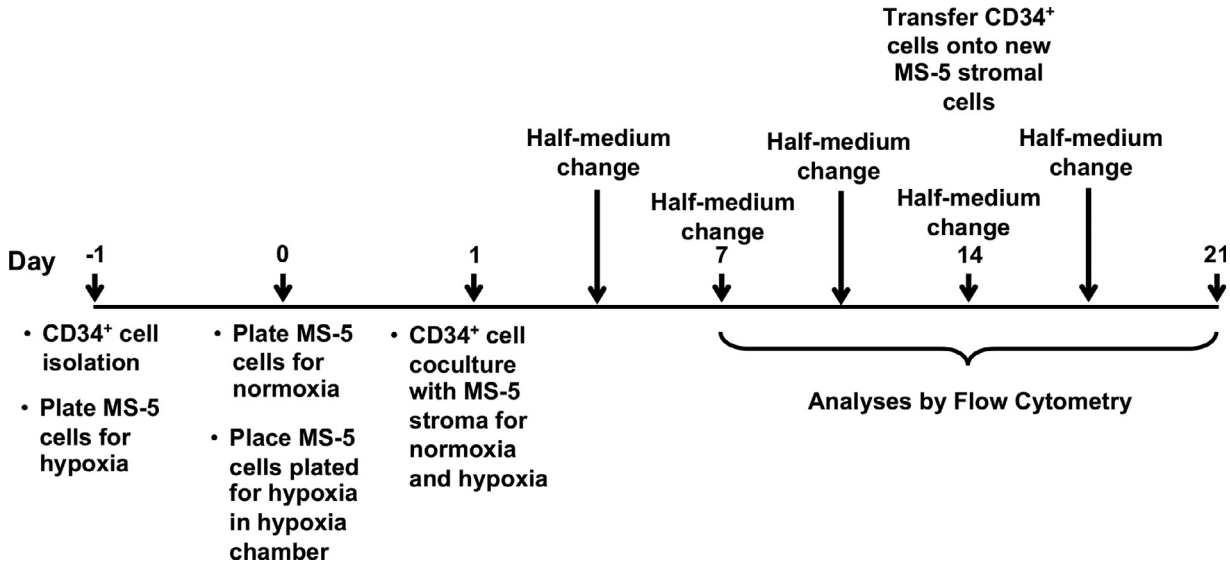

Figure E1. Experimental timeline. Schematic for experimental timeline of myelo-erythroid differentiation of $CD34^+$ HSPCs in hypoxia or normoxia. $CD34^+$ cells were isolated and stimulated for 48 hours, and then cocultured with MS-5 stromal cells in normoxia (21% oxygen) or hypoxia (1% oxygen). Half-medium changes were carried out every 3-4 days. On day 14, the cultures in hypoxia and normoxia were transferred onto freshly seeded MS-5 cells. Flow cytometry analysis was performed on days 1, 7, 14, and 21.

Table E1. List of identified metabolites in fresh medium and spent medium from cultures of CD34+ cells in normoxia and hypoxia. Samples are labeled as experiment number, normoxia (N) or hypoxia (H), and day 4 and FM is fresh medium. 13C3-Lactate and 13C5-15N-Glutamic acid were internal standards

Sample ID	QC1	Exp6 H D4	FM1	Exp5 N D4	Exp2 H D4	Exp2 N D4	QC2	Exp5 H D4	Exp3 N D4	Exp6 N D4	FM2	QC3	Exp1 H D4	Exp1 N D4	Exp3 H D4	FM3	Exp4 N D4	Exp4 H D4	QC4	CV (QC)	% > 1000 %
Malate		1397655.96	2266508.38	730667.10	2188196.35	2368429.89	2792994.07	1399844.75	2455016.32	2550787.49	2601032.89	837933.95	1419899.05	2830772.70	2408844.25	2541736.64	943912.66	2765250.31	2272654.90		
1407890.68	0.72	61.29																			
Methylguanidine	317517.84	578526.02	363540.15	386433.51	431654.70	396724.12	319451.11	625987.16	594213.87	431361.49	353010.39	312354.73	711532.11	539924.72	632827.17	478640.96	432304.62	510429.81	317419.33	0.96	61.29
Threonine		10981456.12	19203113.64	12712801.29	14440617.04	17425830.08	15941635.78	10865398.27	23023716.59	20966072.70	17205607.18	12593030.13	10766157.04	26311905.98	19070436.45	23044853.36	17656287.97	17665590.37	20682601.28		
11105625.64	1.34	61.29																			
2/3-Aminoisobutyric acid/ Dimethylglycine	254299.74	794519.28	215058.29	190471.73	650699.89	236241.53	247217.67	881101.71	192636.69	172761.31	3353379.41	254503.72	2148168.06	206947.63	1385467.83	164501.27	179929.93	558587.53	249010.46	1.47	61.29
Homoserine/ Threonine		10981456.12	19203113.64	12658479.02	14440617.04	17425830.08	16325527.08	10865398.27	23023716.59	20757423.91	17205607.18	12593030.13	10766157.04	26311905.98	19070436.45	23044853.36	17708046.55	17313623.95	20682601.28		
11152286.83	1.52	61.29																			
Xylitol	44591.67	35093.77	21623.05	41658.12	42054.25	50169.79	45123.45	31313.04	43893.86	36316.04	11735.27	43865.42	37601.20	40523.47	42149.96	22871.63	41484.66	31710.95	43357.22	1.76	61.29
4-Methylvaleric acid/Hexanoic acid		1837552.94	908727.34	291066.32	3024464.27	868181.57	3355132.31	1810982.40	986368.63	3048702.86	3064680.39	237923.61	1760642.53	1104242.15	3279023.84	1010295.10	263067.61	3625541.65	1133854.90		
1823659.92	1.85	61.29																			
alpha-KG	890892.00	607265.22	85876.26	1427000.56	357667.74	1272741.17	891633.60	663197.34	1338878.42	1624693.02	73931.71	922333.41	510861.71	1215350.77	486417.84	103409.54	1797686.88	617008.77	925039.60	2.07	61.29
Methionine		3756913.75	3571418.82	8123996.34	4260022.20	3116500.63	3156401.97	3667994.44	4465367.61	4507731.73	4788576.01	9003882.33	3702808.25	4409661.76	4476157.00	4954199.09	10478632.06	5121001.21	5981247.07		
3859101.98	2.23	61.29																			
4-Methyl-2-oxopentanoic acid/Keto-leucine/ Ketoisoleucine	282928.87	231932.13	15717.81	617315.14	243728.54	560501.30	293523.01	252289.18	503479.84	559322.41	11652.39	298535.17	281909.74	572172.87	262732.46	13213.92	627294.85	297047.58	295402.86	2.31	61.29
13C3-Lactate		1007366.37	876655.09	1025153.62	873031.41	816392.95	900330.31	978946.71	898983.02	969479.88	1073296.21	967265.60	1027187.59	884740.66	915551.62	787800.17	882493.91	1028266.41	875531.49		
1030289.68	2.34	61.29																			
R5P	38561.57	109139.15	1376.37	88059.18	152165.05	57665.39	38663.51	122824.88	58756.95	84318.60	1674.06	37215.77	139772.60	65495.86	131258.64	1924.56	68203.87	138899.44	39520.08	2.47	61.29
6-Methyl-DL-Tryptophan	79843.46	61465.26	158903.84	85203.19	64234.87	96501.51	82617.65	75455.46	121101.67	98255.14	175717.41	83835.66	82110.89	101461.34	62806.91	188634.59	107786.09	58978.06	79657.37	2.54	61.29
Glucose		4116829.57	3293063.90	7321112.59	5992496.11	2672126.84	6168177.10	4318773.80	2823114.96	6731540.65	6601858.75	7480996.92	4092461.69	2798828.34	5722125.91	3046909.20	6287492.49	6325906.92	3335169.98		
4075582.59	2.73	61.29																			
Aspartate	56496.39	48323.57	15784.10	63503.31	55470.74	76455.20	54629.86	57643.69	76064.12	86300.17	21838.63	58700.93	62935.01	86423.19	38955.80	21587.45	72723.97	48815.35	57117.60	2.97	61.29
Mannose		1256717.51	936097.80	2144568.78	1718696.24	846960.12	1618432.20	1236090.12	979452.94	1779626.34	1890067.38	2270697.39	1227518.34	826376.81	1694804.02	983329.53	2251877.88	1729362.78	979762.18		
1324412.76	3.48	61.29																			
Phenylalanine		33378733.64	46161244.80	43795886.89	39083478.45	44728735.08	46249616.37	30759908.76	45232888.00	42978616.14	44902587.19	40732179.88	32163486.19	48652991.55	44512581.86	44866405.54	41106793.95	42817866.87	41795187.10		
32885994.82	3.53	61.29																			
Sarcosine		4026293.90	3191484.43	707885.42	5779598.79	3239441.29	6123775.93	3793836.74	3585911.11	7647247.46	5568574.25	693578.97	3874428.00	5938759.41	6879797.16	4922167.00	1021536.22	6045842.08	3078164.04		
3705830.13	3.54	61.29																			
Imidazole	159002.68	157305.26	102223.36	127734.64	183595.29	115544.16	161528.19	143135.77	145344.50	129600.74	136188.03	155344.52	164983.96	149761.27	145335.07	133498.48	130328.82	174626.93	148073.84	3.75	61.29
Alanine		4116148.54	3247467.72	775958.18	5783733.32	3457066.79	6591317.40	4302839.99	3889079.94	7997820.59	5837989.90	748234.16	4323413.33	5855397.09	7037426.58	5217248.53	1023657.87	6054072.50	3010072.82		
4534534.38	3.96	61.29																			
Dihydroxyacetone	150407.36	152012.11	46225.40	151509.49	245966.86	207106.99	136447.92	191088.88	193507.82	154393.10	50349.60	143584.66	336288.14	215545.30	227704.05	57969.77	178128.31	174087.82	144583.57	3.98	61.29
Glycine	175453.42	304952.75	136469.45	372622.21	287117.41	395416.36	170129.53	339130.03	446661.70	379743.09	135278.44	161052.86	330572.11	388621.57	311584.02	173696.96	373655.34	291647.67	161794.87	4.14	61.29
Carnosine	122383.02	205353.50	188588.49	261827.33	197760.76	224317.18	113918.28	232642.08	250061.52	239466.98	164681.55	123317.98	252124.08	230880.29	238105.74	209418.51	253163.35	203667.91	114273.34	4.28	61.29
pregnenolone sulfate	9071.10	3028.22	4454.24	2526.19	10487.41	4738.04	8919.27	2415.93	2460.94	1734.42	2021.08	9811.34	2450.20	5155.24	4352.01	3347.03	3658.82	3858.54	9441.58	4.29	61.29
alpha-Ketoisovaleric acid/Maleic acid	237308.62	143864.13	14696.68	436867.91	135252.62	471174.54	233547.89	143301.27	411306.73	415776.63	13673.24	255614.14	165019.24	438693.51	151603.05	10654.03	462527.57	180657.83	234779.20	4.29	61.29
Isoleucine		169679240.19	246726656.23	289648671.29	198373086.10	269589920.33	191449411.80	184897997.22	273987095.31	194506088.84	195744189.16	298355365.98	184831752.33	299569879.08	190146514.26	289865572.62	321240166.24	198830652.92	259813189.94		
186035587.09	4.30	61.29																			
Pyroglutamic acid		3842675.36	7794816.56	5271713.97	7116275.81	5020312.37	6356161.12	3592792.96	8785329.02	7328551.33	7983399.53	6166242.86	3471359.96	7263415.02	6144404.54	5855338.14	6637674.36	7170950.12	7071501.16		
3718077.30	4.38	61.29																			
3-Phenyllactic acid	156201.82	72351.88	4540.73	183081.12	101274.91	159590.61	162860.62	96926.40	160058.20	162705.73	4221.76	164913.49	100620.72	158502.79	96668.30	5235.61	217673.43	84540.33	173908.95	4.44	61.29
Glutaconic acid	807318.67	1423292.89	61841.96	931856.89	1556466.00	1055703.37	889798.95	1564133.04	1104196.41	1147151.00	66584.91	836150.05	1826016.36	1153248.41	1636880.38	54251.18	1205101.16	1426338.50	878398.41	4.47	61.29
TMAO	620895.50	592400.50	618657.43	731295.25	644622.44	856164.05	619165.33	611392.24	3183051.74	745009.63	860202.01	679494.60	722685.32	873421.28	704415.24	972398.24	690923.76	703373.41	627724.05	4.51	61.29
Pyridoxine		2850077.46	4014361.72	4618219.57	4120580.85	3736932.34	3928731.42	2801022.92	4203577.76	4087441.94	3857780.59	4583034.68	2621825.79	4237762.64	4347729.45	3818569.85	5737729.16	4530252.16	4437582.26		
2947069.99	4.86	61.29																			
Valine		24613188.72	32995469.43	26142473.98	23927894.31	39099622.34	21397442.32	26549268.80	37500010.60	21946418.38	22841178.86	27832166.47	27643380.04	38330254.17	22132743.07	36946080.20	25320891.54	22322100.18	39339679.88		
26871153.93	4.88	61.29																			
Citraconic acid	219475.09	172450.94	14679.54	466536.35	199490.52	497984.80	239925.04	194418.62	413590.67	391734.70	10494.49	221133.51	230217.81	460402.22	204914.40	9129.01	473004.73	219638.08	214568.46	4.97	61.29
L-Alloisoleucine/ Leucine/ Norleucine		117652160.72	160445043.95	178591685.02	117557966.77	170183585.79	106553279.04	122718989.38	181003858.87	110139719.06	117789595.37	168188386.84	130920692.68	176712631.49	113457232.39	170869535.64	173309916.48	117092129.31	179807893.58		
116551198.78	5.07	61.29																			
L-(+)-Arabinose	88090.82	67430.90	237536.66	136756.23	57073.92	140352.49	80703.36	79127.31	170037.88	172840.63	191011.66	82435.39	74312.69	153901.28	66878.87	257669.66	161792.31	68545.20	78122.67	5.13	61.29
Stearic acid		33168427.62	14821848.48	28055323.22	23912971.70	16835584.36	14606041.28	34209711.32	14723705.84	20328617.42	22953150.89	18394091.64	32797245.62	12516358.14	24171849.56	11318542.52	16383346.60	17979017.19	21311670.07		
30262262.80	5.14	61.29																			
Glyoxylic acid	38991.44	34469.76	72510.21	67857.65	30834.58	59909.99	43495.88	35582.60	71732.16	64529.02	73436.72	39142.73	32921.07	62263.77	30335.09	75268.23	52234.62	31871.09	41445.17	5.24	61.29

(*continued on next page*)

Table E1 (*Continued*)

Sample ID	QC1	Exp6 H D4	FM1	Exp5 N D4	Exp2 H D4	Exp2 N D4	QC2	Exp5 H D4	Exp3 N D4	Exp6 N D4	FM2	QC3	Exp1 H D4	Exp1 N D4	Exp3 H D4	FM3	Exp4 N D4	Exp4 H D4	QC4	CV (QC)	% > 1000 %
Myristic acid	396143.34	271441.22	413870.47	375647.79	523633.74	300572.19	380921.85	266692.81	405892.85	344668.71	351473.11	366954.54	220042.79	488478.46	177749.89	343157.52	235971.68	313858.77	415233.06	5.32	61.29
Isobutyric acid	376325.62	171920.62	6684.91	729359.29	89967.98	629591.38	388805.06	158593.70	669167.84	621432.33	5576.30	370478.76	172792.34	550772.13	118919.51	3425.65	537101.68	125975.77	341465.17	5.43	61.29
Leucic acid	162937.97	169178.49	5493.68	101744.70	268226.76	116933.49	176775.31	182571.25	103011.52	112779.56	5604.57	186144.64	283807.79	108934.30	281568.87	5563.04	135323.22	221215.77	176000.75	5.44	61.29
2-Deoxycytidine	49500.67	4878.64	18955.15	36886.16	2199.92	5700.10	53366.25	5262.58	20729.60	84555.34	18907.72	51427.36	2814.39	9400.95	3094.27	16510.41	10896.34	4609.40	56394.58	5.58	61.29
Oxaloacetic acid	59925.02	90511.88	1658.92	56564.97	124546.26	54306.00	55889.80	97432.87	55503.29	61304.12	437.33	56711.93	115245.60	47716.48	127110.14	1308.62	63152.86	104098.10	51996.27	5.81	58.06
Choline		3650869.80	17815775.23	17577834.50	2029442.39	18569806.60	1057766.28	3755297.07	18764278.76	762659.42	1761103.13	17652451.13	3581678.61	17090972.14	1378254.40	16202955.32	18547101.62	2357693.25	22140426.71		
4080678.90	5.86	61.29																			
Normetanephrine	68186.79	60647.20	18422.06	175512.48	59777.17	171028.62	67943.96	64101.77	207739.79	183049.60	23022.45	67810.96	68218.36	197297.92	75131.20	23367.47	204304.54	65438.40	60093.20	5.98	61.29
HIAA	23651.45	26918.39	28360.12	19795.25	52347.41	22162.52	22862.22	34028.80	25533.10	26329.63	30369.85	24149.38	70221.41	17502.46	69151.93	36290.41	25751.87	26203.81	21018.83	5.99	61.29
Uridine	2653.85	2036.96	729.99	7116.63	3410.47	1397.73	2419.62	2621.33	3473.68	13417.03	1961.32	2361.21	4138.50	1484.54	3474.46	2301.09	3887.47	2727.50	2326.10	6.05	58.06
3-Methyl-2-oxovaleric acid		3952538.56	3185150.73	59429.85	8086922.81	3139219.56	8149821.05	4235138.91	2042895.13	7026028.89	7041568.81	37746.83	3628535.53	3873280.77	7838613.97	3569556.06	45907.25	8324697.94	3483351.78		
3986126.20	6.30	61.29																			
Amino valerate	11859.14	40362.18	9736.78	24074.17	27989.44	27842.60	10199.10	45715.32	32802.47	22835.16	12332.96	10987.30	69081.00	62085.43	39896.31	32743.00	25802.05	48909.62	11420.50	6.37	61.29
9-Octadecynoic acid	396846.84	128944.79	534513.82	285992.49	382816.27	261260.55	349502.09	171706.34	259221.09	277395.31	461660.38	405348.76	125547.69	313297.57	103607.56	459971.70	267760.85	177662.09	381112.92	6.42	61.29
Lactate		10674283.36	13155510.22	758686.85	5289603.38	16332112.39	7171585.43	10926196.41	15204602.21	5181654.88	4511470.04	786815.95	12292133.70	15949882.30	6157406.47	18023951.29	829376.31	5062511.92	14651483.39		
11704141.29	6.49	61.29																			
13C5-15N-Glutamic acid		2250230.62	2410582.51	2121243.75	1741726.98	2450579.47	1617658.98	2126020.10	2144588.26	1879572.30	1739629.56	2186006.17	2003114.77	2409893.52	1650123.57	1828041.12	1989497.99	1932954.04	2300804.19		
1936717.29	6.66	61.29																			
Methylmalonic acid		5192431.95	5679889.36	6459155.02	8450104.38	6491073.12	8943814.58	5221051.66	6022484.02	9515018.93	9329165.79	6592868.60	5535945.90	7283646.39	9842735.09	6663498.62	7844995.00	9271010.74	6668659.93		
5980441.60	6.69	61.29																			
Norvaline		23127493.79	31276682.58	23340875.31	22762327.18	37445983.77	20364546.12	23080229.51	35966747.10	20917288.25	21508878.18	25237631.64	26444950.56	36122905.49	20442786.34	34802926.38	18247358.45	20956525.73	37413953.32		
25175227.12	6.73	61.29																			
Succinate		5185772.63	5683357.36	6442667.16	8450652.80	6492232.94	8945497.16	5219666.48	6037610.90	9488483.52	9329165.79	6593902.47	5542022.16	7279262.25	9820868.10	6671683.62	7846630.32	9276342.44	6678857.82		
5983070.41	6.75	61.29																			
2HG	57767.07	93513.56	49774.05	83962.18	115128.06	85080.63	66036.04	94191.84	84621.38	60839.62	38703.09	58996.63	121084.79	66122.66	112643.81	38444.22	74553.99	128047.51	65114.57	6.78	61.29
Glutamic acid		3178065.23	2093558.85	981544.12	3542732.91	2436806.68	3424308.63	2833385.32	2203599.15	3124837.96	3680300.32	1150168.15	2999542.88	2521224.26	3535622.24	2615208.65	1172157.47	3022814.20	2175914.68		
3314740.38	6.81	61.29																			
Serine	182278.25	108707.42	915436.10	181461.05	93592.25	130502.85	208464.46	120450.12	329561.48	360093.47	892059.48	209751.77	111593.36	203493.58	87842.22	960512.94	256019.95	112505.84	212737.26	6.95	61.29
4-Pyridoxic acid	168035.25	54538.34	39350.67	512293.78	46392.27	371901.92	156749.56	61385.72	428022.61	485534.83	38022.91	151582.29	61712.52	478728.65	44850.53	43543.41	541610.55	47485.38	141893.20	7.04	61.29
Pipecolinic acid	912836.90	682034.73	524990.20	1115093.45	806432.00	1043722.45	912323.84	754606.24	1223065.36	1374855.21	693936.71	994637.26	859929.11	1155620.03	915830.65	554659.21	1164971.84	713062.57	1056589.59	7.22	61.29
Xylose	125048.62	124340.24	13322.61	72748.54	152545.61	88124.21	136317.70	127560.09	69713.54	55523.39	11619.59	140054.70	126162.77	75270.72	146744.13	15147.30	78174.11	143878.96	149687.47	7.39	61.29
Acetylcarnitine		4672764.73	3734980.41	4771717.50	5706794.51	4793773.19	6294920.27	4081130.29	3252433.83	6850944.94	5816386.10	5466059.81	4286900.70	3255069.19	6562853.62	3015681.34	4797770.88	6486340.39	4189139.87		
4788131.79	7.40	61.29																			
2-Aminobutyric acid	252204.32	13369504.62	12578671.01	1772485.91	14038780.98	1026095.24	211620.11	15386769.01	936556.23	1711292.13	10552417.85	225280.25	14142681.39	1217941.54	14554112.09	13899346.67	2115503.06	15484463.06	235916.40	7.41	61.29
Metanephrine	598311.15	1271288.00	949920.51	1259997.18	1330343.87	1190809.57	526355.46	1523180.96	1445626.02	1234149.75	1059051.35	523894.81	1415327.80	1290005.17	1602947.57	1342058.77	1545048.78	1232360.10	507196.42	7.51	61.29
Lysine		3406146.72	5889704.03	5195004.51	5534690.25	5060596.93	4835674.02	2871861.78	5902157.30	5877978.19	6534979.66	4918591.26	2977736.76	6773835.88	5259876.25	6275679.48	6214705.40	5818985.13	5863332.64		
3056702.03	7.52	61.29																			
Proline		17889129.33	23172119.96	3057064.65	14063821.76	25480162.65	13444955.61	19686437.12	25811567.84	10936885.67	12021480.33	3433548.46	16393376.62	24661537.91	15014011.71	27202359.01	3008418.31	17981196.09	22935787.69		
18930625.69	7.83	61.29																			
Dulcitol		1011857.11	1288754.09	803082.12	1044135.23	1481867.00	1289179.73	897665.45	1401077.40	1364935.87	913059.47	874521.64	1045519.33	1822643.85	1215375.14	1609763.85	955650.51	985346.51	1377281.23		
901699.27	7.86	61.29																			
2-Methylbutyric acid/Valeric acid	326083.79	178992.32	164758.39	467491.60	172142.19	533261.39	291207.59	175390.66	741177.74	628671.59	146742.09	318543.02	191916.75	566115.06	186100.98	137732.13	550860.65	162498.46	353444.67	7.94	61.29
Ribose	125183.85	124967.28	13599.48	73558.25	152559.26	90115.19	135347.15	141042.19	69104.56	58501.41	12136.87	144798.41	124518.43	78113.68	146357.34	15169.54	78803.88	145590.44	150316.57	7.95	61.29
Phenylpyruvic acid	36579.13	4508.34	803.94	89145.39	3473.99	62761.38	31289.25	4245.03	59734.24	139285.15	488.45	34670.05	4290.91	47253.16	7623.51	453.09	121531.77	5390.80	37749.00	8.05	51.61
Suberic acid	149319.34	250117.97	9610.57	189247.43	170225.67	182101.88	159377.00	270004.27	157720.79	192322.52	13966.61	139128.70	284059.65	187603.15	301861.45	9410.30	210878.33	235105.58	131913.97	8.27	61.29
Nicotinamide		2374328.27	2604828.80	2972323.23	2161198.59	2866658.05	2207627.83	2220172.37	2572850.41	2373356.39	2121558.69	2825783.68	2545028.17	2977296.73	2197403.91	2735702.23	2854993.62	2136159.14	2794711.26		
2693174.23	8.35	61.29																			
Lactose	25223.89	22737.39	30232.82	43672.84	18468.08	30746.92	23090.60	25959.89	34876.20	44569.50	22182.79	20640.51	18980.08	33950.39	19690.41	25489.74	33448.57	27867.46	24205.91	8.46	61.29
Tryptophan		5207406.67	10263260.64	7799405.96	5926706.35	6861294.44	4782154.85	4593669.34	10905385.57	6294035.86	6764644.91	8865052.35	5223268.88	10653682.38	5228521.55	7744302.32	9840860.76	5738004.29	8011289.74		
4414365.61	8.59	61.29																			
D-(+)-Cellobiose	27201.73	22231.99	24072.03	35224.70	18103.53	31869.11	22942.32	23177.54	33346.33	39251.97	29722.48	22631.54	19356.76	34005.09	19775.56	26505.57	31321.79	27079.64	24514.99	8.59	61.29
Pentadecanoic acid	418443.79	289823.47	447819.12	351886.50	641208.27	501744.34	442692.01	229432.69	569098.46	326976.51	324528.81	454324.13	241069.99	458545.10	267278.75	326866.20	406751.31	348760.71	515567.74	9.03	61.29
NADPH	6814.27	7016.40	4578.93	5911.55	6073.41	6789.86	6841.65	6068.38	6212.30	3214.04	5129.96	8050.94	5772.27	8522.75	5830.72	4708.58	5326.89	6496.69	6614.15	9.25	61.29
2-Hydroxyphenylacetic acid/3-Hydroxyphenylacetic acid	62789.62	30944.13	24270.50	48166.28	36580.03	54566.76	67231.18	34962.16	48317.11	45342.69	38027.46	64467.56	31564.95	51757.10	38576.79	44915.79	53696.28	28888.91	53826.50	9.34	61.29
N-Acetyl-D-galactosamine	22148.68	25415.31	44596.56	43782.25	27692.76	46546.57	21646.70	27149.72	64838.37	58987.48	64915.43	19282.74	38497.71	65912.63	32962.30	99558.51	63700.51	26312.20	24257.61	9.36	61.29
Sorbitol	819653.96	1044608.22	719911.99	817187.86	1289059.21	953417.30	771191.03	1365307.28	1061781.47	973109.46	762165.47	959440.09	1337425.34	1129204.19	1420342.60	830796.21	984558.58	1356947.74	865278.87	9.39	61.29
Arginine		42870060.75	65946068.41	57231680.12	56382807.12	75875114.08	56984503.73	53723392.13	75826157.96	59316956.64	66644178.35	71474202.98	49518481.38	93650306.73	60203943.02	78677168.83	82079472.17	57724159.11	69620397.46		
51194283.55	9.40	61.29																			
D-Mannose 6-Phosphate (disodium salt hydrate)	12986.49	6130.75	3989.37	27967.95	16717.48	49186.95	14042.62	14827.29	66975.20	48886.69	12558.73	13223.45	18824.06	61896.06	17681.58	11457.46	59574.97	10213.05	15933.69	9.52	61.29

