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A recently developed approach in tumor therapy using *Salmonella*

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Abstract

There are three main approaches in cancer treatment: surgery, chemotherapy, and radiotherapy. Recently, the use of bioengineered bacteria as therapeutic agents has been shown to have some valuable properties in the treatment of cancer, which do not exist in conventional approaches. Bacteria in particular can target tumors, and they can preferentially proliferate and accumulate within tumors and inhibit the growth of cancer cells by inducing cytotoxicity. Thus, bacteria can be easily detected in tumor sites. Moreover, bacteria-derived factors exert an immunostimulatory effect. Over the past decade, *Salmonella*, *Clostridium*, and other bacterial genera have been shown to inhibit tumor growth and promote the survival rate in animal models. Clinical trials for cancer treatment with bacteria have shown improved results by combination with other therapeutic methods such as chemotherapy or radioactive agents. This review is an effort to introduce the use of healthy bacteria in tumor therapy. We specifically focus on *Salmonella*, which has been extensively used in tumor therapy. Therefore, in this review study, we discuss the merits, mechanisms, and attenuated strains of a combination therapy compared to other therapeutic approaches in *Salmonella*-mediated cancer therapy.

Key words: cancer therapy, combination therapy, *Salmonella*, tumor targeting

Abbreviations

AB	– antibodies
TAR	– aAspartate receptors
Baf A1	– bafilomycin A1
BCR	– B-cell receptor
BCRP	– breast cancer resistance protein
Dcs	– dendritic cells
IgM	– immunoglobulin M
IFN-γ	– interferon-gamma
IL-1β	– interlukin-1β
LPS	– lipopolysaccharide
LTA	– lipoteichoic acid
MHC-II	– major histocompatibility class II
MAPK	– mitogen-activated protein kinase
MDR1	– multidrug resistance mutation 1
MRP1	– multidrug resistance protein 1
NK	– natural killer
NF-κB	– nuclear factor-κb
Nod	– nucleotide oligomerization domain
NLRs	– nod-like receptors
PAMPs	– pathogen-associated molecular patterns
PRRs	– pattern recognition receptors
TRG	– ribose/galactose receptor
SCV	– *Salmonella* -containing vacuole
Th1	– T helper 1
TLRs	– toll-like receptors
TNF-α	– tumor necrosis factor-alpha
TNFSF14	– tumor necrosis factor superfamily member 14
T3SS	– type III secretion system

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Introduction

Cancer has been one of the leading causes of morbidity and mortality for decades (Kural-Seyahi et al., 2003; Resnick et al., 2012). Cancer therapies are limited to surgical removal, radiation, chemotherapy, and immunotherapy (Perry et al., 1987). These methods encounter problems such as drug resistance, pharmacological or toxicity concerns in a majority of cases, and a risk of damage to healthy tissues or incomplete eradication of cancer (Mukherjee et al., 2016). Unfortunately, the nonspecific targeting of anticancer agents leads to many side effects, and the poor drug delivery fails to produce the desired outcome in several cases (Brigger et al., 2012, Bahrami et al., 2017). The major challenge in cancer therapy is to differentiate between cancerous and normal body cells. To address this problem, researchers have devoted considerable efforts to engineer drugs to provide more efficient treatments, which can potentially detect cancer cells and prevent their growth by inhibiting proliferation (Hare et al., 2017). Chemotherapy, radiotherapy, and surgery are currently used in cancer treatment, despite the fact that they have several disadvantages. For example, cancer patients do not usually respond to the single-agent chemotherapy regimen and are therefore switched to multi-agent chemotherapy regimens, which in turn increase both side effects and toxicity (Bower et al., 1997, Lurain and Nejad, 2005). In addition, drug resistance (King and Jarvis, 2007), damage to healthy cells (Lushbaugh and Casarett, 1976), or hypopituitarism (Melmed et al., 2009) occur in conventional cancer therapy. On the other hand, a nanotechnology approach seems to be extremely valuable in cancer therapy and offers considerable advantages such as effective prevention tools, more reliable diagnostics, considerable imaging techniques, efficient cancer cell targeting, and improvement in the quality of life throughout cancer care period (Gharbavi et al., 2018; Gharbavi et al., 2019; Gharbavi et al., 2020).

The pathophysiological changes in diseased tissues may improve vascular permeability along with impaired lymphatic drainage in tumors that allows an enhanced permeability and retention effect of nanoparticles in tumors (Maeda al., 2000; Sahoo et al., 2007; Parveen et al., 2007). One of the most critical obstacles of nanoparticle use in cancer treatment is variations in particle size used in the nanoscale materials, which can induce extensively diverse changes in their properties, including toxicity (Xia et al., 2006; Boverhof and David, 2010).

