

EFFECTS OF FOLIC ACID WITHDRAWAL ON TRANSCRIPTOMIC PROFILES IN MURINE TRIPLE-NEGATIVE BREAST CANCER CELL LINES

Supplementary Table 1: Joined pathway analysis

Pathways	Total	Hits	Raw P-value	minus log P-value	FDR	Impact	Hits – metabolites	Hits – genes
E-Wnt								
Pantothenate and CoA biosynthesis	46	4	7.9E-06	11.8	2.58E-03	0.17	beta-Alanine; Aspartate	<i>Vnn1; Vnn3</i>
M-Wnt								
JAK-STAT signaling pathway	165	5	7.0E-04	7.3	1.20E-02	1.14		<i>Irf9; Stat1; Stat2; Il15; Il19</i>
Alanine, aspartate and glutamate metabolism	66	5	8.9E-06	11.6	3.66E-04	0.48	Alanine; Aspartate; Asparagine; Glutamate; Glutamine	
beta-Alanine metabolism	64	3	2.6E-03	5.9	2.95E-02	0.31	beta-Alanine; Aspartate; Histidine	
Phenylalanine, tyrosine and tryptophan biosynthesis	43	3	8.2E-04	7.1	1.28E-02	0.29	Tryptophan; Tyrosine; Phenylalanine	
Pyrimidine metabolism	123	4	1.9E-03	6.3	2.60E-02	0.26	UDP-glucose; beta-Alanine; Glutamine	<i>Cmpk2</i>
Prolactin signaling pathway	83	4	4.4E-04	7.7	9.55E-03	0.26	Tyrosine; ATP; Glucose	<i>Stat1</i>
D-Glutamine and D-glutamate metabolism	17	2	2.4E-03	6.0	2.91E-02	0.25	Glutamate; Glutamine	
Arginine biosynthesis	42	3	7.7E-04	7.2	1.26E-02	0.23	Aspartate; Glutamine; Glutamate	
Aminoacyl-tRNA biosynthesis	118	16	1.9E-20	45.4	3.09E-18	0.22	Tryptophan; Leucine; Tyrosine; Alanine; Isoleucine; Valine; Methionine; Serine; Aspartate; Proline; Glutamate; Glutamine; Phenylalanine; Histidine; Asparagine	<i>Qrs11</i>
Epstein-Barr virus infection	232	8	6.0E-06	12.0	2.81E-04	0.21		<i>Stat1; Stat2; Blnk; Irf9; Oas2; H2-D1; H2-K1; H2-Q7</i>
Herpes simplex virus 1 infection	439	9	9.4E-05	9.3	2.80E-03	0.16		<i>Ccl5; Oas2; Stat1; Stat2; Irf9; Bst2; H2-D1; H2-K1; H2-Q7</i>
Galactose metabolism	78	3	4.6E-03	5.4	4.15E-02	0.15	Myo-Inositol; UDP-Glucose; Glucose	
Hepatitis C	162	5	6.4E-04	7.4	1.16E-02	0.15		<i>Stat1; Stat2; Irf9; Oas2; Rsad2</i>
Valine, leucine and isoleucine biosynthesis	27	3	2.1E-04	8.5	5.59E-03	0.15	Leucine; Isoleucine; Valine	
Taurine and hypotaurine metabolism	33	3	3.8E-04	7.9	8.78E-03	0.14	Alanine; Taurine; Glutamate	
Histidine metabolism	71	3	3.5E-03	5.7	3.59E-02	0.13	Aspartate; Glutamate; Histidine	
Pantothenate and CoA biosynthesis	46	3	1.0E-03	6.9	1.49E-02	0.12	Valine; beta-Alanine; Aspartate	
Osteoclast differentiation	131	4	2.4E-03	6.0	2.91E-02	0.12		<i>Stat1; Stat2; Irf9; Blnk</i>
