Supplementary Tables

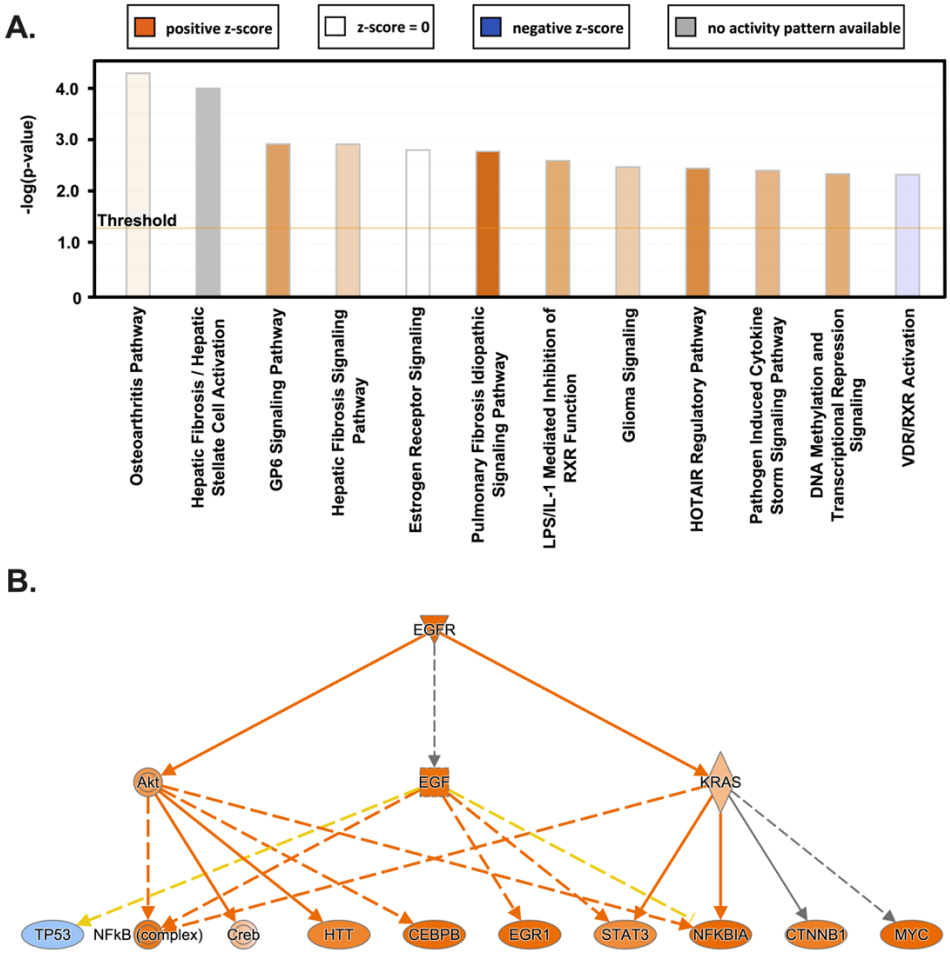
Supplementary Table 1: Description and primer sequences for genotyping and selected genes tested by RT-qPCR.

