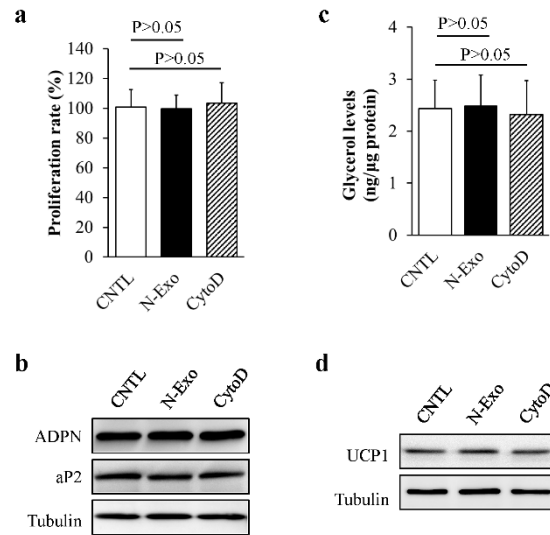
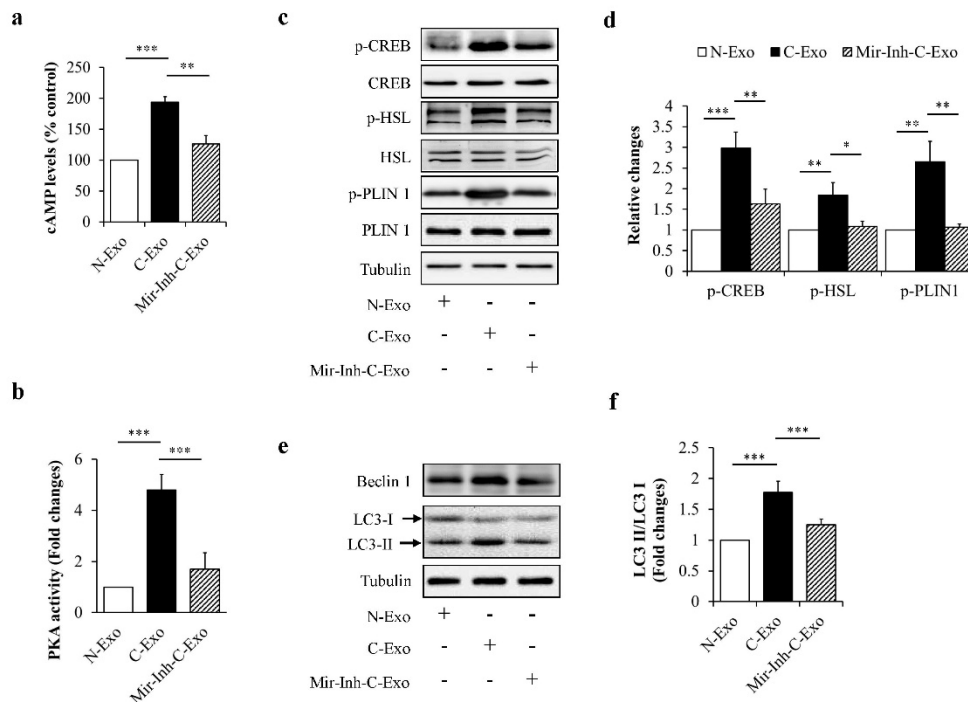


