Supplemental Information

Hydrogen sulfide is a regulator of hemoglobin oxygen carrying capacity via controlling 2,3-BPG production in erythrocytes

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Table S1. Metabolites identified by LC/MS/MS in erythrocytes of CSE knockout mice and wild type mice using positive ion model

No.	Metabolites	Adduct	VIP	m/z	RT(s)	FC(CSE/WT)	*P* value	ESI
1	Xanthine	(M+H)+	3.0	153.0399	409.594	2.718496	2.39E-06	+
2	L-Citrulline	(M+H)+	3.4	176.1026	745.693	2.264544	1.58E-06	+
3	Xanthosine	(M+H)+	1.2	285.0827	603.345	3.253237	1.51E-05	+
4	1-Methylhistamine	(M+H)+	1.4	126.1016	618.601	2.658647	6.48E-06	+
5	N-Acetylneuraminic acid	(M+H)+	2.0	310.1132	735.083	2.054706	3.71E-06	+
6	Taurine	(M+H)+	3.0	126.0211	560.389	0.555819	0.00022	+
7	Hypoxanthine	(M+H)+	9.4	137.0452	315.406	1.409968	8.43E-05	+
8	Uridine	(M+H)+	2.7	245.0764	302.893	2.338957	3.06E-05	+
9	UDP-N-acetylglucosamine	$(M+NH_4)+$	1.2	625.1144	846.869	1.989755	2.14E-05	+
10	Uridine 5'-diphosphate	(M+H)+	1.7	405.0093	870.047	1.514867	2.89E-05	+
11	Pyridoxamine	$(M+H-H_2O)+$	1.5	151.0858	57.912	2.914985	0.000914	+
12	UDP-D-Galactose	$(M+NH_4)+$	3.0	584.0889	869.062	1.548528	0.000115	+
13	Arachidonic Acid	(M+Na)+	2.3	327.2317	89.501	1.385576	0.007258	+
14	Nicotinamide	(M+H)+	6.8	123.0546	125.843	1.315883	0.00638	+
15	Oxindole	(M+H)+	2.8	134.0593	56.473	2.723085	0.002996	+
16	D-Mannose 6-phosphate	(M+H)+	2.4	261.0368	887.3445	1.944749	0.0012	+
17	Uracil	(M+H)+	2.2	113.0335	158.6135	2.356268	0.001586	+
18	20-Hydroxyarachidonic acid	$(M+CH_3CN+H)+$	2.2	362.269	88.879	1.528554	0.00637	+
19	2-Pyrrolidineacetic acid	(M+H)+	1.4	130.0855	125.519	1.651085	0.017246	+
20	L-Lysine	(M+H)+	1.9	147.112	985.372	1.370958	0.002068	+
21	Beta-D-Fructose 2-phosphate	$(M+NH_4)+$	1.2	278.0632	885.99	1.882894	0.002325	+
22	Nicotinamide ribotide	M+	1.7	335.0638	889.761	1.399347	0.001656	+
23	Adenosine	(M+H)+	1.0	268.1038	319.473	1.700916	0.002282	+
24	2-oleoyl-sn-glycero-3-phosphocholine	(M+Na)+	2.3	810.5999	169.423	2.846154	0.005393	+
25	1-Stearoyl-sn-glycerol	(M+H)+	5.7	359.3155	67.246	0.540699	0.005148	+
26	PC(16:0/16:0)	(M+H)+	3.1	734.5688	206.993	2.071174	0.005347	+
27	1-Stearoyl-rac-glycerol	$(M+H-H_2O)+$	3.0	341.305	67.249	0.523568	0.0055	+
28	Phosphorylcholine	(M+H)+	1.7	184.073	902.51	1.455359	0.00823	+
29	Glycerol 1-myristate	(M+H)+	1.2	303.2528	69.002	0.62677	0.006083	+
30	Creatinine	(M+H)+	3.0	114.0653	316.017	1.331764	0.009251	+
31	L-Gulonic gamma-lactone	$(M+NH_4)+$	2.5	196.0811	242.631	0.458522	0.000504	+
32	D-Mannose	$(M+NH_4)+$	1.8	198.0969	571.963	0.380237	0.014442	+
33	Indole-3-lactic acid	$(M+H-H_2O)+$	1.4	188.0703	480.236	1.377094	0.008023	+
34	L-Glutamate	(M+H)+	2.6	148.0598	770.018	1.267898	0.008789	+

