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镧蛋白工程化细菌外膜囊泡用于协同靶向放射免疫治疗

摘要

靶向放射性核素治疗（TRT）与免疫治疗的联合为增强抗肿瘤免疫提供了强有力的策略，然而适应性递送平台的开发仍面临挑战。本研究报道了一种可编程的” 即插即用” 纳米平台——TRT@LnOMVs，通过将镧蛋白（LanM）展示于减毒鼠伤寒沙门氏菌来源的外膜囊泡（OMVs）表面，实现了多种治疗性放射性核素（如 177Lu、90Y、225Ac）在温和条件下的高效、稳定标记，克服了传统螯合剂方法的局限性。该平台具有模块化特性，可通过脂质插入策略便捷地偶联靶向配体（如 PSMA、FAP）。在前列腺癌模型中，与临床批准的 ^177^Lu-PSMA-617（PluvictoTM）进行头对头比较，PSMA 靶向 TRT@LnOMVs 实现了 90% 的生存率，远超 PluvictoTM 的 25%。单细胞 RNA 测序和转录组分析揭示，TRT@LnOMVs 通过激活先天免疫并重编程免疫抑制性髓系细胞群，从根本上重塑肿瘤免疫微环境，触发强大的抗肿瘤免疫应答。该研究为下一代放射免疫治疗提供了强有力的范式。

关键词

细菌外膜囊泡；放射免疫治疗；镧蛋白；靶向放射性核素治疗；肿瘤免疫微环境

Abstract

The combination of targeted radionuclide therapy (TRT) with immunotherapy offers a potent strategy to amplify anti-tumor immunity, yet the development of adaptable delivery platforms remains challenging. Herein, we report a programmable, “plug-and-play” nanoplatform, termed TRT@LnOMVs, engineered for synergistic radio-immunotherapy. By displaying lanmodulin (LanM) on the surface of outer membrane vesicles (OMVs) derived from attenuated Salmonella typhimurium, this platform enables versatile and high-efficiency radiolabeling of diverse therapeutic radioisotopes (177Lu, 90Y, 225Ac) under mild conditions, circumventing the limitations of conventional chelator-based methods. The platform’s modularity is further demonstrated by the facile incorporation of lipid-conjugated ligands for precision targeting. In a head-to-head comparison with clinically approved 177Lu-PSMA-617 (PluvictoTM), PSMA-targeted TRT@LnOMVs achieved a 90% survival rate in a prostate cancer model, far surpassing the 25% survival rate of PluvictoTM. Single-cell RNA sequencing and transcriptomic analysis revealed that TRT@LnOMVs fundamentally remodel the tumor immune microenvironment by activating innate immunity and reprogramming immunosuppressive myeloid compartments to trigger robust anti-tumor immunity. Collectively, TRT@LnOMVs represent a versatile class of bio-hybrid therapeutics, offering a robust paradigm for next-generation radio-immunotherapy.

Keywords

Outer membrane vesicles; Radio-immunotherapy; Lanmodulin; Targeted radionuclide therapy; Tumor immune microenvironment

Author: Ms 张, 菲菲 (兰州大学)

Presenter: Ms 张, 菲菲 (兰州大学)

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