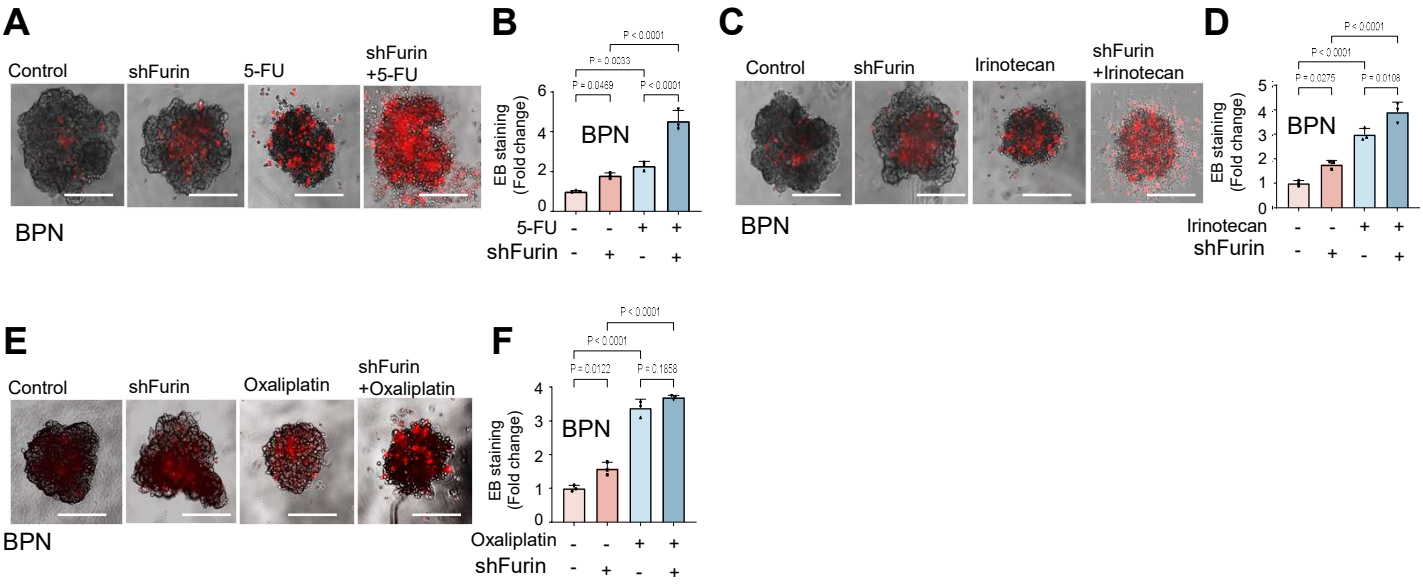
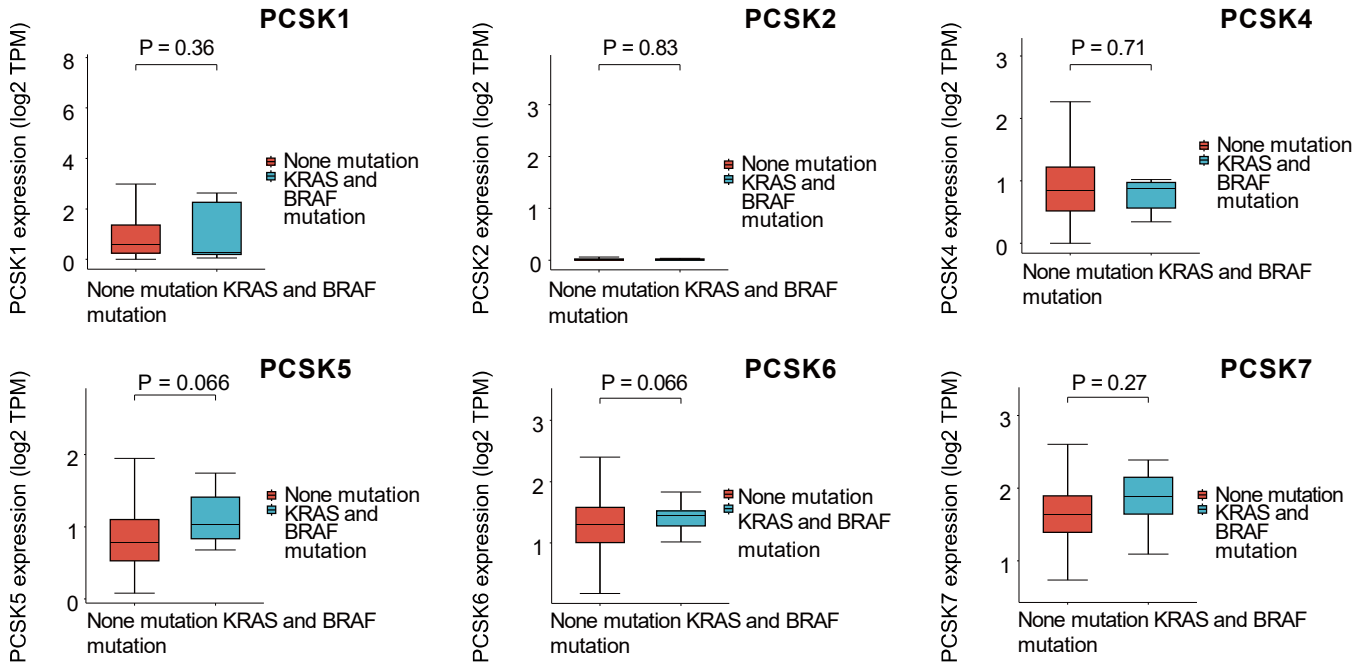
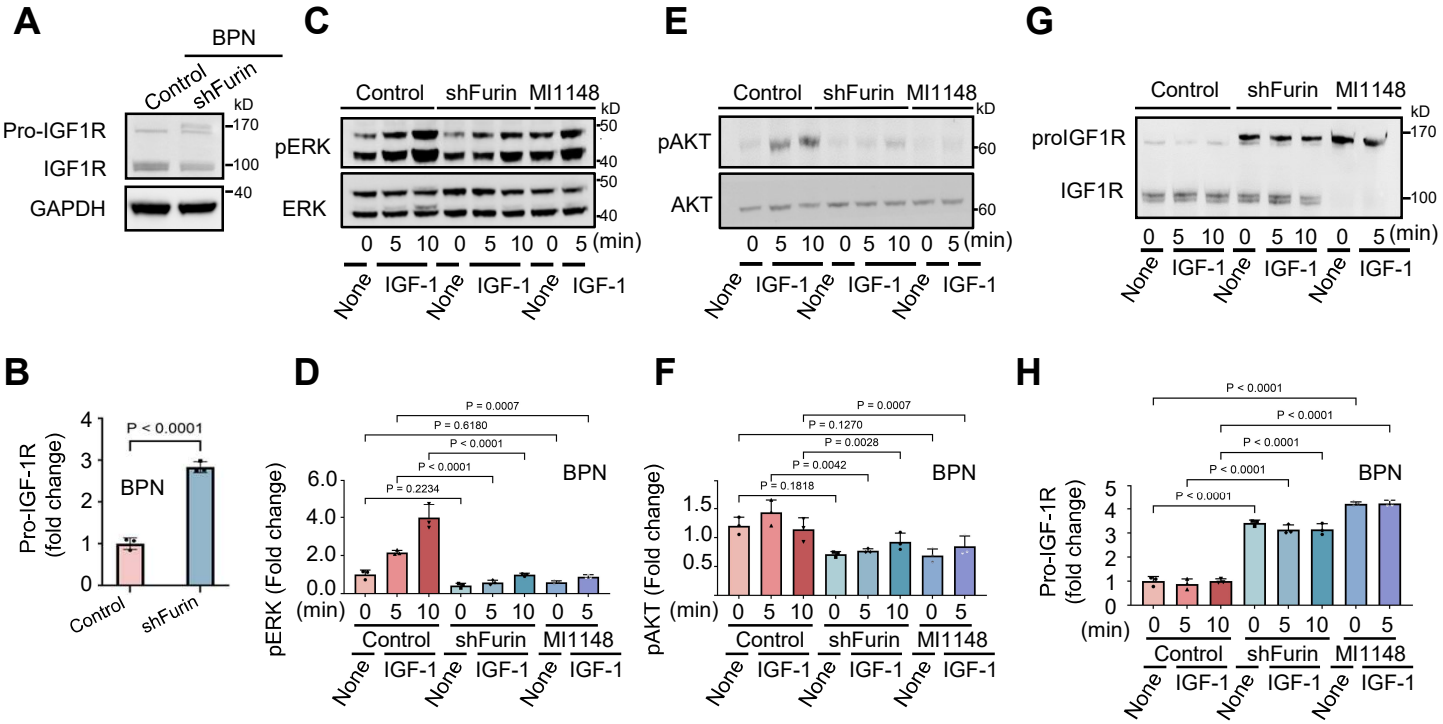


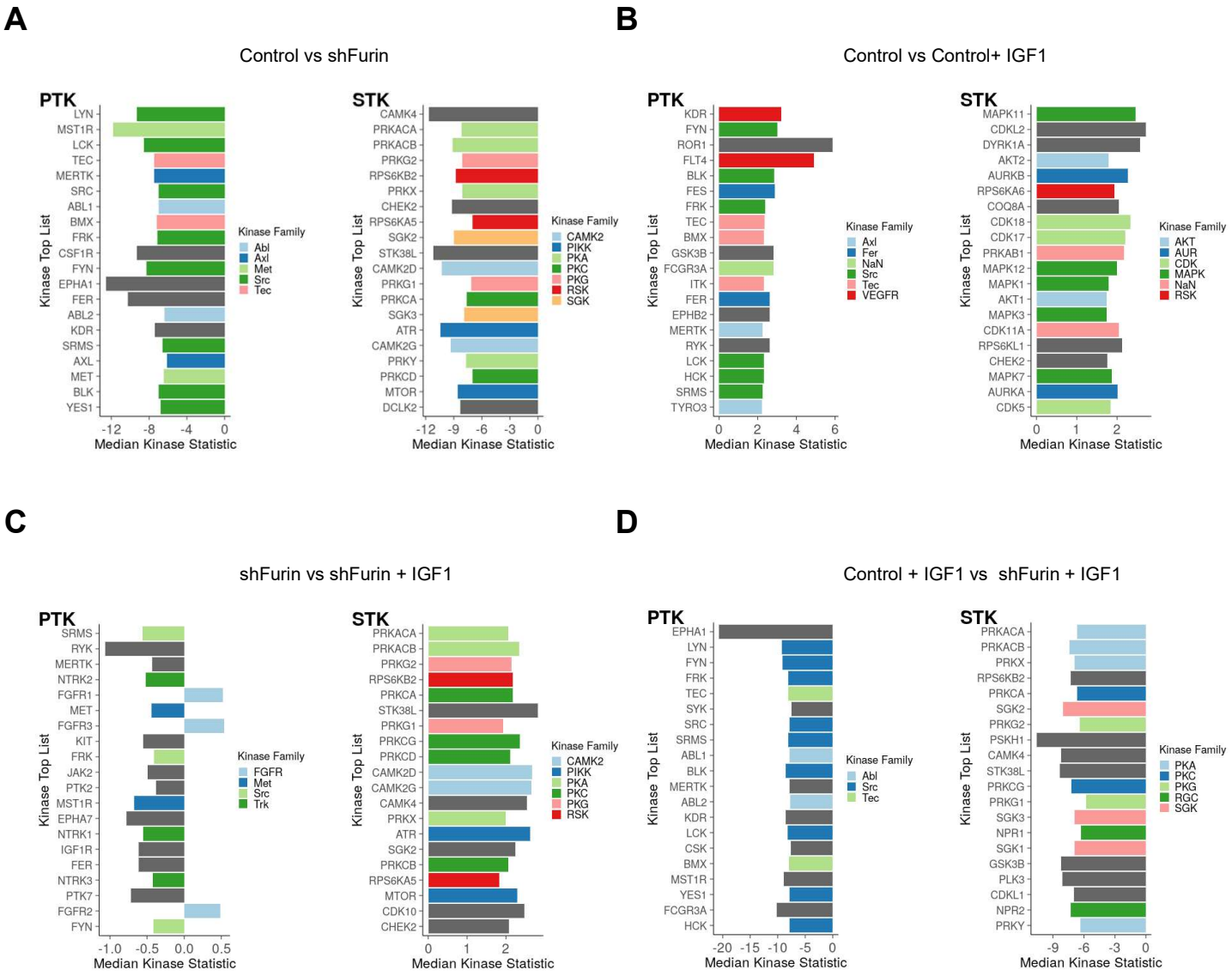
Supplementary Fig. S1. (A, C, E) Representative images of BPN organoids (control and shFurin-expressing) treated with **5-fluorouracil (5-FU, 500 µM)** (A), **irinotecan (10 µM)** (C), or **oxaliplatin (10 µM)** (E). Cytotoxicity was assessed using ethidium bromide (EB) staining. Images are representative of 6 organoids per condition from 3 independent experiments. **(B, D, F)** Quantification of EB staining intensity corresponding to treatments shown in A, C, and E, respectively, expressed as percentage of staining. Scale bars: 500 µm. Data are shown as mean ± SD from three independent experiments. Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparison test.



