Virulence factors of the microbiome: A functional toolkit for cancer progression (Review)

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Received September 6, 2025; Accepted February 11, 2026

DOI: 10.3892/mco.2026.2957

Abstract. The paradigm of cancer biology has shifted to recognize tumor as a complex ecosystem inhabited by a diverse microbiome. Beyond mere association, the molecular mechanisms driven by microbial virulence factors are critical for understanding how these microorganisms contribute to malignancy. The present review describes a virulence factor-centric framework to deconstruct the microbial 'toolkit' and illustrate its role in enabling the Hallmarks of Cancer. The major classes of virulence factors were systematically analyzed, detailing how each contributes to tumor progression. It was described how bacterial adhesins (for example, Fusobacterium adhesin A and Fap2) initiate oncogenic signaling and mediate immune evasion; how secreted toxins drive genomic instability (Colibactin and CDT) and corrupt cellular signaling pathways (CagA and *Bacteroides fragilis* toxin); how degradative enzymes (gingipains and collagenases) dismantle the extracellular matrix to facilitate physical invasion; how viral oncoproteins (Human Papillomavirus E6/E7 and Epstein Barr virus latent membrane protein 1) hijack core cell cycle machinery; and how microbial structural components (lipopolysaccharides and extracellular vesicles) and metabolites (secondary bile acids) sustain a pro-tumorigenic environment. This analysis reveals a pattern of functional convergence, where diverse microbial agents repeatedly target core host pathways such as NF-κB, Wnt/β-catenin and p53. This mechanistic understanding reframes the microbiome as an active orchestrator of malignancy and reveals a new frontier of therapeutic targets. Strategies aimed at neutralizing specific virulence factors or modulating the tumor ecosystem represent a novel and promising pillar in oncology.

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Key words: microbiome, virulence factors, metastasis, hallmarks of cancer, bacterial toxins, oncomicrobes

Contents

1. Introduction

Virulence factors, the molecular weapons used by pathogenic microorganisms to survive and proliferate within a host have been a subject of intense study since the inception of germ theory. While traditionally defined within the context of infectious disease as components that modulate host-microbe interactions to enhance host damage (1,2), the classification of these factors is becoming increasingly complex. A classic example is the AB toxin family, such as Diphtheria toxin, which possesses dual functions: An enzymatic 'A' fragment that drives pathogenicity and a receptor-binding 'B' fragment that facilitates delivery (3,4).

However, an increasing body of evidence suggests that similar microbial components produced by the commensal microbiome can influence the development and progression of non-infectious diseases, including cancer (5,6). The distinction between a helpful symbiont and a harmful pathogen is often fluid. In the context of cancer, a once-benign microbe may acquire 'virulent' behavior during dysbiosis, contributing to carcinogenesis (7). Rather than acting solely as direct carcinogens termed 'oncomicrobes' [for example, *Helicobacter pylori* (*H. pylori*) and human papillomavirus (HPV)] numerous microorganisms function as 'complicit microbes'. These facilitators [for example, *Fusobacterium nucleatum* (*F. nucleatum*)] do not necessarily initiate cancer but create a microenvironment conducive to tumor development (8,9).

The present review offers a unique perspective by moving beyond a catalogue of microbial species to focus on their

functional machinery. It was examined how the microbiome's 'toolkit' actively participates in the 'Hallmarks of Cancer' framework proposed by Hanahan and Weinberg (10-12). This framework, which originally focused on host cell genetics, now formally recognizes the microbiome as a key enabling characteristic of the tumor microenvironment (TME) (10-12). Whether classified as oncomicrobes or complicit microbes, these organisms exploit an arsenal of virulence factors: Adhesins, toxins and enzymes to rewire host signaling, degrade physical barriers, and suppress immune responses.

The present review is organized by the functional class of the virulence factor rather than the specific microbe. A comprehensive summary of these factors categorized by their functional class is provided in Table I. Bacterial adhesins as the initiators of malignant interaction were first explored, followed by secreted toxins as molecular weapons. It was then detailed how degradative enzymes act as an extracellular 'demolition crew' and how viral oncoproteins hijack cellular machinery. Finally, structural components were analyzed, including extracellular vesicles and metabolites, as environmental modulators, before synthesizing these mechanisms into the 'Evade-Endure-Colonize' framework (illustrated in Fig. 1).

2. Bacterial adhesins: Initiating the malignant interaction

Bacterial adhesion represents the critical initiating event in the interplay between the microbiome and cancer. This molecular docking, mediated by surface proteins known as adhesins, provides the anchor necessary for colonization and the delivery of other virulence factors (13). Crucially, adhesion is not a passive process; binding triggers signaling events that can directly promote oncogenesis (14).

