

Supplementary Table I. High-quality annotated metabolites differentially expressed between early-stage (I/II) and advanced-stage (III/IV) differentiated thyroid cancers.

Group: Metabolite Name	Subgroup	P Value	q Value	log ₂ (FC)	m/z	RT (s)	Column/ESI	Adduct	KEGG ID	CID	HMDB ID
Nucleotide Flux											
GMP	Purine Metabolism	1.8E-8	4.1E-5	2.35	364.0646	242	C18-	M+H	C00144	135398631	HMDB0001397
AMP	Purine Metabolism	4.8E-5	0.024	1.51	346.0557	18	C18-	M-H	C00020	6083	HMDB0000045
Uracil	Pyrimidine Metabolism	1.3E-4	0.029	1.05	111.02	22	C18-	M-H	C00106	1174	HMDB0000300
Uracil	Pyrimidine Metabolism	2.4E-4	0.036	1.53	113.0346	41	C18-	M+H	C00106	1174	HMDB0000300
Cytosine	Pyrimidine Metabolism	0.003	0.128	1.10	112.0507	38	C18-	M+H	C00380	597	HMDB0000630
2-Methylaminoadenosine	tRNA/Modified Nucleosides	0.003	0.135	1.88	261.1085	61	C18-	M+H-2H2O	C03218	439946	—
2'-Deoxyinosine 5'-phosphate (dIMP)	Purine Catabolism	0.004	0.146	1.40	333.0605	68	C18-		C06196	135398614	HMDB0006555
Guanine	Purine Salvage	0.011	0.241	0.75	150.0424	23	C18-	M-H	C00242	135398634	HMDB0000132
Ribose 5-phosphate	Pentose Phosphate Path	0.014	0.254	2.42	231.0262	160	C18-	M+H	C00117	439167	—
CTP	Pyrimidine Metabolism	0.015	0.264	1.28	517.955	52	C18-	M+Cl	C00063	6176	HMDB0000082
5-Aminoimidazole	Purine Biosynthesis	0.031	0.335	1.05	128.0193	92	C18-	M+2Na-H	C05239	484	HMDB0003929
dATP	DNA Precursor	0.043	0.367	-0.92	557.9782	285	C18-	M-H+HCOONa	C00131	15993	HMDB0001532
Protein/AA Turnover											
Iminoaspartate	Aspartate Metabolism	5.0E-5	0.024	1.80	96.0081	27	C18-	M+H-2H2O	C05840	796	HMDB0001131
3-Methylcrotonylglycine	Amino Acid/Leucine Branch	0.002	0.124	1.06	158.081	75	C18-	M+H	C20828	169485	—
Imidazole acetaldehyde	Histidine Catabolism	0.002	0.126	1.25	111.0554	71	C18-	M+H	C05130	150841	HMDB0003905
delta-Guanidinovaleric acid (δ -GVA)	Arginine Catabolism	0.003	0.128	1.61	182.0908	54	C18-	M+Na	C13688	160464	HMDB0250978
2-Oxobutanoate	Methionine/Cysteine Catabolism	0.004	0.159	0.64	101.0244	22	C18-	M-H	C00109	58	HMDB0000005
4-Methylthio-2-oxobutanoic acid (MTOB)	Methionine Salvage	0.007	0.198	0.96	149.0266	74	C18-	M+H	C01180	473	HMDB0001553
Aspartate	Central AA Metabolism	0.007	0.198	1.11	134.0448	67	C18-	M+H	C00049	5960	HMDB0000191
Histidine	Essential AA Pool	0.008	0.205	0.98	156.0767	75	C18-	M+H	C00135	6274	HMDB0000177
Asparagine	Nitrogen Salvage	0.011	0.235	1.02	133.0607	76	C18-	M+H	C00152	6267	HMDB0000168
Citrulline	Urea Cycle/NO Signaling	0.016	0.279	0.94	174.0885	20	C18-	M-H	C00327	9750	HMDB0000904
N6-Hydroxy-lysine	Modified Lysine/Hydroxylation	0.017	0.279	1.94	163.1077	113	C18-	M+H	C01028	439370	—
Phenol	Tyrosine Catabolism	0.018	0.279	0.85	95.0493	51	C18-	M+H	C00146	996	—
S-Allyl-cysteine	Sulfur Amino Acids	0.021	0.291	1.31	206.0213	232	C18-	M+2Na-H	C16759	9793905	HMDB0034323
β -Alanyl-lysine	Dipeptide/Autophagy	0.025	0.311	1.58	218.1499	64	C18-	M+H	C05341	440638	HMDB0060442