Influenza A	169	6	8.2E-05	9.4	2.70E-03	0.12		<i>Stat1; Stat2; Irf9; Oas2; Ccl5; Rsad2</i>
Glycine, serine and threonine metabolism	90	4	6.0E-04	7.4	1.15E-02	0.11	Creatine; Serine; Aspartate; Tryptophan	
Human papillomavirus infection	364	6	4.6E-03	5.4	4.15E-02	0.11		<i>Stat2; Stat1; Irf9; H2-D1; H2-K1; H2-Q7</i>
Arginine and proline metabolism	128	4	2.2E-03	6.1	2.89E-02	0.10	Creatine; Phosphocreatine; Glutamate; Proline	
Measles	145	4	3.5E-03	5.7	3.59E-02	0.10		<i>Stat1; Stat2; Irf9; Oas2</i>
Glyoxylate and dicarboxylate metabolism	93	5	4.8E-05	10.0	1.73E-03	0.08	Formate; cis-Aconitate; Serine; Glutamate; Glutamine	
Cysteine and methionine metabolism	115	4	1.5E-03	6.5	2.12E-02	0.08	Serine; Methionine; Alanine; Aspartate	
Kaposi sarcoma-associated herpesvirus infection	221	6	3.6E-04	7.9	8.78E-03	0.08		<i>Stat2; Stat1; Irf9; H2-D1; H2-K1; H2-Q7</i>
Ascorbate and aldarate metabolism	76	3	4.3E-03	5.5	4.09E-02	0.07	Myo-Inositol; UDP-Glucose; UDP-Glucuronate	
Nitrogen metabolism	36	3	4.9E-04	7.6	9.96E-03	0.07	Glutamine; Glutamate; Formate	
NOD-like receptor signaling pathway	215	8	3.4E-06	12.6	1.86E-04	0.06	ATP	<i>Stat1; Stat2; Ifi204; Irf9; Ccl5; Gbp5; Oas2</i>
Graft-versus-host disease	67	3	3.0E-03	5.8	3.25E-02	0.04		<i>H2-D1; H2-K1; H2-Q7</i>
Central carbon metabolism in cancer	104	16	2.2E-21	47.5	7.33E-19	0.00	Glucose; Glutamine; Glutamate; Serine; Leucine; Isoleucine; Phenylalanine; Methionine; Alanine; Asparagine; Aspartate; Proline; Tyrosine; Histidine; Tryptophan; Valine	
Protein digestion and absorption	141	16	3.7E-19	42.5	4.00E-17	0.00	Glutamate; Glutamine; Aspartate; Proline; Alanine; Phenylalanine; Valine; Leucine; Isoleucine; Methionine; Tryptophan; Serine; Asparagine; Histidine; Tyrosine; beta-Alanine	
Mineral absorption	81	12	6.0E-16	35.1	4.88E-14	0.00	Glucose; Valine; Leucine; Isoleucine; Proline; Tryptophan; Serine; Asparagine; Glutamine; Alanine; Methionine; Phenylalanine	
ABC transporters	186	15	1.0E-15	34.5	6.64E-14	0.00	Taurine; Alanine; Myo-Inositol; Glucose; Aspartate; Glutamine; Glutamate; Histidine; Valine; Leucine; Isoleucine; Proline; Serine; Phenylalanine	<i>Abcg1</i>
Allograft rejection	64	3	2.6E-03	5.9	2.95E-02	0.00		<i>H2-D1; H2-K1; H2-Q7</i>
Type I diabetes mellitus	73	3	3.8E-03	5.6	3.76E-02	0.00		<i>H2-D1; H2-K1; H2-Q7</i>
Autoimmune thyroid disease	82	3	5.3E-03	5.2	4.65E-02	0.00		<i>H2-D1; H2-K1; H2-Q7</i>

