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Advances in the Study of Bacterial-mediated Antitumor Therapy

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ABSTRACT

Tumors, due to their complex pathophysiological properties and potential drug resistance, make it difficult for traditional treatment modalities, including radiotherapy, chemotherapy and immunotherapy, to completely eliminate tumor cells. As an emerging therapeutic strategy, bacteriotherapy demonstrates its unique advantages, which are highly targeted. Whether applied alone or in combination with nanotechnology, bacterial therapy can effectively prevent tumor recurrence and metastasis. With the help of genetic engineering technology, it is possible to enable bacteria to express anti-cancer drugs, and these bacteria are able to precisely target the tumor area and release therapeutic molecules to induce apoptosis of tumor cells. Bacteria-targeted therapy has great potential for development in the field of tumor therapy. The paper reviews the research progress of bacterial therapies, introduces the principle of various bacterial therapies for tumor treatment, the research progress of bacterial therapies combined with nanotechnology, and the limitations of this therapy.

KEYWORDS

Bacteriotherapy; Tumor therapy; Targeting; Anti-tumor

1. INTRODUCTION

Cancer has long been one of the key factors contributing to human mortality. Although modern medicine has made remarkable progress in cancer treatment technology, traditional treatments, including surgery, chemotherapy and immunotherapy, still have limitations in the face of challenges such as cancer diversity, drug resistance and side effects during treatment. Bacteria as carriers can deliver anticancer drugs directly and precisely to the tumor microenvironment region, preventing drug inactivation during transport, and have the ability to synthesize, release, and activate drugs autonomously in situ, which helps to reduce the toxicity of the drugs to normal tissues and ensures the effectiveness of the drugs [1].Tumor microenvironments (TMEs) are characterized by hypoxia, acidosis, and necrosis, and bacteria are able to recognize and exploit these properties, thereby enhancing their specificity for tumors [2].In recent years, bacterial-mediated antitumor therapeutic strategies have been developed to take advantage of the properties of bacteria and the specific hypoxic microenvironment of tumors.

2. ADVANCES IN BACTERIOTHERAPY RESEARCH

Bacterial therapy has gradually entered the researchers' field of vision since more than 150 years ago, and bacteria have become a hotspot of research due to their tumor-targeting and intra-tumor proliferation characteristics. Bacteria capable of targeting tumors have achieved significant results in

the treatment of tumors, such as Salmonella, Escherichia coli, Clostridium difficile, and Listeria monocytogenes, in clinical tests [3].

2.1. Rationale for the Use of Bacteria in the Treatment of Tumors

Bacteria have unique biological characteristics that enable them to specifically localize and act on tumor tissues, because tumor areas are characterized by hypoxia, acidic environment and abundant nutrients, which provide a favorable growth environment for bacteria, thus enhancing their selective colonization of tumor sites. Secondly, bacteria carry a variety of immune-activating substances that can regulate the tumor microenvironment and activate the host's immune system, as well as certain bacteria are also able to directly penetrate the tumor cell membrane, in which the internal structure of the cell is destroyed or the tumor cells are directly killed through the secretion of toxins, and at the same time, they are able to inhibit the generation of tumor blood vessels, limiting the growth and metastasis of tumors. Bacteria can also be used as biocarriers for antitumor drugs and therapeutic genes, and they have flagella, which can actively free themselves in the vascular system and diffuse into tumor tissues, participating in tumor therapy through a variety of mechanisms [4].

