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REVIEW

Uncommon Gram-Negative Opportunists as Drivers of Cancer-Related Immunomodulation: The Virulence Machinery of Aeromonas, Shewanella, and Morganella Species

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Abstract

Immunosuppression and tissue destruction related to cancer provide a niche of permissible colonization by opportunistic bacteria, although the role of uncommon gram-negative pathogens in tumor-associated immune modulation has not been studied in detail. New findings point to Aeromonas, Shewanella, and Morganella organisms that were historically considered either environmental or low-virulence provirulence organisms as potential active mediators of cancer-related immunomodulation by having highly complex virulence systems. These bacteria have a repertoire of pathogenic determinants such as type III and type VI secretion systems, iron acquisition mechanisms, endotoxin reorganization, biofilm formation, and outer membrane vesicle release that allow them to withstand antagonistic tumor microenvironment and a direct contact with host immune pathways. Along with the cancer environment, these opportunists can contribute to immune dysregulation through cytokine profile distortion, phagocytic dysfunction, persistent inflammation, and immune evasion. Their redox-adaptive capacities and metabolic flexibility also favor their survival in hypoxic environments, nutrient-scarcity and oxidative stress, which are the hallmarks of solid tumors. Most importantly, the communication between these bacteria and tumor-related immune cells, including macrophages and neutrophils can strengthen pro-tumorigenic inflammation and suppress efficient antitumor immunity. Simultaneously, antimicrobial resistance characteristics and stress-regulated virulence determinants increase their clinical usefulness in immunocompromised cancer patients. The current review has identified the mechanistic roles of the Aeromonas, Shewanella and Morganella species as unorthodox yet biologically important mediators of immune homeostasis to cancer. Their virulence mechanisms and contact with the host can reveal new biomarkers of infection-mediated tumor pathogenesis and be useful in combination therapy with microbial-specific factors and immune dysfunction in cancer management.

Keywords: Aeromonas- Shewanella- Morganella- Cancer Immunomodulation- Virulence Factors- Opportunistic Infections

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1. Introduction

The relationship between cancer and immune disturbance has been recognized for over a century. The detrimental effects of malignancy on host defences can be direct or indirect. Inflammation, an aetiological agent in oncogenesis, which may arise from cancer chemotherapeutics or a compromised immune system, can augment oncogenic risk [1]. Bacteria capable of modulating immunity are emerging as associated agents in various settings. Rare taxa, including Aeromonas, Shewanella, and Morganella species, have been implicated. These Gram-negative opportunists, capable of colonizing and infecting immunocompromised individuals, are among the taxa associated with increased risk of cancer [2].

2. Epidemiological Context of Cancer-Associated Immunomodulation

The terms "oncogenic immunomodulation" or "cancer-associated immunomodulation" encapsulate the many ways that the immune system can be altered in cancer. The predominance of cancer-associated

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immunomodulation is detailed for other microbes. While inflammatory and infectious processes increase cancer risk, disseminated disease with Gram-positive pathogens such as Staphylococcus and Streptococcus or with opportunistic pathogens such as Pseudomonas or Candida is more frequently cited, potentially drawing attention away from Gram-negative biochemical strategy choices that contribute to advanced solid tumors [3]. Cancer-associated factors further modify local microenvironment conditions that can shape the capacity of the invading bacteria to influence tumor immunity; Aeromonas in particular modifies tumor microenvironments, including via the expression of biofilms. Microbes are known to affect tumorigenesis not only during an established cancer state but also during early phases through innate and adaptive immune pathways, metabolism, coordinated tissue disease control. Occasional case reports or survey papers note that the environmental and commensal opportunists Aeromonas, Morganella, or Shewanella can become systemic in advanced cancers [4]. The development, microbiological traits, and high-impact virulence factors of these similar, low-GC Gram-negative opportunistic microbes occurring together as common causes of such advanced-stage oncoimmunomodulation have not previously been examined [5].