(*continued on next page*)

Table E1 (*Continued*)

Sample ID	QC1	Exp6 H D4	FM1	Exp5 N D4	Exp2 H D4	Exp2 N D4	QC2	Exp5 H D4	Exp3 N D4	Exp6 N D4	FM2	QC3	Exp1 H D4	Exp1 N D4	Exp3 H D4	FM3	Exp4 N D4	Exp4 H D4	QC4	CV % (QC) > 1000 %
Citrate	951845 9.39	7295216.91	13189136.48	18718001.29	9971184.81	23191352.75	7821423.15	6350289.87	32898470.54	21537798.19	10326462.97	7941842.04	7075891.02	22909784.73	6645550.63	13676838.06	24466380.08	7590104.27	8964220.09	9.56 61.29
4-Hydroxybenzoic acid	11998.80	6638.69	6795.64	11597.72	8739.54	18828.70	12802.49	8144.09	24070.67	7477.12	4286.95	14879.09	12432.45	15536.34	10938.82	4625.45	11906.45	11200.26	12597.08	9.59 61.29
Trehalose	21475.24	19594.21	19479.88	21249.07	19641.24	19011.88	18715.51	18120.48	25584.79	17540.73	19478.60	19398.78	17447.74	21180.23	24564.98	23128.19	22799.10	17846.01	23208.52	9.87 61.29
Palmitic acid		21343366.94	13388750.25	28781267.99	19274738.19	24984031.55	13060322.13	26009392.48	16115817.56	18796701.97	18496829.26	17139890.32	21609621.33	10833306.03	23552566.79	11341221.15	15949468.24	14046334.64	15335703.19	
21525364.19	9.99	61.29																		
Lauric acid	184527.11	148180.93	187360.01	196920.00	261540.14	175240.30	198843.15	121212.05	194063.67	186052.76	157669.08	201250.53	108310.88	180818.18	115165.86	156340.42	156890.61	167309.28	233602.00	10.1361.29
Adipic acid	24789.66	2565.84	2415.37	145226.85	6473.00	184151.85	22138.81	8689.88	216738.60	158282.45	1584.32	24661.59	5590.83	181773.16	4756.70	2872.16	135130.86	6563.40	28440.01	10.3761.29
5-Aminolevulinic acid		3913300.37	3935383.70	1640687.38	4101648.79	3013342.33	5426309.10	3500414.51	5017930.45	9170960.67	4762196.45	1789381.42	3230497.12	10036590.41	7329768.26	7227566.53	2732604.45	4793153.25	3011838.92	
3098755.06	10.47	61.29																		
4-Hydroxyphenyl-acetic acid/Mandelic acid	60543.56	32731.62	27014.39	36633.66	34749.57	44249.92	66937.82	34345.91	48663.00	41896.51	26112.19	70982.14	33118.60	52166.24	38134.43	34358.60	54030.38	25059.81	55930.60	10.5061.29
2-Aminoadipic acid	83548.03	100660.91	66096.07	90617.76	83787.50	107689.03	82965.06	141076.20	165199.46	122014.55	73613.44	67895.69	167427.04	111037.03	121295.90	83134.97	103017.57	87157.83	70809.92	10.6461.29
4-Imidazoleacetic acid	106258.26	99098.78	28735.45	123691.29	124770.45	123148.01	100732.90	135531.60	140932.76	111830.75	38998.34	119595.48	143771.17	183348.52	156396.20	33019.73	134585.68	119312.95	127736.84	10.8561.29
Raffinose	10188.82	17417.24	19054.85	22454.70	16528.04	19878.89	9796.83	15106.41	21999.85	17298.87	14668.16	12373.33	19129.59	18163.43	16588.39	20587.07	18942.22	14593.52	10312.32	10.8661.29
F6P/G6P	13826.10	7512.01	8508.71	39753.01	21140.25	51676.84	14722.93	10932.62	88309.15	56374.98	14176.20	11304.48	21325.73	73514.16	18528.26	11323.28	48996.57	7081.59	13688.15	10.9261.29
Nonadecanoic acid	614773.75	184537.60	275918.84	240049.94	491666.81	247204.01	553081.92	165958.79	265913.29	306885.37	222601.91	563867.42	132674.63	291291.90	123672.55	197353.82	273599.60	229329.02	469145.35	10.9761.29
Creatinine		1915119.48	1142099.45	1188366.93	1118618.97	1338197.91	1185568.80	1864061.38	1268974.46	1223258.38	1144967.34	1338280.56	2220390.28	1397009.39	1189263.48	1615488.37	1224839.84	1278474.10	1599896.71	
2331987.37	10.98	61.29																		
Hydroxyproline		4075835.43	3817615.47	1557706.54	4399294.33	2697233.87	5529135.24	3577669.64	4904779.06	9360710.69	4848105.00	1696720.91	3316073.67	9971909.35	7261790.54	7236410.33	2618746.81	4769456.86	3047527.66	
3183690.30	11.13	61.29																		
L-(-)-Arabitol	73437.56	49205.96	40367.99	69662.14	62045.86	71929.63	77267.93	54421.95	79587.28	64423.02	43339.56	93698.07	60507.23	78097.37	64235.45	49988.92	71821.24	59572.54	77735.66	11.1661.29
Glutamine		14154188.47	59822707.05	62267601.58	28550894.64	65612004.24	27448222.01	14798970.03	60467017.04	30127071.88	29288665.78	72903450.65	17893160.18	78867163.55	33036548.48	75976195.48	79573246.22	22003831.13	67613535.05	
17184764.78	11.31	61.29																		
Phenylacetic acid	32382.24	39826.92	25906.05	36968.20	39885.82	42561.15	41338.95	33893.80	42207.68	41970.28	25808.14	38658.51	43009.57	40295.53	46186.03	28046.90	34139.02	38625.88	42061.98	11.4061.29
Picolinic acid	72166.67	85460.17	46995.47	64035.18	71424.80	51822.74	75200.42	88758.52	54189.34	70324.83	53648.48	62594.62	78928.35	54465.01	78757.03	42700.41	67051.51	89946.66	58998.03	11.4361.29
4-Hydroxy benzaldehyde	69215.11	9764.38	54419.33	119471.08	25887.21	131032.03	74536.47	11487.00	182678.43	150676.16	43455.75	87457.89	16519.72	111520.71	13190.50	35886.03	163525.46	15114.89	68460.15	11.7361.29
Aconitic acid	51556.09	67209.59	9909.53	62350.71	75925.35	70272.08	45761.56	60726.81	80718.11	51305.85	10213.44	39014.66	82429.32	61374.16	61188.11	13550.71	51544.76	31833.92	42459.87	11.9461.29
Quinolinic acid	23754.38	38304.97	26218.31	16488.97	35827.88	16864.69	20496.76	41553.97	13470.67	13344.48	10240.74	21521.48	43672.32	13322.68	44502.17	10237.48	10144.04	49185.79	17719.00	12.0061.29
Creatine		15298450.71	34564582.92	16709184.82	32376865.12	30374462.59	25351565.81	15563976.78	41646839.22	42475321.92	32191540.77	16017926.95	19678489.97	55291273.87	39972591.41	59303962.21	32550333.24	38732017.88	34472912.41	
16392896.18	12.06	61.29																		
p-Tolylacetic acid/4-Ethylbenzoic acid	1679.11	1593.17	1149.00	1831.58	755.61	1879.82	1459.72	943.97	1900.01	1724.67	1129.42	1961.62	1128.92	1364.09	1720.87	687.37	1484.50	555.90	1739.51	12.0748.39
Caprylic acid	168948.37	243238.61	184149.83	157774.85	171243.14	181313.26	148010.80	99855.26	220708.75	126154.84	69353.14	191923.60	96813.22	183889.45	82147.86	86686.68	109642.74	169419.59	193923.33	12.3361.29
Urocanic acid	661323.02	1283934.87	1280677.84	1134380.93	1162416.71	1131321.49	526189.31	1234141.79	1487490.76	1305554.43	1278809.04	646750.77	1508268.07	1367451.98	1597491.29	1768061.68	1304628.17	1278716.94	711348.86	12.3461.29
Acetamide	259761.92	397411.52	406685.56	313760.35	312550.55	302332.10	240470.13	296344.44	387458.13	378701.24	376143.74	302917.57	310613.12	405755.82	232057.05	366495.36	341609.35	199983.08	230484.56	12.4161.29
Pantothenic acid		2713999.68	4051521.90	3834008.78	4497094.21	3990142.87	4400137.62	2155702.76	4250848.37	4549418.10	4236237.13	4807647.56	2716606.36	4462685.27	5586401.45	4120926.55	4072543.05	4856980.15	3605535.20	
2934438.63	12.65	61.29																		
Glycocyamine	177059.03	134719.35	188951.78	166528.12	161376.05	108707.19	208253.91	206742.85	154822.31	125082.67	160311.35	162521.91	206924.48	162787.69	196374.89	130365.29	140223.51	192084.76	158982.48	12.7061.29
Taurine	23971.82	16613.76	37512.76	25599.41	70764.04	24811.91	27566.76	27341.73	26591.43	33195.26	44270.09	27304.78	47725.59	30978.67	44950.26	51820.28	33862.43	19469.17	32588.90	12.7561.29
D-Mannitol	313670.67	407325.92	267452.15	325969.90	485473.77	388973.65	299437.02	486036.61	392679.32	314920.27	269214.14	328539.20	502716.80	376501.62	561119.08	271963.86	330531.33	476071.50	397929.32	13.0461.29
Ornithine	206369.20	642967.48	633582.32	402916.35	430810.67	329960.21	227288.63	632677.91	462764.59	481886.54	578663.98	280899.22	382676.84	620212.79	504308.79	675638.78	427703.82	592777.82	252667.00	13.3261.29
Fructose/Galactose	952611.62	1289745.91	1119725.09	1424003.41	1550372.09	1477840.24	785429.06	1228341.76	1727722.63	1447438.06	858259.64	733057.10	1691829.37	993688.30	1368990.00	1289312.27	1443769.59	1465017.36	720899.81	13.3861.29
Adenosyl-L-homocysteine	4433.44	13749.21	1212.94	42255.97	16599.97	55578.90	3383.38	16529.32	49368.75	65676.63	443.49	3346.74	19029.54	50148.79	19446.79	386.03	50825.37	21878.35	3922.33	13.6254.84
Cytosine	63366.30	180116.22	277459.56	262653.07	142482.33	112929.68	57989.44	198968.12	208844.50	363622.61	247095.31	68809.72	198328.44	126902.76	139610.01	329965.68	234349.38	140755.32	79539.23	13.6561.29
Asparagine	167141.85	433050.98	3377.97	575352.74	500027.60	488207.53	212434.41	569902.85	543319.59	701774.88	4511.83	227290.30	529785.20	571901.64	557475.96	5659.12	672760.46	583376.90	228080.85	13.7261.29
G1P	12841.81	2869.66	3239.79	33136.61	19260.85	51496.51	12235.24	16800.13	93285.74	60470.15	12790.08	9375.58	18790.08	64028.37	17506.45	11620.77	51818.06	11545.53	10505.12	14.1461.29
AMP	19499.82	48732.60	3784.36	64485.57	104752.43	93768.09	17870.31	36204.48	96512.94	89975.73	844.58	13882.05	59109.48	36712.37	35986.71	2359.65	39304.93	15444.83	16223.10	14.2258.06
2-Pyrrolidinone	3474.22	4312.21	4278.46	4416.71	4529.52	4831.94	4047.24	4864.50	4219.94	4842.64	3965.10	4114.05	4877.76	5661.60	4031.02	5136.73	4627.60	4107.57	4911.79	14.2961.29
Cystine	724246.27	1539499.48	1382126.35	1241854.66	1433973.77	1051416.70	578254.98	1344024.76	1364534.88	1412314.84	1292243.99	589405.13	1676188.67	1175726.60	1411747.40	1696609.88	1265352.04	1356832.90	517618.90	14.4761.29
Carnitine		4608144.84	7043134.55	5496108.95	7786141.03	6880847.51	7658554.86	3691703.72	9890134.47	10257736.94	10613789.79	5787027.39	4266590.26	8488142.72	8361429.93	7830568.41	7576587.58	10752789.32	7738546.12	
5237991.76	14.53	61.29																		
Benzoic acid	80115.75	63117.60	18419.75	61092.75	69383.47	101358.34	65684.45	50651.13	112618.54	60023.15	9437.08	93941.03	85220.45	74914.96	67678.42	19989.88	74102.59	50087.40	87363.91	14.8261.29
5-Methylcytidine	25265.68	11105.29	16895.79	33052.73	9934.40	15594.37	21109.74	14147.19	39971.45	30163.77	21021.57	21529.03	10006.85	42280.02	10717.75	20790.34	41975.13	9987.92	17331.83	15.2261.29
Acetohydroxamic acid	2980.44	3546.23	2812.33	3564.20	2789.66	3705.70	2653.15	2844.34	13467.01	3130.42	4781.55	2202.59	3142.49	3491.06	3366.25	3589.86	2688.15	2576.78	2161.69	15.6261.29
6-Hydroxynicotinic acid	49867.58	78222.93	81092.82	93753.40	84892.13	103964.15	44504.56	83551.47	114621.82	79624.06	78842.98	33638.55	90465.42	92765.14	83277.51	91176.55	85331.70	79310.91	45304.77	15.8861.29
Tyrosine		6088656.30	5521260.93	3164657.66	4985128.11	5964821.54	4488715.39	4485689.31	6919513.40	4164895.55	3787277.03	4180943.49	4354635.17	6113567.65	4257430.94	5720847.75	3055848.37	5165069.16	6309623.79	
4872129.62	15.96	61.29																		
Cytidine	192341.28	450818.28	665072.37	544344.09	298214.21	202587.11	135042.48	482611.07	423396.78	549246.80	605275.60	144790.26	482504.49	213233.10	342145.98	750368.51	471165.00	334333.33	153618.72	16.0561.29
Acetyl-L-glutamine	49226.53	49102.82	9526.27	95697.33	77986.52	204813.03	37134.31	52551.07	219840.08	93579.03	7635.38	36997.45	114613.06	197780.38	107805.61	15208.93	89964.61	49139.73	34645.68	16.6761.29
Putrescine	1648.14	5689.33	2820.78	7296.38	6857.41	5710.36	1816.73	8079.70	6061.16	6734.33	2719.19	2189.89	8461.92	7948.73	8843.39	5111.25	3622.72	5439.89	2393.05	16.9161.29

(*continued on next page*)

Table E1 (*Continued*)

