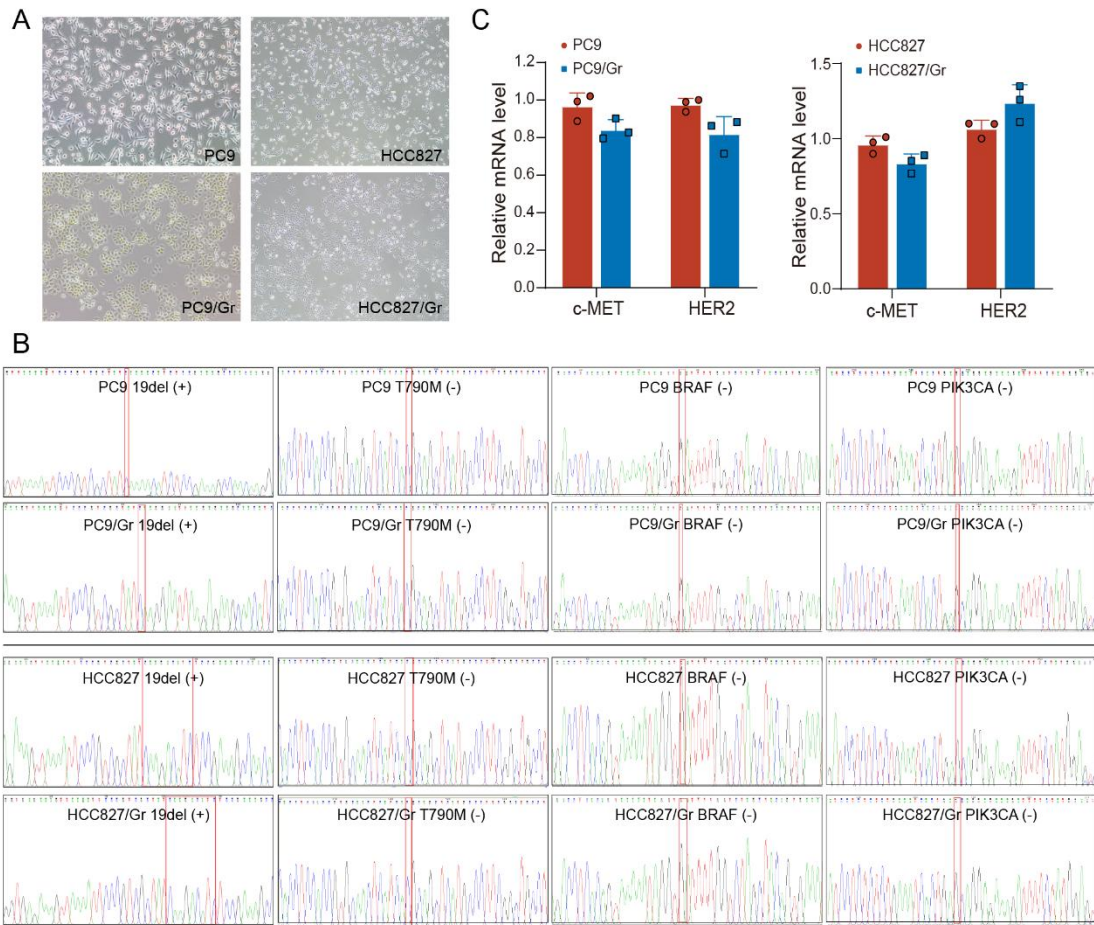
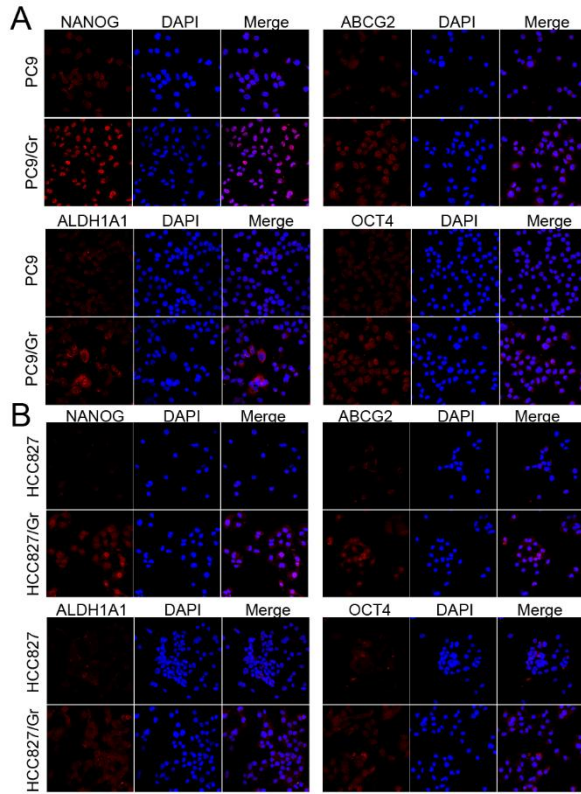