Gene Symbol	Gene Name	Gene Function	Forward Sequence (5' → 3')	Reverse Sequence (5' → 3')
Genotyping				
Erbb2^{tm1Mll}	Erb-b2 receptor tyrosine kinase 2	ERBB tyrosine kinase receptor	GATGAATTGCCCGTCGTT	GCCCTCTTGTTCTACTTCTGGG
Tg(Vil-Cre)20Syr	Transgene	Cre recombinase expression	GTGATGAGGTTCGCAAGAAC	AGCATTGCTGTCACTTGGTC
ERBB family members				
Egfr	Epidermal Growth Factor Receptor	ERBB tyrosine kinase receptor	GCATCATGGGAGAGAACAACA	CTGCCATTGAACGTACCCAGA
Erbb2	Epidermal growth factor receptor 2	ERBB tyrosine kinase receptor	GAGACAGAGCTAAGGAAGCTGA	ACGGGGATTTTCACGTTCTCC
Erbb3	Epidermal growth factor receptor 3	ERBB tyrosine kinase receptor	TCTGCATTAAAGTCATCGAGGAC	CAGCCGTACAATGTGGGCAT
Erbb4	Epidermal growth factor receptor 4	ERBB tyrosine kinase receptor	TCCCCCAGGCTTTCAACATAC	GCACCCTGAGCTACTGGAG
Egf	Epidermal Growth Factor	Growth Factor ligand	TTCTCACAAGGAAAGAGCATCTC	GTCCTGTCCCGTTAAGGAAAAC
Tgfa	Transforming growth factor alpha	Growth Factor ligand	CACTCTGGGTACGTGGGTG	CACAGGTGATAATGAGGACAGC
Areg	Amphiregulin	Growth Factor ligand	GCCTCCGAAGTGTGGTATCC	CCTGGTACTGTCCAAACGCA
Epgn	Epigen	Growth Factor ligand	GGGGGTTCTGATAGCAGTCTG	TCGGTGTTGTTAAATGTCCAGTT
Btc	Betacellulin	Growth Factor ligand	AATTCTCCACTGTGTGGTAGCA	GGTTTTCACTTTCTGTCTAGGGG
Hbegf	Heparin-binding Egf	Growth Factor ligand	CGGGGAGTGCAGATACCTG	TTCTCCACTGGTAGAGTCAGC
Ereg	Epiregulin	Growth Factor ligand	CTGCCTCTTGGGTCTTGACG	GCGGTACAGTTATCCTCGGATTC
Nrg1	Neuregulin 1	Growth Factor ligand	TCAGCAAGTTAGGAAACGACAG	ACATAGGGTCTTTCAGTTGAGGC
Nrg2	Neuregulin 2	Growth Factor ligand	GGATGGCAAGGAACTCAACC	TCGGCCTCACAGACGTACT
Nrg3	Neuregulin 3	Growth Factor ligand	TTACGCTGTAGCGACTGCATC	GCCTACCACGATCCATTTAAGC
Nrg4	Neuregulin 4	Growth Factor ligand	CACGCTGCGAAGAGGTTTTTC	CGCGATGGTAAGAGTGAGGA
RNA sequencing validation				
Col1a1	Collagen Type 1 Alpha 1 Chain	Extracellular matrix structural constituent	GACTGGAAGAGCGGAGAGTA	CCATGTTGCAGTAGACCTTGA
Ctnnb1	Catenin beta 1	Transcription regulator	TGAGGACCAGGTGGTAGTTAAT	GTACAATGGCAGACACCATCT
Jun	Jun proto-oncogene	Transcription regulator	CAAGAACGTGACCGACGAG	TGTTCTGGCTATGCAGTTCAG
Mapk4	Mitogen-activated protein kinase 4	Serine/threonine kinase	CGTCAACAGTGAAGCCATTGA	GGCTCATGTAAGGATGCTGAAG
Reference genes				
Actb	Beta Actin	Cytoskeletal structural protein	GGCTGTATTCCCCTCCATCG	CCAGTTGGTAACAATGCCATGT
Gapdh	Glyceraldehyde 3-phosphate dehydrogenase	Glycolysis pathway enzyme	AGGTCGGTGTGAACGGATTTG	GGGGTCGTTGATGGCAACA

Supplementary Table 2: Top human molecular signatures overlapping with expression signatures of *Erbb2*-deficient colon tumors.