Sample ID	QC1	Exp6 H D4	FM1	Exp5 N D4	Exp2 H D4	Exp2 N D4	QC2	Exp5 H D4	Exp3 N D4	Exp6 N D4	FM2	QC3	Exp1 H D4	Exp1 N D4	Exp3 H D4	FM3	Exp4 N D4	Exp4 H D4	QC4	CV % (QC) > 1000 %
Betaine	26694026.52	36758110.64	38634178.23	47595911.26	36503437.76	46076557.08	31294025.33	36690895.10	44235880.94	42073187.35	46766794.41	35319710.02	39955524.42	42769756.11	41137604.12	45259599.55	49991123.66	44640080.11	40082624.20	17.1261.29
Heptadecanoic acid	314814.71	163297.60	228234.12	224270.45	250796.21	195993.58	287748.49	132653.84	234299.68	184713.71	277637.58	257213.37	148413.63	291115.90	156322.06	264499.14	177454.22	170750.03	382730.44	17.2361.29
Citrulline	87422.56	274021.80	404992.92	218401.02	232945.81	265326.02	59837.95	288560.42	245706.77	225848.07	334890.72	90168.72	381884.11	260195.02	283237.97	418407.51	291226.14	317123.56	78922.01	17.3261.29
2-Hydroxybenzoic acid	8629.72	9978.57	6962.42	12970.31	8558.65	16391.20	12172.27	12082.65	16022.68	12587.95	7013.54	8369.77	13744.77	9676.12	16744.15	5249.73	17685.21	14570.58	9175.82	18.3261.29
Adonitol	1989.16	1198.40	2816.89	4303.98	689.57	2083.94	2357.21	221.46	3751.36	4057.24	5273.94	2729.86	1457.77	2608.37	1124.00	2993.66	2838.17	1102.88	1789.16	18.7454.84
Indole-3-lactic acid	109880.08	191667.37	164274.04	114797.70	158719.97	104985.94	107285.85	195445.79	120897.78	122860.58	139677.90	72153.20	194254.56	100532.96	153304.50	176384.90	116963.01	155256.46	86828.45	19.0061.29
3-Hexenedioic acid	8478.80	8975.09	4314.46	8231.04	9940.44	10094.25	12977.94	9082.81	6143.99	7740.29	6495.52	13800.69	9667.49	8315.07	14173.14	7282.89	8769.20	15573.61	12229.00	19.8161.29

Table E2. List of identified metabolites in fresh medium and spent medium from cultures of MS-5 cells in normoxia and hypoxia. Samples are labeled as MS-5 cells normoxia (N) or hypoxia (H), and day 4 and FM is fresh medium. 13C3-Lactate and 13C5-15N-Glutamic acid were internal standards

Compounds	FM	MS-5 N-1	MS-5 N-2	MS-5 N-3	MS-5 N-4	MS-5 H-1	MS-5 H-2	MS-5 H-3	MS-5 H-4
Citraconic acid	344865	230074	183820	196185	168106	173963	417016	220013	229614
Serine	255115	36697	34350	89979	29054	72570	101651	32208	213245
Norvaline	8654780	15063039	16144215	15216125	16439547	14375248	9914960	16376614	9556454
L-Alloisoleucine/Leucine/Norleucine	91303814	125815719	137714479	134885982	145011672	128365769	105738158	136513022	104808036
Asparagine	326601	408185	418182	254337	305686	281927	320335	454044	216889
Isoleucine	91512488	124949549	137738713	133820174	144056991	129525205	105253080	138342315	105083534
Valine	9839649	16959422	18454579	17121724	18461669	16564824	11366268	18708583	10804205
Glucose	6551167	3346103	3373447	4003075	3639667	4201892	6194651	3646433	6666389
Sorbitol	700797	943380	944501	982909	896289	952672	817725	847672	332699
Fumarate	217146	105440	81949	94726	69279	69262	268919	90915	133267
Glyoxylic acid	68503	34895	32414	49688	36058	40757	63686	37086	70726
Homoserine/Threonine	6761510	8142612	8189782	7876716	9005973	7912996	6989180	8451411	7714452
Threonine	6761510	8142612	8189782	7876716	9005973	7912996	6989180	8451411	7714452
Methionine	3301966	3908536	4536153	4366010	4661934	4147131	3179859	4287057	3513780
Sarcosine	2332677	1623577	1674786	1228896	1710722	1401988	2988195	1621848	2320729
Alanine	2412726	1627287	1774936	1382773	1757850	1332217	3007805	1719816	2091095
Kynurenine	28280	61747	61461	28525	79746	31024	8109	63303	44378
Phosphocreatine	47160	46544	31873	101436	29555	17877	26516	19383	34112
Dihydroxyacetone	97210	96527	137587	186487	82682	114245	155858	102739	168532
4-Methyl-2-oxopentanoic acid/Ketoleucine/ Ketoisoleucine	439159	288226	247748	288022	250974	245966	601131	294186	303727
Isobutyric acid	253586	116557	115788	213431	92882	195347	362268	149938	270637
4-Methylvaleric acid/Hexanoic acid	2020782	866647	803390	852327	673344	318080	2329568	926745	1297160
2-Methylbutyric acid/Valeric acid	757669	192595	180958	133994	196198	114975	332314	178888	558477
Hydroxyproline	1026192	656909	686745	715299	913816	724083	1086978	766991	1280966
Mannose	1950082	1160799	924553	1355667	1082742	1336172	2033806	1009843	1915233
TMAO	391453	298973	418393	304567	443572	402230	299403	349502	458580
Glutamine	7446374	30171003	28826677	35620219	27282200	34178207	14801462	31196434	6419593
2-Aminoadipic acid	28353	25728	28436	36612	40905	34537	41177	27254	37053
alpha-Ketoisovaleric acid/Maleic acid	306965	165498	120581	157262	111375	112904	369737	135526	204067
13C3-Lactate	721215	636742	747276	739351	653771	694705	722984	711991	909618
Lactate	2285015	10176171	10723490	10377737	9756358	10752694	3985733	10773833	1254662
Adipic acid	45630	264137	345568	404055	119120	471901	132311	346754	94734
Methylguanidine	186753	213993	196478	212756	215020	205846	176125	201989	181817
Pyridoxine	1702216	2260621	1779762	2083706	2367273	2195595	2356701	2076982	1211614
9-Octadecynoic acid	128831	54594	42876	65215	57665	48041	128132	56079	116650
HIAA	15832	14911	21146	9911	26253	9337	9177	19027	16031
2-Aminobutyric acid	405000	5865445	5347933	4870469	5960468	5260179	1173402	5748658	907191
Glutamic acid	2741892	1601579	1598607	1199201	1767108	1217954	2421655	1849575	1953610
3-Methyl-2-oxovaleric acid	5501524	3334165	3062982	3735959	3166060	3120920	7896909	3765074	4091919
Histamine	59267	42528	43373	50721	26201	53469	64151	49919	51088
5-Aminolevulinic acid	962045	666043	688408	718727	910486	729690	1087159	773566	1241384
Tryptophan	3085788	3353981	4081384	4313606	4842866	3893613	2788486	4334400	2435940
Pipecolinic acid	696450	405514	510359	361988	497564	379658	627118	463132	621015

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Table E2 (*Continued*)

Compounds	FM	MS-5 N-1	MS-5 N-2	MS-5 N-3	MS-5 N-4	MS-5 H-1	MS-5 H-2	MS-5 H-3	MS-5 H-4
3-hydroxykynurenine	5205	7745	3438	2200	3634	3447	4993	1924	3656
2/3-Aminoisobutyric acid/Dimethylglycine	254022	3371001	2911227	2244270	4215792	2846113	716846	3640764	81698
Nicotinamide	1377661	1276317	1283416	1331132	1589386	1401913	1278413	1495636	1096639
Myristic acid	165063	108932	114671	138277	113915	110623	121871	72260	175766
Uridine	3519	1680	2654	1543	2065	1570	948	2492	1504
L-(+)-Arabinose	192325	76964	75204	110953	76617	100321	153320	86124	179269
Quinolinic acid	49296	41873	51680	53035	50106	51509	54767	49611	53261
Aspartate	69504	50232	39813	30043	44155	27122	81511	34122	53129
Stearic acid	2323052	1618297	1332232	2428447	1489808	1814716	2222668	1487340	2482501
Phenylalanine	23121771	23787647	21992085	23653625	22125567	22220306	22152969	22346772	19887876
Dulcitol	879381	1000104	1019436	1054806	984396	1020143	974847	1083979	356535
Glycine	161287	105506	98790	90936	112907	96678	139288	105319	129434
L-(-)-Arabitol	55812	43224	46327	53034	43282	56648	66414	48600	51613
Phenylpyruvic acid	52375	9606	6948	7179	9294	6317	30853	7833	29571
3-Phenyllactic acid	45062	85586	61888	24420	76601	27020	38007	82500	26042
Isovaleric acid	511260	240812	208830	381923	229659	392227	434829	259172	533945
Malate	951474	1101513	1323446	1137268	1354858	941527	1020125	1468236	874129
Nonadecanoic acid	130677	92992	110679	139506	95981	102992	104069	61861	159727
D-Mannitol	252954	326663	312169	307139	343536	355788	300036	325003	96323
4-Hydroxyphenylacetic acid/Mandelic acid	21000	6666	6861	7373	5834	6526	25264	9436	13363
2-Deoxycytidine	88466	16719	15058	57325	10067	49517	23800	11882	231067
6-Methyl-DL-Tryptophan	46154	22820	25784	30597	27615	27513	42449	27408	55271
Adonitol	29038	19927	20074	24204	19104	24556	31447	21199	21220
Oxaloacetic acid	53799	77218	105497	75915	54721	96620	89118	96430	51895
2-Hydroxyphenylacetic acid/3-Hydroxyphenylacetic acid	22772	6607	6786	6850	5971	6426	24724	9602	13496
Pentadecanoic acid	202665	123782	74273	241326	88380	86708	122815	72636	212403
Metanephrine	419614	383269	394690	478225	475766	399992	581682	408814	327362
Ribose	29252	71107	80063	75982	61943	82767	40601	70987	16015
Caprylic acid	129602	71502	110594	78708	124455	122847	149083	112130	140255
Xylose	29252	71690	80253	76055	61938	83364	39956	71903	16134
Pyroglutamic acid	3725319	3076119	3883461	3206949	4176584	2987963	3444940	3919170	4460492
Normetanephrine	59079	29168	27585	22504	28978	19821	64931	29709	33138
Succinate	7344974	5218342	5279109	5461562	5524063	5262155	8013218	5534803	7154703
Ethylmalonic acid	4794	2605	3519	4237	3914	3307	2993	2743	5969
Creatinine	1034690	940259	838853	928380	972753	960547	1082261	878649	755089
Creatine	4166732	4871985	4923835	4340364	6022525	5802456	5680648	5167608	6206867
Trehalose	16572	9553	8988	13980	5464	14096	13040	6231	3420
Methylmalonic acid	7353523	5222372	5279019	5454792	5522345	5260750	8013218	5535630	7157598
Lauric acid	194409	111715	130115	115042	128113	94333	147301	106571	166463
belta-Hydroxyisovaleric acid	3580	23771	10468	4709	11700	4479	3186	11412	1177
Imidazole	28333	31583	42119	22913	80464	52467	21985	29882	34605
Heptadecanoic acid	436232	173716	526068	264564	502029	573517	191011	284832	350022
Xylitol	30865	25919	26543	31345	28646	31097	37490	31857	24718
Ornithine	240730	228502	198663	143312	233752	147634	272720	209598	257069
Leucic acid	57222	106915	118742	48237	97278	48803	101040	120078	39578

(*continued on next page*)

Table E2 (*Continued*)

Compounds	FM	MS-5 N-1	MS-5 N-2	MS-5 N-3	MS-5 N-4	MS-5 H-1	MS-5 H-2	MS-5 H-3	MS-5 H-4
Benzoic acid	146088	170345	146849	47399	125701	51075	55028	143524	161513
Phenylacetic acid	50534	45293	47197	28979	57228	44212	36762	50491	61213
Cytidine	138354	103365	99088	92659	153927	88861	67026	107448	82247
Palmitic acid	2774909	1779001	1568277	1792342	1996430	1918529	2006991	1512900	2538182
Acetylcarnitine	3219482	4162658	4154382	4455694	3607602	5171927	4004118	3787427	2962943
Tyrosine	2712569	2609585	2923543	2599089	3273800	3046439	2626324	3033433	1887264
Cystine	373612	461111	401687	452445	588658	504564	497941	394192	311626
4-Pyridoxic acid	43074	8683	8351	7472	10755	9278	65366	9312	15864
4-Hydroxybenzaldehyde	78659	8163	11157	9575	7079	6488	40841	10401	32337
Glycocyamine	64267	69498	64407	77074	62737	72895	65243	73913	46010
pregnenolone sulfate	3163	2560	6570	2266	1851	2203	2994	2108	3312
13C5-15N-Glutamic acid	1280394	1448063	1150207	1192599	1305559	1356009	1174642	1210580	1263436
Picolinic acid	38898	42128	43119	42317	45607	39227	43740	42789	31832
Lysine	2558919	3193173	2581842	2543576	2930707	2661670	2703349	2746108	2170591
3-Methyladipic acid	8691	6259	4339	5750	5701	5121	7454	5295	8168
Betaine	21175156	15556778	19637757	17259630	18271990	16262356	19324180	17610780	16305541
2-Pyrrolidinone	2719	1880	1820	2611	2193	2336	2510	1878	2258
alpha-KG	877429	561329	612823	693953	738184	681156	775252	702740	1010848
Carnosine	98291	119211	99215	91290	99862	93639	120792	89985	73767
Arginine	19372941	24842693	21002238	21820792	26258623	24269860	22428136	21477142	15411805
Citrulline	112371	128242	156096	179618	73573	206783	193483	139351	83048
Fructose/Galactose	1331050	16040520	15205022	13607011	15698625	14144484	3264949	14804741	477682
N-Acetylmuramic Acid	16966	2639	1672	3472	1869	3563	20171	1855	13387
D-(+)-Cellobiose	42993	21500	23619	75609	13037	85759	19138	19963	45052
Lactose	42585	23266	21637	67080	12482	87852	18954	20177	43099
Erythrose	2634	2580	2910	3471	3152	2817	3731	3198	2247
malonic acid	64233	7764	7898	28571	9215	32779	47391	8546	45422
Levulinic acid	141080	5537	6284	80264	4409	85930	185895	10292	113055
Urocanic acid	366557	309608	270056	232024	439126	263759	207452	268601	49167
4-Imidazoleacetic acid	54913	55707	55099	43301	54317	43539	69294	49235	65826
Carnitine	3790712	3029504	2449149	2269357	2962291	2460366	3431502	2799358	2474530
2HG	62800	86690	76374	65150	83741	61935	63380	85781	56142
Cytosine	92609	55174	61095	46032	80501	47633	39568	40027	57495
Histidine	4215148	3730253	1804909		1045772	3988274	5579941	2602455	2580622
R5P	67609	127026	132011	72750	105527	85745	83029	142372	57149
Glyceric acid	21826	12274	15146	14140	11981	12374	13565	14028	20484
2-hydroxybutyric acid/Malonic acid	8131	5298	4019	9251	3805	11696	11165	4361	5065
Pantothenic acid	1481478	1681725	1527000	1780311	1700868	1410302	2241615	1441138	1275849
6-Hydroxynicotinic acid	18802	21262	19379	16522	26496	18180	14926	19532	6501
Proline	5967145	15524093	14198086	8804861	16312269	10075192	7953585	16346920	3441861
D-Xylonic Acid (Lithium Salt)	313377	299597	274094	241374	467705	271699	292350	279549	211294
N-Acetyl-D-galactosamine	63250	19058	22448	22124	27667	18387	56075	19586	29198
2-Methylglutaric acid	381144	213107	212659	284891	294678	272960	306388	270909	353304
4-Hydroxy-3-methylbenzoic acid	5549	1635	1674	2584	1350	1184	6476	1716	3517
2-Hydroxybenzoic acid	11259	12064	13885	11345	11266	6311	10354	11915	16761

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Table E2 (*Continued*)

Compounds	FM	MS-5 N-1	MS-5 N-2	MS-5 N-3	MS-5 N-4	MS-5 H-1	MS-5 H-2	MS-5 H-3	MS-5 H-4
Acetyl-L-glutamine	25969	26843	23581	14855	29780	15359	53306	25320	12904
Capric acid	104630	68908	100690	48836	104082	84959	94097	85841	127677
Adenosyl-L-homocysteine	29858	15077	13103	6234	5081	9835	34175	22748	3664
N-Acetylneuraminic acid	23372	18456	22346	18403	20903	19946	25995	21367	18684

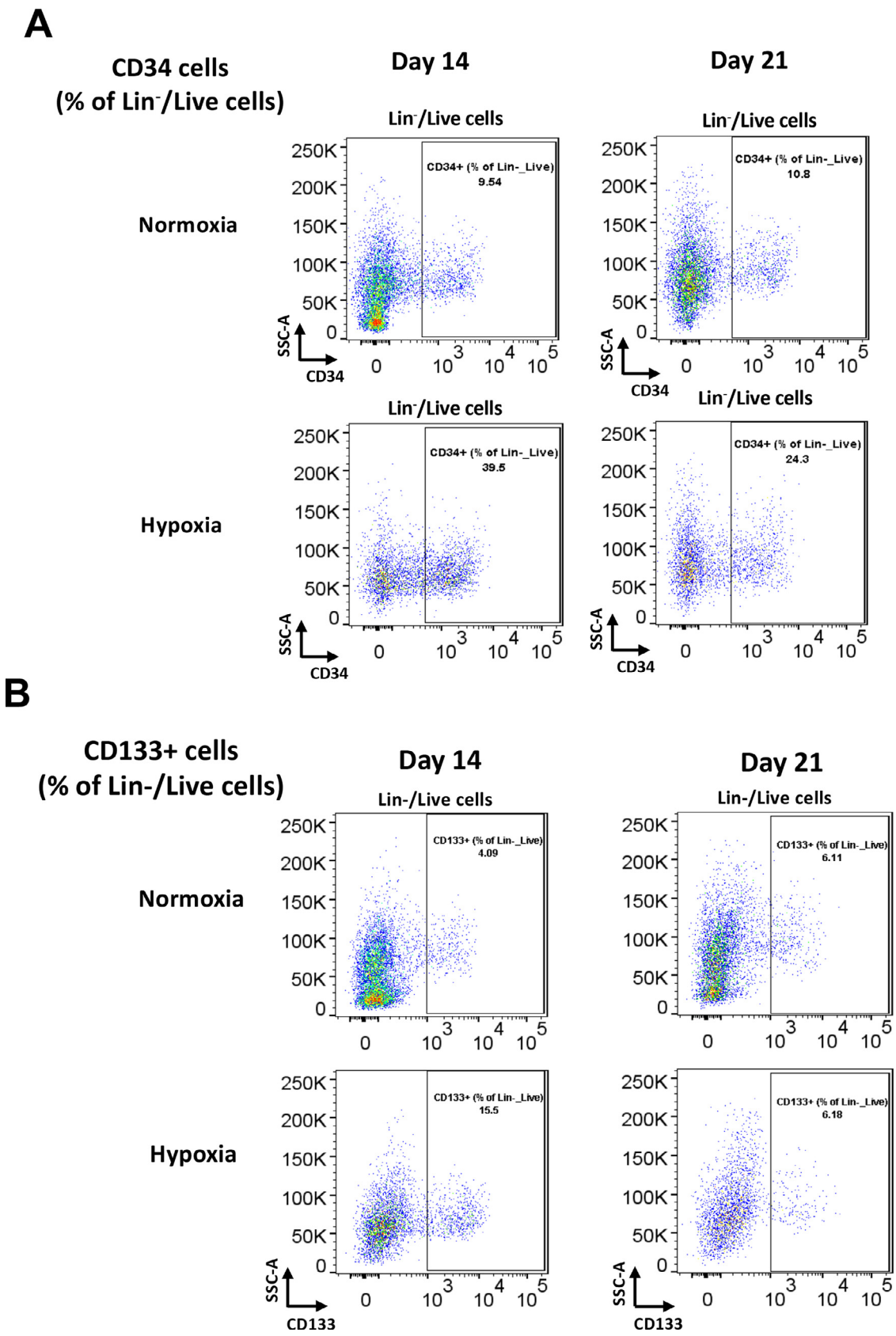

Figure E2. Hypoxia inhibits expansion of the stem and progenitor cells. Representative scatter plots for $CD34^+$ (A) and $CD133^+$ (B) cells in cultures incubated in normoxia or hypoxia. Plots for immunophenotyping performed on days 14 and 21 are shown.

