Supplementary Figure 1

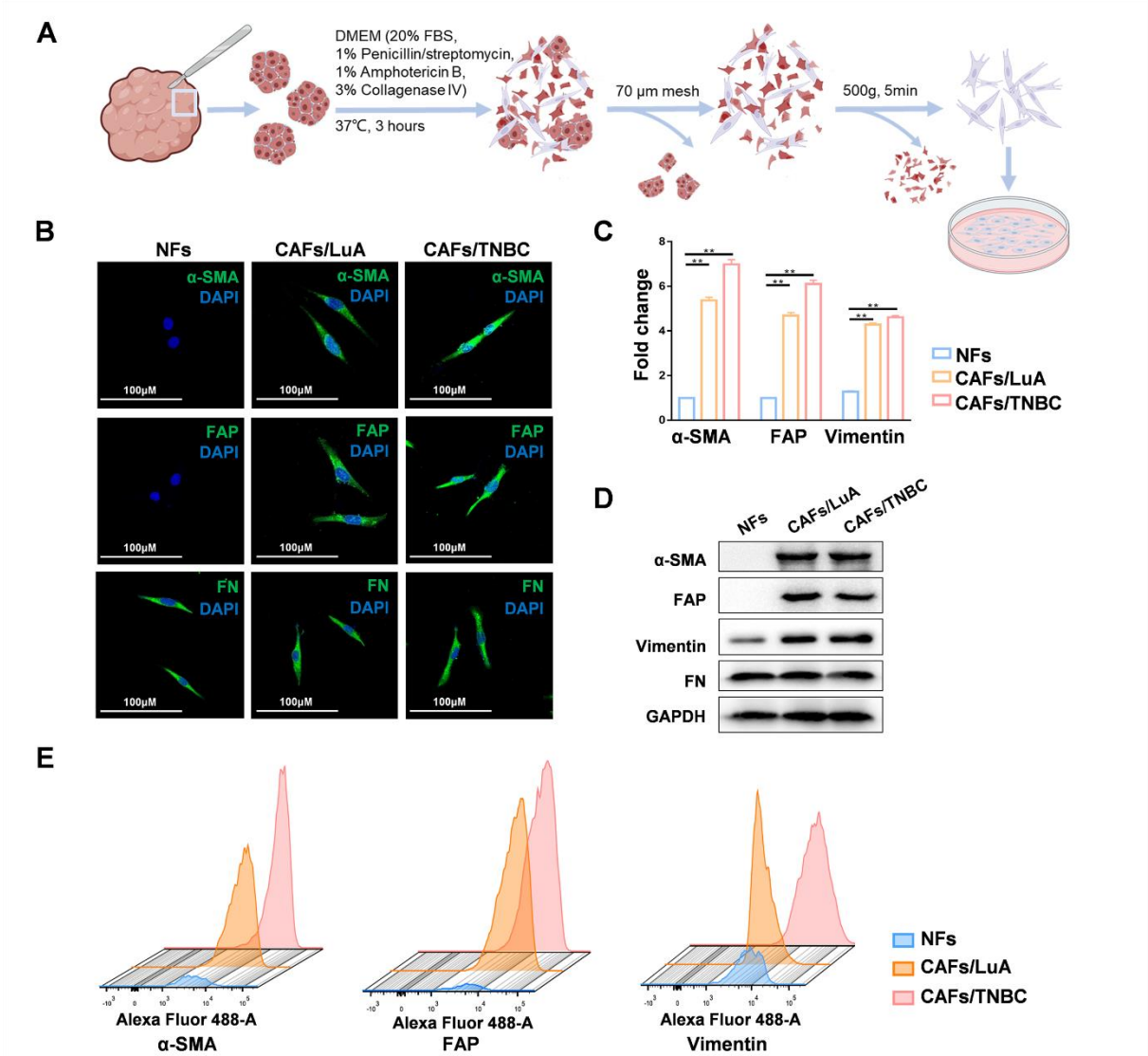

Fig.S1 Identification of fibroblasts. (A) Schematic diagram of fibroblast extraction. **(B-E)** The extracted fibroblasts were examined by the determination of CAFs-specific proteins α-SMA, FAP, and vimentin by immunofluorescence **(B)**, ELISA **(C)**, immunoblots **(D)**, and flow cytometry **(E)**, respectively. FN serves as a fibroblast protein control. Data shown represent the results of at least three biologically independent experiments. $*P < 0.05$, $**P < 0.01$.

