- 2 Supplementary figure 1. Proliferation of WT and Adam17-/- 4T1 and E0771 cells
- 3 A) Relative cell proliferation of WT and Adam17^{-/-} (A17^{-/-}) 4T1 (left) and E0771 (right) cell lines,
- 4 analyzed over a period of 44h (n=3). Mean and standard deviation indicated. Two-sided, unpaired
- 5 Student's t-test was applied to test for significant differences.

6

- 7 Supplementary figure 2. Marker expression in macrophages co-cultured with either WT or
- 8 *Adam17*-/- cells
- 9 A) Relative IL-10, CCR7, IL6, cMyc, CCl2 and iNOS mRNA expression in macrophages co-cultured
- with WT or *Adam17*-/- (A17-/-) 4T1 cells, determined by qRT-PCR (n=4). β₂ microglobulin (B2M)
- was used as a housekeeping gene. B) Relative IL-10, CCR7, IL6, cMyc and CCl2 mRNA expression
- in macrophages co-cultured with WT or *Adam17*-/- E0771 cells determined by qRT-PCR (n=4). B2M
- was used as a housekeeping gene. Mean and standard deviation indicated. Two-sided, unpaired
- Student's t-was applied to test for significant differences: $p \le 0.05$, $p \le 0.01$.

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- Supplementary figure 3. Cancer cells educate macrophages towards an invasion promoting
- phenotype via an ADAM17-dependent soluble factor in several mouse cancer cell lines
- A) Left: Protein expression of ADAM17 in WT and Adam17-/- (A17-/-) E0771 cell lines, determined
- by Western blot (representative of 3 repeats). β-actin was used as a loading control. *Right:* Average
- amount of invaded cells/field of WT E0771 cell lines together with BMDM educated by WT or
- 21 Adam17^{-/-} E0771 cells (n=3). B) Left: Protein expression of ADAM17 in WT and Adam17^{-/-} MC38
- 22 cell lines, determined by Western blot (representative of 3 repeats). β-actin was used as a loading
- control. *Right*: Average amount of invaded cells/field of WT MC38 cell lines together with BMDM

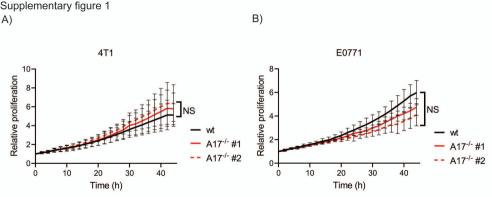
- educated by WT or Adam17^{-/-} MC38 cells (n=3). Data were analyzed by one way ANOVA with
- Dunnetts multiple comparison test.: * $p \le 0.05$.

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- 27 Supplementary figure 4. HB-EGF and AREG siRNA efficiency in 4T1 and E0771 cells
- 28 A) HB-EGF and B) AREG knock-down efficiency in 4T1 and E0771 measured by qRT-PCR (n=3).
- 29 β₂ microglobulin (B2M) was used as a housekeeping gene. Mean and standard deviation indicated.
- 30 Data in E were analyzed by one way ANOVA with Dunnetts multiple comparison test.

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- 32 Supplementary figure 5. CXCL1 expression upon CSF-1 and HB-EGF treatment
- A) CXCL1 mRNA expression in BMDM upon CSF-1, HB-EGF and CSF-1 and HB-EGF treatment
- 34 (n=3). Data in E were analyzed by one way ANOVA with Dunnetts multiple comparison test.



Supplementary figure 2 A) IL-10 CCR7 IL-6 сМус iNOS CCL2 1.5-1.5 1.5 1.5 0.055 Relative expression Relative expression Relative expression Relative expression Relative expression Relative expression 1.0 1.0 1.0-0.9 0.8 0.5 0.5 2-0.7 0.0 0.0 0.6 0.0 0.0 × Ma all #1 * Ma Alti ** * we alt #1 * WO ELT! ** * we art ** * Wo all #1 wan, *Novi wan, * Man * Man' * Wan! сМус CCL2 CCR7 IL-6 iNOS IL-10 1.5-1.2-1.5-1.5-3. Relative expression Relative expression Relative expression Relative expression Relative expression Relative expression 1.0 1.0 1.0 1.0 0.5 0.8 0.0 * Ma ATT #2 0.6 *Maa11 #2 0.0 0.0 * No ATT ** * Wast, #5 *MaA11 ** * wast ** * Man' want, * Man' * Man' * Man' *No NT B) CCL2 CCR7 IL-6 сМус IL-10 1.2-2.5-1.5-1.5-1.5-Relative expression Relative expression Relative expression Relative expression 1.1-2.0-Relative expression 1.0-1.0-1.0 1.0 1.5-0.9 1.0-0.5 0.5 0.8 0.5-0.0 0.7 0.0 * we art ** * we art ** 0.0 * We alt #1 0.0 * we alt ** * wa all ** * Man' *Non' *Non' * Man' * NO NI IL-6 сМус CCL2 IL-10 CCR7 1.5 1.5-1.5-1.5 Relative expression Relative expression 1.0 Relative expression Relative expression Relative expression 1.0-1.0 1.0-1.0-0.9 0.8 0.5 0.5 0.7 * we salt #\$ *Mari*** *Marit ** 0.6 0.0 0.0 × Ma Part #2 0.0 × Ma ATT #2 0.0 *Non' * Man! wan's Trans. * Man!

Supplementary figure 3 A) E0771 150 Average amount of cells/field A17-/-100-#1 #2 WT ADAM17 50 β-actin B) MC38 Average amount of cells/field A17-/-15 WT #1 #2 ADAM17 10 β-actin

Supplementary figure 4 A) 4T1 E0771 1.5-1.5 Relative expression 1.0 1.0 4T1 E0771 1.5-1.5

