Supplemental Figure Legends

Supplementary Figure 1

Sepp1 message is decreased in human cancer and tumors from mice subjected to the AOM/DSS protocol. **(A)** Human *SEPP1* mRNA expression at various stages of colon tumorigenesis (10-normals, 6-adenomas, 33-Stage I, 76-Stage 2, 82-Stage 3, 59-Stage 4 for combined total of 250 CRC samples, GSE17538). **(B)** Mouse *Sepp1* mRNA expression in tumors (n = 5) isolated from AOM/DSS mice relative to adjacent non-malignant mucosa (n = 5), normalized to GAPDH. ***P < 0.001, 2-tailed unpaired t test.

Supplementary Figure 2

Crypt apoptosis is increased and crypt proliferation is decreased in *Sepp1*$^{-/-}$ AOM/DSS-treated colons. **(A)** Quantification (left) and images (right) of crypt apoptosis (average TUNEL^{+}/crypt; WT, 7; *Sepp1*$^{+/-}$, 6; *Sepp1*$^{-/-}$, 7). Intratumoral protein expression of cleaved caspase-3, caspase-3, cleaved PARP, and β-actin as a loading control with three replicates within each genotype (bottom right). Quantification is shown in Figure 3. **(B)** Representative images of TUNEL staining within the tumor high-powered field. **(C)** Quantification (left) and representative images (right) of crypt proliferation (average ki67^{+}/crypt; WT, 8; *Sepp1*$^{+/-}$, 5; *Sepp1*$^{-/-}$, 8). **(D)** Representative images of ki67 staining within the tumor high-powered field. **(E)** Quantification (left) and representative images (right) of DNA damage (average 8-OHdG^{+}/crypt; WT, 8; *Sepp1*$^{+/-}$, 5; *Sepp1*$^{-/-}$, 8). **(F)** Representative image of 8-hydroxyguanine staining within the tumor high-powered field. All images were taken at 40x magnification. *P < 0.05, **P < 0.01, ***P < 0.001, 1-way ANOVA, Newman-Keuls Multiple Comparison Test.

Supplementary Figure 3

Proliferation and DNA damage are increased in *Sepp1*$^{\Delta 240\text{-}361/\Delta 240\text{-}361}$ colons post-AOM/DSS administration. **(A)** Representative intratumoral proliferation staining as determined by ki67 positivity. **(B)** Crypt and **(C)** intratumoral DNA damage as measured by 8-hydroxyguanine staining. Images taken at 40x magnification.

Supplementary Figure 4

Crypt proliferation and crypt and tumor apoptosis are unaltered in *Sepp1*$^{\Delta 240\text{-}361/\Delta 240\text{-}361}$ colons. **(A)** Quantification of crypt proliferation (ki67^{+} cells/crypt; WT, 8; *Sepp1*$^{\Delta 240\text{-}361/\Delta 240\text{-}361}$, 7). **(B)** Quantification of crypt (TUNEL^{+} cells/crypt; WT, 8; *Sepp1*$^{\Delta 240\text{-}361/\Delta 240\text{-}361}$, 8) and **(C)** intratumoral (TUNEL^{+} cells/tumor HPF; WT, 5; *Sepp1*$^{\Delta 240\text{-}361/\Delta 240\text{-}361}$, 13) apoptosis.

Supplementary Figure 5

Proliferation and DNA damage are increased in colons of *Sepp1*$^{U40S/U40S}$ mice. **(A)** Representative images of proliferation in crypts (ki67^{+} cells/crypt) and **(B)** tumors (ki67^{+} cells/tumor HPF). **(C)** Representative images of DNA damage in crypts (8-OHdG^{+} cells/crypt) and **(D)** tumors (8-OHdG^{+} cells/tumor HPF). HPF is 40x magnification.

