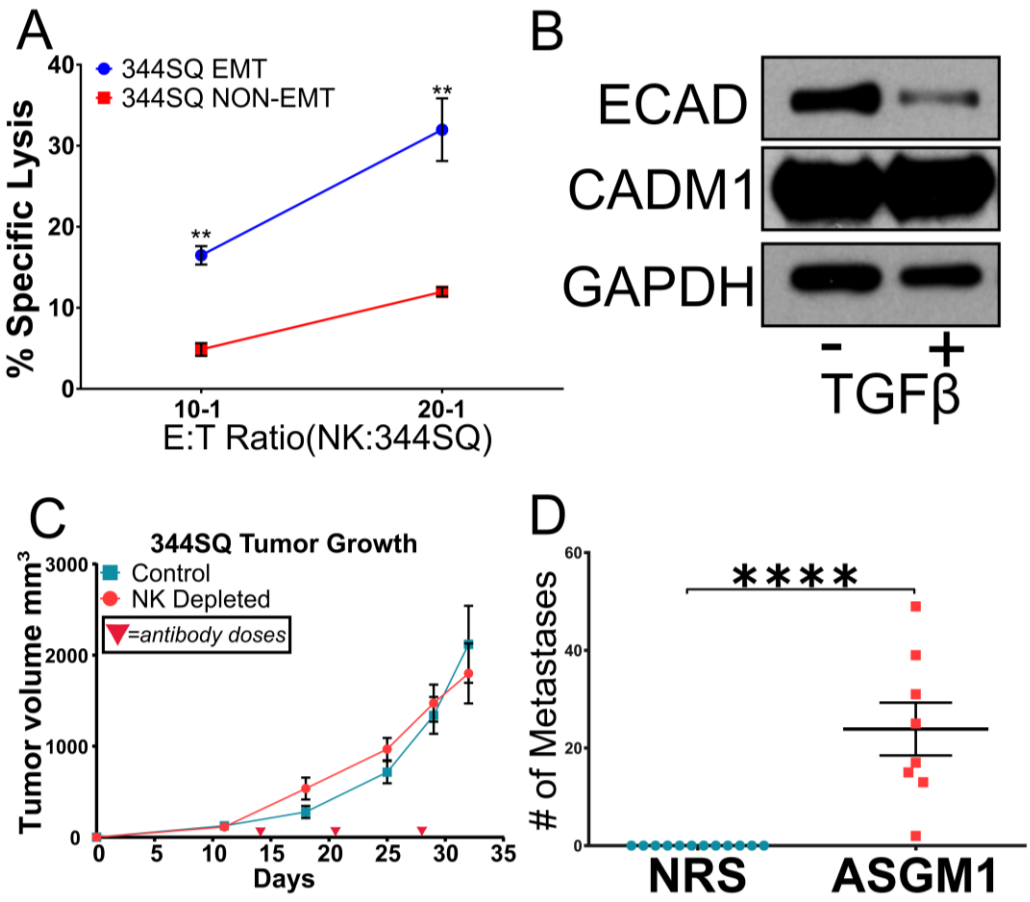
Supplemental Figures



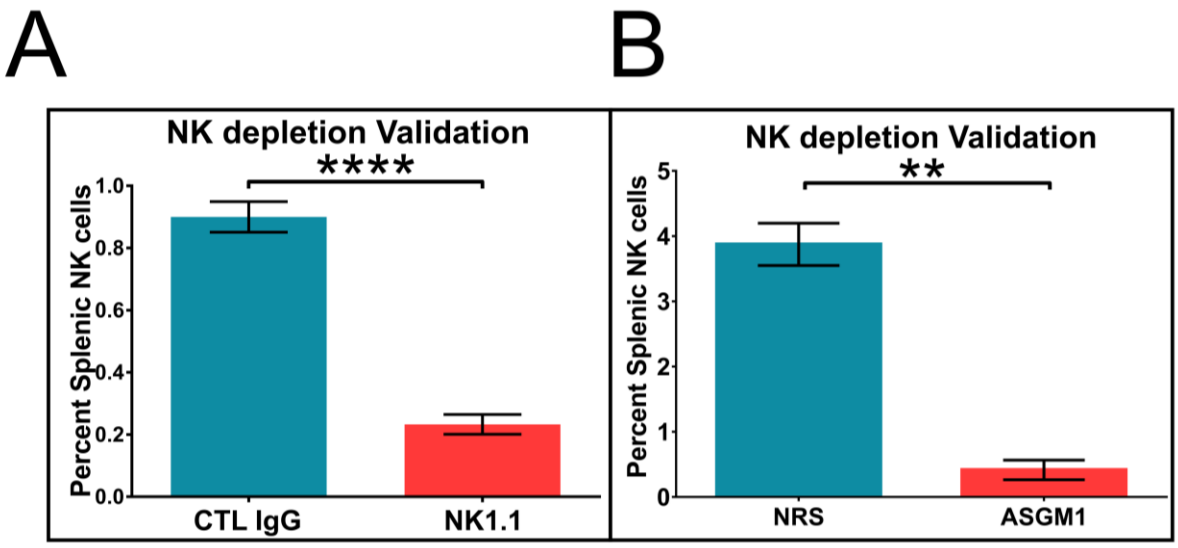
Supplemental Figure 1. EMT-ed Murine 344SQ Cells are Susceptible to NK Mediated Cytotoxicity, Related to Figures 1 and 2

(**A**) To test murine 344SQ lung cancer EMT susceptibility to NK cells, cancer cells were treated with TGFβ for 72 hours and co-cultured with isolated splenic NK cells (CD45+,NK1.1+, CD3e-) from C57BL/6 mice in a cytotoxicity assay as described in Figure 1B. mean±SEM shown, significance was determined by unpaired, two-tailed, t-test.

(**B**) Western immunoblot analysis of ECAD, CADM1, and GAPDH protein levels pre- and post-EMT 344SQ cells.

