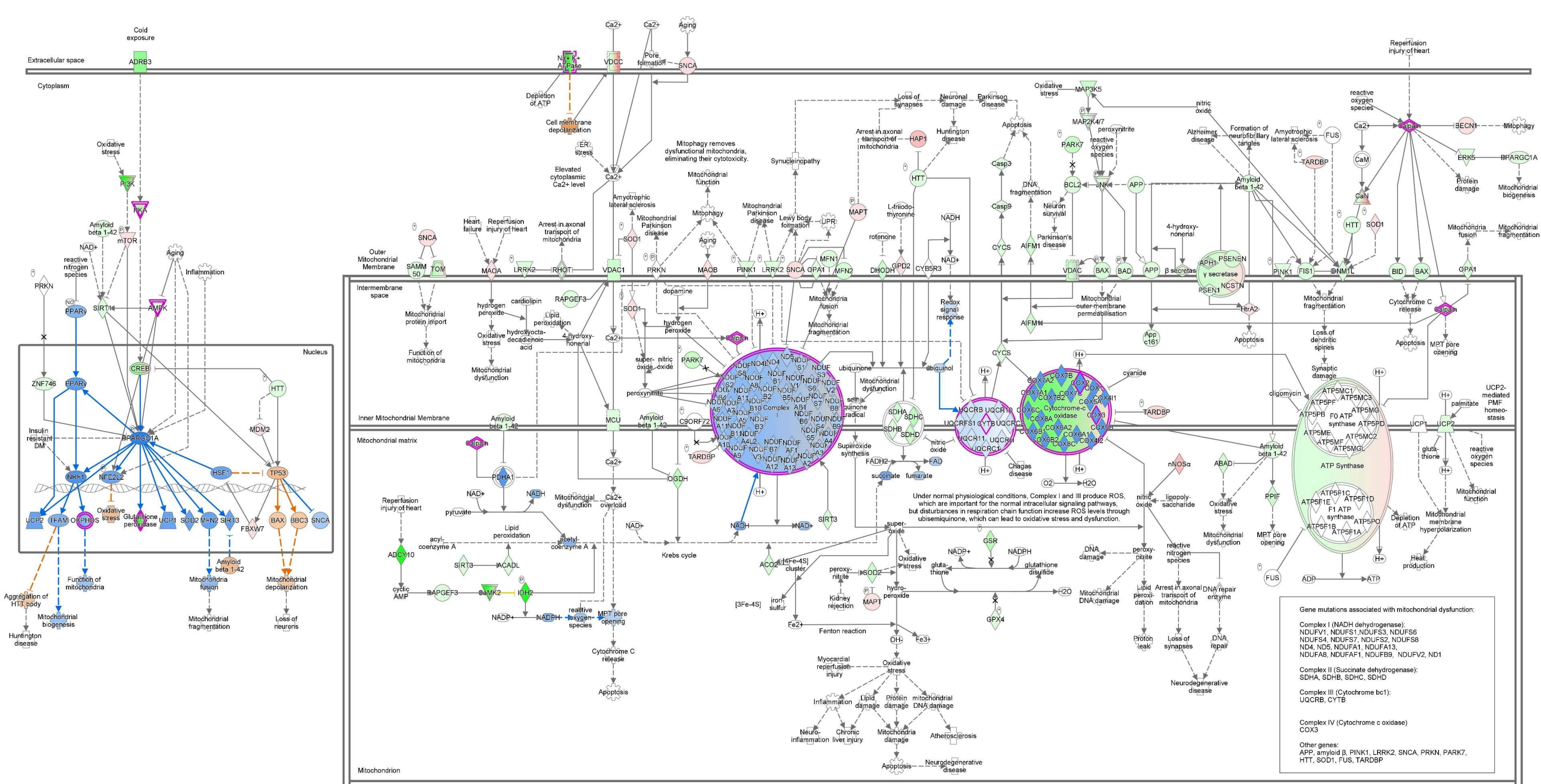


**Figure S1. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway: Chemical Carcinogenesis – DNA adducts.**

A KEGG pathway ‘Chemical Carcinogenesis – DNA adduct’ enriched liver tissues from mice fed fructose water, which was retrieved from transcriptome for KEGG pathway terms.