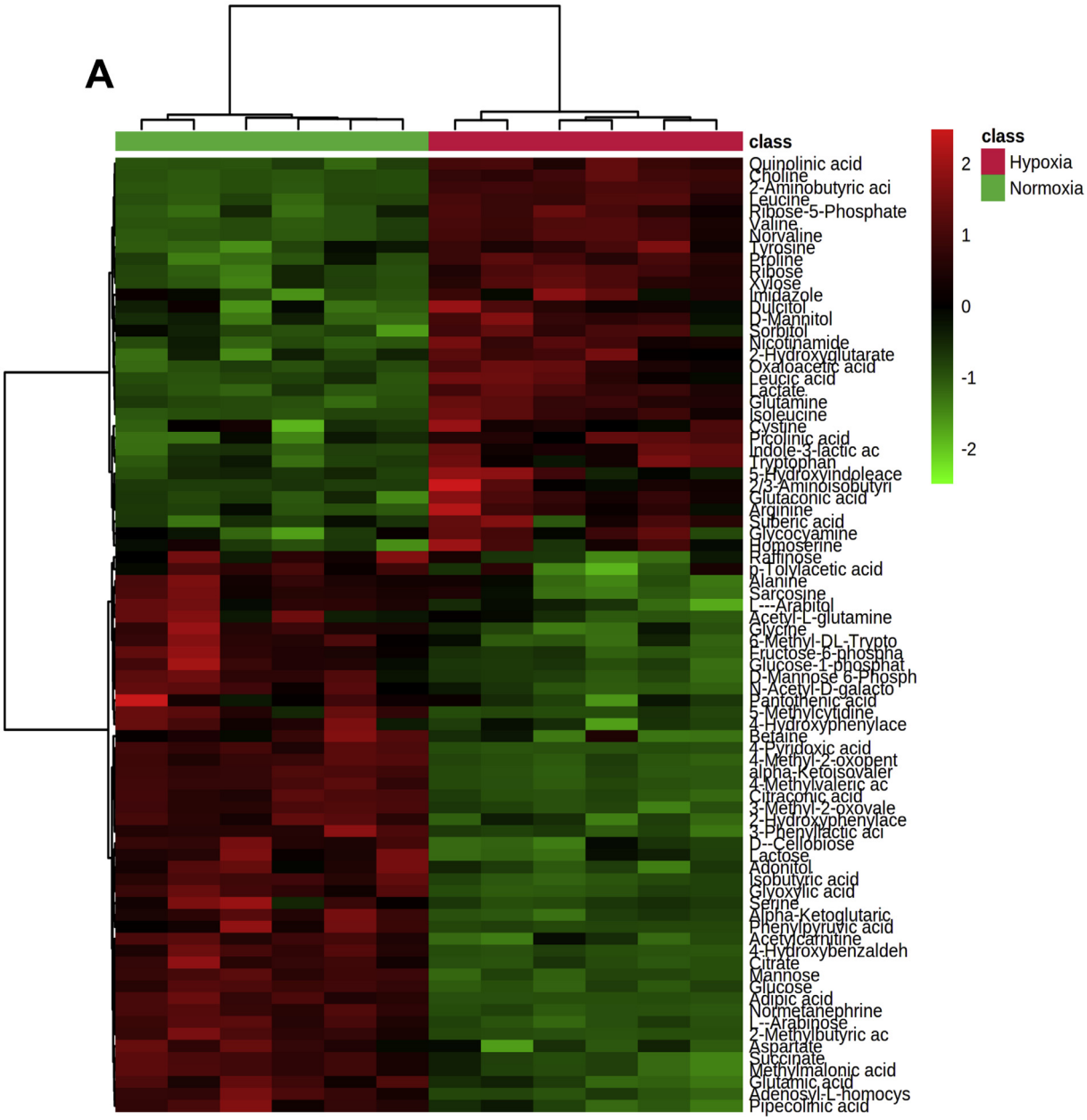

Figure E3. Hypoxia causes a metabolic shift in the CD34$^+$ cells. Metabolite profiling comparing levels in spent medium of cultures incubated in normoxia or hypoxia to levels in fresh medium. (A) Heat map representation of fold change in metabolites in hypoxia or normoxia. (B) Graph of fold change in metabolites that are significantly different ($p < 0.05$) between medium from normoxia and hypoxia cultures. Statistical analysis was performed in MetaboAnalyst.

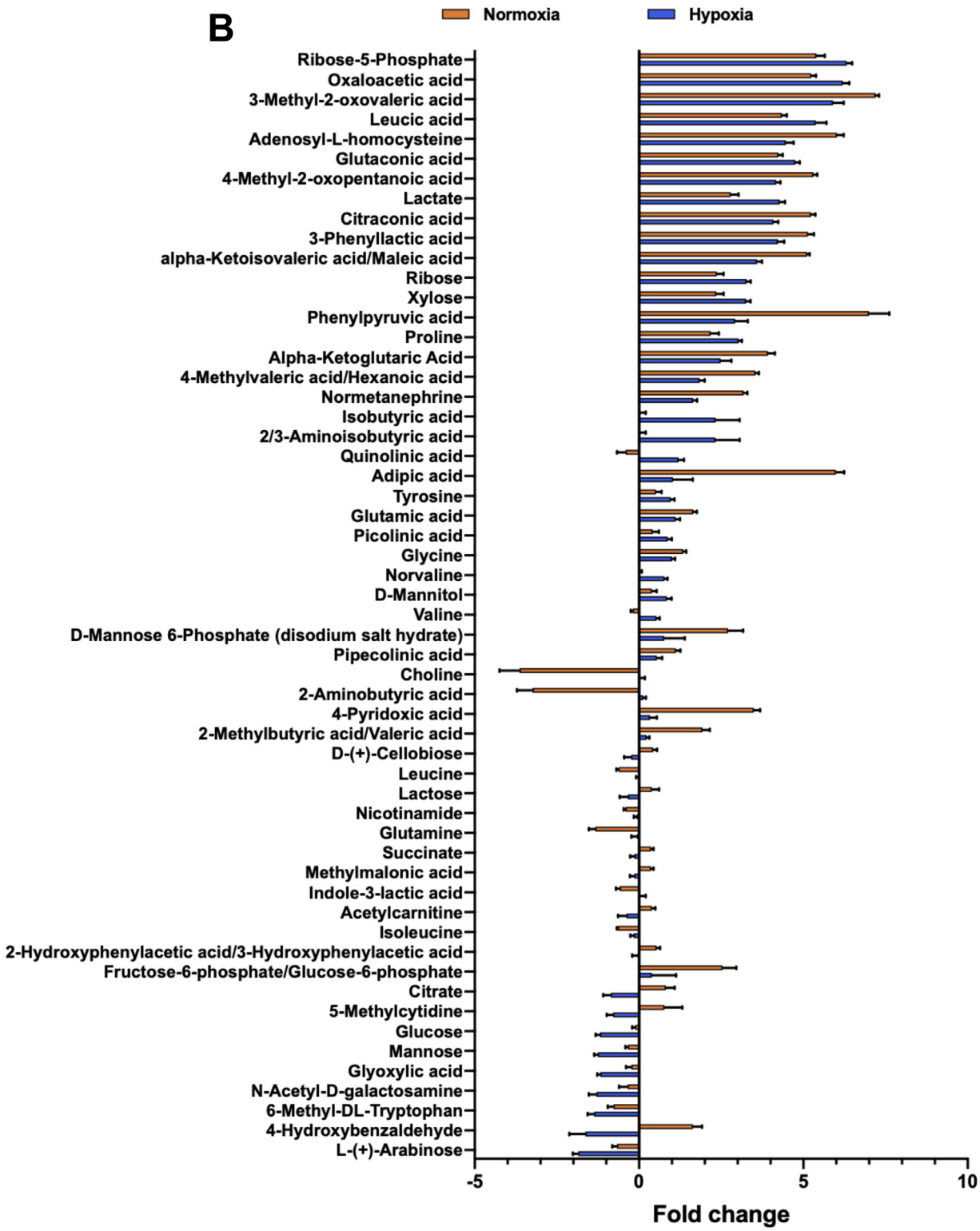

Figure E3. Continued.

Table E3. List of metabolites that significantly changed in the spent medium of CD34+ co-cultures relative to fresh medium in normoxia.

Sample ID	Normoxia	*P*-value
Choline	0.08624623	5.4059E-08
2-Aminobutyric acid	0.11053036	2.6427E-07
Serine	0.25962546	4.7162E-05
Glutamine	0.40057862	0.00013069
Methionine	0.47143679	0.00059151
9-Octadecynoic acid	0.55805333	7.7938E-05
Cytidine	0.56613052	0.04104889
6-Methyl-DL-Tryptophan	0.58536351	0.00072776
Citrulline	0.60995152	0.00021856
L-(+)-Arabinose	0.62982558	0.00028602
Isoleucine	0.63789562	8.2889E-06
Leucine	0.64657272	2.6769E-06
Taurine	0.65313315	0.01374881
Tryptophan	0.65634056	0.00555253
Indole-3-lactic acid	0.66639276	0.00022387
Ornithine	0.69390987	0.03363796
5-Hydroxyindoleacetic acid	0.70674765	0.0280946
Nicotinamide	0.7549103	6.8709E-05
Mannose	0.79086512	0.00071692
Pyridoxine	0.80058708	0.01909436
Valine	0.87160887	0.00280845
Carnosine	1.22252177	0.00913645
Sorbitol	1.27237754	0.04396603
Methylmalonic acid	1.28987857	0.00524438
Succinate	1.2902666	0.00513616
Acetylcarnitine	1.31383686	0.00400842
D-Mannitol	1.31597634	0.01692835
Picolinic acid	1.34487266	0.0393333
D-(+)-Cellobiose	1.35118414	0.00699011
Tyrosine	1.43871019	0.01264926
2-Hydroxyphenylacetic acid/3-Hydroxyphenylacetic acid	1.45426804	0.03006403
Phenylacetic acid	1.47129331	0.00271879
4-Hydroxyphenylacetic acid/Mandelic acid	1.50793639	0.02416206
L-(-)-Arabitol	1.60666813	0.00116481
2-Hydroxyglutarate	1.71990246	0.00850632
Citrate	1.78319467	0.02597473
p-Tolylacetic acid/4-Ethylbenzoic acid	1.84870081	0.00782083
Xylitol	1.90319347	0.001077
Pipecolinic acid	2.18506991	0.0002713
2-Hydroxybenzoic acid	2.32919609	0.0116719
Glycine	2.53274825	4.2477E-05
5-Aminolevulinic acid	2.71222365	0.04314563
Hydroxyproline	2.88669912	0.0352636
Malate	3.04695456	6.9282E-05
Glutamic acid	3.14661609	2.3892E-05
4-Hydroxybenzaldehyde	3.17036881	0.00332875
Dihydroxyacetone	3.51964799	0.00062304
2-Methylbutyric acid/Valeric acid	3.84318152	0.00087707
Aspartate	4.11605422	0.0001192
Benzoic acid	4.20129402	0.0087986
4-Imidazoleacetic acid	4.4127849	0.00137074
Proline	4.58673842	0.00103968
Xylose	5.1464227	0.00032129
Ribose	5.1930513	0.00026431
Aconitic acid	5.36461594	0.00092318
Fructose-6-phosphate/Glucose-6-phosphate	6.02771494	0.00964743
D-Mannose 6-Phosphate (disodium salt hydrate)	6.78645897	0.00546105
Lactate	7.00522771	0.00052434
Alanine	7.27976769	0.00011906
Sarcosine	7.33286294	8.5226E-05
Glucose-1-phosphate	7.94575994	0.0136457

(*continued*)

Table E3 (*Continued*)

Sample ID	Normoxia	*P*-value
Normetanephrine	9.08467573	6.4458E-06
4-Pyridoxic acid	11.3321011	8.1698E-05
4-Methylvaleric acid/Hexanoic acid	11.6683857	2.8019E-06
Acetyl-L-glutamine	12.1510314	0.02623156
Alpha-Ketoglutaric Acid	15.2791014	0.00019053
Glutaconic acid	18.9424254	6.7249E-06
Suberic acid	19.6253654	9.0371E-06
Leucic acid	20.4619665	2.3124E-05
AMP	22.827629	0.01670402
alpha-Ketoisovaleric acid/Maleic acid	34.664999	3.664E-07
3-Phenyllactic acid	35.5146983	7.1519E-05
Citraconic acid	37.8471008	6.0766E-06
Oxaloacetic acid	38.0278722	1.0497E-05
4-Methyl-2-oxopentanoic acid	39.6345225	2.9525E-06
Ribose-5-Phosphate	42.6646289	0.00037718
Adipic acid	64.3843976	0.00029006
Adenosyl-L-homocysteine	65.4284844	0.00011725
Isobutyric acid	123.218488	2.6296E-05
Asparagine	131.064251	6.5166E-05
Phenylpyruvic acid	137.814423	0.02061056
3-Methyl-2-oxovaleric acid	147.044285	1.8707E-06

Table E4. List of metabolites that significantly changed in the spent medium of CD34+ co-cultures relative to fresh medium in hypoxia.

Sample ID	Hypoxia	*P*-value
Serine	0.11277691	1.5891E-09
2-Deoxycytidine	0.21484877	1.5247E-05
L-(+)-Arabinose	0.27824692	3.1156E-07
Adonitol	0.33238795	0.00109115
4-Hydroxybenzaldehyde	0.33945454	0.00274186
9-Octadecynoic acid	0.36544348	0.00693911
6-Methyl-DL-Tryptophan	0.3884956	3.5975E-05
N-Acetyl-D-galactosamine	0.4116632	0.02000297
Mannose	0.42094444	6.3108E-07
Glucose	0.4401434	2.0746E-05
Glyoxylic acid	0.44213528	2.8911E-07
Methionine	0.47481453	0.00199821
Cytosine	0.5489073	0.00152124
Citrate	0.55743666	0.00087295
Cytidine	0.56298769	0.00309838
5-Methylcytidine	0.58287937	0.00205505
Citrulline	0.71968777	0.02150607
Pyridoxine	0.78694823	0.01571151
Raffinose	0.83550597	0.04237544
2-Methylbutyric acid/Valeric acid	1.17583997	0.038051
L-(-)-Arabitol	1.29113539	0.03150266
NADPH	1.33720413	0.00433504
Imidazole	1.37023407	0.02099061
Threonine	1.42350906	0.05050989
Valine	1.45223769	0.00055341
Pipecolinic acid	1.46093576	0.00984419
Phenylacetic acid	1.49159593	0.00550488
Xylitol	1.64756159	0.00707642
Sorbitol	1.67959611	0.00215125
Dulcitol	1.70224612	0.00588917
Norvaline	1.70744767	0.00041207
D-Mannitol	1.80364422	0.00106991
Putrescine	1.82263836	0.0357772
Picolinic acid	1.8331408	0.00044674
Tyrosine	1.95855637	0.00018943
Glycine	2.00430474	0.00012304
2-Hydroxybenzoic acid	2.06568555	0.02963327
Glutamic acid	2.17397995	0.00025074
Quinolinic acid	2.31373508	0.00355612
2-Hydroxyglutarate	2.51123174	0.00086161
Aspartate	2.78415166	0.00207274
Malate	2.93309783	6.6682E-05
Normetanephrine	3.13726198	5.0121E-05
Benzoic acid	3.35105678	0.0036788
4-Methylvaleric acid/Hexanoic acid	3.61625554	8.9637E-05
4-Imidazoleacetic acid	4.20413374	0.00058171
Dihydroxyacetone	4.24571115	0.01398476
Alanine	4.57066623	0.00991176
Sarcosine	4.61732922	0.01179264
Aconitic acid	5.38944415	0.00775302
Alpha-Ketoglutaric Acid	5.70991698	0.00176391
Acetyl-L-glutamine	6.08038835	0.03093061
Phenylpyruvic acid	7.83130302	0.00765058
Proline	8.20289366	1.9388E-06
Xylose	9.61520332	1.0633E-05
Ribose	9.6751641	7.5666E-06
alpha-Ketoisovaleric acid/Maleic acid	12.0929972	2.9825E-05
Citraconic acid	17.0965264	1.4729E-05
4-Methyl-2-oxopentanoic acid	18.0844054	9.6915E-06
3-Phenyllactic acid	18.8339823	4.9712E-05
Lactate	19.587286	2.0052E-05

(*continued*)

Table E4 (*Continued*)

Sample ID	Hypoxia	*P*-value
Adenosyl-L-homocysteine	22.3546448	0.00019857
Suberic acid	26.4862619	0.00042595
Glutaconic acid	27.0849387	1.0027E-05
Isobutyric acid	27.6334748	0.00165934
Leucic acid	42.4046412	0.00093114
3-Methyl-2-oxovaleric acid	61.0530539	0.00054081
Oxaloacetic acid	74.0169502	6.5718E-05
Ribose-5-Phosphate	80.1852711	2.3417E-05
Asparagine	117.059097	1.5017E-05

Table E5. List of metabolites that differed significantly in spent medium of CD34+ coculture in hypoxia versus normoxia.

