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Bacteria–Tumor Spheroid Co-Culture Model Labeled with Multi-Metal Nanoparticles and Its X-ray Fluorescence Imaging Study

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Abstract

Recent studies have revealed the presence of diverse bacteria within solid tumors of cancer patients. The intrinsic tumor-targeting properties of these bacteria, along with the selective colonization observed in animal models, have renewed interest in employing bacteria as carriers for cancer therapy. However, due to the limitations of current in vivo imaging technologies, the spatiotemporal distribution of bacteria within tumors remains difficult to capture accurately, hindering systematic studies of their mechanisms of action and safety. Meanwhile, metal nanoparticles (NPs), owing to their tunable properties and multifunctionality, have demonstrated great potential in integrated tumor diagnosis and therapy. Three-dimensional tumor spheroids, as in vitro models of solid tumors, provide a reliable platform to study NP delivery, diffusion, and intercellular interactions.

In this study, we established a bacteria–tumor spheroid co-culture system labeled with multiple NPs. In situ labeling was achieved via bacterial intracellular reduction. Lactobacillus has been verified to generate gold nanoparticles (AuNPs), and we further attempted the synthesis of self-fluorescent selenium nanoparticles (SeNPs) for early-stage imaging and tracking bacterial dispersion. Simultaneously, Ni, Bi, Fe, and Au NPs were used to label different tumor cell lines, establishing both homogeneously mixed and core–shell structured 3D tumor spheroid models. Using multi-element synchronous detection and high-resolution visualization through X-ray fluorescence imaging (XFI), this system enables non-destructive imaging of multi-metal labels, allowing systematic investigation of interactions between bacteria and tumor cells.

Progress

In our preliminary studies, we successfully synthesized AuNPs using Lactobacillus and conducted initial in vivo reduction experiments for SeNPs to track bacterial dispersion. Additionally, we prepared and functionalized Ni, Bi, Fe, and Au nanoparticles with controlled sizes and efficient cellular uptake, and constructed multi-layered tumor spheroid models based on 4T1, MCF-7, and HeLa cell lines. XFI experiments were performed at the P06 beamline of the DESY synchrotron in Germany. Clear and stable imaging signals were obtained in 2D cell layers, and partial 3D tumor spheroid samples were successfully imaged, preliminarily demonstrating their feasibility as XFI targets and providing a good signal-to-noise ratio.

Innovation and Significance

The novelty of this study lies in the first integration of bacterial intracellular reduction and cellular uptake pathways to achieve a systemically designed multi-metal labeling strategy. A multi-scale "fluorescence–XFI" imaging approach was employed to achieve multi-level visualization of bacteria and tumor spheroids. This platform not only overcomes the limitations of current in vivo imaging in terms of resolution and multi-element detection but also offers a high-throughput, accessible approach to study the dynamic behavior of bacteria in the tumor microenvironment and explore tumor–microbiota interaction mechanisms. The system holds significant value for fundamental research and potential clinical translation.

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