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Oncogenic potential of *Salmonella* infection: a short review

Abrar Alhussainy[1], Hussam W. Al-Humadi[2], Rafal J. Al-Saigh[3,*]

[1]*Department of Pharmacology and Toxicology, College of Pharmacy, University of Babylon, Hillah, Iraq*
[2]*College of Pharmacy, University of Babylon, Hillah, Iraq*
[3]*Department of Clinical Laboratory Sciences, College of Pharmacy, University of Babylon, Hillah, Iraq*

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ABSTRACT

Salmonella infections, whether typhoidal or non-typhoidal, represent a major global health burden. While acute infections primarily manifest as gastroenteritis, chronic infections have been increasingly associated with severe long-term complications, including inflammatory bowel disease, gallbladder cancer, and colorectal cancer. Emerging evidence indicates that *Salmonella* infections may promote tumorigenesis through multiple mechanisms, such as chronic inflammation, DNA damage, and the manipulation of host cell signalling pathways. Specifically, *Salmonella* effector proteins, including AvrA, SopE, SopE2, and SopB, have been shown to play a critical role in activating oncogenic pathways such as Wnt/β-catenin, PI3K/Akt, and MAPK, which drive cellular transformation and tumour progression. Additionally, *Salmonella* infection can disrupt the gut microbiome, leading to dysbiosis, which may further contribute to cancer risk. Environmental factors, lifestyle choices, and genetic predispositions also modulate the risk of developing these cancers. This short review highlights the urgent need for further research in order to unravel the complex interactions between *Salmonella* infections, host factors, and cancer development, with the goal of improving prevention, early detection, and therapeutic strategies.

*** CORRESPONDING AUTHOR:**
Rafal J. Al-Saigh, Department of Clinical Laboratory Sciences, College of Pharmacy, University of Babylon, Hillah, Iraq; e-mail: phar.rafal.jalil@uobabylon.edu.iq

1. Introduction

Salmonella enterica, a species that includes both typhoidal and non-typhoidal subspecies which can be responsible for typhoid fever and severe gastroenteritis. The primary mode of transmission is through the consumption of contaminated food or water. *Salmonel-*

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la infections are a significant global health burden, causing millions of cases of gastroenteritis annually, with high mortality rate[1]. Beyond acute gastroenteritis, chronic *Salmonella* infections have been linked to inflammatory bowel disease, colon cancer, and gallbladder cancer; they can contribute to tumorigenesis through mechanisms such as chronic inflammation and DNA damage[2]. This short review focuses on the role of *Salmonella* infection in the development of colorectal and gallbladder cancer, by discussing the interplay between the gut microbiome, host factors, and environmental influences.

2. Experimental models of *Salmonella* infection-linked tumorigenesis

A study by van Elsland *et al.*[3] has revealed that a low repetitive exposure to *Salmonella* infection can increase the risk of colon cancer, and so can a single high-dose exposure to the bacterium. These findings suggest that even subclinical or asymptomatic *Salmonella* infections could predispose individuals to colon cancer[3]. The same study has also found that invasive *Salmonella* bacteria could be recovered from colonic tumours of mice exposed to azoxymethane and dextran sodium sulfate; an experimental model used for the induction of inflammatory colorectal cancer[3].

In addition to chemically-induced models of cancer, researchers have used a mouse model with a conditional deficiency in the adenomatous polyposis coli (APC) gene, which is critical for suppressing tumour growth in the colon[4]. While *Salmonella* infection did not increase the number of tumours in those mice, it accelerated tumor growth, likely through the activation of the β-catenin pathway which promotes the hyperproliferation of intestinal epithelial cells[4].

As bile juice is secreted from the liver and transferred to the gallbladder for storage during a chronic *Salmonella* infection, it releases various types of toxins in the gallbladder. These toxins are carcinogenic[5].