2.2. Advances in the Study of Different Bacteria in Tumor Therapy

2.2.1. Gram-negative bacteria

(1) Salmonella

Salmonella are Gram-negative bacteria, possessing parthenogenetic anaerobic properties, capable of aerobic and anaerobic respiration, and able to grow not only in the hypoxic necrotic zone of the tumor, but also to survive in the aerobic tumor region [5]. Salmonella induces the expression of vascular interferon, which increases blood flow to the tumor, thereby increasing the number of bacteria escaping. Salmonella also triggers cellular autophagy by down-regulating the AKT/mTOR signaling pathway, which plays an important role in the regulation of apoptosis and autophagy, and is able to inhibit the expression of oncoproteins, such as P-glycoprotein (P-gp), hypoxia-inducible factor (HIF), and matrix metalloproteinase-9 (MMP-9), which can inhibit tumor angiogenesis, immunosuppression, drug resistance, andmetastasis. In addition, Salmonella can inhibit angiogenesis by suppressing the expression of vascular endothelial growth factor (VEGF), which in turn inhibits tumor growth, e.g., in melanoma, Salmonella infection induces the up-regulation of connexin 43 (Cx43), which in turn down-regulates HIF1α and VEGF, reduces the number of blood vessels around the tumor, and cuts off the blood supply to the tumor. The ability of Salmonella to activate the immune system is also part of its antitumor effect, which restores the immunogenicity of the tumor microenvironment, promotes immune cell infiltration and tumor-specific immune response, reduces the expression of the immunosuppressive molecule IDO, and activates the host immune response. The LPS and flagellar components of Salmonella activate host immunity, induce tumor necrosis factor alpha (TNF-α) and CD8+ T cell responses, and effectively clear tumors [6].

(2) Escherichia coli (E. coli)

Escherichia coli (E.coli) is a Gram-negative bacterium, a probiotic with parthenogenetic anaerobic properties, and a tumor-targeting bacterium with strong tumor-targeting and colonization abilities. Escherichia coli Nissle 1917 (E.coli Nissle 1917, EcN) shows a clear growth advantage at the necrotic and hypoxic junction of tumor tissues, and the serum-sensitive lipopolysaccharide contained in its outer membrane contributes to its rapid exclusion from normal organs. Metabolomic analysis revealed that the metabolic pattern of EcN was significantly different from that of pathogenic strains, and that it possessed an extensive iron uptake system with inhibitory effects on harmful microorganisms in the intestinal tract. In addition, it produces a variety of proteins and compounds with anti-microbial and anti-tumor properties. The podocarp structure of EcN makes it easy to be cleared in the serum environment, and its flagellum and chemotactic receptor contribute to its

penetration and migration in tissues, allowing it to accumulate in regions farther away from the vascular system [7]. The team of Yufei Tan from Shandong University achieved the first-ever demonstration of yew-diene (yew-diene) by Gibson multifragament assembly by Gibson multifragment assembly [8,9]. For the first time, paclitaxel diene (paclitaxel precursor compound) was successfully constructed in an efficient biosynthetic system to achieve the delivery of the terpene anticancer drug paclitaxel, which has good therapeutic effects on a variety of cancers. The research team has constructed an efficient biosynthetic system of paclitaxel diene in EcN, which not only lays the foundation for the development of paclitaxel-targeted delivery system, but also provides a reference for the heterologous expression of other terpenoids in EcN.

2.2.2. Gram-positive bacteria

(1) Clostridium difficile (bacterium causing gut infection)

Clostridium histolyticum is a Gram-positive bacterium that is exclusively anaerobic and can therefore colonize necrotic areas of tumors where oxygen is scarce. Clostridia currently used in cancer therapy include Clostridium histolyticum (C. histolyticum), Clostridium acetobutylicum (C. acetobutylicum), Clostridium tetani (C. tetani), and Clostridium tumefaciens (C. sporogenes).Evidence suggests that germination of Clostridium spores in tumor cells activates key transcription factors, such as hypoxia-inducible factor-1 (HIF-1), as well as a variety of cytokines, including TNF-α, IL-2, and IL-12 The activation of these molecules has a potential inhibitory effect on controlling the growth and spread of tumor cells, and thus Clostridium sporogenes has the potential to be a therapeutic agent for the treatment of cancer.It has also been revealed that specific toxins produced by Clostridia, such as cytosine deaminase and nitroreductase, may play an important role in destroying tumor cells[3].