(**C**) To assess the effect of NK cell depletion on primary tumor growth and metastasis of murine 344SQ tumor cells, cells were implanted subcutaneously into the dorsal flanks of in C57BL/6 mice. Mice were treated with ASGM1 at indicated time points to deplete NK cells. Mean±SEM shown.

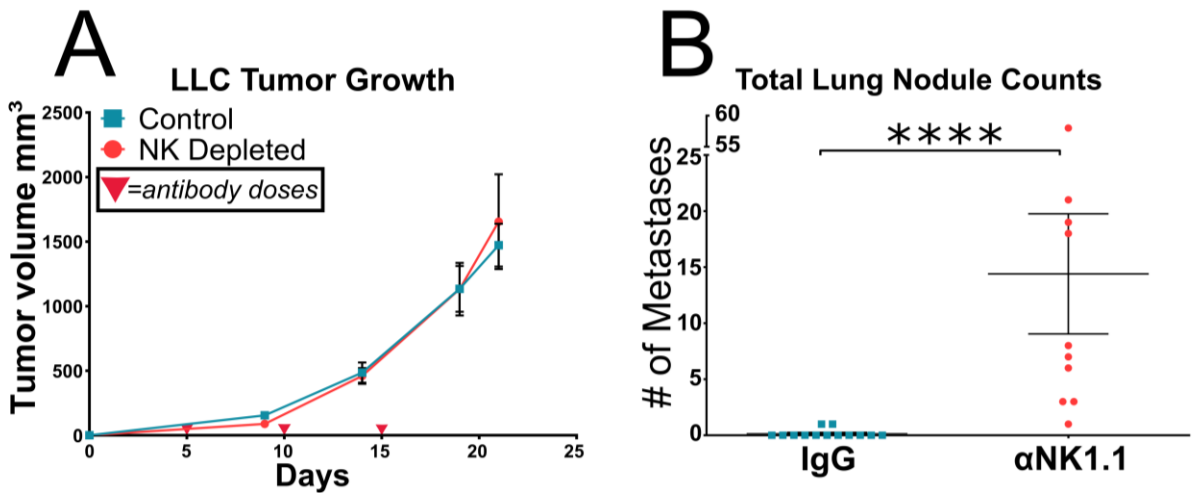
(**D**) Overt lung nodules were counted on the excised lungs to assess spontaneous metastasis. Pooled data is shown from two experiments n=4 mice per group. Error bars are SEM and Mann-Whitney U test was performed, *P < 0.05, **P < 0.01, ***P < 0.001.