In general, three different areas can be distinguished in tumor sites: area with epithelial tumor cells, hypoxic area, and necrotic area, as shown in Figure 1. Radiotherapy uses ionizing radiation to irradiate tumor cells, which causes DNA damage in the cells and controls their proliferation. Ionizing radiation causes the formation of free radicals in cells, which subsequently results in cancer cell death (Patriciu et al., 2007). Ionizing radiation does not precisely discriminate between tumor and healthy cells; hence, radiotoxicity to healthy tissues is considered as one of the critical limiting factors in cancer treatment by radiotherapy (Hainfeld et al., 2008, Paulides et al., 2013). Additionally, many clinical studies indicate that due to poor vascularization, the hypoxic and necrotic tumor regions are more resistant to ionizing radiation, which is considered as another major drawback of tumor therapy (Yan et al., 2020).

Chemotherapy is one of the most commonly used strategies in cancer therapy, but some of its drawbacks often limit its efficacy (Jahandideh et al., 2017). Two main processes limit the efficiency of chemotherapy: first, the expression of genes involved in drug resistance, such as MDR1 (multidrug resistance mutation 1), MRP1 (multidrug resistance protein 1), and BCRP (breast cancer resistance protein) (Efferth et al., 2003; Wu et al., 2014); second, hypoxic tumor regions are resistant to chemotherapy because of their distance from the vasculature, which leads to poor drug delivery and eventually results in anticancer drug resistance.

Because of these drawbacks, radio-chemotherapy is not efficient in cancer treatment. Cancer therapy using bacteria is a promising method in addressing such pressing problems. It has already been reported 200 years ago that cancer patients were in remission after being infected with bacteria (Morrissey et al., 2010). Between 1890 and 1930, William B. Coley, an American physician, conducted a set of experiments to treat cancer patients by using bacteria such as *Streptococcus pyogenes*, *Serratia marcescens*, and bacterial products, termed "Coley's vaccine" or "Coley's toxin." Coley believed that "the toxin" from dead cells of *Streptococcus pyogenes* and *Serratia marcescens* were capable of stimulating immune system response to fight cancer. In 1962, Coley's toxin for cancer treatment was banned, but pre-

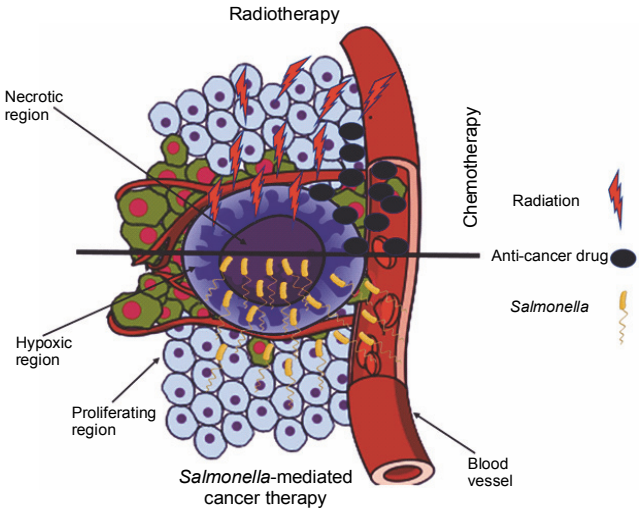

Fig. 1. Schematic representation of the mechanisms underlying the therapeutic effects of different cancer therapies (chemotherapy, radiotherapy, and *Salmonella*-mediated cancer therapy)

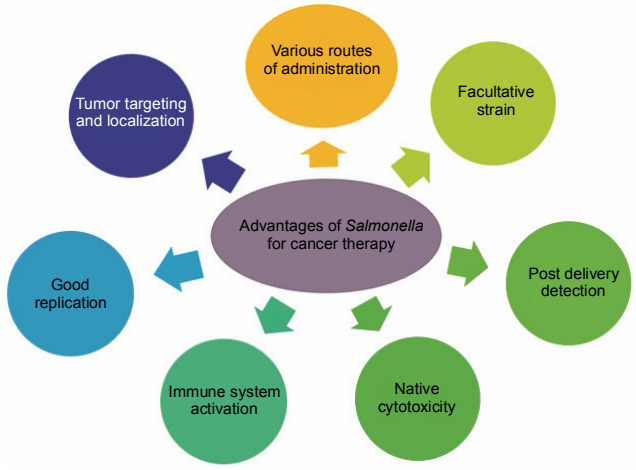

Fig. 2. Advantages of *Salmonella* as an antitumor agent

sently, bacteriotherapy is considered a novel therapy (Goodman and Walsh, 2001; Bandura, 2017). In this procedure, bacteria are used as anticancer agents with many advantages prominently in terms of their genes that can easily be manipulated. Additionally, bacteria can be engineered to overcome the drawbacks of conventional cancer therapy (radiation and chemotherapy) (Minton, 2003; Felgner et al., 2016; Hill et al., 2016; Nguyen and Min, 2017).

