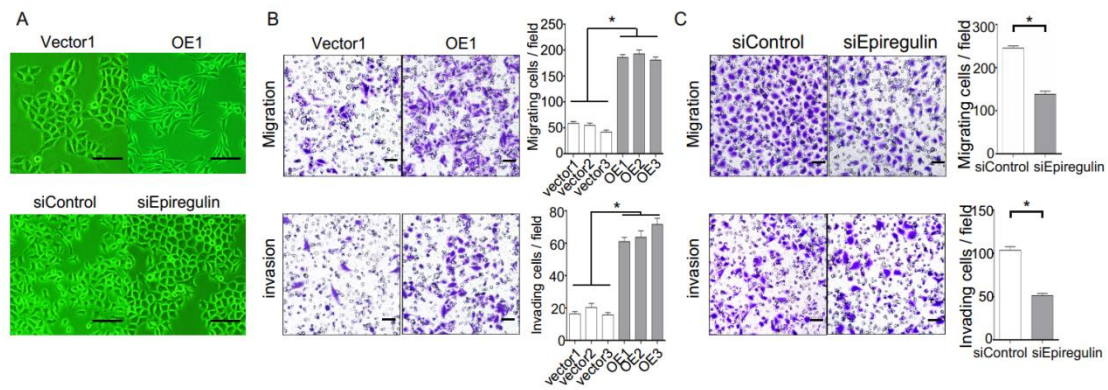**Supplementary data**

Figure S1 Epiregulin induces a prometastatic phenotype in SACC cells.

(A) Phase-contrast photomicrographs showing morphological changes in epiregulin-overexpressing OE cells and siEpiregulin cells compared to controls. Scale bar = 100 μm. (B, C) Migration and invasion assays (scale bar = 50 