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Pathway	Metabolites	Genes	FDR	Metabolites	Genes	FDR	Metabolites	Genes	Metabolites	Genes
metM-Wnt										
Alanine, aspartate and glutamate metabolism	66	5	4.3E-06	12.4	2.36E-04	0.46	Fumarate; Aspartate; Asparagine; Glutamine; Glutamate			
Pyrimidine metabolism	123	4	1.1E-03	6.8	2.59E-02	0.26	UDP-glucose; beta-Alanine; Glutamine			<i>Cmpk2</i>
Arginine biosynthesis	42	4	1.7E-05	11.0	7.96E-04	0.26	Aspartate; Fumarate; Glutamate; Glutamine			
D-Glutamine and D-glutamate metabolism	17	2	1.8E-03	6.3	3.65E-02	0.25	Glutamate; Glutamine			
Galactose metabolism	78	4	2.0E-04	8.5	7.15E-03	0.18	Mannose; Glucose; UDP-Glucose; Myo-Inositol			
Valine, leucine and isoleucine biosynthesis	27	3	1.3E-04	8.9	5.44E-03	0.15	Isoleucine; Valine; Leucine			
Aminoacyl-tRNA biosynthesis	118	12	9.5E-15	32.3	1.55E-12	0.13	Tryptophan; Tyrosine; Leucine; Isoleucine; Valine; Serine; Aspartate; Proline; Glutamate; Glutamine; Asparagine			<i>Gars</i>
Pantothenate and CoA biosynthesis	46	3	6.6E-04	7.3	1.65E-02	0.12	beta-Alanine; Aspartate; Valine			
Glycine, serine and threonine metabolism	90	4	3.4E-04	8.0	1.01E-02	0.11	Aspartate; Tryptophan; Serine; Creatine			
Arginine and proline metabolism	128	4	1.3E-03	6.7	2.80E-02	0.10	Creatine; Phosphocreatine; Glutamate; Proline			
Pyruvate metabolism	69	3	2.1E-03	6.1	4.11E-02	0.08	Formate; Lactate; Fumarate			
Ascorbate and aldarate metabolism	76	3	2.8E-03	5.9	4.85E-02	0.07	Myo-Inositol; UDP-glucuronate; UDP-glucose			
Nitrogen metabolism	36	3	3.2E-04	8.1	1.01E-02	0.07	Formate; Glutamine; Glutamate			
Glyoxylate and dicarboxylate metabolism	93	4	3.9E-04	7.9	1.05E-02	0.06	Formate; Glutamate; Glutamine; Serine			
Amino sugar and nucleotide sugar metabolism	157	4	2.7E-03	5.9	4.85E-02	0.05	Glucose; Mannose; UDP-Glucose; UDP-glucuronate			
Central carbon metabolism in cancer	104	13	3.9E-17	37.8	1.27E-14	0.00	Fumarate; Asparagine; Aspartate; Glucose; Glutamate; Glutamine; Leucine; Isoleucine; Proline; Serine; Tryptophan; Tyrosine; Valine			
Protein digestion and absorption	141	12	8.3E-14	30.1	9.09E-12	0.00	Glutamate; Glutamine; Aspartate; Valine; Serine; Proline; Isoleucine; Leucine; Asparagine; Tryptophan; Tyrosine; beta-Alanine			
ABC transporters	186	12	2.3E-12	26.8	1.90E-10	0.00	Glucose; Glutamate; Aspartate; Glutamine; Valine; Taurine; Myo-Inositol; Leucine; Serine; Proline; Mannose; Isoleucine			
Mineral absorption	81	9	1.3E-11	25.1	8.35E-10	0.00	Glucose; Valine; Leucine; Isoleucine; Proline; Tryptophan; Serine; Asparagine; Glutamine			

Results of joined pathway analysis based on transcriptomic and metabolomic data. Identified pathways unique for M-Wnt cells are highlighted in orange. Identified pathways unique for metM-Wnt^{liver} cells are highlighted in green. Only pathways with a FDR P -value <0.05 are shown. Total reflect the total number of metabolites / genes within a pathway. Hits represent the number of metabolites / genes identified within our dataset.