(2) Listeria monocytogene

Listeria monocytogenes is a parthenogenetic anaerobic Gram-positive intracellular rod-shaped bacterium. Listeria monocytogenes can be used as a potent carrier of drugs for the treatment of cancer because during infection, Listeria monocytogenes is able to penetrate the intestinal epithelium and further translocate to organs such as the spleen and liver, where it is phagocytosed by antigen-presenting cells (APCs), a process that activates the adaptive immune system, leading to increased levels of pro-inflammatory cytokines, enhanced Listeria-specific CD4+ T-cell responses and enhanced protein antigen delivery via MHCclass I molecules delivering protein antigens to CD8+ T cells. Notably, Listeria monocytogenes achieves spreading and survival within host cells by producing specific proteins, such as Listeriolysin (LLO) and Actin Assemble Inducing protein (ActA), which help the bacteria evade the host's immune response while facilitating its intracellular spreading in the host cell. A significant advantage of Listeria monocytogenes over other bacterial vectors is that it triggers a milder humoral immune response, which makes it less likely to be inhibited by neutralizing antibodies, and therefore more efficiently and accurately delivers cancer drugs to the tumor cell region [3].

3. APPLICATION OF BACTERIAL-MEDIATED TUMOR THERAPY

3.1. Bacteria Combined with Nanotechnology in Tumor Diagnosis and Treatment

Nanotechnology has been widely used in recent years and also involved in tumor therapy and played an effective role. Nanotechnology has obvious advantages in drug delivery, such as increasing the solubility of difficult-to-solve drugs, helping drugs escape lysosomes, avoiding clearance and controlling release. As nanotechnology develops, it is combined with engineered bacteria to effectively deliver therapeutic drugs and imaging molecules to inhibit tumor development. For example, nanoparticles are attached to the surface of bacteria and reach the tumor microenvironment for diagnosis and treatment by injection [9].

3.1.1. Nanoengineering of bacterial surfaces

The modification of bacterial surfaces can make them effective in directing nanomedicines to tumor cells, the microenvironment of TEMs, and the release of nanomedicines.2022 In 2022, Yuet Li of Southwest Medical University investigated a new approach to lung cancer treatment using an anaerobic bacterium-mediated targeted drug delivery system in order to improve the efficacy of lung cancer treatment[10]. The core principle of the study was to use anaerobic Bifidobacterium infantis (B. infant, Bi) as a preimplantation target and implant it into the tumor hypoxic region, and then the therapeutic drug adriamycin (DOX) was enriched into the tumor hypoxic region by the nanomedicine modified by the Bifidobacterium infantis-specific antibody (Ab-DOX-s-s-NPS), which was actively targeting inside the tumor tissue.In the tumor region, the nanomedicine particles were able to release rapidly in the acidic microenvironment of the tumor, thus enhancing the therapeutic effect. Through a series of experiments, it was confirmed that this drug delivery strategy could increase the drug concentration in the tumor region, significantly reduce the toxic side effects in other systemic systems, and have good anti-tumor effect and biosafety.

3.1.2. Synergistic therapy

In 2022, Yao Meiat Linyi University developed a pH-programming-responsive tumor synergistic therapeutic nanoplatform based on single-atom catalysts, which not only enables effective drug delivery, but also targeted multimodal combination therapy can achieve efficient and precise tumor treatment [11]. Various nanomaterials (H2O2-inducible nanomaterials, PH-responsive nanomaterials, glutathione-responsive nanomaterials, hypoxia-inducible nanomaterials) have been investigated in cancer based on the microenvironment of tumors, and single-atom catalysts have been investigated for use in cancer therapies such as photodynamic therapy, chemodynamic therapy and photothermal therapy. By designing nanomedicines capable of responding to TME properties, precise treatment of tumors has been achieved while reducing side effects on normal tissues.