Imidazole acetaldehyde	Histidine Catabolism	0.025	0.313	0.28	169.0619	17	C18-	M+Hac-H	C05130	150841	HMDB0003905
4-Guanidinobutanal	Arginine/Putrescine Path	0.027	0.320	0.93	152.0787	228	C18-	M+Na	C02647	559	—
Pipecolate	Lysine Catabolism	0.029	0.330	1.02	130.0862	71	C18-	M+H	C00408	439227	HMDB0000070
Leucyl-leucine	Dipeptide/Autophagy	0.030	0.330	2.22	245.1859	26	C18-	M+H	C11332	94244	HMDB0028933
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	C18-	M+H	C02218	123991	HMDB0003609
2-Amino-6-oxoheptanedioate	Lysine Metabolism	0.035	0.345	-0.71	190.0711	233	C18-	M+H	C03871	194695	—
N6-Acetyl-lysine	Protein Acetylation	0.038	0.356	1.32	189.1233	47	C18-	M+H	C02727	92832	HMDB0000206
Methylguanidine	Arginine/Creatine Path	0.039	0.357	0.63	118.035	91	C18-	M+2Na-H	C02294	10111	HMDB0001522
O-Succinyl-homoserine	Methionine Metabolism	0.040	0.357	1.78	220.0816	66	C18-	M+H	C01118	439406	—
Lysine	Essential AA Pool	0.040	0.357	0.96	147.1128	75	C18-	M+H	C00047	5962	HMDB0000182
D-erythro-1-(Imidazol-4-yl)glycerol 3-phosphate (IGP)	Histidine Biosynthesis	0.041	0.359	1.36	283.0072	50	C18-	M+2Na-H	C04666	440431	HMDB0012208
Pipecolate	Lysine Catabolism	0.048	0.388	0.54	128.0718	23	C18-	M-H	C00408	439227	HMDB0000070
Phenylacetylglutamine	Phenylalanine/Gut Microbiome	0.048	0.388	1.20	263.104	22	C18-	M-H	C04148	92258	HMDB0006344
Membrane Integrity											
3-Ketosphinganine	Sphingosine Synthesis	7.4E-5	0.028	2.70	298.2741	24	C18-	M+H	C06121	9839212	—
3-Dehydroosphinganine	Sphingosine Synthesis	2.0E-4	0.033	3.38	300.2897	24	C18-	M+H	C02934	439853	HMDB0001480
Oleoylglycerone phosphate (Oleoyl-DHAP)	Plasmalogen Precursor	0.002	0.123	1.84	433.2365	166	C18-	M-H	C03630	5280612	—

(continued)

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sn-Glycero-3-phospho-1-inositol (GroPIns)	PI-Signaling Byproduct	0.014	0.261	2.18	333.0593	147	C18-	M-H	C01225	45480545	HMDB0011649
Phosphodimethylethanamine	Membrane Synthesis/Methylation	0.014	0.263	0.71	192.0397	42	C18-	M+Na	C13482	151438	HMDB0060236
Lipid Remodeling											
(6Z,9Z,12Z)-Octadecatrienoic acid (γ -Linolenate)	Linolenic Acid Path	1.1E-4	0.028	2.47	279.232	24	C18-	M+H	C06426	5280933	HMDB0003073
Linoleate	Essential Fatty Acids	0.002	0.118	2.53	281.2476	29	C18-	M+H	C01595	5280450	HMDB0000673
9-Hydroxy-12-oxo-octadecadienoate	Oxylipin Path	0.004	0.145	1.37	309.207	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	HMDB0003229
(9Z)-Octadecenoic acid (Oleate)	Monounsaturated Fatty Acids	0.004	0.161	2.28	283.2633	29	C18-	M+H	C00712	445639	HMDB0000207
16-Hydroxypalmitate	Omega-Oxidation	0.008	0.205	0.29	271.2279	148	C18-	M-H	C18218	10466	HMDB0006294
Stearidonic acid (Stearidonate)	Omega-3 Metabolism	0.010	0.235	1.55	277.2163	23	C18-	M+H	C16300	5312508	HMDB0006547
Dodecanoic acid (Laurate)	Medium-Chain Fatty Acids	0.012	0.244	0.85	199.1703	156	C18-	M-H	C02679	3893	HMDB0000638