Compared with the previously applied cancer therapy methods, bacteriotherapy is one of the recent methods that has several advantages, including the oral administration route (Levine et al., 1987; Clairmont et al., 2000), high proliferative capacity without adopting external agents (Pawelek et al., 1997), extendibility of the therapeutic effect, sufficient tissue penetration, and the flexibility of delivery along with facilitation of host's immune response (Juris et al., 2002).

This method can also be combined with other therapeutic methods such as chemotherapeutic drugs (Mercado-Lubo et al., 2016; Yang et al., 2018), radiotherapy, and noninvasive monitoring techniques (Jiang et al., 2010; Barker et al., 2015). Neil S. Forbes, in a review article, stated that bacteria are tiny programmable "robot factories," which can be directed to tumor cells (Forbes, 2010). The accumulation of bacteria in tumor cells is approximately 1000-fold higher than that in healthy cells, and these agents induce severe toxicity in cancer cells (Maeda, 2012).

Several types of bacteria (anaerobes and facultative anaerobes) have been used in animal models or human clinical trials to treat tumor cells by destruction (Zhao et al., 2005; Arrach et al., 2008; Arrach et al., 2010; Taniguchi et al., 2010; Leschner et al., 2012). General tumor treatment strategies, including chemotherapy, radiotherapy, and *Salmonella* therapy, are schematically shown in Figure 1. Facultative anaerobic bacteria such as *Salmonella, Escherichia, Shigella, Vibrio*, and *Listeria* are used owing to their ability to target and colonize vasculature and hypoxic tumor regions (Ryan et al., 2006).

Salmonella as an antitumor agent

Several bacterial species such as *Salmonella, Clostridium, Escherichia*, and *Bifidobacterium* have been used as anticancer agents (Pawelek et al., 2003; Ryan et al., 2006; Theys et al., 2006; Van Mellaert et al., 2006; Chen et al., 2009; Kimura et al., 2010; Leschner and Weiss, 2010).

Evidence shows that *Salmonella* and *Clostridium* have been used successfully for treatment purposes (Dang et al., 2001; Cheong et al., 2006; McCarthy, 2006; Wei et al., 2007).

Importantly, although the aforementioned pathogens have been directly used in animal models, live genetically modified organisms have been conventionally used in human trials (Toso et al., 2002; Heimann and Rosenberg, 2003). Given that *Bifidobacterium*, *Clostridium*, and *Salmonella* are obligate anaerobes and colonize the areas devoid of oxygen, they must be injected into solid tumors in a spore form to preferentially target and

replicate in the hypoxic/necrotic regions (Xu et al., 2009; Liu et al., 2014).

Given that *Salmonella* has several potential advantages (as presented in Fig. 2) in therapeutic tumor targeting, genetic modifications have been introduced to improve its tumor-targeting or tumor therapy. As such, some *Salmonella* strains, including *YB1*, *VNP20009,* and *SL7207*, have been genetically modified to preferentially target and replicate in the hypoxic and necrotic regions of tumors and therefore inhibit tumor growth (Heimann and Rosenberg, 2003; Yu et al., 2012).

Some of the main characteristics of *Salmonella* are indicated below:

- *Salmonella* is a facultative anaerobic strain with the potential to grow regardless of oxygen presence and can colonize vasculature and hypoxic tumor regions (Nguyen et al., 2010; Guo et al., 2011; Li et al., 2012; Hong et al., 2013; Jeong et al., 2014).
- Several routes of administration have been reported for *Salmonella* delivery as an anticancer agent, such as intravenous (IV), intraperitoneal (IP), intratumoral, and oral (Urashima et al., 2000; Zhang et al., 2007; Yang et al., 2008; Ganai et al., 2009).
- Tumor-targeting ability of *Salmonella* has enabled it to play a significant therapeutic role in solid tumor treatment such as therapies related to colon (Nguyen et al., 2010; Guo et al., 2011; Hong et al., 2013; Jeong et al., 2014), fibrosarcoma (Roider et al., 2011), bladder (Iyer et al., 2016; Koshiol et al., 2016; Vagholkar et al., 2016), liver (Nguyen et al., 2010; Hartono et al., 2012; Koshiol et al., 2016), pancreas (Felgner et al., 2016), lung (Lee et al., 2005), melanoma (Lee et al., 2005; Chen et al., 2012; Kaimala et al., 2014), breast (Ganai et al., 2009), and prostate cancers (Chen et al., 2012).
- *Salmonella* and its derivatives prefer solid tumors to normal tissue; they are located or they can be localized specifically at tumor sites, which helps to reduce toxic side effects of systemic delivery (Kasinskas and Forbes, 2006, 2007).
- Unlike other bacteria, *Salmonella* has a high rate of replication at tumor sites, thus requiring a low dose to effectively target tumors (Lee et al., 2005; Roider et al., 2011).
- *Salmonella* has the potential for metabolic activation and is capable of continuous production of cytolysin A to attack tumors, which can lead to improvement in delivery efficiency (Chen et al., 2012; Kaimala et al., 2014).
- Immune system activation: *Salmonella* bound to nucleotide oligomerization domain (Nod)-like receptors (NLRs) induces the activation of caspase-1 and subsequent secretion of proinflammatory cytokines such as IL-1β, IL-18, TNF-α, and IFN-γ as well as pyroptosis (inflammatory cell death).
- This leads to improvement of the immunosuppressive conditions and helps to maintain an innate adaptive response (de Zoete and Flavell, 2013; Perez-Lopez et al., 2013).
- Self-relied cytotoxicity: the natural toxicity of bacteria capable of producing virulence factors leads to the sensitization of the immune system along with neutrophil infiltration and antitumor immune responses (Sznol et al., 2000; Hoffman and Zhao, 2006; Lee et al., 2008).
- Post-delivery functionality: four different strategies are used to identify bacteria in tumors, including bioluminescence, fluorescence, magnetic resonance, and positron emission imaging (Urashima et al., 2000; Soghomonyan et al., 2005; Hoffman and Zhao, 2006; Steele-Mortimer, 2008).

Salmonella-mediated tumor therapy

Distribution of Salmonella in host cells

Salmonella embodies a bacterial system that invades nonphagocytic cells by modulation. In cancer therapy, *Salmonella* can potentially enter the cells through both Trigger and Zipper processes (Velge et al., 2012). In the Zipper mechanism, the Rck protein is expressed on *Salmonella's* outer cell membrane and interacts with its receptor on the host cell membrane, which leads to phosphorylation of at least one tyrosine kinase. The activation of class I PI 3-kinase leads to the activation of protein kinase B (aka Akt). The activation of the guanosine triphosphatase protein (GTPase) Rac1, the downstream molecule of the Akt/PI 3-kinase activation, and the GTPase Cdc42 trigger actin polymerization *via* the Arp2/3 complex (Mijouin et al. 2012).

The mechanism controlling Cdc42 during the Rck-induced signaling pathway is still unknown (Mijouin et al., 2012; Velge et al., 2012; Wiedemann et al., 2012). However, several studies have demonstrated that *Salmonella* invades host cells only *via* the Trigger entry mechanism (Stender et al., 2000; Steele Mortimer, 2011; Cossart and Helenius, 2014).

In the Trigger mechanism, *Salmonella* bacterial effectors, including SipA, SipC, SopB, SopE, SopE2, which are induced by type III secretion system (T3SS), are directly injected into host cells. While SipA and SipC directly bind to actin, SopE, SopE2, and SopB activate the Rho GTPases, leading to host cell cytoskeleton remodeling via cellular proteins, such as WASP/Scar/WAVE/WASH, which activate the Arp2/3 complex. Thus, the formation of membrane ruffles and internalization is induced by the recruitment of the exocyst complex and is manipulated by SipC and SopE via the Ras-related protein RalA (Chen et al., 1996; Schlumberger and Hardt, 2006). Following the entry into the host cells, *Sal-*

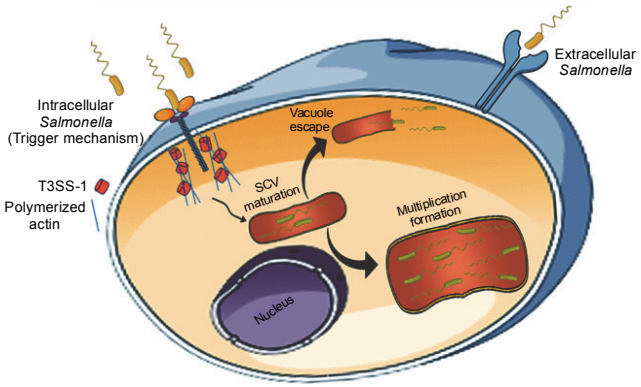

Fig. 3. Intracellular *Salmonella* invades nonphagocytic host cells through the Trigger mechanism

monella replicates within a membrane-bound compartment termed *Salmonella*-containing vacuole (SCV).