Supplementary Figure 2

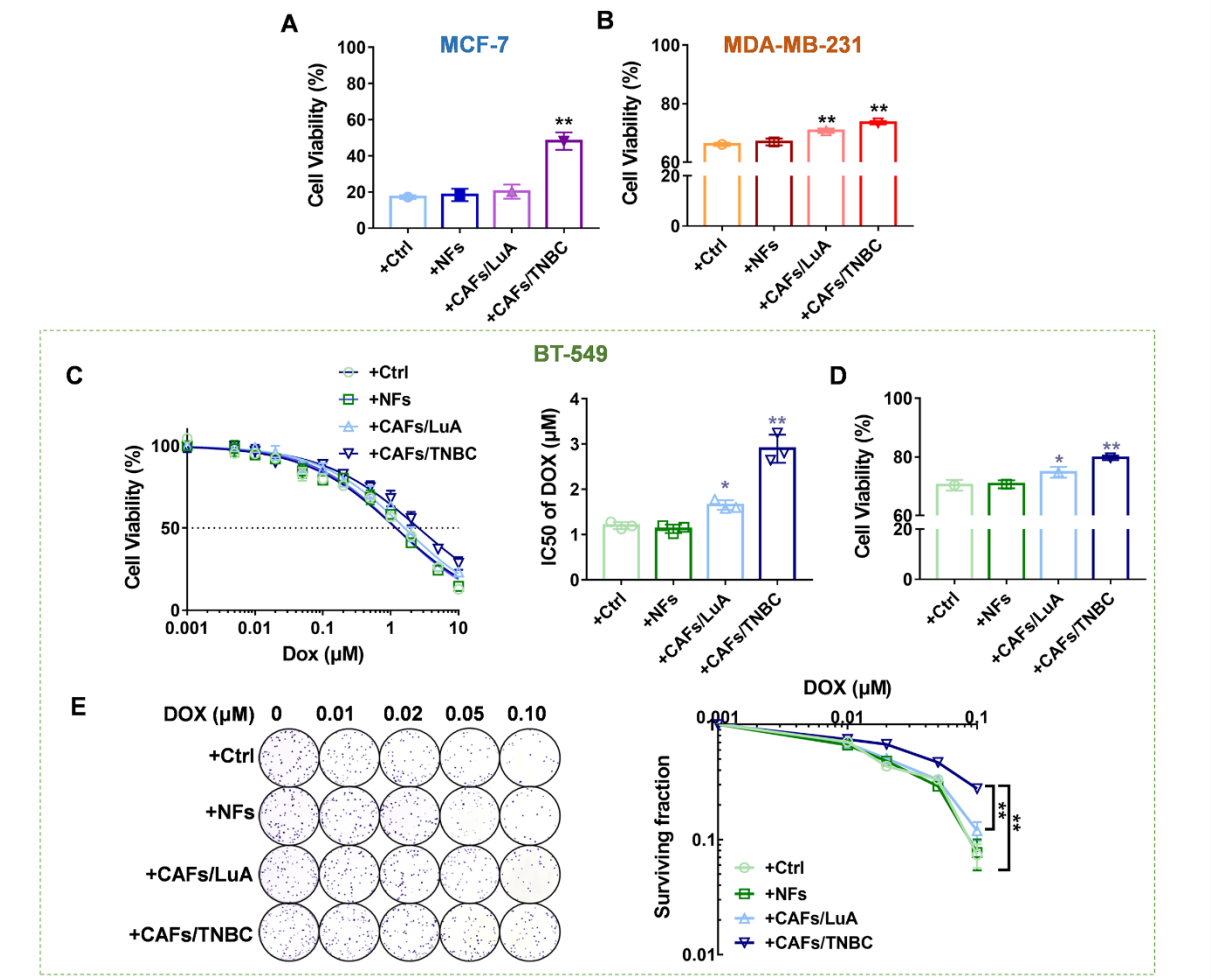

Fig.S2 CAFs reduced DOX sensitivity of BC cells. (A, B) Cell viability of BC cells post 0.5μM DOX treatment for 48 h. **(C-D)** Cell viability of BT-549 cells was measured by an MTT assay. **(E)** After cell-fibroblasts incubation and drug treatment, DOX resistance was analyzed by colony survival assay. Data shown represent the results of at least three biologically independent experiments. *$P < 0.05$, **$P < 0.01$.