3. Aeromonas Species: Virulence Factors and Immunomodulatory Interactions

A significant association exists between aeromonad infections and wide-ranging extraintestinal manifestations, including septicemia, soft-tissue wound infections, and gastroenteritis, particularly in patients undergoing immunosuppressive treatments. Aeromonas virulence trends cross multiple oncological settings worldwide and also extend to Shewanella and Morganella species, underscoring their relevance in cancer-infection interactions across similar environmental and pathobiological contexts. This section evaluates the immunomodulatory actions of opportunistic Aeromonas species in humans, focusing on relevant virulence traits and their integration within a cancer framework [6, 7]. Aeromonas species engaged in oncogenic operations express cytolysins, lipases, and flagellin without deploying two prominent virulence factors, i.e., enterotoxins and adherent fimbriae, that remains integral to gastrointestinal disease. Nonetheless, human clinical isolates comprise a broad variety of species and therefore constitute but one recipient of pathogen–tumor cooperation. The virulence determinants deployed often depend on the specific conditions encountered inside different hosts, e.g., species, habitat, and milieu, including fish and amphibians in a wider ecological context, suggesting the coexpression of pathogenic factors towards shaping tumor-microenvironmental outreach (Figure 1) [8, 9].

3.1. Toxin Production and Host Immune Signaling

Bacteria produce a wide array of virulence factors enabling pathogens to regulate host immune responses, which can favor bacterial survival, replication, and spread during infection. Strikingly, some cancer-associated

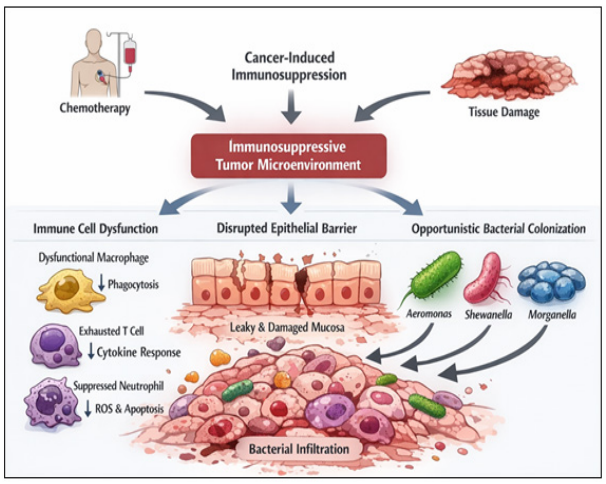

Figure 1. Overview of Cancer-Associated Immunosuppression and Opportunistic Gram-Negative Colonization

microbes engage immunosuppression-, inflammation-, apoptosis-, and metabolic remodeling-inducing factors to exacerbate tumorigenesis. Aeromonas species exemplify how the virulence machinery of common environmental opportunists can co-opt evolutionarily conserved pathways for cancer-related immunomodulation [10, 11]. Shewanella and Morganella species have comparable cancer-related immunomodulatory mechanisms, which integrate both innate and adaptive arms of the host immune system. Such associations between low-abundance taxa highlight how even rare opportunistic pathogens may be associated with high-profile cancer-related immunomodulation as well as identify their commonality in lineages of virulence machinery across the microbiome [12, 13].

3.2. Biofilm Formation and Tumor Microenvironment

Bacteria in biofilms are capable of triggering tumor microenvironment alteration that promotes cancer development. Particularly, the production of local biofilms changes the bioavailability of metabolites including amino acids and carbohydrates and biofilms adjust immune cell invasion by releasing extracellular matrix components that induce immune cell attraction [14]. Moreover, biofilms also secrete extracellular polymeric compounds which provide greater resistance to chemotherapeutic agents thus increasing the viability of the tumor cells. The Aeromonas species produce type IV pili involved in the development of biofilm, and such structures play a significant role in the development of local infections. The formation of biofilm promotes local invasion of medium- and high-grade tumors, changes the microenvironment and metabolome around, and promotes the development of peripheral metastases. Immunocellular invasion of tumors infested with Aeromonas species reveals that neutrophils, dendritic cells, and macrophages are more frequently observed whereas T and natural killer cells are less frequent, which indicates that local infections recapitulate to form the tumor microenvironment in a way that facilitates cancer development [15, 16].