Supplemental Figure 2. NK depletion validation, Related to Figure 2 and Supplemental Figure 3

(**A**) A single injection of 200ug of anti-NK1.1(clone: PK136) or CTL IgG was administered to C57BL/6 mice i.p. and 5 days later spleens were harvested and assessed for NK cells(CD45+,NK1.1+, CD3e-), n=3 per group, mean±SEM is shown.

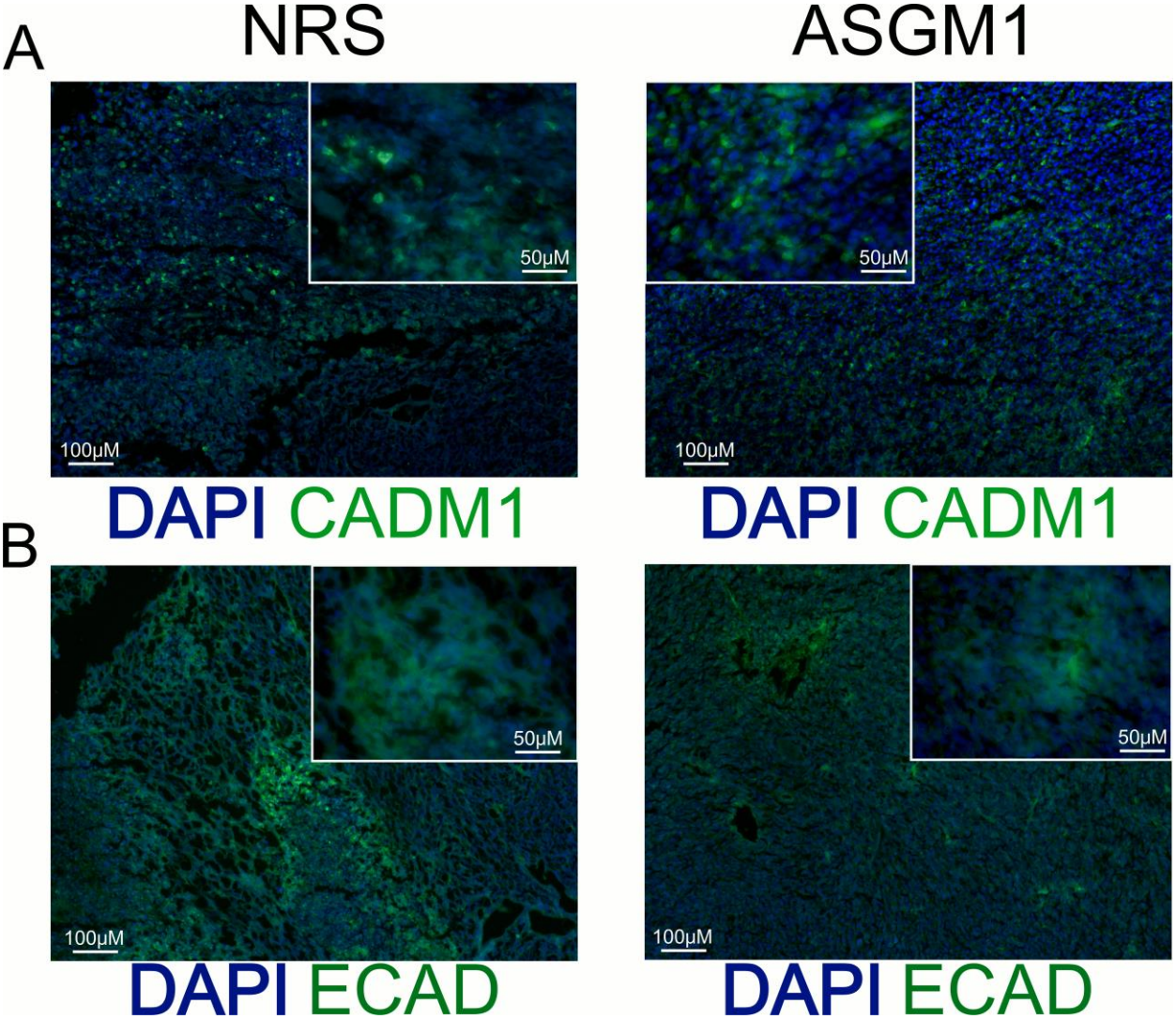
(**B**) A single injection of 25ul of anti-Asialo GM1(ASGM1) or control normal rabbit serum(NRS) was administered to C57BL/6 RAG1$^{-/-}$ mice and 7 days later spleens were harvested and assessed for NK cells(CD45+,NK1.1+, CD3e-), n=3 per group, mean±SEM is shown. Significance was determined by unpaired, two-tailed, t-test.



