**Figure S1. Estrogen and anti-estrogen response of MDA-MB-330 and BCK4 cells. A-B.** Estrogen and anti-estrogen dose response in (**A**) MDA-MB-330 (6 days) and (**B**) BCK4 (7 days) cells. E2: Estradiol (100 pM); 4-OHT: 4-hydroxytamoxifen (100 nM); Fulv: Fulvestrant (ICI 182, 780, 100 nM). Graphs show representative data (n=6) from two-three experiments. BCK4 data was expressed as the maximum versus minimum growth for either treatment context. **C.** Nanostring-based expression of ILC E2-regulated gene code-set (from ref. 15) in BCK4 cells with the indicated treatments for 24hrs. Genes were excluded from analysis if all treatment groups had average raw expression counts <24. +, canonical ER target gene. Control: vehicle (Ethanol). **D.** Bars represent average fold change for all genes in the indicated group ± SEM. **E.** Top, Genes from groups 1 and 2 were overlapped with genes previously identified as being regulated by tamoxifen as an agonist (ref. 15). Bottom, Cells were treated as described above with 1μM 4OHT for 3 or 24hrs. BCK4 data are repeated from (**C**).
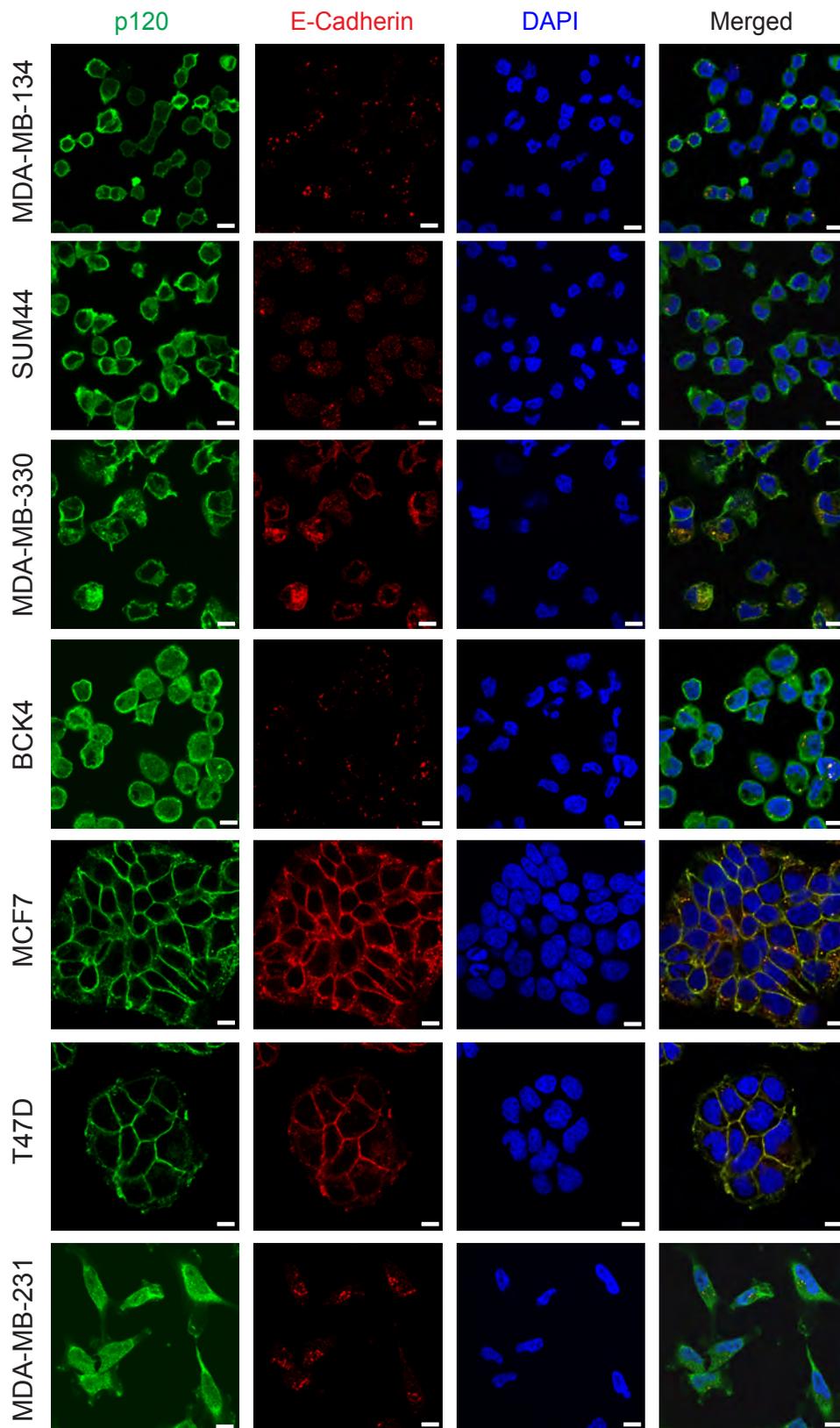
Figure S2. p120 and E-cadherin co-immunofluorescence staining in ILC and IDC cells. p120 (green), E-cadherin (red), DAPI (blue) and merged co-immunoflorescence images of ILC and IDC cell lines. Scale bar: 10 μm.
