

Supplement for

Title: Transcriptomic adjustment to decreasing oxygen reveals novel functional strategies for extreme hypoxia tolerance in the copepod *Tigriopus californicus*

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This file contains the following items:

Tables S1, S4, and S5

Figures S1-S11

Other supplemental files:

Tables S2 and S3 are uploaded as separate excel documents.

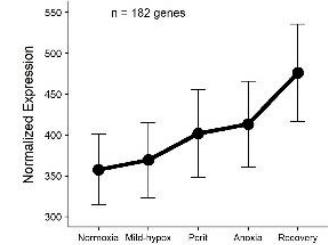
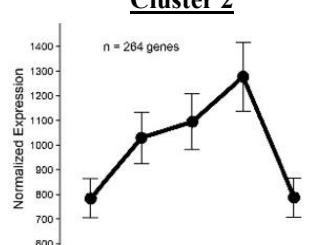
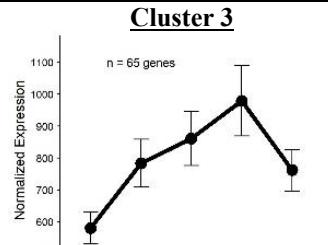
Upon submission, all supplementary files are freely available for review at this Github link:

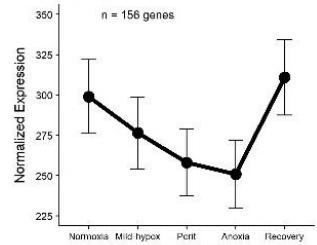
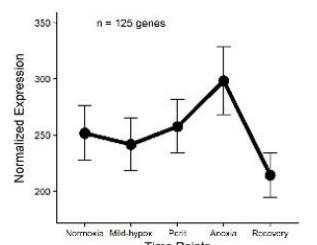
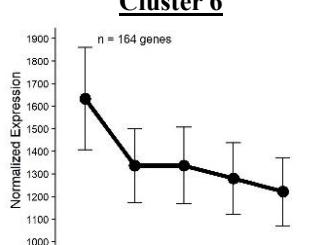
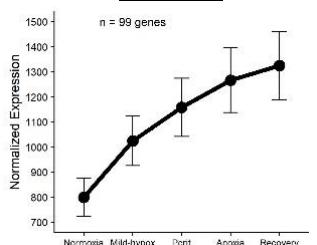
<https://github.com/mjp0044/Hypoxia-time-series-gene-expression>

Table S1. Summary of RNA-seq read processing. Sample replicates are listed where C = normoxia, 3.5 = mild hypoxia, 0.5 = P_{crit} , A = anoxia, and R = recovery sampling points.

Sample	Raw reads	Percent retained after trim	Total mapped	Percent mapped	Uniquely mapped	Percent counted
Average	14,721,690	91.10%	12,768,055	95.43%	10,377,819	77.66%
Min	9,296,007	88.92%	8,519,329	94.16%	7,217,475	74.84%
Max	17,740,487	97.48%	15,139,948	96.38%	11,886,378	80.96%
0.5-1	15,080,682	90.39%	13,042,446	95.68%	10,559,447	77.46%
0.5-2	15,066,384	90.30%	12,866,570	94.57%	10,488,187	77.09%
0.5-3	16,352,714	89.18%	13,980,632	95.87%	11,322,965	77.65%
0.5-4	14,173,108	90.30%	12,213,780	95.43%	9,937,041	77.64%
0.5-5	15,420,160	90.23%	13,246,498	95.20%	10,667,103	76.66%
0.5-6	11,043,075	96.17%	10,102,560	95.12%	8,364,220	78.75%
3.5-1	14,476,481	91.62%	12,782,737	96.38%	10,377,008	78.24%
3.5-2	9,296,007	97.33%	8,519,329	94.16%	7,217,475	79.77%
3.5-3	15,640,161	89.78%	13,465,718	95.90%	10,967,343	78.11%
3.5-4	14,354,239	89.21%	12,184,688	95.16%	9,904,052	77.35%
3.5-5	13,265,079	89.93%	11,363,570	95.26%	9,193,371	77.06%
3.5-6	16,113,538	91.66%	14,143,855	95.76%	11,586,855	78.45%
A-1	17,740,487	89.52%	15,139,948	95.33%	11,886,378	74.84%
A-2	14,881,716	94.52%	13,364,222	95.01%	10,858,084	77.19%
A-3	12,735,602	91.48%	11,180,066	95.97%	8,965,773	76.96%
A-4	15,890,635	89.06%	13,539,623	95.67%	10,896,969	76.99%
A-5	14,137,237	90.34%	12,256,955	95.97%	9,998,329	78.28%
A-6	15,499,781	95.17%	14,079,068	95.45%	11,551,500	78.31%
C-1	14,184,895	90.98%	12,417,484	96.22%	10,210,518	79.12%
C-2	13,418,024	90.03%	11,557,566	95.68%	9,480,287	78.48%
C-3	15,671,108	91.27%	13,694,425	95.75%	11,002,387	76.93%
C-4	15,725,830	89.66%	13,476,971	95.58%	10,876,383	77.14%
C-5	15,201,451	90.24%	13,123,455	95.67%	10,722,031	78.16%
C-6	16,714,325	90.60%	14,443,593	95.38%	11,774,587	77.75%
R-1	9,764,254	97.48%	9,076,983	95.36%	7,705,652	80.96%
R-2	13,633,312	88.92%	11,495,975	94.83%	9,287,748	76.62%
R-3	17,051,950	89.04%	14,552,705	95.85%	11,863,513	78.14%
R-4	16,607,656	89.34%	14,060,646	94.77%	11,263,233	75.92%
R-5	16,630,154	89.01%	14,130,335	95.46%	11,245,707	75.97%
R-6	15,880,651	90.23%	13,539,256	94.48%	11,160,431	77.88%

