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Analysis of S.typhimurium in Cancer Treatment

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Abstract. Cancer is widely considered one of the most intractable diseases, with high annual mortality rates, creating an urgent need for effective treatments. With the development of medical technology, humans have a better understanding of tumors, and a variety of treatments have proven feasible, including chemotherapy and radiotherapy. Recent advances in medicine have led to the widespread investigation of viruses and bacteria for their anti-tumor abilities, with Salmonella typhimurium demonstrating broad therapeutic potential. Extensive research has demonstrated that S.typhimurium's broad specificity and unique selective growth properties enable oncolytic activity in a wide range of hypoxic tumor regions. Furthermore, its robust targeting mechanisms lay the foundation for drug delivery. This paper summarizes the characteristics and mechanisms of S. typhimurium as an oncolytic bacterium and delivery vehicle, analyzing the entire process of tumor cell invasion and elimination in cancer therapy. It also highlights the current applications of this bacterium and demonstrates its immense potential in cancer therapy.

Keywords: S.typhimurium, cancer treatment, delivery, oncolytic bacteria

1. Introduction

S.typhimurium is a bacteria. According to the taxonomy, it belongs to the Pseudomonadati kingdom, Pseudomonadota phylum, Gammaproteobacteria class, Enterobacterales order, Enterobacteriaceae family, Salmonella genus, Salmonella enterica species and Salmonella enterica I subspecies [1]. It was separated from the Gram-negative bacillary bacteria group and recognized as the facultative anaerobic flagellated single-celled organism. It is usually found in the intestines of organisms and replicate through binary fission. The symptoms of being affected by these bacteria are abdominal cramps and diarrhea [2]. Although it is harmful to humans, scientists have found that it can contribute to various types of cancer treatment, including melanoma, colorectal cancer and breast cancer. This type of bacteria has shown great potential in oncology, and it has been widely discussed in this field. Researchers worldwide have done several experiments to test the availability of this bacteria in treating cancer; they have so far found S.typhimurium can act as an oncolytic bacterium to invade into the tumor cells and kill them as both natural ones and genetically edited ones [3], which could successfully clean the cancer cells inside the Mus musculus. This paper mainly discloses the mechanisms of treatments using S.typhimurium and summarize the characteristics of the bacteria that make its high efficacy. It will further highlight the potential of its cancer treatment.

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2. The antitumor mechanism of S.typhimurium

2.1. Main properties

Compared with other oncolytic bacteria, S.typhimurium has several unique antitumor properties that made it outstanding among the oncolytic bacteria and showed great significance in applying them to various tumor treatments [4]. These properties establish strong targeting of S. typhimurium.

2.1.1. Select growth

Different from normal cells, cancer cells are not dependent on high concentrations of oxygen. In fact, it survives in hypoxic conditions (oxygen% <1%) [5]. Blood vessels are an important pathway for transporting nutrients and oxygen. As a tumor continues to grow, it will exceed the oxygen supply range of nearby blood vessels. As the tumor grows, it further causes vascular abnormalities, thus forming an internal tumor microenvironment. The tumor itself relies on hypoxia-inducible factor (HIF) to survive [6]. This environment limits conventional tumor treatments, such as radiotherapy: this method does not work well in the tumor microenvironment with extremely low oxygen content and shows poor results [7]. The facultative anaerobic characteristics of Salmonella typhimurium make it suitable for this environment. Related studies have shown that this bacterium has a strong ability to reproduce in the tumor microenvironment, nearly a thousand times that of other cells [8], This is due to the replication ability of Salmonella typhimurium. This method can minimize the spread of bacterial toxicity while precisely targeting the interior of tumor cells, showing high tumor specificity [9].

