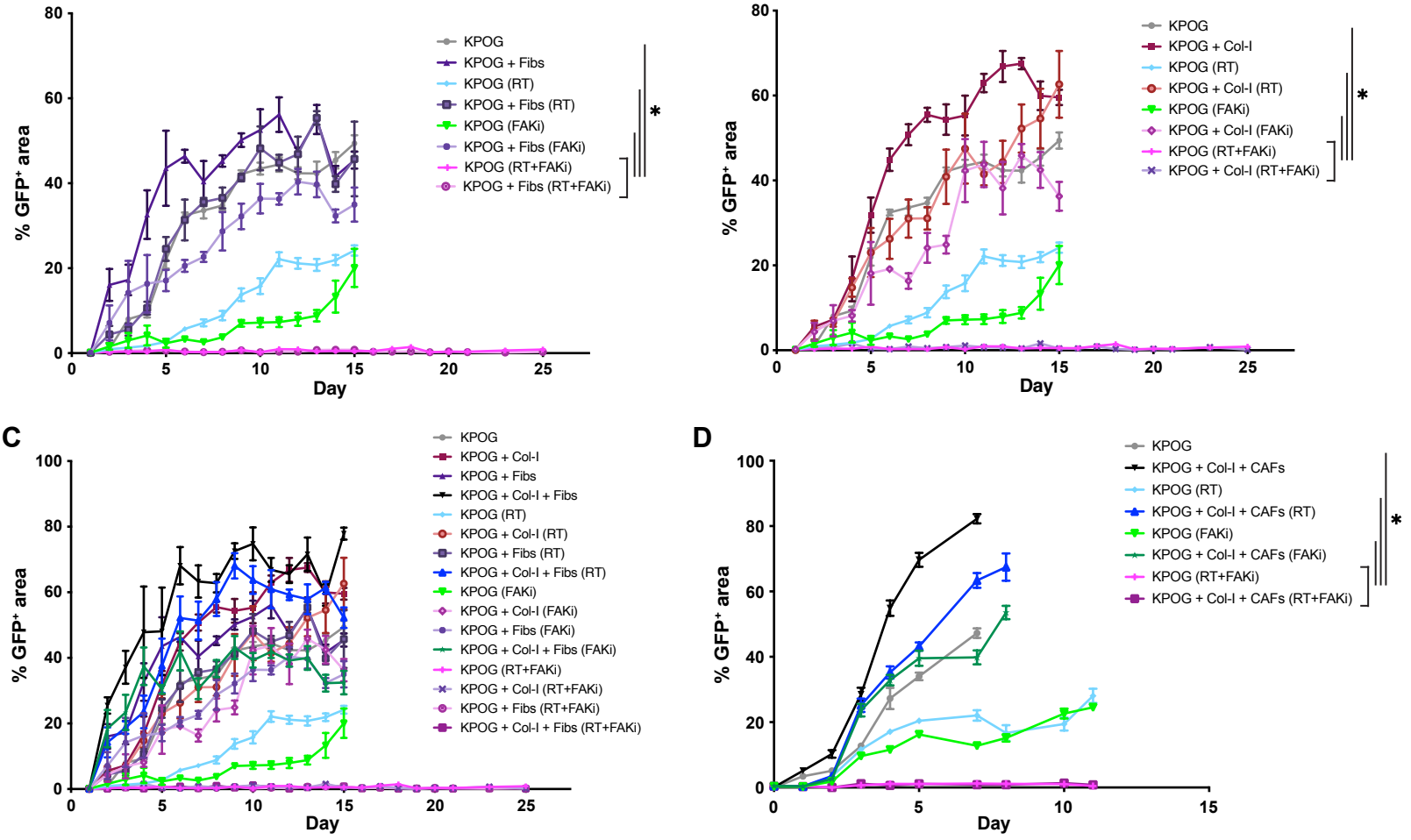
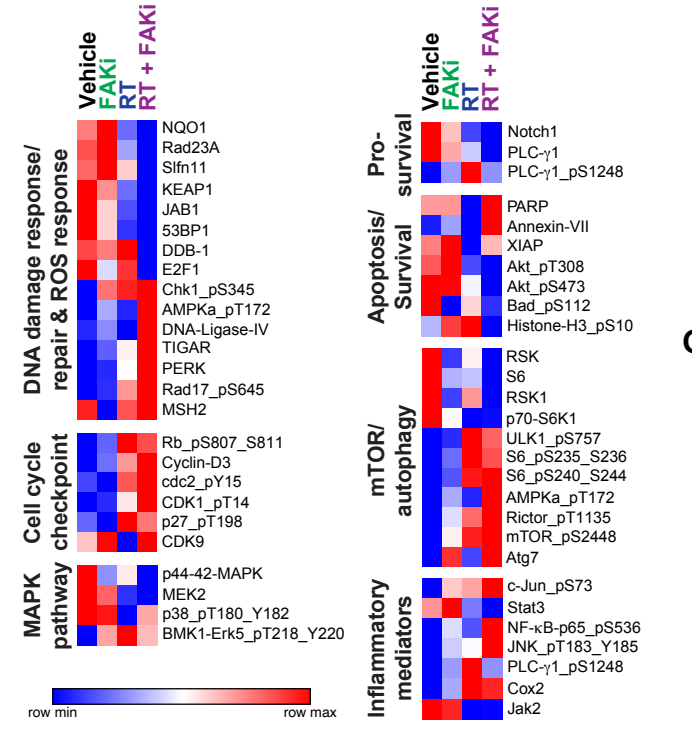