Supplementary Figure 6

Apoptosis is unaltered in colons of *Sepp1*$^{U40S/U40S}$ mice post-AOM/DSS protocol. **(A)** Quantification of crypt (TUNEL^{+} cells/crypt; WT, 7; *Sepp1*$^{U40S/U40S}$, 7) and **(B)** intratumoral (TUNEL^{+} cells/tumor HPF; WT, 6; *Sepp1*$^{U40S/U40S}$, 17) apoptosis in colons of mice treated with the AOM/DSS protocol.

Supplementary Figure 7

Oxidoreductase proteins are alternatively regulated at the mRNA level in *Sepp1*$^{-/-}$ tumors, but expression of other selenoproteins is unaltered. **(A)** RNAseq analysis of significantly-altered antioxidant genes.

Supplementary Figure 8

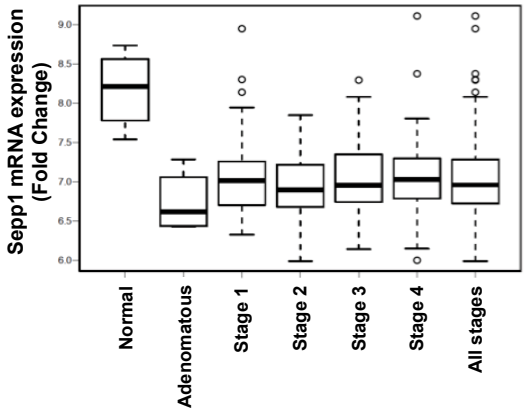
Ingenuity pathway analysis of alterations in Canonical Signaling in *Sepp1*$^{-/-}$ tumor RNAseq data relative to WT data. The Wnt pathway was one of the most significantly altered pathways (highlighted in red).

Supplementary Figure 9

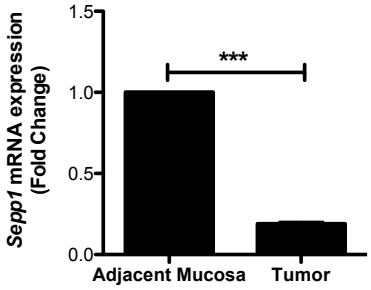
Ingenuity pathway analysis of *Sepp1*$^{-/-}$ tumor RNAseq data relative to WT data. WNT pathway alterations demonstrated in a pathway map. Genes highlighted with red are overexpressed and genes highlighted

with green are suppressed. Intensity of color indicates extent of expression where darker color indicates a greater expression change.