35	Cytosine	(M+H)+	1.0	112.0493	453.808	1.529537	0.015906	+
36	GDP-glucose	(M+H)+	1.7	606.0842	921.896	1.342224	0.011911	+
37	Allopurinol riboside	(2M+H)+	4.9	537.1681	411.961	1.470336	0.023725	+
38	S-Lactoylglutathione	(M+H)+	1.8	380.1122	761.714	3.88661	0.008716	+
39	Cellobiose	$(M+NH_4)+$	1.2	360.1497	753.445	1.545841	0.020222	+
40	L-Pyroglutamic acid	(M+H)+	1.5	130.0491	770.078	1.217886	0.01304	+
41	Betaine	(M+H)+	11.6	118.0856	514.84	0.303261	0.012237	+
42	Adenosine monophosphate	(M+H)+	2.8	348.0704	830.974	1.303344	0.045364	+
43	Glutathione disulfide	(M+H)+	4.8	613.1595	962.884	1.110997	0.048303	+
44	Cytidine	(M+H)+	1.0	244.0924	453.8275	1.399592	0.047718	+
45	L-Tryptophan	(M+H)+	1.3	205.0967	480.2455	1.437256	0.027627	+
46	D-Erythrose 4-phosphate	(M+H)+	1.0	201.0155	765.015	1.27206	0.033801	+
47	1-Palmitoylglycerol	$(M+H-H_2O)+$	4.0	313.2738	67.931	0.627025	0.011437	+
48	Nicotinamide adenine dinucleotide	(M+H)+	3.8	664.1158	844.401	1.270499	0.040986	+
49	Diethanolamine	$(M+H-H_2O)+$	3.5	88.07484	411.7195	0.387521	0.024573	+
50	Choline	M+	13.9	104.1065	426.088	1.83864	0.04973	+
51	1,2-dioleoyl-sn-glycero-3-phosphatidylcholine	(M+H)+	4.7	786.599	100.102	0.523646	0.024671	+

VIP, variable importance in the projection. RT, retention time. FC, Fold change. LC, liquid chromatography. ESI, electrospray ionization. MS, mass spectroscopy

Table S2. Metabolites identified by LC/MS/MS in erythrocytes of CSE knockout mice and wild type mice using negative ion model