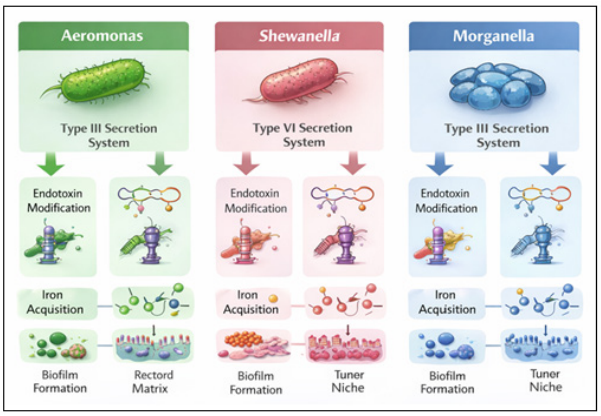

Figure 2. Virulence Machinery of Aeromonas, Shewanella, and Morganella Species

3.3. Metabolic Modulation and Immunometabolism

Bacteria are also able to regulate host metabolism to avoid immune reactions, especially cancer models [17]. With respect to Aeromonas, limited data indicate that effects on host metabolism shift immunity away from pro-inflammatory profiles elicited by pathogenic microbes, including tumor-associated pathogens, towards pro-tumorigenic immunity. Morganella strains produce gut-associated lipopolysaccharides with distinct acylation patterns that dampen LPS-mediated pro-inflammatory signaling and induction of Th1-type cytokines [18]. Proteolytic enzymes hijack host protease-activated signaling, promoting tumor formation in murine models of colon cancer (Figure 2) [19, 20].

4. Shewanella Species: Pathogenic Traits and Immune Quieting

Shewanella species possess several pathogenic traits that influence anti-tumor immunity and tumor evasion mechanisms. Collectively, these traits can be seen as immune "quieting" strategies that may facilitate tumor progression [21]. Shewanella outer membrane vesicles are capable of stimulating multiple Toll-like receptors, including TLR2, TLR3, and TLR4, and inhibit pro-inflammatory cytokines such as IL-1β, IL-2, IL-6, TNF-α, and IFN-γ while promoting the anti-inflammatory cytokine IL-10. In tumors, Shewanella produces important environmental electron donors that couple with the quorum-sensing autoinducer N-acyl homoserine lactones from incipient biofilms to activate the anaerobic electron transport system, resulting in non-canonical Redox [22, 23]. This strongly favored the growth of Shewanella and other redox-related organisms of enteric origin that were negatively correlated with Th1-type cells. Tetrathionate and other iron sources such as heme and transferrin were utilized. The binding of tfxA186 to the tfxA308 of the invading bacterium accelerated the cleavage of transferrin in tumors. These systems can rapidly cleave and obtain iron from serum components. These strategies may play important roles in the progression of Shewanella-associated tumors, in particular, a marked reduction of immune infiltrates that characterize the evolution of cancer [24, 25].