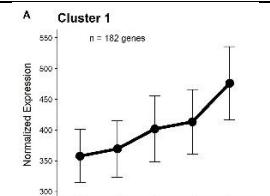
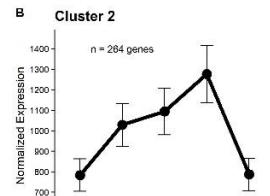
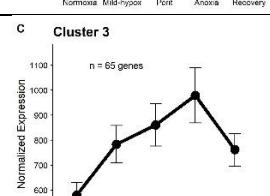
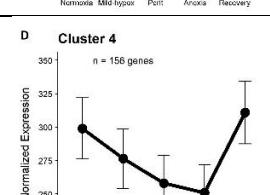
Table S4 Top 10 genes in each maSigPro cluster, arranged by statistical significance, along with possible roles that may relate to hypoxia response and reoxygenation stress during recovery. Additionally, the top 10 significant genes that responded significantly at P_{crit} only.

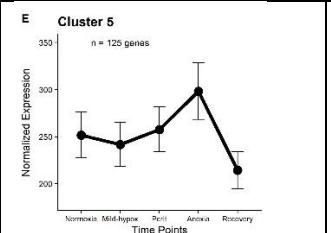
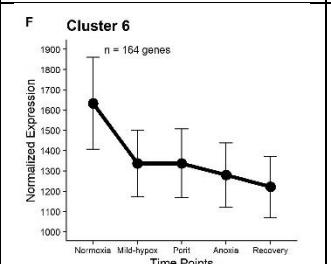
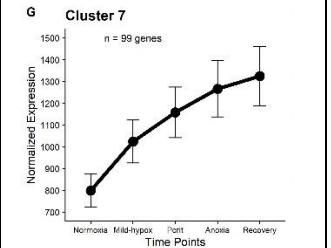
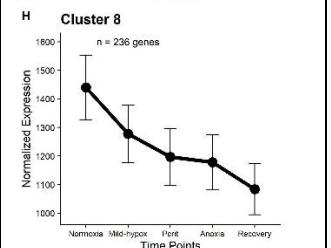
Cluster	Gene ID (TCAL)	Gene Annotation	Known Functional Role(s) [references listed as superscripts]
Cluster 1  n = 182 genes	01682 12432 00370 04867 12088 06799 09070 14535 03517 11503	ninaB hmp Flavohemoprotein B3GALT1 SLC13A5 tim (timeless) CHAC2 aos (giant-lens) per Mgst3 At5g337910	Carotenoid dual-oxygenase and isomerase ¹ Nitric oxide detoxification and redox homeostasis ² Biosynthesis of glycoproteins and glycolipids ³ Citrate transport within neurons ⁴ Circadian clock and DNA damage checkpoint ⁵ Glutathione degradation for antioxidant homeostasis ⁶ Photoreceptor axon pathfinding and cell determination ⁷ Regulation of circadian rhythm ⁸ Cell detoxification via glutathione reactions ⁹ Mitochondrial chaperone ¹⁰
Cluster 2  n = 264 genes	01551 05776 04965 07926 06511 02126 03439 10671 05534 09693	cuticle-like DDO Siah1 Tmem9 Pyx (pyrexia) Gbs-76A Hsp68Bb Dipetalogastin homolog arrd-17 SPCC1494.01	Exoskeleton modification ¹¹ Deamination of D-aspartate for cell detoxification ¹² Positive inducer of HIF-1 α through PHD degradation ¹³ Regulation (+) of Wnt pathway and intracellular pH reduction ¹⁴ Heat stress response and circadian temperature synchronization ¹⁵ Regulation (-) glycogen binding and (+) glycogen biosynthesis ¹⁶ Heat shock protein ¹⁷ Thrombin inhibitor to protect fibrinogen-related proteins ¹⁸ Responds to osmotic stress and stimulation after starvation ¹⁹ 2-oxoglutarate-dependent dioxygenase ²⁰
Cluster 3  n = 65 genes	08675 06802 07801 08592 17390 12220 03482 08955 07840 08629	norP Venom carboxylesterase-6 CYP6J1 Nrf-6 Nose Slc12a3 homolog Cyp49a1 Glutathione reductase (Gsr) AHCYL2 UGP2 Tret1	Phototransduction in photoreceptors ²¹ Lipolytic activity to generate free fatty acids ²² Oxidoreductase related to cell detoxification (GSH) ²³ Lipid transport ²⁴ Sodium and chloride homeostasis and receptor for cytokines ²⁵ Estrogen hormone biosynthesis ²⁶ Mitochondrial oxidative stress resistance and cell detoxification ²⁷ Regulation of sodium/bicarb transport and magnesium sensitivity ²⁸ Generates precursors to glycogen ²⁹ Trehalose sugar transporter for chitin synthesis ³⁰