Metabolite	Hypoxia-1	Hypoxia-2	Hypoxia-3	Hypoxia-4	Hypoxia-5	Hypoxia-6	Normoxia-1	Normoxia-2	Normoxia-3	Normoxia-4	Normoxia-5	Normoxia-6	*P*-value
Ribose-5-Phosphate	6.40406181	6.52661731	6.3133927	6.39502102	6.21758312	6.04714897	5.31045593	5.12675777	5.15381165	5.36890583	5.73752563	5.67490306	2.4977E-05
Oxaloacetic acid	6.27930017	6.39127028	6.42066769	6.13253236	6.03706905	5.93076761	5.00714821	5.19377218	5.22523367	5.41150863	5.25256936	5.36864458	2.3296E-06
3-Methyl-2-oxovaleric acid	6.2004706	5.89732045	6.08265918	6.04739069	5.27752967	5.91827617	7.2175131	7.2736829	7.05962402	7.30431244	7.26250536	7.0628114	3.3864E-06
Leucic acid	5.68191861	5.60045761	5.67049228	5.32245868	5.045464	4.93555056	4.30046276	4.40269265	4.21981009	4.6134139	4.20195806	4.35051006	3.7979E-05
Adenosyl-L-homocysteine	4.57302652	4.37596614	4.60431771	4.7742897	4.36981317	4.1041348	5.97100077	6.11932303	5.94838401	5.99033477	5.72394109	6.36016598	2.7552E-07
Glutaconic acid	4.975345	4.74491938	4.81759421	4.61896172	4.75200854	4.61587789	4.31234862	4.18484985	4.24964214	4.37579958	4.00482565	4.30470063	5.2633E-05
4-Methyl-2-oxopentanoic acid	4.28450864	4.0745505	4.18286977	4.35996933	4.12435367	4.00297799	5.3057264	5.27599302	5.12120932	5.43841901	5.41528248	5.27295542	2.099E-08
Lactate	4.3282056	4.36237122	4.50457514	4.20570656	4.25916789	4.05032703	2.95505462	3.17502388	2.70614479	2.67258527	2.73589141	2.50632951	1.4041E-07
Citraconic acid	4.27344799	4.06676868	4.10546991	4.20557674	4.0296149	3.85663452	5.2733433	5.38655021	5.11865213	5.31230312	5.29243801	5.04032541	5.231E-08
3-Phenyllactic acid	4.36348834	4.37283782	4.30567579	4.11227254	4.30952257	3.88766342	5.01906916	5.02893669	5.03315754	5.47672625	5.22704395	5.05682597	6.877E-06
alpha-Ketoisovaleric acid/Maleic acid	3.70253634	3.41555862	3.58020088	3.83316181	3.49895345	3.50460897	5.11311538	5.21616359	5.02011671	5.18944137	5.10709916	5.03571068	9.9641E-10
Ribose	3.11377142	3.40678188	3.34690724	3.3393278	3.2935389	3.11896252	2.44105937	2.64725442	2.26426519	2.45375091	2.35437146	2.02395577	3.7395E-06
Xylose	3.14777669	3.42173107	3.36579323	3.3373461	3.16366748	3.1267837	2.40265136	2.63010081	2.2920015	2.45725341	2.35348074	1.96365828	5.5782E-06
Phenylpyruvic acid	2.77126414	2.46657148	3.60043495	3.10047811	2.75575465	2.84257652	6.23231836	6.64178466	6.57046575	7.59516924	7.14806783	7.79187724	8.4621E-08
Proline	3.02356844	3.07068015	3.16503742	2.91890614	3.08932344	2.93369572	2.30761535	2.14837089	1.85050805	2.56779475	2.21329456	1.98692054	1.4619E-05
Alpha-Ketoglutaric Acid	2.43236683	1.91805426	2.3616302	2.70472497	2.80887216	2.68176071	3.6827347	3.74930099	3.82238689	4.24750368	3.91434783	4.10152908	4.2306E-06
4-Methylvaleric acid/Hexanoic acid	1.99475037	1.64776274	1.86647063	2.0329298	1.83189271	1.71361338	3.56495983	3.59806309	3.45988899	3.70988997	3.44837306	3.46743007	6.2829E-10
Normetanephrine	1.70701916	1.51645398	1.84627111	1.6469966	1.61722346	1.53730025	3.23916244	3.03302448	3.31356422	3.28950796	3.0703603	3.13102132	7.5419E-10
Isobutyric acid	3.50070873	1.77766657	2.86797514	1.55745782	2.21498258	2.06575632	0.12494484	0.31594045	0.02156245	-0.0768839	0.005257	-0.1355384	2.0054E-05
2/3-Aminoisobutyric acid	3.50070873	1.77766657	2.86797514	1.55745782	2.21498258	2.06575632	0.12494484	0.31594045	0.02156245	-0.0768839	0.005257	-0.1355384	2.0054E-05
Quinolinic acid	1.26057241	0.97493634	1.28772894	1.43209459	1.18883988	1.0713852	-0.4522515	-0.1121345	-0.4363148	-0.8454949	-0.1446389	-0.4498927	1.7717E-07
Adipic acid	1.08046834	1.29184125	0.84736901	1.31184993	1.71674162	-0.0431561	6.10340076	6.12215748	6.35721769	5.67561877	5.77956981	5.90376291	4.2864E-09
Tyrosine	0.97498425	0.93944878	0.8791989	1.0205236	1.15363994	0.82796788	0.45295461	0.52927377	0.42125196	0.73175805	0.68060114	0.28413334	0.00029264
Glutamic acid	1.22730725	1.17817469	1.28010877	1.01480519	1.03304497	0.95914081	1.71514637	1.668995	1.53696378	1.48907475	1.71804493	1.77300568	1.8088E-05
Picolinic acid	0.81550393	0.67138589	0.8123691	1.00402958	0.98484552	0.93021227	0.28029237	0.20854837	0.27297176	0.58023095	0.51382615	0.64899508	0.0006028
Glycine	1.09192401	0.88860024	1.0065804	0.91118592	1.12879747	0.97554497	1.32532457	1.35033113	1.52614088	1.2686668	1.26467233	1.29198235	0.00012724
Norvaline	0.79674065	0.84863756	0.7430355	0.84740299	0.79049042	0.58891493	-0.0245769	-0.0301091	0.00852677	0.01123048	0.13047802	0.04876288	1.7951E-08
D-Mannitol	0.89834942	0.847997	1.05691013	0.81978202	0.84966863	0.59478811	0.48126104	0.5282772	0.54195631	0.293393	0.27334484	0.22359301	0.00030078
Valine	0.57494066	0.60361165	0.52187862	0.61244216	0.54334822	0.35872605	-0.2173549	-0.2660982	-0.2295515	-0.2050645	-0.1048449	-0.1719005	1.3384E-08
D-Mannose 6-Phosphate (disodium salt hydrate)	1.28526797	1.11404824	1.19493776	0.4031068	0.94094603	-0.3331646	3.00253694	2.67096487	3.1163163	2.94739575	1.85646437	2.66213123	0.00010743
Pipecolinic acid	0.67172926	0.57906477	0.76259208	0.40154135	0.48323632	0.33735823	1.0981056	0.95117692	1.17993984	1.10973355	1.04660322	1.34871778	4.8871E-05
Choline	-0.0797534	0.03996984	-0.1567301	0.29369227	0.05499976	-0.0198332	-3.7109778	-4.0920309	-4.562219	-2.9371699	-3.1533307	-3.3577678	5.9001E-08
2-Aminobutyric acid	0.09526619	0.08462827	0.13663703	0.22603094	0.21689996	0.0141572	-3.4415192	-3.6884893	-3.8200025	-2.6454707	-2.9005905	-2.9512525	9.8018E-09
4-Pyridoxic acid	0.57429702	0.16262059	0.11386151	0.19621908	0.56663685	0.39600535	3.52986718	3.16558127	3.36834607	3.70791488	3.6276304	3.55023382	1.0458E-10
2-Methylbutyric acid/Valeric acid	0.34359464	0.18671572	0.29919993	0.10354161	0.21368675	0.24301232	1.90420578	1.81795343	2.29292986	1.86479791	1.62805114	2.05541698	9.3983E-09
D-(+)-Cellobiose	-0.3856502	-0.4822151	-0.3547697	0.09871517	-0.1257637	-0.1858531	0.42725529	0.33366408	0.39903278	0.30867202	0.47809202	0.6342688	4.8805E-05
Leucine	0.00623946	-0.0480733	-0.0422701	0.03129043	0.04085445	-0.1330851	-0.633008	-0.7235796	-0.6758208	-0.5875135	-0.5817854	-0.5789456	1.1096E-08
Lactose	-0.5537618	-0.5932134	-0.5007559	0.00032647	-0.1019702	-0.2931854	0.28517059	0.14218555	0.32398543	0.26368712	0.64847732	0.67779764	0.00030874
Nicotinamide	0.03117741	-0.0234553	-0.0909133	-0.0601255	-0.1794559	-0.1616352	-0.4070204	-0.4003236	-0.2958933	-0.4478007	-0.4309884	-0.457695	1.1817E-05
Glutamine	0.1532288	-0.1122339	0.09935191	-0.068882	-0.2300439	-0.2454989	-1.1021086	-1.3694455	-1.2351051	-1.6883796	-1.3126255	-1.275821	2.8552E-07
Succinate	0.02693535	-0.1381405	-0.0988048	-0.0972543	-0.2428763	-0.3301095	0.45899088	0.32430268	0.40931809	0.37669681	0.2422043	0.38488877	6.0246E-06
Methylmalonic acid	0.02630522	-0.1398971	-0.1020746	-0.1009576	-0.2479941	-0.3324888	0.46070079	0.32253252	0.41184829	0.37436859	0.2406119	0.38338999	6.2735E-06
Indole-3-lactic acid	0.18962536	-0.1018371	-0.1519201	-0.133667	0.19844532	0.17028171	-0.7606411	-0.698115	-0.4945276	-0.5422621	-0.5692202	-0.4712936	2.7391E-05
Acetylcarnitine	-0.5557397	0.00272626	-0.6659416	-0.1917794	-0.5569082	-0.3573306	0.45588488	0.39575002	0.51786433	0.43896644	0.25424334	0.2816856	4.0883E-05
Isoleucine	-0.0280106	-0.1801351	-0.0755187	-0.2334263	-0.1567939	-0.3079864	-0.6837818	-0.6739303	-0.6510787	-0.6193545	-0.6226783	-0.6419247	5.2815E-07
2-Hydroxyphenylacetic acid/3-Hydroxy-phenylacetic acid	-0.132155	0.08057611	0.15725229	-0.2599609	0.01531456	-0.1608122	0.58127355	0.65753883	0.48205145	0.6343387	0.47754063	0.39038752	1.946E-05
Fructose-6-phosphate/Glucose-6-phosphate	1.10476729	1.09216469	0.90190013	-0.485672	0.14081513	-0.4005482	2.89019294	2.38168883	3.1547337	2.30485174	2.00323526	2.50722589	0.00010017
Citrate	-0.9247733	-0.4299317	-1.0152933	-0.8235684	-1.080857	-0.8807356	0.77018594	0.78780896	1.29224142	0.86502243	0.47864953	0.6810931	4.1624E-07
5-Methylcytidine	-0.9130225	-0.9235054	-0.814012	-0.9157546	-0.4135067	-0.7627682	1.16594342	-0.2729988	1.08493743	1.15550238	0.81073764	0.67878533	6.3253E-05
Glucose	-1.2815863	-1.3484171	-1.1590687	-1.0286602	-1.2691221	-1.0469893	-0.249887	-0.1415953	-0.015504	-0.1051675	-0.1832819	-0.0435682	1.409E-08
Mannose	-1.4114208	-1.3759287	-1.160559	-1.1658021	-1.1662575	-1.2315713	-0.3752087	-0.4417292	-0.3047538	-0.346087	-0.3550129	-0.2178916	1.4487E-08
Glyoxylic acid	-1.1663204	-1.2607777	-1.284338	-1.2130811	-1.0541642	-1.1000032	-0.246962	-0.3025575	-0.042737	-0.5003446	-0.1228448	-0.1954073	1.7693E-07
N-Acetyl-D-galactosamine	-0.9047545	-1.379997	-1.128702	-1.4537695	-1.4085671	-1.5037999	-0.1289871	-0.6308595	-0.1526939	-0.1782366	-0.7191862	-0.2891313	5.5917E-05
6-Methyl-DL-Tryptophan	-1.0814983	-1.4356968	-1.4681282	-1.5588665	-1.2034412	-1.4992779	-0.7762235	-0.8485282	-0.5209405	-0.6889849	-1.0281664	-0.8225476	0.00018739
4-Hydroxybenzaldehyde	-1.4505745	-0.8025527	-1.775237	-1.5787841	-1.9747105	-2.2090735	1.30442918	1.5370368	2.01642321	1.85663228	1.40377889	1.73856823	5.51E-08
L-(+)-Arabinose	-1.7362778	-2.1170053	-1.8883192	-1.8528182	-1.6457192	-1.8764613	-0.6860079	-0.818955	-0.5421599	-0.6138716	-0.8564021	-0.5185742	9.2691E-08

Table E6. Comparison of metabolites in medium from cultures of MS-5 cells did not show any signifcant differences in hypoxia versus normoxia on day 4.

Label	Hypoxia-1	Hypoxia-2	Hypoxia-3	Hypoxia-4	Normoxia-1	Normoxia-2	Normoxia-3	Normoxia-4	*P*-value
Citraconic acid	-0.9872478	0.27407162	-0.6484408	-0.5868191	-0.5839318	-0.9077349	-0.8138143	-1.0366568	0.26739538
Serine	-1.8136917	-1.3275178	-2.9856015	-0.2586346	-2.7973711	-2.8927172	-1.5034804	-3.1342711	0.19393313
Norvaline	0.73201811	0.19611048	0.92006829	0.14297897	0.7994441	0.89944849	0.81403224	0.92560174	0.11463705
L-Alloisoleucine/Leucine/Norleucine	0.49151395	0.21174973	0.58029194	0.19900297	0.46256561	0.5929336	0.5629938	0.66742234	0.10699044
Asparagine	-0.2122064	-0.0279469	0.47530336	-0.5905703	0.32169452	0.35660229	-0.3607864	-0.0954777	0.62561358
Isoleucine	0.50119277	0.20182258	0.59620235	0.19949676	0.44930563	0.58989395	0.5482555	0.6545995	0.1451476
Valine	0.75144443	0.20808054	0.92702178	0.13491489	0.78540854	0.90730032	0.79914951	0.90785448	0.13480296
Glucose	-0.6407107	-0.0807279	-0.8452632	0.02515443	-0.9692667	-0.9575251	-0.7106409	-0.8479426	0.06936222
Sorbitol	0.44298346	0.2226198	0.27451014	-1.0747752	0.4288429	0.43055621	0.4880617	0.35496793	0.23891832
Fumarate	-1.6485208	0.30850689	-1.2560701	-0.7043435	-1.0422394	-1.4058609	-1.1968284	-1.6481667	0.30522382
Glyoxylic acid	-0.7491168	-0.1051899	-0.8852895	0.04607433	-0.9731434	-1.0795462	-0.463268	-0.9258446	0.15443083
Homoserine/Threonine	0.2268792	0.04777856	0.32184732	0.19021888	0.2681468	0.27648018	0.22024944	0.41353718	0.21370239
Threonine	0.2268792	0.04777856	0.32184732	0.19021888	0.2681468	0.27648018	0.22024944	0.41353718	0.21370239
Methionine	0.32878891	-0.0543615	0.37666286	0.08969938	0.24330369	0.4581445	0.40299067	0.49760376	0.11262921
Sarcosine	-0.7345101	0.35728828	-0.5243461	-0.0074076	-0.5228089	-0.4780081	-0.9246206	-0.4473796	0.22643302
Alanine	-0.8568321	0.31804752	-0.4884081	-0.2064043	-0.5681934	-0.4428955	-0.8030971	-0.4568505	0.35923381
Kynurenine	0.13360332	-1.8021755	1.16249193	0.65006289	1.12658711	1.11988931	0.01244563	1.49563015	0.25829712
Phosphocreatine	-1.3994529	-0.8306978	-1.2827666	-0.4672827	-0.0189676	-0.565227	1.10493433	-0.6741593	0.08285467
Dihydroxyacetone	0.23295503	0.68105591	0.07980809	0.79384621	-0.0101713	0.50116797	0.93989867	-0.2335302	0.65541356
4-Methyl-2-oxopentanoic acid/Ketoleucine/ Ketoisoleucine	-0.8362817	0.45293652	-0.5780128	-0.5319664	-0.6075408	-0.8258672	-0.6085623	-0.8072028	0.28648658
Isobutyric acid	-0.3764345	0.51458271	-0.7581065	0.09388476	-1.1214353	-1.1309851	-0.2487041	-1.4489976	0.06435073
4-Methylvaleric acid/Hexanoic acid	-2.6674166	0.20514941	-1.1246652	-0.6395551	-1.2213925	-1.3307357	-1.2454298	-1.5854901	0.65165932
2-Methylbutyric acid/Valeric acid	-2.7202093	-1.1890161	-2.0824953	-0.4400682	-1.9759838	-2.0658974	-2.4993712	-1.9492443	0.35730187
Hydroxyproline	-0.5030719	0.08302284	-0.4200176	0.31993207	-0.6435331	-0.5794523	-0.5206805	-0.167324	0.17309911
Mannose	-0.5454272	0.06064809	-0.9494005	-0.026014	-0.7484141	-1.0767029	-0.5245301	-0.8488424	0.14906045
TMAO	0.03918242	-0.3867489	-0.1635373	0.22833498	-0.3888224	0.09602039	-0.362078	0.18032989	0.81809969
Glutamine	2.19846677	0.99112992	2.06677119	-0.2140551	2.01855273	1.95279461	2.25808644	1.87335007	0.22597008
2-Aminoadipic acid	0.28464197	0.53833775	-0.0570325	0.38608948	-0.140161	0.00421802	0.36881572	0.52877623	0.64342627
alpha-Ketoisovaleric acid/Maleic acid	-1.4429711	0.26842586	-1.1795	-0.5890293	-0.8912574	-1.3480659	-0.9649007	-1.462642	0.32775262
13C3-Lactate	-0.054028	0.00353519	-0.0185695	0.33483195	-0.1797193	0.05121261	0.03583087	-0.1416429	0.29149375
Lactate	2.23442266	0.80264172	2.23725611	-0.864902	2.15491932	2.23049901	2.18321638	2.09413911	0.19981183
Adipic acid	3.37042968	1.53587855	2.92585798	1.05389985	2.53323187	2.92091508	3.14649714	1.38436123	0.69870934
Methylguanidine	0.14043472	-0.0845307	0.11314606	-0.0386434	0.19643286	0.07323716	0.18806908	0.2033401	0.08152191
Pyridoxine	0.36719837	0.46935507	0.28707519	-0.4904822	0.40930552	0.06427102	0.29173821	0.47581243	0.54557085
9-Octadecynoic acid	-1.4231354	-0.0078481	-1.1999426	-0.1432924	-1.2386606	-1.5872296	-0.9822006	-1.1597075	0.20158624
HIAA	-0.76181	-0.7867464	0.2652052	0.01802176	-0.0864655	0.41754176	-0.6757387	0.7296391	0.35159916
2-Aminobutyric acid	3.69911809	1.53470365	3.8272314	1.1634846	3.85624676	3.72298758	3.5880669	3.8794318	0.13798392
Glutamic acid	-1.1707076	-0.1791773	-0.567976	-0.4890275	-0.7756742	-0.7783538	-1.1930937	-0.6337794	0.34943754
3-Methyl-2-oxovaleric acid	-0.8178572	0.52145717	-0.5471512	-0.4270521	-0.7225034	-0.8448916	-0.5583508	-0.7971401	0.21511797
Histamine	-0.1485253	0.11424347	-0.2476388	-0.2142434	-0.4788143	-0.4504302	-0.2246446	-1.1776027	0.0842145
5-Aminolevulinic acid	-0.3988192	0.17638736	-0.3145786	0.3677737	-0.5304872	-0.4828388	-0.4206589	-0.0794666	0.16504154
Tryptophan	0.3354711	-0.1461558	0.4901938	-0.3411589	0.12023631	0.40342001	0.48325591	0.65022249	0.19364873
Pipecolinic acid	-0.8753164	-0.1512818	-0.5885943	-0.1653906	-0.7802655	-0.4485057	-0.9440747	-0.485136	0.34125134
3-hydroxykynurenine	-0.5945549	-0.0599903	-1.4357829	-0.5096303	0.57336747	-0.5983266	-1.2423897	-0.5183379	0.68224786

(*continued on next page*)

Table E6 (*Continued*)

Label	Hypoxia-1	Hypoxia-2	Hypoxia-3	Hypoxia-4	Normoxia-1	Normoxia-2	Normoxia-3	Normoxia-4	*P*-value
2/3-Aminoisobutyric acid/Dimethylglycine	3.4859676	1.49670988	3.84121588	-1.6365723	3.73015171	3.51860199	3.14322091	4.05277834	0.20296417
Nicotinamide	0.02517674	-0.1078659	0.11853892	-0.3291309	-0.1102332	-0.102231	-0.0495663	0.20624927	0.6449802
Myristic acid	-0.5773634	-0.4376603	-1.191743	0.09064003	-0.5995869	-0.5255144	-0.2554543	-0.5350572	0.86107299
Uridine	-1.1643965	-1.8921944	-0.4978597	-1.2263561	-1.0667004	-0.4069956	-1.1894229	-0.7690212	0.35171505
L-(+)-Arabinose	-0.9389194	-0.326999	-1.1590547	-0.1014193	-1.3212851	-1.3546592	-0.793595	-1.3278043	0.09238329
Quinolinic acid	0.06335475	0.15183698	0.00919032	0.11160968	-0.2354491	0.06813628	0.10547494	0.02351364	0.3028964
Aspartate	-1.3576267	0.2298994	-1.0263901	-0.3875949	-0.4684876	-0.8038537	-1.2100624	-0.654517	0.7127799
Stearic acid	-0.3562762	-0.063728	-0.6432848	0.09577362	-0.5215432	-0.8021734	0.06401336	-0.6408929	0.38596366
Phenylalanine	-0.0573723	-0.0617509	-0.0491845	-0.2173615	0.0409615	-0.0722665	0.03281024	-0.0635365	0.16043092
Dulcitol	0.21421179	0.14868816	0.30177712	-1.3024393	0.18559045	0.21321159	0.26241803	0.16275114	0.3767293
Glycine	-0.7383682	-0.211558	-0.6148624	-0.3174122	-0.6123031	-0.7071909	-0.8267039	-0.5144934	0.2149107
L-(-)-Arabitol	0.02145053	0.25091267	-0.1996179	-0.1128398	-0.3687413	-0.2687208	-0.0736568	-0.3668067	0.07415608
Phenylpyruvic acid	-3.0515063	-0.763465	-2.7412021	-0.8246925	-2.4468444	-2.9141586	-2.8669767	-2.4944788	0.22806193
3-Phenyllactic acid	-0.7378812	-0.245645	0.87248304	-0.7910685	0.92546372	0.45774882	-0.8838451	0.76545218	0.37414296
Isovaleric acid	-0.3823668	-0.2336078	-0.9801439	0.06263479	-1.0861459	-1.2917229	-0.4207738	-1.1545595	0.08435989
Malate	-0.0151609	0.10051057	0.62584811	-0.122317	0.21125104	0.47606365	0.25733675	0.50990595	0.2800524
Nonadecanoic acid	-0.3434715	-0.3284635	-1.0788992	0.28960355	-0.490825	-0.2396225	0.09432271	-0.4451829	0.76964843
D-Mannitol	0.49214324	0.24626119	0.36157852	-1.3929167	0.36892853	0.3034528	0.28001726	0.44158672	0.37910365
4-Hydroxyphenylacetic acid/Mandelic acid	-1.6861093	0.26669436	-1.1541376	-0.6521432	-1.6554874	-1.6138903	-1.5100585	-1.8478206	0.09009311
2-Deoxycytidine	-0.8371964	-1.8941494	-2.8962966	1.38511637	-2.4036099	-2.5545625	-0.6259565	-3.1354213	0.33381527
6-Methyl-DL-Tryptophan	-0.7463397	-0.1207241	-0.7518561	0.26006764	-1.0161533	-0.8399768	-0.5930635	-0.7410011	0.13379218
Adonitol	-0.2418653	0.11498105	-0.4539442	-0.4525158	-0.5432157	-0.5326121	-0.2626953	-0.6040653	0.19056514
Oxaloacetic acid	0.84474277	0.72813782	0.84190297	-0.0519829	0.52135826	0.97155094	0.49680606	0.02451609	0.77385953
2-Hydroxyphenylacetic acid/ 3-Hydroxyphenylacetic acid	-1.8252571	0.11865191	-1.2458492	-0.7547266	-1.7851833	-1.7466178	-1.7330754	-1.9312037	0.07969972
Pentadecanoic acid	-1.2248551	-0.7226078	-1.4803334	0.06770799	-0.7112931	-1.4481806	0.25188702	-1.1973005	0.90399075
Metanephrine	-0.0690907	0.47116831	-0.0376173	-0.3581745	-0.1307044	-0.0883418	0.18862742	0.18119005	0.85724729
Ribose	1.50052051	0.47298045	1.27901973	-0.8691085	1.28145647	1.45260053	1.37712255	1.08240619	0.24241366
Caprylic acid	-0.0772244	0.20202844	-0.2089145	0.11396497	-0.8580296	-0.2288137	-0.7195034	-0.0584628	0.06766379
Xylose	1.51088934	0.44987737	1.29751684	-0.8584282	1.29323677	1.45602017	1.37850796	1.08228973	0.24362105
Pyroglutamic acid	-0.3182003	-0.1128841	0.07318498	0.2598395	-0.2762514	0.05997982	-0.2161614	0.16496019	0.80415478
Normetanephrine	-1.5756078	0.13626275	-0.9917419	-0.8341561	-1.0182553	-1.0987574	-1.3924579	-1.0276837	0.41839265
Succinate	-0.4811019	0.12562508	-0.4082239	-0.0378646	-0.4931641	-0.4764612	-0.4274422	-0.4110261	0.13775522
Ethylmalonic acid	-0.535705	-0.6796354	-0.8054726	0.31625991	-0.8799436	-0.4460628	-0.1781857	-0.2925848	0.9405441
Creatinine	-0.1072695	0.06485068	-0.2358385	-0.4544783	-0.1380674	-0.3027073	-0.1564101	-0.0890522	0.92516186
Creatine	0.47774782	0.44713967	0.3105809	0.57494932	0.22559403	0.24086674	0.05890054	0.53145259	0.14450394
Trehalose	-0.2334607	-0.3458024	-1.4112059	-2.2766588	-0.7947193	-0.8826727	-0.2453821	-1.6007102	0.75000844
Methylmalonic acid	-0.4831654	0.12394687	-0.4096865	-0.0389591	-0.4937286	-0.478164	-0.4309098	-0.413153	0.13731677
Lauric acid	-1.0432568	-0.4003263	-0.8672772	-0.2238923	-0.7992694	-0.5793058	-0.7569318	-0.6016761	0.80888787
belta-Hydroxyisovaleric acid	0.32321764	-0.1682122	1.67252025	-1.6048371	2.73117112	1.54795444	0.39546164	1.70847712	0.11241544
Imidazole	0.88892719	-0.3659624	0.07679413	0.28849773	0.15666556	0.57198821	-0.3063157	1.5058602	0.59666599
Heptadecanoic acid	0.39474116	-1.1914353	-0.6149823	-0.3176486	-1.3283594	0.2701543	-0.7214764	0.20267577	0.94256663
Xylitol	0.01080448	0.28053463	0.04563945	-0.3204084	-0.2519605	-0.2176392	0.02226439	-0.1076371	0.34127082
Ornithine	-0.7053886	0.18000525	-0.1997898	0.09474047	-0.0752082	-0.2770914	-0.748254	-0.0424363	0.63673379
Leucic acid	-0.2295989	0.820285	1.06933022	-0.5318694	0.9018227	1.05318869	-0.2464285	0.76554395	0.51730691