μm) in OE cells and siEpiregulin cells compared to controls.
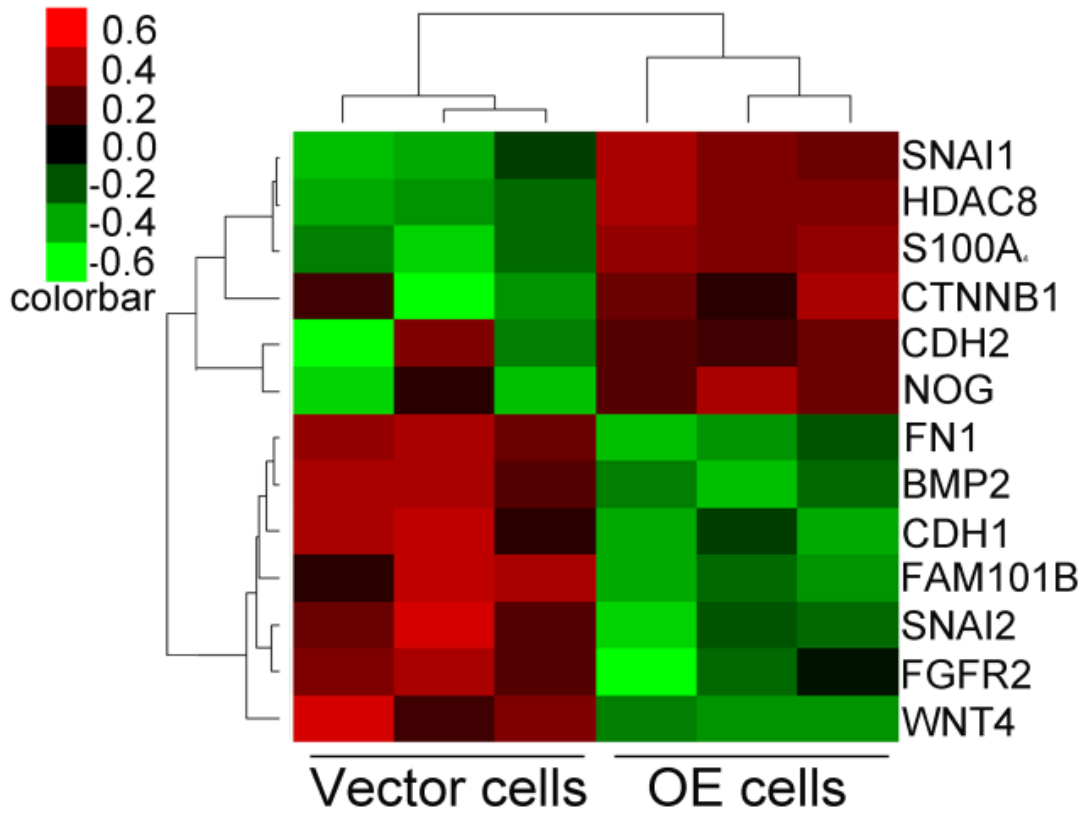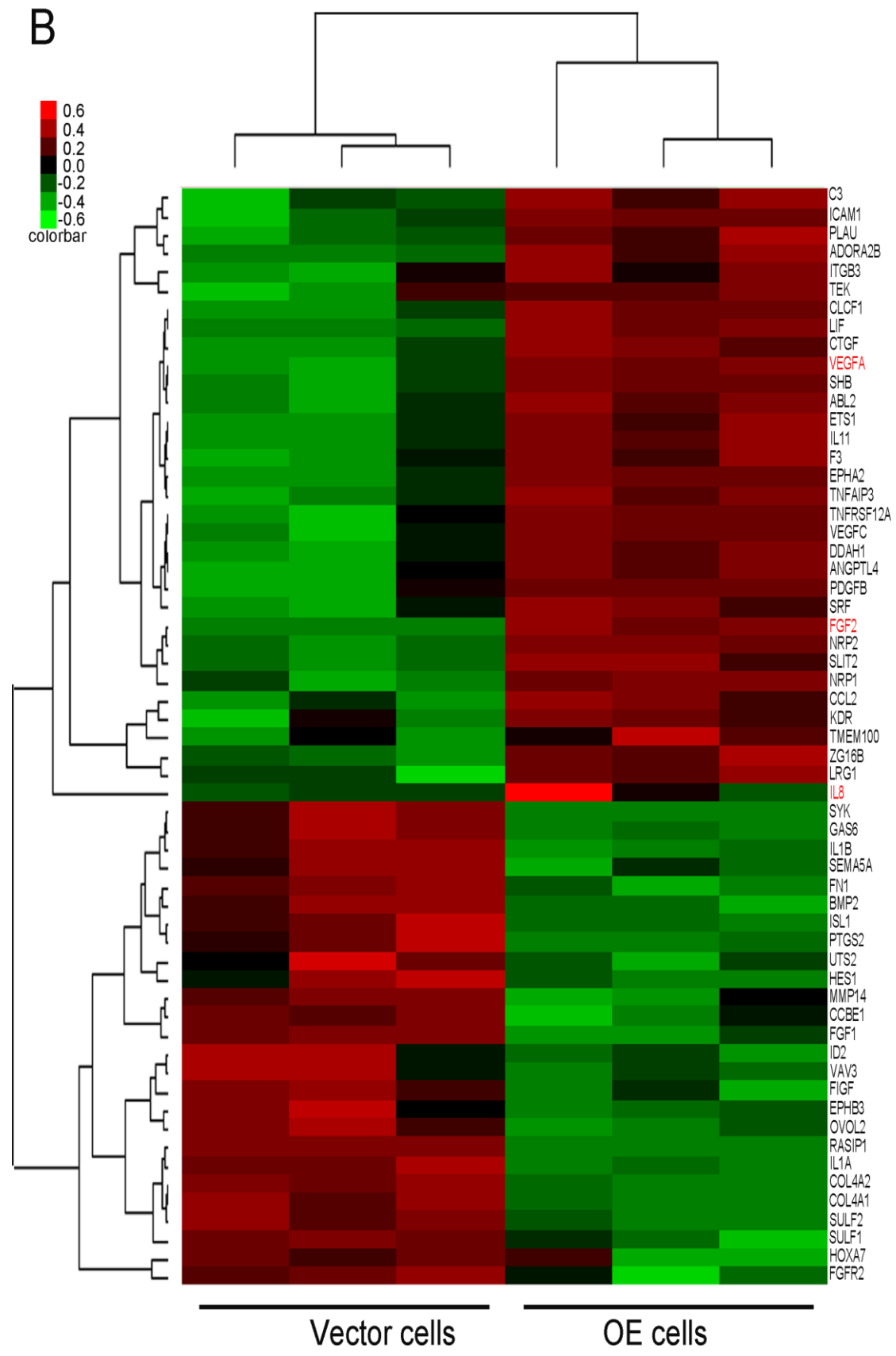
Figure S2: Heatmap analysis of microarray data showed differentially expressed genes related to EMT (A) and angiogenesis (B) processes in OE cells. Red square: up-regulated genes; green square: down-regulated genes.