Abbreviations: KEGG, Kyoto Encyclopedia of Genes and Genomes





**Figure S2. Canonical Pathway: Mitochondrial dysfunction.** Colonic transcriptomics suggests that IDH2 KO-induced mitochondrial dysfunction is linked to the suppression of Complex IV and V in comparison to WT mice. Blue/red indicate observed inhibition/activation, while green/orange represent predicted inhibition/activation. Abbreviations: IDH2, isocitrate dehydrogenase 2; KO, knockout; WT, wild type

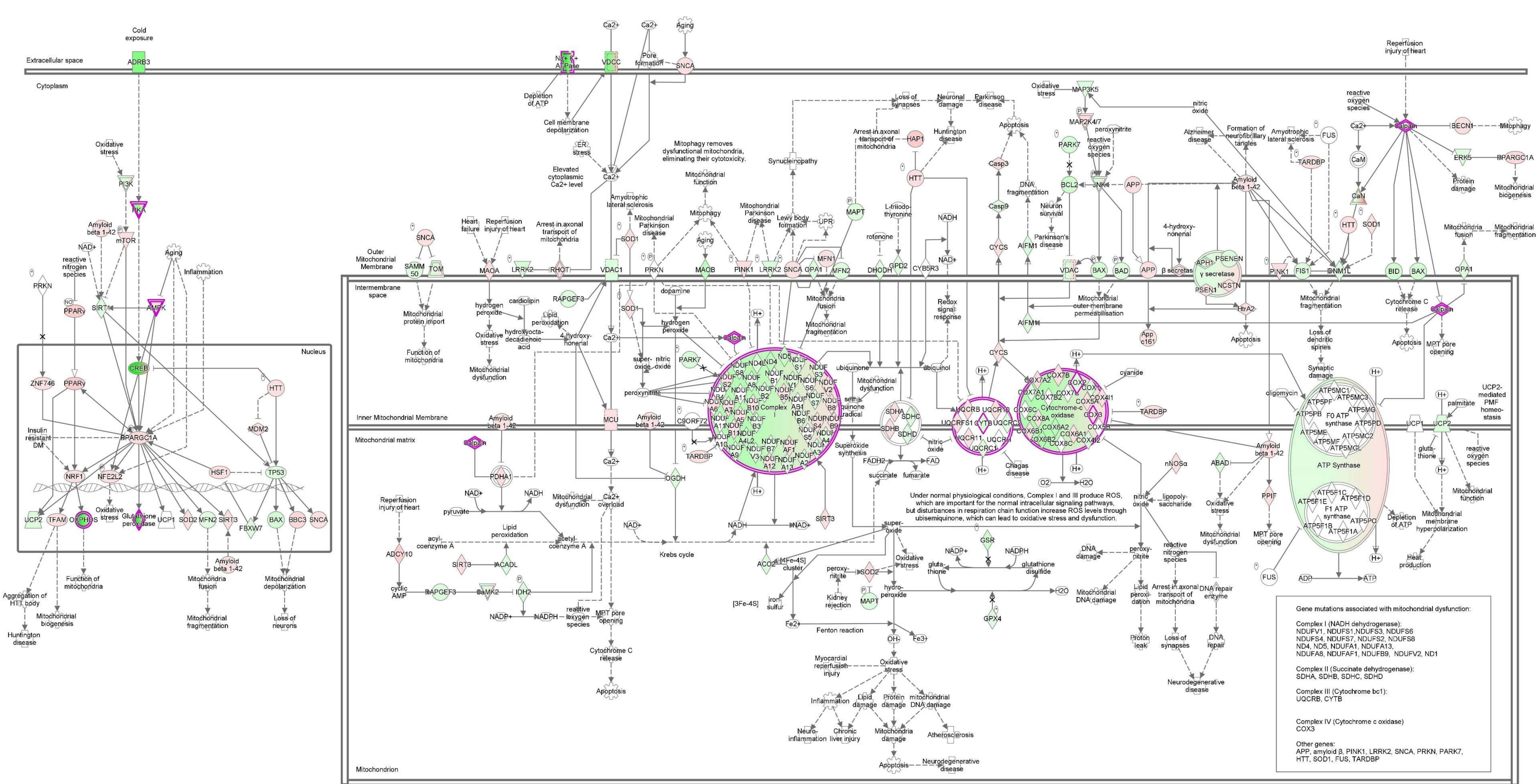




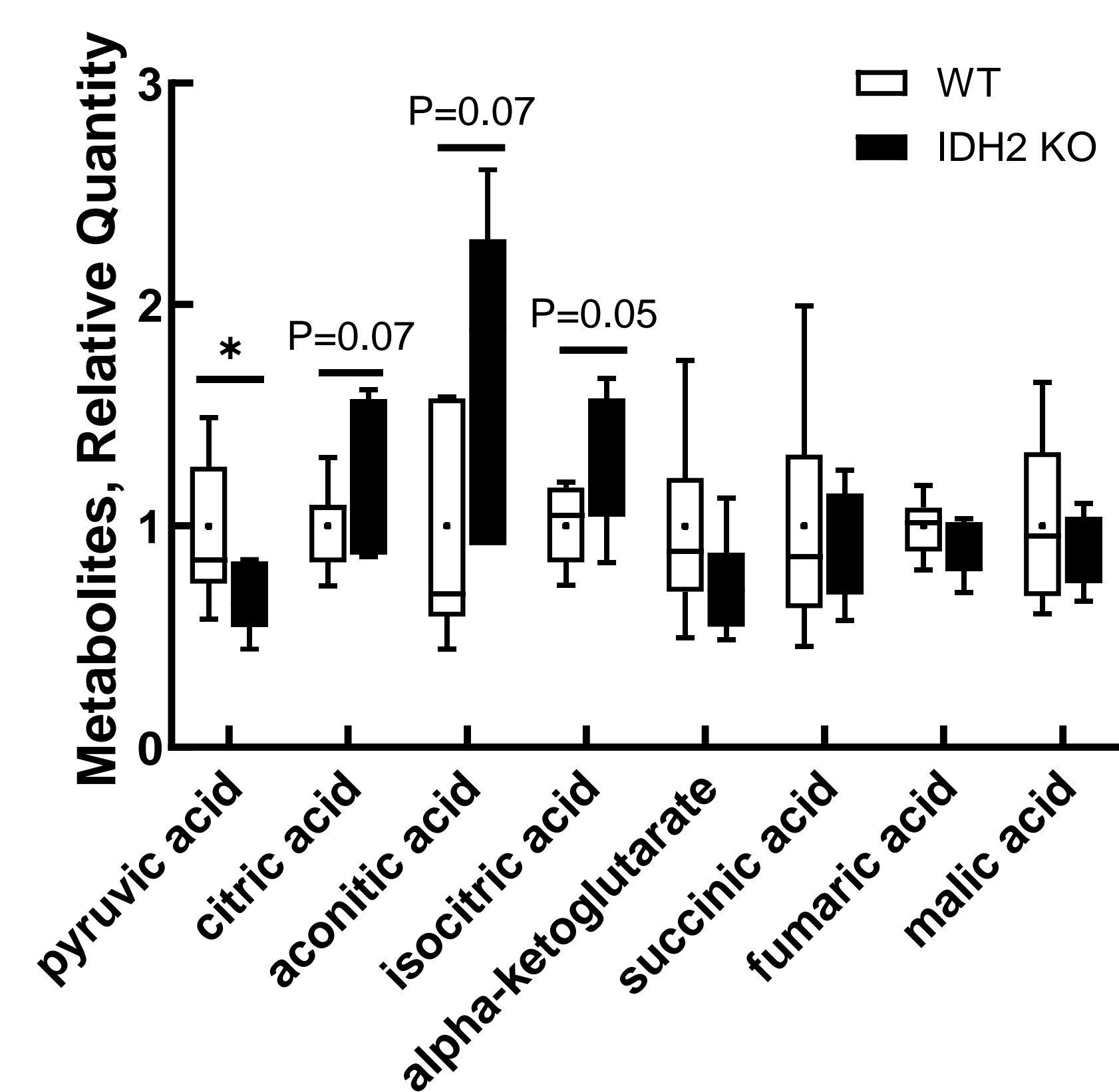












**Figure S6. Plasma metabolomics revealed that isocitrate dehydrogenase 2 (IDH2) knockout (KO) may induce reductive TCA cycle.**

Key metabolites of the TCA cycle in plasma of mice to validate IDH2 KO-mediated metabolic shift. Data are present as mean  $\pm$  standard error of the mean (n=6 per group). A p-value of 0.05 or less was considered statistically significant; \*p<0.05.

Abbreviations: IDH2, isocitrate dehydrogenase 2; KO, knockout; WT, wild type

**Table S1. Activated or inhibited canonical pathways<sup>1</sup> in colon tissues by IDH2 knockout**

Canonical Pathways	-log(p-value)	z-score <sup>2</sup>