4.1. Outer Membrane Vesicles and Cytokine Alteration

Shewanella putrefaciens, a member of the Shewanella genus, is a gram-negative bacillus, ubiquitous in nature, and commonly found in aquatic environments [26]. Shewanella species are emerging pathogens associated with human infections predominantly among immunocompromised individuals. Pattern recognition receptors like Toll-like receptors result in immune recognition of bacterial invasion and consequently, the immune response (innate and adaptive). The responses can be avoided, evaded or down-regulated by the secretion or presentation of a variety of effectors by Shewanella species. The evidence is increasing on the issue of the possible role of Shewanella spp. in oncogenic processes [27].This is caused by lipopolysaccharides released by bacterial populations that alter the physicochemical makeup of the tumor microenvironment and lead to redox shift changes and tumor progression. Shewanella spp. have been reported to induce several hemophores and other iron acquisition factors, which induce the release of interleukin-10 (IL-10), interleukin-4 (IL-4), and transforming growth factor-b (TGF-b) [28]. This creates an interesting paradox since even immunocompromised hosts, which are generally at high risk of becoming infected by bacteria, have reduced rates of Shewanella infection. The ability of Shewanella spp. to take advantage of or regulate the immune system to sustain their own survival is becoming increasingly felt; pathophysiological conditions due to the presence of Shewanella infections can weaken these lofty barriers to the benefit of the malignant cell occupancy and proliferation [29].

Bacterial outer membrane vesicles (OMVs) are important in the interactions of the host with the pathogen and innate bacterial defense. Their biologically active proteins are capable of controlling the host cells with the effector proteins and can be involved in the signaling and trafficking group processes. OMV production is stress inducing and helps in the modulation of immunity during infections. OMVs of S. aureus and S. putrefaciens have been demonstrated to shift the overall bone marrow-derived dendritic cells cytokine responses, favoring Th2. Suspensions of living S. putrefaciens suppressed tumor development and increased survival in a mouse orthotopic tumor model of the bladder, and subsequent studies suggested that live bacteria were able to suppress the generation of cytokines caused by a prevalent clinical pathogen (Figure 3) [30, 31].

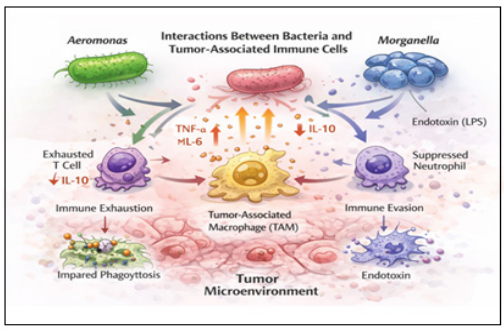

Figure 3. Bacterial–Immune Cell Interactions within the Tumor Microenvironment

4.2. Electron Transfer Systems and Redox Imbalance in Tumors

The conversion of aerobic to anaerobic conditions produces reactive oxygen species (ROS) that cause redox imbalance in favor of tumor growth and progression [32]. Aerobic respiration produces harmful byproducts, prompting stochastic mutations in host cells, while fermentation of carbohydrates, proteins, and lipids generates reduced electron carriers. Accumulation of these metabolites in tumors further alters the redox balance. Cancer cells produce excessive ROS to maintain redox equilibrium, but higher concentrations induce cell apoptosis or senescence [33]. Pathophysiological conditions related to tumorigenesis, such as inflammation, hypoxia, and elevated ROS/RNS, boost anaerobic growth of diverse pathogens, including Shewanella spp [34].

4.3. Iron Acquisition and Immune Response Modulation

Aeromonas and Shewanella spp. are known to promote tumor immunity, while Morganella spp. exhibit potentiation of tumor development through strategies observed in their commensal lifestyle. Pathogenic Shewanella spp. exploit strategies sustaining an immune-quiescent state and even dampening pre-existing immune responses. Outer membrane vesicles can alter tumor-associated macrophages (TAMs) toward anti-inflammatory activation and modify the th2-th9 cytokine balance, while strategies for iron acquisition modulate cytokines, toll-like receptors, inflammasome activation and patterns of M1/M2 macrophage polarization [35, 36]. Operons involved in iron homeostasis and electron transfer systems similarly confer advantages to Aeromonas. Both emerge in the flesh and through aquatic sources, notably in gastrointestinal infections, which co-occur with acr antigen detection and fecal excretion [37]. Morganella spp. are frequently detectable in the gut of cancer patients and are implicated in other biomedically relevant infections [38, 39].

