

Supplementary Table I.

High-quality annotated metabolites with differential abundance between early-stage (I/II) and advanced-stage (III/IV) differentiated thyroid cancers.

Group: Metabolite Name	Subgroup	P Value	q Value	$\log_2(\text{FC})^*$	m/z	RT (s)	Column/ESI	Adduct	KEGG ID	CID
Nucleotide Flux										
GMP	Purine Metabolism	1.8E-8	4.1E-5	2.35	364.0646	242	HILIC+	M+H	C00144	135398631
AMP	Purine Metabolism	4.8E-5	0.024	1.51	346.0557	18	C18-	M-H	C00020	6083
Uracil [†]	Pyrimidine Metabolism	1.3E-4	0.029	1.05	111.0200	22	C18-	M-H	C00106	1174
Uracil [†]	Pyrimidine Metabolism	2.4E-4	0.036	1.53	113.0346	41	HILIC+	M+H	C00106	1174
Cytosine	Pyrimidine Metabolism	0.003	0.128	1.10	112.0507	38	HILIC+	M+H	C00380	597
2-Methylaminoadenosine	tRNA/Modified Nucleosides	0.003	0.135	1.88	261.1085	61	HILIC+	M+H-2H2O	C03218	439946
2'-Deoxyinosine 5'-phosphate (dIMP)	Purine Catabolism	0.004	0.146	1.40	333.0605	68	HILIC+		C06196	135398614
Guanine	Purine Salvage	0.011	0.241	0.75	150.0424	23	C18-	M-H	C00242	135398634
Ribose 5-phosphate	Pentose Phosphate Path	0.014	0.254	2.42	231.0262	160	HILIC+	M+H	C00117	439167
CTP	Pyrimidine Metabolism	0.015	0.264	1.28	517.9550	52	C18-	M+Cl	C00063	6176
5-Aminoimidazole	Purine Biosynthesis	0.031	0.335	1.05	128.0193	92	HILIC+	M+2Na-H	C05239	484
dATP	DNA Precursor	0.043	0.367	-0.92	557.9782	285	C18-		C00131	15993
Protein/Amino Acid Turnover										
Iminoaspartate	Aspartate Metabolism	5.0E-5	0.024	1.80	96.0081	27	HILIC+	M+H-2H2O	C05840	796
3-Methylcrotonylglycine	Amino Acid/Leucine Branch	0.002	0.124	1.06	158.0810	75	HILIC+		C20828	169485
Imidazole acetaldehyde [†]	Histidine Catabolism	0.002	0.126	1.25	111.0554	71	HILIC+	M+H	C05130	150841
delta-Guanidinovaleric acid (δ-GVA)	Arginine Catabolism	0.003	0.128	1.61	182.0908	54	HILIC+	M+Na	C13688	160464
2-Oxobutanoate	Methionine/Cysteine Catabolism	0.004	0.159	0.64	101.0244	22	C18-	M-H	C00109	58
4-Methylthio-2-oxobutanoic acid (MTOB)	Methionine Salvage	0.007	0.198	0.96	149.0266	74	HILIC+	M+H	C01180	473
Aspartate	Central AA Metabolism	0.007	0.198	1.11	134.0448	67	HILIC+	M+H	C00049	5960
Histidine	Essential AA Pool	0.008	0.205	0.98	156.0767	75	HILIC+	M+H	C00135	6274
Asparagine	Nitrogen Salvage	0.011	0.235	1.02	133.0607	76	HILIC+	M+H	C00152	6267
Citrulline	Urea Cycle/NO Signaling	0.016	0.279	0.94	174.0885	20	C18-	M-H	C00327	9750