## Supplemental Data



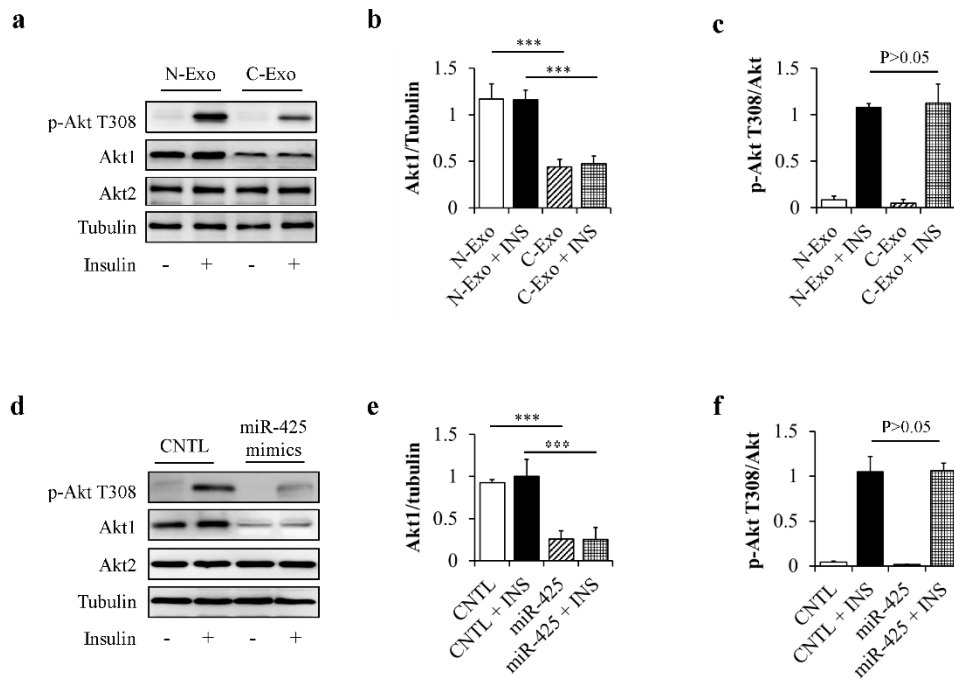
Suppl. Figure 1

**Supplemental Figure 1. N-Exo and CytoD did not affect preadipocyte proliferation, adipogenesis, lipolysis, and adipocyte browning.** HPA-v cells were incubated with 50  $\mu\text{g/L}$  of exosomes or 2  $\mu\text{g/mL}$  of CytoD for 24 h (for cell proliferation) or 7 days (for adipocyte differentiation), respectively. Adipocyte differentiation was induced using a standard protocol. **(a)** Effects of N-Exo and CytoD on cell proliferation. **(b)** Effects of N-Exo and CytoD on the protein levels of aP2 and ADPN. Mature adipocytes were incubated with 50  $\mu\text{g/L}$  of exosomes or 2  $\mu\text{g/mL}$  of CytoD for 24 h. **(c)** Effects of N-Exo and CytoD on glycerol concentration in culture medium. **(d)** Effects of N-Exo and CytoD on UCP1 protein levels. Data are presented as mean  $\pm$  SD,  $n=3$ . N-Exo: normal (NL20) cell-derived exosomes; aP2: adipocyte protein 2; ADPN: adiponectin; CytoD: cytochalasin D.



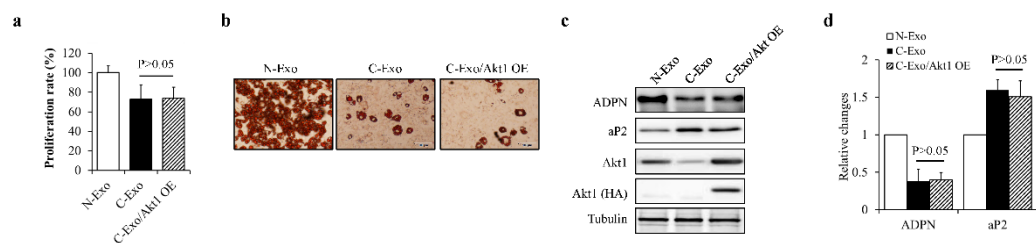
Suppl. Figure 2

**Supplemental Figure 2. Inhibition of miR-425-3p mitigated the effects of C-Exo on cAMP/PKA signaling and lipophagy.** Mature adipocytes were incubated with 50  $\mu\text{g/L}$  of exosomes for 24 h. **(a)** Effect of exosomes on the intracellular cAMP concentration. **(b)** Effect of exosomes on the intracellular PKA activity. **(c, d)** Effect of exosomes on the protein or phosphorylated protein levels of CREB, HSL, and PLIN 1. **(e, f)** Effect of exosomes on the protein levels of beclin 1 and LC3. Data are presented as mean  $\pm$  SD,  $n=3$ ;  $*p < 0.05$ ,  $**p < 0.01$ ,  $***p < 0.001$  vs indicated group. N-Exo: normal (NL20) cell-derived exosomes; C-Exo: cancer (A549) cell-derived exosomes; Mir-Inh-C-Exo: cancer (A549) cell-derived exosomes with miR-425-3p inhibition.