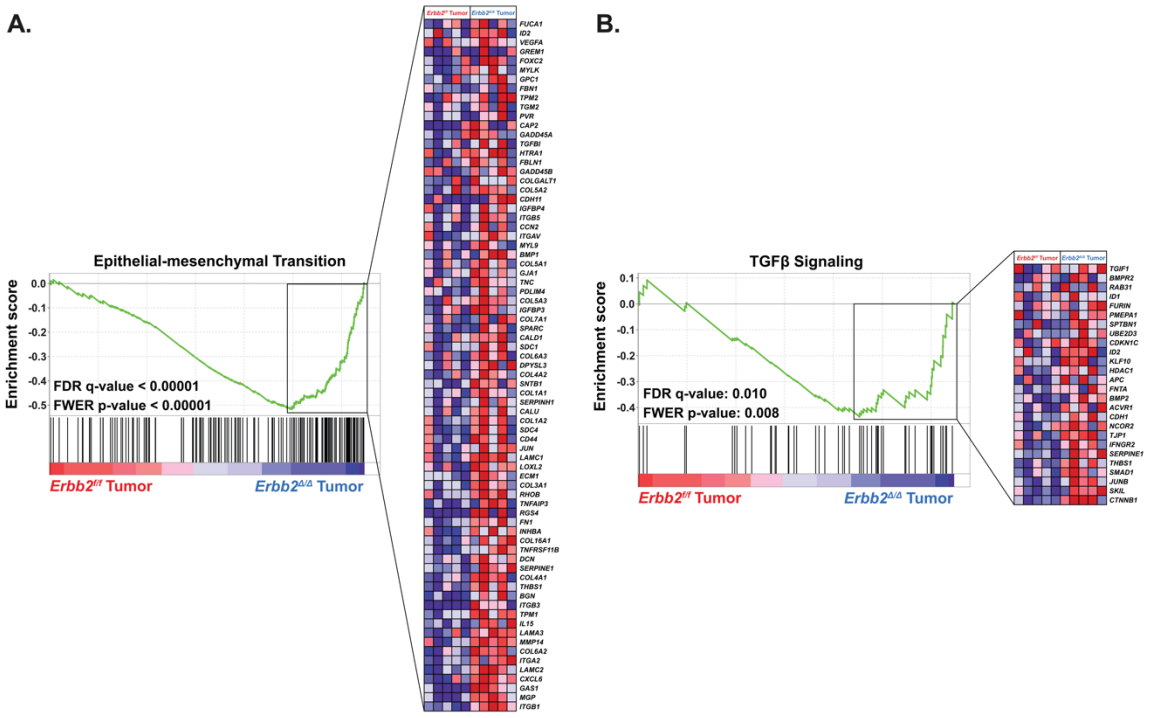
Gene Set Name	Description	p-value	FDR q-value
Hallmark – Epithelial to Mesenchymal Transition	Genes defining epithelial to mesenchymal transition, as in wound healing, fibrosis and metastasis	1.19E-10	2.85E-8
EGFR upregulation	Genes up-regulated in MCF-7 cells (breast cancer) positive for ESR1 and engineered to express ligand-activatable EGFR	5.63E-10	6.72E-8
MEK upregulation	Genes up-regulated in MCF-7 cells (breast cancer) positive for ESR1 stably over-expressing constitutively active MAP2K1 gene	5.83E-9	4.64E-7
LEF1 upregulation	Genes up-regulated in DLD1 cells (colon carcinoma) over-expressing LEF1	3.01E-7	1.2E-5
Hallmark – TNFα signaling via NFκB	Genes regulated by NF-kB in response to TNF	4.26E-7	1.46E-5
IL2 upregulation	Genes up-regulated in Sez-4 cells (T lymphocyte) that were first starved of IL2 and then stimulated with IL2	1.6E-6	4.78E-5
KRAS upregulation	Genes up-regulated in four lineages of epithelial cell lines over-expressing an oncogenic form of KRAS gene	3.23E-6	7.73E-5
Hallmark – IL2 STAT5 signaling	Genes up-regulated by STAT5 in response to IL2 stimulation	1.53E-5	2.26E-4
Hallmark – TGFβ signaling	Genes up-regulated in response to TGFB1	2.92E-5	3.88E-4
PTEN downregulation	Genes down-regulated in HCT116 cells (colon carcinoma) upon knockdown of PTEN by RNAi	3.31E-5	4.16E-4

