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# Infection by *Salmonella enterica* Promotes or Demotes Tumor Development

Marco A. Hernández-Luna, Paola Muñóz-López,
Carlos A. Aguilar-González and Rosendo Luria-Pérez

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## Abstract

Cancer is a disease that claims the lives of millions of people every year around the world. To date, multiple risk factors that may contribute to its development have been described. In recent years, a factor that has been associated to cancer development is the presence of bacterial infections that could contribute to its occurrence not only by favoring the inflammatory process, but also through the release of proteins that trigger tumorigenesis. One of the bacterial species that have recently generated interest due to its possible role in cancer development is *Salmonella enterica*. Nevertheless, for more than a decade, attenuated strains of *Salmonella enterica* have been proposed as a treatment for different neoplasms due to its bacterium tropism for the tumor microenvironment, its oncolytic activity and its ability to activate the innate and adaptive immune responses of the host. These two facets of *Salmonella enterica* are addressed in detail in this chapter, allowing us to understand its possible role in cancer development and its well-documented antitumor activity.

**Keywords:** *Salmonella*, cancer, live-attenuated bacterial vector, tumor selectivity, immunotherapy

## 1. Introduction

In recent years, cancer has become a worldwide public health problem, and millions of people die of this disease every year in the world [1]. Despite the efforts made to understand the mechanisms involved in carcinogenesis to better develop new therapeutic strategies, the cure

for cancer remains unsolved. Among the causes that have been associated with cancer origin and development, it is found physical and chemical agents as well as biological processes such as inflammation [2], this inflammation has been associated with the presence of infectious biologic agents; these may be viral like human papilloma virus associated to cervical cancer [3], or bacterial like *Helicobacter pylori* in the development of gastric cancer [4], or *Escherichia coli* (*E. coli*) in the development of colon cancer [5]. In this context, *Salmonella enterica* has also been associated with the development of neoplasms that affecting the gastrointestinal tract such as gallbladder cancer [6] and colon cancer [7]. On the other hand, since more than a decade, attenuated strains of *Salmonella enterica* have been evaluated as adjuvants in the treatment of different neoplasms [8], including colon cancer [9] due to its great affinity for tumor tissue [10, 11], its oncolytic activity and the induction of the innate and adaptive immune response against the tumor [12].

The role of *Salmonella enterica* in cancer is a provocative issue to debate, for that reason, in this chapter, we document these two facets of *Salmonella enterica* as a promoter of the development of gastrointestinal tract neoplasms and as a bacterium with antitumor activity and with potential use in cancer treatment.

## 2. Infection by *Salmonella enterica* and colon cancer

*Salmonella enterica* genus comprises a wide range of bacteria, including species such as *Salmonella typhi* and *Salmonella paratyphi*, for which natural host is human and *Salmonella typhimurium*, which has mouse as its natural host [13]. The fact that *S. typhimurium* causes the same type of infection in the mouse than in the human has allowed us to understand in great detail the pathogenicity and immunogenicity of these bacteria [14]. Nevertheless, the infection by *Salmonella enterica* has recently begun to be associated with the development of neoplasia of the gastrointestinal tract such as colon cancer [7] and gallbladder cancer [6].

The role of *Salmonella enterica* infection in cancer development is currently under investigation. *Salmonella enterica* capacity to modulate host's inflammatory response [15], contributing to neoplasm development has been documented, showing that chronic inflammation induced by bacterial infection causes DNA damage and increases cell proliferation and migration, factors associated with cancer development [16]. Likewise, it has been suggested that at least two proteins of *Salmonella enterica* could trigger the development of colon cancer; the first one, the typhoid toxin, a cyclomoduline similar to *E. coli* CDT protein [17]; which increases cell survival and is capable of favoring dysbiosis [18], a process known as a risk factor for developing inflammatory bowel disease and colon cancer [19]; the second protein of *Salmonella enterica* is the effector protein AvrA, secreted via the type 3 secretion system [20], and that has been detected in stool samples obtained from patients with colon cancer [21].

