**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

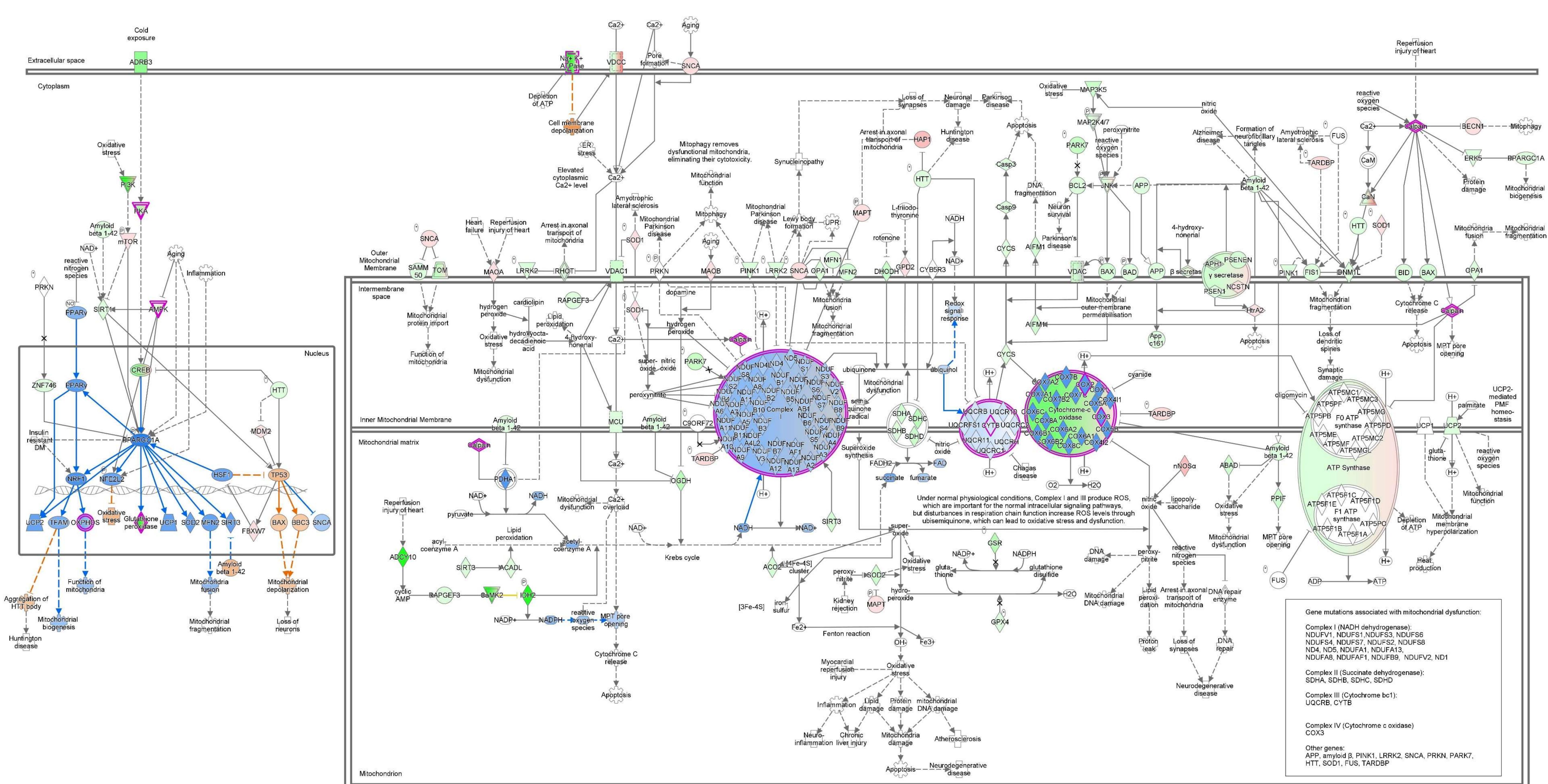


Figure S2. Canonical Pathway: Mitochondrial dysfunction.