N6-Hydroxy-lysine	Modified Lysine/Hydroxylation	0.017	0.279	1.94	163.1077	113	HILIC+	M+H	C01028	439370
Phenol	Tyrosine Catabolism	0.018	0.279	0.85	95.0493	51	HILIC+	M+H	C00146	996
S-Allyl-cysteine	Sulfur Amino Acids	0.021	0.291	1.31	206.0213	232	HILIC+	M+2Na-H	C16759	9793905
β-Alanyl-lysine	Dipeptide/Autophagy	0.025	0.311	1.58	218.1499	64	HILIC+		C05341	440638
Imidazole acetaldehyde [†]	Histidine Catabolism	0.025	0.313	0.28	169.0619	17	C18-	M+Hac-H	C05130	150841
4-Guanidinobutanal	Arginine/Putrescine Path	0.027	0.320	0.93	152.0787	228	HILIC+		C02647	559
Pipecolate [†]	Lysine Catabolism	0.029	0.330	1.02	130.0862	71	HILIC+	M+H	C00408	439227
Leucyl-leucine	Dipeptide/Autophagy	0.030	0.330	2.22	245.1859	26	HILIC+	M+H	C11332	94244
4-Imidazolone-5-acetate	Histidine Catabolism	0.035	0.345	0.35	187.0358	179	C18-	M+FA-H	C05133	440570
Dehydroalanine	Post-Translational Modification	0.035	0.345	0.93	88.0394	65	HILIC+		C02218	123991
2-Amino-6-oxoheptanedioate	Lysine Metabolism	0.035	0.345	-0.71	190.0711	233	HILIC+	M+H	C03871	194695
N6-Acetyl-lysine	Protein Acetylation	0.038	0.356	1.32	189.1233	47	HILIC+	M+H	C02727	92832
Methylguanidine	Arginine/Creatine Path	0.039	0.357	0.63	118.0350	91	HILIC+	M+2Na-H	C02294	10111
O-Succinyl-homoserine	Methionine Metabolism	0.040	0.357	1.78	220.0816	66	HILIC+		C01118	439406
Lysine	Essential AA Pool	0.040	0.357	0.96	147.1128	75	HILIC+	M+H	C00047	5962
D-erythro-1-(Imidazol-4-yl)glycerol 3-phosphate (IGP)	Histidine Biosynthesis	0.041	0.359	1.36	283.0072	50	HILIC+	M+2Na-H	C04666	440431
Pipecolate [†]	Lysine Catabolism	0.048	0.388	0.54	128.0718	23	C18-		C00408	439227
Phenylacetylglutamine	Phenylalanine/Gut Microbiome	0.048	0.388	1.20	263.1040	22	C18-	M-H	C04148	92258
Membrane Integrity										
3-Ketosphingosine	Sphingosine Synthesis	7.4E-5	0.028	2.70	298.2741	24	HILIC+	M+H	C06121	9839212
3-Dehydroosphinganine	Sphingosine Synthesis	2.0E-4	0.033	3.38	300.2897	24	HILIC+	M+H	C02934	439853
Oleoylglycerone phosphate (Oleoyl-DHAP)	Plasmalogen Precursor	0.002	0.123	1.84	433.2365	166	C18-	M-H	C03630	5280612
sn-Glycer-3-phospho-1-inositol (GroPIns)	PI-Signaling Byproduct	0.014	0.261	2.18	333.0593	147	C18-	M-H	C01225	45480545
Phosphodimethylethanolamine	Membrane Synthesis/Methylation	0.014	0.263	0.71	192.0397	42	HILIC+	M+Na	C13482	151438

