

## Supporting Information

### **SPION decorated exosome delivered TNF- $\alpha$ targeting cancer cell membrane through magnetism**

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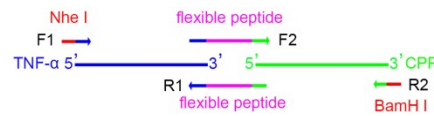
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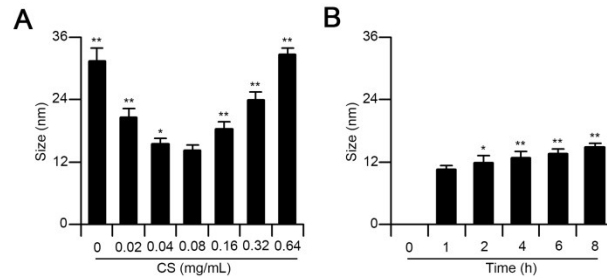
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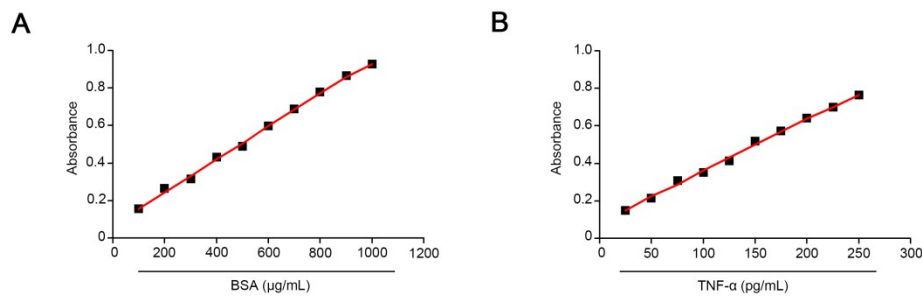
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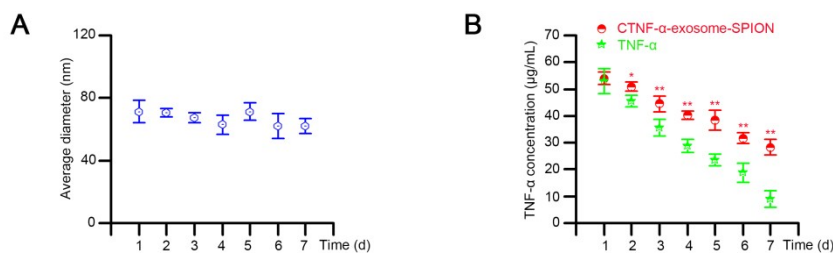
**Fig. S1.** The consists of primer sequences of overlapping PCR.



**Fig. S2.** Size distribution of carboxylated CS decorated SPIONs. (A) Size distribution of SPIONs was measured in the presence of different concentrations of carboxylated CS; (B) Size distribution of SPIONs was measured in the presence of 0.08 mg/mL CS at the different reaction time. Six independent experiment, significance levels are shown as \* $p < 0.05$  and \*\* $p < 0.01$ .

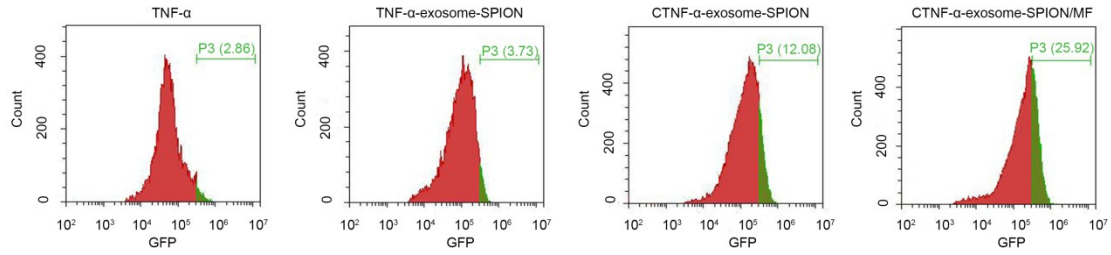


**Fig. S3.** The standard curve of BSA or TNF- $\alpha$ . (A) Concentration standard curve of BSA protein assay with the BCA kit for protein standards concentration; (B) Concentration standard curve of TNF- $\alpha$  assay with the TNF- $\alpha$  kit.