3.1.3. Gene therapy

HU et al researchers effectively delivered a DNA vaccine encoding vascular endothelial growth factor receptor 2 for tumor immunotherapy by modifying cationic polymers on the surface of engineered bacteria and piggybacking plasmid DNA nanoparticles, which enhanced the ability of plasmid DNA to escape from phagocytic vesicles [9]. A significant reduction in tumor volume was detected by positron emission tomography (PET) in mice, suggesting that the cationic polymers on the surface of the engineered bacteria not only acted as a protonate buffer, but also enhanced the bacteria's tolerance in acidic environments.

3.2. Application of Bacteria As Drug Carriers

In 2022, Zhenguo Liang, University of Chinese Academy of Sciences, modified and extracted NK-Exo-N3, an exosome modified with -N3 motifs on its membrane proteins by bioorthogonal glycometabolic modification and coupled with YB1 modified with -DBCO motifs on bioorthogonal glycometabolic modification [12]. YB1-NK-Exo, a drug delivery system with hypoxic tumor targeting and synergistic tumor immunotherapy, was constructed.YB1-HA-Ce6 showed good tumor targeting ability, cytotoxicity and immune activation effects in in vitro and in vivo experiments. In particular, it demonstrated significant anti-tumor effects under acoustic/photodynamic synergistic therapy. It was demonstrated that the use of attenuated Salmonella YB1 and NK cell exosomes as delivery carriers could effectively deliver the drugs to tumor tissues and improve the efficiency of tumor treatment through the synergistic effect of acoustic/photodynamic therapy and immunotherapy.

4. SAFETY AND TARGETING

While the use of bacteria in tumor therapy has potential, it also carries the risk of possible toxicity to the host. To reduce this risk, researchers have used genetic engineering techniques to modify Salmonella to reduce its virulence. This involves deleting their virulence genes or introducing trophic defects, such as Salmonella with the aroA gene deleted, so that it can only grow in tumor tissue, thus enhancing its targeting of tumors without affecting healthy tissue. For example, Salmonella typhimurium strain VNP20009 was attenuated by deletion of the msbB and purI genes and showed better tumor targeting and inhibition in a mouse tumor model [2]. However, its performance in clinical cancer therapy is not satisfactory, mainly due to the lack of tumor specificity and antitumor activity.

Genetic engineering techniques have also been used to improve the tumor targeting of bacteria [13]. For example, specific recognition of tumor cells is enhanced by expressing specific peptides or fusion proteins on the bacterial surface. In addition, bacteria capable of delivering functional nucleic acid molecules to tumors have been constructed through a biotin-streptavidin binding approach and tracked by bioluminescence imaging, and despite some success in animal models, the study of tumor targeting of bacteria is still facing challenges in clinical applications. Further research is needed to optimize the tumor targeting of bacteria to ensure their efficacy and safety in clinical trials. Researchers are working to develop more effective methods through gene editing techniques to improve the specificity of bacterial therapies and reduce potential side effects, while maintaining or enhancing their antitumor activity.

Scientific experiments have demonstrated that some genetically modified bacteria, which are able to carry anticancer drugs and exhibit enhanced proliferation in the tumor microenvironment, are inhibited in normal tissues. These bacteria do not cause significant immune responses or serious toxic side effects. For example, by introducing genes such as cytosine deaminase, nitroreductase, or TNF-α into Clostridium difficile, their targeted tumor-killing effect can be enhanced [14]. At the present level of biotechnology, bacterial therapy can be applied in combination with traditional radiotherapy, chemotherapy and immunotherapy to complement each other's advantages and improve the overall therapeutic effect, while reducing the toxic side effects of single treatment modalities.

5. SUMMARY AND OUTLOOK

Scientific and technological advances continue to drive breakthroughs in the field of cancer therapy, and researchers have made remarkable progress in this area. As a new strategy for cancer treatment, therapy using bacteria has received high attention due to its ability to naturally target tumors, excellent penetration, immunomodulatory function, and potential for genetic engineering. Compared with conventional tumor therapies, bacterial therapy has the ability to selectively attack tumors and genetic engineering due to its high specificity, controllable drug release, and ability to dissolve tumors, which can accurately express a variety of anticancer proteins, effectively inhibit tumor growth, and improve the survival rate of patients. It is ideal for achieving targeted tumor therapy and an effective complement to traditional therapies.