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

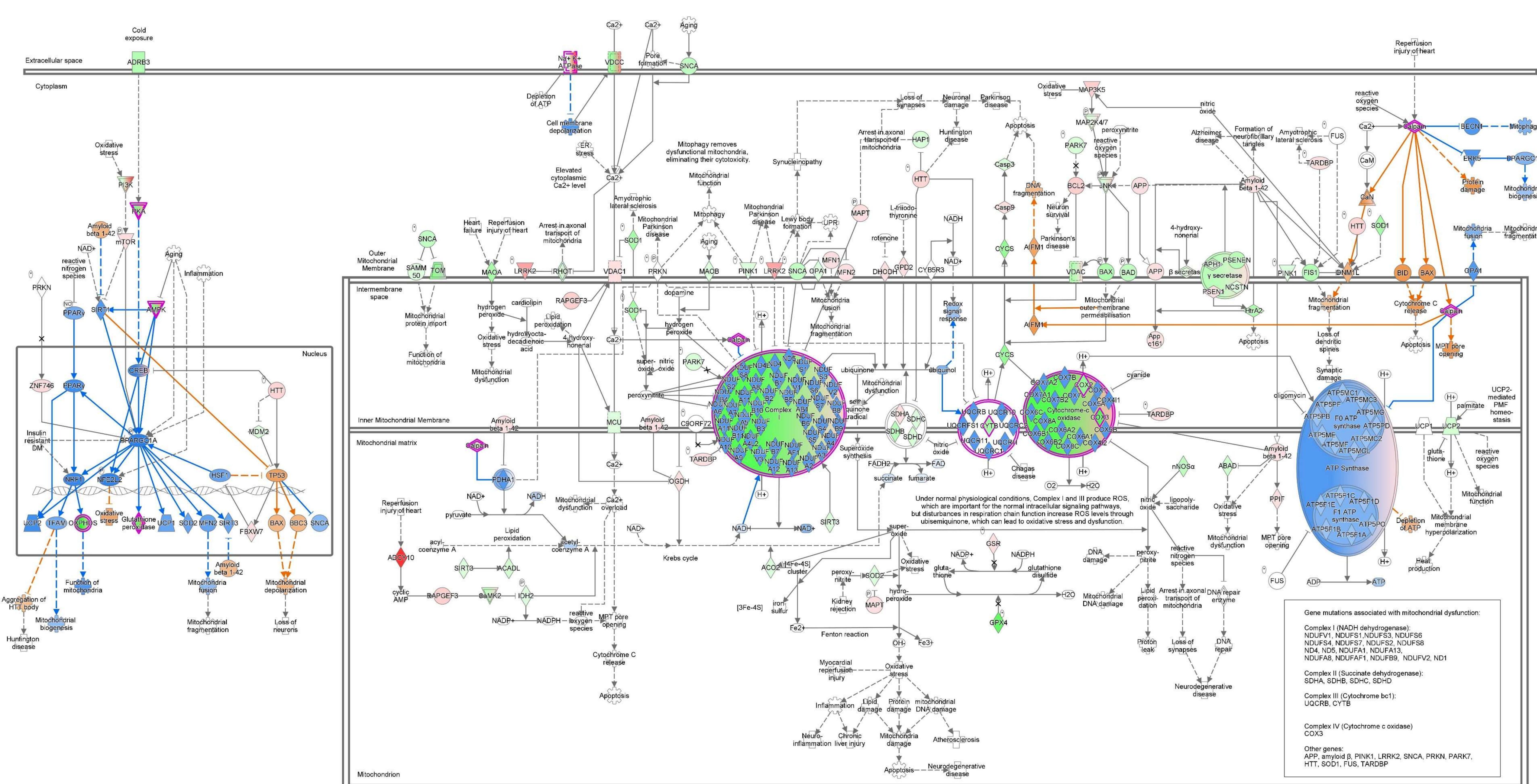


Figure S3. Canonical Pathway: Mitochondrial dysfunction.

Colonic transcriptomics reveals that 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (PhIP)-mediated mitochondrial dysfunction is linked to the suppression of Complex I and IV in WT mice. Blue/red indicate observed inhibition/activation, while green/orange represent predicted inhibition/activation.

