**Supplementary Figure Legends**

**Supplementary Figure 1: Clonal variability introduced by the *TP53, KRAS,* and *MYC* manipulations**

A) mRNA expression levels of *TP53* (green), *MYC* (red) and *KRAS* (blue) using qRT-PCR in 20 single-cell clonal populations isolated from HBECPKM normalized to human reference (methods). Expression levels of clones were rank sorted for each gene. B) Representative immunofluorescence images of P53 and MYC protein levels in parental HBEC and HBECPKM, scale bar = 50 µM. C) Quantification of the immunofluorescence images for nuclear amount of P53 and MYC protein expression showing the distribution of each protein level across ~3000 cells per cell line.

**Supplementary Figure 2: Quantitation of signaling alterations for -CATENIN, P65, FOXO1 and p-ERK1/2**

A), B) Downregulated (blue), baseline and upregulated (yellow) fraction of cells in -CATENIN, P65, FOXO1 and p-ERK1/2 signaling in oncogenically manipulated HBECs compared to the parental HBEC as described in Fig. 1B. C) Quantification of signaling alteration for the signaling markers as above in parental and oncogenically manipulated HBECs as described in Fig. 1B.

**Supplementary Figure 3: Comparison between parental HBEC and HBECPKM cells for their sensitivity to the MEK inhibitor AZD6244**

MTS assay of parental HBEC and HBECPKM cells for their response to MEK inhibitor AZD6244. x-axis: concentration of AZD6244 in µM; y-axis: percent viability, with 100% corresponding to DMSO control conditions for each respective cell line. Error bars represent standard deviation (n = 8 technical replicates). Solid curves were constructed using a sigmoidal curve fit.

**Supplementary Figure 4: Similar distributions of SMAD2/3 signaling with total or phospho antibodies**

Downregulated (blue), baseline and upregulated (yellow) fraction of cells assayed for total or phospho- SMAD2/3 signaling in HBECPKM compared to parental HBEC as described in Fig 1B.

**Supplementary Figure 5: Alterations of p-STAT3 signaling in high EGF growth condition**

Quantification of downregulated (blue), baseline and upregulated (yellow) fraction of cells in p-STAT3 signaling in oncogenically manipulated HBECs compared to the parental HBEC. Graphs are as described in Fig. 1D, 1E except the cell lines were grown in a higher EGF (50 vs. 5000 pg/mL) condition.

**Supplementary Figure 6: Identification of lower EGF concentration (<5000 pg/mL) in which both parental HBEC and HBECPKM grow healthy colonies**

Equal number of cells from each cell line were seeded (200 cells/well) in 6-well plates. Varying concentrations of EGF (0, 0.5, 5, 50, 500, 5000 pg/mL) were added in the growth media KSFM. After 14 days media was removed. The colonies were stained with crystal violet and the colonies were counted. Based on the above colony formation assays we identified 50 pg/mL as the lowest concentration of EGF for viable growth of colonies for both parental HBEC and HBECPKM. Hence, we chose 50 pg/mL of EGF throughout the remainder of our studies.

**Supplementary Figure 7: Stattic treatment reduces the level of p-STAT3**

Western blot showing p-STAT3, total STAT3, GAPDH (loading control) protein expression before and after Stattic treatment in HBECPKM cells.

**Supplementary Figure 8: SMAD2/3 signaling alteration is not simply due to change in cell size from parental HBEC to HBECPKM**

A) Distribution of cell sizes for parental HBEC (top) and HBECPKM (bottom) cells. Cells are binned into small, medium and large categories based on their size with equal number of cells in each category. B) Quantification of alterations in SMAD2/3 signaling as described in Fig. 1C, individually on cells of small, medium and large sizes.

**Supplementary Figure 9: siRNA mediated knockdown of BCL6**

A, C) Confirmation of BCL6 knockdown based on gene expression. Relative BCL6 gene expression using qRTPCR for (left to right): parental HBEC transfected with non- target control, parental HBEC transfected with siRNA against BCL6, HBECPKM transfected with non-target control and HBECPKM transfected with siRNA against BCL6. Error bars are as in Fig 2B (*n* = 6 technical replicates); the expression of BCL6 in each cell line with siBCL6 is normalized to BCL6 expression with siNTC. B, D) Confirmation of BCL6 knockdown based on protein expression. Western blot showing BCL6 protein expression in HBECPKM transfected with non-target control and siRNA against BCL6. 2 siRNAs (siBCL61 and siBCL62) were used and the one with better knock down ability (siBCL61) was chosen for further experiments.