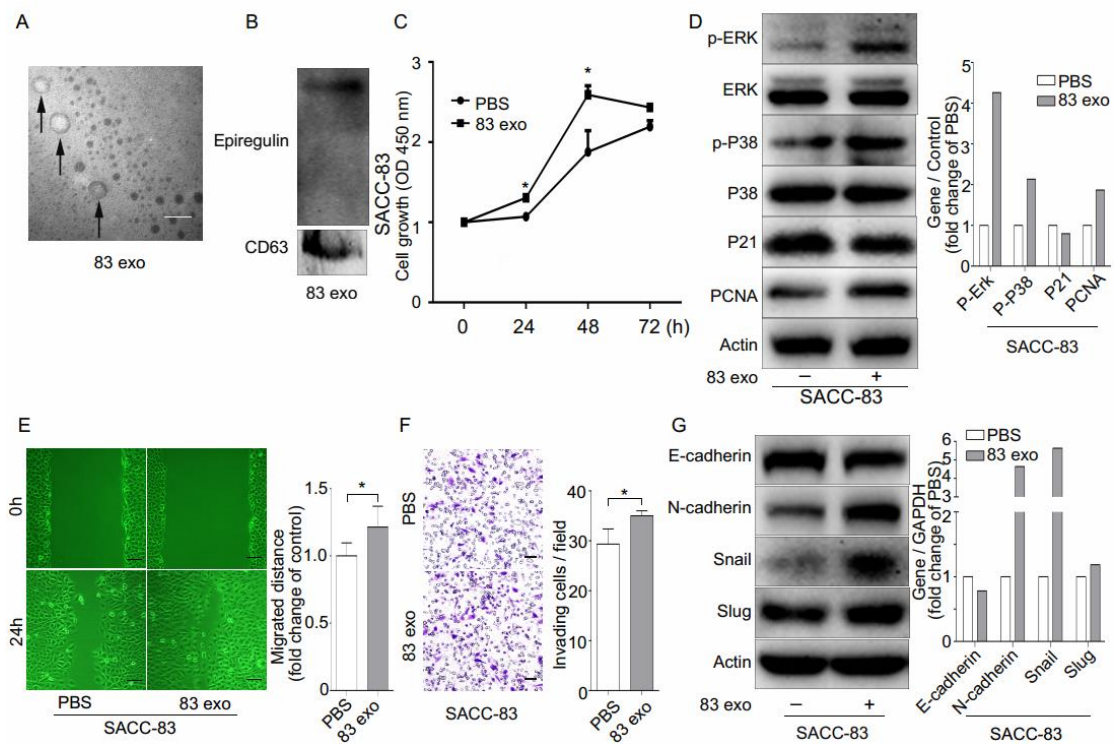
Figure S3: Exosomes derived from SACC-83 cells (83 exo) enhance the proliferation, migration, and invasion of SACC cells. (A) Electron microscopy image of 83 exo (approximately 30–100 nm in diameter; scale bar = 100 nm). (B) Western blot analysis of the exosomal marker CD63 and epiregulin (mainly full-length proepiregulin) in 83 exo. (C) CCK8 cell proliferation assays of SACC-83 cells after co-culturing with 83 exo for 24 hours, 48 hours, and 72 hours. (D) Western blot assay of the expression of phosphorylated (p)-ERK, ERK, p-P38, P38, P21, and PCNA in SACC-83 cells after incubation with or without 83 exo. (E) Migration of SACC-83 cells in a wound healing assay, and quantification of the scratch closure 16 hours incubation with or without 83 exo. Scale bar = 100 μm. (F) Representative images and quantification of the invasive ability of SACC-83 cells (i.e., ability to penetrate the membrane with matrigel) after incubation with or without 83 exo. Scale bar = 50 μm. (G) Western blot assay indicating the expression of E-cadherin, N-cadherin, Slug, and Snail in SACC-83 cells after incubation with or without 83 exo. All data are expressed as mean ± SD, *$P < 0.05$.
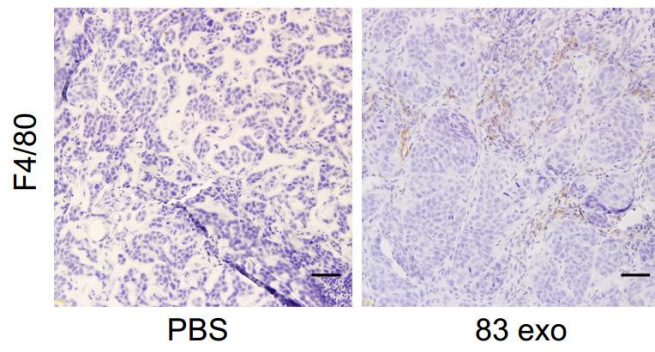
Figure S4: Exosomes derived from SACC-83 cells induce aberrant distribution of macrophages *in vivo*, as shown via immunohistochemical staining for F4/80.