Tetradecanoic acid (Myristate)	Saturated Fatty Acids	0.017	0.279	1.09	227.2017	200	C18-	M-H	C06424	11005	HMDB0000806
Decanoic acid (Caprate)	Medium-Chain Fatty Acids	0.018	0.279	0.74	171.139	107	C18-	M-H	C01571	2969	HMDB0000511
Dihomo-γ-linolenate	Prostanoid Precursors	0.018	0.279	2.28	307.2633	24	C18-	M+H	C03242	5280581	HMDB0002925
Octadecanoic acid (Stearate)	Saturated Fatty Acids	0.023	0.303	1.58	285.2789	19	C18-	M+H	C01530	5281	HMDB0000827
9,10-Epoxystearate*	Oxylipin Path	0.024	0.307	0.77	297.2437	252	C18-	M-H	C19418	15868	HMDB0247617
Erucic acid (Eruccate)	Very-Long-Chain Fatty Acids	0.024	0.311	1.29	397.3324	289	C18-	M+Hac-H	C08316	5281116	HMDB0002068
1-Dodecanol	Fatty Alcohols	0.032	0.337	2.16	231.1702	29	C18-	M+2Na-H	C02277	8193	HMDB0011626
3-Hydroxytetradecane-tricarboxylate	Lipid Metabolism	0.035	0.345	1.74	369.1871	64	C18-	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	HMDB0003073
(9Z)-Octadecenoic acid (Oleate)	Monounsaturated Fatty Acids	0.039	0.357	1.11	281.2486	250	C18-	M-H	C00712	445639	HMDB0000207
Hexadecanoic acid (Palmitate)	Saturated Fatty Acids	0.040	0.357	0.47	255.2328	243	C18-	M-H	C00249	985	HMDB0000220
9,10-Epoxystearate*	Oxylipin Path	0.047	0.385	0.90	299.2582	31	C18-	M+H	C19418	15868	HMDB0247617
16-Oxopalmitate	Omega-Oxidation	0.048	0.388	0.42	271.2268	23	C18-	M+H	C19614	15931626	-
Epigenetic Signaling											
S-Adenosyl-L-homocysteine (SAH)	Methylation Cycle Marker	2.9E-4	0.039	1.70	385.128	73	C18-	M+H	C00021	439155	HMDB0000939
Acetylglutamate	Urea Cycle Regulation	9.4E-4	0.076	1.29	188.0565	17	C18-	M-H	C00624	70914	HMDB0001138
8-Amino-7-oxononanoate	Biotin (B7) Metabolism	0.001	0.094	2.03	188.1281	40	C18-	M+H	C01092	173	HMDB0240687
3'-Phosphoadenylyl sulfate (PAPS)	Universal Sulfate Donor	0.002	0.115	2.22	573.9672	23	C18-	M+H+HCOONa	C00053	10214	HMDB0001134
Formate	Folate Cycle Entry	0.003	0.135	1.09	90.9768	53	C18-	M+2Na-H	C00058	284	HMDB0000142
1-Methylnicotinamide	Nicotinate/Nicotinamide Path	0.008	0.205	2.86	137.071	47	C18-	M+H	C02918	457	HMDB0000699
5-Methylcytosine	Epigenetic DNA Modification	0.019	0.283	0.39	124.0515	225	C18-	M-H	C02376	65040	HMDB0002894
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	C18-	M+H+2H2O	C22458	4474067	-
Nicotinurate	Nicotinate/Nicotinamide Path	0.026	0.320	0.51	181.0608	238	C18-	M+H	C05380	68499	HMDB0003269
Choline	Methyl Donor/Phospholipids	0.027	0.320	1.25	104.1071	36	C18-	M+H	C00114	305	HMDB0000097
N6-Methyl-lysine	Histone Methylation	0.030	0.330	1.01	161.1285	67	C18-	M+H	C02728	164795	HMDB0002038
Choline	Methyl Donor/Phospholipids	0.037	0.355	1.05	170.0799	26	C18-	M+H+HCOONa	C00114	305	HMDB0000097
Nicotinamide	NAD+ Precursor	0.038	0.356	1.81	123.0553	34	C18-	M+H	C00153	936	HMDB0001406
Steroid Metabolism											
Pregnan-21-ol	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	287.237	25	C18-	M+H	C00899	5280382	HMDB0006216