Supplementary Figure 3

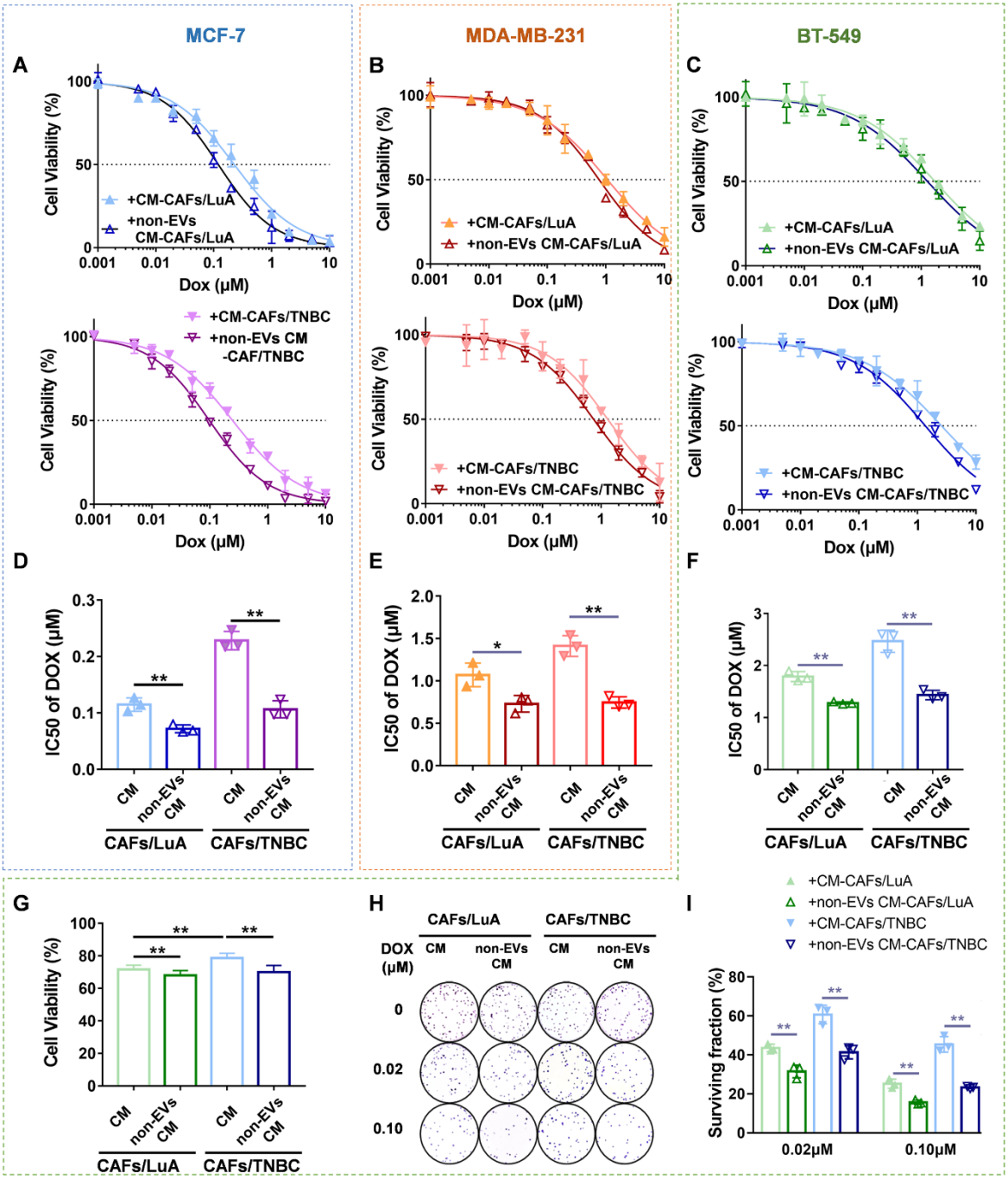

Fig.S3 EVs derived from CAFs contributed to DOX resistance in BC cells. (A-C) The percentage of live BC cells relative to total cells was counted over time post-DOX treatment. **(D-F)** The IC50 values of the recipient cells were calculated. **(G)** Cell viability of BT-549 was measured by an MTT assay. **(H, I)** The cell survival rate was determined using a colony survival assay. Data shown represent the results of at least three biologically independent experiments. $*P < 0.05$, $**P < 0.01$.