AvrA is a multifunctional protein. On the one hand, AvrA is responsible for decreasing the inflammatory response by inhibiting signaling pathways such as the one induced by NF-κB [22] or suppressing the secretion of cytokines such as IL-12, IFN-$\gamma$ and TNF-$\alpha$ [23] as well as inhibiting IL-6

transcription and increasing IL-20 transcription [24]. On the other hand, AvrA would favor tumor formation in the intestinal epithelium by activating cell proliferation pathways such as Wnt/β catenin pathway [25], associated with colon cancer [26], through two post-translational modifications, β catenin phosphorylation (activation) and deubiquitination of it (decreasing degradation) [7]. Also, AvrA activates Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway [27], which also plays an important role in carcinogenesis because it is involved in apoptosis regulation, cell proliferation and differentiation as well as on the inflammatory response [28]. In addition, AvrA has acetyl transferase activity and one of its targets is p53 [29]; when it is acetylated, it causes cell cycle arrest and apoptosis inhibition by decreasing proapoptotic proteins such as Bax [30]. AvrA mechanisms are summarized in **Figure 1**.
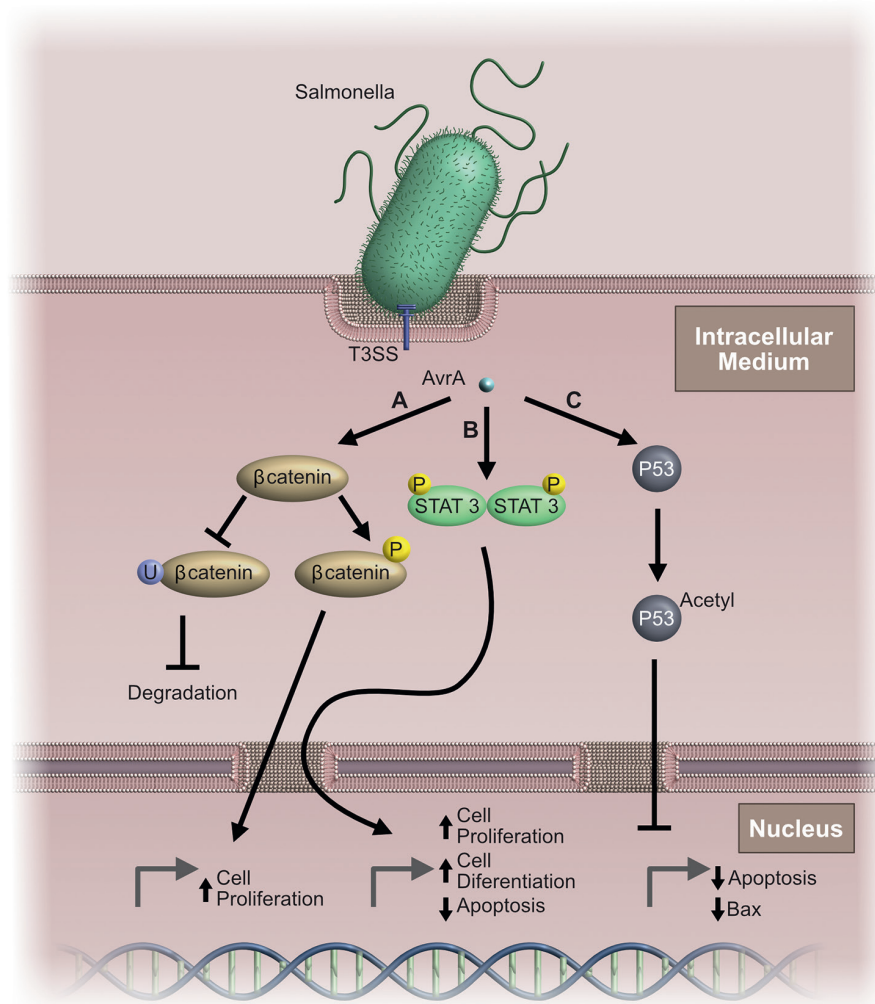