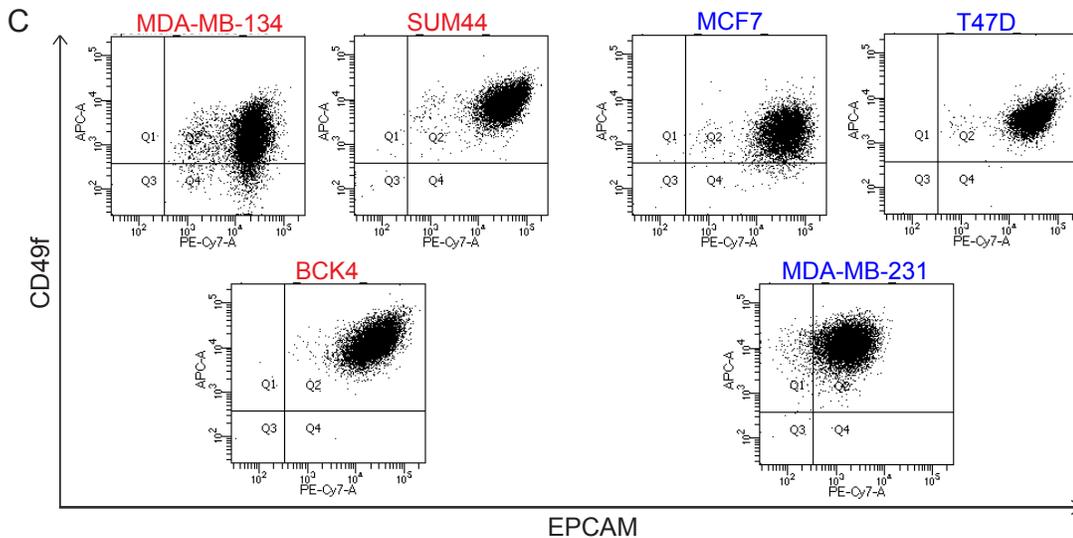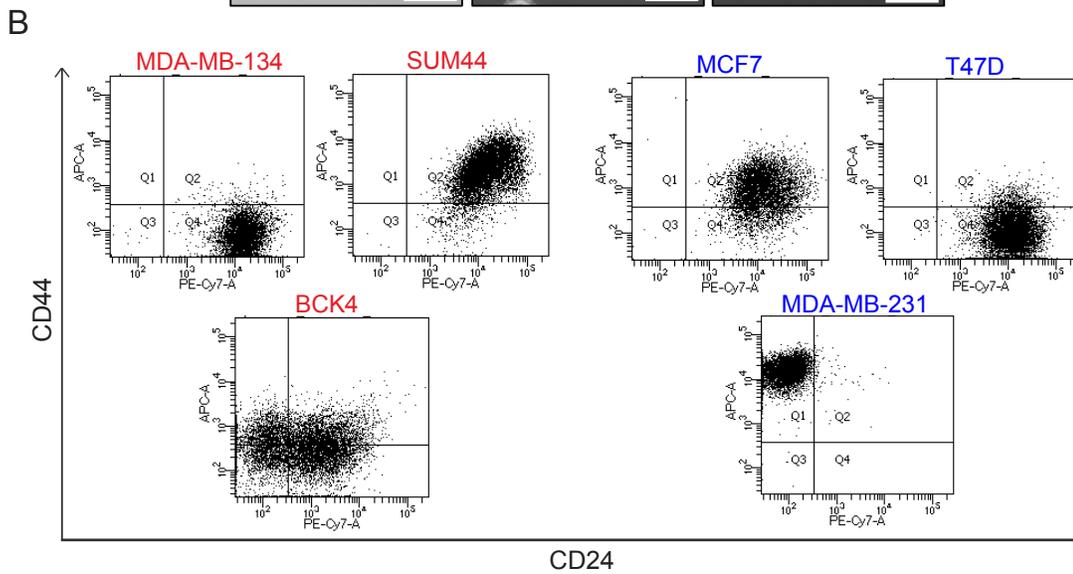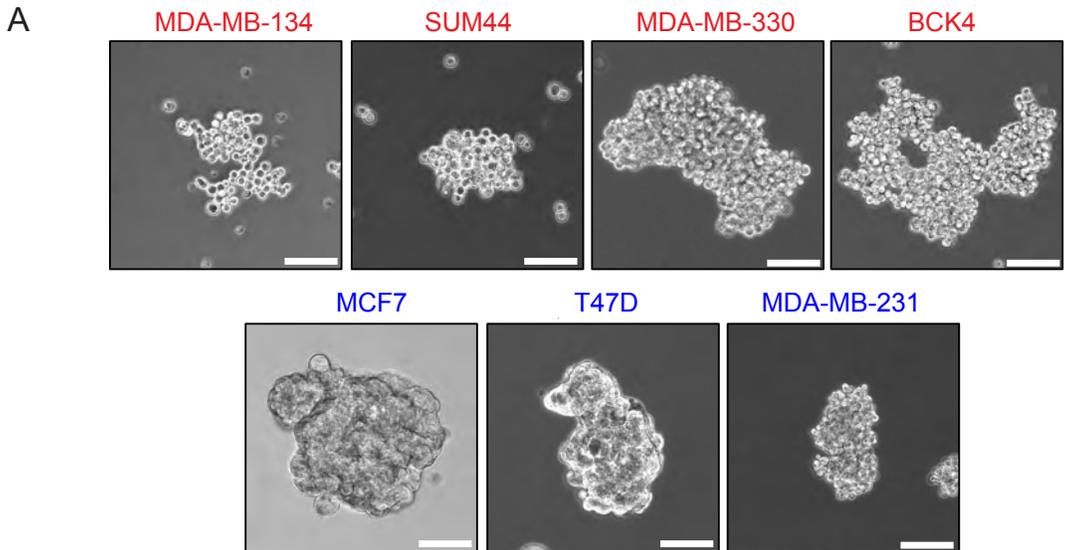
**Figure S3. Human ILC cell lines do not form robust mammospheres. A.** Phase contrast light microscopy images of mammospheres from ILC (red; top) and IDC (blue; bottom) cell lines in 6-well 2D and ULA plates 7 days post plating. Scale bar: 100 μm. **B-C.