5. Morganella Species: Enteric Opportunists in Oncologic Contexts

Morganella morganii, a facultative gram-negative enterobacterium prevalent in the intestines of humans and other mammals, stands as a significant opportunistic pathogen responsible for a range of nosocomial and community-acquired infections [40]. Wound infections, bacteremia, and UTIs are the most common types of infections, with an exceptionally high rate observed among the various populations, including neonates, postoperative patients, patients receiving neutropenic chemotherapy, and patients with diabetes. The clinical burdensomeness of the organism has just been one of the factors that have made the organism notorious, in addition to its unquestionable intrinsically resistant repertoire against a number of antibiotics and antiseptics [41, 42]. Morganellalong has come into the limelight of recent years as a bloodstream pathogen as well as an emerging player in infectious disease scenarios, not to mention that it appears in enterobacterial genera within the environment of significance. New evidence implicates Morganella species in inflammation in cancer and assumes that individual metabolic and virulence strategies can counteract the anticancer effects of inflammation [43, 44]. Morganella, one of the genera within the family of Morganellaceae, has high metabolic adaptability, which is attained by the use of discrete two-partner secretion systems. The structure of bacterial multi-drug efflux pumps is also a factor in the significant survival benefit of the organism in complex host infection environments as well as in contaminated waters in the recovery of industrial actions [45, 46].

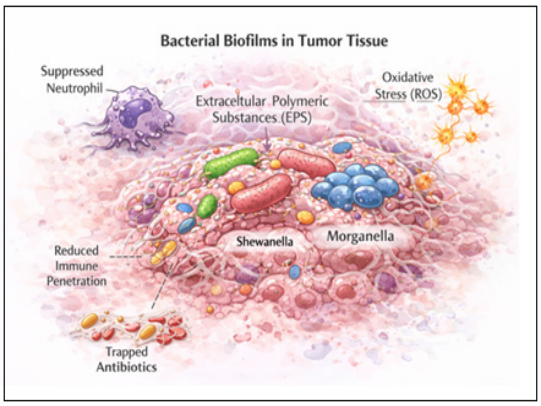

Figure 4. Biofilm Formation and Persistence of Opportunistic Pathogens in Tumor Niches

5.1. Proteolytic Enzymes and Immune Evasion

The types of enterobacteria present in the gastrointestinal microbiota differ dramatically between healthy individuals and those affected by cancer. In patients treated with both immunotherapy and antibiotics, the predominant strains shift to M. morganii, which is involved in urinary tract infections and is frequently found in cancer patients with maximum immunosuppression [47, 48]. The Salmonella genus has been under extensive investigation for possible use as an anticancer agent, and several other Enterobacteriaceae possess similar traits to Morganella that might facilitate tumor development. Morganella possesses several virulence factors that allow for immune evasion, such as lipopolysaccharides that differ from those produced by closely related Enterobacteriaceae. No experimental evidence has been published that explicitly associates Morganella opportunism with cancer; nevertheless, the correlation between the presence of certain opportunistic bacteria, including Morganella species, in heavily immunosuppressed cancer patients undergoing treatment with antibiotics and enhanced tumor growth and dissemination provides reasonable grounds for linking the genus with immunomodulation related to tumorigenesis (Figure 4) [49, 50].

5.2. Lipopolysaccharide Variants and Inflammatory Cascades

Morganella spp. are Gram-negative, oxidase-negative, enteric bacilli belonging to the Enterobacteriaceae family. They are opportunistic pathogens found in surface waters worldwide and associated with infections in humans

