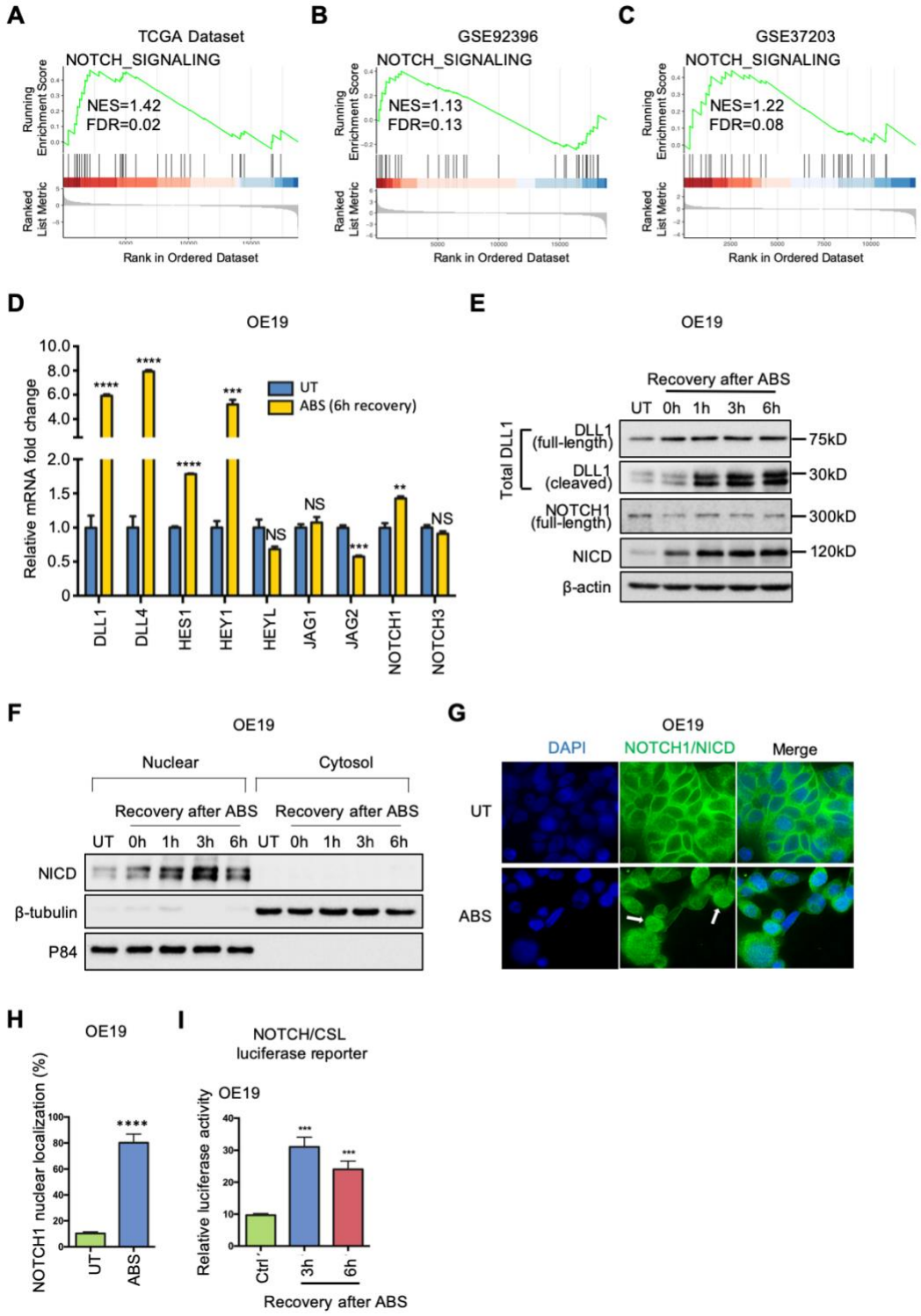
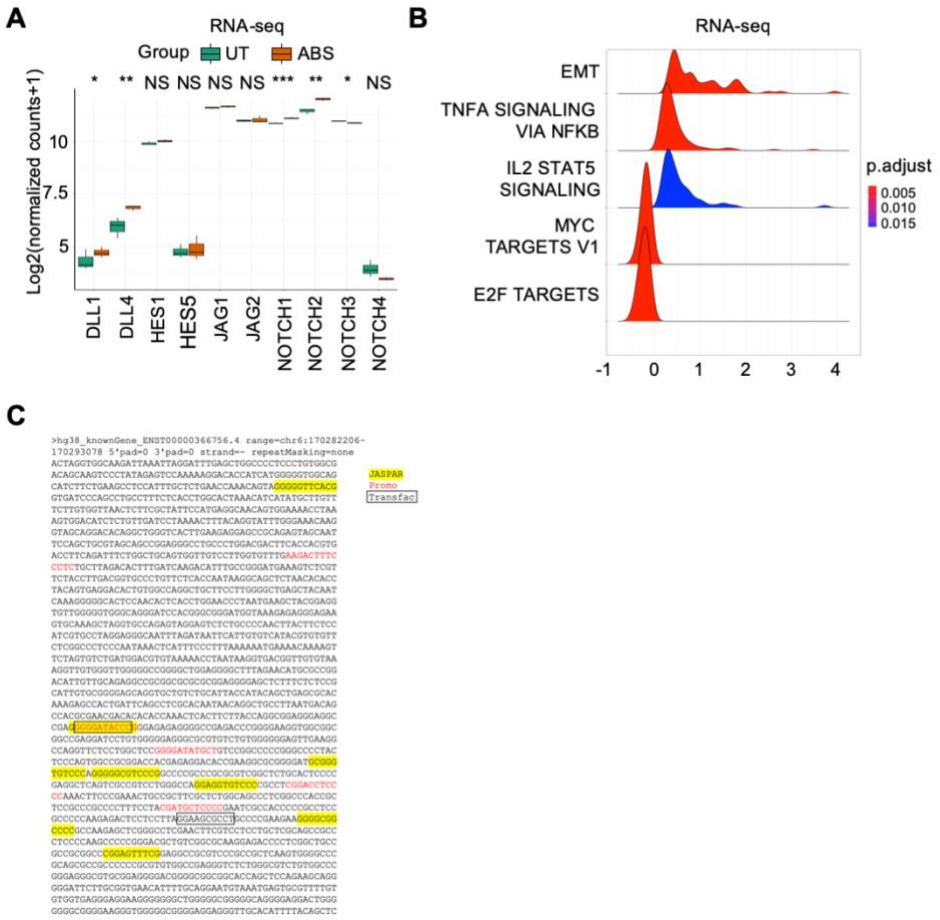
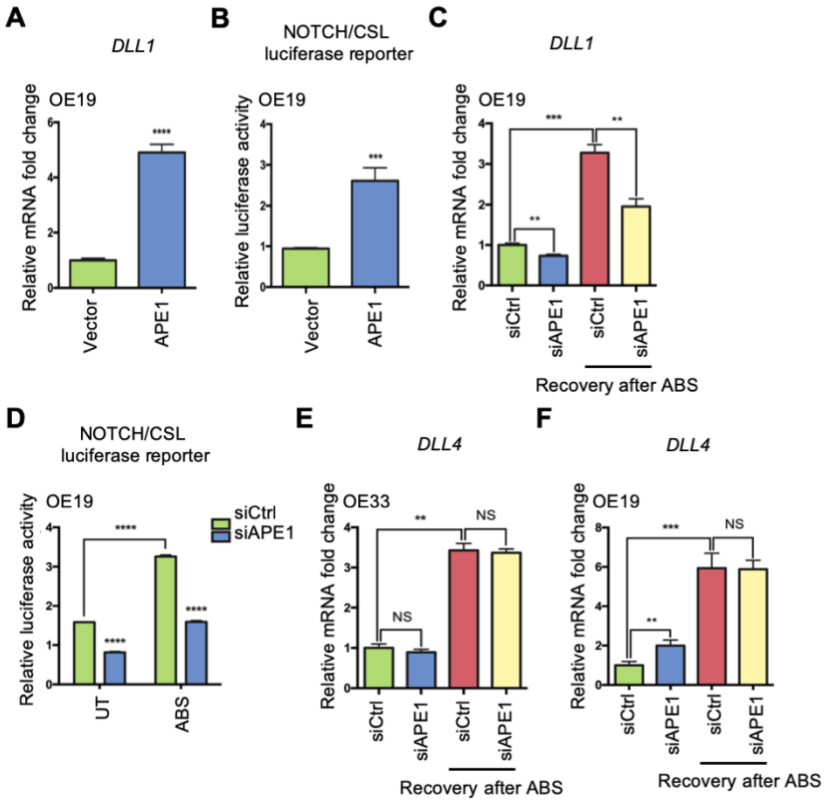


Supplemental Figure 1. NOTCH signaling is dysregulated in human EAC tissues and ABS-treated EAC cell line models. (A-C) GSEA displays that NOTCH signaling pathway was enriched in human EAC tissues in TCGA-EAC database (A) and GEO datasets including GSE92396 (B) and GSE37203 (C). (D) qRT-PCR showing mRNA expression levels of key components of NOTCH pathway in OE19 cells after 6h-recovery from ABS exposure. (E) Western blots of total DLL1 (including full-length DLL1 at 75kDa and cleaved DLL1 at

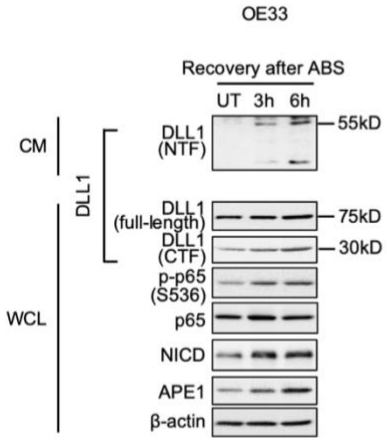
30kDa), full-length NOTCH1 (300kDa), active NOTCH1 intracellular domain (NICD, 120kDa) and β-actin in OE19 cells during indicated recovery time courses after ABS exposure. (F) OE19 cells were harvested for cytosol/nuclear fractionation during 6h-recovery after ABS exposure. Induction of NICD was examined by Western blots. β -tubulin and p84 were used as loading control for cytosol fraction and