Supplemental Figure 3. LLC Tumors Spontaneously Metastasize with NK Cell Depletion, Related to Figure 2

(**A**) To assess the effect of NK cell depletion on primary tumor growth and metastasis of murine LLC tumor cells, cells were implanted subcutaneously into the dorsal flanks of in C57BL/6 mice. 200μg Anti-NK1.1 was administered every 5 days to deplete NK cells. Mean±SEM shown. See also Supplemental Figure 2.

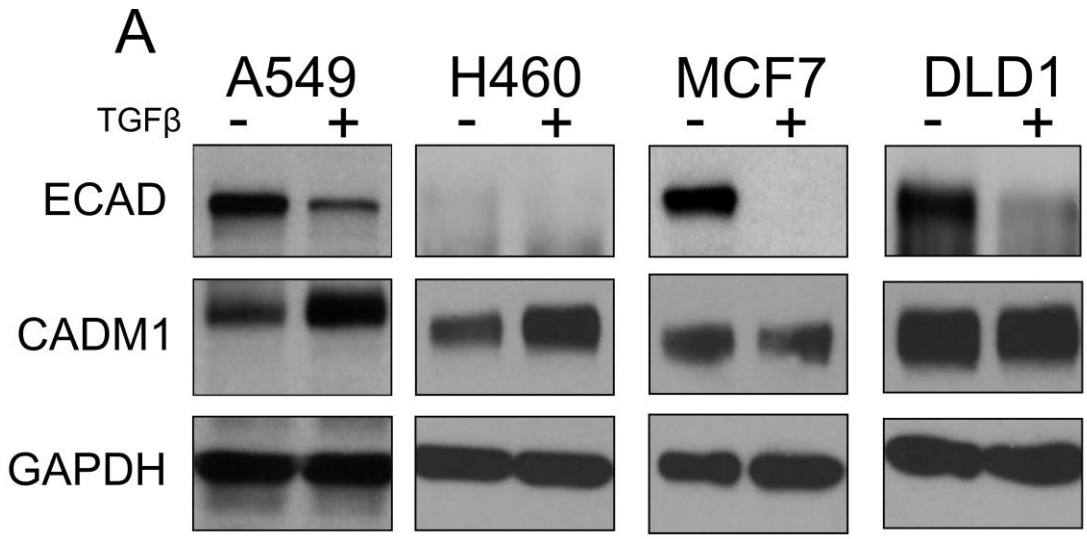
(**B**) Spontaneous metastatic lung nodules were quantified from (**A**), pooled data from two experiments is shown, n=5 mice per group. Error bars are SEM and Mann-Whitney U test was performed, *P < 0.05, **P < 0.01, ***P < 0.001.



Supplemental Figure 4: CADM1 and E-cad Protein Levels in A549 Tumors in NK depleted and Control mice, Related to Figures 2, 5,

