | m+4: 62%| m+4: 64%|
|             |         |           |       |         | m+6: 4% | m+6: 3% |
| shGPT2-1    | m+0: 87%| m+0: 86% | --   | --      | m+0: 22%| m+0: 20%|
|             | m+3: 13%| m+3: 14% |       |         | m+3: 2% | m+3: 3% |
|             |         |           |       |         | m+4: 2% | m+4: 3% |
|             |         |           |       |         | m+5: 74%| m+5: 74%|
|             |         |           |       |         | m+6: 9% | m+6: 8% |
| shGLS-1     |         |           |       |         | m+0: 59%| m+0: 63%|
|             |         |           |       |         | m+1: 45%| m+1: 43%|
|             |         |           |       |         | m+5: 65%| m+5: 69%|
|             |         |           |       |         | m+4: 57%| m+4: 57%|
| shGLS-2     |         |           |       |         | m+0: 57%| m+0: 54%|
|             |         |           |       |         | m+3: 0% | m+3: 0% |
|             |         |           |       |         | m+4: 0% | m+4: 0% |
|             |         |           |       |         | m+5: 67%| m+5: 66%|
|             |         |           |       |         | m+4: 57%| m+4: 57%|

Indicated derivatives of SW480 cells were pulsed with $^{13}$C-glucose, $^{13}$C-glutamine, or $^{15}$N-glutamine for indicated time and the relative abundance of $^{12}$C- and $^{13}$C-isotopologues was determined by LC-MS/MS. Values represent percentage of indicated metabolite pools for all detectable isotopologues (m+n), with m+0 representing the unlabeled fraction.
Supplemental Experimental Procedures

Plasmids

Murine lactate dehydrogenase-B (LDHB) cDNA was purchased from Open Biosystems and cloned into the retroviral vector pBabePuro3 (Morgenstern and Land, 1990). shRNA’s targeting murine lactate dehydrogenase-A (LDHA) and murine glutamic pyruvate transaminase 2 (GPT2) were cloned into the retrovirus vectors pSUPERRetro.hydro and .puro (OligoEngine) respectively. shRNAs targeting human GPT2 and human glutaminase (GLS) were purchased from Open Biosystems and expressed with pLKO.1 vector system. shRNA resistant GPT2 cDNA was generated by restriction digest removal of shRNA target sequence within 3’ UTR of a full length murine cDNA. Both full length cDNAs were purchased from Open Biosystems and cloned into the lentiviral vector pLenti6/UbC/V5-GW/lacZ. For shRNA target sequences and mutagenesis primer sequences see below.

Measurement of senescence associated-β-gal and acidic-β-gal activity

Senescence associated and acidic β-gal activity was performed as described previously (Debacq-Chainiaux et al., 2009). Briefly, cells were washed twice with PBS and fixed in PBS containing 2% formaldehyde (vol/vol) and 0.2% glutaraldehyde for 5 min. at room temperature. After the end of 5 min. fixation solution was removed and cells were washed twice with PBS. Staining solution containing 40 mM citric acid/Na phosphate buffer, 5 mM K4[Fe(CN)6] 3H2O, 5 mM K3[Fe(CN)6], 150 mM sodium chloride, 2 mM magnesium chloride and 1 mg ml−1 X-gal in distilled water, was calibrated to pH 6 to detect senescence associated β-gal activity and to pH 4 for acidic β-gal activity as a positive control. Staining solution was added to wells and cells were incubated at 37°C for 16 hrs. After the incubation, cells were washed twice with PBS and imaged using bright field microscopy. Percentages were calculated by counting at least 100 cells from each condition.

