Abstract

The traditional perception of intratumoral bacteria as harmful agents that contribute to cancer progression and metastasis is being increasingly challenged by emerging evidence suggesting their potential therapeutic value. This thesis explores the underappreciated anticancer potential of bacteria isolated from the tumor microenvironment and aims to redefine their role from passive residents or malignancy promoters to active therapeutic agents. During a broader investigation into bacterial anticancer properties, three bacterial strains, *Cutibacterium acnes, Acinetobacter radioresistens,* and *Bacillus thuringiensis*, were isolated from tumor tissues and evaluated for their tumor-suppressive capabilities. Among them, *C. acnes*, a non-pathogenic anaerobe from the Propionibacteriaceae family, exhibited superior tumor growth inhibition when administered intravenously in murine models. Histological and molecular analyses indicated immune cell infiltration and activation in response to the bacterial presence, suggesting that *C. acnes* exerts its antitumor effects, at least in part, through immune stimulation. Moreover, colony assays confirmed its specific localization within the hypoxic tumor microenvironment, reinforcing its natural tumor-homing ability and biocompatibility.

Despite its promise, monotherapy with *C. acnes* did not achieve complete tumor regression. It could only facilitate tumor growth suppression, underscoring the need for a multimodal approach to tackle cancer's complexity. To address this, the study integrated bacterial immunotherapy with nanotechnology and chemotherapy. Leveraging the amphiphilic and immunogenic nature of bacterial components, a nanohybrid platform was developed by functionalizing graphene oxide (GO) with *C. acnes* biomolecules and loading it with camptothecin (CPT), a hydrophobic chemotherapeutic agent. The resulting CPT–CA–GO complex exhibited improved aqueous dispersibility and was designed to exploit GO's photothermal properties upon near-infrared (NIR) laser exposure. Upon systemic administration and targeted irradiation, this multifunctional nanocomposite facilitated enhanced tumor accumulation, localized heating, chemotherapeutic drug release, and immune system activation, collectively contributing to marked tumor suppression.

This thesis highlights two major insights: first, that certain intratumoral bacteria possess intrinsic therapeutic properties and can serve as safe, cost-effective agents for immunomodulation; and second, that combining biologically derived agents with smart nanomaterials and classical drugs can synergistically enhance therapeutic outcomes. By avoiding genetically modified organisms and relying instead on naturally occurring bacterial strains, this approach offers translational promise with fewer biosafety concerns. Overall, the study presents a novel paradigm in cancer therapy, where intratumoral bacteria, once considered merely opportunistic or pathogenic, are re-envisioned as key elements in a multimodal therapeutic arsenal. These findings not only expand the landscape of oncolytic and immunotherapeutic strategies but also encourage the broader scientific community to revisit the tumor microbiome as a resource for cancer treatment innovation.

Keywords: Cancer, tumor-isolated bacteria, tumor suppression, immunology, Hybrid nanoarchitectonics, photothermal therapy, graphene oxide, drug delivery