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Supporting Information

Hyaluronic acid modified doxorubicin loaded Fe_3O_4 nanoparticles effectively inhibit breast cancer metastasis

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Figures

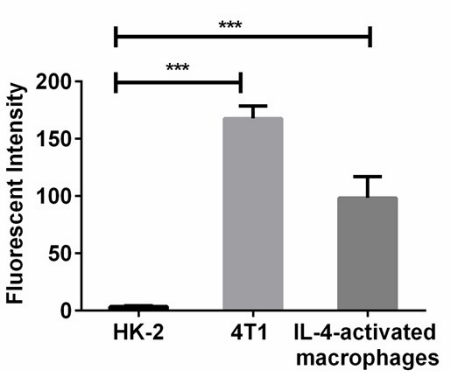

Fig. S1. The results of CD44 receptor expression in 4T1 cells and IL-4 activated macrophages we used in this study tested via flow cytometry with HK-2 cells as a negative control. Data represent mean ± SD (n = 5), ***, $p < 0.001$.

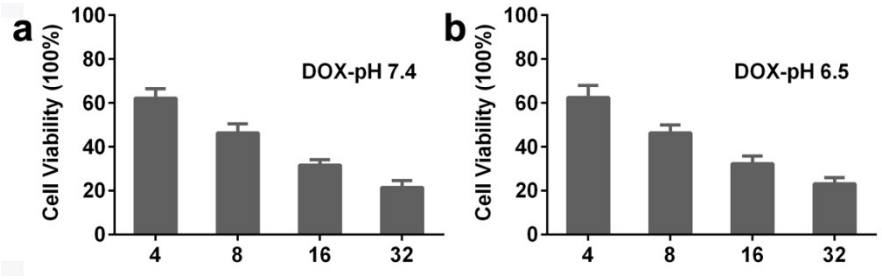

Fig. S2. *In vitro* cell viability of free DOX against TAMs at pH 7.4 (a) and pH 6.5 (b).

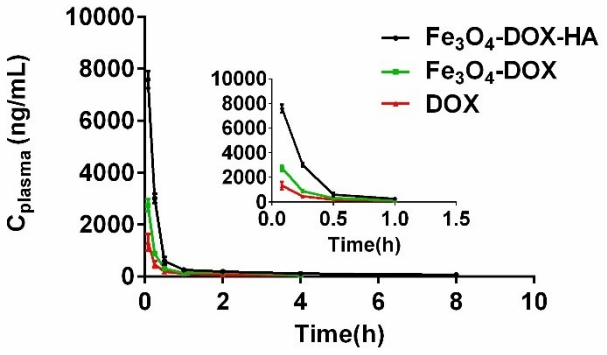

Fig. S3. *In vivo* pharmacokinetic profiles after intravenous injection of free DOX, Fe_3O_4-DOX-HA and Fe_3O_4-DOX in rats. Data represent mean ± SD (n = 5).

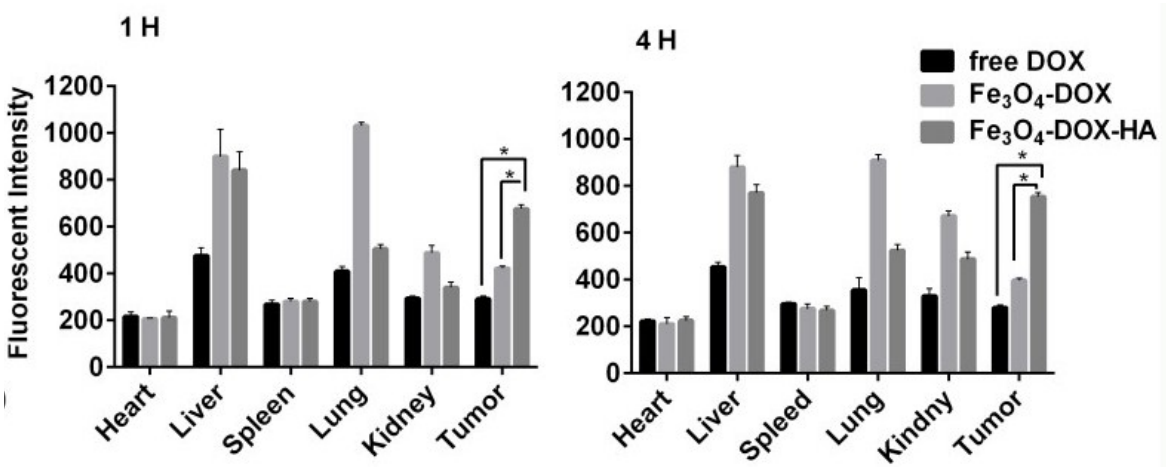

Fig. S4. The fluorescence intensity of DOX in tumors and vital organs in all the three groups at 1 and 4 h after administration. Data represent mean ± SD (n = 5), *, $p < 0.05$.