Abbreviations: IDH2 isocitrate dehydrogenase 2· KO knockout· PhIP 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine· WT wild type

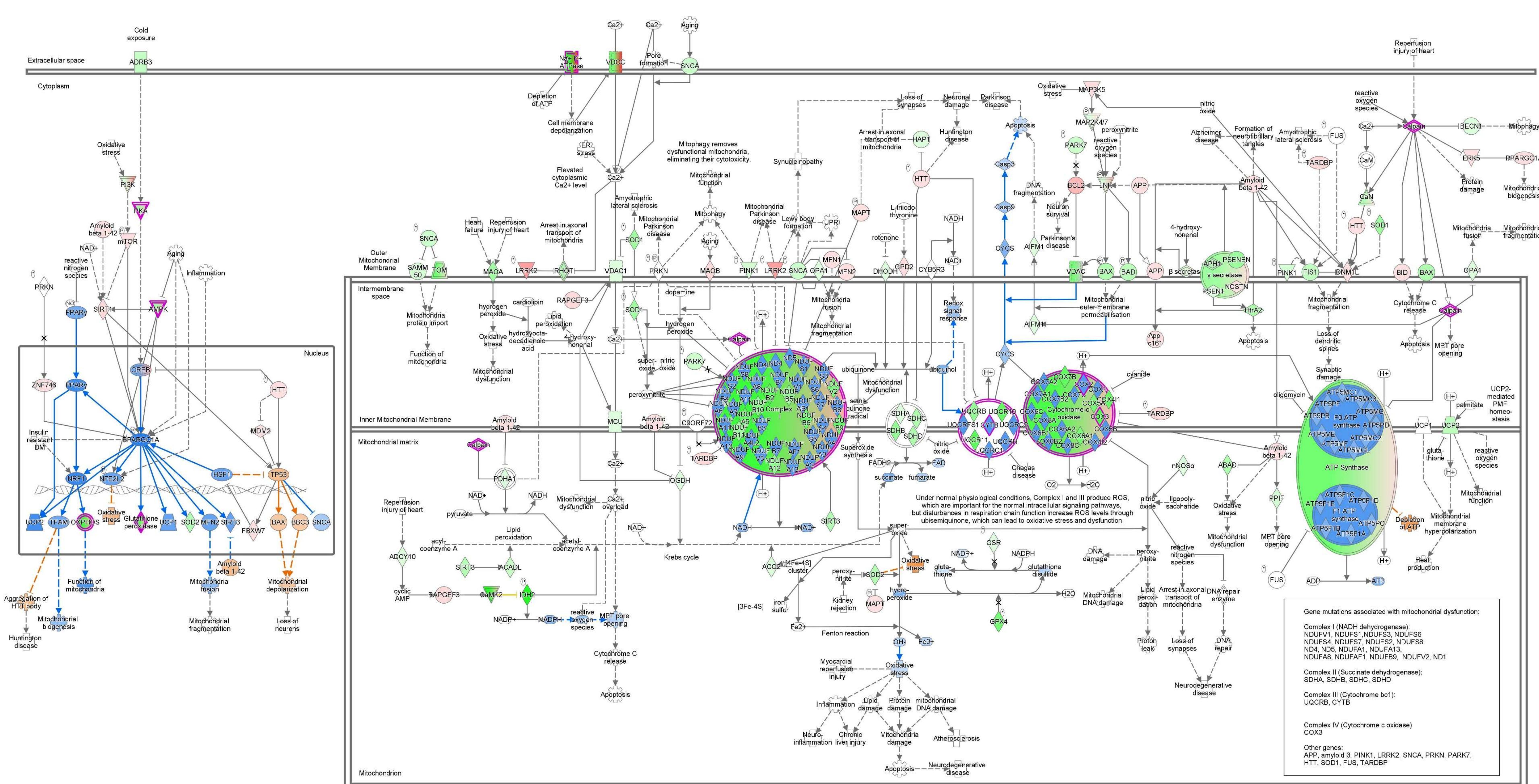


Figure S4. Canonical Pathway: Mitochondrial dysfunction.

Colonic transcriptomics suggests that IDH2 KO exacerbates PhIP-mediated mitochondrial dysfunction via overall suppression of the electron transport chain. Blue/red indicate observed inhibition/activation, while green/orange represent predicted inhibition/activation.