1 **Supporting Information**



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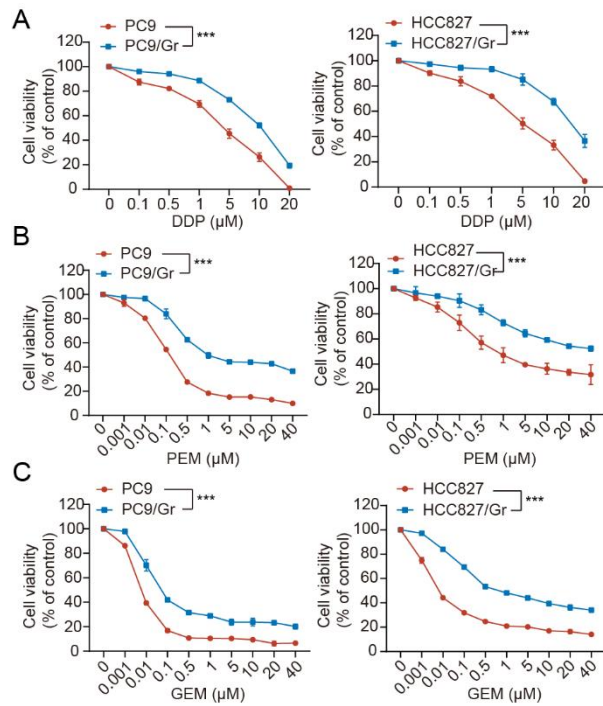
3 **Supplementary Figure S1.** A. The morphology of lung cancer cells (PC9 and HCC827) and
 4 gefitinib resistant lung cancer cells (PC9/Gr and HCC827/Gr). B. Sanger sequencing for EGFR
 5 T790M, BRAF and PIK3CA of PC9 and PC9/Gr, HCC827 and HCC827/Gr cells. C. The
 6 expression of C-MET and HER2 in PC9 and PC9/Gr, HCC827 and HCC827/Gr cells was detected
 7 by qRT-PCR.



8

9 **Supplementary Figure S2.** A. Immunofluorescence staining of stemness related genes NANOG,
 10 ABCG2, ALDH1A1 and OCT4 in PC9 and PC9/Gr cells. B. Immunofluorescence staining of
 11 stemness related genes NANOG, ABCG2, ALDH1A1 and OCT4 in HCC827 and HCC827/Gr
 12 cells.

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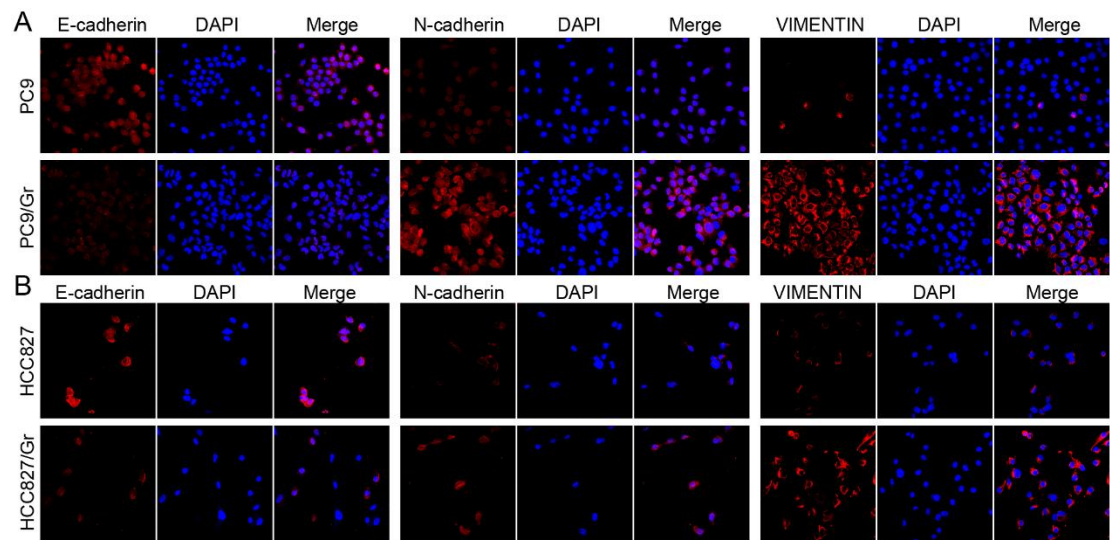


