Proceedings of the 9th World Congress on Recent Advances in Nanotechnology (RAN 2024)
London, United Kingdom –April 8 – 10, 2024
Paper No. NDDTE 104
DOI: 10.11159/nddte24.104

Integration of Modified Cell Membrane-coated Nanoparticles with Photothermal Therapy to Enhance Ferroptotic Tumor Cell Death

Lu Bai[1], Yanan Tan[2], Min Luo[2], Xinyuan Guan[1†]
[1] Department of Clinical Oncology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong, China
lubai21@connect.hku.hk ; xyguan@hku.hk
[2] Department of Clinical Oncology, The University of Hong Kong-Shenzhen Hospital, 1 Haiyuan 1 Rd, Futian District, Shenzhen, China
tanyn@hku-szh.org ; luom9@hku-szh.org
[†]Corresponding Author

Extended Abstract

Background: Biomimetic nanoparticles are engineered by combining natural cell membranes with drug delivery nanoparticles to mimic autologous cells for immune evasion and prolonged blood circulation[1]. Cell membrane-coated nanoparticles commonly exploit the passive targeting enhanced permeability and retention (EPR) effect to efficiently access tumor tissues. By leveraging the ligand-receptor interaction, the modification of cell membrane proteins enables them to selectively bind to tumor molecules, thereby greatly enhancing drug delivery efficiency. Our preliminary studies showed elevated chemokine CXCL12 secretion in the tumor microenvironment. CXCL12 specifically binds to the transmembrane receptor CXCR4 and plays an important role in tumor growth and metastasis. Based on this, modifying cell membranes to enhance CXCR4 expression may serve as an effective means to target tumor regions characterized by elevated CXCL12 secretion, thereby enabling precise diagnosis and targeted drug delivery.

Ferroptosis is an iron-dependent form of cell death driven by lipid peroxidation. Increasing evidence shows the potential of regulating ferroptosis in cancer therapy. The ferroptosis inducer RSL3 inhibits glutathione peroxidase 4 (GPX4) activity and interferes with its catalytic redox glutathione, thereby hindering the reduction process of intracellular lipid peroxide[2]. Nevertheless, its poor solubility and inconsistent drug distribution in the bloodstream present constraints on its clinical utility[3]. Therefore, encapsulating the RSL3 molecule within cell membrane-coated nanoparticles may improve its bioavailability. In the meanwhile, studies have found that the heat generated during photothermal therapy not only enhances the consumption of intracellular reducing glutathione but also accelerates the Fenton reaction, leading to increased lipid peroxide accumulation[4], [5]. Thus, combining photothermal therapy with RSL3 may synergistically enhance ferroptosis in tumors.

This project aims to construct a modified cell membrane-coated photosensitive nanoparticle loaded with a ferroptosis inducer. This drug delivery system is designed to actively target tumor sites as well as synergistically enhance ferroptotic tumor cell death.

Methods: The chemokine receptor CXCR4 is overexpressed on the cell membrane through lentivirus transfection and is validated by RT-qPCR and western blotting. The migration ability of CXCR4-overexpressed cells towards CXCL12 is validated by a transwell migration assay. RSL3 is loaded into near-infrared responsive nanoparticles through solvent diffusion and is then encapsulated with CXCR4-overexpressed cell membranes (CXCR4-MNVs). The photothermal effect of CXCR4-MNVs is recorded by a thermal imaging camera. The tumor-targeting ability of CXCR4-MNVs is validated in vivo and the ferroptotic effect of CXCR4-MNVs on tumor cells is evaluated by functional assays.

Results: We successfully constructed CXCR4-overexpressed cells and validated their enhanced chemoattraction towards CXCL12. The in vivo results displayed that CXCR4-MNVs can reach tumor regions with minimal off-target effects. When exposed to near-infrared light, the NPs' temperature was raised to over 50 °C. The cell viability assay and lipid peroxidation assay showed that near-infrared light irradiation and RSL3 synergistically inhibited tumor cell growth through ferroptosis.

Conclusion: These results demonstrate the specific targeting and ferroptosis-enhancing capabilities of CXCR4-MNVs within tumor cells. This suggests that the CXCR4-MNVs system might be a potential treatment modality for cancer.

Keywords: Membrane-coated nanoparticles, targeted drug delivery, ferroptosis, photothermal therapy, cancer treatment

References

[1] W. Meng, S. Xue, and Y. Chen, "The role of CXCL12 in tumor microenvironment," *Gene*, vol. 641, no. February 2017, pp. 105–110, 2018, doi: 10.1016/j.gene.2017.10.015.

[2] Z. Wang, S. Wu, C. Zhu, and J. Shen, "The role of ferroptosis in esophageal cancer," *Cancer Cell Int.*, vol. 22, no. 1, pp. 1–12, 2022, doi: 10.1186/s12935-022-02685-w.

[3] T. Xu, W. Ding, X. Ji, X. Ao, Y. Liu, W. Yu, and J. Wang, "Molecular mechanisms of ferroptosis and its role in cancer therapy," *J. Cell. Mol. Med.*, vol. 23, no. 8, pp. 4900–4912, 2019, doi: 10.1111/jcmm.14511.

[4] Y. Jiang, X. Zhao, J. Huang, J. Li, PK. Upputuri, H. Sun, X. Han, M. Pramanik, Y. Miao, H. Duan, K. Pu, and R. Zhang, "Transformable hybrid semiconducting polymer nanozyme for second near-infrared photothermal ferrotherapy," *Nat. Commun.*, vol. 11, no. 1, pp. 1–13, 2020, doi: 10.1038/s41467-020-15730-x.

[5] H. Ranji-Burachaloo, P. A. Gurr, D. E. Dunstan, and G. G. Qiao, "Cancer Treatment through Nanoparticle-Facilitated Fenton Reaction," *ACS Nano*, vol. 12, no. 12, pp. 11819–11837, 2018, doi: 10.1021/acsnano.8b07635.