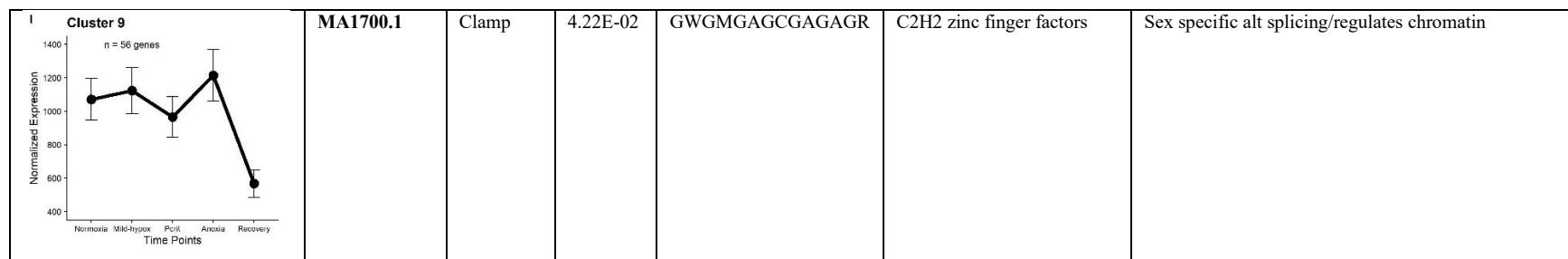
Cluster 4  n = 156 genes	02557 08167 15032 11065 14798 04178 05313 13736 00225 05545	Ets98B Ptchd3 colt SIK2 Gmcl1 Atxn11 CPPED1 Chitin deacetylase 5 mucin-5AC METTL9	Transcription factor binding during cell differentiation ³¹ Sperm development or function ³² Gas filling of trachea and epithelial morphogenesis ³³ Fatty acid oxidation and glucose metabolism ³⁴ Nuclear envelope protein involved in spermatogenesis ³⁵ Repressor of Notch signaling ³⁶ Apoptosis promoter and inhibits glucose uptake in adipocytes ³⁷ Conversion of chitin to chitosan ³⁸ Extracellular matrix structural constituent of internal epithelia ³⁹ Methylation in mitochondria incl. electron transport subunits ⁴⁰
Cluster 5  n = 125 genes	11456 10176 02167 13139 04517 15195 16261 11277 01071 04316	AVT3B TACR2 nhr-14 Slc18b1 Heat shock 70 kDa cognate 4 setd7 Jph3 Dat HMCN1 Gls	Neutral amino acid transport ⁴¹ Receptor for tachykinins (neural, muscular) ⁴² Immune regulator and enabler of steroid binding activity ⁴³ Translocation of polyamines from cytosol to secretory vesicles ⁴⁴ Used in protein degradation for healthy embryogenesis ⁴⁵ DNA damage response and heterochromatin organization ⁴⁶ Forms junctional complexes between plasma membrane and ER ⁴⁷ Dopamine and noradrenaline transport ⁴⁸ Influences components of epidermal or epithelial structure ⁴⁹ Glutaminase used in energy prod. and acid-base homeostasis ⁵⁰
Cluster 6  n = 164 genes	11302 12235 13288 07499 00248 08165 01675 07652 12109 04108	Spns2 (spinster homolog) D4Des slc46a1 Luciferin 4-monoxyganase CTDSPL2 gst-6 glutathione transferase Tret1-2 homolog GstD1 NDRG3 ATP13A3	Lipid transporter required for immune response ⁵¹ Biosynthesis of polyunsaturated fatty acid docosahexaenoic acid ⁵² Transport of folate across cell membranes in acidic conditions ⁵³ Fatty-acyl-CoA biosynthesis for downstream ATP production ⁵⁴ Regulator of transcription by RNA polymerase II ⁵⁵ Cell detoxification against oxidative stress ⁵⁶ Trehalose sugar transporter for chitin synthesis ³⁰ Insect glutathione transferase for cell detoxification ⁵⁷ Lactate signaling during hypoxia ⁵⁸ Transport of polyamines to the cytosol ⁵⁹
Cluster 7  n = 99 genes	14591 08242 12804 00766 05569 05663 11917 01737 08982 08241	cwo transcription factor Leech-der. tryptase inh. c lcc2 Laccase-2 Slc22a1 lhpp fabG SQOR Slc22a7 Soma ferritin Dipetalogastin homolog	Circadian pacemaker and regulator of Clock gene ⁶⁰ Tryptase inhibitor ⁶¹ Used to make exoskeleton insoluble and hard ⁶² Transporter critical for uptake of cations and toxins ⁶³ Metabolizes phosphate and inhibits aerobic glycolysis ⁶⁴ Fatty acid synthesis ⁶⁵ Detoxifies mitochondria from sulfides for hypoxia resistance ⁶⁶ Hub gene for excretion of toxic anions during hypoxic stress ⁶⁷ Storage of iron ions during hypoxia ⁶⁸ Thrombin inhibitor to protect fibrinogen-related proteins ¹⁸