14

15 **Supplementary Figure S3.** The sensitivities of PC9 and PC9/Gr, HCC827 and HCC827/Gr cells

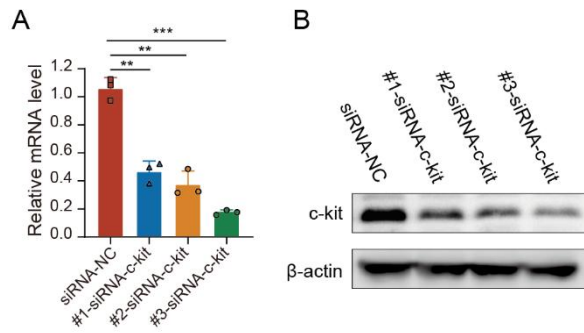
16 to cisplatin (A), pemetrexed (B), and gemcitabine (C). *: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$.

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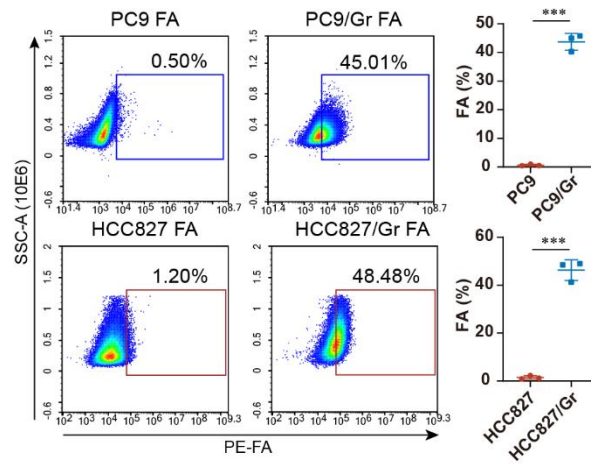
Supplementary Figure S4. A. Immunofluorescence staining of EMT related markers E-cadherin, N-cadherin, and Vimentin in PC9 and PC9/Gr cells. B. Immunofluorescence staining of EMT related markers E-cadherin, N-cadherin, and Vimentin in HCC827 and HCC827/Gr cells.



23

24 **Supplementary Figure S5.** A. The relative c-kit mRNA expressions after interference with
 25 #1-siRNA-c-kit, #2-siRNA-c-kit, and #3-siRNA-c-kit in PC9/Gr cells were detected by qPCR. B.
 26 The relative c-kit protein expressions after interference with #1-siRNA-c-kit, #2-siRNA-c-kit, and
 27 #3-siRNA-c-kit in PC9/Gr cells were detected by Western blot. *: $P < 0.05$; **: $P < 0.01$; ***: $P <$
 28 0.001.

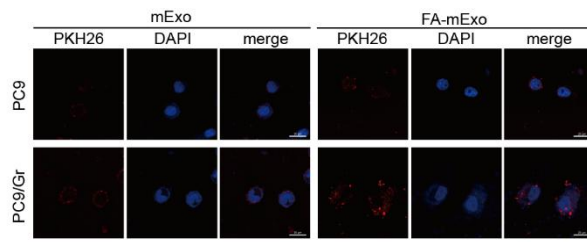
29



30

31 **Supplementary Figure S6.** Flow cytometry analysis of folate receptor- α in PC9 and PC9/Gr,
 32 HCC827 and HCC827/Gr cells. *: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$.

