Original Article

SALMONELLA IN ONCOLOGY: A NOVEL APPROACH TO CANCER MANAGEMENT

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Abstract: The hypoxic microenvironment of tumor tissue provides a conducive environment for the growth of facultative and anaerobic bacteria. Researchers have exploited this property of bacteria for the clinical management of cancer. Among the different bacteria, Salmonella is the most preferred choice due to its genetic manipulability. In this article, we discuss the mechanism of Salmonella-host interaction and the ways in which this bacterium can be used for cancer treatment. Salmonella can be genetically engineered to deliver anticancer agents or act as a therapeutic for cancer treatment. The ability of Salmonella to grow in the hypoxic microenvironment and its chemotaxis ability make it a promising candidate for anticancer therapy. However, Salmonella-based drug delivery also has its challenges, and future work needs to focus on enhancing its target-specificity and patient-safety abilities for its successful use in cancer treatment. Several types of cancer, including pancreatic, prostate, breast, spinal-cord cancers, and some tumor metastases, have been successfully treated by S. typhimurium, making it a potential candidate for cancer therapy in the future

Keywords: Salmonella, tumor, bacterial therapy, hypoxic microenvironment, genetic engineering

Introduction

Tumor growth is associated with an abnormal increase in cell growth that may lead to the insufficient vascularization of the tumor tissues, resulting in a hypoxic or anoxic microenvironment. This microenvironment provides a promising opportunity for the growth of facultative and anaerobic bacteria, which can be used for the clinical management of cancer. Bacteria can be genetically engineered to either deliver anticancer agents or themselves act as therapeutics in the treatment of cancer. Salmonella, a Gram-negative rod-shaped motile bacteria of family Enterobacteriaceae, is a preferred bacterium for cancer therapy. It is a facultative anaerobe that localizes

efficiently in the hypoxic microenvironment of tumors. This article focuses on the different mechanisms of Salmonella-host interaction and the various ways in which this bacterium can be used for cancer treatment. Several challenges need to be addressed before Salmonella-based therapy can be used extensively, such as enhancing the target-specificity and patient-safety abilities of these bacteria. However, several types of cancer, including pancreatic, prostate, breast, spinal-cord cancers, and some tumor metastases, have been successfully treated by S. typhimurium, making it a potential candidate for cancer therapy in the future.

Bacterial therapy:

By the end of 19th century, Dr. William B. Coley initiated the bacterial therapy to treat cancer by injecting his novel preparation called 'Coley's toxin', that contained a mixture of killed and attenuated bacterial species which can induce inflammation without resulting in bacteraemia. But the subsequent introduction of radiotherapy replaced this technique in hospitals. However, since last two decades the former one again came into research and clinical trials.

***Salmonella*- the most preferred choice:**

There are several characteristics of *Salmonella* which make the microbe very much conducive for clinical management of *in vivo* tumor tissues.

- It is a facultative anaerobe which can grow, colonize and replicate to many generations favourably in the hypoxic microenvironment of the tumor.
- The organism possesses the ability for biosynthesis of flagella and hence is motile to avoid the normal diffusion resistance from the vascular system.
- It can adopt chemotaxis to reach the specific nutrients available in the microenvironment of tumor such as dead and degraded cells, apoptotic neutrophils etc. This ability can also aid in reaching of bacteria to poorly vascularized areas surrounding tumor and for efficient drug delivery to these areas.
- Its T3SS is a well characterized injectisome structure of *Salmonella*, which is well exploited by researchers for drug delivery to the tumor and thus the organism is designated as a significant biocarrier system.
- The structural components of bacteria like lipopolysaccharide (LPS) of outer membrane, flagellin protein of flagella and the surface antigens may interact with toll like receptors (TLRs) of host which can lead to secretion of cytokines and/or chemokines driven by inflammasome formation.
- Some auxotrophs can synthetically grow in the tumor surrounding that is rich in one or more amino acids.
- Serovar *S.* Typhimurium is mostly opted for bioengineering by many researchers as the overall molecular mechanisms involved in its pathogenesis has been explored extensively and murine is a well-established laboratory model for its in vivo host-interaction studies.

VNP20009, genetically engineered *S.* Typhimurium ATCC14028 strain developed at Yale University, is a best example in this aspect as it is stable both genetically and phenotypically either *in vitro* or *in vivo* and has utmost safety profiles. Further examples are A1/A1-R, CRC2631 etc.

Challenges and future perspectives:

As wild STM is pathogenic to human beings, it can infect normal tissues alongside tumors, so it is essential to attenuate STM by genetic manipulations for enhancing the safety of bacterial tumor therapy. With regards to the *Salmonella*-based drug delivery, the payload has to be designed in a manner to reduce the virulence and maximize the safety. For achieving effective drug targeting, the gene responsible for expression of the molecule has to be kept

under the regulation of an inducible promoter. Nevertheless, prostate, breast, pancreatic, spinal-cord cancers and some tumor metastases have been reported to be successfully treated by *S. typhimurium.* Thus, by enhancing the target-specificity and patient-safety abilities of *Salmonella* can pave its way to rise as a promising candidate for anticancer therapy in the future course of work.

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