No.	Metabolites	Adduct	VIP	m/z	RT(s)	FC(CSE/WT)	*P* value	ESI
1	Xanthine	(M-H)-	2.5	151.0272	410.595	4.168839449	8.86E-07	-
2	L-Citrulline	(M-H)-	2.3	174.0897	736.273	2.735780032	8.7E-07	-
3	UDP-N-acetylglucosamine	(M-H)-	2.0	606.076	823.417	2.165541407	2.19E-06	-
4	N-Acetylneuraminic acid	(M-H)-	1.3	308.0998	710.515	1.939334432	1.25E-06	-
5	Xanthosine	(M-H)-	1.1	283.0694	585.034	3.079430453	1.6E-05	-
6	Cholesteryl sulfate	(M-H)-	3.0	465.3049	48.776	0.403468005	7.8E-06	-
7	Phenylacetylglycine	(M-H)-	1.6	192.0676	358.4425	4.6266632	2.41E-05	-
8	Uridine diphosphate glucose	(M-H)-	3.0	565.0493	845.314	1.705024489	1.94E-05	-
9	Uridine	(M+CH_3COO)-	1.2	303.0847	298.248	2.609409881	1.72E-05	-
10	Hypoxanthine	(M-H)-	5.6	135.0322	312.661	1.61698252	2.33E-05	-
11	L-Arginine	(M-H)-	1.6	173.1057	975.815	2.653089595	2.4E-05	-
12	D-Ribose 5-phosphate	(M+CH_3COO)-	1.3	289.0345	878.92	1.93541291	8.97E-05	-
13	L-Lactic acid	(M-H)-	10.0	89.02504	438.061	1.502669985	5.3E-05	-
14	Uracil	(M-H)-	2.8	111.0206	159.055	2.796231544	0.000359	-
15	Fructose 6-phosphate	(M-H)-	4.0	259.0243	864.402	2.302727634	0.00075	-
16	m-Chlorohippuric acid	M-	6.3	213.0187	174.534	0.382090299	0.001312	-
17	D-Aspartic acid	(M-H)-	1.2	132.0311	764.461	2.102392928	0.001059	-
18	D-Fructose 2,6-bisphosphate	(M-H)-	5.7	338.9903	961.626	1.504976204	0.002999	-
19	Adenosine 5'-diphosphate	(M-H)-	2.0	426.0233	877.154	1.320433635	0.002115	-
20	Dodecanoic acid	(M-H)-	2.5	199.1712	86.5085	0.575542205	0.002665	-
21	Indoxyl sulfate	(M-H)-	6.2	212.0035	52.68	3.158198063	0.002956	-
22	L-Tryptophan	(M-H)-	1.2	203.0841	474.488	1.9736578	0.002739	-
23	L-Glutamate	(M-H)-	3.0	146.0468	751.23	1.558090472	0.002993	-
24	Guanosine diphosphate mannose	(M-H)-	1.3	604.0715	898.404	1.35303503	0.004699	-
25	Inosine	(M-H)-	6.8	267.075	405.399	1.402563722	0.00985	-
26	1-Stearoyl-sn-glycerol	(M-H)-	1.1	357.3019	65.7745	0.533632788	0.003328	-
27	Nicotinamide adenine dinucleotide	(M-H)-	2.9	662.1036	827.11	1.478558322	0.004327	-
28	myo-Inositol	(M-H)-	1.2	179.0574	747.753	1.397204543	0.003849	-
29	9-OxoODE	(M-H)-	1.5	293.213	87.253	2.086004736	0.007043	-
30	L-Malic acid	(M-H)-	1.2	133.0152	769.968	1.333857648	0.007789	-
31	Phosphoenolpyruvate	(M-H)-	1.2	166.9762	960.352	1.230767031	0.01152	-
32	Allantoin	(M-H)-	2.8	157.0382	337.161	1.350291169	0.012133	-
33	D-Ribulose 1,5-bisphosphate	(M+CH_3COO)-	1.1	369.0007	968.302	1.377690792	0.022483	-
34	2,3-bisphosphoglycerate	(M-H)-	5.6	264.9538	960.331	1.208877467	0.015664	-
35	L-Arabinono-1,4-lactone	(M+CH_3COO)-	1.6	207.0523	116.5005	0.440045923	0.005526	-
36	L-Ascorbic acid	(M+Na-2H)-	1.1	197.0079	229.591	1.716003145	0.014859	-
37	Adenosine monophosphate	(M-H)-	1.8	346.0575	810.835	1.37334	0.023654	-
38	16-Hydroxy hexadecanoic acid	(M-H)-	1.0	271.2287	124.4	0.572348353	0.000753	-
39	Glutathione disulfide	(M-H)-	6.1	611.1464	949.058	1.289559755	0.016896	-
40	12,13-EpOME	(M-H)-	2.1	295.2287	113.9925	1.706026527	0.02629	-
41	L-Arabinose	(M-H)-	4.3	149.0464	196.981	0.48149178	0.010563	-
42	Alpha-D-Glucose	(M-H)-	5.4	179.0577	574.8085	0.60964915	0.003381	-
43	Myristic acid	(M-H)-	3.7	227.2026	84.996	0.586378089	0.005415	-
44	3-Hydroxybutyric acid	(M-H)-	1.4	103.0408	453.532	0.394865515	0.020681	-
45	Palmitoleic acid	(M-H)-	6.7	253.2186	82.816	0.616121698	0.004102	-
46	Myristoleic acid	(M-H)-	1.6	225.1875	84.574	0.547681144	0.010531	-

47	D-Lyxose	$(M-H_2O-H)^-$	4.7	131.0359	196.444	0.497185381	0.025904	-

VIP, variable importance in the projection. RT, retention time. FC, Fold change. LC, liquid chromatography. ESI, electrospray ionization. MS, mass spectroscopy.

Table S3. The enriched metabolic pathways in CSE knockout mice compared with WT mice