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Table E6 (*Continued*)

Label	Hypoxia-1	Hypoxia-2	Hypoxia-3	Hypoxia-4	Normoxia-1	Normoxia-2	Normoxia-3	Normoxia-4	*P*-value
Benzoic acid	-1.5161413	-1.4085937	-0.0255448	0.14481333	0.22162257	0.00749664	-1.6239008	-0.2168404	0.64037554
Phenylacetic acid	-0.1928152	-0.4590375	-0.0012272	0.2765843	-0.1579652	-0.0985582	-0.8022439	0.17946749	0.64488683
Cytidine	-0.6387399	-1.0455679	-0.3647243	-0.7503269	-0.420615	-0.4815804	-0.5783594	0.15388267	0.14070332
Palmitic acid	-0.532438	-0.4674046	-0.8751209	-0.1286439	-0.641371	-0.8232573	-0.6305924	-0.4750163	0.43330731
Acetylcarnitine	0.68387367	0.31465648	0.23439013	-0.1197967	0.37067698	0.36780583	0.46882203	0.1642123	0.72746913
Tyrosine	0.16746471	-0.046614	0.16129232	-0.5233618	-0.0558385	0.10805873	-0.0616528	0.27130696	0.5118422
Cystine	0.43349697	0.41443451	0.0773585	-0.2617239	0.30357387	0.10453174	0.27620223	0.65588926	0.43218813
4-Pyridoxic acid	-2.2149126	0.60172349	-2.2096355	-1.4410542	-2.3105301	-2.366773	-2.5272217	-2.0017957	0.19374817
4-Hydroxybenzaldehyde	-3.5996367	-0.9455904	-2.9188392	-1.2824208	-3.2683587	-2.8176189	-3.038208	-3.4738856	0.19134747
Glycocyamine	0.18174242	0.02174585	0.20175067	-0.482129	0.11289409	0.00314024	0.26216675	-0.0347607	0.56543745
pregnenolone sulfate	-0.5218222	-0.0792184	-0.5854167	0.06640992	-0.3051484	1.05460002	-0.481144	-0.7729861	0.73635166
13C5-15N-Glutamic acid	0.08277972	-0.1243656	-0.0808884	-0.0192343	0.17753724	-0.1546932	-0.1024778	0.02808068	0.80367154
Picolinic acid	0.01215189	0.16925794	0.13754471	-0.2892169	0.1150842	0.14862846	0.12154212	0.22955994	0.22364392
Lysine	0.05679805	0.07921408	0.10185465	-0.2374453	0.3194568	0.0128671	-0.0086754	0.19571493	0.28912134
3-Methyladipic acid	-0.7630941	-0.2215062	-0.7148891	-0.0895383	-0.4735883	-1.0021561	-0.5959582	-0.6083051	0.32078303
Betaine	-0.3808348	-0.1319643	-0.2659125	-0.3770088	-0.4448277	-0.1087414	-0.2949697	-0.2127376	0.80620409
2-Pyrrolidinone	-0.2190347	-0.1153878	-0.5338772	-0.2680294	-0.5323416	-0.5791357	-0.0584727	-0.310169	0.58479294
alpha-KG	-0.3652957	-0.1786159	-0.32029	0.20421245	-0.6444336	-0.5178101	-0.338443	-0.2493007	0.13300984
Carnosine	-0.0699488	0.29739426	-0.1273737	-0.4140822	0.27838674	0.0134998	-0.1066015	0.02287733	0.4643938
Arginine	0.32512336	0.21126739	0.14875975	-0.3300058	0.35877912	0.11650083	0.17166118	0.43874876	0.30576017
Citrulline	0.87984808	0.78393735	0.31045417	-0.4362508	0.19059974	0.47416426	0.67666252	-0.6110194	0.64199844
Fructose/Galactose	3.40960288	1.29449584	3.47542259	-1.4784355	3.59108425	3.51391124	3.35371353	3.56000154	0.1683481
N-Acetylmuramic Acid	-2.2514621	0.24963676	-3.1930817	-0.3418124	-2.6845468	-3.3429091	-2.2887866	-3.1822354	0.12647834
D-(+)-Cellobiose	0.99618652	-1.1676573	-1.1067692	0.06749017	-0.9997616	-0.864151	0.81445648	-1.7214803	0.61966713
Lactose	1.04472999	-1.1678386	-1.0776297	0.01730991	-0.8721192	-0.9768415	0.65553769	-1.770486	0.56304879
Erythrose	0.09690499	0.50230745	0.27991519	-0.229254	-0.0298834	0.14376453	0.39809653	0.2590128	0.87140674
malonic acid	-0.9705395	-0.4387	-2.9099437	-0.4999217	-3.0483824	-3.0236972	-1.1687587	-2.8012158	0.12600541
Levulinic acid	-0.7152773	0.39797499	-3.7767528	-0.3194873	-4.6706938	-4.4882428	-0.8136858	-4.9990174	0.0975578
Urocanic acid	-0.4748155	-0.8212572	-0.4485712	-2.8982264	-0.2435936	-0.4407773	-0.6597613	0.26059801	0.19963105
4-Imidazoleacetic acid	-0.3348381	0.33558326	-0.1574624	0.26151042	0.02071175	0.00487928	-0.342746	-0.015743	0.57348707
Carnitine	-0.6235938	-0.1436276	-0.4373712	-0.6153123	-0.3233859	-0.6301862	-0.7401828	-0.355754	0.7187753
2HG	-0.0200087	0.01326397	0.44989405	-0.161683	0.46510149	0.28231762	0.05300144	0.41517008	0.19713709
Cytosine	-0.9591877	-1.2268134	-1.2101742	-0.6877136	-0.7471613	-0.6000961	-1.0085117	-0.2021445	0.12043094
Histidine	-0.0798178	0.40466708	-0.6957078	-0.7078621	-0.1763087	-1.2236524	-5.9963249	-2.0110006	0.16025266
R5P	0.34283779	0.2964006	1.07437843	-0.2424858	0.90983686	0.96537117	0.1057327	0.64232532	0.42191255
Glyceric acid	-0.8187331	-0.6861564	-0.6377363	-0.0915493	-0.8304395	-0.5271091	-0.6262635	-0.8652965	0.42505469
2-hydroxybutyric acid/Malonic acid	0.52451094	0.45747902	-0.8987707	-0.6828683	-0.6179829	-1.0165926	0.18617721	-1.0955323	0.34509498
Pantothenic acid	-0.0710321	0.5975017	-0.0398278	-0.2155784	0.18290529	0.04366369	0.26509269	0.19923465	0.59412623
6-Hydroxynicotinic acid	-0.048533	-0.3330571	0.05495437	-1.5321452	0.17739187	0.04360882	-0.1864967	0.49488889	0.17847513
Proline	0.7556949	0.41456495	1.45390621	-0.7938494	1.37939637	1.25058387	0.5612598	1.45084485	0.21907681
D-Xylonic Acid (Lithium Salt)	-0.2058889	-0.1002017	-0.164797	-0.5686456	-0.0648752	-0.1932274	-0.3766275	0.57769995	0.33157802
N-Acetyl-D-galactosamine	-1.7823689	-0.1737066	-1.6912335	-1.1151918	-1.7306591	-1.4944716	-1.515446	-1.1928947	0.47685323
2-Methylglutaric acid	-0.4816449	-0.314975	-0.4925261	-0.1094251	-0.8387554	-0.8417914	-0.4199245	-0.3711953	0.13831385
4-Hydroxy-3-methylbenzoic acid	-2.2285394	0.22287583	-1.693169	-0.6578803	-1.762927	-1.7289186	-1.1026177	-2.0392535	0.36445838
2-Hydroxybenzoic acid	-0.8351354	-0.1208894	0.08170104	0.57402993	0.0996304	0.30244906	0.01097878	0.00089756	0.57420786

(*continued on next page*)

Table E6 (*Continued*)

Label	Hypoxia-1	Hypoxia-2	Hypoxia-3	Hypoxia-4	Normoxia-1	Normoxia-2	Normoxia-3	Normoxia-4	*P*-value
Acetyl-L-glutamine	-0.7577037	1.03750768	-0.0365121	-1.0089686	0.04775628	-0.1391645	-0.8058392	0.19755396	0.97520566
Capric acid	-0.3004565	-0.1530748	-0.2855565	0.28720268	-0.6025511	-0.0553752	-1.0992756	-0.0075751	0.30383456
Adenosyl-L-homocysteine	-1.6021125	0.19482448	-0.3923763	-3.0265677	-0.9857647	-1.1882158	-2.2598673	-2.5549028	0.53006208
N-Acetylneuraminic acid	-0.2286805	0.15345367	-0.1293958	-0.3229765	-0.3406899	-0.0647636	-0.3448388	-0.1610701	0.4687919

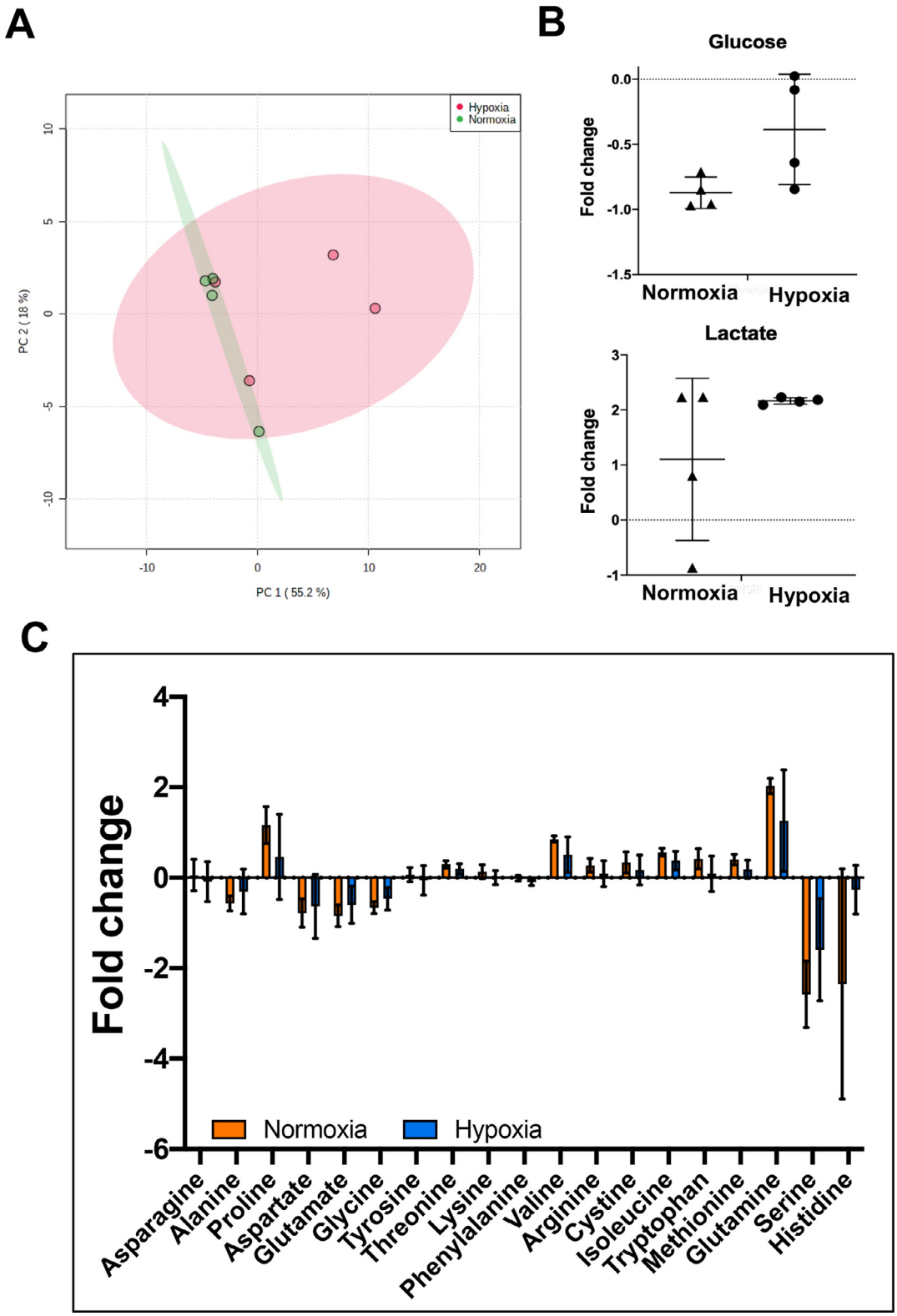


Figure E4. Hypoxia does not affect metabolic profile of MS-5 cells. (A) Principal component analysis of samples on the basis of fold change in metabolites in spent medium relative to fresh medium from MS5 cell cultures incubated in hypoxia or normoxia. (B) Fold change in glucose and lactate in spent medium relative to fresh medium from MS5 cell cultures incubated in normoxia or hypoxia. (C). Fold change in amino acids in spent medium relative to fresh medium from MS5 cell cultures incubated in normoxia or hypoxia. Spent medium was collected on day 4 of culture. Statistical analysis was performed in MetaboAnalyst.

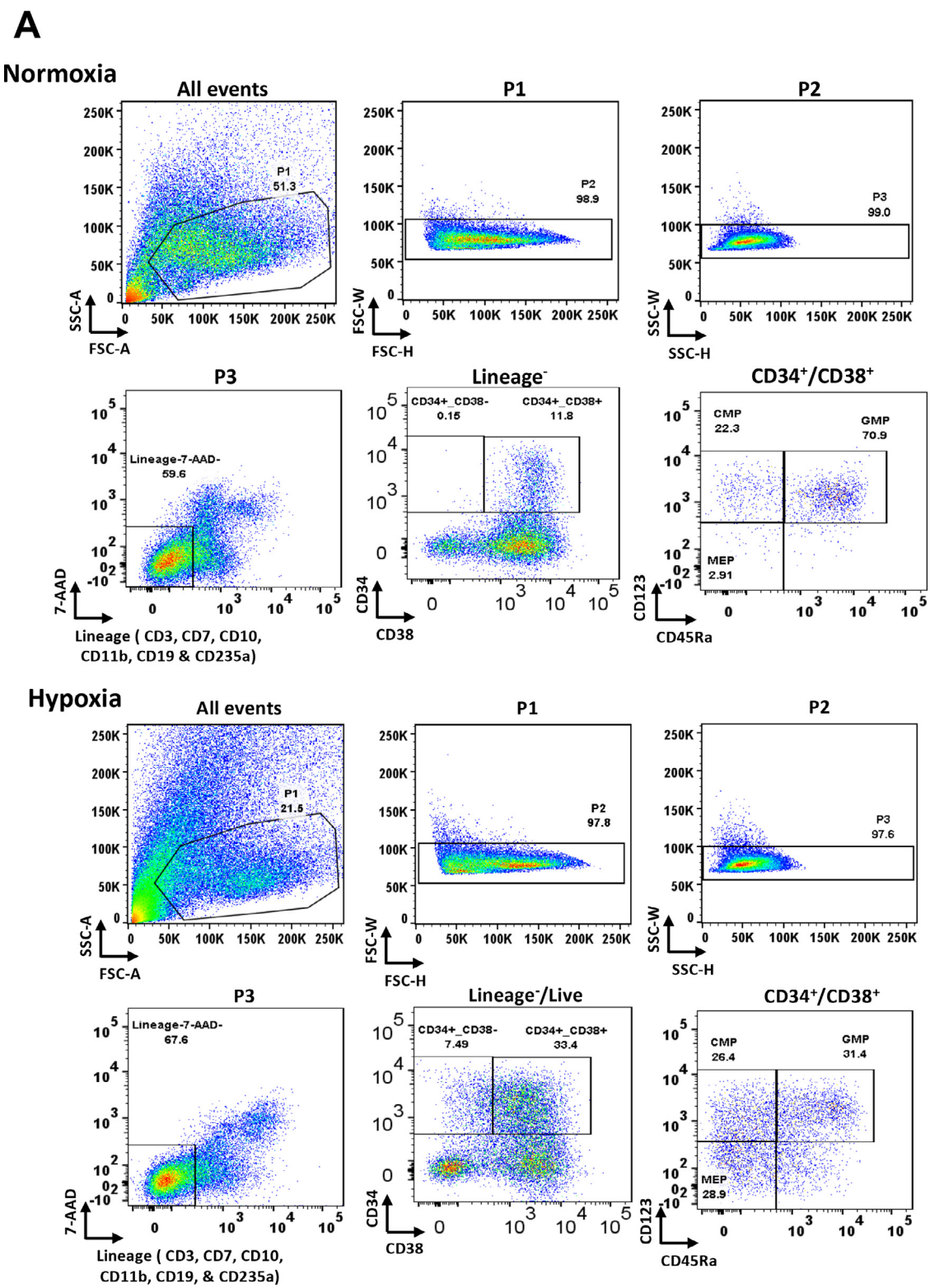


Figure E5. Hypoxia promotes development of common myeloid progenitors and megakaryo-erythroid progenitors. (A) Representative scatter plots showing the gating strategy for immunophenotyping of the progenitor cells in cultures incubated in normoxia or hypoxia. Plots for flow cytometry performed on day 21 are shown. MPP, multipotent progenitor ($CD34^+/CD38^+$); CMP, common myeloid progenitor ($CD45Ra^-/CD123^+$); GMP, granulocyte-monocyte progenitor ($CD45Ra^+/CD123^+$); MEP, megakaryo-erythroid progenitor ($CD45Ra^-/CD123^-$). (B) Fold change in the percentage of progenitor cells calculated relative to day 1 is shown.

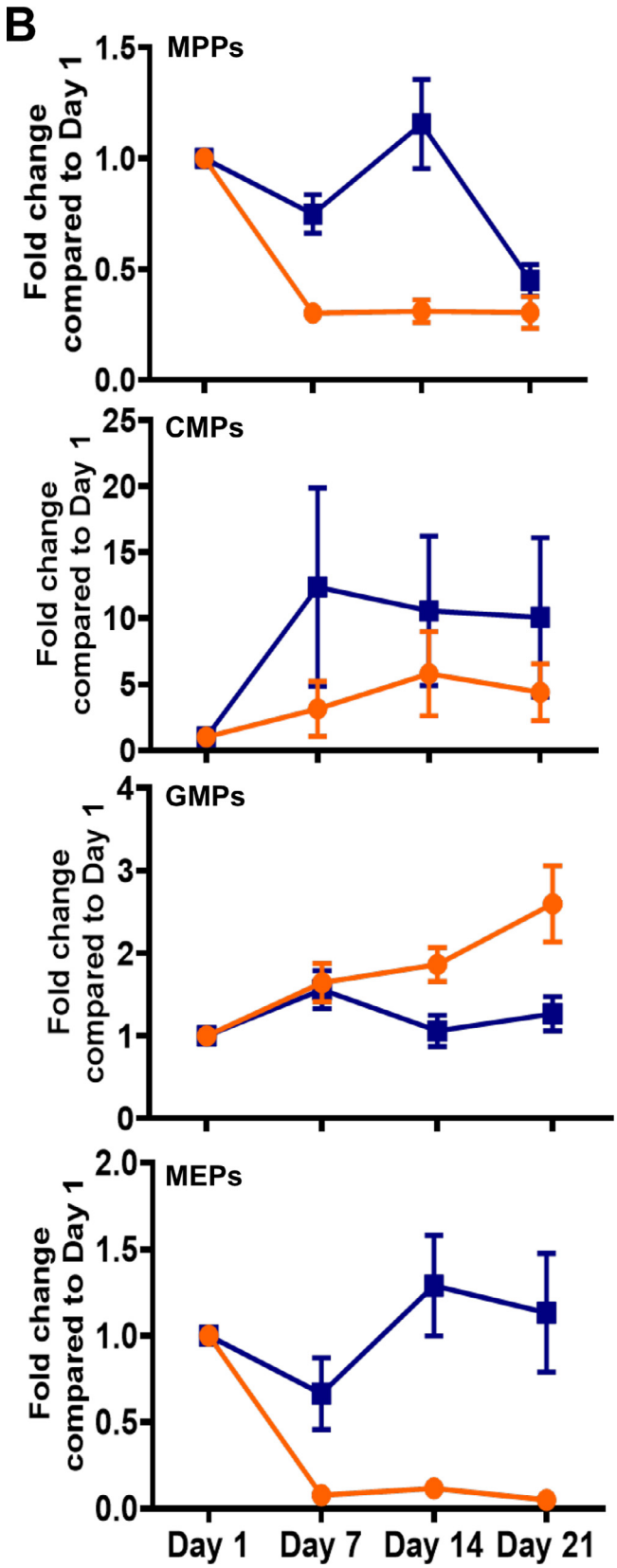


Figure E5. Continued.