**Figure 1. Oncogenic activity of the *Salmonella enterica*.** Once AvrA is released and internalized via the type 3 secretion system of *Salmonella enterica*, it exerts its oncogenic effect by modulating the following signaling pathways (1) phosphorylation and deubiquitination of β catenin, promoting cellular proliferation [7, 25], (2) STAT3 phosphorylation, fostering cell proliferation and differentiation as well as decreasing apoptosis [27] and (3) acetylation of the p53 transcription factor that decreases apoptosis by transcriptional downregulation of proapoptotic proteins such as Bax [29].

## 3. Infection by *Salmonella enterica* and gallbladder cancer

Gallbladder cancer is the main type of neoplasm that affects the bile ducts. Even though the incidences of this neoplasm is low worldwide compared to other types of cancer that affect the gastrointestinal tract, the high incidence in some geographic regions like South America [31, 32] and Southeast Asia [33, 34] have generated a particular interest on studying the causes that contribute to the development of this type of neoplasm on these population.

The main risk factor for developing gallbladder cancer is cholelithiasis, gallstone formation (GSD), which favors the inflammatory process and damage to the epithelium [35]. Likewise, a second risk factor that has begun to be associated with the development of this neoplasia is the infection with *Salmonella enterica* [33], which enters the gallbladder directly from the bloodstream or through the bile [36]. Interestingly, a high incidence of *Salmonella enterica* has been reported in geographic regions where there is a higher number of gallbladder cancer cases [6], and several studies have shown its presence in biopsies of patients with gallbladder cancer [32, 37–39], where different serotypes of *Salmonella enterica* such as *S. typhi*, *S. paratyphi*, *S. typhimurium* and *S. choleraesuis* have been found [37].

To date, there is a little information about how an infection with *Salmonella enterica* would participate in the development of gallbladder cancer. One of the main proposed mechanisms is the induction of chronic inflammation in the gallbladder [40], which is recurring in patients with cholelithiasis [39]. Since *Salmonella enterica* can go unnoticed for years, and it has the ability to form biofilm on gallstones constituted by cholesterol [38]; the inflammation would increase immune cell recruitment, including activated macrophages expressing COX-2 [41], which is an enzyme that plays a role in the development of tumors in the gastrointestinal tract [42, 43]. In addition, the inflammatory process causes alterations in the *TP53* gene, increasing the risk to develop gallbladder cancer [44]. Lastly, in another study, it was shown that infection with *S. typhimurium* in cell lines and gallbladder organoids produces malignant transformations, by activating the MAPK and AKT pathways, which were associated with the development of gallbladder tumors in a murine model [6].