<p>Cluster 8</p> <p>n = 236 genes</p>	13810 09890 05274 11475 01161 09874 07649 09466 09716 12742	urad clpX EHD4 xsc mmlH agmo Similar to oxlT nad Epmerase dehydratase Similar to oxlT TMEM68	Purine catabolic processes in the peroxisome ⁶⁹ Unfolded protein response in mitochondria ⁷⁰ Membrane reorganization and endosomal transport ⁷¹ Conversion of taurine to sulfite and acetate ⁷² 4-methylmuconolactone transporter in aromatics metabolism ⁷³ Alkylglycerol monooxygenase involved in cuticle stability ⁷⁴ Uptakes oxalate from the gut ⁷⁵ Helps regulate cell surface properties ⁷⁶ Uptakes oxalate from the gut ⁷⁵ Alternative triglyceride synthesis and mitochondrial stability ⁷⁷
<p>Cluster 9</p> <p>n = 56 genes</p>	02439 11523 01542 12977 03519 05698 12659 112107 05177 05281	CD63 Venom toxin 11-like mdh CG9705 CG13624 PNKP rost (rolling stone) NA ⁺ /H ⁺ exchanger beta Slc12a3 homolog XK-related 6-like	Promotes cell survival, cell adhesion, sequestration of pigment ⁷⁸ Secretes OcyC11 like compound affecting cell adhesion ⁷⁹ Needed for citric acid cycle and NADH supply to mitochondria ⁸⁰ Cold shock protein needed for mRNA 3'-UTR binding activity ⁸¹ (+) regulator of transcription involved with TORC1 signaling ⁸² DNA damage repair following oxidative damage ⁸³ Needed for myoblast fusion during muscle growth and repair ⁸⁴ Important for insulin secretion during homeostasis ⁸⁵ Sodium and chloride homeostasis and receptor for cytokines ²⁵ Blood antigen production ⁸⁶
<p>P_{crit} cluster</p>	16451 03260 06219 09416 03107 11030 06987 12876 09258 05028	Basic proline-rich isoform X1 Sell L-selectin Mrc2 C-type P4HA1 resilin pro-resilin Sc5d Lathosterol oxidase FUCA1 Compound eye opsin BCRH2 cuticle 7-like ANKS1A	Cell growth ⁸⁷ Endothelial cell growth ⁸⁸ Extracellular collagen modification ⁸⁹ Key enzyme in collagen synthesis ⁹⁰ Cuticle development ⁹¹ Cholesterol biosynthesis and prevention of cell death ⁹² Fucose-containing glycoprotein degradation ⁹³ Photoreceptor activity ⁹⁴ Exoskeleton modification ⁹⁵ Ephrin signaling pathway and neuron pathway regulation ⁹⁶

Table S5 Significantly enriched motifs in the promoter region (maximum 1000bp upstream) of genes in each maSigPro cluster. Within each cluster, motifs are arranged by statistical significance along with possible roles that may relate to hypoxia response and reoxygenation stress during recovery.