Interferon alpha/beta signaling	10.7	3.606
Role of Hypercytokinemia/hyperchemokinema in the Pathogenesis of Influenza	8.53	2.887
ISGylation Signaling Pathway	5.52	2.53
Pathogen Induced Cytokine Storm Signaling Pathway	2.61	2.496
DDX58/IFIH1-mediated induction of interferon-alpha/beta	2.29	2.236
Activation of IRF by Cytosolic Pattern Recognition Receptors	5.45	2.121
Neuroinflammation Signaling Pathway	3.76	2.111
Interferon Signaling	3.85	2
Antigen Presentation Pathway	2.67	2
SPINK1 Pancreatic Cancer Pathway	2	2
Immunogenic Cell Death Signaling Pathway	1.42	2
Death Receptor Signaling	1.33	2
Glucose metabolism	1.58	-2
Coronavirus Pathogenesis Pathway	2.07	-2.121
The citric acid (TCA) cycle and respiratory electron transport	2.98	-2.236
O-linked glycosylation	1.69	-2.236
Ion channel transport	2.93	-2.333
Gap Junction Signaling	1.39	-2.333
Serotonin Receptor Signaling	2.55	-2.84

<sup>1</sup>Activity states were predicted by the IPA software using differentially expressed genes.

<sup>2</sup>Calculated activity score. Positive and negative values indicate predicted activated and predicted inhibited, respectively.