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A Bacterial Nanomedicine Combines Photodynamic-Immunotherapy and Chemotherapy for Enhanced Treatment of Oral Squamous Cell Carcinoma

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Bacterial therapy is an emerging hotspot in tumor immunotherapy, which can initiate antitumor immune activation through multiple mechanisms. *Porphyromonas gingivalis* (Pg), a pathogenic bacterium inhabiting the oral cavity, contains a great deal of pathogen associated molecular patterns that can activate various innate immune cells to promote antitumor immunity. Owing to the presence of protoporphyrin IX (PpIX), Pg is also an excellent photosensitizer for photodynamic therapy (PDT) via the in situ generation of reactive oxygen species. This study reports a bacterial nanomedicine (nmPg) fabricated from Pg through lysozyme degradation, ammonium chloride lysis, and nanoextrusion, which has potent PDT and immune activation performances for oral squamous cell carcinoma (OSCC) treatment. To further promote the tumoricidal efficacy, a commonly used chemotherapeutic drug doxorubicin (DOX) is efficiently encapsulated into nmPg through a simple incubation method. nmPg/DOX thus prepared exhibits significant synergistic effects on inhibiting the growth and metastasis of OSCC both in vitro and in vivo via photodynamic-immunotherapy and chemotherapy. In summary, this work develops a promising bacterial nanomedicine for enhanced treatment of OSCC.

1. Introduction

Oral squamous cell carcinoma (OSCC), known to be the most common malignancy in the oral and maxillofacial region, often exhibits the phenotype of aggressiveness, metastasis, and poor prognosis.[1,2] Current treatment modalities for OSCC include surgery, radiotherapy, chemotherapy, or a combination of these strategies depending on the extent of the disease. Unfortunately, various limitations also exist, and the overall survival of OSCC patients remains relatively unchanged for the last several decades.[1,3] Immunotherapy, combating tumors via activating specific immunity, has been demonstrated as an emerging strategy with improved clinical outcomes.[4,5] However, these immune activation approaches targeting single mechanism usually display a poor response rate due to tumor resistance, and only a minority of patients experience long-term benefits in clinic.[6] It is widely accepted that the multi-mechanism-mediated immunotherapy is a more efficient strategy for tumor treatment.[7]

Bacterial therapy, a newly emerged hotspot in tumor immunotherapy based on the live bacteria and their derived materials, can initiate the antitumor immune remodeling via multiple mechanisms.[8] Innate immune cells, such as dendritic cells (DCs), macrophages, and neutrophils existed in tumor microenvironment can be activated via recognition of their pattern recognition receptors by large amounts of pathogen associated molecular patterns (PAMPs) expressed on the surface of bacteria.[9–11] Activated innate immune cells in tumor microenvironment can secrete various pro-inflammatory cytokines to further recruit multiple immune cells, thus promote tumor antigen presentation and trigger antitumor immunity.[12] A representative example is the bacillus Calmette-Guerin, an attenuated live Mycobacterium bovis strain, which has been used as an effective reagent with good biocompatibility for immunotherapy of superficial bladder cancer.[13] Some bacteria can secrete specific metabolites, toxins, and enzymes to exert direct antitumoral effects,[14,15] which together with their potent immune enhancing action provide the great potential of bacteria therapy in dealing with cancers. In addition, combining bacterial biomaterials with nanotechnology can not only preserve the immune activation effects of bacteria, but also acquire numerous superiorities of nanocarriers in cancer therapy, such as improved solubility, increased

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The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/smll.202304014

DOI: 10.1002/smll.202304014