According to the data presented earlier, infection with *Salmonella enterica* could be a factor associated with the development of neoplasms in the gastrointestinal tract, where the chronic inflammatory process induced by the bacteria, as well as some of its effector proteins would be responsible for triggering the tumor process. However, more studies are needed in order to better understand the role of *Salmonella enterica* in carcinogenesis.
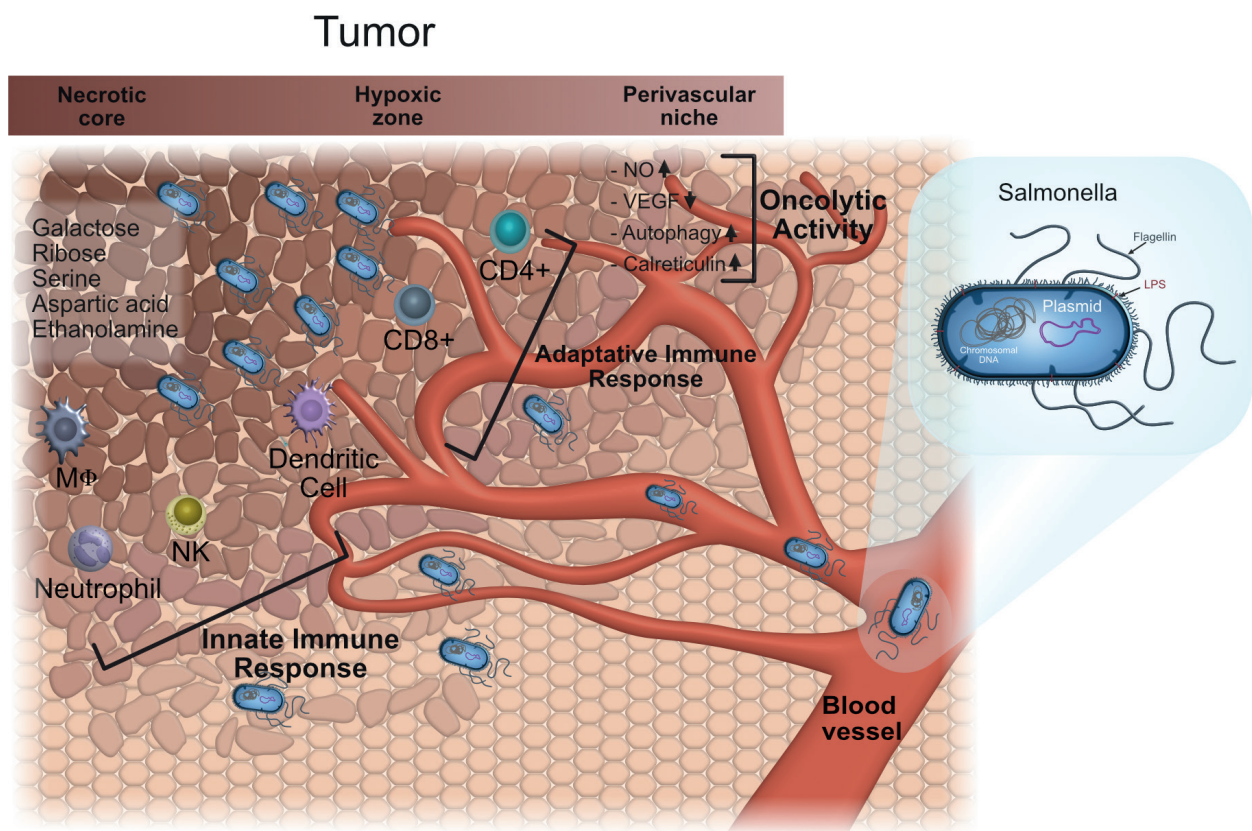
## 4. Antitumor activity of *Salmonella enterica*

Contrary to carcinogenesis induction, infection by bacteria such as *Salmonella enterica* facilitates the elimination of tumor cells [11]. The use of bacteria and their derivatives to treat cancer was first documented by William Coley over a century ago, using "Coley's Toxin," a compound of *Streptococcus pyogenes* and *Serratia marcescens* extract intended for the treatment of patients with sarcoma, carcinoma, lymphoma, melanoma and myeloma [45]. Since 1976,

subsequent studies led to the use of the attenuated strain of *Mycobacterium bovis* (Bacillus de Calmette-Guérin, BCG) administered intravesically as immunotherapy against superficial transitional cell bladder carcinoma [46].

To date, *Salmonella enterica* is one of the most studied bacteria in the fight against cancer [11]. Results of a phase I clinical trial with *S. typhimurium* strain VNP20009 showed that the bacterium does not lead to severe adverse effects and it is well tolerated by patients with metastatic melanoma, metastatic renal carcinoma, carcinoma of the head and neck and esophageal adenocarcinoma [47–49]. The mechanisms implicated in the ability of *Salmonella enterica* to eliminate tumors remain under scrutiny, but its tropism for the tumor microenvironment, its oncolytic activity and its ability to activate the innate and adaptive immune responses of the host have been documented (**Figure 2**).