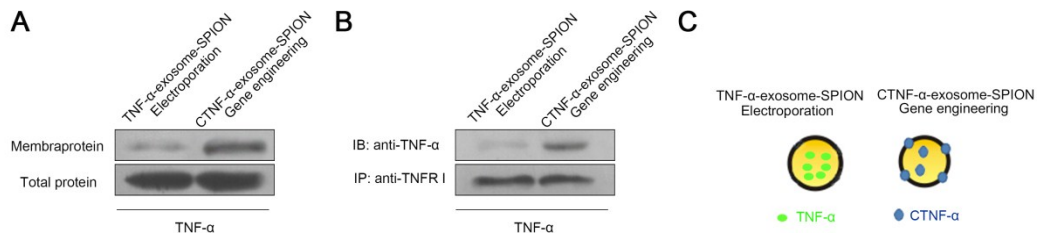


**Fig. S4.** Stability of CTNF- $\alpha$ -exosome-SPION in serum. (A) Change in size of CTNF- $\alpha$ -exosome-SPIONs stored at 4°C in PBS; (B) Change in TNF- $\alpha$  concentration of TNF- $\alpha$  or CTNF- $\alpha$ -exosome-SPIONs stored at 37°C in serum. Six independent experiment, significance levels are shown as \* $p < 0.05$  and \*\* $p < 0.01$ .

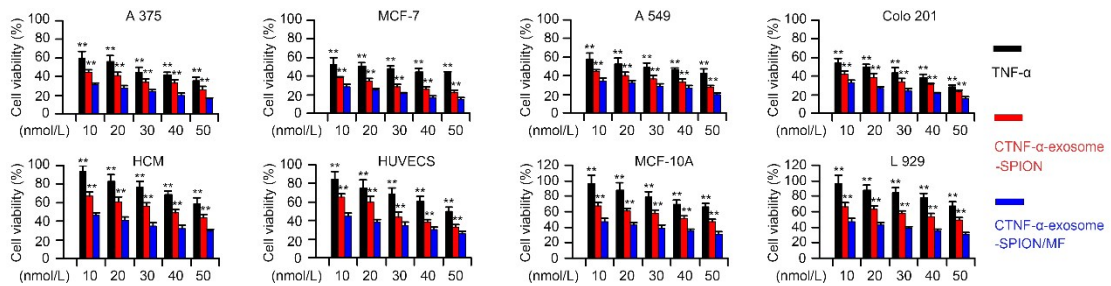
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**Fig. S5.** The binding efficiency of CTNF- $\alpha$ -exosome-SPIONs with or without MF. The cells were incubated with TNF- $\alpha$ , TNF- $\alpha$ -exosome-SPION, CTNF- $\alpha$ -exosome-SPION and CTNF- $\alpha$ -exosome-SPION//MF for 1 h, the cellular binding efficiency of CTNF- $\alpha$ -exosome-SPIONs analyzed by detecting the fluorescence intensity of TNF- $\alpha$  via flow cytometry assay.

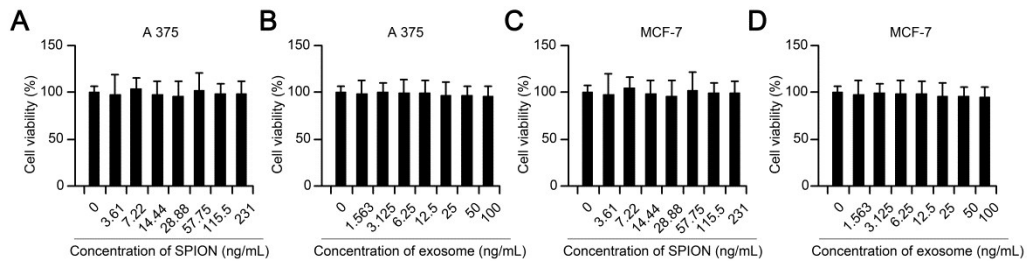


**Fig. S6.** The mechanism of CPP mediated TNF- $\alpha$  anchoring to the cell membrane. (A) TNF- $\alpha$  content in exosome membrane were detected by Western blot; (B) Binding abilities of TNF- $\alpha$  and TNFR I were analyzed by CO-IP; (C) The structure diagram of TNF- $\alpha$ -exosome-SPION or CTNF- $\alpha$ -exosome-SPION.

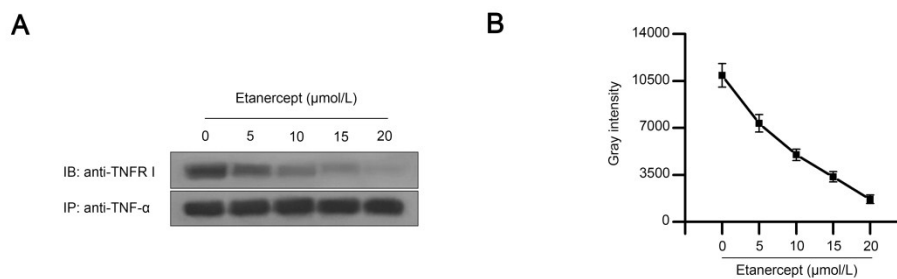


**Fig. S7.** Cytotoxic effects of TNF- $\alpha$ , CTNF- $\alpha$ -exosome-SPION and CTNF- $\alpha$ -exosome-SPION/MF on tumor cell lines (A375, MCF-7, A549 and Colo 201) and normal cell lines (HCM, HUVECS, MCF-10A and L 929). The cells were treated increasing concentration (10, 20, 30, 40 and 50 nmol/L) of TNF- $\alpha$ , CTNF- $\alpha$ -exosome-SPION and CTNF- $\alpha$ -exosome-SPION/MF, cell viability was examined by MTT.

