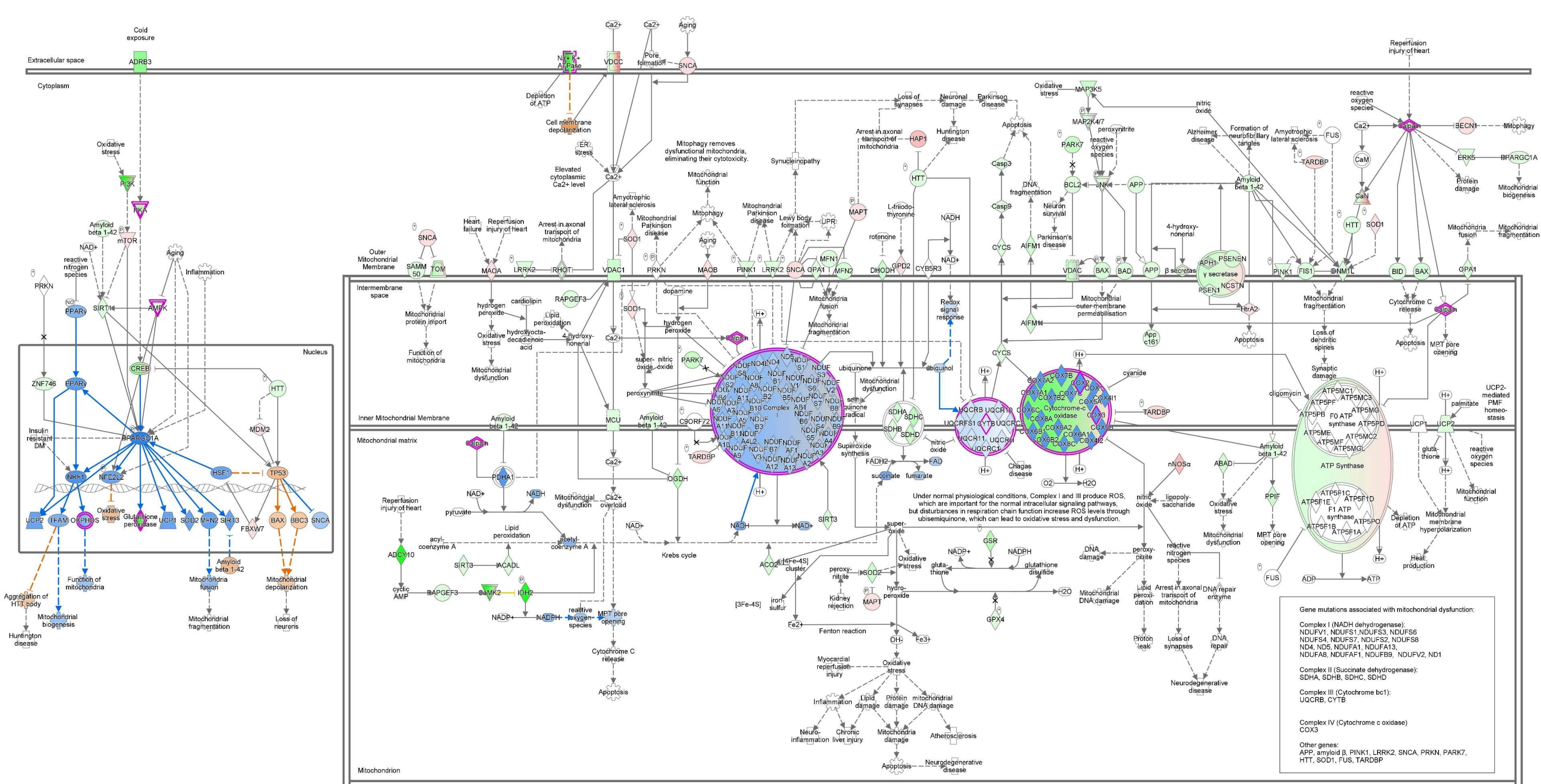


**Figure S1. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway: Chemical Carcinogenesis – DNA adducts.**

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.