Supplementary Figure 4

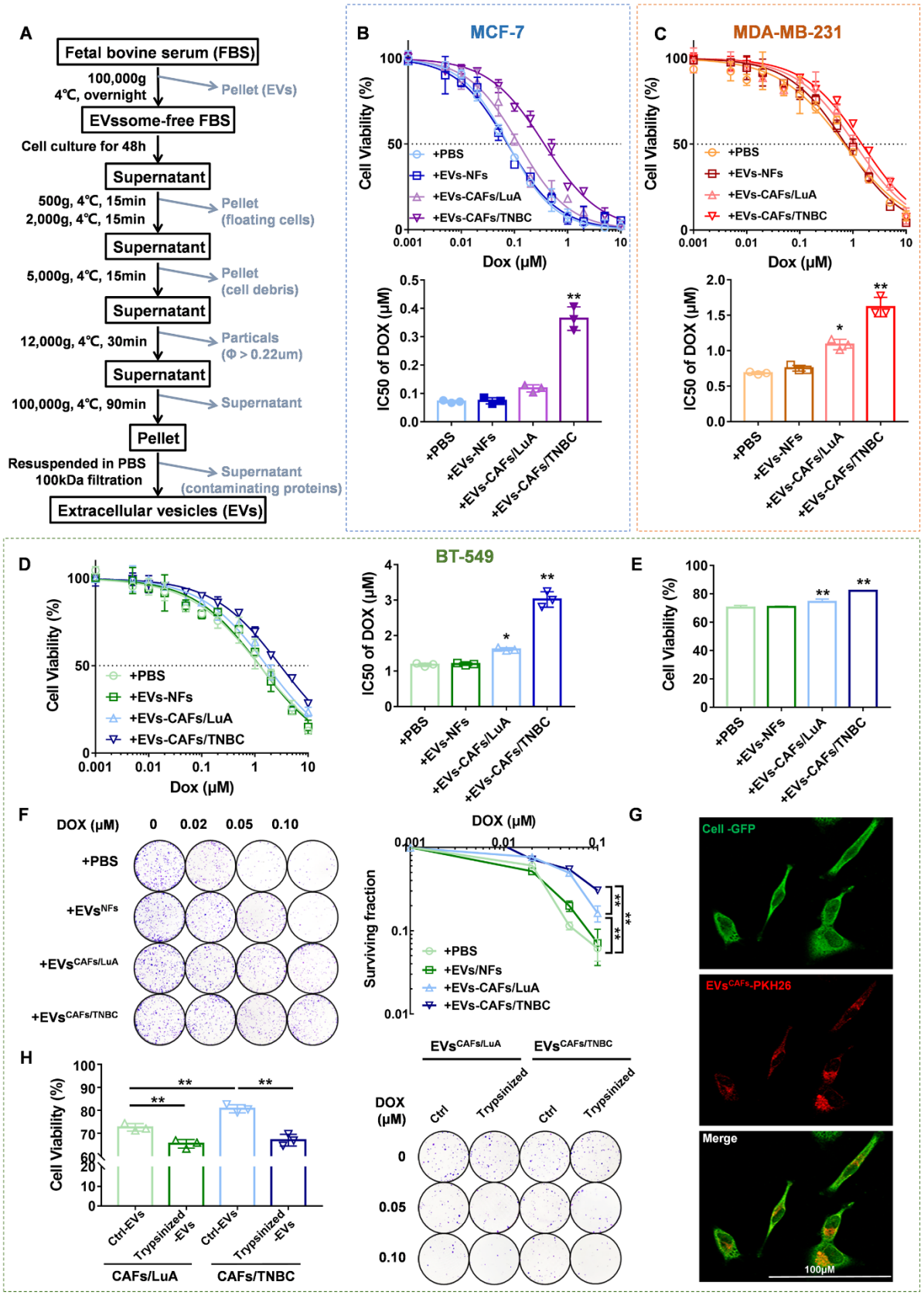

Fig.S4 CAFs/TNBC-derived EVs reduced the sensitivity of BC cells to DOX. (A)

Schematic diagram of EVs extraction. **(B-E)** Cell viability was measured by an MTT assay. **(F)** The cell survival rate was determined using a colony survival assay. **(G)** After incubation with PKH26-labeled EVs, BT-549 cells (labeled with GFP) were observed using a confocal microscope. **(H)** Cell viability and cell survival rate were measured by an MTT assay and colony survival assay, respectively. Data shown represent the results of at least three biologically independent experiments. $*P < 0.05$, $**P < 0.01$.