** FACS plots of ILC (red; left) and IDC (blue; right) cell lines co-stained for (**B**) CD44/CD24 and (**C**) CD49f/EPCAM. Gating was done using isotype-stained samples.
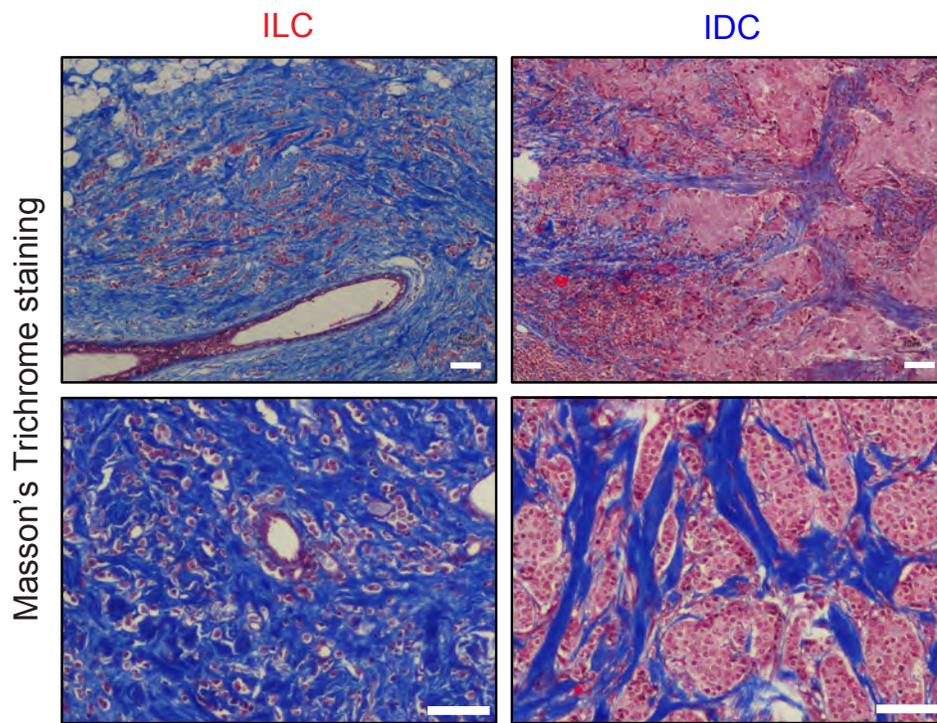
Figure S4. Higher Collagen deposition in human ILC versus IDC tumors. ILC (red; left) and IDC (blue; right) tumors from a tissue microarray stained with Masson's Trichrome. Cytoplasm and muscle fibers stain red, whereas Collagen displays blue coloration. Scale bar: 100 µm.