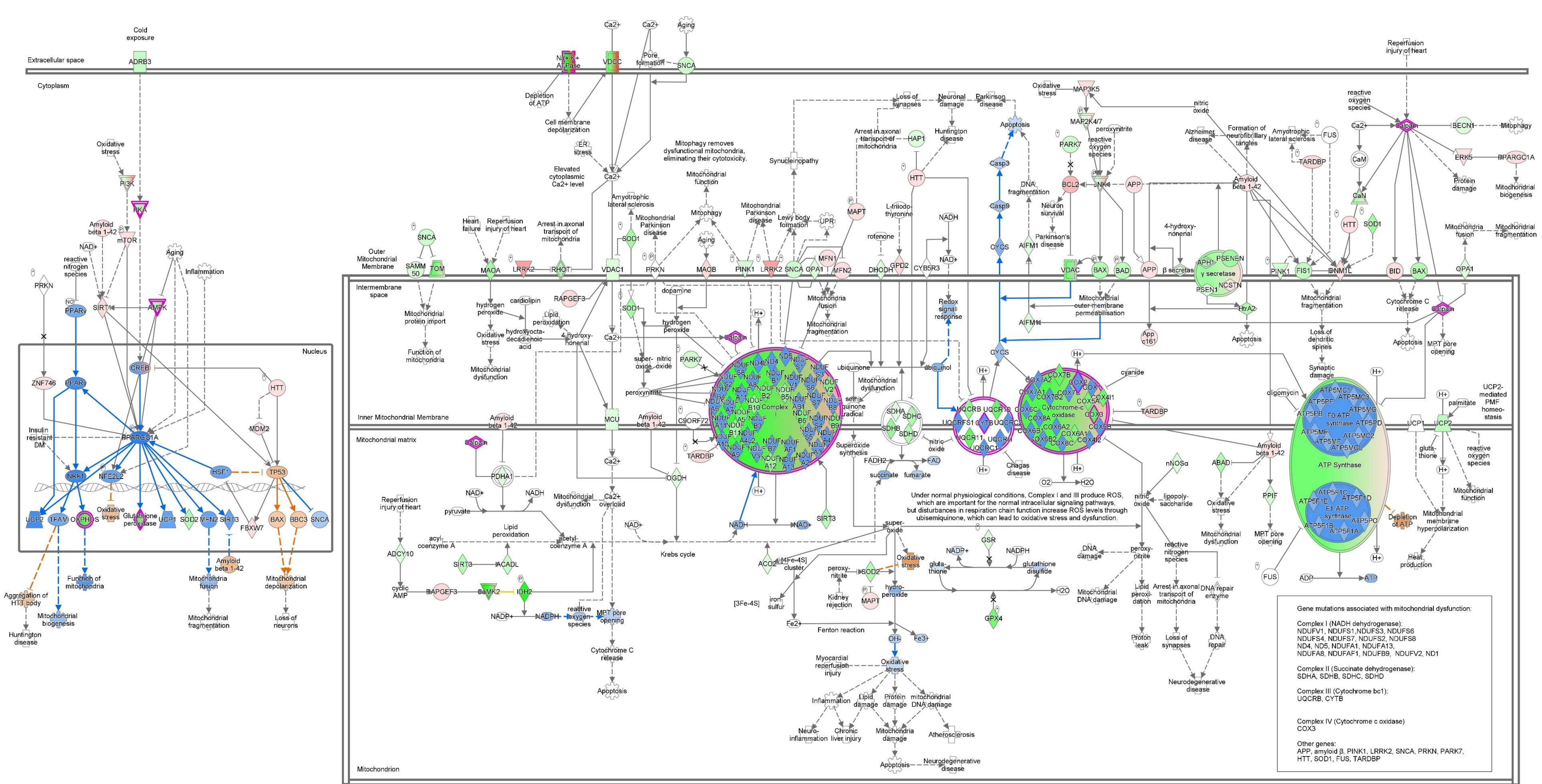
Blue/red indicate observed inhibition/activation, while green/orange represent predicted inhibition/activation.