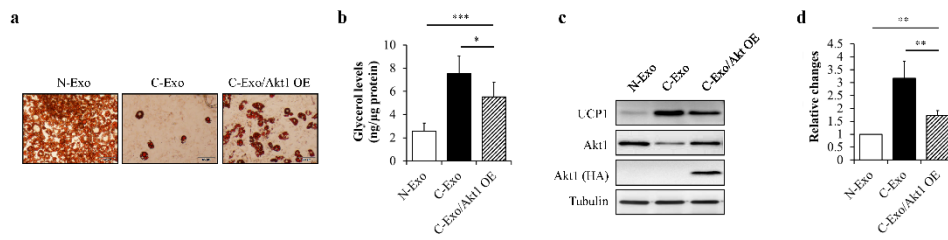
Suppl. Figure 3

**Supplemental Figure 3. C-Exo and miR-425-3p mimics suppressed insulin signaling.** Mature adipocytes were starved serum for 6 h and then incubated with 50  $\mu\text{g/L}$  of exosomes for 24 h, following by stimulation with 100 nM of insulin for 10 min. **(a)** Effect of exosomes on Akt1 levels and phosphorylation. **(b)** Quantitative analysis of Akt1 protein levels in (a). **(c)** Quantitative analysis of Akt1 phosphorylation in (a). **(d)** Effect of miR-425-3p mimics on Akt1 levels and phosphorylation. **(e)** Quantitative analysis of Akt1 protein levels in (d). **(f)** Quantitative analysis of Akt1 phosphorylation in (d). Data are presented as mean  $\pm$  SD,  $n=3$ ;  $***p < 0.001$  vs indicated group. N-Exo: normal (NL20) cell-derived exosomes; C-Exo: cancer (A549) cell-derived exosomes; CNTL: control; INS: insulin.



Suppl. Figure 4

**Supplemental Figure 4. Akt1 overexpression had no effect on the C-Exo-reduced proliferation and differentiation in human preadipocytes.** HPA-v cells were overexpressed with Akt1 and then incubated with 50  $\mu\text{g/L}$  of exosomes for 24 h (for cell proliferation) or 7 days (for adipogenic differentiation), respectively. Adipocyte differentiation was induced using a standard protocol. Oil red O staining and western blot were performed at day 7 of adipogenic differentiation. **(a)** Effect of exosomes on cell proliferation. **(b)** Effect of exosomes on oil red O staining. **(c, d)** Effect of exosomes on the protein levels of aP2 and ADPN. Data are presented as mean  $\pm$  SD,  $n=3$ . N-Exo: normal (NL20) cell-derived exosomes; C-Exo: cancer (A549) cell-derived exosomes; aP2: adipocyte protein 2; ADPN: adiponectin; OE: overexpression.



Suppl. Figure 5

**Supplemental Figure 5. Akt1 overexpression partly mitigated the effects of C-Exo on adipocyte lipolysis and white adipocyte browning.** Mature adipocytes were overexpressed with Akt1 and then incubated with 50 μg/L of exosomes for 24 h. **(a)** Effect of exosomes on oil red O staining. **(b)** Effect of exosomes on glycerol concentration in culture medium. **(c, d)** Effect of exosomes on UCP1 protein levels. Data are presented as mean ± SD, n=3; \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  vs indicated group. N-Exo: normal (NL20) cell-derived exosomes; C-Exo: cancer (A549) cell-derived exosomes; OE: overexpression.

**Supplemental Table 1. Mutations of has-miR-425-3p-binding site**

<b>Gene</b>	<b>3' UTR WT</b>	<b>3' UTR Mutant</b>
CEBPA	5'-CUUCCCGAG-3'	5'-CUCAAAGCG-3'
GATA2	5'-UUUCCCGAA-3'	5'-UUCAAAGCA-3'
IGFBP4	5'-CUUCCCGAU-3'	5'-CUCAAAGCU-3'
MMP15	5'-CUUCCCGAU-3'	5'-CUCAAAGCU-3'
PDE4B	5'-CUCCCGAAC-3'	5'-CUAAAAGAC-3'