Previous studies have shown that SifA, SseF, and SseG are involved in the formation of *Salmonella*-induced filaments (Sifs) that are required for maintaining the SCV (Salcedo and Holden, 2003; Boucrot et al., 2005; Abrahams and Hensel, 2006). After formation, the SCV proceeds to maturation and mediates the virulent factors for secretion into the cytoplasm. This process also facilitates the delivery of nutrients to SCV and leads to *Salmonella* replication and SCV-lysosome fusion (the autophagy response), wherein the bacterial cells are likely to disappear. As shown in Figure 3, a segment of bacteria can be released from the SCV that efficiently target the cytosol of epithelial cells.

Targeting the components of cancer cells

The main vague point about *Salmonella* is specifically the way it migrates to the tumor region. Several studies have described the interaction of *Salmonella* and tumor aggregates by using 3D cell culture chip (Barrila et al., 2010; Ravi et al., 2017). As previously reported, *Salmonella* preferentially accumulates in internal tumor region boundaries and can directly destroy tumor cells (Rosenberg et al., 2002; Yu et al., 2012).

Flagella are surface appendages of *Salmonella* and play a critical role in the interaction of *Salmonella* with host cells through multiple functions such as motility and chemotaxis, leading to the attraction of *Salmonella* in the tumor microenvironment structure by increasing the likelihood of contact (Jones et al., 1992; Dang et al., 2001). For example, aspartate receptors (TAR) on the *Salmonella* surface detect the aspartate secreted by the existing cancer cells through chemotaxis transmitted to tumor cells. Ribose/galactose receptor (TRG) also supports transmitting *Salmonella* to necrotic tissue (Kasinskas and Forbes, 2006; Kasinskas and Forbes, 2007).

Several interacting mechanisms are used to control tumor accumulation; as *Salmonella* surrounds the chaotic vasculature of tumors (Forbes et al., 2003), it allows for a tremendous influx of blood into tumors and promotes inflammation (Leschner et al., 2009), transmits chemotaxis towards tumors compounds, (Kasinskas and Forbes, 2006, 2007) and finally, enables preferential antitumor replication in tumor-specific microenvironment scales (Nuyts et al., 2001; Forbes et al., 2003; Kasinskas and Forbes, 2006) as well as clearance protection initiated by the immune system (Sznol et al., 2000).

These mechanisms enable *Salmonella* to accumulate in tumor sites at ratios higher than 1000/1 compared to other organs such as the liver and spleen. Bacterial growth in tumor tissues causes nutrient depletion in cancer cells and induces antitumor immune response, leading to tumor cell death (Sznol et al., 2000).

Salmonella and the immune system

Interaction of Salmonella with macrophages

Tumors limit the maturation and infiltration of the immune cells, which results in immunosuppression and exclusion from the immune system tracking (Sznol et al., 2000). As mentioned before, *Salmonella* can survive and proliferate intracellularly *via* SCV, especially in macrophages.

Microbial products, termed pathogen-associated molecular patterns (PAMPs), include lipopolysaccharides, flagella, and peptidoglycans, which are strong agonists for pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), especially TLR-4 and TLR-5 (Sfondrini et al., 2006; Lee et al., 2008), scavenger receptors, mannose receptors, and NOD-like receptors (NLRs).

Macrophages have the potential of recognizing microbial products via PRRs and transducing signals through NF-κB or MAPK, which consequently leads to a pro-inflammatory effect, and cytokines through consistent and adaptive immune responses. In addition, *Salmonella* is capable of inducing continuous signals with effectors secreted by T3SS (Bruno et al., 2009). One of the most common questions that can be asked is how, despite the

presence of a host immune system, does *Salmonella* evade the tumor cells? Indeed, *Salmonella* can utilize several strategies.

One of the strategies used is the prevention of dendritic cells (DCs) from activating antigen-specific T cells. This may be achieved in two ways: Firstly, preventing SCV acidification with Bafilomycin A1 (Baf A1) causes a significant decrease in the frequency of persisters (Helaine et al., 2014). Secondly, *Salmonella* is capable of inducing macrophage death in a caspase 1-dependent manner. *Salmonella*-mediated NLRC4 and NLRP3 can activate caspase 1, which then initiates a proinflammatory cell death termed pyroptosis, leading to the modulation of the macrophage function (Mazurkiewicz et al., 2008; Figueira and Holden, 2012). *Salmonella* also has the capacity to escape the immune system via the secretion of sipB protein and can induce dendritic cell death in a caspase 1-dependent manner, thus impairing the antigen presenting process and the adaptive immunity (Halici et al., 2008). Furthermore, *Salmonella* can induce ubiquitination of major histocompatibility class II complex (MHC-II) by T3SS effectors such as ssaV and can cause subsequent removal of the mature MHC-II-peptide complex from the cell surface, which then leads to the modulation of DC function (Halici et al., 2008).