Group: Metabolite Name	Subgroup	P Value	q Value	$\log_2(\text{FC})^*$	m/z	RT (s)	Column/ESI	Adduct	KEGG ID	CID
Lipid Remodeling										
(6Z,9Z,12Z)-Octadecatrienoic acid (γ -Linolenate) [†]	Linolenic Acid Path	1.1E-4	0.028	2.47	279.2320	24	HILIC+	M+H	C06426	5280933
Linoleate	Essential Fatty Acids	0.002	0.118	2.53	281.2476	29	HILIC+	M+H	C01595	5280450
9-Hydroxy-12-oxo-octadecadienoate	Oxylipin Path	0.004	0.145	1.37	309.2070	222	C18-	M-H	C21923	45934096
(9Z)-Hexadecenoic acid (Palmitoleate)	Monounsaturated Fatty Acids	0.004	0.146	1.60	253.2173	213	C18-	M-H	C08362	445638
(9Z)-Octadecenoic acid (Oleate) [†]	Monounsaturated Fatty Acids	0.004	0.161	2.28	283.2633	29	HILIC+	M+H	C00712	445639
16-Hydroxypalmitate	Omega-Oxidation	0.008	0.205	0.29	271.2279	148	C18-	M-H	C18218	10466
Stearidonic acid (Stearidonate)	Omega-3 Metabolism	0.010	0.235	1.55	277.2163	23	HILIC+	M+H	C16300	5312508
Dodecanoic acid (Laurate)	Medium-Chain Fatty Acids	0.012	0.244	0.85	199.1703	156	C18-	M-H	C02679	3893
Tetradecanoic acid (Myristate)	Saturated Fatty Acids	0.017	0.279	1.09	227.2017	200	C18-	M-H	C06424	11005
Decanoic acid (Caprate)	Medium-Chain Fatty Acids	0.018	0.279	0.74	171.1390	107	C18-	M-H	C01571	2969
Dihomo- γ -linolenate	Prostanoid Precursors	0.018	0.279	2.28	307.2633	24	HILIC+	M+H	C03242	5280581
Octadecanoic acid (Stearate)	Saturated Fatty Acids	0.023	0.303	1.58	285.2789	19	HILIC+	M+H	C01530	5281
9,10-Epoxystearate ^{†\$}	Oxylipin Path	0.024	0.307	0.77	297.2437	252	C18-	M-H	C19418	15868
Eruic acid (Erucate)	Very-Long-Chain Fatty Acids	0.024	0.311	1.29	397.3324	289	C18-	M+Hac-H	C08316	5281116
1-Dodecanol	Fatty Alcohols	0.032	0.337	2.16	231.1702	29	HILIC+	M+2Na-H	C02277	8193
3-Hydroxytetradecane-tricarboxylate	Lipid Metabolism	0.035	0.345	1.74	369.1871	64	HILIC+	M+Na	C04529	5460247
(6Z,9Z,12Z)-Octadecatrienoic acid (γ -Linolenate) [†]	Linolenic Acid Path	0.037	0.355	1.11	277.2173	201	C18-	M-H	C06426	5280933
(9Z)-Octadecenoic acid (Oleate) [†]	Monounsaturated Fatty Acids	0.039	0.357	1.11	281.2486	250	C18-	M-H	C00712	445639
Hexadecanoic acid (Palmitate)	Saturated Fatty Acids	0.040	0.357	0.47	255.2328	243	C18-	M-H	C00249	985
9,10-Epoxystearate ^{†\$}	Oxylipin Path	0.047	0.385	0.90	299.2582	31	HILIC+	M+H	C19418	15868
16-Oxopalmitate	Omega-Oxidation	0.048	0.388	0.42	271.2268	23	HILIC+	M+H	C19614	15931626
Epigenetic Signaling										
S-Adenosyl-L-homocysteine (SAH)	Methylation Cycle Marker	2.9E-4	0.039	1.70	385.1280	73	HILIC+	M+H	C00021	439155
Acetylglutamate	Urea Cycle Regulation	9.4E-4	0.076	1.29	188.0565	17	C18-	M-H	C00624	70914