## 4.1. Tumor selectivity of *Salmonella enterica*

For over a decade, the use of live-attenuated strains of *Salmonella enterica* as a therapeutic alternative against cancer [8, 11] has been favored by this bacterium's ability to effectively and selectively colonize the tumor microenvironment [8, 12]. Several studies have described



**Figure 2.** *Salmonella enterica* **selectivity for the tumor, oncolytic activity and induction of immune response.** Once *Salmonella enterica* reaches the tumor tissue, attracted by molecules such as aspartate, serine, ribose/galactose [50, 51] and ethanolamine [53], it induces its antitumor oncolytic activity promoting cell death via nitric oxide production [74], decreased angiogenesis [78], autophagy activation [79, 80], activation of immunogenic death [81] and activation of the innate and adaptive antitumor immune responses [74, 87, 89–91].

how *Salmonella enterica* infects and replicates within tumors in murine models in a 1:1000 ratio compared to normal tissue [10]. Although the mechanisms of tumor selectivity are still controversial, *in vitro* studies mimicking the tumor microenvironment have shown that *Salmonella enterica* migrates to the tumor tissue due to attraction by certain molecules such as amino acids and carbohydrates that allow the bacteria to arrive and penetrate the tumor tissue and then direct to the necrotic area [50, 51]. In addition, ethanolamine, a molecule found in elevated concentrations in different types of neoplasia [52], has also been found to act as a chemotactic agent because the deletion of the *eutC* gene (part of the operon encoding the enzyme ethanolamine-ammonia-lyase (EAL) which metabolizes ethanolamine [53]) in *Salmonella enterica*, decreased its colonization in a murine model of breast cancer [54].

Other studies have referred that *Salmonella enterica* migration involves motility proteins such as the CheA/CheY system [50, 51, 55], proteins fliA, fliC and flgE [56] and the *motAB* gene, the flagellar motor of the bacteria [54]. The *Salmonella enterica* metabolic pathways of aromatic amino acids (*aroA*) and purines (*purA*) are also relevant since mutations in these metabolic pathways lead to decreased recruitment in tumor tissue [56, 57].

On the other hand, the microenvironment in the tumor characterized by (1) hypoxia [58], (2) acidity [59] and (3) necrosis contributes to bacterial proliferation [11]. The permanence of *Salmonella enterica* in tumor tissue may be fostered by low macrophage and neutrophil activity [60], suppression of the immune response mediated by cytokines such as TGF-β, and the difficult access of anti-Salmonella antibodies and factors of the complement pathway due to the irregular growth of blood vessels in the tumor [61].

## 4.2. Oncolytic activity of *Salmonella enterica*

Several studies have documented the antitumor activity of *Salmonella enterica* in murine cancer models, including lung cancer [62], carcinoma of the colon [57, 63], prostate cancer [64], T-cell metastatic lymphoma [65] and B-cell lymphoma [66], among others. In these studies, *Salmonella enterica* inhibited tumor growth and its metastases, while also increasing the lifespan of the mice. These results are consistent with reports in murine models of xenotransplants of breast cancer [67] and prostate cancer [68, 69], using auxotrophic strains of *S. typhimurium* such as the A1 strain (deficient in leucine and arginine synthesis) and the A1-R strain (deficient in leucine and arginine synthesis but with a greater capacity to eliminate tumor cells); these do not cause any injuries in the host because the bacterium has greater affinity for the tumor tissue [67]. Other studies have shown that the A1-R strain inhibits the formation of metastases in bone of murine breast cancer models [70] as well as metastases from osteosarcoma [71], pancreatic cancer [72] and dorsal spinal cord gliomas [73].

