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Research Article

Integration of CoAl-Layered Double Hydroxides on Commensal Bacteria to Enable Targeted Tumor Inhibition and Immunotherapy

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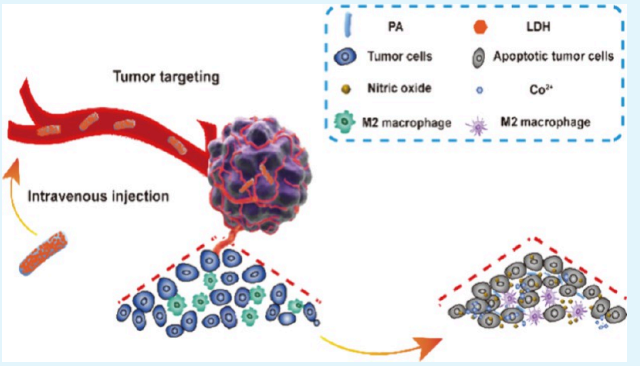
ABSTRACT: Combining targeted therapy and immunotherapy brings hope for a complete cancer cure. Due to their selective colonization and immune activation capacity, some bacteria have the potential to realize targeted immunotherapy. Herein, a biohybrid system was designed and synthesized by cladding NO_3^--intercalated cobalt aluminum layered double hydroxides (LDH) on anaerobic *Propionibacterium acnes* (PA) (PA@LDH). In this system, the covering of LDH reduces the pathogenicity of PA to normal tissues and alters its surface charge for prolonged in vivo circulation. Once the tumor site is reached, the acid-responsive degradation of LDH enables PA exposure. PA can colonize and convert nitrate ions to nitric oxide (NO) through denitrification. Then, NO reacts with intracellular $O_2^{\cdot-}$ to produce toxic reactive nitrogen species $ONOO^-$ and induce tumor cell apoptosis. In addition, cobalt ions released from LDH can inhibit the activity of superoxide dismutase (SOD), thus increasing the level of $O_2^{\cdot-}$ and further enhancing the antitumor effect. Moreover, PA exposure activates M2-to-M1 macrophage polarization and a range of immune responses, thereby achieving a sustained antitumor activity. In vitro and in vivo results reveal that the biohybrid system eliminates solid tumors and inhibits tumor metastasis effectively. Overall, the biohybrid strategy provides a new avenue for realizing simultaneous immunotherapy and targeted therapy.



KEYWORDS: *biohybrid system, layered double hydroxides, propionibacterium acnes, targeted therapy, immunotherapy*

1. INTRODUCTION

Methods to precise tumor ablation include photothermal therapy,[1] photodynamic therapy,[2] and sonodynamic therapy.[3] By responding to the tumor microenvironment (TME) or external field, nanomaterials produce a biotoxic substance (such as reactive oxygen species, ROS) or sufficient thermal energy to eliminate the primary tumor. However, these therapeutic strategies usually cannot prevent tumor invasion and metastasis.[4] To enhance the efficacy of cancer therapy, many studies are committed to achieving simultaneous precise tumor treatment and immune activation.[5−7] Immunotherapy aims at activating the immune system to obtain a durable antitumor response. It has been considered to have unparalleled advantages over traditional methods in eliminating disseminated metastatic tumor. Nevertheless, systemic toxicity remains unsolved for the clinical translation of cancer immunotherapy.[8] Simultaneous implementation of targeted therapy and immunotherapy can compensate for their limitations and thus improve the therapeutic efficacy.[9]

Recently, some bacteria-based biohybrid systems show potential in synergistic cancer therapy.[10−12] Anaerobic or facultative anaerobic characteristics enable bacteria to possess hypoxia tropism for active tumor targeting.[13,14] In addition, the immunogenicity of bacteria facilitates it with immune activity.[13,15,16] *Propionibacterium acnes* (PA), as an anaerobic bacterium with oxygen tolerance, is a commensal organism in human skin.[17] The hypoxic TME is preferential for PA to proliferate and metabolize. According to Silobrcic's study, up to 50% of tumor-bearing mice were cured after a single injection of inactivated PA suspension.[18] PA can increase the expression of inducible nitric oxide (NO) synthase (iNOS) and promote macrophage M1 polarization.[19] PA can also increase the phagocytosis of macrophages, promote the maturation of dendritic cells, and induce proinflammatory cytokine secretion.[20] Therefore, PA has great potential to simultaneously achieve tumor targeting and immunotherapy. However, as a Gram-positive bacterium, PA can be pathogenic under certain circumstances and cleared quickly by the immune system.[21] The pathogenicity of bacteria is derived

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