Supplemental Figures



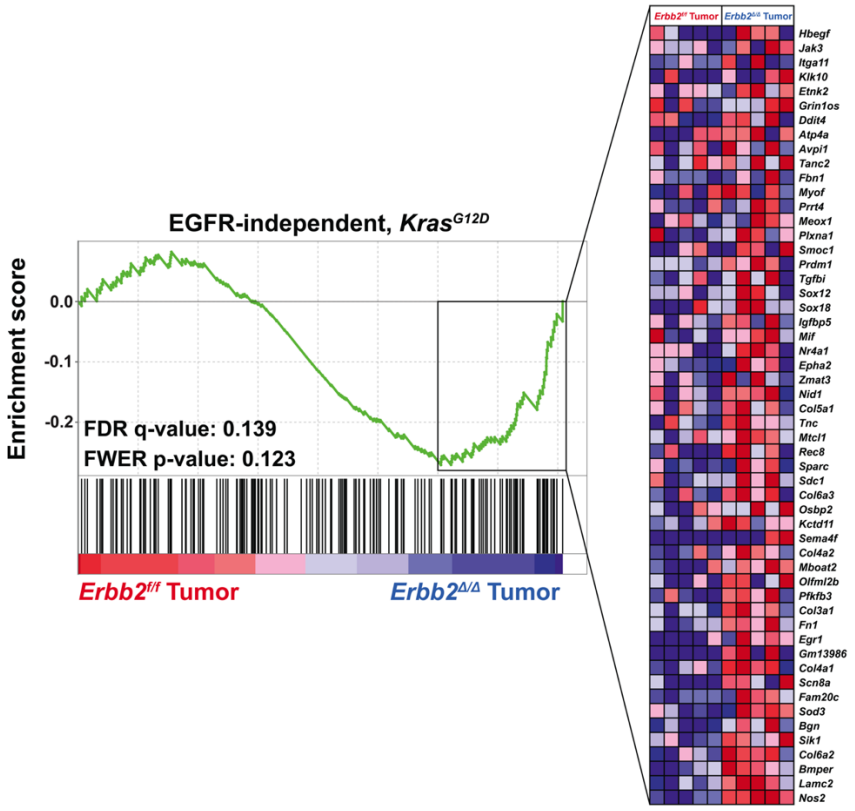
Supplementary Fig. 1: Transcriptomic analysis of *Erbb2*-deficient intestinal polyps.

A Top significant canonical pathways altered in *Erbb2*-deficient tumors as predicted by IPA. **B** Prediction of activation of EGFR in *Erbb2*-deficient intestinal polyps. Blue indicates negative activation z-scores, while orange indicates positive activation z-scores.



Supplementary Fig. 2: Gene set enrichment analysis (GSEA) reveals enrichment of oncogenic hallmarks in *Erbb2*-deficient *Apc*$^{Min/+}$ colon tumors.

GSEA analysis of hallmarks of **A** epithelial to mesenchymal plasticity and **B** TGFβ signaling oncogenic human molecular signatures. The green line indicates the enrichment score of each ranked gene in the pathway represented by black lines below the X axis. Heatmaps display the relative gene expression of markers in the leading-edge subset. Heat map is displayed as a spectrum from high expression (dark red) to low expression (dark blue).



Supplementary Fig. 3: The *Kras*^{G12D} mutation modifies enrichment of the *Erbb2*-deficient tumor transcriptomic profile with EGFR-independent CRC.

GSEA of genes upregulated in the EGFR-independent with *Kras*^{G12D} activating mutation (*Apc*$^{f/f}$, *Egfr*$^{f/f}$, *Kras*$^{G12D/+}$) oncogenic mouse molecular signature. Green line indicates enrichment score of each ranked gene in the pathway represented by black lines below the X axis. Heatmaps display the relative gene expression of markers in the leading-edge subset. Heat map is displayed as a spectrum from high expression (dark red) to low expression (dark blue).