Salmonella Pathogenicity Island 1 (SPI-1), which promotes the phagocytosis of bacteria in nonphagocytic cells, can suppress this process in DCs in a phosphatidylinositol 3-kinase (PI3K)-dependent manner (Bueno et al., 2010; Oppong et al., 2013).

Interaction of Salmonella with B cells

Host B cells are necessary for the antitumor activity to help *Salmonella* by controlling their distribution around the tumor region. In this sense, the B-cell receptor (BCR) is composed of immunoglobulin molecules that form a type 1 transmembrane receptor protein usually located on the outer surface of a lymphocyte type known as B cells (Fahy et al., 2004; Westphal et al., 2008; Lee et al., 2011).

Bacteria are recognized by the BCR and induce *Salmonella* internalization followed by B cell differentiation (variation) and secretion of anti-*Salmonella* antibodies (AB) by *Salmonella*-specific B cells (Anuforom, 2015).

Antibodies produced by B cells lead not only to a slightly lower quantity of bacteria in the tumor sites but also to a decrease in inflammation and cytokine production in the intact organs after systemic *Salmonella* treatment (Maaser et al., 2004). Furthermore, B cells regulate the proliferation of *Salmonella*-specific CD4+ T cells, which enhance *Salmonella*-specific production of AB (Alaniz et al., 2006).

Therefore, after the administration of *Salmonella* , their exit from tumor cells is very slow as compared to that from other organs such as liver and spleen, which are under constant surveillance by the host immune system. B cells specify the dissemination of *Salmonella* in tumor organs and prevent their spread to the healthy organs. Anti-*Salmonella* IgM antibodies are present in tumor microenvironment (Barr et al., 2009).

Interaction of Salmonella with T cells

Salmonella, which has been shown to cause T-cell activation, induces response of both anti-*Salmonella*-specific and tumor antigen-specific and expression of Connexin 43 as a gap junction protein induced by lipopolysaccharide (LPS), lipoteichoic acid (LTA), and flagellin of bacteria (Maybeno et al., 2012).

This protein also creates junctions through melanoma cancer cells to immune dendritic cells. As a result, the dendritic cells use the protein transferred from the tumor cells to T cells in order to stimulate the T-cell response, subsequently leading to target and cleanse the tumor cells at the affected site. Consequently, *Salmonella* inhibits tumor growth by utilizing T cells.

On the other hand, the cross-presentation of tumor antigen increases the infiltration of CD8+ T cells in *Salmonella*-treated tumors and enhances the immune system response (Avogadri et al., 2005). Such responses, while enhancing the antitumor efficacy of *Salmonella* expressing cytokines, also increase immunity and prevent tumor growth (Fig. 4) (Sorenson et al., 2008).

Interaction of Salmonella with cytokines

Salmonella infection usually induces both antigen-recognizing T and B cells to mediate immunity that leads to the inhibition of tumor growth and metastasis. In such situations, the levels of circulating and hepatic natural killer (NK) cells, hepatic CD4+, and CD8+ T lymphocytes, splenic neutrophils, and macrophages are increased (Mittrücker and Kaufmann, 2000; Feltis et al., 2002). The expression of cytokines such as TNF-α, IFN-γ, IL-1, IL-6, IL-12, and IL-18 is subsequently eleva-