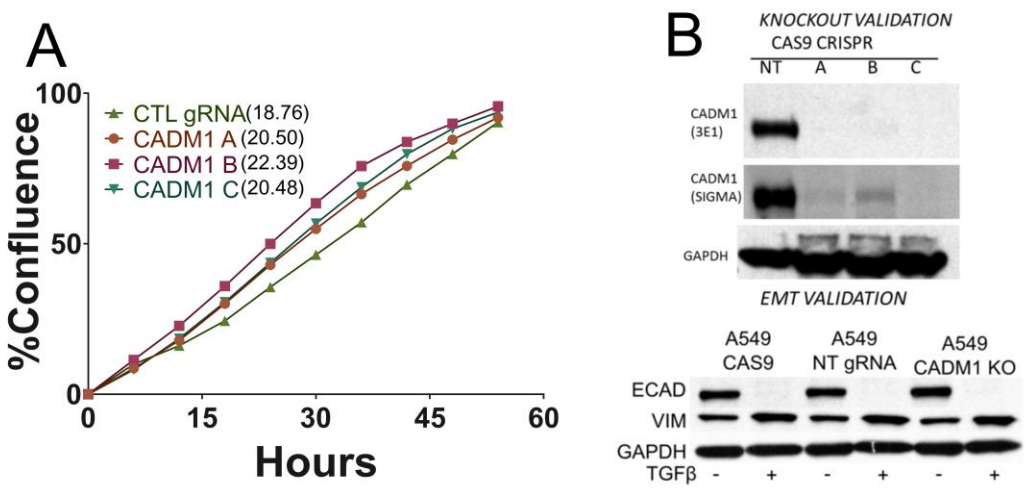
(**A**) A549 tumors grown subcutaneoulsy in RAG1$^{-/-}$ with NK cells depleted (ASGM1) or control (NRS) immunolabeled for CADM1 in green and nuclei were stained with DAPI in blue. Scale bars are 100 micron for large images and 50 micron for insets.

(**B**) Same tumors were immunolabeled for ECAD in green and nuclei were stained with DAPI in blue. Scale bars are 100 micron for large images and 50 micron for insets.



Supplemental Figure 5. CADM1 and ECAD Protein Levels Correlate to EMT-induced Susceptibility to NK Cells, Related to Figures 1 and 5

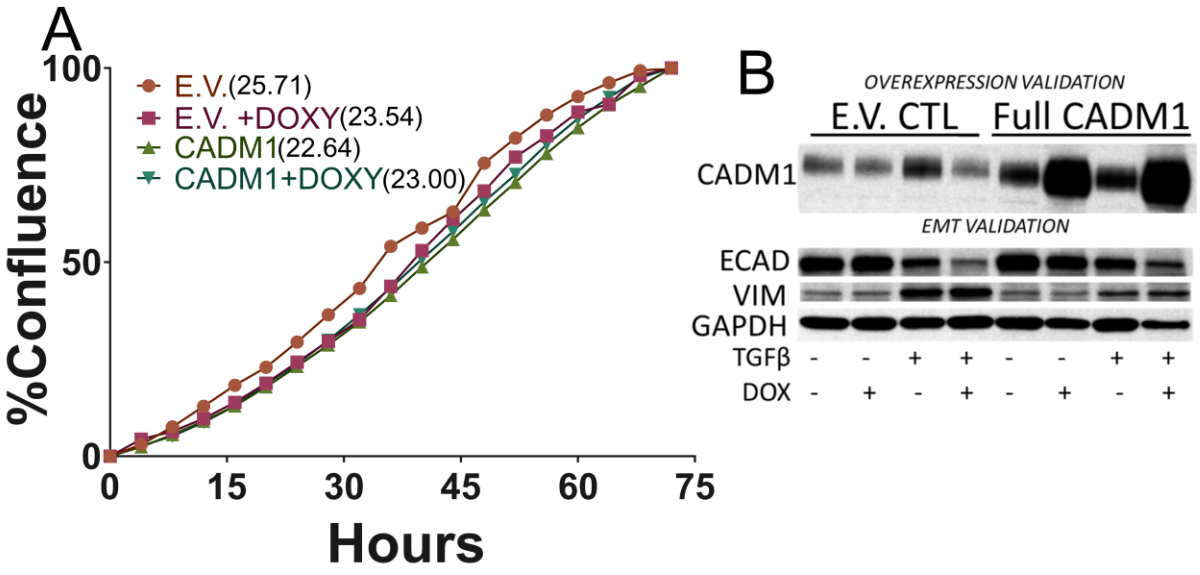
(**A**) Western immunoblot analysis of ECAD, CADM1, and GAPDH in response to TGFβ after 3 days for A549, and 6 days for MCF7, H460, and DLD1. Immunoblots were cropped for clarity of each cell line used.