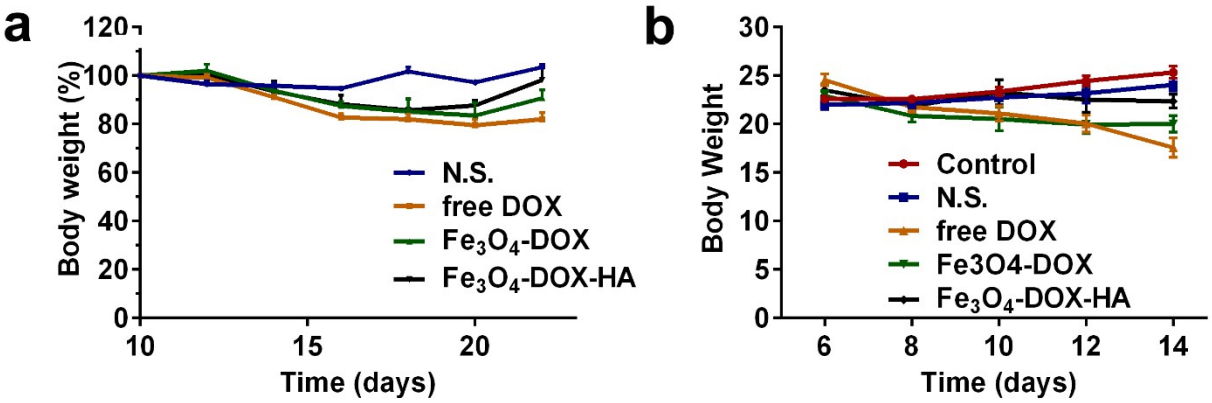

Fig. S5. Body weight in tumor-bearing female BALB/c mice were recorded in *in vivo* antitumor (a) and anti-metastasis study (b).

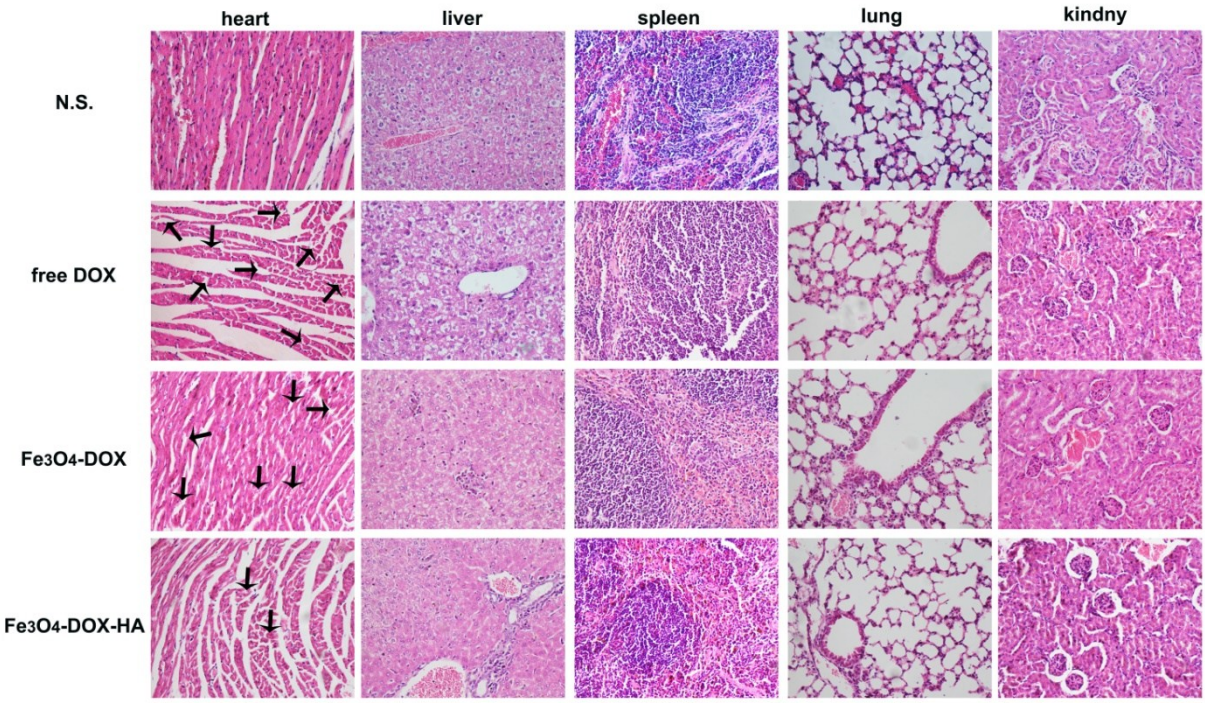

Fig. S6. Safety evaluation of free DOX, Fe_3O_4-DOX and Fe_3O_4-DOX-HA, magnification: 200×.

Tables

Table S1. Pharmacokinetic parameters of free DOX, Fe_3O_4-DOX and Fe_3O_4-DOX-HA (mean ± SD，n = 5).

Sample	Free DOX	Fe_3O_4-DOX	Fe_3O_4-DOX+HA
Dose (mg/kg)	2.0	2.0	2.0
C_{max} (ng/ml)	1476.5 ± 325.6	2974.6 ± 218.5	7197.3 ± 293.1[a, b]
T_{max} (min)	5	5	5
$AUC_{(0-t)}$ (min·ng/ml)	36,982	80,655	193,867 [a, b]
$t_{1/2}$ (min)	27.58	85.32	184.96 [a, b]

[a], $p < 0.01$ vs. Fe_3O_4-DOX group.

[b], $p < 0.001$ vs. free DOX group.

Table. S2. Median survival and ILS of mice bearing 4T1 tumors treated with saline and various DOX formulations (n = 10).

Groups	Median (days)	ILS (%)
		Fe_3O_4-DOX+HA
N.S.	36	38.9***
DOX	36	38.9***
Fe_3O_4-DOX	40	25*
Fe_3O_4-DOX-HA	50	/

Median: the median survival.

ILS (increase in life span) = (T/C - 1) × 100%, where T and C represent the mean survival time (days) of the treated and control animals, respectively. p values: were calculated by using the log-rank (Mantel-Cox) test, *, $p < 0.05$, ***, $p < 0.01$.