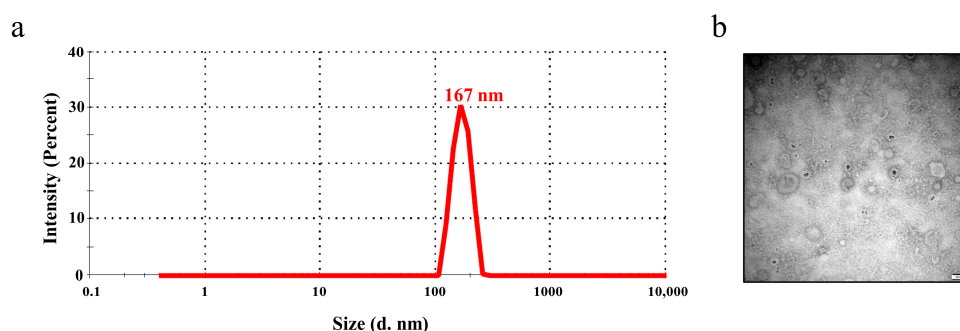


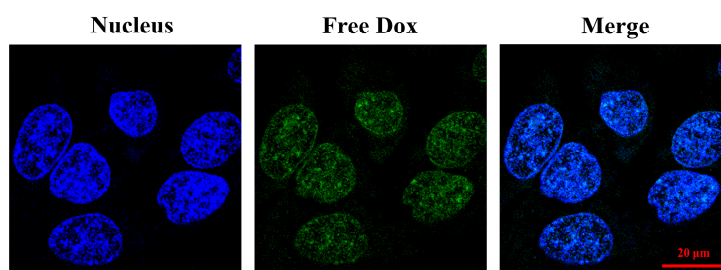
## 1. Doxorubicin loading into MSCs-EVs.

No.	Methods	Doxorubicin loading condition	Encapsulation efficiency (EE%)	Drug loading efficiency (DL%)
1	Incubation	Incubation at 37°C for 30 min	17.40%	8.00%
2	Ultrasound	8% amplitude, 3 cycles of 10 s on and 10 s off cooling period	34.20%	14.6%
3	Electroporation	Electroporation at 150 V, 1 ms, 5 pulses in 0.2 cm cuvette	12.16%	5.73%
4	Freeze-thaw cycles	Freezed at -80°C for 30 min and thawed at RT thrice.	14.33%	6.69%

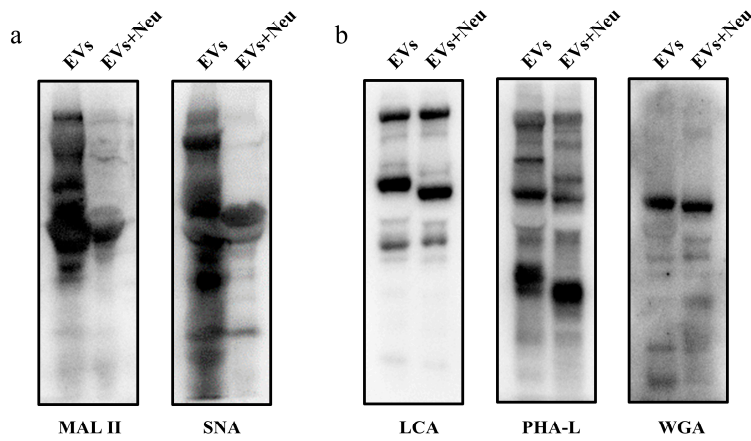
**Table S1. Efficiency of Dox loading into EVs by different drug loading methods.** Loading capacity for Dox in EVs was measured by microplate reader at an absorbance wavelength of 480 nm. The drug encapsulation efficiency (EE%) was calculated by dividing the amount of loaded drug by which of total drug. The drug loading efficiency (DL%) was calculated by dividing the amount of loaded drug by which of drug-loaded EVs.



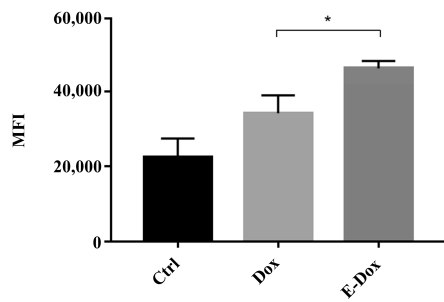
**Figure S1. Characterization of drug-loaded EVs.** (a) The size distributions of drug-loaded EVs based on intensity by DLS measurements. The peak diameters were at 167 nm. (b) Representative TEM images of drug-loaded EVs. Scale bar = 100 nm.



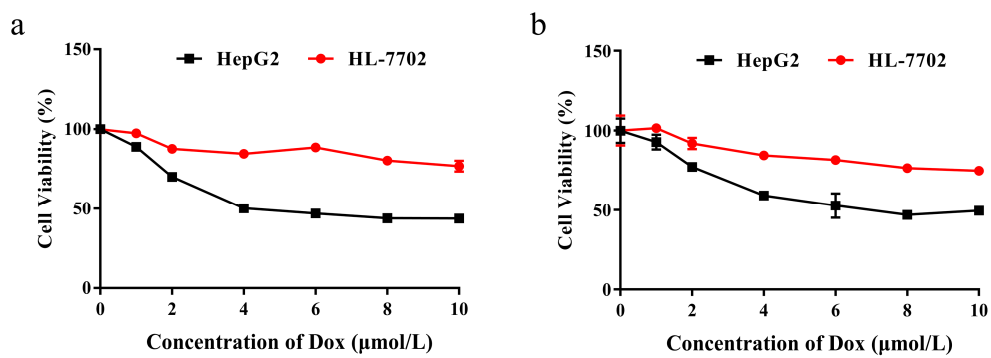
**Figure S2. Cellular uptake of free Dox.** HepG2 cells were incubated with free Dox (10 μmol/L) for 1 h and photographed under confocal microscopy. Blue, Hoechst 33258 for nucleus. Green, autofluorescence of Dox. Scale bar, 20 μm.



**Figure S3. The glycosylation changes of EVs treated with Neu.**(a) The level of  $\alpha$ -2,3 and  $\alpha$ -2,6 sialic acid of EVs were detected by lectin blotting with 4 U neuraminidase treatment at 37°C for 30 min. (b) Levels of fucose, complex type N-glycans and GlcNAc on EVs was detected by lectin blotting under the same treatment conditions as (a).



**Figure S4. Statistics for Figure 2B.** The data were presented as the mean values  $\pm$  SD. \*  $p < 0.05$



**Figure S5. Cell viability assay.** (a, b) HepG2 and HL-7702 cells were treated with desialylated Dox-loaded EVs and free Dox at different concentrations for 48 h.