**Supplemental** **Methods**

**CD8+ T Cells**

CD8+ T cells were purified with the EasySep mouse CD8+ T cell isolation kit (Stemcell Technologies) from the spleens of naïve/tumor bearing BALB/c mice according to the manufacturer’s instructions. CD8+ T cell purity was at least 90–95%.

**NK Cells**

Splenocytes from naïve BALB/c mice were cultured in complete alpha MEM medium supplemented with 1000 IU/ml rmIL-2 for 72 hours. NK cells were negatively isolated from the lymphokine-activated splenocytes with the EasySep mouse NK cell isolation kit (Stemcell Technologies). Dead cells were removed using the dead cell removal kit (Miltenyi Biotec). NK cell purity was at least 95%.

**CD8+ T Cell Activation Assay**

CD8+T cells were cultured overnight in complete RPMI-1640 supplemented with 125 ng/ml anti-CD3 and 50 U/ml rmIL-2, and then cultured alone (control; CTR) or co-cultured with BM-derived M1- or M2-Mφs ±rmSEMA3A or Mφs flow sorted from 4T1-3A+ or 4T1-CTR tumors O/N. Activation of CD8+ T cells was assessed by flow cytometric analysis of IFN- secretion.

**Cytotoxicity Assay**

NK cells were pre-activated with rmIL-2 for 4 days, then incubated O/N with or without conditioned medium from M1- or M2-polarized Mφs for 36 hours or in 0,4 μm transwell inserts above Mφs flow sorted from 4T1-3A+ or 4T1-CTR tumors. NK cells were then incubated with 51Cr-labeled 4T1 target cells for 4 hours. Supernatants were collected, and the radioactivity was measured in a gamma counter (Wallac Oy, Uppsala, Sweden). Specific lysis was measured using the following formula: % specific lysis = (experimental release-spontaneous release)/(maximum release - spontaneous release) × 100.

**Wound healing assay**

BM-derived M0-, M1- and M2-Mφs were cultured in monolayers in 6-well plates ±rmSEMA3A. A scratch was made with a 200 μl pipet-tip and the migration of cells into the cleaned area was monitored after 24 and 48h. Images were acquired using a Leica DM1740M Light microscope and analyzed and quantified using ImageJ software.

**Proliferation Assay**

4T1-CTR and 4T1-3A+ tumor cells were seeded at a density of 2×103 cells in 100 µl volume per well in 96-well plates in serum free RPMI-1640 medium. Six replicates were seeded for each cell line and time point. To evaluate proliferation at each time point, an XTT labeling mixture was prepared by mixing XTT labeling reagent and the electron-coupling reagent according to the manufacturer’s protocol [Cell Proliferation Kit II (XTT), Roche]. Cell viability was measured at a wavelength of 490 nm (with 650 nm as a reference) using a microplate reader.

**Metabolic flux analysis**

The oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) of 4T1-CTR and 4T1-3A+ cells were measured using a Seahorse XF24 Extracellular Flux Analyzer (Seahorse Bioscience). Cells (3-4 x 104 cells/well in 250 µl medium) were plated in XF24 cell culture plates the day before analysis and allowed to attach. Before loading the plates in the XF Analyzer cell culture medium was replaced with 500 µl DMEM medium buffered at pH 7.4, containing 2 mM glutamine and 1 mM sodium pyruvate and plates were equilibrated at 37C without CO2 for 1 h. Measurements of OCR and ECAR were obtained before (baseline) and after the sequential addition of the following reagents: glucose (25 mM), oligomycin (1 M), FCCP (1 M) and rotenone/antimycin A (1 M). All measurements during each step were acquired 3 times every 6 min and expressed, respectively as pmol/min (OCR) and mpH/min (ECAR) after normalization to total amount of proteins per well (Bradford assay). Data presented were acquired from five independent experiments and five wells per plate were used as technical replicates. Basal OCR and ECAR are calculated in presence of glutamine and sodium pyruvate from the last measurements before addition of glucose while glucose-stimulated ECAR was calculated from the last measurement after addition of glucose. Maximal respiration was calculated from the third measurement after the addition of the mitochondrial uncoupler FCCP. Comparison between cell lines was performed using the paired T-test.

**Lentiviral Vectors**

Lentiviral vector expressing murine SEMA3A downstream of the cytomegalovirus (CMV) promoter was purchased from GeneCopoeia. An empty vector was used as a control. Concentrated vesicular stomatitis virus-G protein (VSV-G)-pseudotyped lentivirus stocks were produced and titrated as described previously (1). Tumor cells were transduced by incubation with concentrated lentivirus for 12 hours in the presence of 8 μg/ml sequa-brene (Sigma), and successfully transduced cells were selected with the appropriate antibiotics.

**Tumor Dissociation**

To obtain single-cell suspensions of tumors for flow cytometry and flow sorting, tumors were minced in dissociation buffer containing TrypLe and Stem Cell Pro Accutase (Life Technologies) at a 1:1 ratio and incubated at 37°C for 30 min. Suspensions were passed through a 19 G needle, filtered, and washed with PBS containing 10% FBS.

**RNA Extraction and cDNA Synthesis**

Total RNA was extracted from cultured 4T1 cells, BM-derived Mφs, and flow-sorted myeloid cells/tumor cells from 4T1-3A+ tumors and 4T1-CTR tumors. Cells were collected in RLT buffer and homogenized using a syringe with a 20G needle. RNA was extracted using RNeasy Mini Kit (Qiagen) according to the manufacturer’s instructions. RNA was then reverse-transcribed with the QuantiTect Reverse Transcription kit (Qiagen). Genomic DNA was eliminated from the RNA using gDNA Wipeout Buffer for 2 min at 42°C. RNA was then mixed with Quantiscript Reverse transcriptase, Quantiscript Reverse transcriptase buffer, and Reverse transcriptase primer mix and incubated at 42°C for 15 min, and the reaction was stopped by heating for 3 min at 95°C.

**Gene Expression Correlation Analyses**

The Uppsala dataset has been extensively described previously (2-4) and is publically available at the NCBI Gene Expression Omnibus (GEO; Accession number GSE3494). The gene expression profiling of this cohort has previously been approved by the Ethics Committee at the Karolinska Institutet together with additional amendments*.* To test for correlations between *SEMA3A* and *CD8A* and *B*, probes corresponding to these genes were extracted from the dataset for each tumor and a Spearman’s rank correlation was performed. In the case of multiple probes mapping to the same gene, the average expression of all probes was used. All analyses were performed using the R Statistical language (*R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2014. http://www.R-project.org/).

**Statistics**

Statistical analyses were performed with GraphPad Prism software version 6.0. Student’s t-test, one-way ANOVA, or two-way ANOVA were used. P-values less than 0.05 were considered significant.

References

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