Pathways	Total	Hits	*P* value	-log(P)	FDR	Impact
Fructose and mannose metabolism	21	6	0.000518	7.5664	0.042437	0.30437
Amino sugar and nucleotide sugar metabolism	37	7	0.002507	5.9888	0.10278	0.18595
Ascorbate and aldarate metabolism	9	3	0.009502	4.6563	0.20432	0
Galactose metabolism	26	5	0.009967	4.6085	0.20432	0.00677
Purine metabolism	68	8	0.023701	3.7422	0.34885	0.14521
Nicotinate and nicotinamide metabolism	13	3	0.027757	3.5843	0.34885	0.44643
Pyruvate metabolism	23	4	0.02978	3.5139	0.34885	0.09
Linoleic acid metabolism	6	2	0.036101	3.3214	0.37004	0
Glycolysis or Gluconeogenesis	26	4	0.044607	3.1099	0.40642	0.11167
Glutathione metabolism	26	3	0.15505	1.864	1	0.10686
Pyrimidine metabolism	41	4	0.16772	1.7854	1	0.13441
Histidine metabolism	15	2	0.18637	1.68	1	0.10753
Lysine biosynthesis	4	1	0.19568	1.6313	1	0
Pentose and glucuronate interconversions	16	2	0.20606	1.5796	1	0.2
Glycerophospholipid metabolism	30	3	0.20918	1.5645	1	0.20648
Synthesis and degradation of ketone bodies	5	1	0.23837	1.4339	1	0
Biotin metabolism	5	1	0.23837	1.4339	1	0
D-Glutamine and D-glutamate metabolism	5	1	0.23837	1.4339	1	1
Pentose phosphate pathway	19	2	0.26616	1.3237	1	0.24174
Starch and sucrose metabolism	19	2	0.26616	1.3237	1	0.30462
Citrate cycle (TCA cycle)	20	2	0.28629	1.2507	1	0.0452
Arachidonic acid metabolism	36	3	0.29643	1.2159	1	0.32601
Butanoate metabolism	22	2	0.32637	1.1197	1	0
Lysine degradation	23	2	0.34622	1.0607	1	0
Taurine and hypotaurine metabolism	8	1	0.35348	1.0399	1	0.42857
Alanine, aspartate and glutamate metabolism	24	2	0.36588	1.0055	1	0.25949
alpha-Linolenic acid metabolism	9	1	0.3879	0.94702	1	0
Nitrogen metabolism	9	1	0.3879	0.94702	1	0
Vitamin B6 metabolism	9	1	0.3879	0.94702	1	0.07843
Arginine and proline metabolism	44	3	0.41511	0.87921	1	0.20617
Phenylalanine metabolism	11	1	0.45139	0.79542	1	0
Glycine, serine and threonine metabolism	31	2	0.49582	0.70155	1	0
Aminoacyl-tRNA biosynthesis	69	4	0.50278	0.68761	1	0
Pantothenate and CoA biosynthesis	15	1	0.55952	0.58068	1	0
beta-Alanine metabolism	17	1	0.6054	0.50187	1	0
Glyoxylate and dicarboxylate metabolism	18	1	0.62654	0.46754	1	0
Fatty acid biosynthesis	43	2	0.67615	0.39133	1	0
Porphyrin and chlorophyll metabolism	27	1	0.77289	0.25762	1	0
Inositol phosphate metabolism	28	1	0.78514	0.24189	1	0.11163
N-Glycan biosynthesis	36	1	0.86234	0.1481	1	0
Tryptophan metabolism	40	1	0.88993	0.11662	1	0.17715
Biosynthesis of unsaturated fatty acids	42	1	0.90159	0.10359	1	0
Primary bile acid biosynthesis	46	1	0.92139	0.081871	1	0.02976
Steroid hormone biosynthesis	72	1	0.98204	0.018119	1	0

The enriched metabolic pathways were analyzed using MetaboAnalyst 4.0 based on differentiated metabolites in erythrocytes of CSE mice compared with WT mice. FDR, false discovery rate.

Table S4. Identification of the proteins interacted with BPGM by LC/MS/MS

ProteinID	Accession	-10lgP	Coverage (%)	#Peptides	#Unique	Avg. Mass	Description
1	sp|P49222|EPB42_MOUSE	347.82	69	57	13	76756	Erythrocyte membrane protein band 4.2
11	Q3UV95|Q3UV95_MOUSE	326.03	52	45	1	74867	Erythrocyte membrane protein band 4.2
7	E9Q397|E9Q397_MOUSE	310.55	27	52	45	246259	Spectrin beta chain erythrocytic
12	sp|P08032|SPTA1_MOUSE	273.11	15	38	37	279863	Spectrin alpha chain erythrocytic 1
13	G5E8J2|G5E8J2_MOUSE	260.81	19	32	26	202518	Ankyrin 1 erythroid
16	E9QNT8|E9QNT8_MOUSE	260.81	19	32	26	204196	Ankyrin-1
15	sp|Q02357|ANK1_MOUSE	260.81	19	32	26	204226	Ankyrin-1
17	G8JL84|G8JL84_MOUSE	260.81	19	32	26	204258	Ankyrin-1
18	D3YTV8|D3YTV8_MOUSE	260.81	19	32	26	205851	Ankyrin-1
19	D3Z5M4|D3Z5M4_MOUSE	260.81	19	32	26	206910	Ankyrin-1