Supplemental Figure 6. CADM1 Deletion Does Not Effect Cell Growth or EMT, Related to Figure 5

(**A**) Confluence percentage as calculated by an Incucyte Imager, EssenBio INC. of A549-CAS9 with indicated signal guide RNAs against CADM1 and a non-targeting (NT) construct. Doubling times were not significantly different, shown in parentheses.

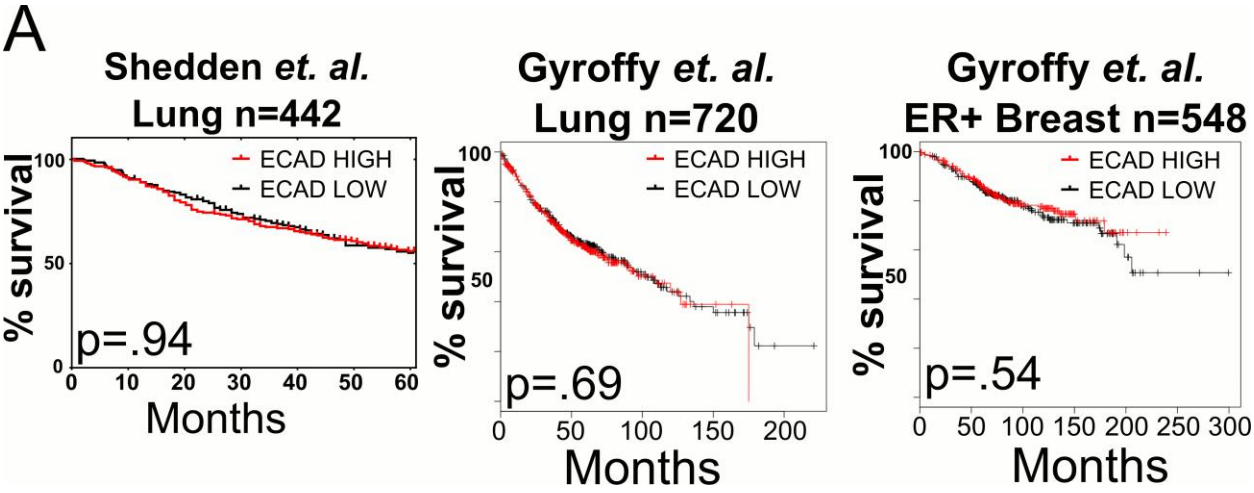
(**B**) Western immunoblot validation of CADM1 deletion utilizing two separate antibodies. 3E1 recognizes the N-Terminal of CADM1 while SIGMA recognizes the C-Terminal domain. Clone C was chosen as our CADM1 KO cell line and TGF-β-induced EMT was validated as seen by ECAD loss and Vimentin (VIM) increases.



Supplemental Figure 7. CADM1 Overexpression Does Not Effect Cell Growth or EMT, Related to Figure 7

(**A**) Confluence percentage as calculated by an Incucyte Imager, EssenBio INC. of A549 doxycycline-inducible overexpression of CADM1 or with an Empty Vector (E.V.) control. Doubling times were not significantly different shown in parentheses with or without doxycycline or induced CADM1 expression.

(**B**) Western immunoblot validation of CADM1 overexpression and TGF-β-induced EMT was validated as seen by ECAD loss and Vimentin (VIM) increases.



Supplemental Figure 8: E-cadherin expression in Patient Cohorts does not reveal survival benefit, related to Figure 8

(**A**) Lung adenocarcinoma patient cohort, Shedden et al.,-lung (n=442), was stratified into low and high CADM1 expressing groups and assessed for overall survival. Lung adenocarcinoma patient cohort, Gyroffy et al. –lung (n=720), was stratified into low and high CADM1 expressing groups and assessed for overall survival. Breast carcinoma patient cohort, Gyroffy et al.,-ER+ breast (n=548), was stratified into low and high CADM1 expressing groups and assessed for overall survival. Datasets shown here are Kaplan-Meier survival curves with Log-Rank p-values comparing the groups.