This paper summarizes the research progress of different bacteria for tumor treatment and bacteria combined with nanotechnology for tumor treatment. Currently, bacteria for tumor treatment mainly work by acting as drug carriers, inhibiting tumor angiogenesis, and activating the immune system. With the further understanding of oncology as well as immunology, the application of bacteria in the treatment of tumors is promising.

Despite the great therapeutic potential of genetically engineered bacteria, they face many challenges in clinical application as living drugs, including potential bacterial toxicity, genetic instability, difficulty in proliferation control, low targeting efficiency, risk of nonspecific infections, and insufficient drug yield. Future research will aim to find a balance between reducing bacterial toxicity

and maintaining its targeting ability [3]. For example, by controlling the expression of specific genes, engineered bacterial strains such as YB1 are made to survive only in low oxygen environments, which usually occurs in the hypoxic regions of tumors, thus reducing the damage to healthy organisms. Therefore, improving the safety and targeting of bacteria is a priority for researchers today, and more extensive and in-depth studies of bacteria are needed to solve today's human problem - cancer treatment.

REFERENCES

[1] Wang, M., Su, W.Y. (2019). Bacteria: a new weapon against cancer. World Latest MedicineInformation.

[2] Liu, D., Mei, Q. B., Zhang, M. L.et al. (2023). Progress of bacterial targeted tumor therapy. Chinese Contemporary Medicine, 30 (08): 32-37.

[3] Liu, C.L., Dong, Y.X., Guo, X. (2021). Application of synthetic biology in promoting preclinical and clinical advances of bacterial anti-cancer therapy. Journal of Integration Technology, 10(04), 78-92.

[4] Shi, E. Y., Wang, N., Zhao, X. Y.et al. (2024). Advances in bacterial-mediated tumor therapy. Chinese Journal of Bioengineering, 44(2), 112-123.

[5] Chen, X., Zhang, W. J., Chen, Y. L.et al. (2024). Advances in Salmonella-mediated tumor therapy. Microbiology Bulletin (4).

[6] Lü, Z. R., Li, D. Y., Zhu, Y. Y.et al. (2024). Advances in Salmonella-mediated tumor-targeted therapy. Journal of Pharmacy, 59(1), 17-24.

[7] Li, Y. T., Cui, T. Q., Zhang H. L.et al.(2023). Progress of tumor-targeting bacterium escherichia coli nissle 1917 in cancer therapy. Chinese Journal of Bioengineering, 43(6), 54-68.

[8] Tan, Y. F. (2023). Heterologous expression study of the anticancer drug paclitaxel precursor paclitaxel diene in tumour-targeting bacteria. (Doctoral dissertation, Shandong University).

[9] Xue, X., Zhang, Y.Y., Wang, H.J. (2024). Progress of bacteria based on combined nanotechnology for tumour diagnosis and treatment. Chinese Journal of Biological Products, 37(1), 117-124.

[10] Li, Y. (2022). Anaerobic bacteria mediated 'smart missile' targeting tumor hypoxic area enhances the therapeutic outcome of lung cancer. Chemical Engineering Journal, 438, 135566-.

[11] Yao, M. (2023). Tumour microenvironment responsive functional materials for multimodal cancer therapy research. (Doctoral dissertation, Linyi University).

[12] Liang, Z.G. (2022). Bacteriophage-based biomimetic nanoparticles for tumour therapy (Master's thesis, University of Chinese Academy of Sciences (Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences)). M.S.

[13] Ren, H. Z., Yang, T. H., Wang, J. (2024). Bacteria-mediated synergistic therapeutic strategies for tumours. Chinese Journal of Tumour Biotherapy, 31(3), 296-302.

[14] Cui, C., Tu, Q., Zhang, Y. M. (2021). Research progress of bacteria for targeted therapy of tumours. Chinese Journal of Antibiotics, 46(5), 8.