2.1.2. Broad tumor specificity and motility

As mentioned in 2.1.1, Salmonella Typhimurium has a strong selective growth ability. As a facultative anaerobic bacterium, it can invade the low-oxygen or hypoxic environment inside the tumor and survive and reproduce in this environment. Since each tumor has a similar tumor microenvironment, that is, a low-oxygen and hypoxic environment, it can be applied to the treatment of various tumors. Relevant studies have shown that Salmonella Typhimurium has been proven to play an effective role in the treatment of various cancers such as melanoma, lung cancer, and breast cancer [10]. At the same time, unlike other bacteria, this bacterium has extremely strong motility, which enables the bacteria to move to the core necrotic area of the tumor and deeply penetrate and disperse the drug into the host body. This ability can also help significantly improve the bacterial aggregation ability, thereby enhancing the anti-tumor ability [11].

2.2. Invasion mechanism

Before S. Typhimurium can successfully invade and kill tumor cells, the mechanism by which it invades humans needs to be understood.

2.2.1. Invade by SPI-1 system

Salmonella typhimurium has multiple different entry pathways, one of which is through the T3SS-1 type III secretion system [12]. This system includes two distinct virulence-associated T3SSs, SPI-1 and SPI-2, and the two different toxins play completely different roles in host cells. Studies have shown that SPI-1 plays an important role in the process of bacterial invasion of host cells: SPI-1 can

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help Salmonella typhimurium invade the host's M cells and epithelial cells and promote its reproduction [13]. This bacterium contains the Salmonella invasion protein, which encodes four effector factors, SipA, SipB, SipC, and SipD, which play different roles. The absence of SipA does not play a decisive role in the invasion process, but is more used to catalyze the aggregation rate of the bacteria in epithelial cells and activate and regulate molecules or proteins involved in subsequent immune responses with the combination of actin. The remaining three proteins combine with other protein polymers to form a transport protein channel connecting the host cell nucleus and bacteria, providing conditions for bacterial invasion [14]. In addition, effector factors such as SopE and SopE2 also play a role in mediating invasion. Studies have shown that SopE can activate multiple proteins such as CDC42 and Rac-1 in the Rho GTPases family, thereby affecting the transmission and transport of information within the cell, providing conditions for the invasion of S.typhimurium [15].

2.2.2. Immune evasion mechanism (SPI-2 system)

In addition to SPI-1, which is used for invasion, there is also SPI-2 in the T3SS system. Unlike the previous one, this gene is mainly used to ensure that the bacteria can successfully survive and replicate in the host body while spreading the virus to the host body. Studies have shown that S.typhimurium needs to survive in a salmonella-containing vacuole (SCV) in the host body, which provides a place for bacteria to survive. The initial formation of SCV is related to the SipA protein in SPI-1. This protein determines the positioning of SCV and has an important impact on protecting bacteria [16]. In addition to the SipA protein, SPI-2 also prevents bacteria from the immune system in different ways. First, SPI-2 can affect the rhythm and amount of cellular transport in the host body. It contains an effector factor, SifA, which, together with SipA-N, promotes the movement of SCVs within host cells. At the same time, the SpiC protein within SPI-2 stabilizes SCVs by inhibiting the binding of phagosomes and lysosomes, preventing them from transforming into mature phagolysosomes [16-18]. This is a way for pathogens to evade immunity because phagolysosomes contain a variety of hydrolytic enzymes to engulf pathogens [18]. One of them is NADPH oxidase, which contains multiple protein forms, including Rap1A. Another mechanism is the effector protein carried by SPI-2, which can prevent macrophages containing NADPH enzyme from approaching, eliminating the possibility of phagocytosis [19]. This allows the further treatment of cancer cells.

2.3. Tumor clearance mechanism

As an oncolytic bacterium, Salmonella Typhimurium has multiple mechanisms to eliminate target tumor cells after successful invasion.