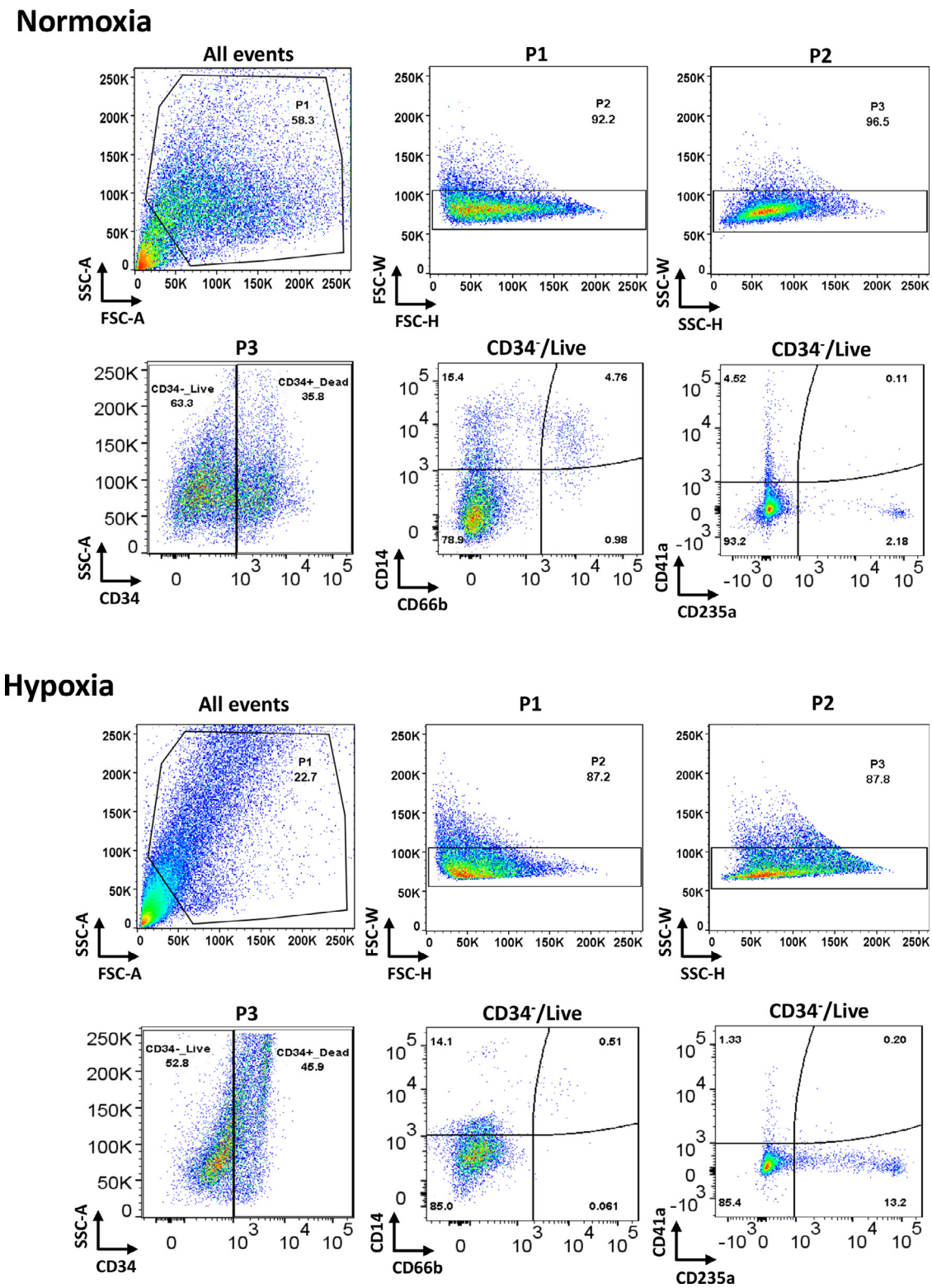


Figure E6. Hypoxia promotes erythroid differentiation of CD34$^+$ cells. Representative scatter plots showing the gating strategy for immunophenotyping of the lineage cells in cultures incubated in normoxia or hypoxia. Plots for flow cytometry analysis performed on day 21 are shown. Lineage cells were monocytes (CD14$^+$/CD66b$^-$), granulocytes (CD14$^-$/CD66b$^+$), megakaryocytes (CD41a$^+$/CD235a$^-$), and erythroid (CD41a$^-$/CD235a$^+$).

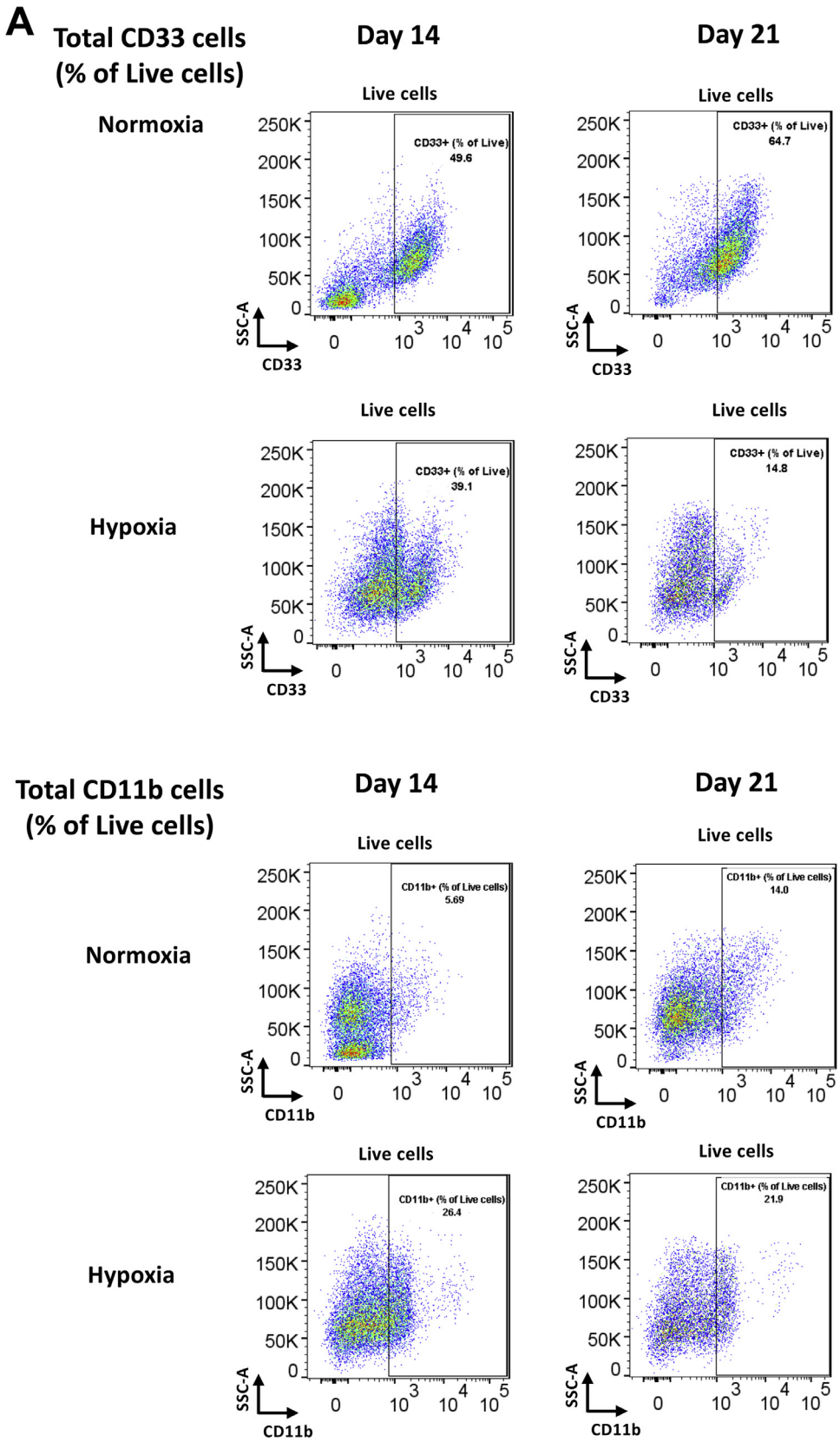


Figure E7. Hypoxia enhances expression of myeloid markers during myelo-erythroid differentiation of CD34$^+$ cells. (A) Representative scatter plots for immunophenotyping for CD33 and CD11b in cultures incubated in normoxia or hypoxia. (B) Quadrant plots for CD34/CD33 and CD34/CD11b expression in the live cell population in normoxia and hypoxia on days 14 and 21 are shown.

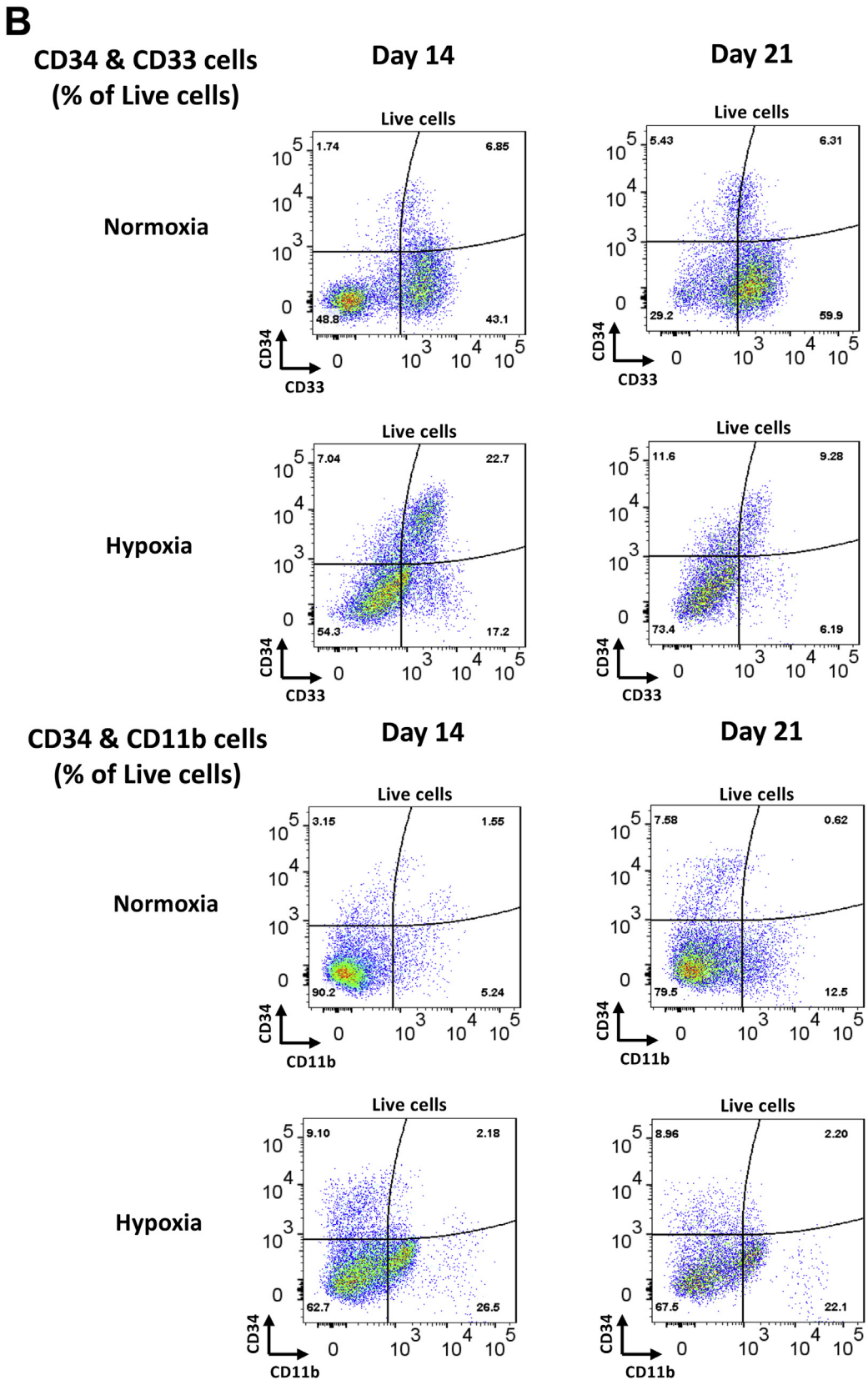


Figure E7. Continued.

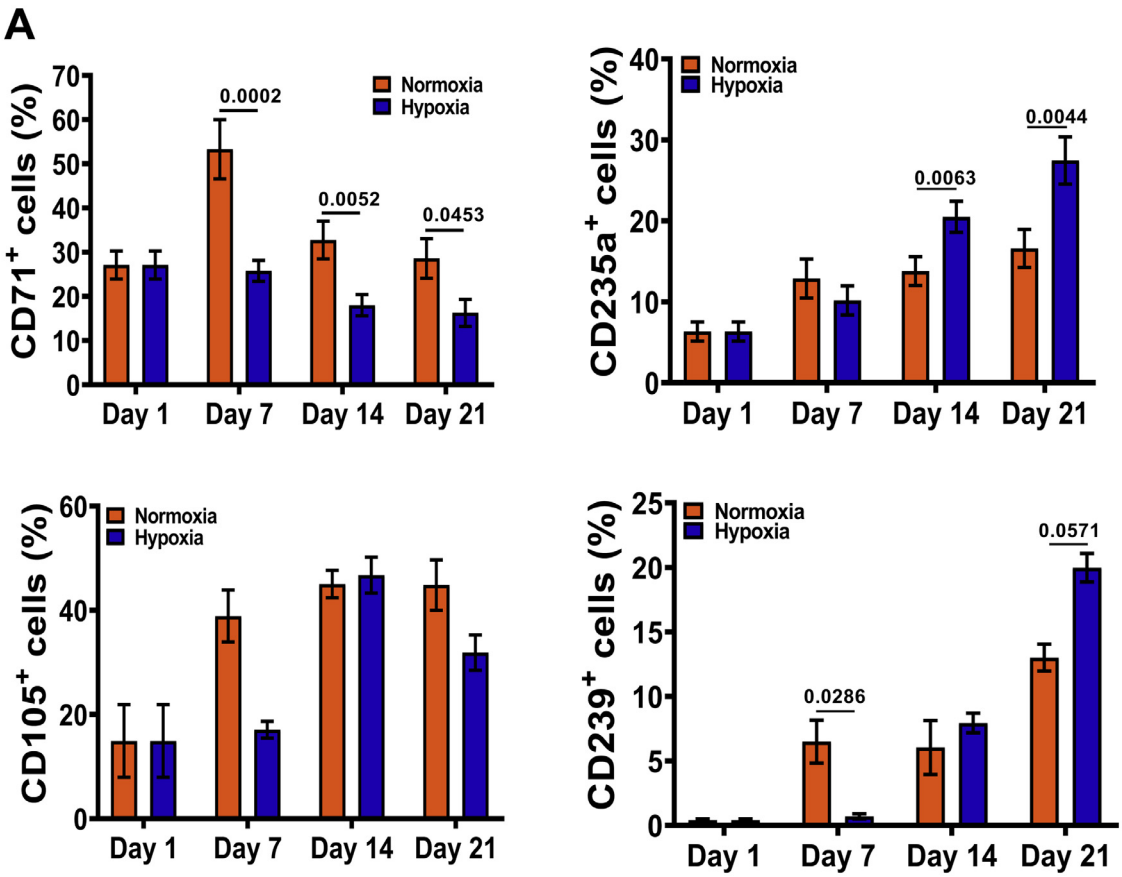


Figure E8. Hypoxia enhances expression of late erythroid markers. (A) Percentages of $CD71^+$, $CD105^+$, $CD235a^+$, and $CD239^+$ cells in the $CD34^-$/Live population for cultures incubated in normoxia or hypoxia. Data are represented as mean with standard error (n = 4). Statistical analysis was performed using the Mann-Whitney test, and p-values ≤0.05 were considered significant (* = $p < 0.05$, ** = $p < 0.005$, *** = $p < 0.0005$). (B) Representative scatter plots for immunophenotyping for $CD71^+$ and $CD105^+$ cells in cultures incubated in normoxia or hypoxia. (C) Representative scatter plots for immunophenotyping for $C235a^+$ and $CD239^+$ cells in cultures incubated in normoxia or hypoxia. Plots for immunophenotyping performed on days 1, 7, 14, and 21 are shown.

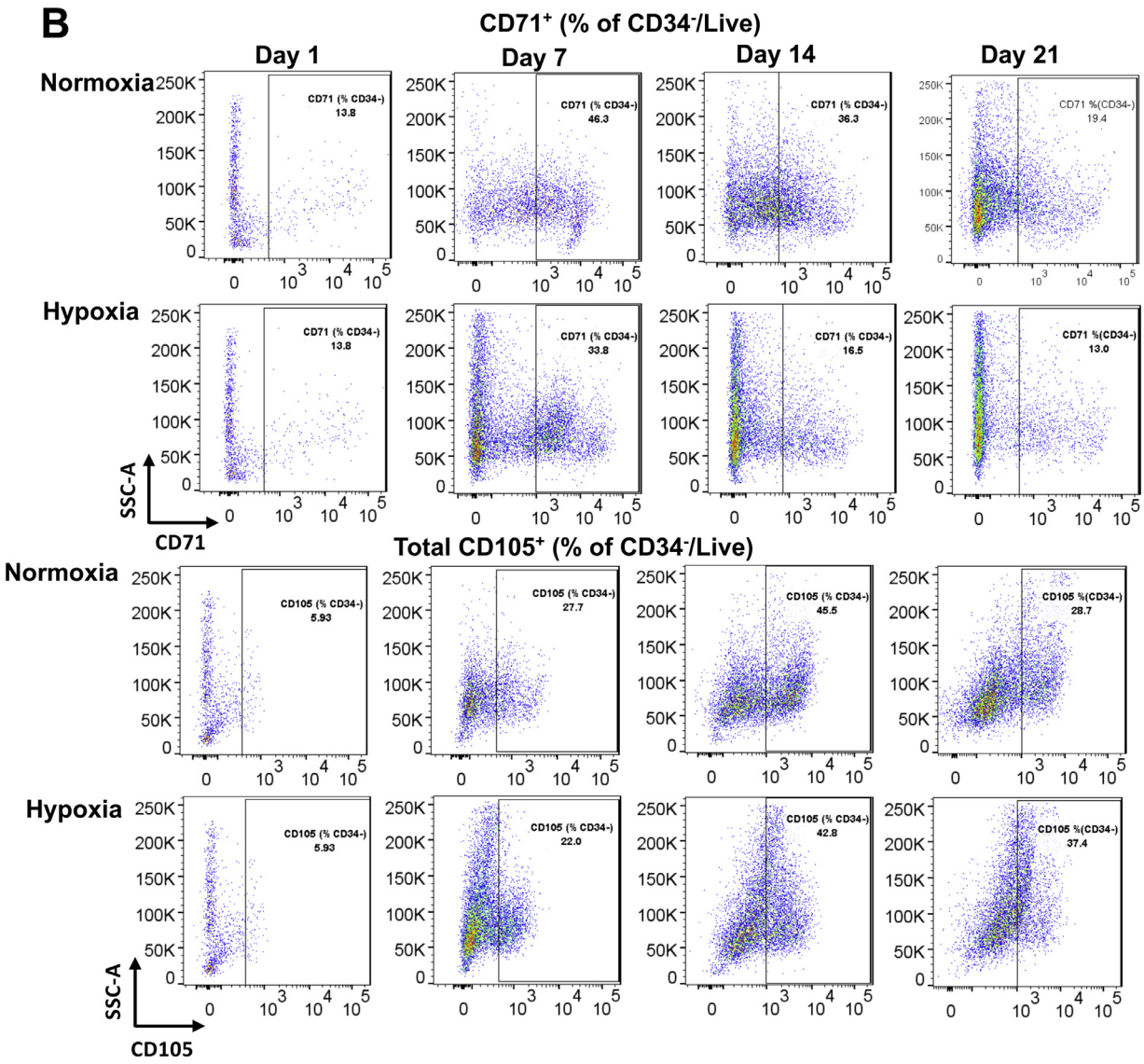


Figure E8. Continued.