LC-MS/MS Methodology

Cells were maintained in culture as indicated above. Cellular media of murine cells was changed to serum free medium with HEPES (10mM) 24 hours and again one hour prior to metabolite extraction or metabolic tracer addition, while human colon cancer cell media was only changed one hour prior. The same conditions were used for measurements in hypoxia, except cells were moved to 1% oxygen for the indicated time prior to extraction. For all labeling experiments, labeling medium was prepared from serum free media with HEPES (10mM), lacking either glucose or glutamine and supplemented with either 12C or U-13C labeled glucose (2 g/L) or 12C or U-13C, or α-15N labeled glutamine (300 mg/L) (Cambridge Isotope Laboratories). Isotope labeling experiments were performed at a time at which label accumulation had plateaued of the metabolic pools of interest had plateaued, i.e. approaching pseudo-steady state, as verified by empirical analysis of their labeling kinetics. Glucose labeling was based upon total 13C labeling (i.e. the sum of all isotopologues) of a given metabolite pool, as a percentage of total pool size over time (see Fig S5 and Table S5-7). Glutamine-derived citrate labeling in the murine-derived colon cells was an exception, as its labeling did not always plateau (Fig S5B); however, this did not impact our conclusions. Labeled (13C) or control medium (12C) was aspirated at indicated times and metabolic activity was quenched with immediate addition of 4 ml of -78°C methanol: water (80:20). Plates were stored on dry ice for at least 10 minutes following quenching. Cells were scraped, and the resulting suspension vortexed vigorously, then centrifuged at 4°C for 5 minutes at 2000 x g. Supernatants were collected and remaining cell pellets were re-extracted twice more with 80% methanol. All extractions were pooled for each sample. Extracts were then either dried under nitrogen gas and resuspended in 200 µl of 50:50 methanol:water or, for measurement of redox sensitive NAD and NADH levels, were directly analyzed following methanol extraction. Amino acids were derivatized prior to analysis. Specifically, 100 µl of the above methanol extracts was derivatized with 1 µl benzyl chloroformate and 5 µl trimethylamine. All samples were then centrifuged at 4°C for 5 minutes at full speed to pellet insoluble material and analyzed using reverse phase chromatography with an ion-paring reagent in a Shimadzu HPLC coupled to a Thermo Quantum triple quadrupole mass spectrometer running in negative mode with selected-reaction-monitoring (SRM) specific scans. Specific chromatography conditions and mass spectrometry parameters were as described in DeVito et al., 2014; Munger et al., 2008).

LC-MS/MS data were analyzed using the publically available mzrock machine learning toolkit (http://code.google.com/p/mzrock/), which automates SRM/HPLC feature detection, grouping, signal to noise classification, and comparison to known metabolite retention times (Melamud et al., 2010). Extracted ion chromatograms of metabolite-specific SRM peak heights were normalized by their cellular protein content as measured by Bradford assay. For relative quantification, protein-normalized peak heights were further normalized by the maximum value for a specific metabolite measured across the samples run on a given day. This normalization serves to reduce the impact of inter-day mass spectrometry variability while preserving relative differences between samples. For absolute quantifications, the metabolite pool abundances of the mp53/Ras cells were quantified based on comparison to standard curves. Extracts from the mp53/Ras cells were subsequently used as a standard, run in the same sample set, to estimate the absolute metabolite abundances of the YAMC cells and their derivatives.
Measurement of fatty acid biosynthesis.

Fatty acid biosynthesis was evaluated largely as indicated previously (Harwood et al., 2003). Briefly, fatty acid biosynthesis was assayed by measuring the incorporation of [1-14C]-acetic acid (NEN Radiochemicals) into cellular lipids. Following 48 hours without selective drugs, cells were plated in 6-well plates under standard culture conditions and serum starved for 24 hours under indicated oxygen conditions. To begin the assay, 1.25 ml of RPMI containing 1 µCi of 56.2 mCi mmol⁻¹ [1-14C]-acetic acid was added to each well, and cells were incubated at 39°C for 2 h. After incubation, cells were washed with PBS and dissolved in 1 ml of 0.2M KOH. Samples were then saponified by the addition of 0.6 ml of 50% KOH and 4 ml of ethanol, followed by a 2-h incubation at 75°C and then an overnight incubation at room temperature. After saponification, the samples were extracted two times with 9 ml of hexane. The hexane-containing fractions were discarded, and the remaining fractions containing fatty acids were acidified to pH 2 by the addition of 1 ml 12 M HCl. After acidification, the samples were extracted one time with 8 ml hexane. The organic fractions were dried under N2, resuspended in 100 µl of 1:1 chloroform-hexane, dissolved in 2 ml of Ecoscint O liquid scintillation fluid, and assessed for radioactivity using a Beckman LS6500 liquid scintillation counter. Results were normalized for protein content measured by Bradford assay. Significant differences were identified through one-way ANOVA analysis with subsequent Fisher’s LSD post-hoc testing (see Table S1).

