

## Supplemental Materials and Methods

### Cell confluency assays

RD and SMS-CTR parental cells were pretreated with either DMSO or trametinib (10 nM for 72h or 20 nM for 24h) prior to being seeded into 48-well plates at 20-50% confluency and stored at 37° C in the Incucyte ZOOM (Essen Bioscience). After 24h, cells were subjected to varying degrees of IR (0 Gy or 15 Gy), began respective DMSO or trametinib (10 nM) treatment, and placed back in the Incucyte. Total confluency over time was monitored every 4–6 hours over a period of 5 days. Significance was calculated by one-way ANOVA with Dunnett's multiple comparisons tests.

### ChIP-seq

ChIP-seq tracks of antibodies targeting SNAI2 (CST, Catalogue # 9585), and H3K27ac (Active Motif, cat. #39133) were used for the current analysis (GEO datasets GSE137168, GSE85171) (14,19). ChIP-seq fastq files were mapped to human reference genome (hg19) using Bowtie2. High-confidence ChIP-seq peaks were called by MACS2 using default parameters and peaks were visualized using IGV viewer or epigenome browser.

### HiC

HiC chromatin interaction data from Rao et al. 2014 (45) was visualized using Juicebox. Data resolution at 5 kb and human genome version hg19. SNAI2 ChIP-seq peaks were derived from Pomela et al. 2021 GSE137168 (19).

### Supplemental References

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