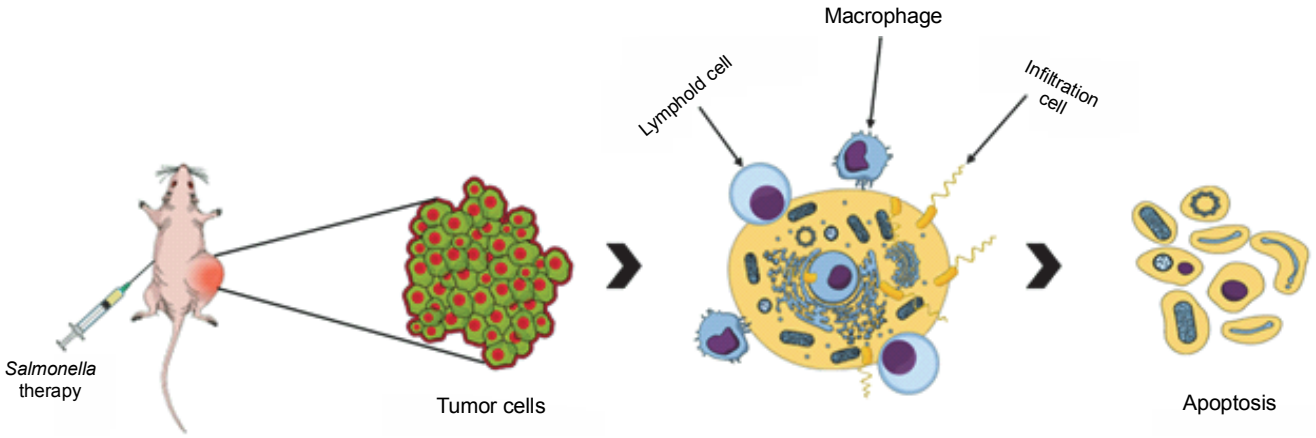

Fig. 4. *Salmonella*-mediated cell death pathway in tumor cells

ted, modulating the immune response and resulting in the inhibition of tumor growth (Weiss et al., 2007).

In addition, *Salmonella* can be engineered to deliver cytokines such as IL-2, IL-18, CCL21, and LIGHT, which exert antitumor effects (Forbes, 2010). Cytokines stimulate the immune cells to inhibit tumor growth by utilizing multiple mechanisms such as the upregulation, proliferation, and migration of immune cells (Marcus et al., 2014).

IL-2 is a signaling molecule that activates the proliferation of B cells and T cells and the cytolytic function of cleansing, which leads to a reduction in angiogenesis, increases necrosis within tumor tissues, and finally, prevents tumor formation (Feltis et al., 2002; Barbé et al., 2005).

IL-18 is produced mainly by activated monocytes, macrophages, and DCs. It has several immunoregulatory functions such as generating IFN-γ from NK and T helper 1 (Th1) cells, thereby enhancing the cytolytic activity of T cells by generating cytotoxicity of NK cells and upregulating MHC class I antigen expression that promotes the differentiation of CD4+ helper T cells into Th1 cells and suppresses angiogenesis by inhibiting the proliferation of endothelial cells. Thus, NK cells, macrophages, and CD8+ T cells mediate the antitumor effects (Gracie et al., 2003; Raupach et al., 2006; Loeffler et al., 2008).

The activities of CCL21 suggest that the effective control in terms of the dynamics of lymphocytes, DCs, and NK cells can possibly impede tumor-induced immunosuppression, thereby optimizing effective immune responses and subsequently resulting in tumor suppression (Loeffler et al., 2009). In addition, CCL21 appears to be involved in antitumor functionality through the binding of the chemokine receptor CXCR3 (Maekawa et al., 2008).

LIGHT, also known as tumor necrosis factor superfamily member 14 (TNFSF14), is a cytokine from the TNF family that is homologous to lymphotoxin that stimulates the proliferation of T cells, induces DC growth and triggers tumor cell apoptosis, thereby leading to tumor suppression (Glenney and Wiens, 2007; Loeffler et al., 2007). IFN-γ (type II interferon) is an important activator of macrophages and stimulates the expression of MHC I and MHC II molecules. It exerts antitumor effects through two mechanisms: preventing tumor cell growth and indirectly stimulating the adaptive immune system response (Böhm et al., 1998). In addition, IFN-γ produces antiangiogenic chemokines, including protein-10 and monokines, through the development of IFN-γ-dependent CD4+ T cells, which enhance the growth of angiogenesis-dependent tumor (Qin and Blankenstein, 2000).

Attenuated *Salmonella* strain as an antitumor agent

To treat cancer, *Salmonella* cells have been extensively studied as antitumor agents. Decades ago, many antitumor features of *Salmonella* were demonstrated (Chorobik et al., 2013), and several attenuated *Salmonella* strains were developed for tumor-targeting studies as presented in Table 1.

Live genetically modified *Salmonella typhimurium* (*VNP20009*)

VNP20009 has been derived from *Salmonella typhimurium* ATCC 14028 that contains most of the characteristics of *Salmonella* (Broadway et al., 2017) and has