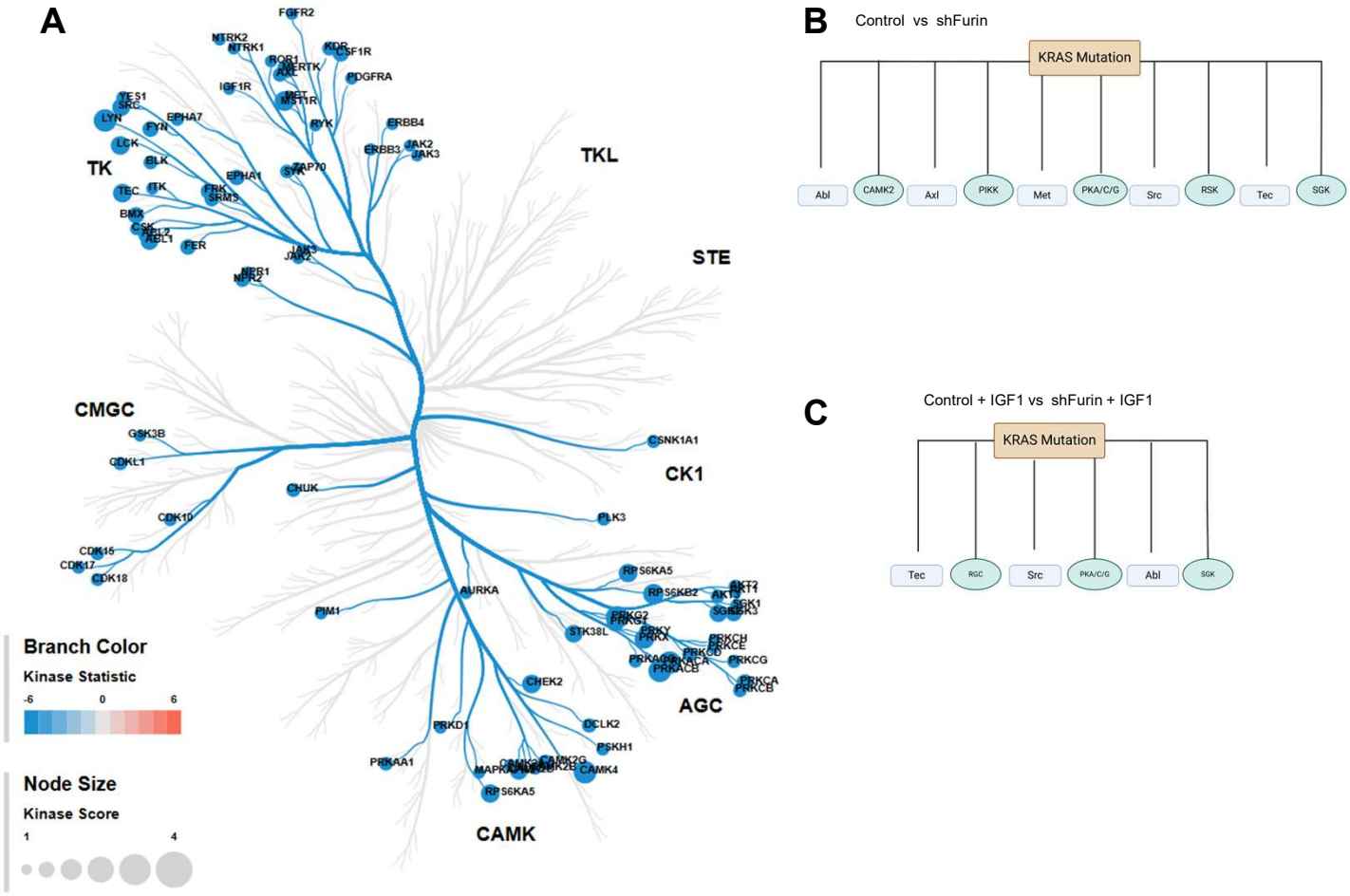
Supplementary Fig. S2. : Expression levels of indicated PCs in COAD and READ mutated tissues (n = 17) and non-mutated tissues (n = 328) were obtained from the TCGA dataset. The central band, boxes, and whiskers of the box plot represent the median, first quartile, third quartile, minimum, and maximum values. COAD: Colon adenocarcinoma, READ : Rectum adenocarcinoma



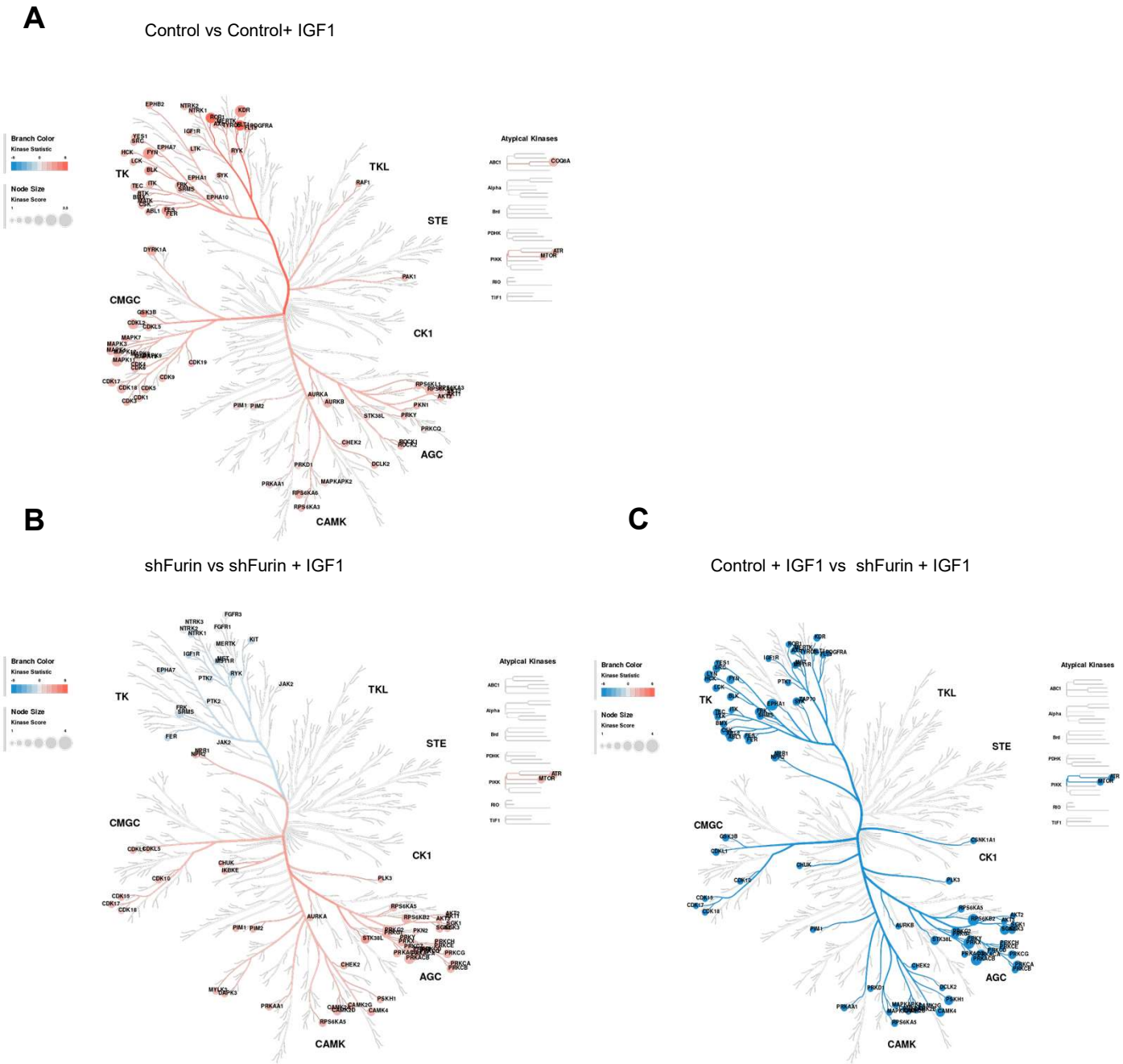
Supplementary Fig. S3. (A) Western blot analysis showing both the precursor form of IGF-1R (Pro-IGF-1R) and the mature, processed form (IGF-1Rβ) in BRAF-mutant control cells (BPN) and in BPN cells with stable shFurin expression. **(B)** Quantification of Pro-IGF-1R accumulation, calculated as the ratio of Pro-IGF-1R to total IGF-1R (Pro-IGF-1R / [Pro-IGF-1R + IGF-1R]), expressed as a percentage. **(C-F)** Immunoblot analysis of phosphorylated and total ERK1/2 (**C, D**) and AKT (**E, F**) in control BPN cells and in BPN cells stably expressing shFurin, following IGF-1 stimulation (100 ng/mL) at the indicated time points. Quantification of phosphorylated proteins (**D, F**) was normalized to total protein levels. **(G)** Western blot analysis of Pro-IGF-1R accumulation in both control BPN and shFurin-expressing BPN cells. **(H)** Quantification of mature IGF-1R levels, calculated as the ratio of IGF-1R to total IGF-1R (IGF-1R / [Pro-IGF-1R + IGF-1R]), shown as a percentage of total receptor. All data are derived from three independent experiments (n = 3 per experiment) and presented as mean ± SD. Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparison test for panels D, F, and H, and an unpaired two-tailed t-test for panel B.