Fusobacterium adhesin A (FadA): A direct activator of the Wnt/β-catenin pathway. The FadA protein, a signature virulence factor of *F. nucleatum*, provides a direct link between a bacterial protein and a core cancer pathway. FadA binds to E-cadherin on colon epithelial cells (15), triggering the internalization of the E-cadherin/β-catenin complex. This releases β-catenin from the membrane, allowing it to translocate to the nucleus and activate the Wnt signaling pathway. This leads to the upregulation of oncogenes such as MYC and cyclin D1 (CCND1), fueling the uncontrolled proliferation characteristic of colorectal cancer (CRC) (16-19).

Fap2: A dual-function adhesin for immune evasion and metastasis. F. nucleatum also employs Fap2, a protein with dual pro-cancer functions. Firstly, Fap2 acts as an immunomodulator by binding to the TIGIT receptor on natural killer (NK) cells and cytotoxic T cells, delivering an inhibitory signal that shields the tumor from immune destruction (20). Secondly, Fap2 functions as a lectin, binding to Gal-GalNAc sugar moieties overexpressed on cancer cells. This interaction allows *F. nucleatum* to 'hitchhike' on circulating tumor cells, facilitating their adhesion to endothelial cells at distant sites and promoting metastasis (21,22).

Blood-group antigen-binding adhesin (BabA)/sialic acid-binding adhesin (SabA) adhesin duo. H. pylori employ a complementary pair of adhesins. BabA binds to Lewis b (Le^b) antigens on healthy gastric cells, establishing the chronic infection required for delivering the CagA oncoprotein (23,24). As infection induces inflammation, the gastric environment changes, and *H. pylori* switches to SabA. SabA binds to sialyl-Lewis x (sLe^x) antigens, which are upregulated on inflamed tissue, creating a feedback loop that perpetuates chronic inflammation (25).

PilG and fimbrial adhesins. Streptococcus gallolyticus utilizes the PilG adhesin to bind collagen types I and IV, which are exposed in the disorganized TME but hidden in healthy tissue. This allows the bacterium to preferentially colonize colorectal tumors (26,27). Similarly, fimbrial adhesins such as FimA [*Porphyromonas gingivalis* (*P. gingivalis*) and FimH [adherent-invasive *Escherichia coli* (*E. coli*)] bind to host integrins and CEACAM6, respectively. These interactions activate Toll-like receptors (TLRs) or stabilize tumor cell adhesion, driving chronic inflammation and invasion (28-30).

Collectively, these adhesins demonstrate how microbes overcome the first hurdle of carcinogenesis: Physical persistence. However, they do more than simply hold on. By targeting molecules such as E-cadherin (FadA), TIGIT (Fap2) and CEACAM6 (FimH), these adhesins directly engage the 'Proliferative Signaling' and 'Avoiding Immune Destruction' Hallmarks. Within the 'Evade-Endure-Colonize' framework, adhesins serve as primary tools for the 'Colonize' phase, allowing microbes to establish a foothold in the tumor niche and physically bridge cancer cells to metastatic sites.

3. Secreted toxins: Molecular weapons targeting host pathways

Beyond adhesion, microbes deploy secreted toxins, specialized weapons that manipulate host biology from a distance. These can be broadly categorized as genotoxins (which damage DNA) or modulating toxins (which hijack signaling) (31).

Genotoxins: Colibactin and Cyto-lethal Distending Toxin (CDT). Colibactin, produced by pks+ *E. coli*, is a potent alkylating agent that creates DNA adducts, leading to double-strand breaks. It leaves a specific 'mutational signature' in human CRC genomes, serving as a molecular fingerprint of bacterial activity (32). Similarly, the CDT, found in *H. pylori* (gastric cancer) and *E. coli* (CRC), functions as a DNase. It translocates to the nucleus and cleaves chromosomal DNA, triggering cell cycle arrest and genomic instability (33,34).

H. pylori toxin arsenal (CagA, VacA and Tipα). H. pylori injects the CagA oncoprotein directly into host cells, where it disrupts cell polarity and promotes epithelial-mesenchymal transition (EMT) (35). Concurrently, the secreted VacA toxin disrupts epithelial barrier integrity and suppresses local T-cell function (36,37), while Tipα binds to STAT3, driving inflammation and proliferation (38).

Modulating toxins: Bacteroides fragilis toxin (BFT), CPAF and Cytotoxic Necrotizing Factor 1 (CNF1). BFT is a metalloprotease that cleaves E-cadherin. This disrupts the intestinal barrier and activates Wnt signaling, while also recruiting T helper 17 (Th17) cells to establish a pro-tumorigenic

Table I. Key microbial virulence factors and their contributions to the hallmarks of cancer.

