**Supplemental Figure 1: Immunohistochemistry analysis of mILC1-iFOXO3.A3 tumors & primary tumor size upon detection of metastasis.**

**A** Expression of FOXO3, Ki67 (cell proliferation marker) and cleaved caspase 3 (apoptosis marker) was determined in tumors either untreated or treated with Dox for 7 days. Treatment of mILC1-iFOXO3.A3 with Dox for 7 days resulted in high levels of FOXO3 expression, low levels of Ki67 expression and increased levels of cleaved caspase 3 (Scalebar FOXO3 & Ki67 = 30m, Cleaved caspase = 100m). Indicating that the observed decrease in tumor size correlates to reduced cell proliferation and increased apoptosis. **B&C** Primary tumor volumes of mILC1-iFOXO3 & iFOXO3.A3 tumors upon metastasis detection by bioluminescent imaging. Black dots represent control tumors (n=8 & n=8), green dots represent early (n=6 & n=6) and blue dots represent late treated tumors (n=6 & n=8). Graph represents the average ±SD, t-test p<0.005=\*\* **.**

**Supplemental figure 2: *Foxo1*, *Foxo3* and *Foxo4* expression levels and depletion in mILC1**

**A** RT-qPCR analysis of *Foxo1, Foxo3* and *Foxo4* expression in mILC1 cells. Graph represents the average of 3 experiments ±SD, mRNA levels are relative to *Gapdh* mRNA levels. **B** Western blot analysis of Foxo1 and Foxo3 expression in mILC1 72 hours after transduction of shLuc, shFOXOs#1, shFOXOs#2, shFOXOs#3. Nonspecific background signal was used to control for loading. **C** RT-qPCR analysis of *Foxo1, Foxo3* and *Foxo4* expression after shFOXOs#3 induction in mILC1-shFOXOs cells. Graph is a representative experiment, average of 3 replicates ±SD, mRNA levels are normalized to *Gapdh* mRNA levels. **D** Colony formation capacity of mILC1-shLuc and mILC1-shFOXOs cells after 7 days of Dox. Shown is a representative experiment. **E** Flow cytometric analysis of Hoechst staining for DNA content in shRNA transduced mILC1 after 72 hours. Shown is a representative histogram and the average percentage of cells with S/G2/M ±SD **F** Flow cytometric analysis of shRNA transduced mILC1 with Propidium Iodide (PI) transferred to suspension culture for 24 hours after 72 hours. A representative experiment is shown with the average of 3 technical replicates ±SD. **G** Western blot analysis of Pkb, phosphor-Pkb-S308 and phosphor-Pkb-S473 expression in mILC1 72 hours after transduction of shLuc, shFOXOs#1, shFOXOs#2, shFOXOs#3. Pkb was used to control for loading

**Supplemental figure 3: Immunohistochemistry analysis of mILC1-shFOXOs tumors & primary tumor size upon detection of metastasis.**

**A** Expression of FOXO1, Ki67 phosphorylated Histone H3 and cleaved caspase 3 was determined in tumors either untreated or treated with Dox for 7 days. Treatment of mILC1-shFOXOs with Dox for 7 days resulted in reduced levels of FOXO1 expression, low levels of Ki67 & pH3 expression and no changes in cleaved caspase 3 levels. Indicating that the observed delay in tumor growth correlates to reduced cell proliferation. **B** Primary tumor volume of mILC1-shFOXOs cells upon metastasis detection by bioluminescent imaging. Black dots represent control tumors (n=6), green dots represent early treated (n=6) and blue dots represent late treated tumors (n=7). Graph represents the average ±SD, t-test p<0.05=\*

**Supplemental figure 4: 3D Spheroid formation of human breast cancer cells**

**A** 10 day 3DSpheroid cultures of MCF7/MDA-MB-231/SKBR3-shFOXOs and -iFOXO3.A3 in Matrigel containing collagen I cultured in the presence of Dox after 1 or after 7 days for shFOXOs and iFOXO3.A3 respectively.

**Supplemental figure 5: Expression of catalase and Sod2 in mILC1**

**A Representative** Flow cytometric analyses of CM-H2DCFA oxidation in MCF7/MDA-MB-231/SKBR3-shFOXOs cells (Grey) treated with Dox for 72 hours (green) or 100M H2O2 as a control for oxidative stress (Blue). **B&C** RT-qPCR analysis of *Catalase* and *Sod2* expression after shLuc, shFOXOs and iFOXO3.A3 induction in mILC1 cells. The graph presents the average of 3 independent experiments ±SD, mRNA levels are normalized to *Gapdh* mRNA levels. **D** Westernblot analysis of Catalase, Sod2 and FOXO3 levels in shLuc, shFOXOs and iFOXO3.A3 before and after Dox treatment for the indicated times. Nonspecific background staining was used to visualize protein loading.