33



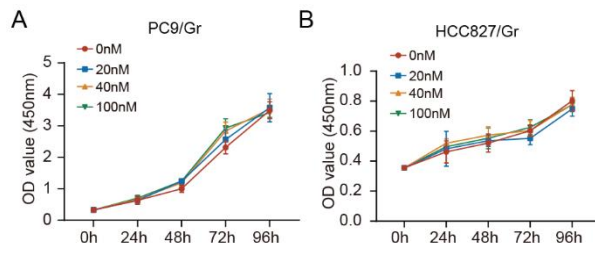
34

35 **Supplementary Figure S7.** Milk exosomes (red fluorescence) with or without FA modification

36 applied on the PC9 and PC9/Gr cells. After 24h incubation, cells were visualized by confocal

37 microscope.

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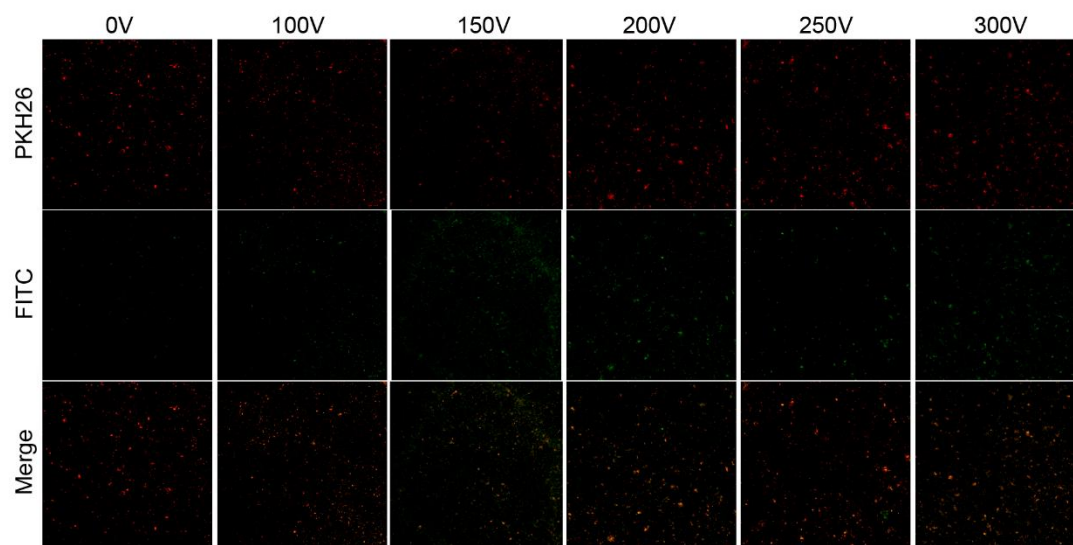


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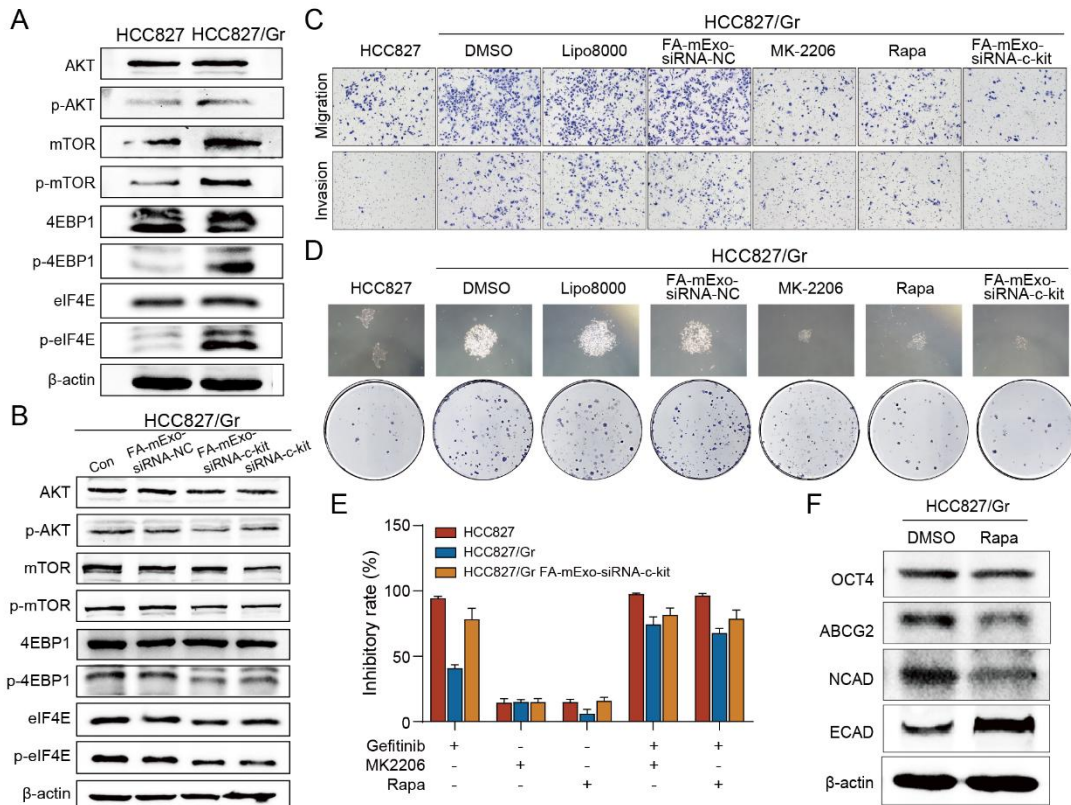
Supplementary Figure S8. Effects of different concentrations of FA on proliferation of PC9/Gr (A) and HCC827/Gr cells (B).