8-Amino-7-oxononanoate	Biotin (B7) Metabolism	0.001	0.094	2.03	188.1281	40	HILIC+	M+H	C01092	173
3'-Phosphoadenylyl sulfate (PAPS)	Universal Sulfate Donor	0.002	0.115	2.22	573.9672	23	C18-	M+H+HCOONa	C00053	10214
Formate	Folate Cycle Entry	0.003	0.135	1.09	90.9768	53	HILIC+	M+2Na-H	C00058	284
1-Methylnicotinamide	Nicotinate/Nicotinamide Path	0.008	0.205	2.86	137.0710	47	HILIC+	M+H	C02918	457
5-Methylcytosine	Epigenetic DNA Modification	0.019	0.283	0.39	124.0515	225	C18-	M-H	C02376	65040
Maleamate	Nicotinate Metabolism	0.023	0.303	0.81	114.0197	17	C18-	M-H	C01596	5280451
8-Amino-7-carboxyamino-nonanoate	Biotin (B7) Metabolism	0.023	0.303	1.65	197.1282	44	HILIC+	M+H+2H2O	C22458	4474067
Nicotinurate	Nicotinate/Nicotinamide Path	0.026	0.320	0.51	181.0608	238	HILIC+	M+H	C05380	68499
Choline [†]	Methyl Donor/Phospholipids	0.027	0.320	1.25	104.1071	36	HILIC+	M+H	C00114	305
N6-Methyl-lysine	Histone Methylation	0.030	0.330	1.01	161.1285	67	HILIC+	M+H	C02728	164795
Choline [†]	Methyl Donor/Phospholipids	0.037	0.355	1.05	170.0799	26	C18-	M+H+HCOONa	C00114	305
Nicotinamide	NAD ⁺ Precursor	0.038	0.356	1.81	123.0553	34	HILIC+	M+H	C00153	936
Steroid Metabolism										
Pregnan-21-al	Progesterogen Metabolism	4.4E-4	0.050	2.12	347.2604	175	C18-	M+FA-H	C00891	439338
11-cis-Retinol	Vitamin A/Retinoids	0.008	0.202	2.90	287.2370	25	HILIC+	M+H	C00899	5280382
Phenolic steroid	Estrogen-like Compounds	0.013	0.254	2.61	279.1712	34	HILIC+	M+Na	C02453	439726
7-Dehydrocholesterol (7-DHC)	Cholesterol Precursor	0.020	0.291	3.39	385.3466	23	HILIC+	M+H	C01164	439423
Estrone	Estrogens	0.030	0.330	1.40	271.1682	252	HILIC+	M+H	C00468	5870
19-Norprogesterone	Progesterogen Metabolism	0.036	0.350	2.04	345.1788	67	HILIC+	M+2Na-H	C14489	228864
Estradiol-17 β	Estrogens	0.038	0.356	2.53	295.1661	39	HILIC+	M+Na	C00951	5757
Cortolone	Cortisol Catabolism	0.049	0.388	-1.43	365.2332	161	C18-	M-H	C05481	160499
Redox Homeostasis										
6-Carboxytetrahydropterin	Biopterin Cycle/Redox	5.4E-4	0.053	2.20	195.0514	212	HILIC+	M+H-NH3	C20239	135911925
Dihydronoepterin	Biopterin Cycle/Redox	8.3E-4	0.073	3.43	256.1043	61	HILIC+	M+H	C04874	135398602
Tetrahydropteridine	Biopterin Cycle/Redox	0.001	0.077	1.47	137.0822	225	HILIC+	M+H	C05650	156
2-(Hydroxysulfanyl)hercynine (HSH-Hercynine)	Ergothioneine Precursor	0.005	0.174	1.54	246.0907	66	HILIC+	M+H	C21731	122706276
Cysteate	Cysteine Metabolism	0.012	0.244	1.87	170.0122	132	HILIC+	M+H	C00506	72886
Hercynine	Histidine/Redox Signaling	0.020	0.289	1.20	198.1237	67	HILIC+	M+H	C05575	440727
3-Bromo-tyrosine	Oxidative Protein Damage	0.027	0.320	0.59	303.9817	51	C18-	M+FA-H	C17079	148708