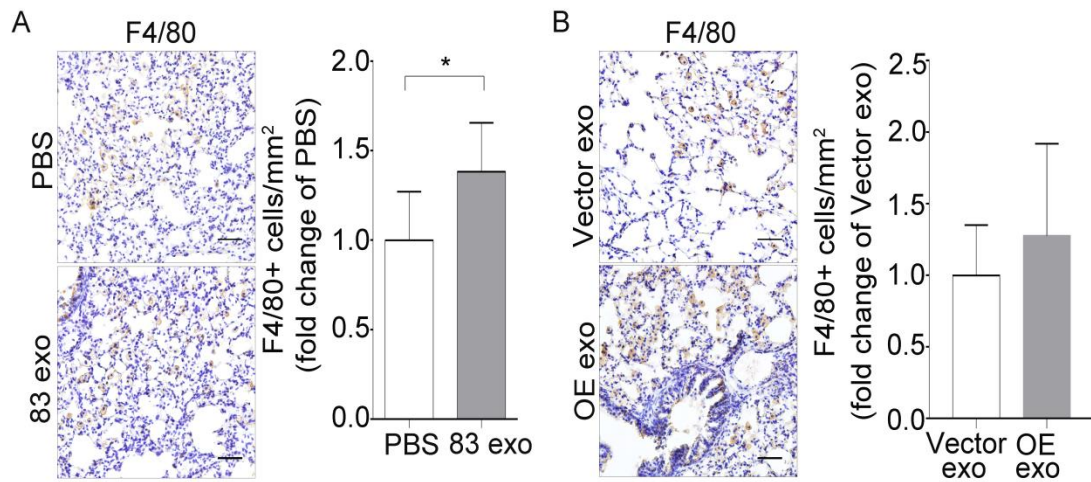
Figure S5: Effects of exosomes on the distribution of macrophages *in vivo*, as shown via immunohistochemical staining for F4/80. **(A)** Representative images of F4/80 immunohistochemical staining of mouse lung in the *in vivo* mouse lung metastasis model with or without 83 exo treatment (n = 6 per group). **(B)** Representative images of F4/80 immunohistochemical staining of mouse lung in the *in vivo* mouse lung metastasis model with Vector exo or OE exo treatment (n = 7 per group). The data are showed as mean ± SD. *, $P < 0.05$.

Table S1: Primers for qRT-PCR.

Gene	Primer sequence (5' to 3')
qRT-PCR (human)	
Epiregulin	F: ATCCTGGCATGTGCTAGGGT
	R: GTGCTCCAGAGGTCAGCCAT
GLI1	F: CTGGACTTTGTGGCTAT
	R: ATGCGATCTGTGATGGA
E-cadherin	F: GACCGGTGCAATCTTCAAA
	R: TTGACGCCGAGAGCTACAC
Fibronectin	F: CAAACTCCGTCACCCTCAGT
	R: GGTGCCAGTGGTTTCTTGTT
Snail	F: CCCCAATCGGAAGCCTAACT
	R: GCTGGAAGGTAAACTCTGGATTAGA
Slug	F: TTCGGACCCACACATTACCT
	R: TTGACGCCGAGAGCTACAC
VEGFA	F: TTCTGAGTTGCCCAGGAGAC
	R: GGAGCAGGAAGAGGATGAGG
FGF-2	F: TCAGTCTTCGCCAGGTCATT
	R: GTATTCGGCAACAGCACACA
IL-8	F: TTTTGCCAAGGAGTGCTAAAGA
	R: AACCCTCTGCACCCAGTTTTC
VEGFR1	F: CTATCACTGCAAAGCCACCA
	R: GCCACACAGGTGCATGTTAG
VEGFR2	F: CAGCATCACCAGTAGCCAGA
	R: GATGCTCCAAGGTCAGGAAG
FGFR1	F: CGGGACAGACTGGTCTTAGG
	R: CTTCACAGCCACTTTGGTCA
FGFR2	F: AAGCTGCTGAAGGAAGGACA
	R: TGCTTGAACGTTGGTCTCTG
GAPDH	F: CCATGGAGAAGGCTGGG
	R: CAAAGTTGTCATGGATGACC
qRT-PCR (mouse)	
VEGFA	F: GAGCAGAAGTCCCATGAAGTGA
	R: CACAGGACGGCTTGAAGATGT
FGF-2	F: AAGGGAGTGTGTGCCAACC
	R: GCCCAGTTCGTTTCAGTGC
IL-8	F: TTTCCACCGGCAATGAAG
	R: TAGAGGTCTCCCGAATTGGA
GAPDH	F: GTGTTTCCTCGTCCCGTAGA
	R: AATCTCCACTTTGCCACTGC