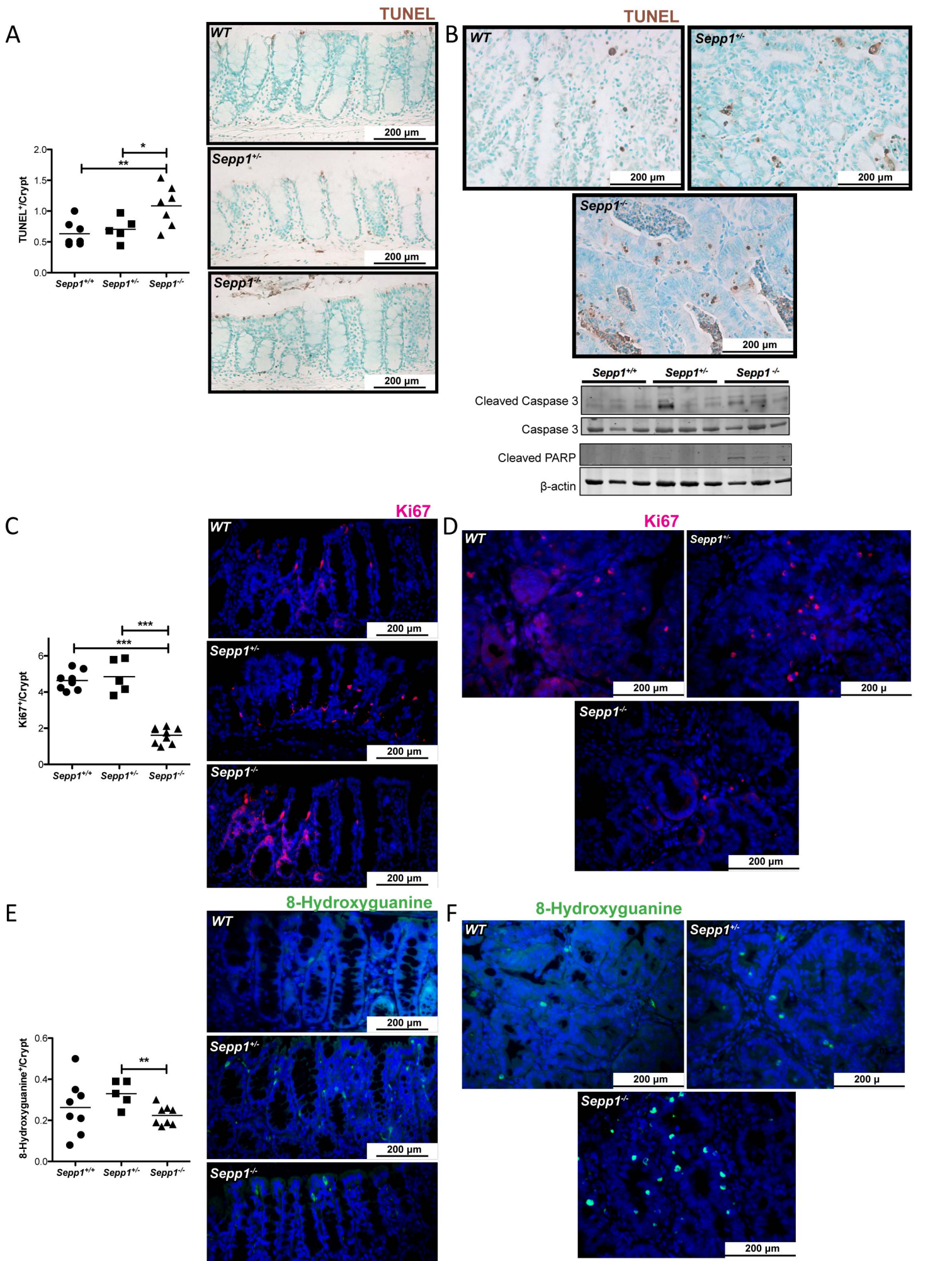
A



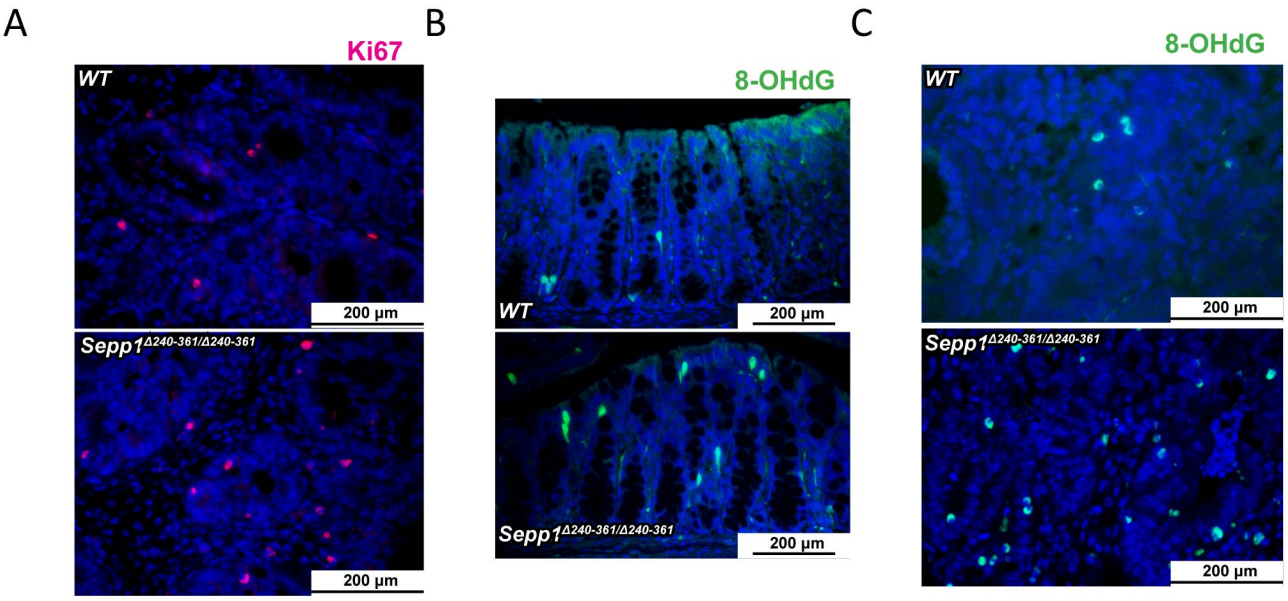
B



Supplementary Figure 1

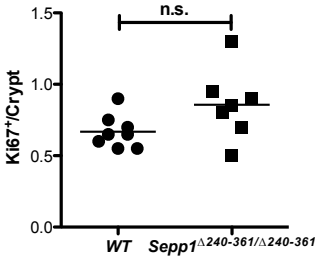


Supplementary Figure 2

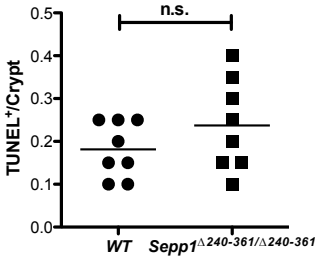


Supplementary Figure 3

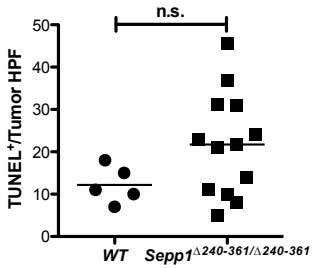
A



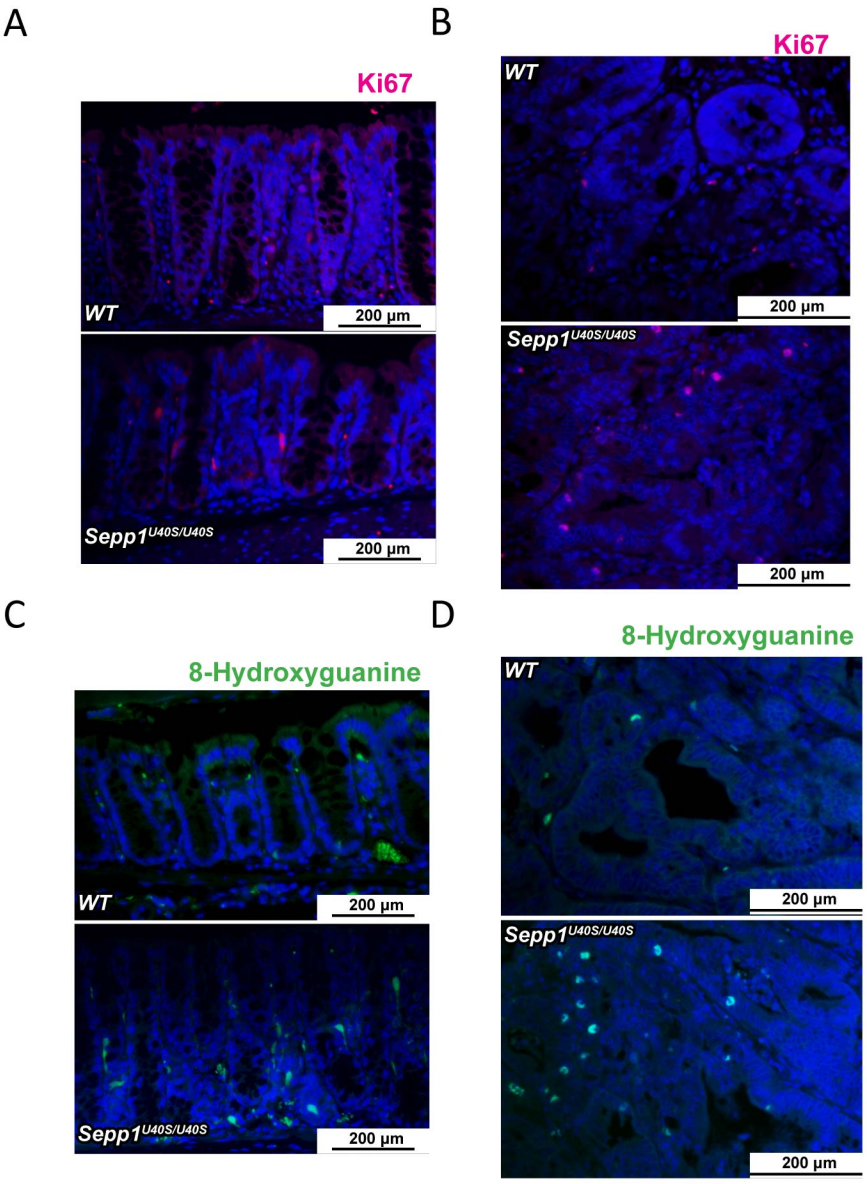
B



C

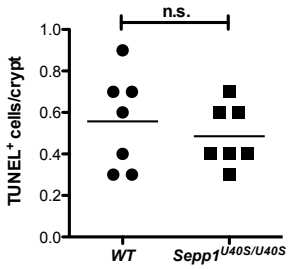


Supplementary Figure 4

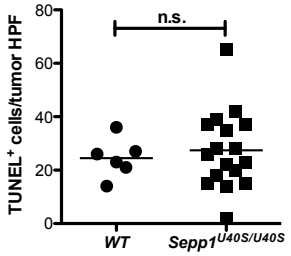


Supplementary Figure 5