Cluster	Motif_ID	Name	p-adj	Consensus sequence	Class	Functional role [references listed as superscripts]
A Cluster 1  n = 182 genes	MA1700.1 MA0205.2 MA0255.1 MA0222.1 MA0015.1 MA0237.2 MA0193.1 MA0247.2	Clamp Trl z exd Cf2 pan schlank tin	4.43E-07 8.83E-04 4.88E-03 1.33E-02 2.77E-02 4.21E-02 4.23E-02 4.39E-02	GWGMGAGCGAGAGR RVAAGAGAGAGR WTGAGTGRDW NTTGACR RTATATRTAB KCGSCKYBTTTGRT CYACYAA WBTCRAGTGS	C2H2 zinc finger C2H2 zinc finger Trithorax Homeo domain C2H2 zinc finger High-mobility group Homeo domain Homeo domain	Sex specific alt splicing/regulates chromatin ⁹⁷ Regulates chromatin structure ⁹⁸ transvection-based gene expression ⁹⁹ Regulation of neural development ¹⁰⁰ Follicle cell fate and muscle gene regulation ¹⁰¹ Regulation of transcription by RNA pol II ¹⁰² Lipid metabolism ¹⁰³ Development of heart and muscle ¹⁰⁴
B Cluster 2  n = 264 genes	MA1700.1 MA0205.2 MA0015.1 MA1457.1 MA0216.2 MA0193.1 MA0451.1	Clamp Trl Cf2 grh cad schlank kni	2.03E-10 1.52E-07 9.42E-05 5.78E-03 1.50E-02 4.01E-02 5.07E-02	GWGMGAGCGAGAGR RVAAGAGAGAGR RTATATRTAB VAAACCAGTTBN RGYMATAAAAM CYACYAA AAWNTAGAGCAS	C2H2 zinc finger C2H2 zinc finger C2H2 zinc finger Grainyhead Homeo domain Homeo domain Nuc rec C4 zinc fingers	Sex specific alt splicing/regulates chromatin Regulates chromatin structure Follicle cell fate and muscle gene regulation Epithelial cell and cuticular development ^{105,106} Regulation of gut AMP levels ¹⁰⁷ Lipid metabolism Regulates segmentation during development ¹⁰⁸
c Cluster 3  n = 65 genes	MA1700.1 MA0205.2 MA0015.1	Clamp Trl Cf2	2.59E-08 4.69E-05 5.18E-02	GWGMGAGCGAGAGR RVAAGAGAGAGR RTATATRTAB	C2H2 zinc finger C2H2 zinc finger C2H2 zinc finger	Sex specific alt splicing/regulates chromatin Regulates chromatin structure Follicle cell fate and muscle gene regulation
D Cluster 4  n = 156 genes	MA1700.1 MA0205.2 MA0015.1 MA0255.1 MA0247.2	Clamp Trl Cf2 z tin	7.79E-08 7.02E-07 2.35E-03 2.56E-03 4.72E-03	GWGMGAGCGAGAGR RVAAGAGAGAGR RTATATRTAB WTGAGTGRDW WBTCRAGTGS	C2H2 zinc finger C2H2 zinc finger C2H2 zinc finger Trithorax Homeo domain	Sex specific alt splicing/regulates chromatin Regulates chromatin structure Follicle cell fate and muscle gene regulation transvection-based gene expression Development of heart and muscle

E Cluster 5  <i>n</i> = 125 genes	MA0205.2 MA1700.1 MA0015.1	Trl Clamp Cf2	1.62E-13 1.83E-13 1.53E-02	RVAAGAGAGAGR GWGMGAGCGAGAGR RTATATRTAB	C2H2 zinc finger C2H2 zinc finger C2H2 zinc finger	Regulates chromatin structure Sex specific alt splicing/regulates chromatin Follicle cell fate and muscle gene regulation
F Cluster 6  <i>n</i> = 164 genes	MA1700.1 MA0205.2 MA0015.1 MA0255.1	Clamp Trl Cf2 z	3.10E-11 3.79E-11 9.35E-06 3.40E-02	GWGMGAGCGAGAGR RVAAGAGAGAGR RTATATRTAB WTGAGTGRDW	C2H2 zinc finger C2H2 zinc finger C2H2 zinc finger trithorax	Sex specific alt splicing/regulates chromatin Regulates chromatin structure Follicle cell fate and muscle gene regulation transvection-based gene expression
G Cluster 7  <i>n</i> = 99 genes	MA0015.1 MA1700.1 MA0255.1 MA0205.2 MA0531.1 MA0249.2	Cf2 Clamp z Trl CTCF twi	1.46E-05 1.87E-05 5.60E-04 5.62E-04 2.24E-02 3.27E-02	RTATATRTAB GWGMGAGCGAGAGR WTGAGTGRDW RVAAGAGAGAGR CCRMYAGRTGGCGCY RNACACATGTN	C2H2 zinc finger C2H2 zinc finger trithorax C2H2 zinc finger C2H2 zinc finger bHLH	Follicle cell fate and muscle gene regulation Sex specific alt splicing/regulates chromatin transvection-based gene expression Regulates chromatin structure Short and long-range chromatin remodeling ¹⁰⁹ Muscle development and Notch activation ¹¹⁰
H Cluster 8  <i>n</i> = 236 genes	MA1700.1 MA0205.2 MA0531.1 MA0015.1	Clamp Trl CTCF Cf2	1.47E-05 2.99E-05 1.18E-02 5.74E-02	GWGMGAGCGAGAGR RVAAGAGAGAGR CCRMYAGRTGGCGCY RTATATRTAB	C2H2 zinc finger C2H2 zinc finger C2H2 zinc finger C2H2 zinc finger	Sex specific alt splicing/regulates chromatin Regulates chromatin structure Short and long-range chromatin remodeling Follicle cell fate and muscle gene regulation