Table 1. Attenuated *Salmonella* strains for targeted cancer therapy

Strains	Genotype	Description	References
VNP20009	Δ *msb*, Δ *purI*	purine auxotrophic mutation and modified lipid A	Toso, Gill et al., 2002; Heimann, Rosenberg, 2003; Nemunaitis, Cunningham et al., 2003; Thamm, Kurzman et al., 2005; Wang, Chen et al., 2013; Coutermarsh-Ott, Broadway et al., 2017
A1-R	leucine and arginine auxotrophs	leucine/arginine-dependent	Zhao, Yang et al., 2005; Zhao, Yang et al., 2006; Zhao, Geller et al. 2007; Momiyama, Zhao et al., 2012; Yano, Zhang et al., 2014
CRC2631	wild-type	decreasing the amount of available wild-type lipopolysaccharide (LPS)	Kazmierczak, Gentry et al. 2016
Δ *ppGpp*	ΔrelA, ΔspoT	defective in ppGpp synthesis; noninvasive to mammalian cells	Nguyen, Kim et al., 2010; Jiang, Park et al., 2013; Kim, Phan et al., 2015
SL3261	ΔaroA	blocked in aromatic synthesis	Lin, Kao et al., 2012; Ye, Li et al., 2013
SL1344	wild-type	virulent laboratory strain (hisG mutant of wild-type 4/74)	Roider, Jellbauer et al., 2011
SA186	ΔznuABC	deletion of the whole znuABC operon, which encodes the high-affinity zinc transporter	Chirullo, Ammendola et al., 2015
NCTC12023	wild-type	isogenic to ATCC 14028	Xiong, Husseiny et al., 2010
SL7207	ΔaroA	aromatic amino acid synthesis depends on *p*-aminobenzoate and 2,3-dihydroxybenzoate	Berger, Soldati et al., 2013; Jarosz, Jazowiecka-Rakus et al., 2013; Li, Yin et al., 2013; Shi, Yu et al., 2016
LH340	ΔphoP, ΔphoQ	cytoplasmic transcriptional regulator (PhoP) and membrane-associated sensor kinase (PhoQ)	Zhang, Gao et al., 2007; Jia, Li et al., 2012; Jarosz, Jazowiecka-Rakus et al., 2013
BRD509	ΔaroA, ΔaroD	aromatic compound-dependent	Al-Ramadi, Fernandez-Cabezudo et al., 2009; Yoon, Choi et al., 2014
S634	ΔaroA	aroA mutation and modified lipid A	Lee, Wu et al. 2004
LVR01	ΔaroC	auxotrophic for certain aromatic compounds	Grille, Moreno et al. 2014
YB1	ΔaroA	engineered to express the essential asd gene under the control of a hypoxia-inducible promoter	Yu, Shi et al. 2015
RE88	ΔaroA, Δdam	defective in DNA adenine methylase; fails to secrete the protein; noninvasive to mammalian cells	Xiang, Mizutani et al., 2005; Lee, Mizutani et al., 2006; Qian, Yan et al. 2011
SB824	ΔaroA, ΔsptP	reduction of virulent gene expression	Roider, Jellbauer et al. 2011
MvP728	ΔpurD, ΔhtrA	adenine-dependent; unable to survive in macrophages	Manuel, Blache et al., 2011; Xu, Hegazy et al., 2014

been intensively investigated for its use in tumor therapy (Felgner et al., 2016). *VNP20009* is a genetically modified strain of *S. typhimurium* that has several advantages such as an excellent safety profile, including *msbB* (lipid A biosynthesis myristoyl transferase) gene deletion, antibiotic susceptibility, and *purI* gene deletion to improve tumor-specific colonization (Clairmont et al., 2000).

VNP20009 growth depends on the level of purine, and it prefers to bind in purine-rich regions, can easily proliferate in these regions, and can be used for tumor tissue colonization. *VNP20009* has been proven to be a promising tumor-target vector that can preferentially accumulate and replicate in a tumor tissue for tumor therapy (Thamm et al., 2005; Ganai et al., 2009; Loeffler et al., 2009; Wang et al., 2013).

Conclusions

Several researchers have found that *Salmonella*-mediated antitumor therapy is a promising therapeutic method that could potentially promote significant tumor suppression and thus prolong survival. *Salmonella*-mediated antitumor therapy has some advantages over other therapies, such as bacterial proliferation, self-targeting, and easy genetic manipulation. In addition, *Salmonella* has multifaceted interplay between the upregulation of immunomodulatory molecules and the downregulation of aggressive phenotype-related proteins to counteract various protumor cellular processes. These characteristics make *Salmonella* an ideal candidate for anticancer therapy.

Moreover, *Salmonella* can be used to improve the survival of cancer patients or can be successfully used to improve the outcomes of the existing treatment strategies.

Most of the problems arising from the use of *Salmonella,* such as its potential toxicity and host immune response against the bacterial agent itself, have been addressed previously or at least have been significantly lessened. Combination therapies with *Salmonella*-mediated therapy and other tumor therapies enhance the curative effects in a synergistic manner. This strategy is a hot topic for future research, but further improvement of the treatment through bioengineering and/or combinatorial approaches may significantly enhance its effectiveness in combating high-grade cancer malignancies.

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