Western Blot

Prior to lysis, cells were grown without selective drugs for a minimum of 48 hr at 39°C, in standard culture media. Cells were lysed for 30 minutes in RIPA buffer (1% NP-40, 0.1% SDS, 0.5% deoxycholic acid, 5 mM EDTA, 50 mM Tris-HCl, pH 7.4, 150 mM NaCl, protease inhibitor cocktail tablet) at 4°C, followed by 10 minutes of centrifugation at 13,000xg to clear insoluble material. Bradford protein assay (Bio-Rad) was used to measure lyysate protein concentrations and 50ug was separated by SDS-PAGE. Protein bands were visualized using horse-radish peroxidase-coupled secondary antibodies (Pierce) and ECL+ kit (Amersham). The following primary antibodies were used: goat polyclonal anti-LDHA (Santa Cruz), mouse monoclonal anti-LDHB (Abcam), rabbit monoclonal anti-GLS (Abcam), rabbit monoclonal anti-GAPDH (Cell Signaling), and mouse monoclonal anti-γ tubulin (Sigma).

Real-time quantitative PCR

Cells were grown without selective drugs for a minimum of 48 hr under standard culture conditions, prior to harvesting for RNA isolation. Total RNA was isolated from cells using RNeasy Mini Kit (Quiagen). cDNA was produced for qPCR analysis by denaturing 5ug RNA at 90°C for 5 minutes, then mixing with 400 µM dNTP mixture, 10 mM DTT, 1x SuperScript II reverse transcriptase buffer, 0.3 ng random hexamer primer, 1µl SuperScript II reverse transcriptase, and 1 µl RNaseOUT RNase inhibitor for a total reaction volume of 50µl (all components from Invitrogen). RT reactions were carried out for 2 hours at 42°C, followed by heat inactivation of RT enzyme by 10 minute incubation at 70°C. SYBR Green-based quantitative PCR was performed by mixing 1µl cDNA/RT reaction with 0.2 μM forward and reverse primer mix of gene-specific qPCR primers (IDT) and 1x Bio-Rad iQ SYBR Green master mix. Reactions were run on an iCycler (Bio-Rad) using the following conditions: 3 minutes at 95°C to activate polymerase, followed by 40 cycles of 95°C for 30 seconds, 60°C for 30 seconds, 72°C for 45 seconds to amplify products, then 40 cycles of 94°C with 1°C step-down for 30 seconds to generate melt curves. Gene expression was calculated using the ΔΔCt method, as previously described (McMurray et al., 2008), and normalized to RhoA. See below for primer sequences.

shRNA target sequences:
The following sequences were targeted for shRNA-mediated knockdown of gene expression:

Murine LDHA shRNA - CATGCGAGCCTTCCCTCTTAAAAAC
Murine GPT2 shRNA - TATCTGGATTATATGGCCTAGC
Human GPT2 shRNA 1 - TATACTGGATCTAGAAATGCCG
Human GPT2 shRNA 2 - ATCTGGAGAGTACACGTTGTC
Human GLS shRNA 1 - TATTTCGAACTGCTTCAGGGC
Human GLS shRNA 2 - ATATACCAACCATGTCTGTGC

RT-PCR Primers
The following gene specific qPCR primers were used:
Murine LDHB Forward - GGGAGCTTGGTTCCTCCAGAC
Murine LDHB Reverse - TGGGTGGAAACCACGATGAT
Murine LDHA Forward - GGAGATCCATCATCTCGCCCTTTGA
Murine GPT2 Forward - CTTTGCCCTGGAAGAGAGAAG
Gene expression in human cancer

GEO: publically available cDNA microarray datasets were used to assess the expression of LDHA, LDHB, and GPT2 in human cancers of colon (Saaf et al., 2007), pancreas (Lowe et al., 2007) and prostate (Lapointe et al., 2004). The ratio of background normalized mean fluorescence intensities of Cy-5 labeled sample and Cy-3 labeled reference mRNA at each microarray element was used as a standardized measure of the abundance for the corresponding mRNAs. Statistical significance in differential gene expression between non-tumor and tumor tissue was determined by using Student’s t-test.