42

43 **Supplementary Figure S9.** The fluorescence intensity of mExo loaded siRNA-c-kit under
44 different electroperforation voltages was observed by confocal microscopy.

45



46

47 **Supplementary Figure S10.** A. Protein expression of mTOR signaling pathway-related
 48 molecules AKT, p-AKT, mTOR, p-mTOR, 4EBP1, p-4EBP1, eIF4E, p-eIF4E in HCC827 and
 49 HCC827/Gr cells. B. Suppression of mTOR signaling pathway after interference of c-kit
 50 expression in HCC827/Gr cells. C. The migration and invasive abilities of HCC827/Gr cells were
 51 assessed with transwell assays after treatment with MK2206 (AKT inhibitor) or rapamycin
 52 (mTOR inhibitor). D. The sphere formation efficiency of HCC827/Gr cells was evaluated after
 53 treatment with MK2206 (AKT inhibitor) or rapamycin (mTOR inhibitor). E. Effects of
 54 AKT/mTOR inhibitors on gefitinib resistance after blocking the mTOR signaling pathway in
 55 HCC827/Gr cells. F. The expression of stem cell-related genes OCT4, ABCG2 and mesenchymal
 56 marker N-cadherin was diminished by MK2206 and rapamycin treatment, and epithelial makers
 57 E-cadherin expression was increased in HCC827/Gr cells. *: $P < 0.05$; **: $P < 0.01$; ***: $P <$
 58 0.001 .

59

60 **Supplementary Table 1.** Primers and probes for qRT-PCR.

KIT_F	CAAGGCTTCTCCAATTCTGC
KIT_R	TGCAGTGGTCCACAGAAGAG
cMET_F	CCAAGTCAGATGTGTGGTCCTTTG
cMET_R	GGTGTTTACGTCAGGATAAGGTGG
HER2_F	GTGTCTGAATTCTCCCGCATGG
HER2_R	CCGCCACTCCTGGTAGATGAG
NANOG_F	CTCCTCCCATCCCTCATAG
NANOG_R	GGCTCCAACCATACTCCA
ABCG2_F	GGGCTTGTGGAAGAATCA
ABCG2_R	GATGGCAAGGGAACAGAA
ALDH1A1_F	TCAAACCAGCAGAGCAAA
ALDH1A1_R	GCCATAACCAGGAACAA
PROM1_F	GCATCCATCAAGTGAAACC
PROM1_R	ACCAGGCCATCCAAATC
OCT4_F	GTTTGTGGCAGGGCTTT
OCT4_R	TGTGTCCCAGGCTTCTTT
SNAI2_F	CTGCGATGCCCAGTCTA
SNAI2_R	CCCCGTGTGAGTTCTAATG
VIM_1F	GAAGAGAACTTTGCCGTTG
VIM_1R	GAAGGTGACGAGCCATTT
ECAD_F	CGACACCCGATTCAAAGT
ECAD_R	GCGTAGACCAAGAAATGGA
NCAD_F	ATCATTGCCATCCTGCTC
NCAD_R	TCCTCCACCTTCTTCATCA

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