Supplementary Figure 5

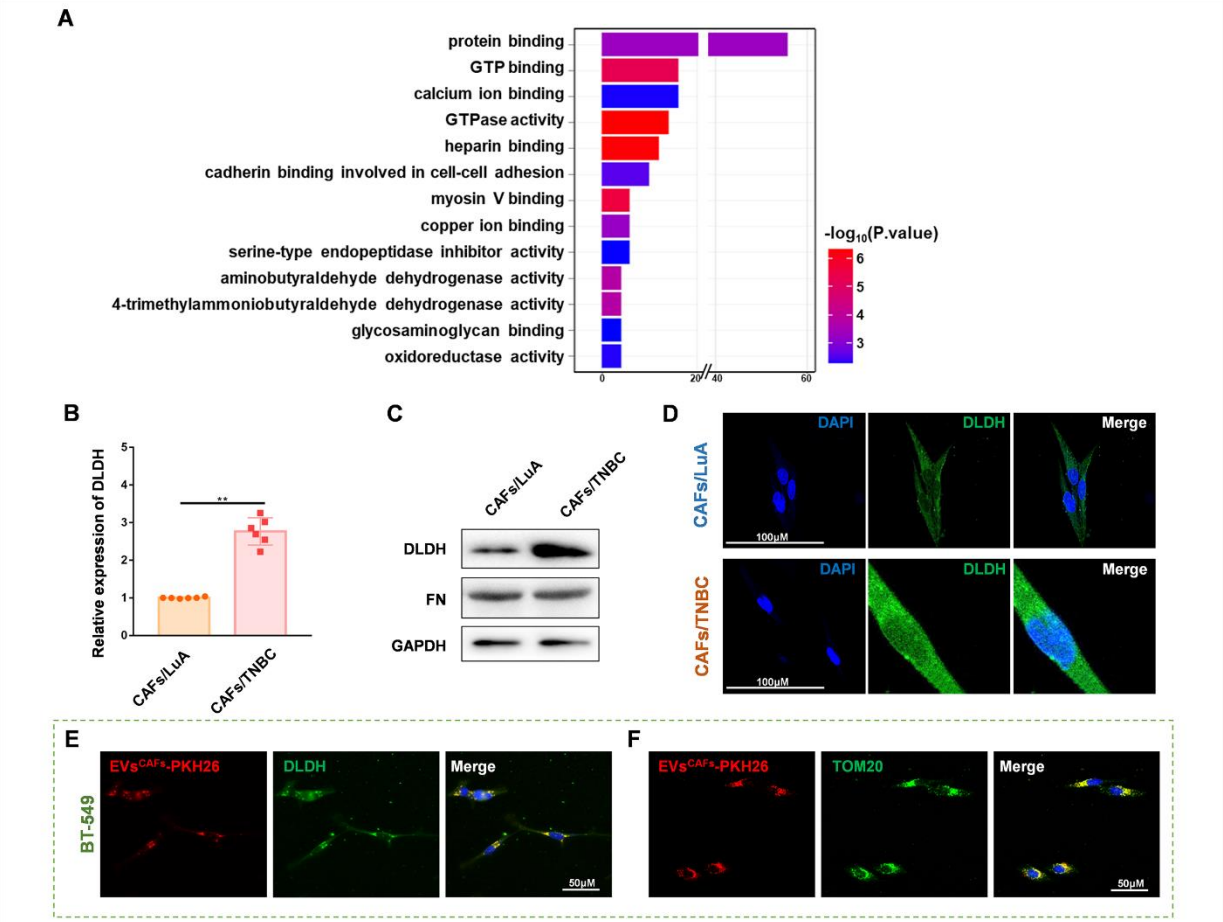

Fig.S5 CAFs-secreted EVs deliver DLDH into the mitochondria of BC cells. (A) Alters in cell binding signals and metabolic pathways were analyzed using KEGG enrichment analysis software. **(B-D)** The levels of DLDH in CAFs/LuA and CAFs/TNBC were quantified by ELISA **(B)**, immunoblots **(C)**, and immunofluorescence **(D)**, respectively. **(E)** Co-localization of DLDH with EVs^{CAFs} in BT-549 cells was analyzed by confocal imaging. **(F)** Co-localization of TOM20 with EVs^{CAFs} in the mitochondria of the recipient cells was examined. **B-F** Data shown represent the results of at least three biologically independent experiments. $^{**}P < 0.01$.