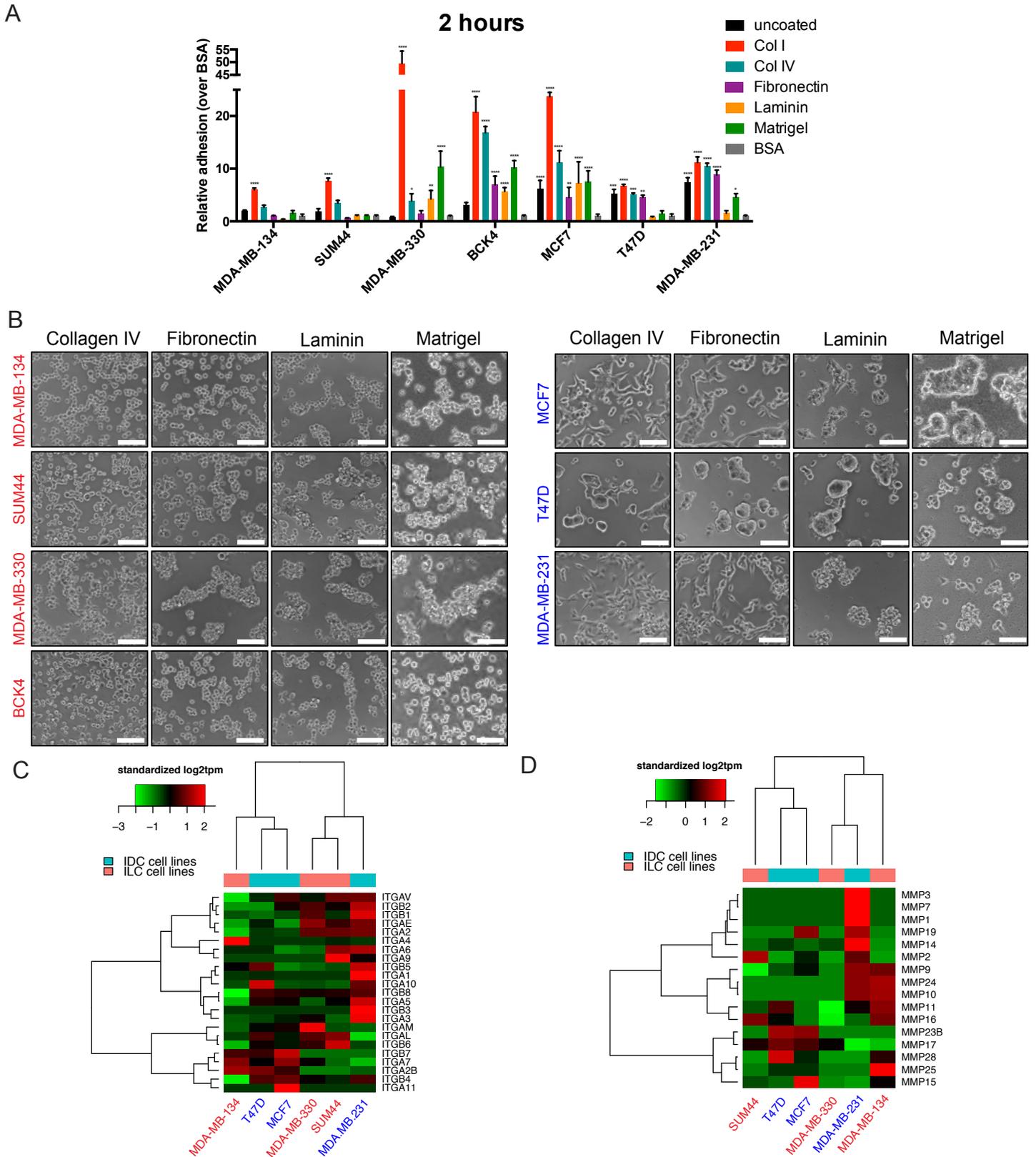
Figure S5. Adhesion of human ILC and IDC cell lines to different ECM proteins. A. Fold adhesion (normalized to BSA) of ILC (red) and IDC (blue) cell lines 2 hours post-plating. Graphs show representative data from two experiments (n=4). p-values are from ordinary one-way ANOVA with Dunnett's multiple comparison test to BSA for each cell line. * $p \leq 0.05$; ** $p \leq 0.01$; **** $p \leq 0.0001$. **B.** Phase contrast light microscopy images of ILC (red; left) and IDC (blue; right) cell lines in plates with the indicated coatings 16 hours post-plating. Scale bar: 100 µm. **C-D.** Unsupervised hierarchical clustering heat map of (**C**) integrin and (**D**) MMP expression in ILC (red) and IDC (blue) cell lines.