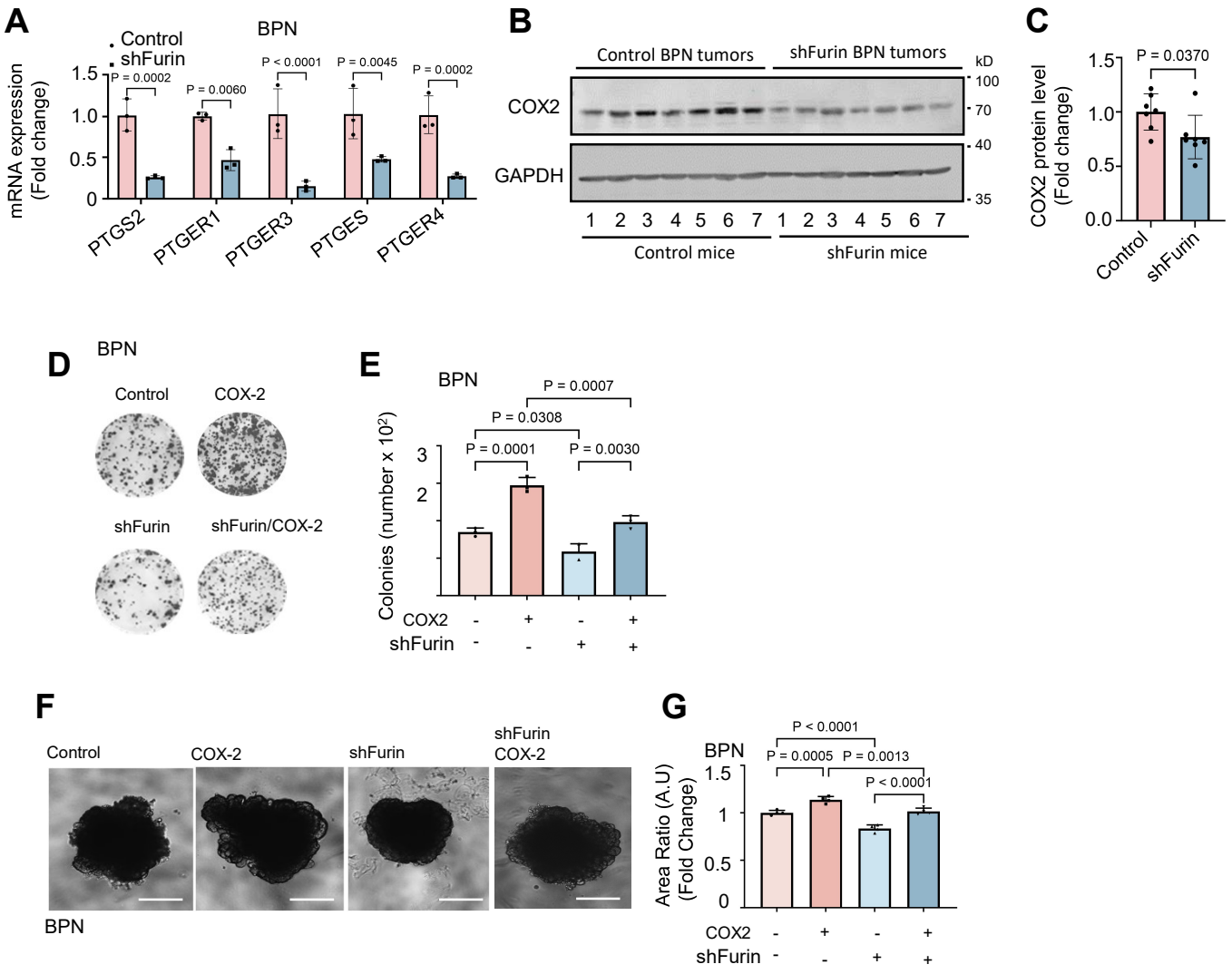
Supplementary Fig. S4: Upstream kinase analysis of PTK and STK of Control vs shFurin (A), Control vs Control+ IGF1, (B), shFurin vs shFurin + IGF1 (C), shFurin vs shFurin + IGF1, showing the top 20 ranked kinases (normalized kinase statistic (log2) < 0: less kinase activity in treated cells; specificity score (log2) > 1.3; white to red bars: statistically significant changes).