Abbreviations: IDH2, isocitrate dehydrogenase 2; KO, knockout; PhIP, 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine

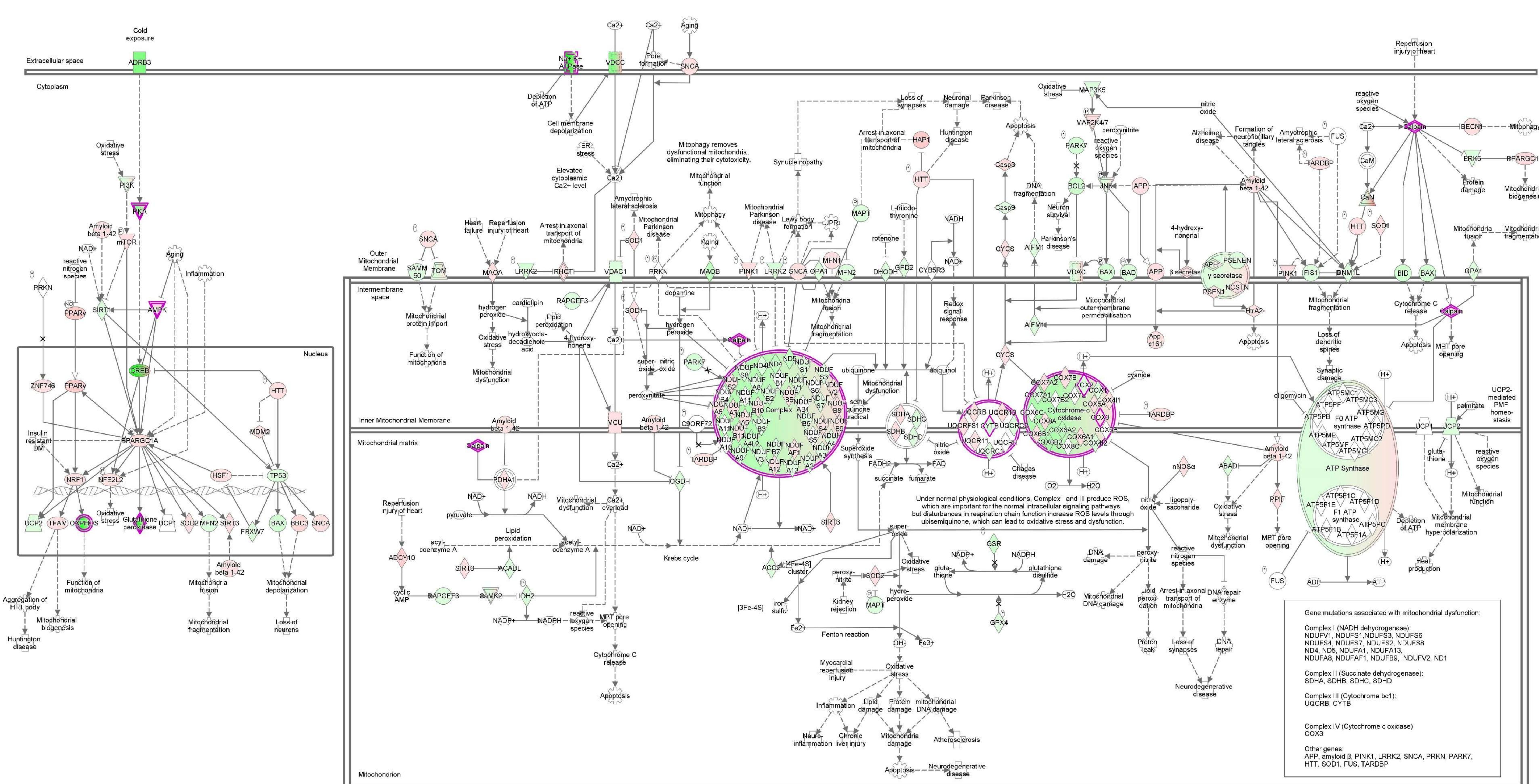


Figure S5. Canonical Pathway: Mitochondrial dysfunction.

Colonic transcriptomics suggests that PhIP treatment in IDH2 KO mice did not significantly alter mitochondrial dysfunction in the colon compared to IDH2 KO mice alone. Red indicates observed inhibition/activation, while green represents predicted inhibition.