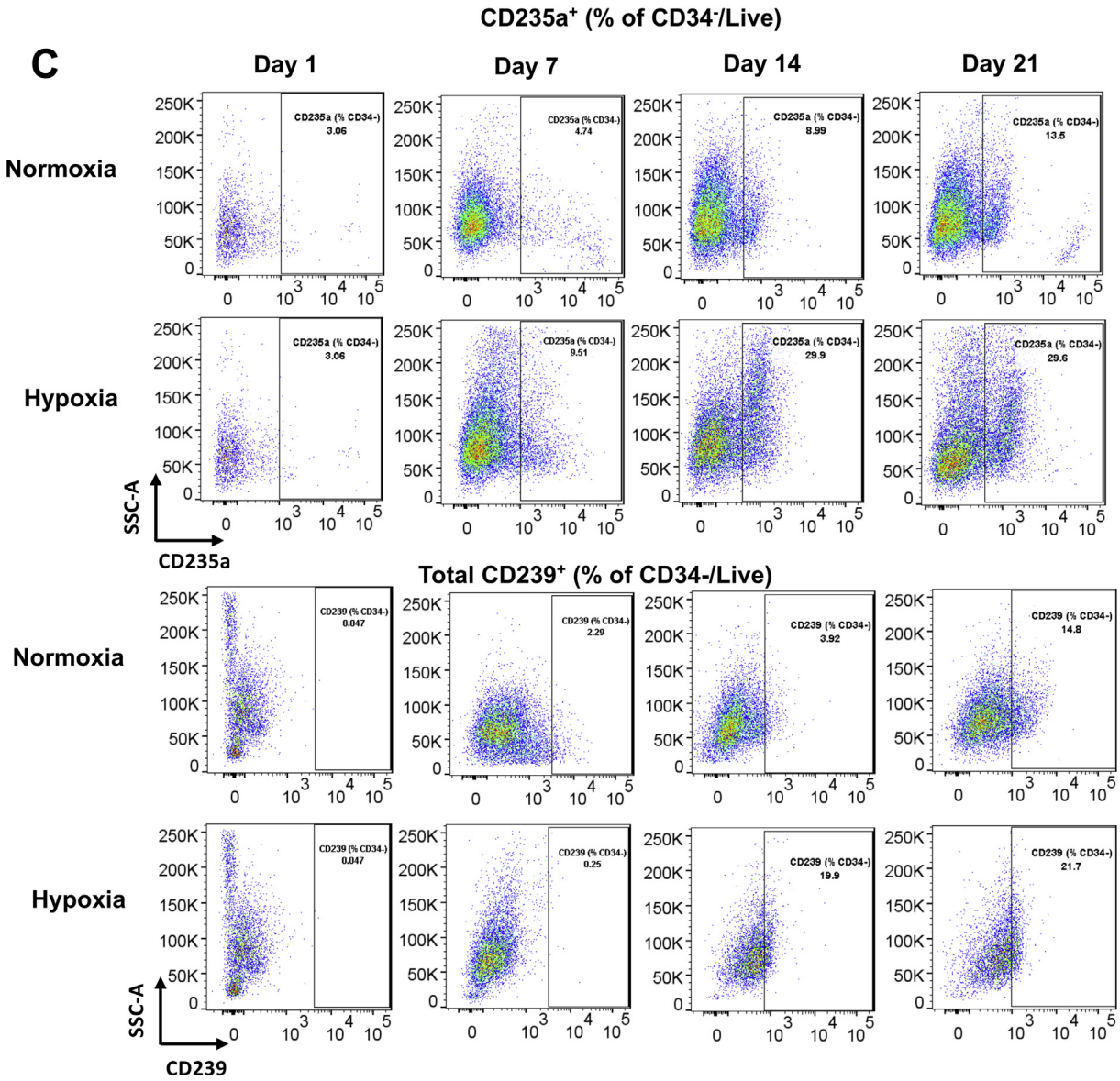
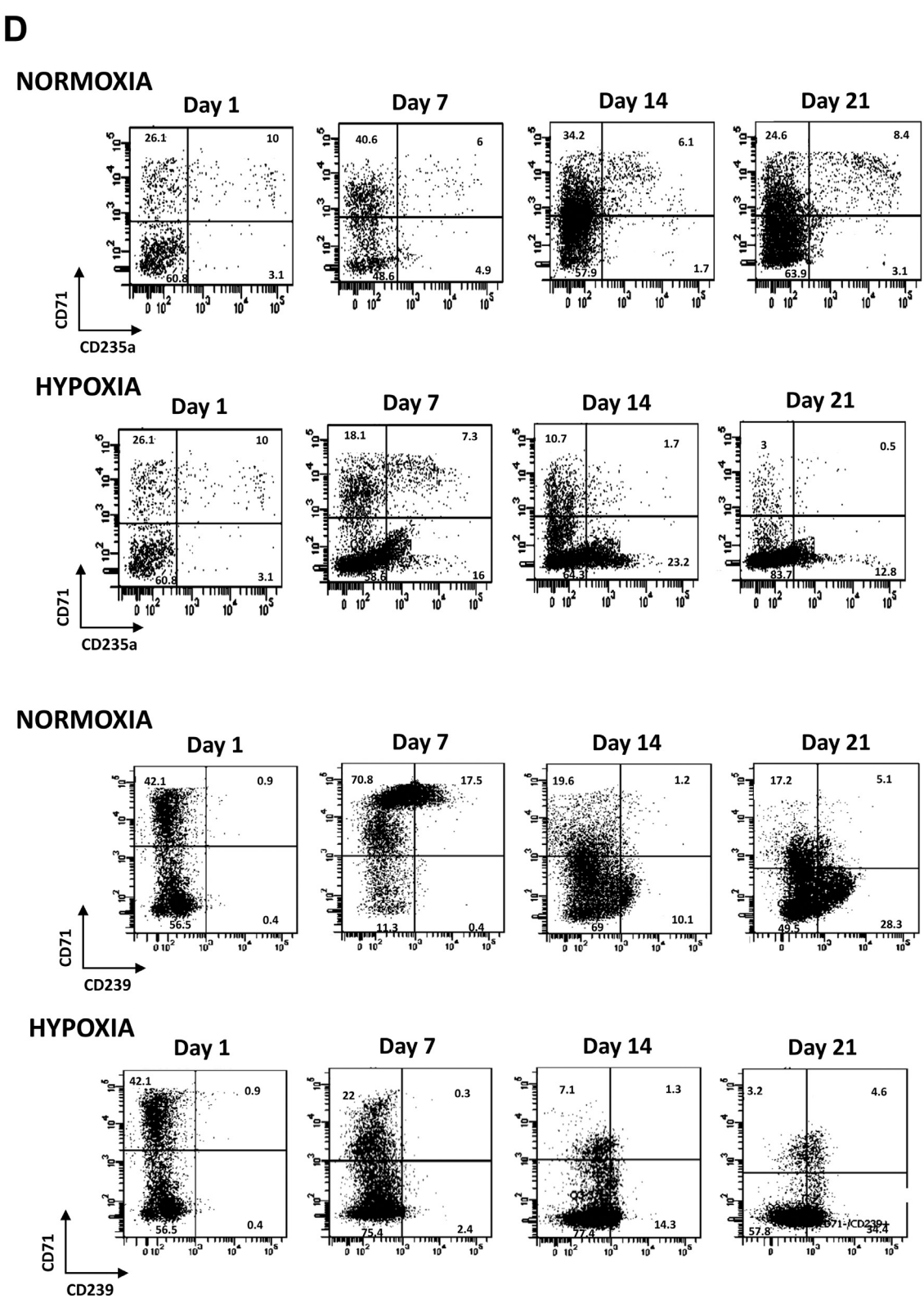


Figure E8. Continued.



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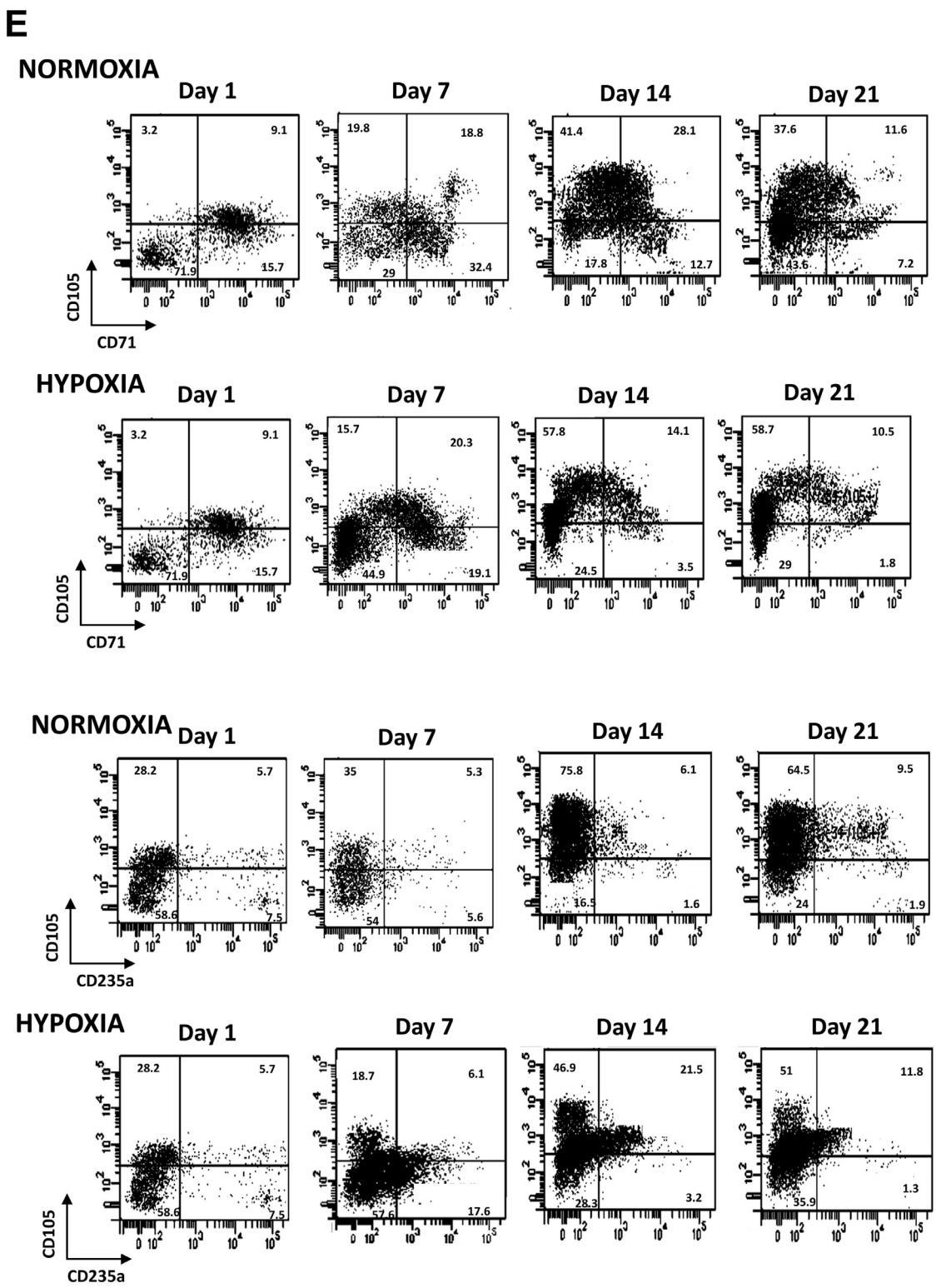

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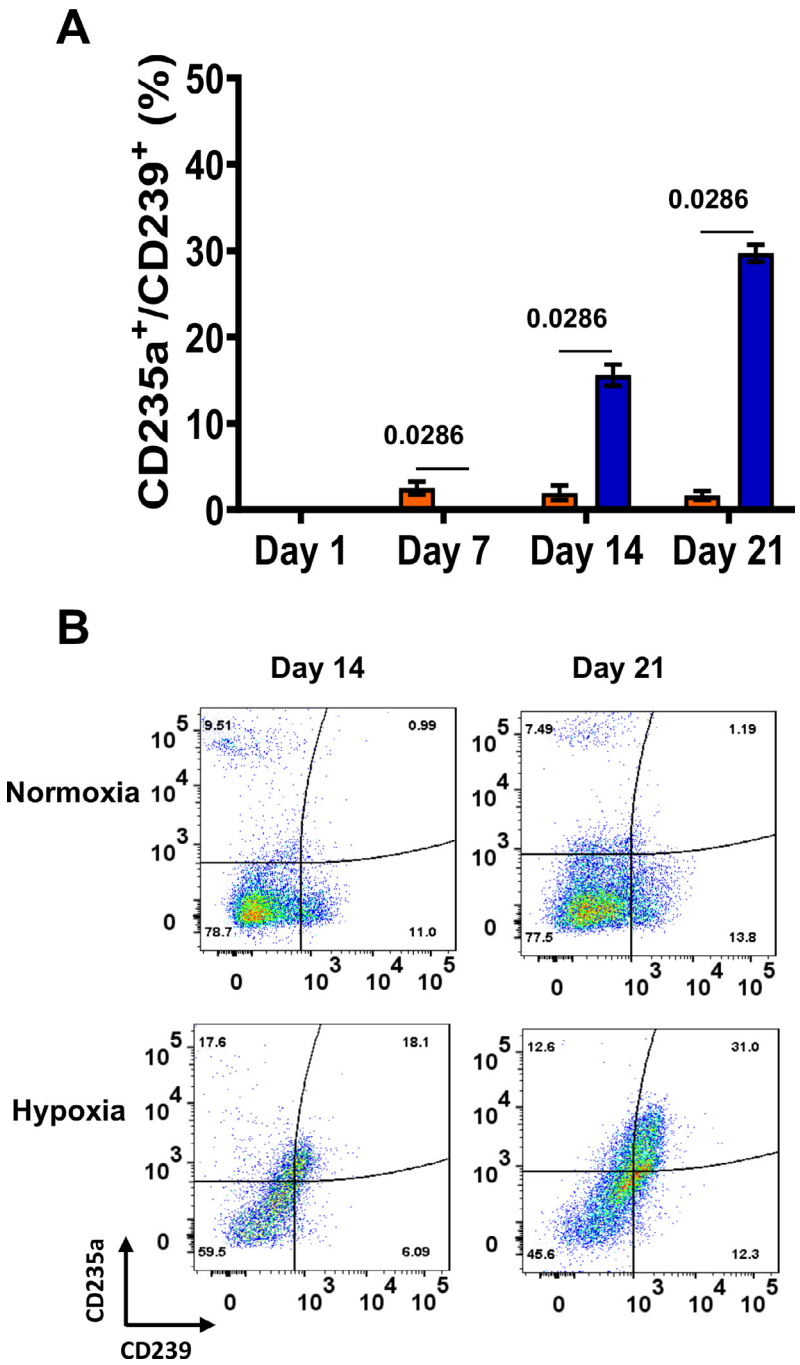

Figure E9. Hypoxia promotes late erythroid markers. Percentage of double positive ($CD235a^+/CD239^+$) cells is higher in hypoxia than in normoxia. The percentage of positive cells in the Lin^-/Live population is shown. Data are represented as mean with standard error (n = 4). Statistical analysis was performed using the Mann-Whitney test, and p-values ≤0.05 were considered significant (* = $p < 0.05$, ** = $p < 0.005$, *** = $p < 0.0005$).

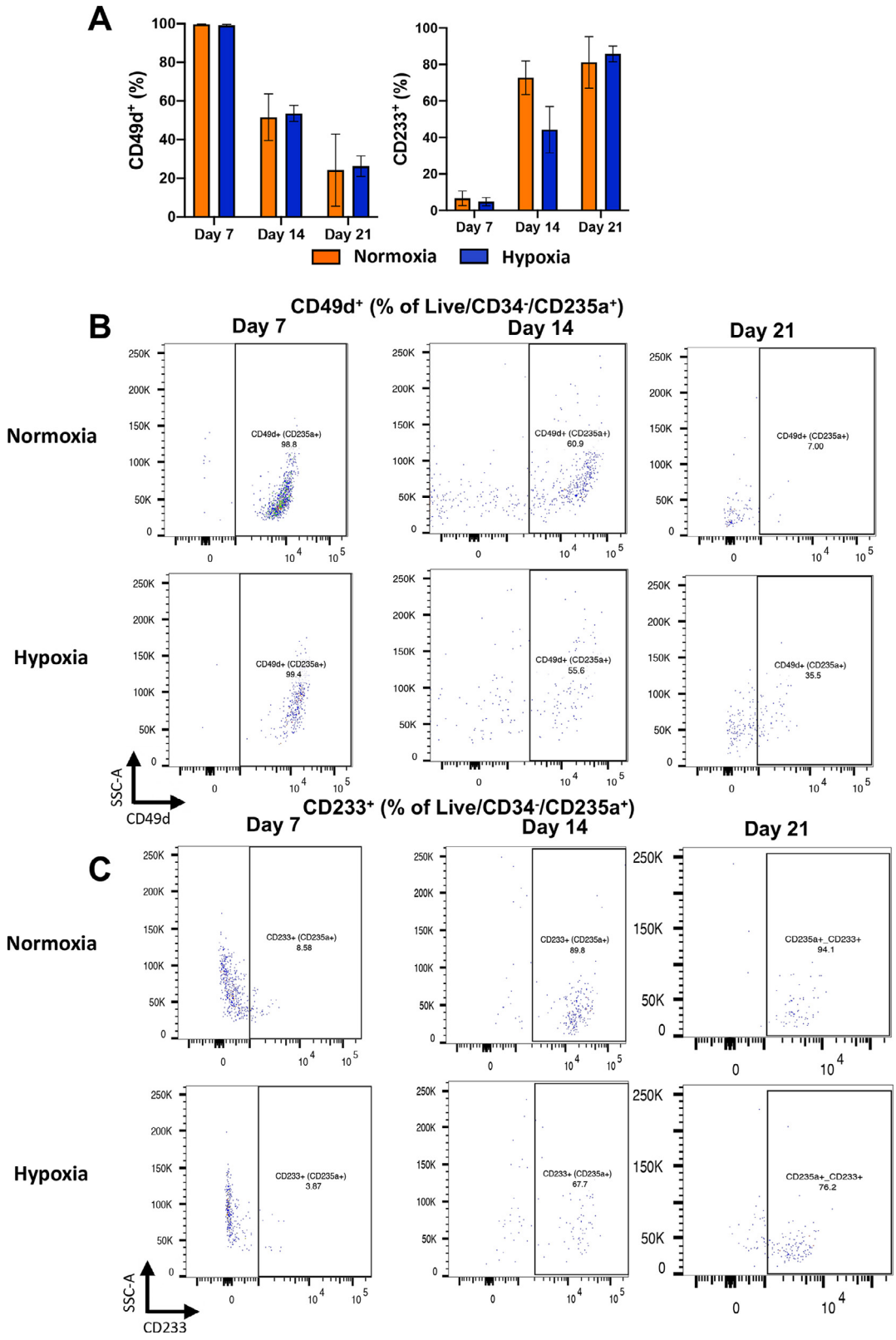

Figure E10. Erythroblast markers are expressed at similar rates in hypoxia and normoxia. (A) Percentage of $CD49d^+$ and $CD233^+$ cells within the $CD235a^+$ cells are shown. Data are represented as mean with standard error (n = 4). (B) Representative scatter plots for immunophenotyping of CD49d within the $CD235a^+$ population in cultures incubated in normoxia or hypoxia. (C) Resepresentative scatter plots for immunophenotyping of CD233 within the $CD235a^+$ population in cultures incubated in normoxia and hypoxia. (D) Representative scatter plots for immunophenotyping for $CD49d^-/CD233^-$, $CD49d^+/CD233^-$, $CD49d^+/CD233^+$, and $CD49d^+/CD233^-$ cells within the $CD235a^+$ population in cultures incubated in normoxia or hypoxia. Plots for immunophenotyping performed on days 7, 14, and 21 are shown.

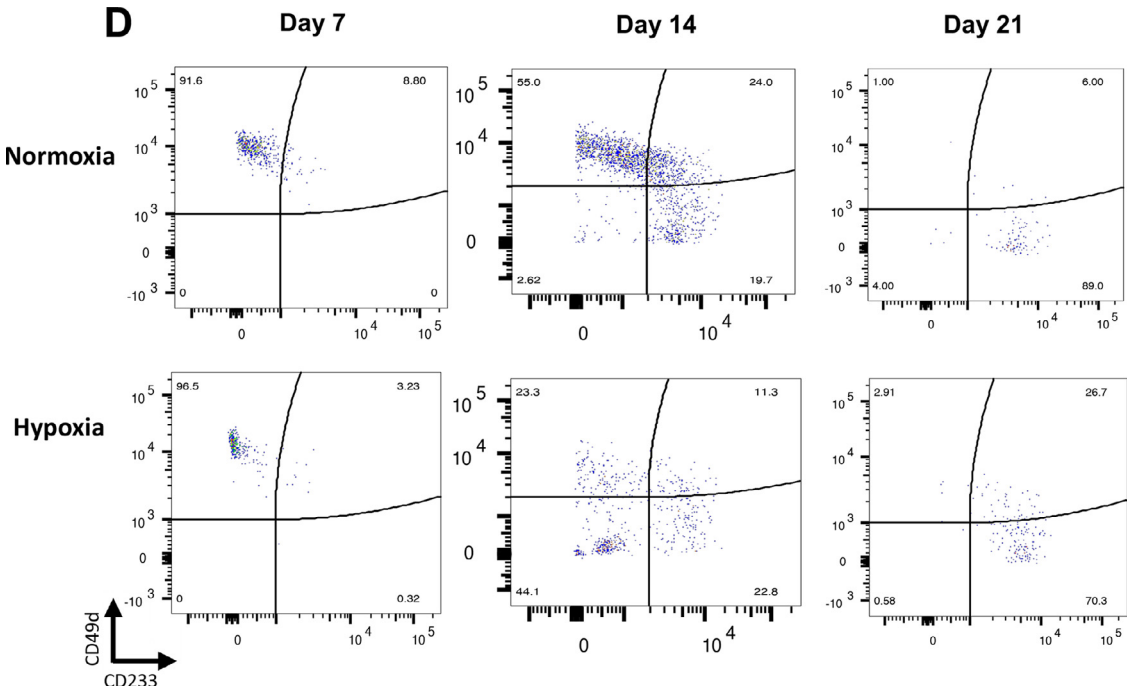

Figure E10. Continued.