TCGA: Level 3 Illumina RNAseq normalized counts were collected for colon, pancreatic and prostate tumors and their corresponding non-tumor tissues. Changes in expression of genes were identified as significantly different by using Benferroni adjusted p-values between tumor and normal samples using t-tests. Relationship between p53/Ras mutational status and expression of genes were studied by partitioning the RNASeq data for the tumors using sample matched somatic mutation information for the presence or absence of Ras and/or p53 mutations. Variance in gene expression between groups were analyzed by using ANOVA F-test in conjunction with Tukey method to determine samples that have means that differ from each other significantly.

Supplemental References

Debacq-Chainiaux, F., Erusalimsky, J.D., Campisi, J., and Toussaint, O. (2009). Protocols to detect senescence-associated beta-galactosidase (SA-betagal) activity, a biomarker of senescent cells in culture and in vivo. Nat Protoc 4, 1798-1806.

DeVito, S.R., Ortiz-Riano, E., Martinez-Sobrido, L., and Munger, J. (2014). Cytomegalovirus-mediated activation of pyrimidine biosynthesis drives UDP-sugar synthesis to support viral protein glycosylation. Proc Natl Acad Sci U S A 111, 18019-18024.

Harwood, H.J., Jr., Petras, S.F., Shelly, L.D., Zaccaro, L.M., Perry, D.A., Makowski, M.R., Hargrove, D.M., Martin, K.A., Tracey, W.R., Chapman, J.G., et al. (2003). Isozyme-nonselective N-substituted biperipidylcarboxamide acetyl-CoA carboxylase inhibitors reduce tissue malonyl-CoA concentrations, inhibit fatty acid synthesis, and increase fatty acid oxidation in cultured cells and in experimental animals. J Biol Chem 278, 37099-37111.

Lapointe, J., Li, C., Higgins, J.P., van de Rijn, M., Bair, E., Montgomery, K., Ferrari, M., Egevad, L., Rayford, W., Bergerheim, U., et al. (2004). Gene expression profiling identifies clinically relevant subtypes of prostate cancer. Proc Natl Acad Sci U S A 101, 811-816.

Lowe, A.W., Olsen, M., Hao, Y., Lee, S.P., Taek Lee, K., Chen, X., van de Rijn, M., and Brown, P.O. (2007). Gene expression patterns in pancreatic tumors, cells and tissues. PLoS One 2, e323.

McMurray, H.R., Sampson, E.R., Compitello, G., Kinsey, C., Newman, L., Smith, B., Chen, S.R., Klevanov, L., Salzman, P., Yakovlev, A., et al. (2008). Synergistic response to oncogenic mutations defines gene class critical to cancer phenotype. Nature 453, 1112-1116.

Melamud, E., Vastag, L., and Rabinowitz, J.D. (2010). Metabolomic analysis and visualization engine for LC-MS data. Anal Chim Acta 682, 9818-9826.

Morgenstern, J.P., and Land, H. (1990). A series of mammalian expression vectors and characterisation of their expression of a reporter gene in stably and transiently transfected cells. Nucleic Acids Res 18, 1068.

Munger, J., Bennett, B.D., Parikh, A., Feng, X.J., McArdle, J., Rabitz, H.A., Shenk, T., and Rabinowitz, J.D. (2008). Systems-level metabolic flux profiling identifies fatty acid synthesis as a target for antiviral therapy. Nat Biotechnol 26, 1179-1186.

Saaf, A.M., Halbleib, J.M., Chen, X., Yuen, S.T., Leung, S.Y., Nelson, W.J., and Brown, P.O. (2007). Parallels between global transcriptional programs of polarizing Caco-2 intestinal epithelial cells in vitro and gene expression programs in normal colon and colon cancer. Mol Biol Cell 18, 4245-4260.