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Salmonella: A PREFERRED MICROORGANISM FOR CLINICAL MANAGEMENT OF CANCER

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Abstract: Ability of both facultative and anaerobic bacteria to grow in hypoxic microenvironment of tumor is exploited by researchers for clinical management of cancer. In few cases, tumor-targeting bacterial monotherapy is executed while better outcomes can be achieved by combination of the former with other anticancer therapies. Bacteria can be genetically engineered to either deliver anticancer agents or itself act as therapeutic on the basis of clinical requirements. *Salmonella*, being a facultative anaerobe, is mostly preferred in this aspect as it is mostly feasible to incorporate genetic manipulations in its case. Here we have focused on the mechanism of *Salmonella*-host interaction and different ways of using the bacteria in treatment of cancer.
Keywords: *Salmonella*, tumor and bacterial therapy.

Introduction

Tumor is an abnormal growth of cells in any part of the body that may either remain localized to its origin as in case of benign tumor or may progress to different body parts as in the case of malignant tumor. The growth of cells is uncontrolled that may lead to insufficient vascularization and hence resulting in hypoxic or anoxic microenvironment.

Salmonella is a Gram-negative rod-shaped motile bacteria of family *Enterobacteriacea*. To date there are more than 2600 serovars of *Salmonella* have been isolated worldwide. Few serovars of the organism are of importance due to their pathogenic ability and many among them are zoonotic with broad host ranges which can spread between animals and humans. This microbe is facultative anaerobe and hence can localize in the hypoxic tumor microenvironment.

Host-*Salmonella* interaction:

Upon oral contamination of *Salmonella*, the pathogen confronts a completely anaerobic environment in host intestine. The two most important regulons are activated for switching the bacterial metabolism from aerobic to anaerobic: *fnr* and *arcA/B* dual-complex. *Salmonella*'s

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ability to invade the enterocytes induces the establishment of host adaptive immune response, thereby subsiding the colonization-resistance exhibited by persistent gut microbiota. During this operation, several neutrophils are recruited to trigger mucosal inflammation and degradation by secreting NOS and ROS which results in destruction of the microbiota. However, *Salmonella* is capable of utilizing both degraded mucosal metabolites as nutrient and nitrate, that is produced from reaction of nitrate oxide (derived from NOS) and superoxide (from ROS), as electron acceptor for anaerobic respiration, thereby able to survive in this milieu.

Invasion is a customized process where the *Salmonella* sense and attach to the enterocytes by fimbrial adhesins followed by induction of genes responsible for expression of a series of proteins for biosynthesis of type-3 secretion system-1 (T3SS1). These genes are found exclusively in the chromosomal region that contains *Salmonella* pathogenicity island-1 (SPI-1). T3SS1, a syringe like structure composed of two membrane bound base-rings, an extracellular appendage, a translocon hole and several effector proteins, is involved in connecting the bacterial cytoplasm to host cytoplasm and translocating the effector proteins from the former to the latter. The effectors entering the enterocyte modulate the cell's signalling systems, thus manipulating the cytoskeletal arrangements, thereby changing the cell's shape to form membrane ruffling and lamellipodia for engulfment of *Salmonella*.

Once the microbe invades host cell, a vacuole is formed as an enclosure of the former and specifically referred as *Salmonella* containing vacuole (SCV) that does not follow the regular endocytic pathway and may remain there for several hours to days. Intracellular survival and replication of Salmonella is mediated by expression of T3SS2. Enterocyte invasion is followed by macrophage invasion, then either the pathogen may persist as intramacrophage-SCV or may get distributed to liver and spleen causing systemic infection and bacteraemia.

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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