Salmonella infection employs various effector proteins in order to manipulate the host cell processes, thereby facilitating the bacterial survival and replication. Two key pathogenicity islands, *SPI-1* and *SPI-2*, encode type III secretion system (T3SS). One such effector, AvrA, activates the Wnt/β-catenin pathway, leading to hyperproliferation and tumorigenesis in the colon. AvrA also inhibits autophagy by regulating the conversion of LC3-I to LC3-II, thereby reducing the levels of Beclin-1; a protein essential for autophagy[6]. This inhibition of autophagy promotes *Salmonella*'s intracellular survival, as suggested by observations in AvrA-deficient *Salmonella* strains[6]. Other effector proteins such as SopE, SopE2, and SopB, can activate oncogenic signalling pathways such as the PI3K/Akt and the MAPK, leading to enhanced cellular proliferation and survival[7]. The Salmonella infection can also induce DNA damage through the release of carcinogenic toxins, such as the cytolethal distending toxin, which creates double-stranded DNA breaks in the host cells[7]. This DNA damage, combined with chronic inflammation, creates a favourable environment for the development of gallbladder cancer[7].

3. Gut microbiome after a *Salmonella* infection

The gut microbiome plays a critical role in human health, and its composition is dynamic, responding rapidly to environmental changes. *Salmonella* infections alter the gut microbiome, affecting the metabolome and increasing inflammation, which may contribute to tumorigenesis. Short-chain fatty acids, produced by the microbiota, are influenced by the ecosystem's structure, available nutrients, and infection. Restoring the microbiome after a *Salmonella* infection has been shown to improve barrier function and suppress inflammation, thereby highlighting the importance of understanding how *Salmonella* infections alter the microbiome and increase cancer risk[8]. Another study has shown that younger patients (under 60 years of age) with serological evidence of a *Salmonella* infection are more likely to develop colon cancer[9]. Additionally, the role of antibiotics in colon cancer risk is unclear. Some studies suggest that antibiotic exposure may increase cancer risk, possibly due to dysbiosis caused by antibiotic-induced changes in the gut microbiome. Fur-

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Table 1. Overview of key studies on *Salmonella* infections and their association with cancer development. Abbreviations used: NTS, non-typhoidal *Salmonella*.

Studies	Key findings
van Elsland *et al.* (2022)[3]	repetitive exposure to NTS increases colon cancer risk in mice; low-dose NTS exposure leads to the development of colonic tumours; invasive *Salmonella* was found in the tumours
Cheng *et al.* (2020)[4]	a mouse model with a conditional deficiency in the adenomatous polyposis coli (APC) gene shows accelerated tumour growth with NTS infection; NTS infection accelerates tumor growth *via* the β-catenin pathway
Scanu *et al.* (2015)[5]	*Salmonella*-induced gallbladder cancer; chronic *Salmonella* infection is linked to gallbladder cancer
Jiao *et al.* (2020)[6]; Stender *et al.* (2000)[7]	*Salmonella* effector proteins manipulate host pathways; AvrA activates the Wnt/β-catenin pathway; SopE/SopE2 facilitate intracellular replication
He *et al.* (2023)[8]	environmental factors influence *Salmonella* infection outcomes; younger patients with a history of a *Salmonella* infection are more likely to develop colon cancer
Sun (2022)[9]	gut microbiome alterations take place after a *Salmonella* infection; the latter disrupts the microbiome, thereby increasing inflammation and cancer risk
McDowell *et al.* (2022)[10]	exposure to antibiotics may increase cancer risk through gut dysbiosis

ther research is needed in order to elucidate the relationship between *Salmonella* infection, antibiotic use, and colon cancer development[10].

4. Conclusion

Salmonella infections are a significant global health concern, with emerging evidence suggesting a link to increased colon cancer risk. Multiple factors, including host genetics, gut microbiome composition, and environmental exposures, contribute to this risk. A better understanding of the mechanisms through which a *Salmonella* infection can contribute to tumorigenesis could lead to new strategies for cancer prevention.

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Conflicts of interest

None exist.

ORCIDs

0009-0008-9963-5247 (A. Alhussainy); 0000-0003-3691-0949 (H.W. Al-Humadi); 0000-0001-7044-2873 (R.J. Al-Saigh)

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