Table S5. Identification of sulfhydration of proteins by LC/MS/MS

Protein ID	Accession	-10lgP	Coverage (%)	#Peptides	#Unique	Avg. Mass	Description
32593	sp|P02088|HBB1_MOUSE	289.24	82	49	2	15840	Hemoglobin subunit beta-1
32605	sp|P01942|HBA_MOUSE	271.96	62	37	35	15085	Hemoglobin subunit alpha
32741	sp|P06467|HBAZ_MOUSE	100.76	6	3	3	16235	Hemoglobin subunit zeta
32742	A7M7S6|A7M7S6_MOUSE	100.76	6	3	3	17990	Hemoglobin subunit zeta (Fragment)
32599	sp|P02089|HBB2_MOUSE	241.84	71	28	2	15878	Hemoglobin subunit beta-2
32596	sp|Q3TTY5|K22E_MOUSE	216.15	17	18	12	70923	Keratin type II cytoskeletal 2 epidermal
32594	A2A513|A2A513_MOUSE	186.89	26	16	12	57041	Keratin type I cytoskeletal 10
32595	sp|P02535|K1C10_MOUSE	186.89	26	16	12	57770	Keratin type I cytoskeletal 10

Table S6. LC-MS/MS fragmentations of mouse Hb

Ion	Sequence	Theoretical mass	Observed mass	Charge	Additional mass	Modification
b17	LRVDPVNFKLLSHC(α-C104)LLV	1948.1200	990.51	2	32.9	SSH
b19	LRVDPVNFKLLSHC(α-C104)LLVTL	2162.2518	1097.57	2	32,8882	SSH
b20	LRVDPVNFKLLSHC(α-C104)LLVTLA	2233.2889	1133.09	2	32.8911	SSH
b21	LRVDPVNFKLLSHC(α-C104)LLVTLAS	2320.3209	1176.61	2	32.8911	SSH
b22	LRVDPVNFKLLSHC(α-C104)LLVTLASH	2457.3798	1245.13	2	32.8802	SSH
b23	LRVDPVNFKLLSHC(α-C104)LLVTLASHH	2594.4387	1313.67	2	32.9013	SSH
b25	LRVDPVNFKLLSHC(α-C104)LLVTLASHHPA	2762.5286	1397.71	2	32.8914	SSH
b26	LRVDPVNFKLLSHC(α-C104)LLVTLASHHPAD	2877.5556	1455.22	2	32.8844	SSH
b27	LRVDPVNFKLLSHC(α-C104)LLVTLASHHPADF	3024.6240	1528.76	2	32.896	SSH
b28	LRVDPVNFKLLSHC(α-C104)LLVTLASHHPADFT	3125.6716	1579.28	2	32.8884	SSH
b30	LRVDPVNFKLLSHC(α-C104)LLVTLASHHPADFTPA	3293.7615	1663.32	2	32.8785	SSH
b31	LRVDPVNFKLLSHC(α-C104)LLVTLASHHPADFTPAV	3392.8299	1712.86	2	32.8901	SSH
b32	LRVDPVNFKLLSHC(α-C104)LLVTLASHHPADFTPAV H	3529.8888	1781.39	2	32.8912	SSH
b33	LRVDPVNFKLLSHC(α-C104)LLVTLASHHPADFTPAV HA	3600.9259	1816.90	2	32.8741	SSH
y28	LLSHC(α-C104)LLVTLASHHPADFTPAVHASLDK	2993.5665	1513.28	2	32.9935	SSH

Table S7. LC-MS/MS fragmentations of human Hb

Ion	Sequence	Theoretical mass	Observed mass	Charge	Additional mass	Modification
b5	LLSHC(α-C104)	554.68	294.12	2	33.56	SSH
b6	LLSHC(α-C104)L	667.84	699.33	1	31.49	SSH
b7	LLSHC(α-C104)LL	781.00	812.43	1	31.43	SSH
b8	LLSHC(α-C104)LLV	880.13	911.55	1	31.42	SSH
b9	LLSHC(α-C104)LLVT	981.24	1012.55	1	31.31	SSH
b10	LLSHC(α-C104)LLVTL	1094.40	563.29	2	32.18	SSH
b11	LLSHC(α-C104)LLVTLA	1165.47	1196.66	2	31.19	SSH
b12	LLSHC(α-C104)LLVTLAA	1236.55	1267.74	1	31.19	SSH
b13	LLSHC(α-C104)LLVTLAAH	1373.69	702.87	2	32.05	SSH
b14	LLSHC(α-C104)LLVTLAAHL	1486.85	759.42	2	31.99	SSH
b15	LLSHC(α-C104)LLVTLAAHLP	1583.97	807.94	2	31.91	SSH
b16	LLSHC(α-C104)LLVTLAAHLPA	1655.03	843.46	2	31.89	SSH
b17	LLSHC(α-C104)LLVTLAAHLPAE	1784.16	907.98	2	31.8	SSH
b18	LLSHC(α-C104)LLVTLAAHLPAEF	1931.34	981.53	2	31.72	SSH
b19	LLSHC(α-C104)LLVTLAAHLPAEFT	2032.45	1031.57	2	30.69	SSH
b20	LLSHC(α-C104)LLVTLAAHLPAEFTP	2129.56	1080.57	2	31.58	SSH