Virulence factor class	Specific virulence factor	Microorganism	Host target/mechanism of action	Consequence (Hallmark of Cancer)	Associated cancer(s)
Bacterial adhesins	*Fusobacterium adhesin A*	*Fusobacterium nucleatum*	Binds E-cadherin, leading to β-catenin release and nuclear translocation	Sustaining proliferative signaling	Colorectal, breast
	Fap2	*Fusobacterium nucleatum*	Binds TIGIT on immune cells (immune evasion) and Gal- GalNAc on tumor cells (metastasis)	Evading immune destruction; activating invasion and metastasis	Colorectal, breast
	Blood-group antigen-binding adhesin/sialic acid-binding adhesin	*Helicobacter pylori*	Bind Lewis b and sialyl-Lewis x antigens for persistent colonization	Tumor-promoting inflammation; enables toxin delivery	Gastric
Secreted toxins	Colibactin	*Escherichia coli* (pks+)	Alkylates host DNA, causing double-strand breaks and a specific mutational signature	Genomic instability and mutation	Colorectal
	CagA	*Helicobacter pylori*	Injected into gastric cells; dysregulates signaling to disrupt cell polarity	Activating Invasion and Metastasis (epithelial-mesenchymal tranistion)	Gastric
	Bacteroides fragilis toxin	*Bacteroides fragilis* (ETBF)	Metalloprotease that cleaves E-cadherin, activating STAT3 signaling	Tumor-promoting inflammation	Colorectal
Degradative enzymes	Gingipains	*Porphyromonas gingivalis*	Cysteine proteases that degrade extracellular matrix components such as collagen and fibronectin	Activating invasion and metastasis	Oral, pancreatic
	Collagenases	*Clostridium, Bacteroides*	Degrade native collagen fibers in the tumor stroma	Activating invasion and metastasis	Pancreatic, breast
Viral oncoproteins	E6/E7	Human Papillomavirus	E6 degrades p53; E7 inactivates Rb	Resisting cell death; avoiding growth suppressors	Cervical, oropharyngeal
	Latent membrane protein 1	Epstein-Barr virus	Constitutively active CD40 mimic; activates NF-κB, JNK, and MAPK pathways	Enabling replicative immortality	Lymphomas, nasopharyngeal
Structural and metabolic	Lipopolysaccharide	Gram-negative bacteria	Binds TLR4; promotes inflammation and primes the lung pre-metastatic niche	Tumor-promoting inflammation; activating invasion and metastasis	(Multiple cancers)
	Fungal β-glucans	*Malassezia* species	Binds Dectin-1; activates the complement cascade	Tumor-promoting inflammation	Pancreatic
	Extracellular Vesicles (microbial extracellular vesicles)	Various bacteria	Long-distance delivery of bioactive molecules; alters distant microenvironments	Activating invasion and metastasis	Lung
	Secondary bile acids (for example, deoxycholic acid)	*Clostridium* species	Induce reactive oxygen species production, causing oxidative DNA damage	Genomic instability and mutation	Colorectal

The present table provides a detailed summary of the principal virulence factors discussed in this review, organized by their functional class. For each factor, the table identifies the producing microorganism, the specific molecular mechanism of action, the primary Hallmark of Cancer it enables, and the associated human malignancies.