Abbreviations: IDH2, isocitrate dehydrogenase 2; KO, knockout; PhIP, 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine

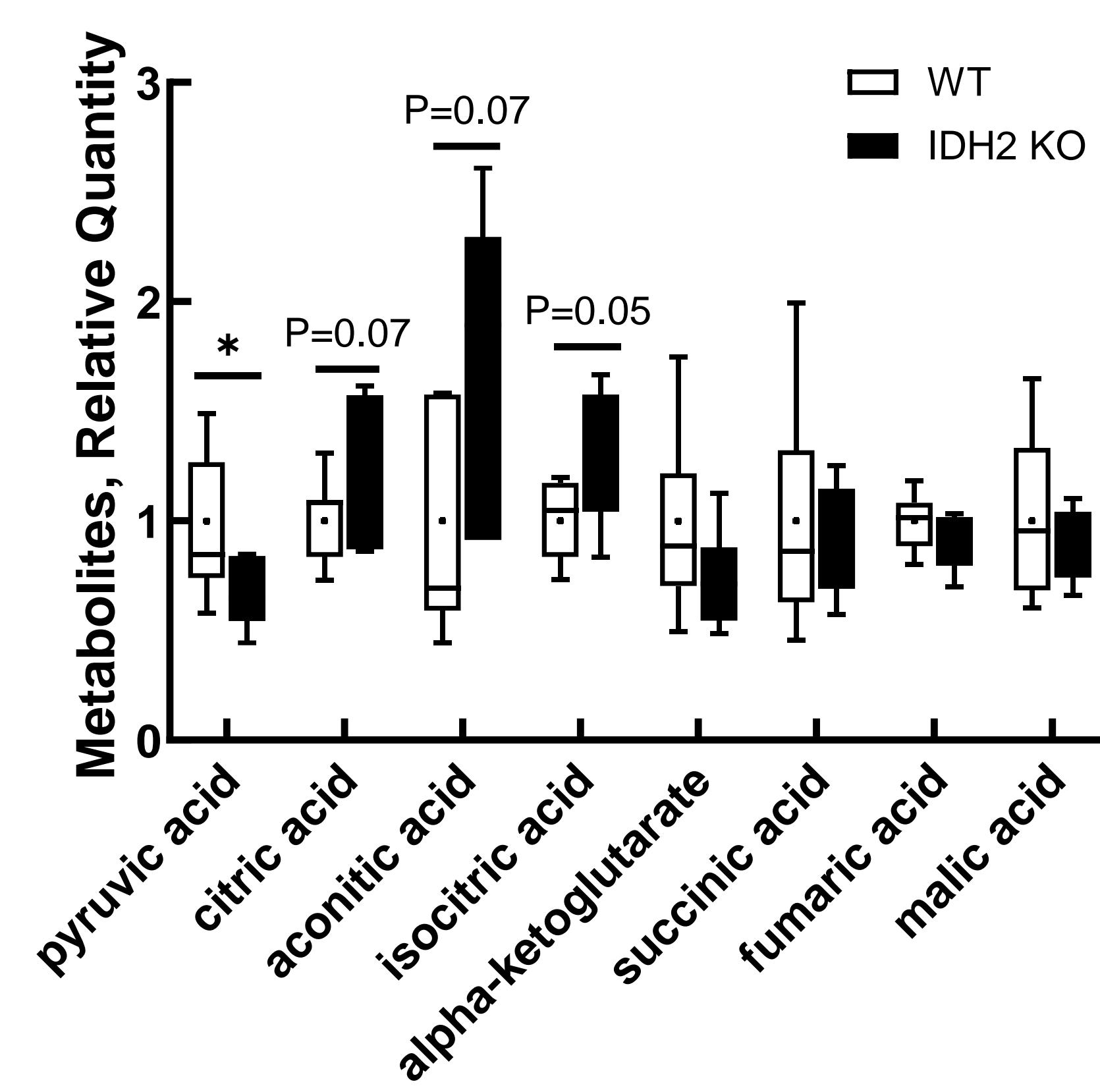


Figure S6. Plasma metabolomics revealed that isocitrate dehydrogenase 2 (IDH2) knockout (KO) may induce reductive TCA cycle.

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 pathways¹ in colon tissues by IDH2 knockout

Canonical Pathways	-log(p-value)	z-score ²
Interferon alpha/beta signaling	10.7	3.606
Role of Hypercytokinemia/hyperchemokinemia 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

¹Activity states were predicted by the IPA software using differentially expressed genes.²Calculated activity score. Positive and negative values indicate predicted activated and predicted inhibited, respectively.