2.3.1. Acting as oncolytic bacteria

Combined with the characteristics of Salmonella typhimurium, it can accumulate inside the tumor by migrating in the tumor blood vessels, thereby further inducing tumor cell death [20]. The T3SS system of Salmonella typhimurium not only allows it to invade host cells, but one of its virulence factors, SpvB, can also directly kill tumor cells. Studies have shown that after the induction of spvB expression, actin depolymerization occurs in cells. At the same time, during the regulation process, it limits the transition from G1 to S in the interphase of mitosis and the transition from G2 in the late interphase to the M phase of mitosis, thereby arresting cell growth and ultimately causing cell death

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[21]. In addition to being a toxin, studies have shown that Salmonella typhimurium can convert nitrates into NO under anaerobic conditions inside tumors, which has been proven to have the ability to eliminate cancer cells. This process is accomplished by the enzymatic action of nitric oxide synthase in the host body. This enzyme has several different isoforms, including nNOS, eNOS, and iNOS. At high concentrations, NO can act as a chemical that induces tumor cell death, while at low concentrations, NO can promote the formation of blood vessels to promote tumor growth [22,23]. Therefore, the concentration of NO produced by bacteria should be controlled during the treatment process.

2.3.2. Activate immune response

Cancer cells are not attacked by the immune system because they not only do not express their own antigens, but also form a tumor microenvironment (TME) containing a variety of inhibitory molecules, thereby escaping T cell recognition to achieve immune escape [24]. As a pathogen, Salmonella typhimurium can stimulate immune responses and help immune cells locate tumor cells. The surface of Salmonella typhimurium contains pathogen-associated molecular patterns (PAMPs), which are recognized by pattern recognition receptors (PRRs) in the host and generate signals corresponding to different specific responses [25]. Among them, the inflammasome (NLRC4) in the host body recognizes bacterial flagellin (fljB and fliC) and lipopolysaccharide (LPS) and further activates caspase-1 protease and releases IL-1β [26,27]. Another possible activation method is to activate the NLRC3 inflammasome through stimuli [28]. After caspase-1 protein is activated, it is cleaved to form mature IL-1β, IL-18 and GSDMD-NT. Among them, GSDMD-NT triggers cell pyroptosis and further releases pro-inflammatory factors [27,29]. IL-1β has been shown to act as a cofactor to activate T cells and a growth factor for B cells, promoting the production of specific antibodies (inducing IL-6). As for IL-18, it can work with other effectors of the Interleukin-1 family to produce Interferon gamma (IFN-γ), which is used to enhance the activity of immune cells such as natural killer (NK) cells and T cells, thereby eliminating tumor cells [30].

2.4. Targeting mechanism

In tumor treatment, Salmonella typhimurium also act as a drug or virus carrier to bring therapeutic substances into the host body.

2.4.1. The possibility of genetic modification

In addition to the good chemical tropism and selective growth mentioned above, Salmonella typhimurium also has strong editability, which makes it an excellent carrier in tumor therapy. To date, attenuated Salmonella typhimurium with minimal side effects has been able to carry a variety of substances into host cells, including cytokines, cytotoxins, and anti-cancer substances such as small interfering RNA (siRNA) [31]. These substances themselves do not have the ability to invade host cells and move to the core of tumor necrosis, but the carrier Salmonella typhimurium can make up for this defect. At the same time, Salmonella typhimurium alone as an oncolytic bacterium cannot achieve a comprehensive cure. This method of combining the transported substances and bacteria to jointly fight tumors can significantly improve the treatment effect while ensuring the targeting of the drug [32].

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2.4.2. Chemotaxis

Chemotaxis is the attraction of cells to chemicals, which serve as signals, leading to directional cell migration. In early experiments, Bren and Eisenbach found that tumors secrete a variety of nutrients, such as aspartate, serine, citrate, and ribose and galactose, which attract ligands carried by S. typhimurium and act as chemotaxis [33]. These receptors play a unique role in the chemotaxis of Salmonella typhimurium. Studies have shown that different receptors can attract bacteria to different degrees: aspartate receptors determine whether Salmonella typhimurium can locate tumor cells and their microenvironment; serine allows bacteria to further break through membrane barriers, allowing them to successfully enter tumor cells; finally, ribose and galactose receptors largely determine the bacteria's potential as oncolytic bacteria and therapeutic carriers, which can attract S. typhimurium into the core of tumor cells, allowing them to disintegrate the tumor from the inside [34]. The properties of these receptors make Salmonella typhimurium highly targeted and show great potential in tumor treatment.