nuclear fraction respectively. (G) Representative immunofluorescent staining images of NOTCH1/NICD in OE19 cells after ABS exposure. DAPI was used for nuclear staining. (H) Percentage of NOTCH1 nuclear localization was quantified using three independent fields. (I) NOTCH/CSL luciferase assays were performed in OE19 cells. All quantification analyses were shown as mean ± SEM. *t test* was performed to analyze the experimental data for two group comparisons. $**p<0.01$, $***p<0.001$, $****p<0.0001$, NS no significance.



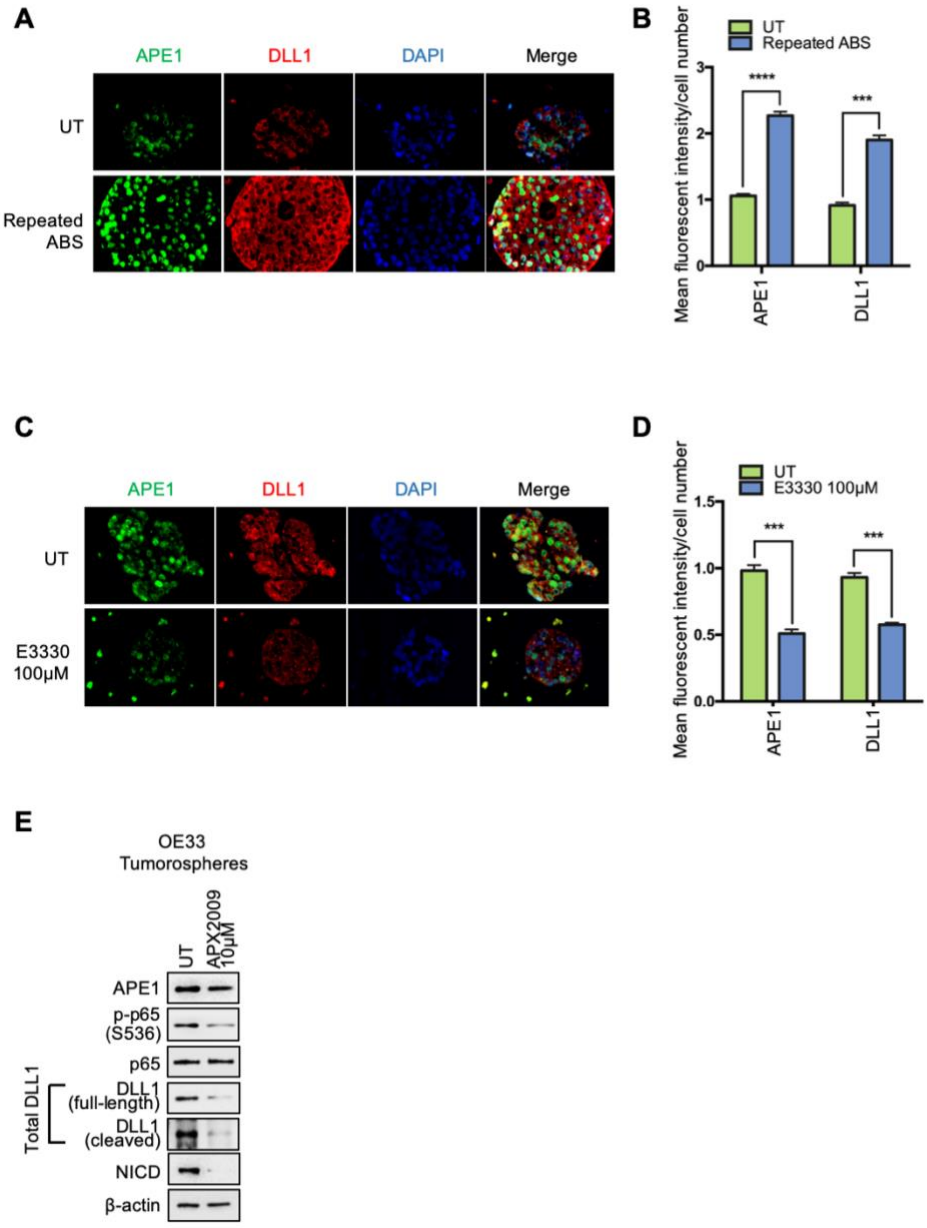
Supplemental Figure 2. NF-κB transcriptionally regulates DLL1in EAC. (A) Grouped boxplot showing gene expression of core NOTCH signaling components in the RNA-seq dataset of OE33 cells, comparing control cells with ABS-treated cells (shCtrl vs shCtrl+ABS). (B) Ridge plot of GSEA results using the RNA-seq dataset of OE33 cells, comparing shCtrl with shCtrl+ABS. (C) Multiple NF-κB binding sites were predicted in DLL1 promoter region by three online software.