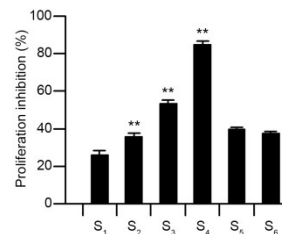
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**Fig. S8.** Effect of SPION or exosome on tumor cell viability. (A) and (B) Anti-cancer activity of different concentrations of SPION or exosome were examined in A375 cells by MTT. (C) and (D) Anti-cancer activity of different concentrations of SPION or exosome were examined in MCF-7 cells by MTT. Six independent experiment, significance levels are shown as \* $p < 0.05$  and \*\* $p < 0.01$ .

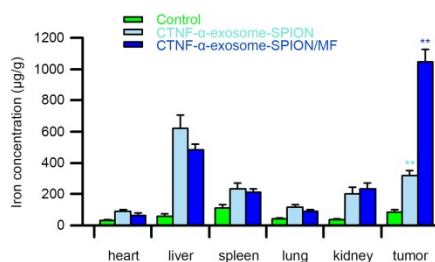


**Fig. S9.** The binding activity of CTNF- $\alpha$  and TNFR I. (A) Effect of etanercept inhibitor on the combination of CTNF- $\alpha$  and TNFR I; (B) The amount of binding TNFR I was analyzed with gray gel scan.

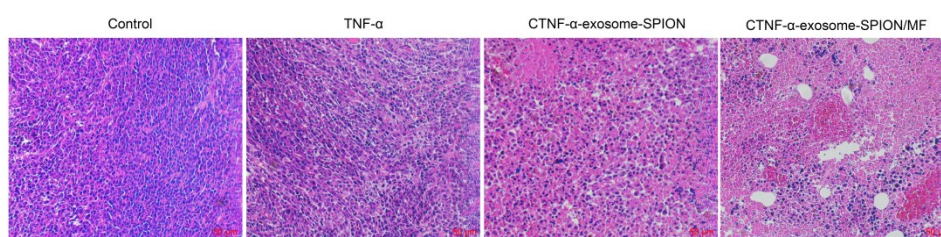


**Fig. S10.** The proliferation inhibition of A375 melanoma cells after different treatments. S<sub>1</sub>: Control, S<sub>2</sub>: TNF- $\alpha$ , S<sub>3</sub>: CTNF- $\alpha$ -exosome-SPION, S<sub>4</sub>: CTNF- $\alpha$ -exosome-SPION/MF, S<sub>5</sub>: CTNF- $\alpha$ -exosome-SPION/MF + Etanercept, S<sub>6</sub>: CTNF- $\alpha$ -exosome-SPION/MF + z-VAD-fmk. Six independent experiment, significance levels are shown as \* $p < 0.05$  and \*\* $p < 0.01$ .

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**Fig. S11.** The distribution of Fe in the major organs (heart, liver, spleen, lung and kidney) and tumors of mice treated with normal saline, CTNF- $\alpha$ -exosome-SPION and CTNF- $\alpha$ -exosome-SPION/MF for 24h. Fe content was measured via ICP-OES.



**Fig. S12.** HE-stained tumor tissues obtained from laboratory mice.

**Table S1.** Sequences of primers used in overlapping PCR and their structural characteristics.

Primers	Sequence <sup>a)</sup>	Comment <sup>b)</sup>
TNF- $\alpha$ -F1	CGGCTAGCTTCCCCAGGGACCTCTCTCT	Restricted site: Nhe I
TNF- $\alpha$ -R1	GTCTCCCACCAGGTCTCCTTGCCGGAGCCGGAGC CGCCGCCGCTCACAGGGCAATGATCCCAAAG	Flexible peptide
CPP-F2	CTTTGGGATCATTGCCCTGTGAGGCGGCGGCGG CTCC GGCTCCGGCAAGGAGACCTGGTGGGAGACB	Flexible peptide
CPP-R2	CGGGATCCCTCGACAAAAGCAATTCCAAGGG	Restricted site: BamH

<sup>a)</sup>The primer sequence; <sup>b)</sup>The recognition sequence of a restriction enzyme and the sequence of flexible peptide.

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