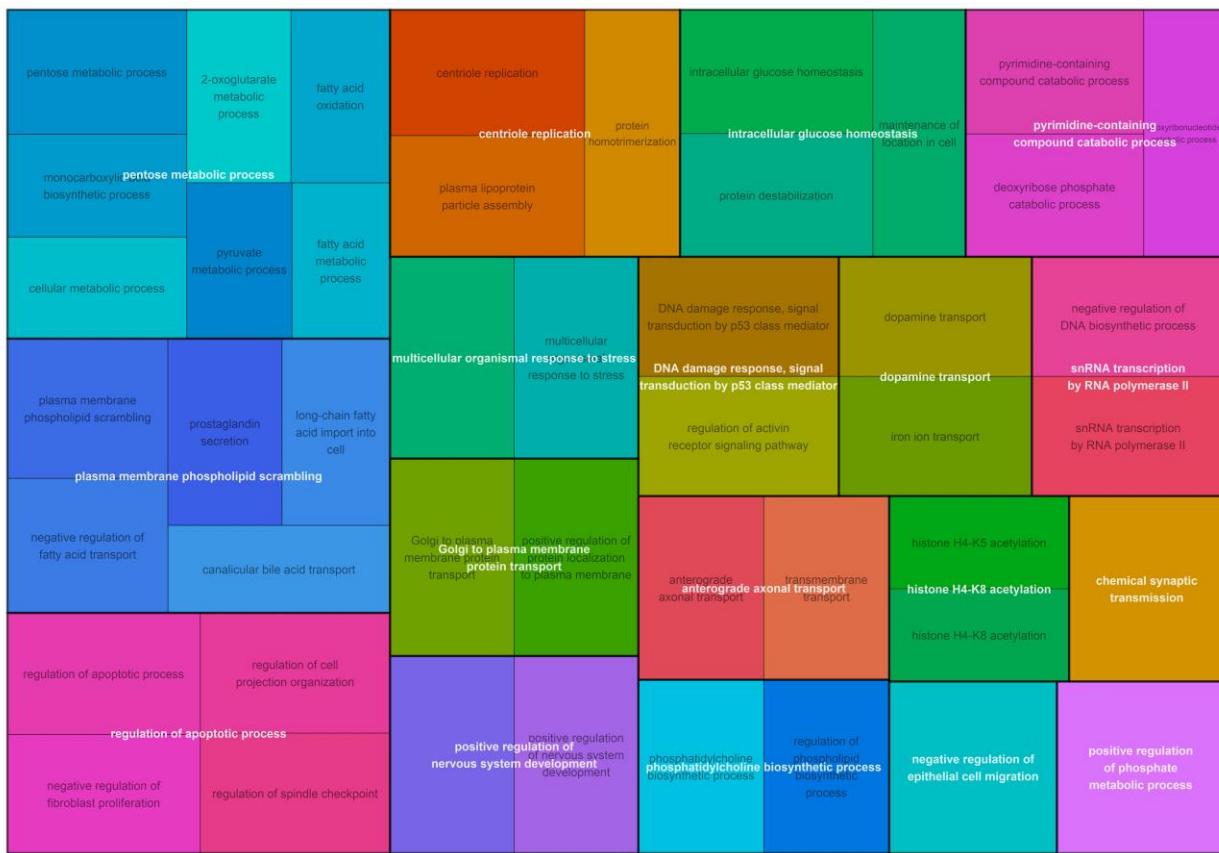


Figure S1: Cluster 2 treemap from rrvgo reduction and grouping of TopGO enrichment analysis of genes. Genes in this cluster increased expression levels steadily through anoxia and then decreased to pre-stress levels during recovery.



Figure S2 Cluster 3 treemap from rrvgo reduction and grouping of TopGO enrichment analysis of genes. Genes in this cluster increased expression levels steadily through anoxia and then decreased during recovery but not to the same level as during normoxia.



Figure S3 Cluster 5 treemap from rrvgo reduction and grouping of TopGO enrichment analysis of genes. Genes in this cluster increased expression levels slowly through P_{crit} , rapidly increased expression levels during anoxia, and then decreased in expression below that during normoxia.