Supplemental Figure 3. NOTCH ligand DLL1, but not other ligands or receptors, could be a downstream target of APE1 in response to ABS. (A) qRT-PCR shows DLL1 mRNA level change after ectopic overexpression of APE1 in OE19 cells. (B) Luciferase reporter assay was performed to confirm NOTCH/CSL transcription activity after APE1 overexpression. (C) and (D) Transient APE1 knockdown abolishes ABS-upregulated DLL1 mRNA expression (C) and NOTCH/CSL luciferase activity (D) in OE19 cells. (E) and (F) qRT-PCR of DLL4 mRNA in OE33 (E) and OE19 (F) cells; Knockdown of APE1 has no suppressive effects on ABS-induced DLL4 transcription. Statistical data are shown as mean ± SEM. **p<0.01, ***p<0.001, ****p<0.0001 and NS no significance as calculated by t test for two group comparisons.



Supplemental Figure 4 Secreted DLL1 is detected to be increased in the conditioned medium of OE33 cells after ABS exposure. Western blots of secreted DLL1 (N-terminal fragment at 55kD) in the conditioned medium, along with total DLL1 (full-length at 75kDa and C-terminal fragment at 30kDa), phosphor-p65, total p65, NICD, APE1 and β-actin in the whole cell lysate of OE33 cells with or without ABS exposure. NTF, N-terminal fragment; CTF, C-terminal fragment; CM, conditioned medium; WCL, whole cell lysate.



Supplemental Figure 5. APE1 and DLL1 are concomitantly expressed in EAC-cell-line-derived tumorospheres. (A) Representative immunofluorescence images of APE1 (green) and DLL1 (red) in the tumorospheres derived from OE33 cells with or without repeated ABS exposure. (B) Quantification of mean fluorescent intensity of APE1 and DLL1 using three independent fields. (C) Representative immunofluorescent images of APE1 (green) and DLL1 (red) in the tumorospheres treated with E3330 (100 μM). (D) Mean fluorescent intensity of APE1 and DLL1 was quantified using three independent fields. (E) Western blots of APE1, phosphor-p65, total p65, total DLL1(full-length and cleaved form), NICD and β-actin in the tumorospheres treated with APX2009. Statistical data are shown as mean ± SEM. ***p<0.001 and ****p<0.0001 as calculated by t test for two group comparisons.