**Supplemental Figure 6: FOXOs control PI3K signaling feedback in human cancer cells.**

**A** RT-qPCR of *RICTOR, IRS1, IRS2, ERBB2, ERBB3, INSR, IGF-1R, EGFR* mRNA expression levels in MCF7/MDA-MB-231/SKBR3-shFOXOs and -iFOXO3.A3 cells. shFOXOs cells were treated with Dox for 72 hours, iFOXO3.A3 were treated with Dox for 16 hours. Shown is a representative experiment with the average of 3 technical replicates ±SD. **B** Western blot analysis of FOXO1, FOXO3, PKB, pPKB-S308, pPKB-S473, IGF-1R, RICTOR, INSR and ERBB3 levels MCF7/MDA-MB-231/SKBR3-shFOXOs and -iFOXO3.A3 cells. shFOXOs cells were treated with Dox for 72 hours, iFOXO3.A3 were treated with Dox for 16 hours. PKB signal was used to control for loading.

**Supplemental figure 7: Restoring GFR-signaling in mILC1-shFOXOs cells is insufficient to rescue cell proliferation and stress kinase induction.**

**A** Western blot analysis of Foxo1, Foxo3, cJun, phospo-cJun, Pkb, pPkb-S308 and pPkb-S473 levels in mILC1-shFOXOs co-expressing a hairpin insensitive GFP-FOXO3 (FOXO3mt). Total Pkb levels were used to control for loading. **B** Western blot analysis of Pkb, pPkb-S308, pPkb-S473 and Foxo1 levels in mILC1-shFOXOs cell constitutively expressing PIK3CA or oncogenic PIK3CAH1047R. Total Pkb levels were used to control for loading. **C** Western blot analysis of Rictor, PIK3CA, cJun, phospho-cJun and Foxo1 levels in mILC1-shFOXOs cell constitutively expressing oncogenic PIK3CAH1047R. Nonspecific background signal was used to control for loading. **D** Western blot analysis of Rictor, Akt, Akt-S473 and Foxo1 levels in cells constitutively expressing RICTOR, myristoylated PKB (myrPKB) or both RICTOR and myrPKB. Total Pkb levels were used to control for loading. **E** Flow cytometric analyses of Annexin-V-FITC and PI stained mILC1-shFOXOs constitutively expressing PIK3CAH1047R, myrPKB, RICTOR, myrPKB & RICTOR or FOXO3mt cultured in suspension in the presence of Dox for 16 hours. **F** Colony forming capacity of mILC1-shFOXOs constitutively expressing PIK3CAH1047R, myrPKB, RICTOR, myrPKB & RICTOR or FOXO3mt cultured in suspension in the presence of Dox for 7 days. **G** Colony forming capacity of mILC1-shFOXOs constitutively expressing myrPKB, RICTOR or myrPKB & RICTOR cultured in the presence of Dox for 7 days in combination with 1mM NAC or 200M Trolox.

**Supplemental figure 8: FOXOs mediated gene expression influences a plethora of cellular processes.**

**A** Heatmap representing the 2Log canonical FOXO target gene mRNA expression in mILC1-iFOXO3.A3 and mILC1-shFOXOs treated with Dox for 8, 16, 48 and 72 hours. **B** Venn diagram representing all differentially expressed genes in mILC1-iFOXO3.A3 cells after 8 hours (blue) or 16 hours (yellow) of Dox treatment. **C** Venn diagram representing all differentially expressed genes in mILC1-shFOXOs cells after 48 hours (green) or 72 hours (red) of Dox treatment. **D** Venn diagram combining all differentially expressed genes in mILC1-iFOXO3.A3 cells after 8 hours (blue), 16 hours (yellow) and mILC1-shFOXOs cells after 48 hours (green) and 72 hours (red) of Dox treatment. Bold numbers represent the overlapping gene-sets used for pathway activity prediction. **E** Heatmap representing pathway activity z-scores (blue: <-0.4, pathway inactive, black: activity status not inferred but altered pathway, yellow: >0.4, pathway active) generated by Ingenuity Pathway Analysis based on differential gene expression in at least three overlapping data-sets of the mILC1-iFOXO3.A3 and mILC1-shFOXOs treated with Dox for 8, 16, 48 and 72 hours. **F** Heatmap representing the 2Log gene mRNA expression mILC1-iFOXO3.A3 and mILC1-shFOXOs treated with Dox for 8, 16, 48 and 72 hours of canonical EMT/metastasis genes combined with genes previously linked to FOXO and metastasis.