Supplementary Figure 6

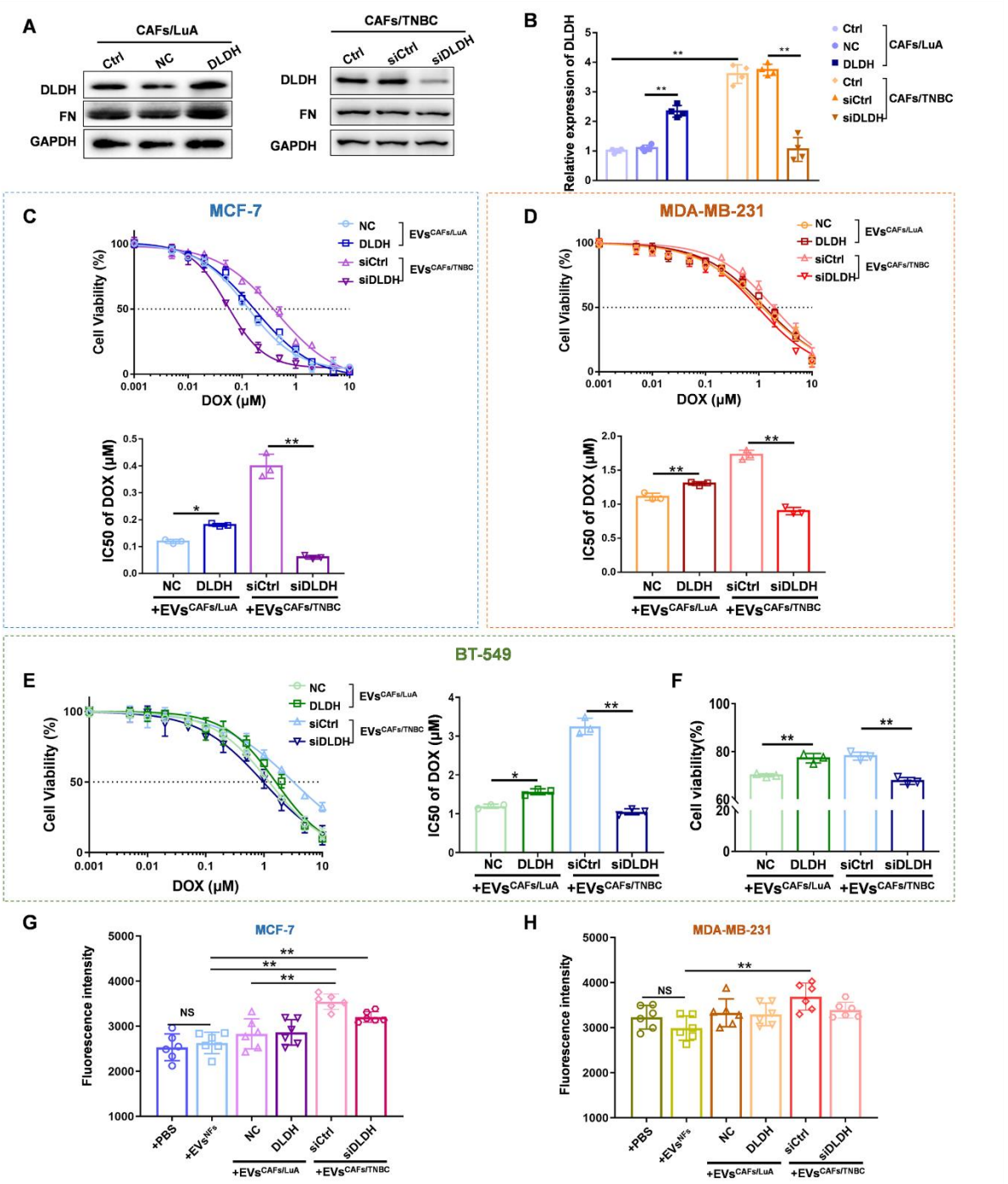

Fig.S6 EVs-DLDH promoted the resistance of BC cells to DOX. (A, B) DLDH was ectopically expressed in CAFs/LuA cells by stably transfecting a human DLDH cDNA construct, and was knocked down in CAFs/TNBC cells using a DLDH siRNA. The level of DLDH in CAFs-derived EVs was measured by western blots **(A)** and ELISA assay **(B)**. **(C-E)** After incubation with EVs derived from DLDH-manipulated CAFs, the percentage of live cells

relative to total cells was counted post-DOX treatment. The IC50 values were calculated. **(F)** Cell viability of BT-549 was measured by an MTT assay. **(G, H)** The tumor volumes of PBS-treated zebrafishes were calculated and plotted, $n \geqq 6$. Data shown represent the results of at least three biologically independent experiments. $*P < 0.05$, $**P < 0.01$.