Phenolic steroid	Estrogen-like Compounds	0.013	0.254	2.61	279.1712	34	C18-	M+Na	C02453	439726	HMDB0244763
7-Dehydrocholesterol (7-DHC)	Cholesterol Precursor	0.020	0.291	3.39	385.3466	23	C18-	M+H	C01164	439423	HMDB0000032
Estrone	Estrogens	0.030	0.330	1.40	271.1682	252	C18-	M+H	C00468	5870	HMDB0000145
19-Norprogesterone	Progesterogen Metabolism	0.036	0.350	2.04	345.1788	67	C18-	M+2Na-H	C14489	228864	-
Estradiol-17β	Estrogens	0.038	0.356	2.53	295.1661	39	C18-	M+Na	C00951	5757	HMDB0000151
Cortolone	Cortisol Catabolism	0.049	0.388	-1.43	365.2332	161	C18-	M-H	C05481	160499	HMDB0003128

(continued)

Group: Metabolite Name	Subgroup	P Value	q Value	$\log_2(\text{FC})$	m/z	RT (s)	Column/ESI	Adduct	KEGG ID	CID	HMDB ID
Redox Homeostasis											
6-Carboxytetrahydropterin	Biopterin Cycle/Redox	5.4E-4	0.053	2.20	195.0514	212	C18-	M+H-NH3	C20239	135911925	HMDB0060410
Dihydronoopterin	Biopterin Cycle/Redox	8.3E-4	0.073	3.43	256.1043	61	C18-	M+H	C04874	135398602	HMDB0002275
Tetrahydropteridine	Biopterin Cycle/Redox	0.001	0.077	1.47	137.0822	225	C18-	M+H	C05650	156	HMDB0001216
2-(Hydroxysulfanyl)hercynine (HSH-Hercynine)	Ergothioneine Precursor	0.005	0.174	1.54	246.0907	66	C18-	M+H	C21731	122706276	—
Cysteate	Cysteine Metabolism	0.012	0.244	1.87	170.0122	132	C18-	M+H	C00506	72886	HMDB0002757
Hercynine	Histidine/Redox Signaling	0.020	0.289	1.20	198.1237	67	C18-	M+H	C05575	440727	HMDB0029422
3-Bromo-tyrosine	Oxidative Protein Damage	0.027	0.320	0.59	303.9817	51	C18-	M+FA-H	C17079	148708	HMDB0005874
DH-Monapterin triphosphate	Biopterin Cycle/Redox	0.037	0.355	1.62	459.9838	167	C18-	M+H-2H2O	C21094	135398606	—
Fatty Acid Oxidation											
Isovalerylcarnitine	Acylcarnitine Shuttle	0.002	0.126	2.67	246.1699	30	C18-	M+H	C20826	169235	—
Butanoylcarnitine	Acylcarnitine Shuttle	0.004	0.153	2.72	232.1543	33	C18-	M+H	C02862	439829	HMDB0002013
Carnitinamide	Acylcarnitine-like	0.015	0.264	1.80	143.1179	35	C18-	M+H-2H2O	C02290	11701090	—
Carnitine	Fatty Acid Transport	0.039	0.357	1.28	162.1125	46	C18-	M+H	C00318	10917	HMDB0000062
Decanoylcarnitine	Acylcarnitine Shuttle	0.041	0.359	1.14	360.2389	154	C18-	M+FA-H	C03299	11953821	HMDB0000651
Bioenergetic Flux											
(2,3-Dihydroxybenzoyl)adenylate (2,3-DHBA-AMP)	Iron Scavenging/Siderophore	0.003	0.130	2.37	506.0677	261	C18-	M+Na	C04030	440201	—
2,3-Dihydroxybenzoate	Iron-Binding/Catechols	0.004	0.154	-0.54	153.0194	22	C18-	M-H	C00196	19	HMDB0000397
D-4'-Phosphopantothenate (P-Pantothenate)	Coenzyme A (CoA) Path	0.005	0.161	-1.04	300.0844	119	C18-	M+H	C03492	41635	HMDB0001016
4-Methyl-2-oxpentanoate (α -Ketoisocaproate)	Leucine Catabolism	0.019	0.281	-1.41	129.0558	23	C18-	M-H	C00233	70	HMDB0000695
5-(2-Hydroxyethyl)-4-methylthiazole (Sulfurol)	Thiamine (B1) Metabolism	0.025	0.313	0.56	142.0339	186	C18-	M-H	C04294	1136	HMDB0032985