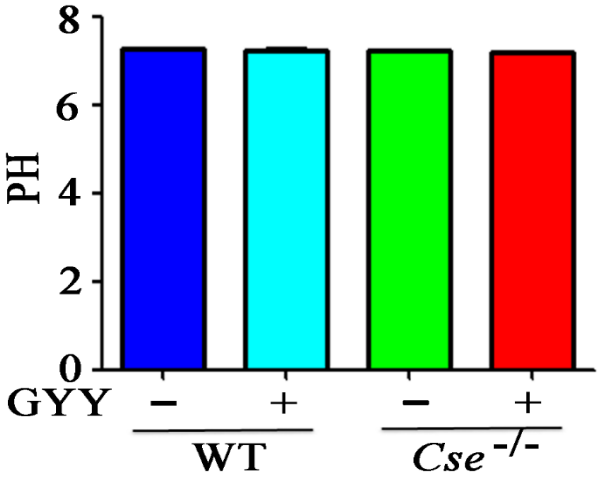

Fig. S1. H_2S treatment has no significant effect on erythrocyte intracellular pH of wild type (WT) and CSE *Cse*$^{-/-}$ mice. WT and C*se*$^{-/-}$ mice were administered with saline or GYY4137 (50 mg/kg). Twenty-four hours later, 100 μl samples of isolated erythrocytes from WT and C*se*$^{-/-}$ mice were lysed in deionized water, then the pH of these diluted cellular lysates was measured. Data are expressed as mean ± SEM (n=10).

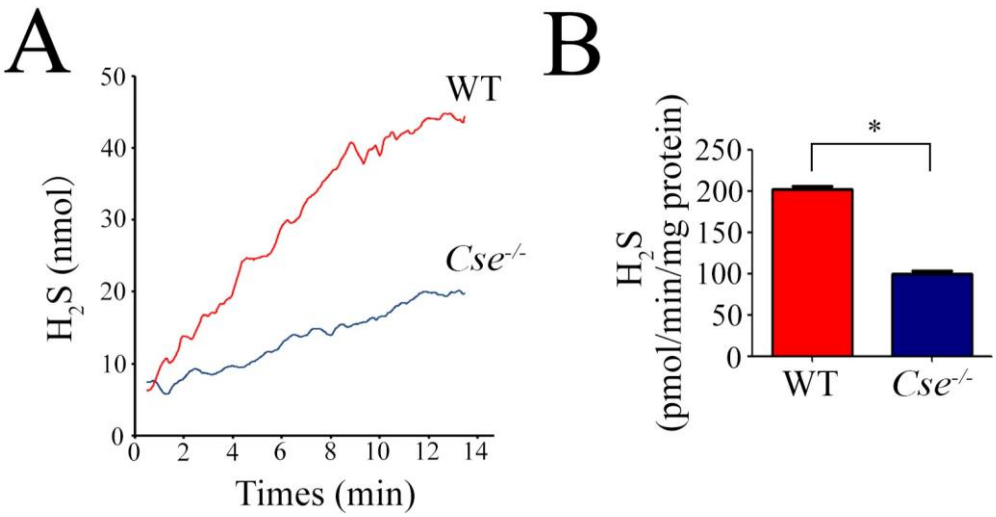

Fig.S2. Erythrocyte H_2S generation in *Cse*$^{-/-}$ mice. A, Representative traces of H_2S production in the homogenate of erythrocytes from WT and C*se*$^{-/-}$ mice. B, cumulative histogram of H_2S generation rates in WT and C*se*$^{-/-}$mice. Data are expressed as mean ± SEM (n=3) * $p<0.05$, vs WT.