A KPOG organoid in vitro
B
% GFP⁺ area
Day
KPOG
KPOG + Fibs
KPOG (RT)
KPOG + Fibs (RT)
KPOG (FAKi)
KPOG + Fibs (FAKi)
KPOG (RT+FAKi)
KPOG + Fibs (RT+FAKi)
KPOG + Col-I
KPOG + Col-I (RT)
KPOG + Col-I (FAKi)
KPOG + Col-I (RT+FAKi)
C
KPOG + Col-I + Fibs
KPOG + Col-I (FAKi)
KPOG + Fibs (FAKi)
KPOG + Col-I + Fibs (FAKi)
KPOG + Col-I (RT+FAKi)
KPOG + Fibs (RT+FAKi)
KPOG + Col-I + Fibs (RT+FAKi)
D
KPOG + Col-I + CAFs
KPOG + Col-I + CAFs (RT)
KPOG (FAKi)
KPOG + Col-I + CAFs (FAKi)
KPOG (RT+FAKi)
KPOG + Col-I + CAFs (RT+FAKi)


E Proteomics (KRAS-INK)
Vehicle
FAKi
RT
RT + FAKi
DNA damage response/ repair & ROS response
NQO1
Rad23A
Slfn11
KEAP1
JAB1
53BP1
DDB-1
E2F1
Chk1_pS345
AMPKa_pT172
DNA-Ligase-IV
TIGAR
PERK
Rad17_pS645
MSH2
Cell cycle checkpoint
Rb_pS807_S811
Cyclin-D3
cdc2_pY15
CDK1_pT14
p27_pT198
CDK9
MAPK pathway
p44-42-MAPK
MEK2
p38_pT180_Y182
BMK1-Erk5_pT218_Y220
row min
row max
Pro-survival
Notch1
PLC-γ1
PLC-γ1_pS1248
Apoptosis/ Survival
PARP
Annexin-VII
XIAP
Akt_pT308
Akt_pS473
Bad_pS112
Histone-H3_pS10
mTOR/ autophagy
RSK
S6
RSK1
p70-S6K1
ULK1_pS757
S6_pS235_S236
S6_pS240_S244
AMPKa_pT172
Rictor_pT1135
mTOR_pS2448
Atg7
Inflammatory mediators
c-Jun_pS73
Stat3
NF-κB-p65_pS536
JNK_pT183_Y185
PLC-γ1_pS1248
Cox2
Jak2

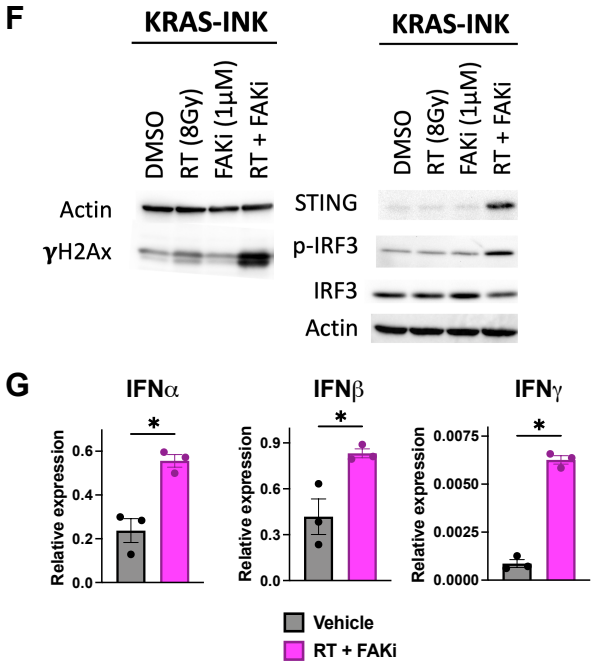

F
KRAS-INK
KRAS-INK
DMSO
RT (8Gy)
FAKi (1μM)
RT + FAKi
Actin
γH2Ax
STING
p-IRF3
IRF3
Actin
G
IFNα
IFNβ
IFNγ
Relative expression
Vehicle
RT + FAKi

Figure S3: Inhibition of Focal Adhesion Kinase overcomes stromal-induced RT resistance

(A-C) Tumor growth analyses of select groups of KPOG organoids co-cultured with fibroblasts (A), KPOG organoids co-cultured with addition of collagen-I (B), and all groups shown (C) when treated with RT +/- FAKi. Cells were cultured as in **Fig. 2A**. n = at least 3/group. **(D)** Tumor growth analysis of KPOG organoids co-cultured with FACS-sorted CAFs from KPC mice and collagen-I treated with RT +/- FAKi. n = at least 4/group. **(E)** RPPA analysis heatmap displaying expression level of proteins related to: (i) DNA damage response/repair and ROS response, (ii) cell cycle checkpoint, (iii) MAPK pathway, (iv) pro-survival, (v) apoptosis/survival, (vi) mTOR/autophagy, and (vii) inflammatory mediators. Proteins were taken from KRAS-INK cells at 24 hours post-treatment. n = at least 3/group. **(F)** Western Blot analysis of γH2Ax, STING, p-IRF3, and total IRF3 proteins from KRAS-INK cells 24 hours post-RT. n = at least 3/group. Representative of at least 3 individual experiments. **(G)** RT-PCR analysis of genes encoding IFNα, IFNβ, and IFNγ proteins from KRAS-INK cells 24 hours post-RT. n = at least 3/group.

All graphs depict mean +/- SEM. "*" denotes $p < 0.05$ by two-tailed t-test or one-way ANOVA as appropriate.