A



B

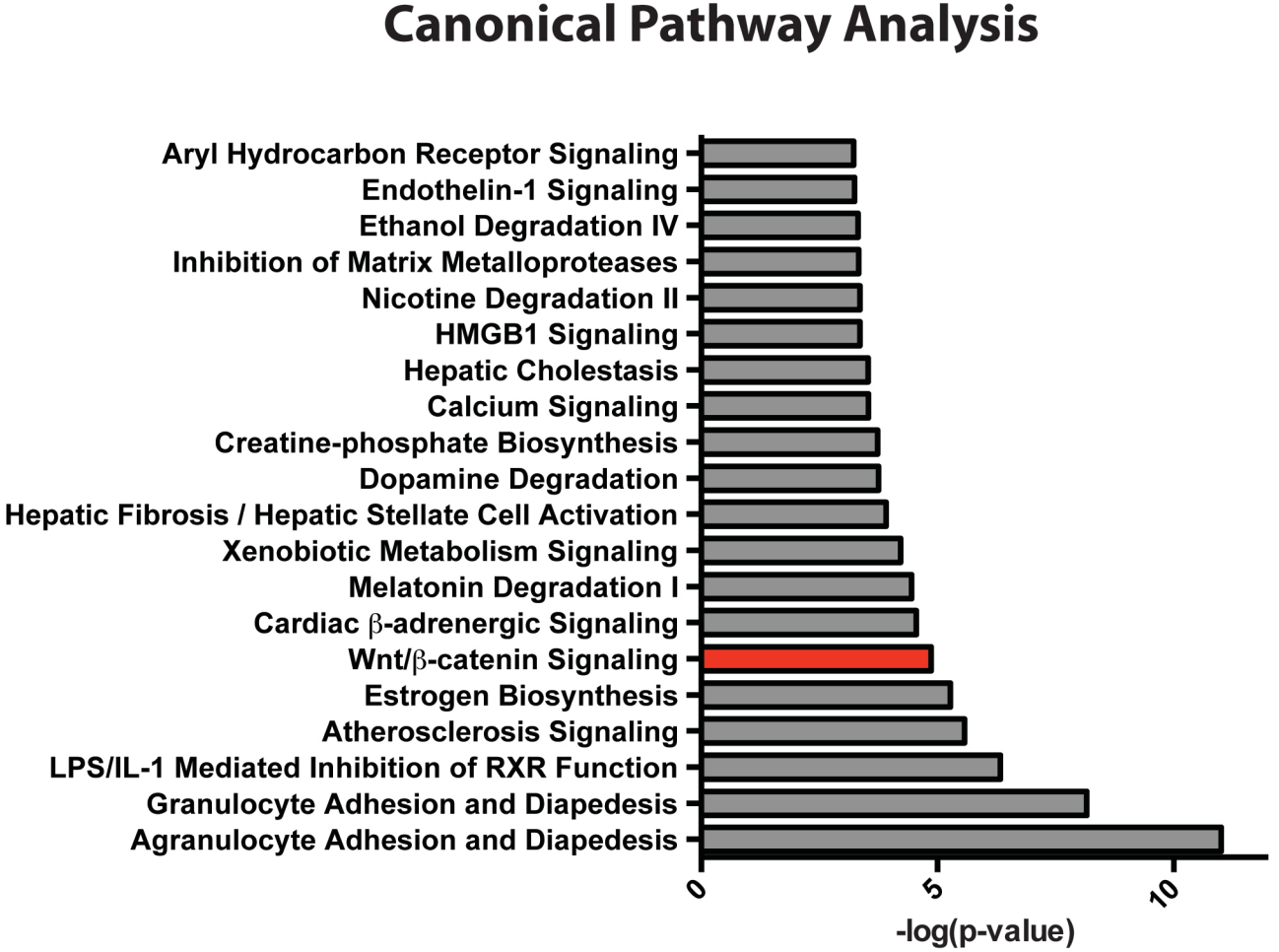


Supplementary Figure 6

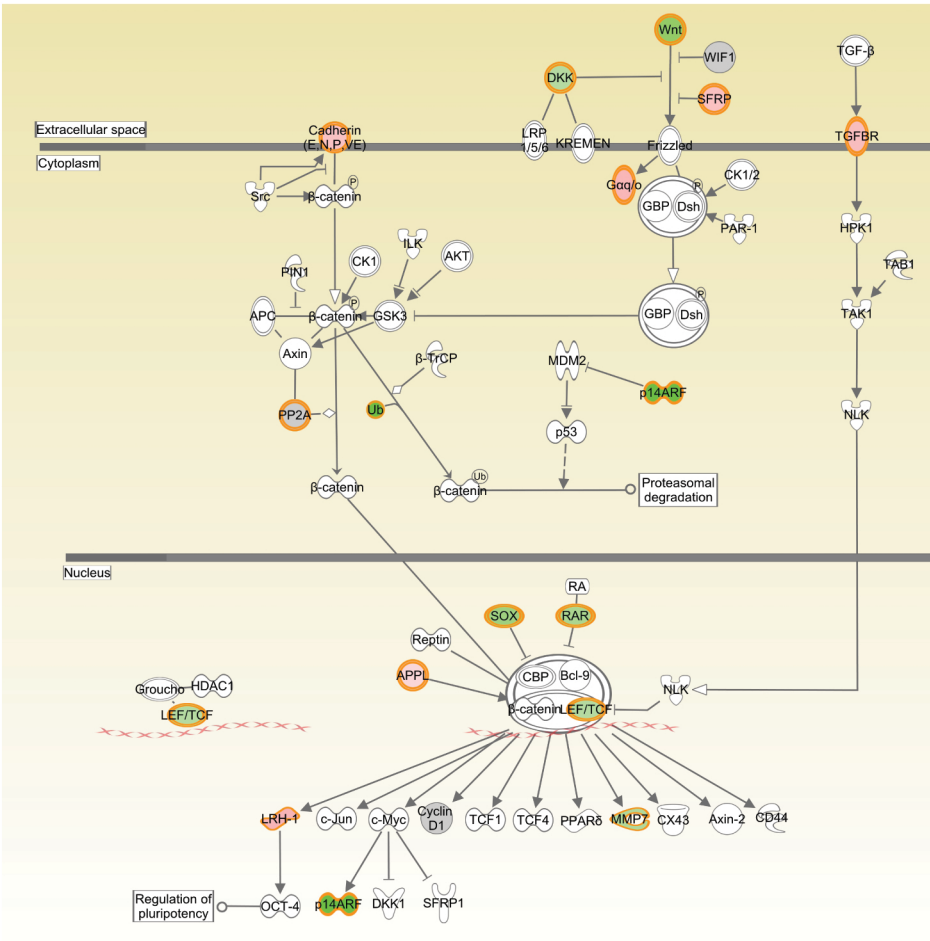
A

Gene Symbol	Gene Name	Enzymatic Activity	Fold Change	P-value
Cyp2b10	Cytochrome P450 2B10	oxidoreductase activity	-2.1	0.0001
Aldh1a1	Retinal dehydrogenase 1	oxidoreductase activity	2	5.00E-05
Hpd	4-hydroxyphenylpyruvate dioxygenase	oxidoreductase activity	2.1	5.00E-05
Hsd3b2	3 beta-hydroxysteroid dehydrogenase/Delta 5-->4-isomerase type 2	oxidoreductase activity	2.2	5.00E-05