Figure S4 Cluster 4 treemap from rrvg reduction and grouping of TopGO enrichment analysis of genes. Genes in this cluster decreased expression levels steadily through anoxia and then increased to pre-stress levels during recovery.

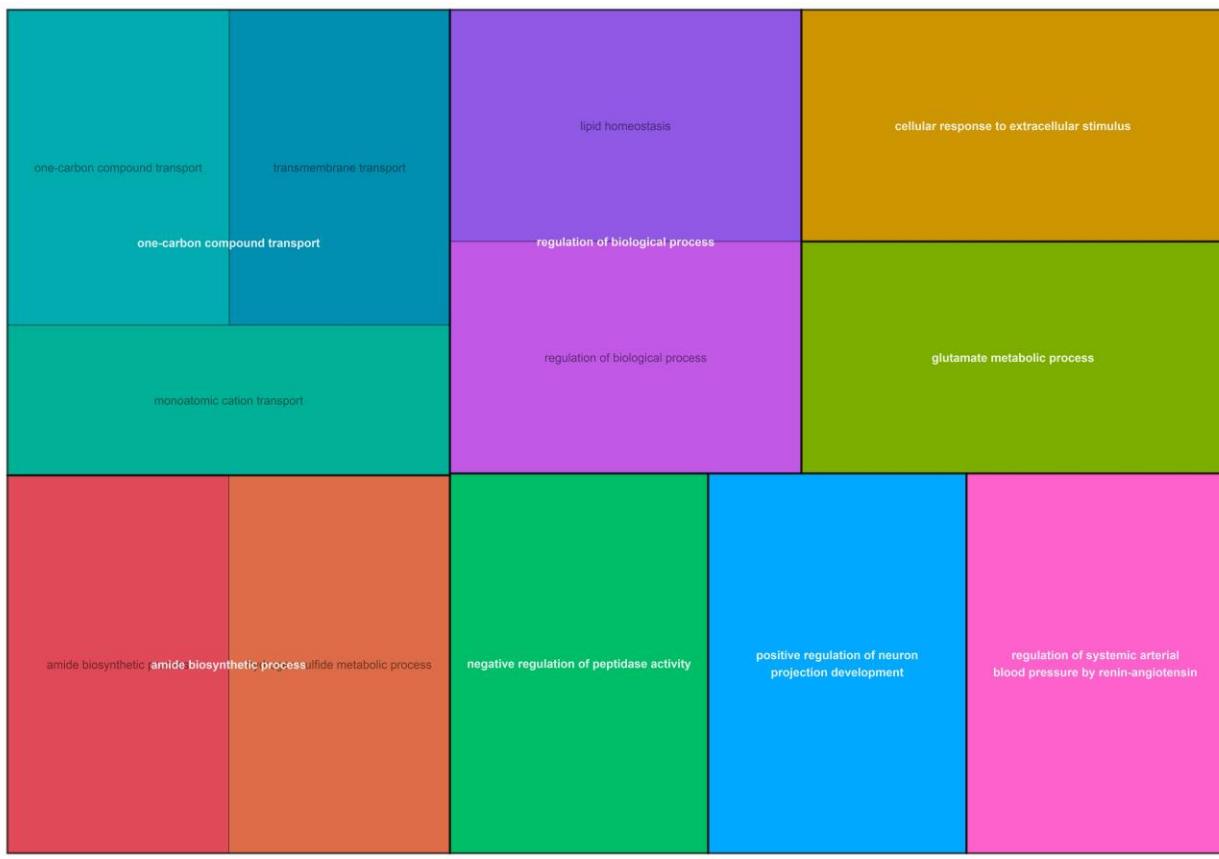


Figure S5 Cluster 7 treemap from rrvgo reduction and grouping of TopGO enrichment analysis of genes. Genes in this cluster increased expression levels steadily all the way through recovery.



Figure S6 Cluster 8 treemap from rrngo reduction and grouping of TopGO enrichment analysis of genes. Genes in this cluster decreased expression levels steadily all the way through recovery.



Figure S7 Cluster 1 treemap from rrvgo reduction and grouping of TopGO enrichment analysis of genes. Genes in this cluster increased expression levels most rapidly when transitioning from anoxia to recovery.



Figure S8 Cluster 9 treemap from rrvgo reduction and grouping of TopGO enrichment analysis of genes. Genes in this cluster decreased expression levels most drastically when transitioning between anoxia and recovery.



Figure S9 Cluster 6 treemap from rrvgo reduction and grouping of TopGO enrichment analysis of genes. Genes in this cluster decreased expression levels most drastically at the start of hypoxia exposure and levels remained mostly stable through recovery.