Acetyl phosphate	High-Energy Intermediate	0.027	0.324	-0.99	138.9802	24	C18-	M-H	C00227	186	HMDB0001494
5-Amino-6-ribitylaminouracil	Riboflavin (B2) Metabolism	0.048	0.388	0.67	275.0996	20	C18-	M-H	C04732	193516	HMDB0011106
Glycan Defense											
Chitobiose	Glucosamine Metabolism	0.003	0.135	1.75	459.14	20	C18-	M+Cl	C01674	439544	HMDB0003556
N-Glycolyl-glucosamine	Hexosamine Biosynthesis	0.020	0.288	1.04	236.0777	16	C18-	M-H	C03146	439921	—
N-Acetyl-9-O-acetylneuraminate (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	C18-	M+H	C00780	5202	HMDB0000259
N1-Acetylspermine	Polyamine Acetylation	0.007	0.198	3.04	245.2335	257	C18-	M+H	C02567	916	HMDB0001186
Kynurenone	Tryptophan/Kynurenone Axis	0.009	0.220	2.22	209.0921	42	C18-	M+H	C00328	161166	HMDB0000684
3-Hydroxyaminophenol	Phenylalanine Branch	0.011	0.239	0.62	126.055	86	C18-	M+H	C14602	5460445	—
N1-Acetylspermidine	Polyamine Acetylation	0.016	0.276	1.36	188.1757	56	C18-	M+H	C00612	496	HMDB0001276
γ -Glutamyltryptamine	Tyramine/Dopamine Path	0.017	0.279	2.53	267.1343	32	C18-	M+H	C20926	10214674	—
N-Methylhistamine	Histamine Metabolism	0.021	0.291	2.29	126.1026	60	C18-	M+H	C05127	3614	HMDB0000898
Kynurenone	Tryptophan/Kynurenone Axis	0.022	0.303	1.41	207.0776	22	C18-	M-H	C00328	161166	HMDB0000684
4-Carboxy-4-hydroxy-2-oxoadipate	Tryptophan/Anthraniolate Path	0.023	0.303	0.80	219.0146	24	C18-	M-H	C04115	130	—
2-Aminomuconate	Tryptophan/Kynurenone Axis	0.027	0.320	1.18	158.0451	34	C18-	M+H	C02220	5280499	HMDB0001241
Leukotriene D4 (LTD4)	Leukotriene Synthesis	0.031	0.335	1.22	555.2725	149	C18-	M+Hac-H	C05951	5280878	HMDB0003080
Histamine	Histidine/Immune Signaling	0.033	0.345	1.44	112.0871	67	C18-	M+H	C00388	774	HMDB0000870
Biliverdin	Heme Degradation/Redox	0.034	0.345	1.73	583.2547	31	C18-	M+H	C00500	5280353	HMDB0001008
2-Aminomuconate semialdehyde	Tryptophan/Kynurenone Path	0.034	0.345	0.31	142.0498	183	C18-	M+H	C03824	5280625	HMDB0001280
Prostaglandin E2 (PGE2)	COX-driven Inflammation	0.035	0.345	0.83	411.2404	152	C18-	M+Hac-H	C00584	5280360	HMDB0001220
Benzylamine	Monoamine Metabolism	0.043	0.367	0.93	91.0544	42	C18-	M+H-NH3	C15562	7504	HMDB0033871
Leukotriene B4 (LTB4)*	Leukotriene Synthesis	0.043	0.368	1.31	335.2224	219	C18-	M-H	C02165	5280492	HMDB0001085
Adrenaline	Catecholamine Signaling	0.044	0.370	-0.55	242.1045	239	C18-	M+Hac-H	C00788	5816	HMDB0000068

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Group: Metabolite Name	Subgroup	P Value	q Value	log ₂ (FC)	m/z	RT (s)	Column/ESI	Adduct	KEGG ID	CID	HMDB ID
5,6-Indolequinone-2-carboxylate 2'-Phospho-cyclic ADP-ribose (2'-P-cADPR) N-Methyltryptamine	Melanogenesis/Dopa Path	0.048	0.388	1.49	235.9932	36	C18-	M+2Na-H	C17938	17796835	–
	Calcium Signaling	0.049	0.388	1.57	622.0327	268	C18-	M+H	C20742	73352906	–
	Tryptophan/Indole Signaling	0.050	0.388	1.05	175.1234	70	C18-	M+H	C06213	6088	HMDB0004370