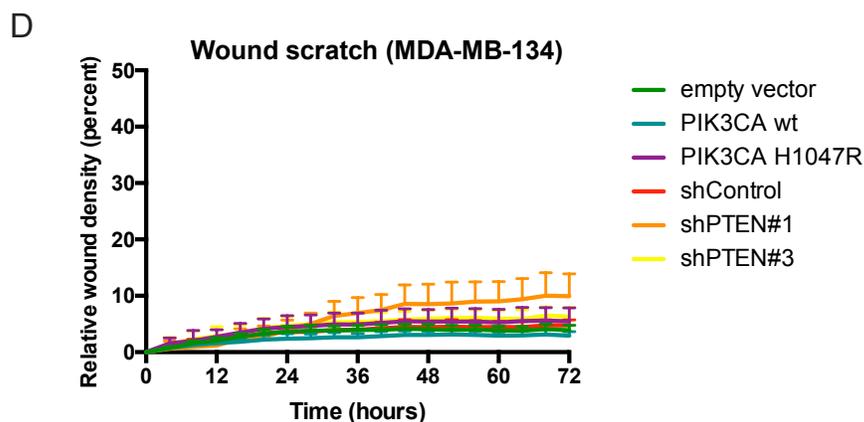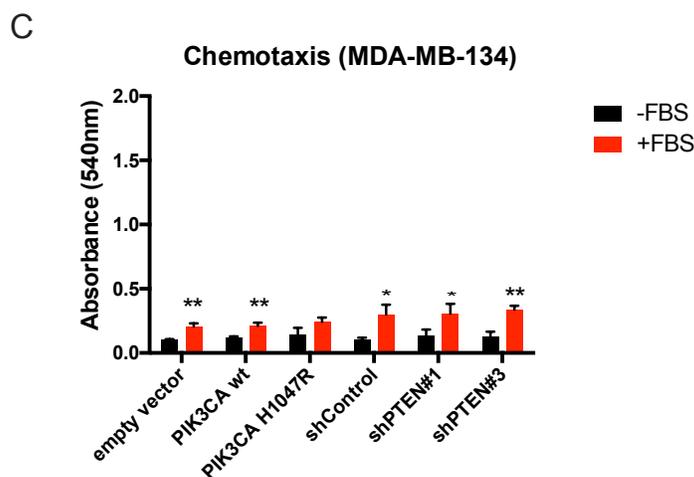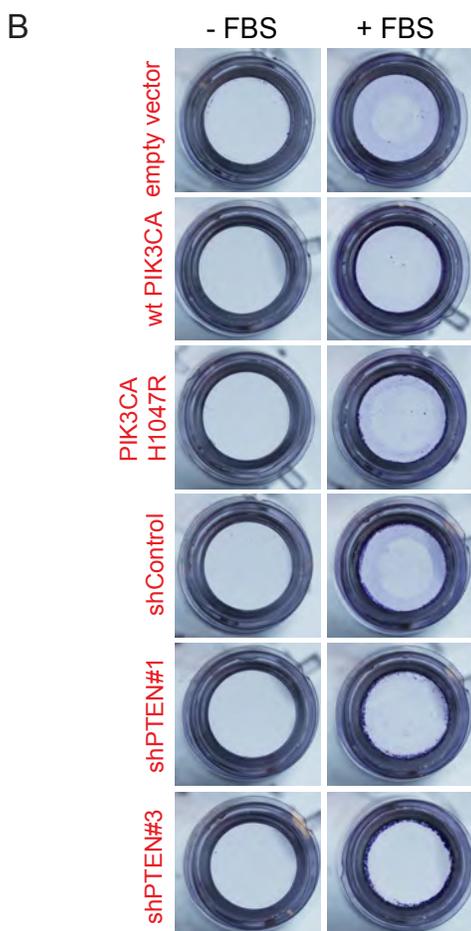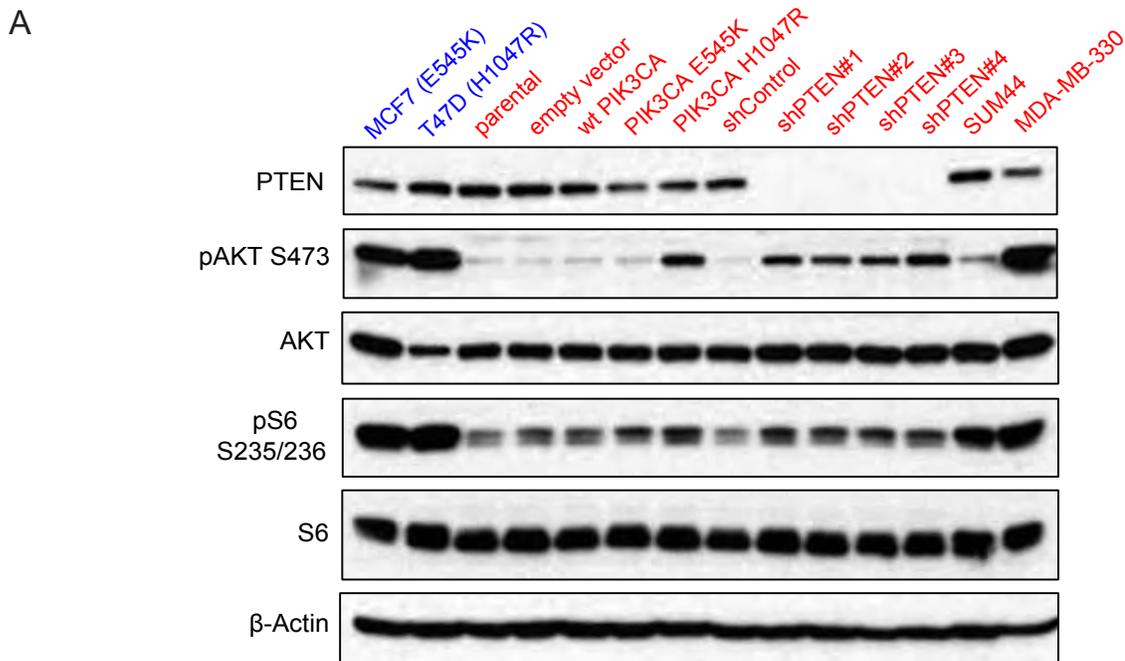
Figure S6. Overexpression of PIK3CA mutants and PTEN knockdown in MDA-MB-134 cells activate downstream PI3K/Akt signaling but do not enhance cell migration. A. Western blotting using the indicated antibodies on whole cell lysates from ILC (red) and IDC (blue) cell lines. β-Actin was used as a loading control. MDA-MB-330 cells harbor HER2 amplification. **B-C. (B)** Images of inserts and (**C**) quantification of haptotaxis in the indicated conditions (n=3). p-values are from unpaired t-test. * p ≤ 0.05; ** p ≤ 0.01. **D.** Relative wound densities from the indicated conditions (n=6-8).