2.5. Mechanism of delivery

The mechanism of Salmonella typhimurium invading host cells is the same as that of SPI-1 in the T3SS system to complete the invasion of epithelial cells, and then use SPI-2 to form salmonella-containing vacuole (SCV) to protect bacteria from attack by immune cells. To verify the drug delivery mechanism, some researchers used GFP technology to identify that the carried drug will be released into the SCV first, and then released into the cytoplasm. This lysis process is controlled by the PsseJ-LysE circuit. When the bacteria enter the SCV, the PsseJ promoter will be activated to cause the bacteria to lyse, thereby releasing the internal drugs [35].

3. Clinical application of Salmonella Typhimurium

As our understanding of Salmonella Typhimurium deepens, numerous studies have confirmed the feasibility and effectiveness of various strains of Salmonella, including VNP20009 and ΔppGpp.

3.1. VNP20009

The first is VNP20009, which is a strain that has been attenuated. By destroying the msbB gene in the bacteria, the amount of TNF-α induced by the bacteria is reduced, thereby significantly reducing toxicity while ensuring basic functions and improving safety of use [36]. At the same time, removal of the purl gene enhanced the ability of bacteria to colonize and grow inside tumors [37]. However, the bacteria still have limitations in clinical application. VNP20009 did not show good efficacy in human trials: the strain had weak colonization ability and could not eliminate tumors, and patients who received large doses also experienced side effects such as inflammation [38].

3.2. ΔppGpp

Compared with VNP20009, ΔppGpp showed good targeting ability and reduced the side effects on the host, especially toxicity. Research data showed that in experiments with mouse colon cancer cell line MC38, the tumor eradication rate of ΔppGpp reached 16.7%, and the host showed a longer life cycle compared to treatment with VNP20009 [39]. Even though this strain showed good therapeutic effects and potential, it still has shortcomings: for example, it showed low anti-tumor effects like

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VNP20009, so compared with oncolytic bacteria, this strain has greater potential as a delivery carrier [39].

4. Conclusion

Overall, Salmonella Typhimurium demonstrates strong potential in a wide range of tumor treatments. Its exceptional targeting properties, broad tumor specificity, chemotaxis, selective growth, and robust colonization capabilities make it suitable for use as an oncolytic bacterium and delivery vehicle for tumor therapy. Multiple currently known mechanisms of invasion and tumor elimination demonstrate promising results, demonstrating the strong potential of Salmonella Typhimurium in tumor therapy, making it a key area of future research in oncolytic bacterial therapy and, ultimately, tumor treatment.

However, this therapy still has shortcomings. When the bacteria act as oncolytic bacteria, they act as tumor suppressors in the host body. When they play an anti-tumor role, T cells are dysfunctional, which further leads to the malfunction of the immune system [40]. When Salmonella typhimurium is used as a transport carrier, some researchers pointed out that although a new CAPPSID system can enable bacteria to carry viruses into the core of the tumor and further treat surrounding and distant tumor cells, how to achieve targeted replication and solve systemic neutralization still requires a lot of research from scientists [41].

At the same time, due to the limited therapeutic effect of oncolytic bacteria, the combination with traditional tumor treatment methods is important research at present. Taking radiotherapy as an example, its effect is directly related to the concentration of oxygen. Hypoxic cells are more resistant to radiotherapy, and because of the hypoxic tumor microenvironment around the tumor, radiotherapy is not very effective. Combining with Salmonella typhimurium can form a complementary effect, allowing the bacteria to treat the hypoxic part, thereby achieving a more efficient and comprehensive therapeutic effect [42].

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