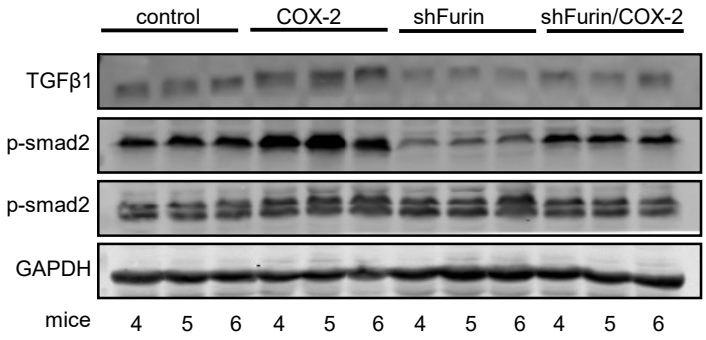
Supplementary Fig. S5 : (A) Kinome tree depicting kinases in control and shFurin-expressing cells, grouped into phylogenetic families. Only kinases with a Kinase Score > 1.3 (above default threshold) are shown. Kinome trees were generated using the CORAL tool (http://phanstiel-lab.med.unc.edu/CORAL/). **(B)** Protein tyrosine kinases (PTKs, blue) and serine/threonine kinases (STKs, green) were downregulated in shFurin-expressing cells. **(C)** Similar downregulation of PTKs (blue) and STKs (green) was observed in shFurin-expressing cells following IGF-1 stimulation.



Supplementary Fig. S6 : Kinome Tree, grouping the kinases in Control vs Control+ IGF1 **(A)**, shFurin vs shFurin + IGF1 **(B)**, shFurin vs shFurin + IGF1 **(C)**, into phylogenetic families. The Coral Trees display all kinases above the default threshold (Kinase Score > 1.3). The Coral Trees were generated using http://phanstiel-lab.med.unc.edu/CORAL/.



Supplementary Fig. S7, (A) Relative mRNA expression levels of PTGS2, PTGER1, PTGER3, PTGER4, and PTGES in control BPN cells and in BPN cells stably expressing shFurin, measured by qRT–PCR and normalized to *GAPDH* (n = 3 independent experiments). **(B)** Western blot analysis of COX2 protein levels in tumors derived from control BPN cells and from shFurin-expressing BPN cells-injected mice (n = 7). **(C)** Quantification of COX2 protein expression in tumors from mice injected with control and shFurin-expressing cells, based on the data shown in (B). **(D, E)** Representative images (**D**) and quantification (**E**) of colony formation by control BPN cells and shFurin-expressing cells, stained with crystal violet (n = 3 independent experiments). **(F)** Representative images of organoid morphology in control and shFurin-expressing BPN cells after 5 days of culture (n = 3–6 organoids per condition from 3 independent experiments). **(G)** Quantification of organoid area after 5 days of culture. Scale bars: 500 µm. All data represent mean ± SD from three independent experiments. Statistical significance was assessed by one-way ANOVA with Tukey's multiple comparison test for (A), (E), and (G), and by two-tailed unpaired *t*-test for (C).



Supplementary Fig. S8:(a)Western blot analysis of TGF-β1, p-Smad2, Smad2, and GAPDH expression in tumors derived from mice injected with control KPN cells, or KPN cells expressing COX2, shFurin, or co-expressing shFurin and COX2.