Figure S10 Treemap from rrvgo reduction and grouping of TopGO enrichment analysis of genes that only showed significant change at the P_{crit} exposure level. Genes in this group increased or decreased expression levels suddenly at P_{crit} and returned to near normoxic levels in anoxia.

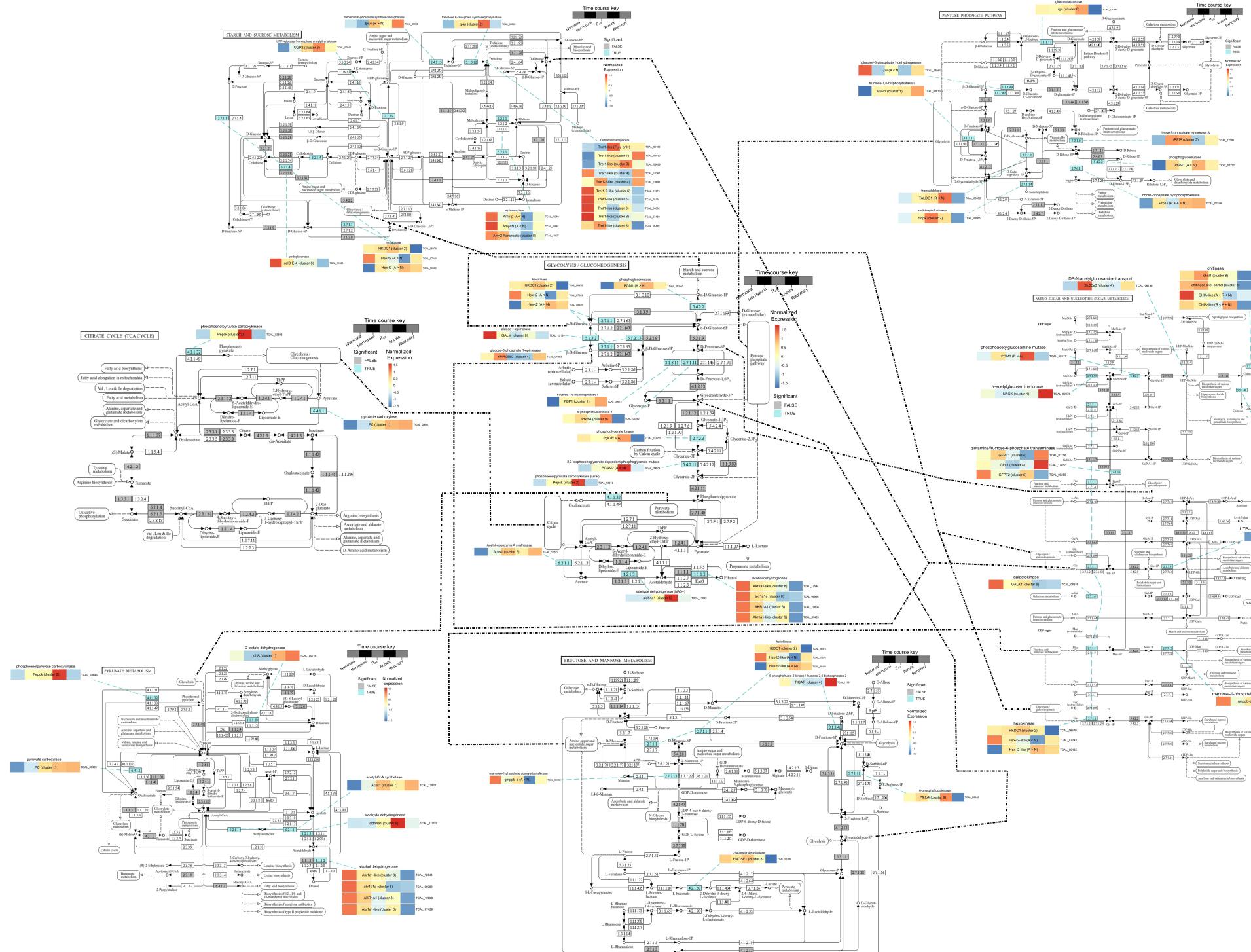


Figure S11 The expression pattern of significant genes identified by maSigPro or DESeq2 in the glycolysis, starch-sucrose, pyruvate, pentose-phosphate, fructose-mannose, TCA cycle, and amino sugar/chitin synthesis pathways. This figure is high resolution, and details can be read by zooming and scrolling to explore the pathways. Significant genes are highlighted light blue on the pathways. Genes highlighted dark grey are genes listed by NCBI and KEGG as being present in the *T. californicus* genome while genes with no highlighting are not. The heat map of each gene has five segments which correspond to the five time points of the hypoxia course: normoxia, mild hypoxia, hypoxia at P_{crit} , anoxia, and recovery.

References for Supplement Tables S4 and S5

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