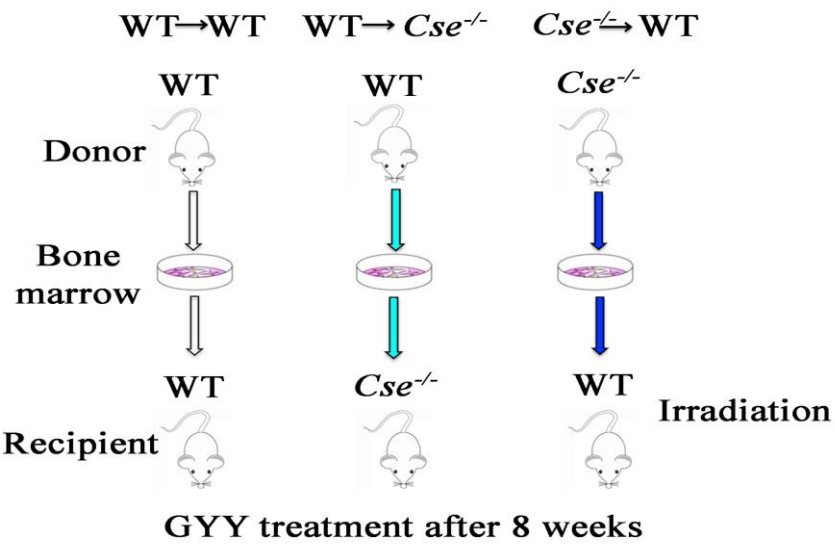

Fig.S3. Protocol of bone marrow transplanted mice. Reciprocal bone marrow transplantation (BMT) was performed between WT and C*se*$^{-/-}$ mice. Eight weeks after BMT GYY 4137 was administrated in ‘WT-*Cse*$^{-/-}$’ mice.

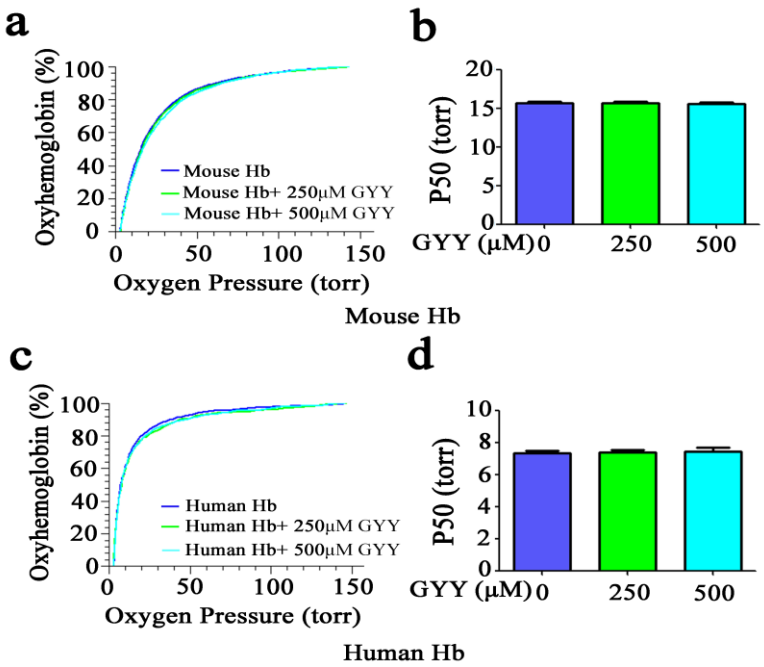

Fig.S4. H_2S treatment has no significant effect on P50 levels of mouse and human Hb. Purified human or mouse Hb was treated with the indicated doses of GYY4137 for 30min, and then were used for determination of oxygen dissociation curve (a&c) and P50 (c&d), respectively. Data are expressed as mean ± SEM (n=3 per group).