and animals. Infections are rare; however, the frequency of identified Morganella spp. infections has markedly increased. Cytotoxicity, hemolysin production, adherence, and resistance to serum are the major virulence factors associated with Morganella spp. [51]. Morganella spp. proteolytic enzymes, such as trypsin-like protease and a chymotrypsin-like serine protease, modulate immune responses through protease-activated pathways and the degradation of immunoglobulins and complement components. In particular, these proteases dampen type I interferon response to double-stranded RNA and inhibit the production of proinflammatory cytokines [52]. Morganella spp. strains from patients with cancer have been shown to possess a distinct lipopolysaccharide, leading to the activation of different transcriptional programs in macrophages and epithelial cells compared to other enteric opportunists. Two different lipopolysaccharides (smooth and rough) occur within the Morganella genus. Smooth lipopolysaccharides undergo extensive O-antigen modification, whereas rough lipopolysaccharides contain truncated O-antigen moieties. The capsular polysaccharides produced by Aeromonas spp., Shewanella spp., and Morganella spp. are a major factor determining adhesion to biotic and abiotic surfaces [53]. Stronger adhesion reduces the transmission risk once colonization occurs and increases the ability of the bacterium to occupy and modify the tumor microenvironment.

5.3. Microbiome-Driven Immunoregulatory Effects in Cancer

Tumor initiation, escape, and promotion are complex processes influenced by microorganisms, including viruses and bacteria. Tumor-associated microbiota generate an immune-suppressive tumor microenvironment (TME) that promotes tumorigenesis, particularly in prostate and liver cancer [54]. Bacteria such as Nevskia ramosa and Staphylococcus aureus enhance Treg-mediated immunosuppression and facilitate melanoma metastasis. In pancreatic ductal adenocarcinoma, the TME is shaped by tumor DNA that programs macrophages through Toll-like receptor (TLR) signaling, with bacterial depletion reprogramming immunity to increase M1-like macrophages, cytotoxic T cells, and activation of CD8+ T and natural killer (NK) cells, thereby enhancing immunotherapy efficacy. Conversely, although many onco-viruses exert tumor-promoting effects, the role of tumor-associated fungi remains obscure. Indeed, a fungal microbiota composition associated with rectal and anal carcinogenesis promotes an oncogenic TME and suppresses immunity to cancer therapies. Fungal proteins engage Dectin-1, augmenting tumor-promoting macrophage populations and inhibiting T cell activation and effector function [55]. Aeromonas, Shewanella, and Morganella species, common members of enteric and aquatic microbial communities, deploy an array of such virulence traits, implicating their onco-promoting potential as well as their distinctive and functionally redundant mechanisms of bacterial immunity. Although such neoplasia-linked opportunism was noted as early as 1860, historical records often lack the specificity to identify these organisms as causative agents of cancer-related immunomodulation. The first of several biogeochemical pathways connecting these bacteria to specific alterations in tumor immunity and progression was elucidated only recently [56, 57].

6. Comparative Analysis of Virulence Machinery Across Species

Species of Aeromonas, Shewanella, and Morganella share increasingly documented associations with human cancers and other malignancies [58]. Comparative analyses of their virulence factors point to a common utility in oncogenic immunomodulation that warrants further examination. The range of immune interactions is determined by differences in secretion systems, surface structures and metabolic characteristics. Production of interventions that address these aspects can also limit virulence and improve anti-cancer immunity. Aeromonas has a flexible complement of type III, type IV and type VI secretion apparatus [59]. The fish-associated strains have Type III secretion, which is lacking in variants that are human associated. Both Aeromonas species have both type IV and type VI systems present in large numbers. Virulence potential is altered by diverse surface structures such as polysaccharides, lipopolysaccharides and TaD tight adherence system which influence biofilm formation. Microbial metabolic potential also has an effect on the microenvironment of the tumour [59]. Morganella has a type IV secretion system, a few proteolytic enzymes and lipopolysaccharides characterized by O-antigenic change. Some strains also have a type VII secretion system and putative toxin genes. Several other genera that are closely related to Morganella are related to non-neoplastic diseases [58, 59].