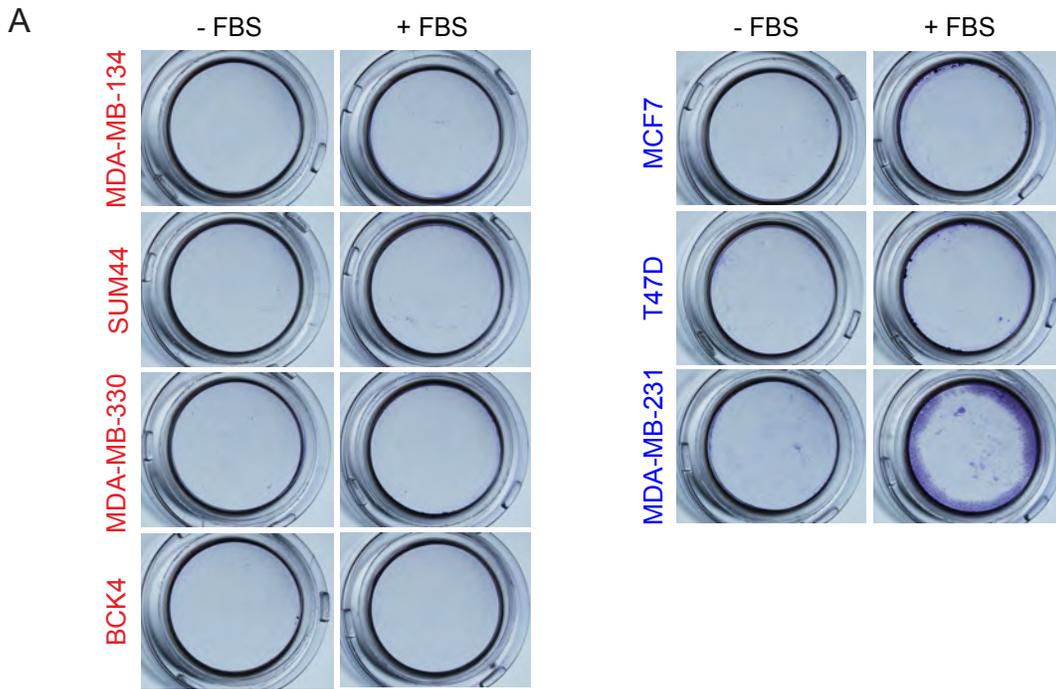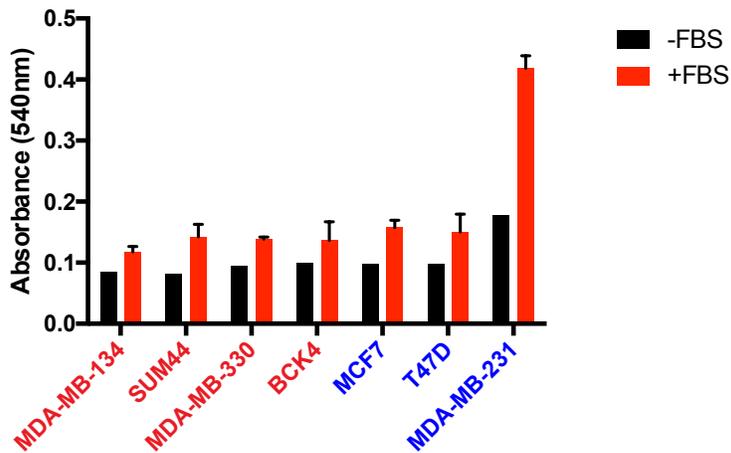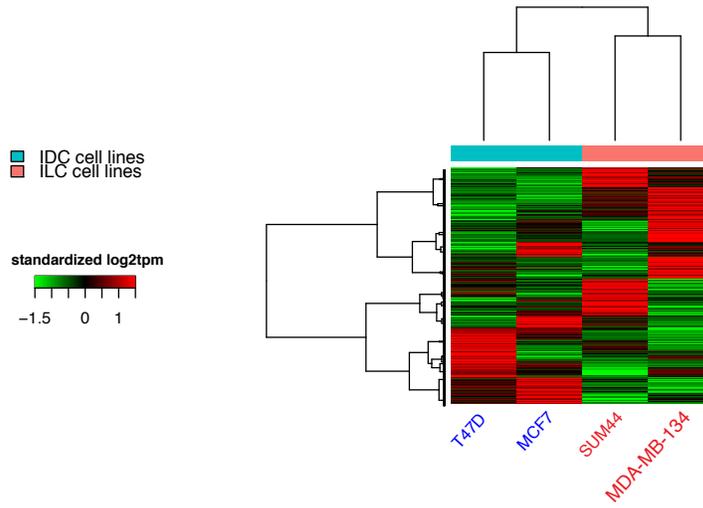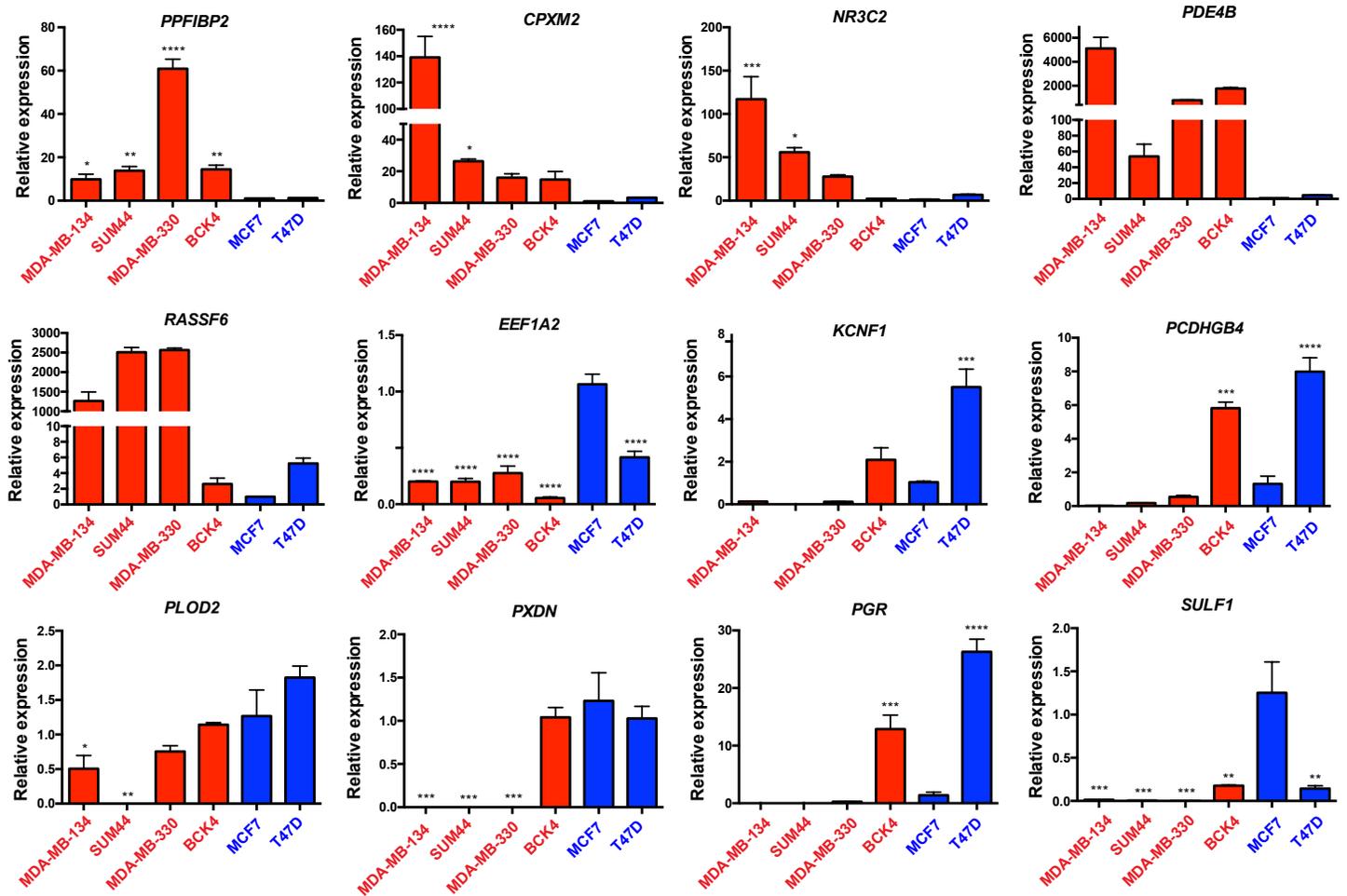
Figure S7. Human ILC cell lines do not exhibit substantial invasion of non-crosslinked Collagen I in transwell Boyden chamber assays. A-B. (A) Images of inserts and (**B**) quantification of amoeboid invasion of non-crosslinked Collagen I (n=1-2) in ILC (red; left) and IDC (blue; right) cell lines.

Figure S8. Differentially expressed genes between human ILC and IDC cell lines and tumors.
A. Unsupervised clustering heat map of ILC (red) and IDC (blue) cell lines using top 1,000 differentially regulated genes. **B**. qRT-PCRs for the ILC-differentially regulated genes in the human ILC (red) and IDC (blue) cell lines. RNA-Seq data from MDA-MB-330 cells was analyzed to see which genes were also differentially expressed in this cell line and primers were used to measure the expression of these genes in all ER+ ILC and IDC cell lines by qPCR. Graphs show expression data from two biological replicates relative to MCF7. p-values are from ordinary one-way ANOVA with Dunnett's multiple comparison test to MCF7.* p ≤ 0.05; ** p ≤ 0.01; **** p ≤ 0.0001. p-values could not be obtained for PDE4B and RASSF6 as they could only be detected in one MCF7 biological replicate.