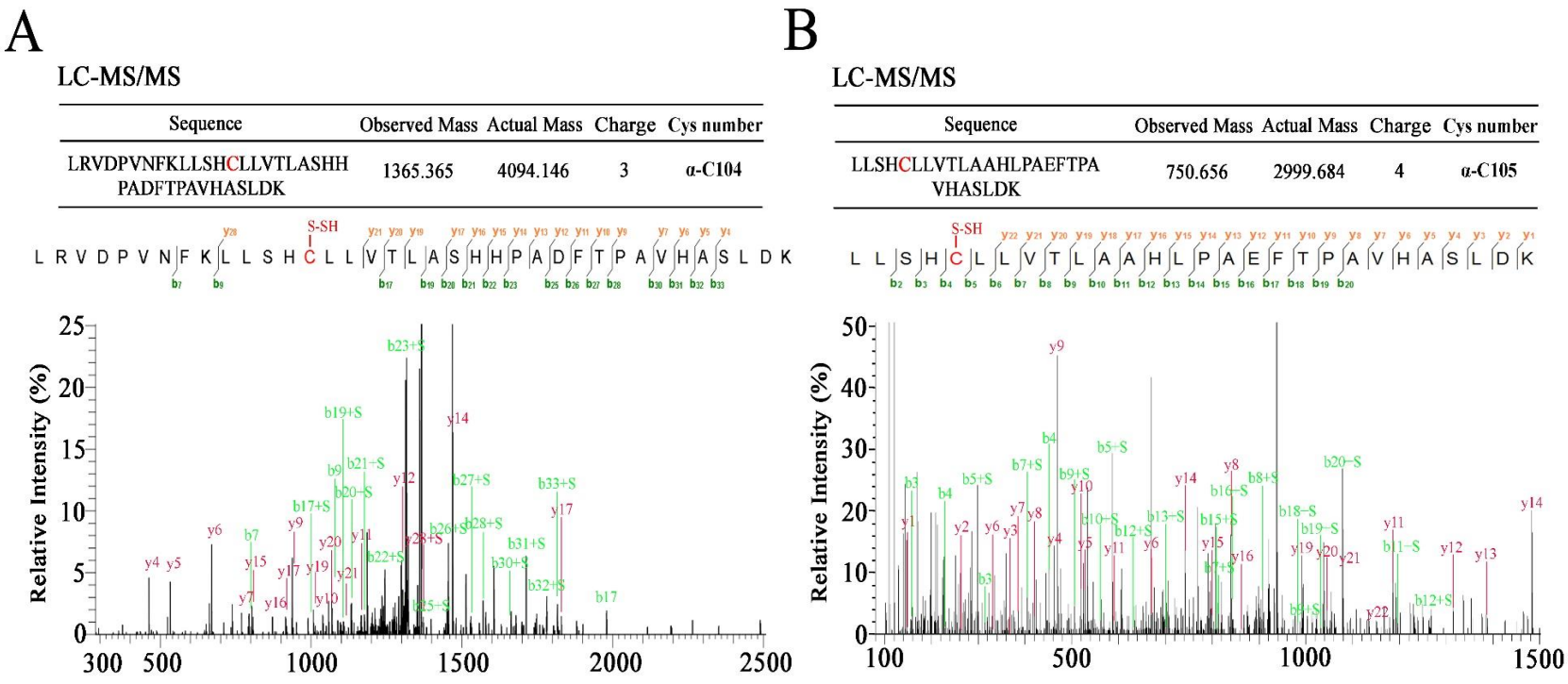

Fig.S5. S-sulfhydration of mouse Hb at cysteine 104 of the α chain and human Hb at cysteine 105 of the α chain. Mass spectrometric analysis demonstrates S-sulfhydration of mouse Hb(A) and human Hb

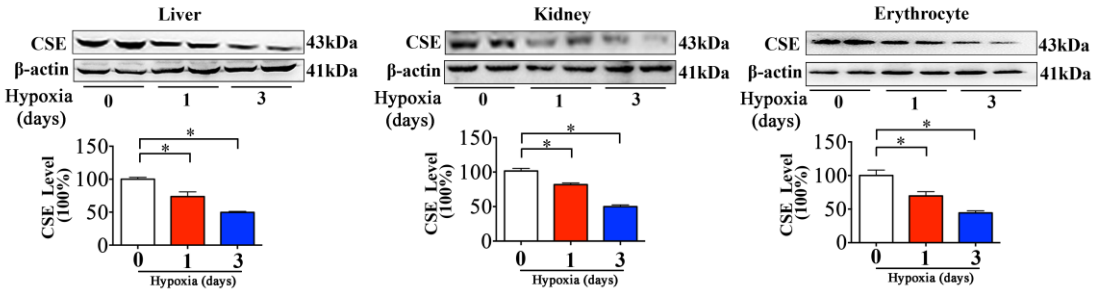

Fig.S6. The effects of hypoxia on CSE expression in liver, kidney and erythrocytes of mice. WT mice were exposed to hypoxia (10% oxygen) for 1-3 days as indicated. The protein levels of CSE were detected in liver, kidney and erythrocytes. Representative protein bands are presented on the top of corresponding histograms. Data are expressed as mean ± SEM (n=6). * $p<0.05$ vs control.