7. Implications for Cancer Immunotherapy and Management

Cancer treatment is progressing rapidly, and new therapies are emerging every day. Additional therapeutic methods are being investigated, including bacteriolysis, which is helping to increase the effectiveness of existing treatments [60]. In recent years, opportunistic pathogens such as Pseudomonas aeruginosa and Clostridium spp. have shown antimicrobial properties, especially when genetically modified. These strains act as a new gene and antigen delivery vector and provide active treatment against solid tumors. These treatments exist for various types of cancer. Bacteria possess the ability to modulate host immunity, which is often beneficial in cases of opportunistic infection. Aeromonas, Shewanella, and Morganella species are undesired and poorly understood opportunistic pathogens that are increasingly associated with cancer in patients. The immunoregulatory roles of these bacteria in tumor biology are being investigated to identify additional measures to improve treatment [60].

7.1. Potential Therapeutic Targets in Bacterial Virulence Pathways

Remarkably high prevalence of opportunistic, antimicrobial-resistant bacteria and their virulence factors

have been observed in tumor-associated microbiomes from cancer patients and in plates from clinical samples containing patient-derived tumor organoids [61]. Several of these pathogens were classified as in the top ten priority pathogens of interest for the development of new antibiotics by the World Health Organization and target numerous pathways involved in cancer-associated immunomodulation. A few of these bacteria such as Aeromonas, Shewanella, and Morganella have been indicated as drivers of oncogenic intra- and extra-tumoral immunomodulation in multiple epidemiological studies. Characterization of their virulence factors shared by the most pathogenic strains indicates the importance of interruption of these bacterial-acquired pathogenicity mechanisms in the context of infection and/ or co-colonization to limit alteration of the immune landscape that could enable the emergence of occult or very slow-growing tumors into a malignant stage while preventing tumor outgrowth [62].

7.2. Strategies to Modulate Microbial Immune Interactions in Tumors

Strategies to modulate microbial immune interactions in tumors encompass the employment of attenuated bacteria such as Listeria monocytogenes and Salmonella typhimurium, along with other tumor-targeting bacterial vectors, as cancer immunotherapeutics [63]. These agents can effectively deliver tumor antigens and bolster antitumor immune responses. The overarching objective of bacterial therapies is to achieve heightened selectivity and more favorable therapeutic outcomes by homing in on the tumor microenvironment. This environment is populated by various immune cell types, including macrophages and neutrophils, which can either spur tumor progression or be co-opted for therapeutic purposes. Consequently, the targeted modulation of macrophage activation and polarization especially with regard to tumor-associated macrophages can profoundly impact immune escape and tumor expansion. Bacterial vectors have also found application in delivering tumor-associated antigens, thereby amplifying the immune system's capacity to recognize and respond to these targets [64].

8. Methodological Considerations in Studying Oncogenic Immunomodulation by Bacteria

Malignant transformation actively reshapes the cancer-affected area, modulating its composition as well as the interaction of the cells present [48]. Early-stage cancer cells often produce immune-suppressor cytokines to create an immunosuppressive tumor microenvironment (TME). Since this phenomenon also occurs in chronic bacterial infection, studies are being made to understand whether specific bacteria can also induce immune modulation in the context of oncogenic inflammation [65]. Such comprehension may aid in the optimization of therapeutic methods. In-depth analysis beyond the identification of bacterial presence is warranted to elucidate the types of modulation they perform and their possible relationship with oncogenic mechanisms.

In conclusion, the immunomodulation associated with cancer has become an important research area that illuminates the fascinating relationship that exists between infectious agents and the development of tumors. It is necessary to know these mechanisms in order to design effective therapeutic interventions. Epidemiological surveys which have taken place in various geographical locations have indicated that unusual Gram negative bacteria, especially Aeromonas, Morganella and Shewanella types are an appreciable percentage of cancer associated opportunistic pathogens. Although they have been known to be associated with malignancies, the virulence mechanisms underlying them have not been well investigated. The information about the relevant bacterial circuits would not only enhance the knowledge of tumor-associated infections but would also reveal the role of such microorganisms in cancer-immunity cycle. A new set of microbial targets would thus be recognized to streamline cancer immunotherapy as well as define strategy-specific interventions to positively redirect bacterial interactions.

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Declaration of Competing Interest

The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.

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