Supplementary Material

Redox dual-responsive and O₂-evolving theranostic nanosystem for highly selective chemotherapy against hypoxic tumor

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Supplementary figures

2. Figure S1. ¹H NMR spectrum of RA-S-S-Cy in C₂D₂N.
3. Figure S2. ¹³C NMR spectrum of RA-S-S-Cy in C₂D₂N.
4. Figure S3. HRMS spectrum of RA-S-S-Cy.
5. Figure S4. HPLC analysis of RA-S-S-Cy.
6. Figure S5. LCMS analysis of RA-S-S-Cy.
7. Figure S6. Long-term-stability study of the size of RA-S-S-Cy@PLGA NPs in RPMI 1640 or DMEM with 10% FBS.
8. Figure S7. Long-term-stability study of the fluorescence of RA-S-S-Cy@PLGA NPs in RPMI 1640 or DMEM with 10% FBS.
9. Figure S8. Specific selectivity of RA-S-S-Cy for GSH. 1, control; 2, Gln; 3, Lys; 4, Glu; 5, His; 6, Leu; 7, Arg; 8, Gly; 9, Met; 10, DTT; 11, Hcy; 12, Cys; 13, Asp; 14, Trp; 15, Ser; 16, GSSG; and 17, GSH (1 mM). Concentration of interference: 100 mM.
10. **Figure S9.** Drug released from RA-S-S-Cy (5 μM) as a function of time in the presence and absence of GSH (1 mM).

11. **Figure S10.** Drug released from RA-S-S-Cy@PLGA NPs as a function of time in the presence and absence of GSH (1 mM) and H₂O₂ (50 μM).

12. **Figure S11.** MTT assay of NCM460 and HCT-116 cells in the presence of different concentrations of empty NPs.

13. **Figure S12.** In vivo fluorescence images of subcutaneous HCT-116 tumor-bearing mice after i.v. injection of 10 mg kg⁻¹ RA-S-S-Cy@PLGA NPs, or RA-S-S-Cy@PLGA NPs (without catalase); Mice pretreated with excessive free cRGD, followed by injection of 10 mg kg⁻¹ RA-S-S-Cy@PLGA NPs. The fluorescence images were acquired using IVIS Spectrum instrument equipped with 675/30 nm excitation and 720/20 nm emission filters.

14. **Figure S13.** Change of relative tumor volume (V/V₀) upon treatments with different concentrations of RA-S-S-Cy@PLGA NPs on tumor-bearing mice.

15. **Figure S14.** H&E stained images of tissue sections from different organs of mice after RA-S-S-Cy@PLGA NPs treatment and the age-matched healthy mice without treatment (control). Scale bars: 100 μm.

16. **Figure S15.** Immuno fluorescence staining with HIF-1α antibodies and corresponding HIF-1α staining of tumor slides from HCT-116 tumor-bearing mice treated with RA-S-S-Cy NPs or RA-S-S-Cy NPs (without catalase) at a dose of 10 mg kg⁻¹.
Scheme S1. Synthesis of RA-S-S-Cy.
Figure S1. $^1$H NMR spectrum of RA-S-S-Cy in C$_3$D$_8$N.
Figure S2. $^{13}$C NMR spectrum of RA-S-S-Cy in C$_5$D$_5$N.
Figure S3. HRMS spectrum of RA-S-S-Cy.

Figure S4. HPLC analysis of RA-S-S-Cy.

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