Although the mechanisms through which *Salmonella enterica* induces tumor cell death are still under study, some proposed mechanisms involve: (1) *apoptosis induction via nitric oxide (NO) production* [74]: NO, the product of nitrate and nitrite degradation (generated by the hypoxic tumor microenvironment) [75] via *Salmonella enterica* nitrate reductase (NirB) [76], could induce the intrinsic apoptotic pathway [77]. (2) *Decreased angiogenesis: Salmonella enterica* inhibits the expression of the transcription factor HIF-1α and thus, the decrease in vascular endothelial growth factor (VEGF) [78]. (3) *Autophagy activation through the AKT/mTOR pathway:* the presence of *Salmonella enterica* in the tumor decreases phosphorylation of the

proteins AKT and mTOR and increases the expression of Beclin-1 and LC3 (microtubule-associated protein 1A/1B-light chain 3) [79, 80], thus promoting autophagy. (4) *Induction* of *immunogenic cell death (ICD):* this type of cell death could be caused by calreticulin (CRT) [81], a protein in the endoplasmic reticulum, when secreted by the cell participating in ICD [82], which increases due to the presence of *Salmonella enterica* in tumor tissue. Other mechanisms involved in tumor cell elimination and fostered by *Salmonella enterica* include the induction of the innate and adaptive immune response, as described later.

### 4.3. Activation of the innate antitumor response by *Salmonella enterica*

The immune response generated against *Salmonella enterica* once it has entered the host [83, 84] plays an important role in tumor recognition due to the recruitment of immune response cells in the tumor and its metastases [85, 86]. In the tumor microenvironment, *Salmonella enterica* induces the reversal of the suppressor environment by facilitating the expression of soluble mediators such as inducible nitric oxide synthase (iNOS) and interferon-γ (IFN-γ), molecules that promote antitumor activity and inhibit the expression of immunosuppressive factors such as arginase-1, interleukin-4 (IL-4), transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF) [8, 87]; also, *Salmonella enterica* decreases the activity of myeloid-derived suppressor cells (MDSCs) [88] and promotes the recruitment of natural killer (NK) cells [89], neutrophils [74], macrophages [87] and T [90] and B lymphocytes [91]. The first studies describing the immunotherapeutic antitumor properties of *Salmonella enterica* were reported by Kurashige S. et al.; whereby with the use of mini cells (vesicles with no genomic DNA) obtained from *S. typhimurium* and administered to a murine sarcoma model [92] and T-cell lymphoma [93], and macrophage activity was restored in the tumor microenvironment and helped eliminate the tumor.

Some studies have documented the ability of *Salmonella enterica* to induce the activation of the inflammasome during the early stages of bacterial colonization, via type NOD receptors (NLR) [94], favoring interleukin-1β (IL-1β) and TNF-α activation [95], and increasing the levels of proinflammatory cytokines and decreasing those of anti-inflammatory cytokines [86] in the tumor microenvironment. The antitumor efficacy of *Salmonella enterica* is further promoted by the induction of the immune response via TLR-MYD88 signaling, thus establishing that cytokine production and modulation may result from the activation of toll-like receptors (TLRs) in the tumor tissue [96].

It is known that bacterial components of *Salmonella enterica*, such as lipopolysaccharide (LPS), flagellin and the CpG sites are recognized by the TLRs, and lead to activation of the signaling pathways inducing the innate and adaptive immune responses. In this context, the interaction of the LPS from *Salmonella enterica* with TLR4 has been shown to contribute to decreased tumor growth and to the recruitment of neutrophils and macrophages [97]. Likewise, the interaction of *Salmonella enterica* flagellin with TLR5 prevented the development of metastases in a murine melanoma model [98]. These results were consistent with the use of a TLR5 agonist used in a murine lymphoma model in which the antitumor effect was associated to the activation of CD8+ lymphocytes and NK cells [99]. Subsequent studies using TLR4 and TLR5 knockout (KO) mice have confirmed their role in the antitumor response mediated by *Salmonella enterica* [100].