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

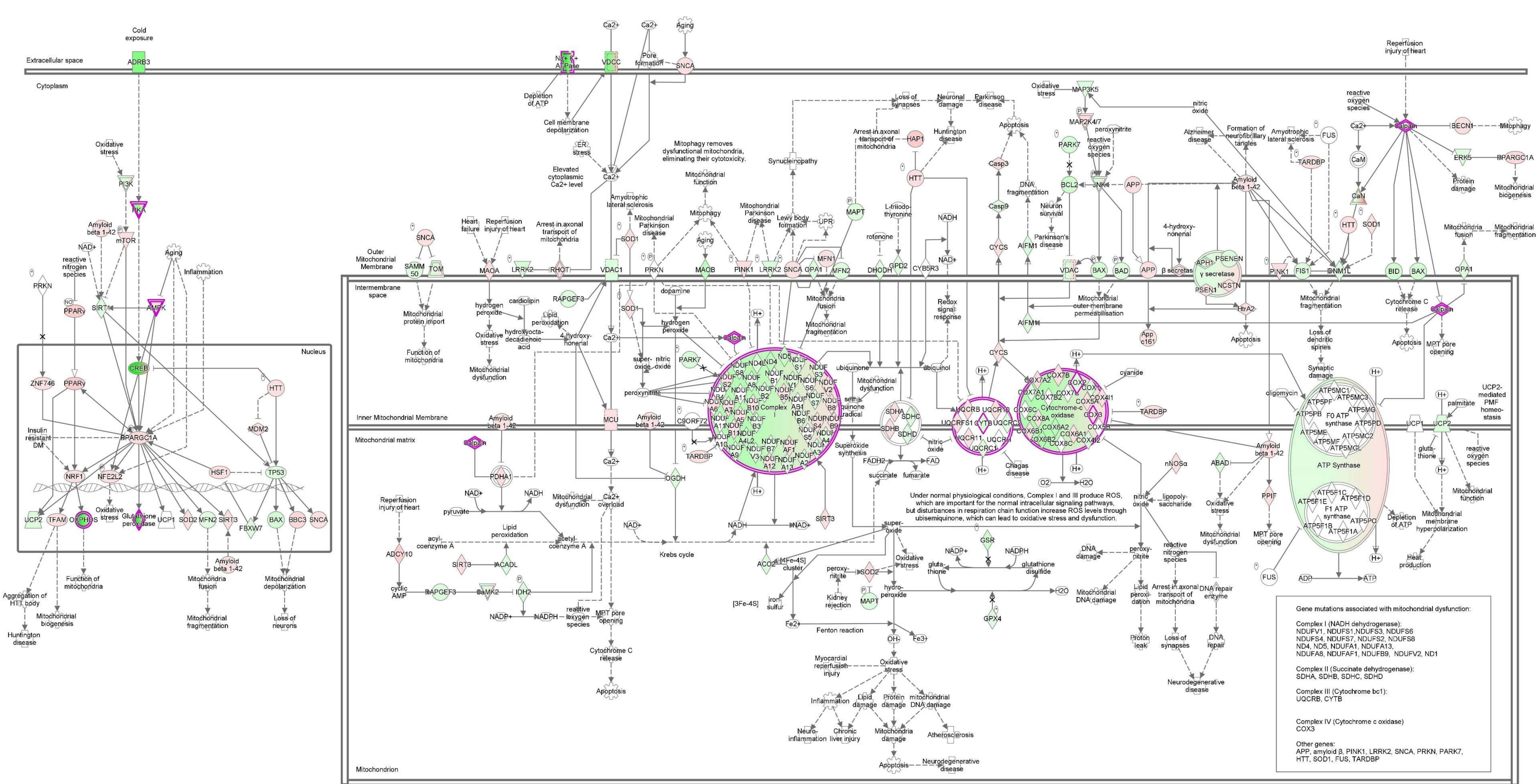










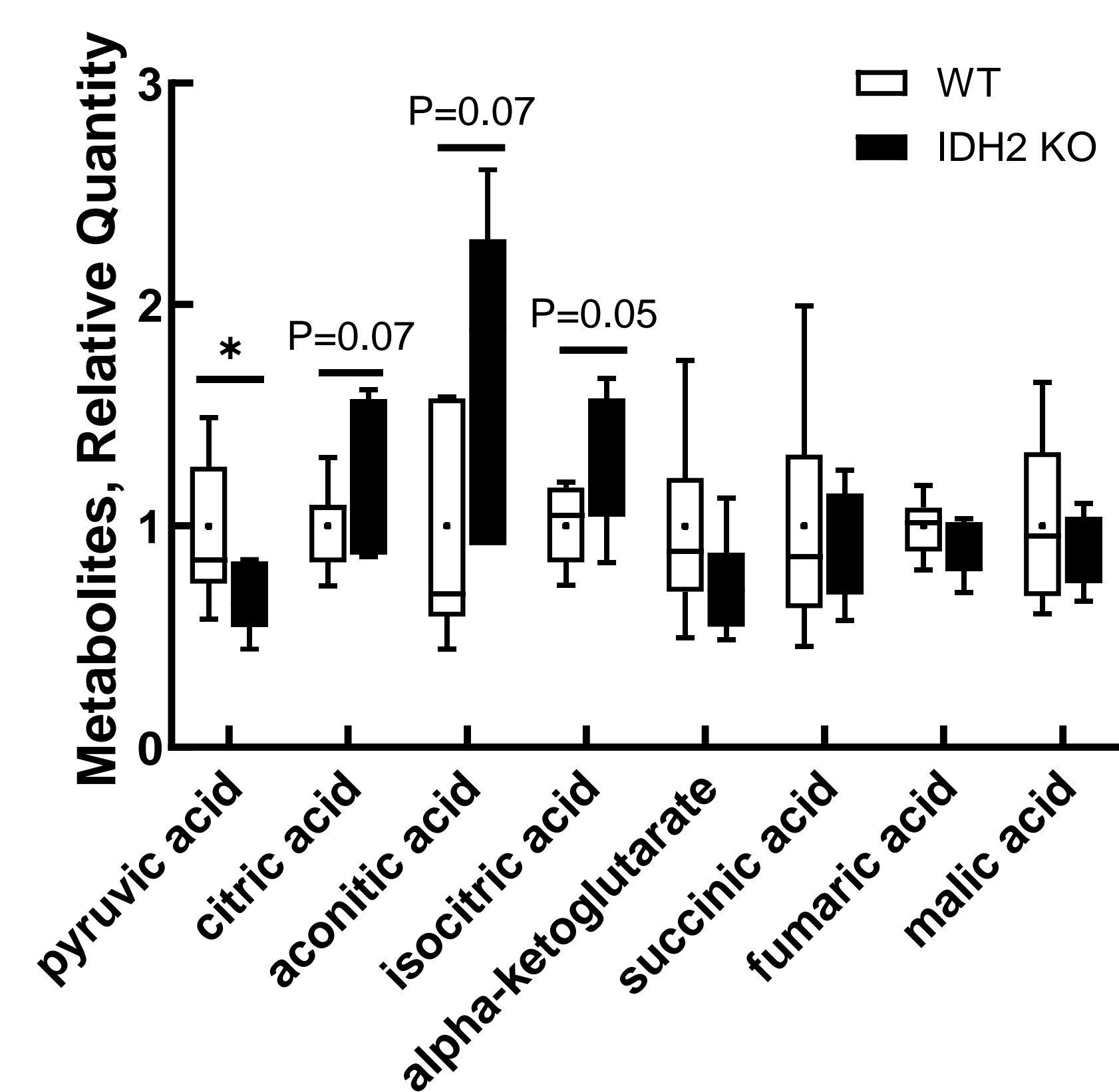


**Figure S5. Canonical Pathway: Mitochondrial dysfunction.**

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