Supplementary Figure 7

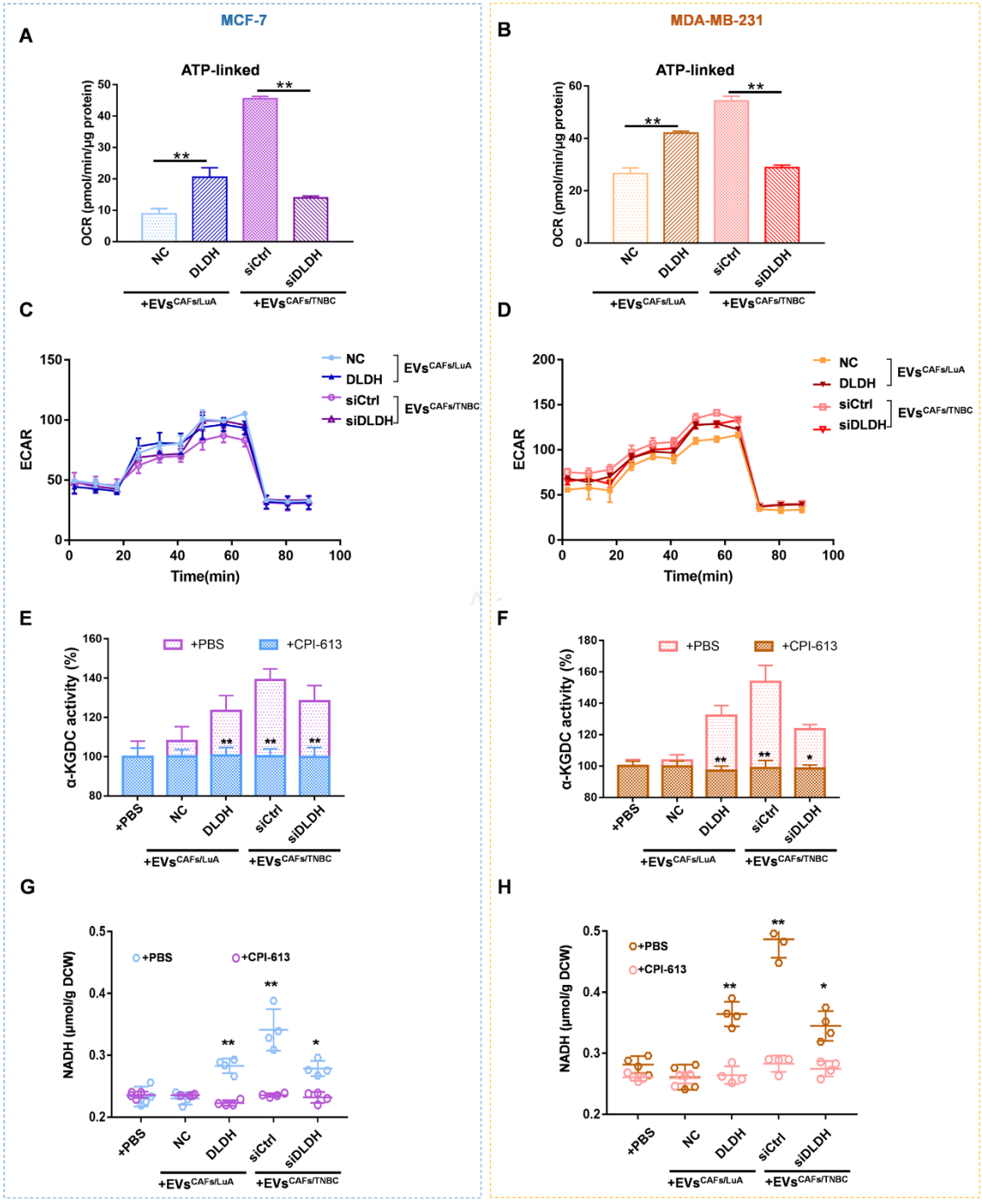

Fig.S7 CAFs-mediated DLDH promoted cellular OXPHOS. (A, B) ATP-linked OCR was calculated. **(C, D)** The effects of EVs on the ECAR of recipient cells were quantified by Seahorse XF Analyzer and representative of two independent experiments. **(E, F)** EVs-incubated cells were treated with CPI-613 for 3h and subsequently measured α-KGDH activity. **(G, H)** The NADH level of the recipient cells was measured. **E-H** Data shown represent the results of at least three biologically independent experiments. *$P < 0.05$, **$P < 0.01$.