Group: Metabolite Name	Subgroup	P Value	q Value	$\log_2(\text{FC})^*$	m/z	RT (s)	Column/ESI	Adduct	KEGG ID	CID
Redox Homeostasis (Continued)										
DH-Monapterin triphosphate	Biopterin Cycle/Redox	0.037	0.355	1.62	459.9838	167	HILIC+	M+H-2H2O	C21094	135398606
Fatty Acid Oxidation										
Isovalerylcarnitine	Acylcarnitine Shuttle	0.002	0.126	2.67	246.1699	30	HILIC+	M+H	C20826	169235
Butanoylcarnitine	Acylcarnitine Shuttle	0.004	0.153	2.72	232.1543	33	HILIC+	M+H	C02862	439829
Carnitinamide	Acylcarnitine-like	0.015	0.264	1.80	143.1179	35	HILIC+	M+H-H2O	C02290	11701090
Carnitine	Fatty Acid Transport	0.039	0.357	1.28	162.1125	46	HILIC+	M+H	C00318	10917
Decanoylcarnitine	Acylcarnitine Shuttle	0.041	0.359	1.14	360.2389	154	C18-	M+FA-H	C03299	11953821
Bioenergetic Flux										
(2,3-Dihydroxybenzoyl)adenylate (2,3-DHBA-AMP)	Iron Scavenging/Siderophore	0.003	0.130	2.37	506.0677	261	HILIC+	M+Na	C04030	440201
2,3-Dihydroxybenzoate	Iron-Binding/Catechols	0.004	0.154	-0.54	153.0194	22	C18-	M-H	C00196	19
D-4'-Phosphopantethenate (P-Pantothenate)	Coenzyme A (CoA) Path	0.005	0.161	-1.04	300.0844	119	HILIC+	M+H	C03492	41635
4-Methyl-2-oxopentanoate (α -Ketoisocaproate)	Leucine Catabolism	0.019	0.281	-1.41	129.0558	23	C18-	M-H	C00233	70
5-(2-Hydroxyethyl)-4-methylthiazole (Sulfurol)	Thiamine (B1) Metabolism	0.025	0.313	0.56	142.0339	186	C18-	M-H	C04294	1136
Acetyl phosphate	High-Energy Intermediate	0.027	0.324	-0.99	138.9802	24	C18-	M-H	C00227	186
5-Amino-6-ribitylaminouracil	Riboflavin (B2) Metabolism	0.048	0.388	0.67	275.0996	20	C18-	M-H	C04732	193516
Glycan Defense										
Chitobiose	Glucosamine Metabolism	0.003	0.135	1.75	459.1400	20	C18-	M+Cl	C01674	439544
N-Glycolyl-glucosamine	Hexosamine Biosynthesis	0.020	0.288	1.04	236.0777	16	C18-	M-H	C03146	439921
N-Acetyl-9-O-acetyleneuraminate (9-O-Acetyl-Neu5Ac) [‡]	Sialic Acid Modification	0.025	0.313	1.52	410.1301	17	C18-	M+Hac-H	C04017	92042744
Immune/Signaling										
Serotonin	Tryptophan Signaling	0.005	0.174	3.76	177.1022	28	HILIC+	M+H	C00780	5202
N1-Acetylspermine	Polyamine Acetylation	0.007	0.198	3.04	245.2335	257	HILIC+	M+H	C02567	916
Kynurenine [†]	Tryptophan/Kynurenine Axis	0.009	0.220	2.22	209.0921	42	HILIC+	M+H	C00328	161166
3-Hydroxyaminophenol	Phenylalanine Branch	0.011	0.239	0.62	126.0550	86	HILIC+	M+H	C14602	5460445
N1-Acetylspermidine	Polyamine Acetylation	0.016	0.276	1.36	188.1757	56	HILIC+	M+H	C00612	496
γ -Glutamyltryptamine	Tyramine/Dopamine Path	0.017	0.279	2.53	267.1343	32	HILIC+	M+H	C20926	10214674
N-Methylhistamine	Histamine Metabolism	0.021	0.291	2.29	126.1026	60	HILIC+	M+H	C05127	3614
Kynurenine [†]	Tryptophan/Kynurenine Axis	0.022	0.303	1.41	207.0776	22	C18-	M-H	C00328	161166
4-Carboxy-4-hydroxy-2-oxoadipate	Tryptophan/Anthranilate Path	0.023	0.303	0.80	219.0146	24	C18-	M-H	C04115	130
2-Aminomuconate	Tryptophan/Kynurenine Axis	0.027	0.320	1.18	158.0451	34	HILIC+	M+H	C02220	5280499
Leukotriene D4 (LTD4)	Leukotriene Synthesis	0.031	0.335	1.22	555.2725	149	C18-	M+Hac-H	C05951	5280878
Histamine	Histidine/Immune Signaling	0.033	0.345	1.44	112.0871	67	HILIC+	M+H	C00388	774
Biliverdin	Heme Degradation/Redox	0.034	0.345	1.73	583.2547	31	HILIC+	M+H	C00500	5280353
2-Aminomuconate semialdehyde	Tryptophan/Kynurenine Path	0.034	0.345	0.31	142.0498	183	HILIC+	M+H	C03824	5280625
Prostaglandin E2 (PGE2)	COX-driven Inflammation	0.035	0.345	0.83	411.2404	152	C18-	M+Hac-H	C00584	5280360
Benzylamine	Monoamine Metabolism	0.043	0.367	0.93	91.0544	42	HILIC+	M+H-NH3	C15562	7504
Leukotriene B4 (LTB4)	Leukotriene Synthesis	0.043	0.368	1.31	335.2224	219	C18-	M-H	C02165	5280492
Adrenaline	Catecholamine Signaling	0.044	0.370	-0.55	242.1045	239	C18-	M+Hac-H	C00788	5816
5,6-Indolequinone-2-carboxylate	Melanogenesis/Dopa Path	0.048	0.388	1.49	235.9932	36	HILIC+	M+2Na-H	C17938	17796835
2'-Phospho-cyclic ADP-ribose (2'-P-cADPR)	Calcium Signaling	0.049	0.388	1.57	622.0327	268	HILIC+	M+H	C20742	73352906
N-Methyltryptamine	Tryptophan/Indole Signaling	0.050	0.388	1.05	175.1234	70	HILIC+	M+H	C06213	6088

* Fold-change was calculated as advanced-stage/early-stage using untransformed peak area values.

[†] Metabolite annotated as a different adduct and/or using different column/ESI.

[‡] Annotated isomers: N-Acetyl-4-O-acetyleneuraminate, N-Acetyl-7-O-acetyleneuraminate

[§] Annotated isomer: 18-Hydroxyoleate

^{||} Annotated isomers: 11H-14,15-EETA, 12(R)-HPETE, 12(S)-HPETE, 15(S)-HPETE, 15H-11,12-EETA, 5(S)-HPETE, 8(R)-HPETE, Hepoxilin A3, Hepoxilin B3

FC, fold-change; RT, retention time; ESI, electrospray ionization; KEGG ID, Kyoto Encyclopedia of Genes and Genomes ID; CID, PubChem Compound ID