Cyp2d9	Cytochrome P450 2D9	oxidoreductase activity	2.2	5.00E-05
Fmo2	Dimethylaniline monooxygenase [N-oxide-forming] 2	oxidoreductase activity	2.2	5.00E-05
Hsd17b13	17-beta-hydroxysteroid dehydrogenase 13	oxidoreductase activity	2.2	5.00E-05
Nos1	Nitric oxide synthase, brain	oxidoreductase activity	2.2	5.00E-05
Cyp2c65	Cytochrome P450, family 2, subfamily c, polypeptide 65	oxidoreductase activity	2.3	5.00E-05
Cyp4b1	Cytochrome P450 4B1	oxidoreductase activity	2.3	0.00065
Cyp4f14	Leukotriene-B4 omega-hydroxylase 3	oxidoreductase activity	2.34	5.00E-05
Hao2	Hydroxyacid oxidase 2	oxidoreductase activity	2.4	5.00E-05
Nrxn2	Protein Nrxn2	oxidoreductase activity	2.5	0.00025
Ddo	D-aspartate oxidase	oxidoreductase activity	2.5	0.00035
Dpyd	Dihydropyrimidine dehydrogenase [NADP(+)]	oxidoreductase activity	2.6	5.00E-05
Hsd3b3	3 beta-hydroxysteroid dehydrogenase/Delta 5-->4-isomerase type 3	oxidoreductase activity	2.6	5.00E-05
Cyp2c55	Cytochrome P450 2C55	oxidoreductase activity	2.7	5.00E-05
Cd163	Scavenger receptor cysteine-rich type 1 protein M130	oxidoreductase activity	3.2	5.00E-05
Cyp2d12	Cytochrome P450, family 2, subfamily d, polypeptide 12	oxidoreductase activity	3.7	5.00E-05
Clvs2	Clavesin-2	oxidoreductase activity	3.8	0.0011
Cyp2e1	Cytochrome P450 2E1	oxidoreductase activity	4.1	5.00E-05

Supplementary Figure 7



Supplementary Figure 8



Supplementary Figure 9