Supplementary Figure 8

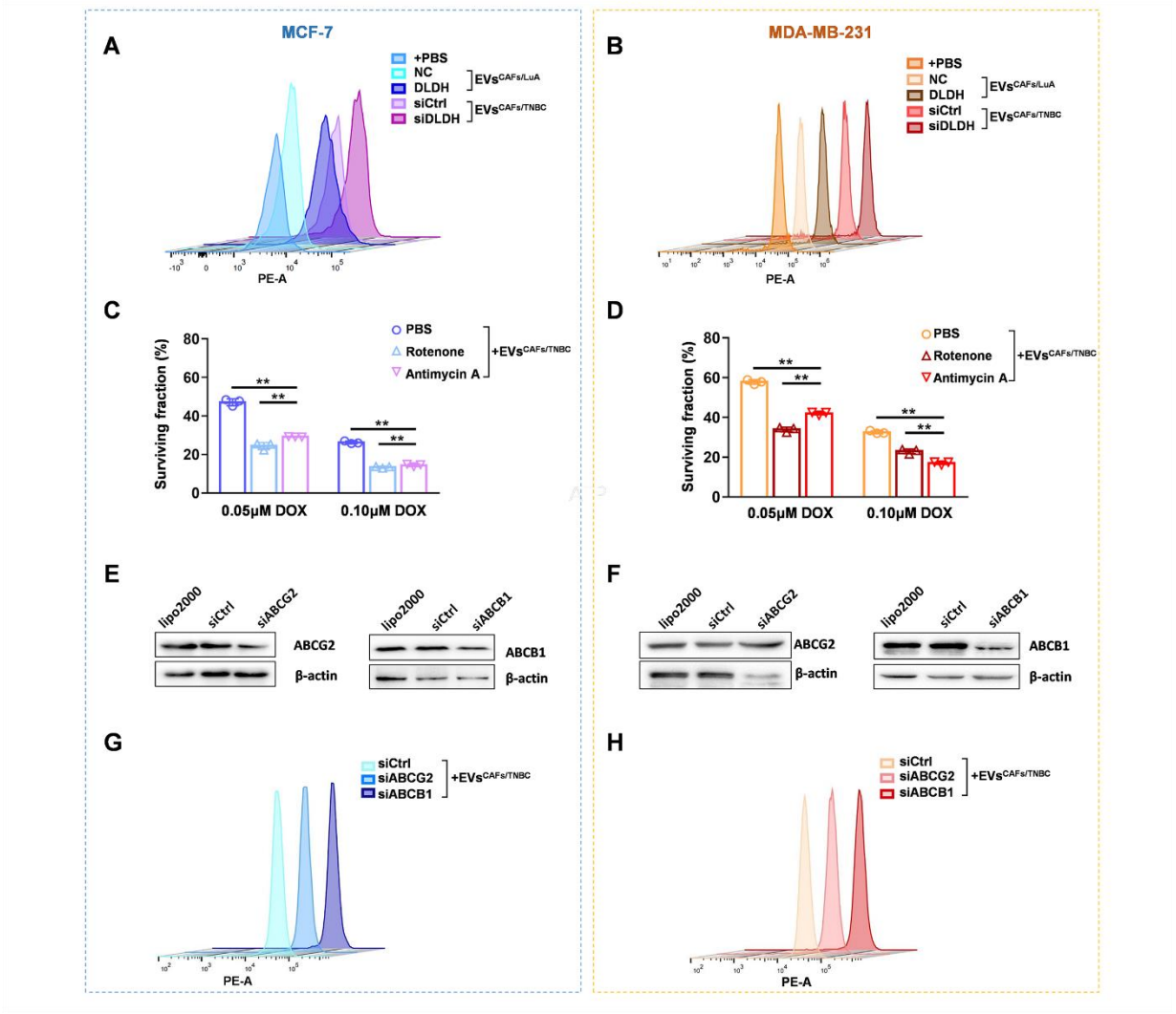

Fig.S8 EVs$^{CAFs/TNBC}$ promoted DOX efflux by enhancing cellular OXPHOS. (A, B) After 0.5 h treatment with DOX, the intracellular DOX content was quantified by flow cytometry. **(C, D)** The EVs-incubated cells were pretreated with Rotenone or Antimycin A followed by DOX treatment. The surviving fraction of cells was determined using a colony survival assay. **(E, F)** The level of ABCG2 or ABCB1 in BC cells was measured by western blots. **(G, H)** After transfection with siRNA, the cells were incubated with EVs$^{CAFs/TNBC}$ followed by DOX treatment for 0.5 h, and the intracellular DOX content was quantified by flow cytometry. Data shown represent the results of at least three biologically independent experiments. $*P < 0.05$, $**P < 0.01$.