The antitumor effects, to which TLRs have been associated, are the recruitment of cells such as macrophages, NK cells, T and B lymphocytes, resulting from increased TNF-$\alpha$ level due to TLR4 activation by LPS [95, 101]. The increased TNF-$\alpha$ would therefore promote bleeding from the blood vessels of the tumor and allow the infiltration by immune response cells [102] that would eliminate the tumor cells. Further, the presence of *Salmonella enterica* in tumor tissue increases the amount of immune response cells in the spleen [81], which subsequently migrate to the tumor and contribute to its eradication.

### 4.4. Induction of the antitumor adaptive immune response by *Salmonella enterica*

Some studies have described that the adaptive immune response induced against *Salmonella enterica* antigens is one of the mechanisms eliminating tumor cells. Tumor cells infected with *Salmonella enterica* and that present these antigens of the bacteria are eliminated by cytotoxic T lymphocytes; this has been documented in the elimination of solid and non-solid tumors [85, 89].

*Salmonella enterica* contributes to the reversal of tumor immune tolerance by decreasing the number of Treg lymphocytes (CD4+ CD25+) in tumor tissue [103] due to the effects of LPS and the Braun lipoprotein (Lpp) of *Salmonella enterica* [104], and the decreased levels of indole-amine 2, 3 dioxygenase 1 (IDO1) (enzyme participating in tryptophan metabolism and associated with the development of immune tolerance by T lymphocytes) [105, 106], precluding the formation of kynurenine and thus favoring the proliferation of T lymphocytes capable of recognizing and eliminating the tumor [79]. Aside from reversing immune tolerance and promoting the recruitment of immune response cells in the tumor microenvironment, *Salmonella enterica* also induces the activation and maturation of T lymphocytes [107], probably as a result of the induced overexpression of gap junction proteins such as connexin 43 (Cx43) [108]; this protein plays a role in B and T lymphocyte activation [109] as well as in antigen presentation to DC [110], thus allowing the transfer of tumor cell preprocessed antigens to DC for their adequate presentation by MHC class I [108], thus generating a specific antitumor response.

Studies conducted by Shilling et al. [111] showed that the *in vitro* activation of DC purified from mice, with cytoplasmic fractions of *S. typhimurium* and with heat shock proteins from tumor cells, prevented tumor formation after regrafting. Further, they showed that activated dendritic cells tended to preferentially localize in the tumor. These studies were consistent with the reports published by Avogadri F et al., which observed that the intravenous administration of *Salmonella enterica* favored cross-presentation of tumor antigens to DC, inducing the activation of CD8^{+} lymphocytes capable of recognizing the tumor [86]. Studies conducted by Grille et al. demonstrated that the administration of *Salmonella enterica* to a murine B-cell lymphoma model induced a local and systemic antitumor response, with the recruitment of CD8^{+} and CD4^{+} lymphocytes in the tumor and the presence of specific antibodies directed against the tumor cells [89].

## 5. Conclusion

The aforementioned data document the duality of the infection caused by *Salmonella enterica*, in which the chronic inflammation promoted by this bacterium induces DNA injury, and some proteins of the bacterium increase cellular proliferation and migration and decrease the

cell death, all these factors are associated with the development of cancer. On the other hand, infection with attenuated strains of *Salmonella enterica* promotes the elimination of tumor cells via intrinsic mechanisms that induce an oncolytic effect on the tumor cell while simultaneously promoting antitumor innate and adaptive immune responses; it appears to be an excellent candidate as a therapeutic alternative against cancer [8].

# Acknowledgements

# Conflict of interest

The authors have no conflict of interest to declare.

# Author details

Marco A. Hernández-Luna[1], Paola Muñóz-López[2,4], Carlos A. Aguilar-González[3,4] and Rosendo Luria-Pérez[4]*

*Address all correspondence to: rluria@himfg.edu.mx

1 Department of Medicine and Nutrition, University of Guanajuato, Leon-Guanajuato, Mexico

2 University of Veracruz, Mexico

3 Metropolitan Autonomous University, Mexico

4 Unit of Investigative Research on Oncological Diseases, Children's Hospital of Mexico Federico Gomez, Mexico City, Mexico

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