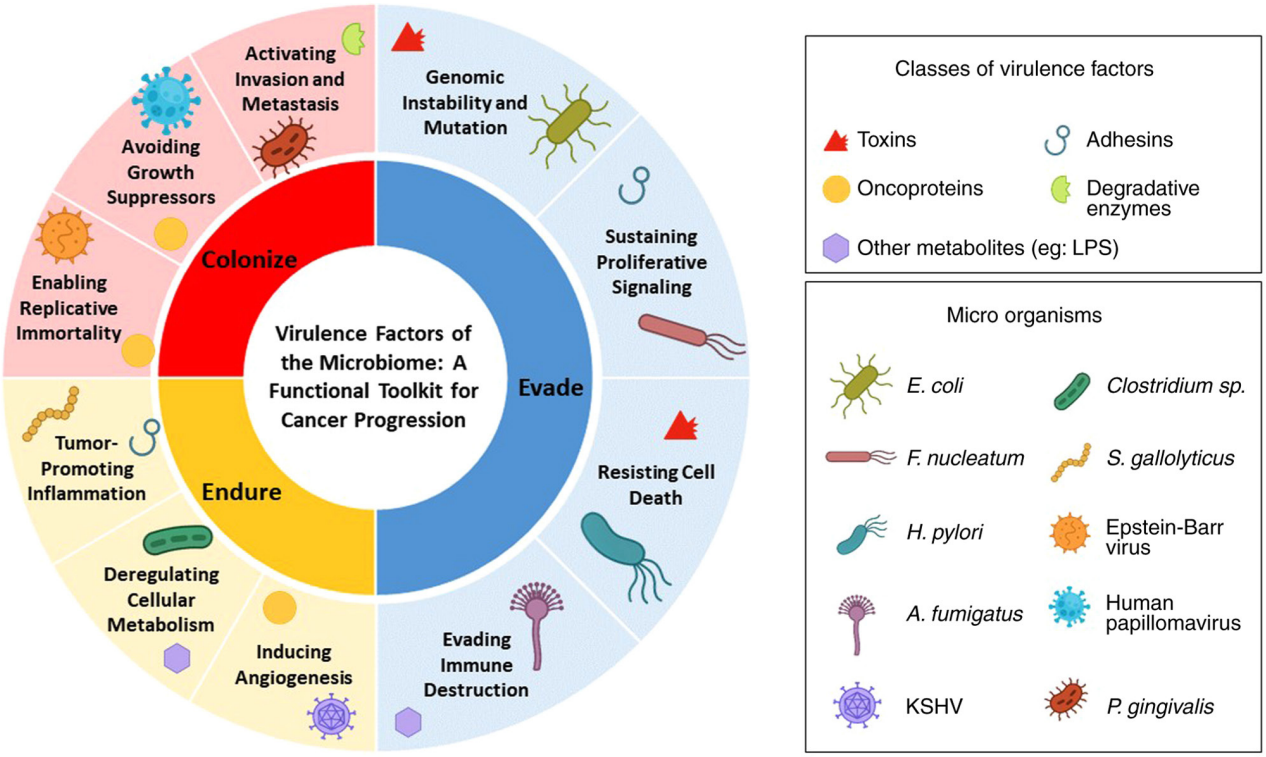

Figure 1. Microbial toolkit for cancer progression. This schematic organizes the classic Hallmarks of Cancer into three functional phases of progression: (blue), (yellow), and (red). The model illustrates how specific microorganisms exploit distinct virulence factors to drive these cancer hallmarks. Representative microbes are paired with icons indicating their primary class of virulence factor: Toxins, adhesins, oncoproteins, degradative enzymes, and other metabolites. The image was generated using Microsoft Copilot. LPS, lipopolysaccharide.

inflammatory environment (39,40). In non-gastrointestinal cancers, *Chlamydia trachomatis* secretes CPAF, a protease that degrades pro-apoptotic proteins and cell cycle regulators, promoting survival in cervical cells (41,42). Additionally, CNF1 from *E. coli* activates Rho GTPases, driving cytoskeletal rearrangement and motility (43,44).

While diverse in mechanism, these toxins converge functionally to enable the 'Genomic Instability' and 'Tumor-Promoting Inflammation' Hallmarks. Genotoxins such as Colibactin and CDT directly mutagenize the host genome, providing the genetic variation required for tumor evolution (the Endure phase). Meanwhile, modulating toxins such as CagA and BFT dismantle cell-cell junctions and induce EMT. This plasticity is essential for cancer cells to detach from the primary tumor, initiating the Evade phase of metastasis.

4. Degradative enzymes: Extracellular demolition crew

While toxins target intracellular pathways, microbial degradative enzymes target the extracellular matrix (ECM), the physical barrier to invasion (45).

Gingipains and hyaluronidases. Gingipains, cysteine proteases from *P. gingivalis*, degrade collagen and fibronectin. In oral squamous cell carcinoma, this activity breaks down the basement membrane, paving the way for invasion (28,46). Similarly, hyaluronidases secreted by *Staphylococcus* and *Clostridium* species cleave hyaluronic acid. This 'liquefies' the ECM in diverse cancer settings - from skin and breast cancer to urogenital tract malignancies, reducing physical resistance to cancer cell migration and facilitating angiogenesis (47,48).

Collagenases: Breaching the barrier. Collagenases from bacteria such as *Clostridium histolyticum* degrade the dense collagen scaffold of the ECM. In the TME, this activity assists cancer cells in breaching the tumor capsule and entering the vasculature (49). Interestingly, this mechanism is being explored therapeutically to 'soften' desmoplastic tumors (such as pancreatic cancer) to improve drug delivery (50).

These enzymes function as the tumor's 'demolition crew'. By degrading the basement membrane and ECM, they directly enable the 'activating invasion and metastasis' Hallmark. In the metastatic cascade, these factors are critical for the transition from the 'Evade' phase (local invasion) to the 'Endure' phase (intravasation into blood vessels). Without this enzymatic assistance, tumor cells would remain physically confined regardless of their genetic mutations.

5. Viral oncoproteins: Master hijackers of cellular machinery

Oncoviruses employ a strategy of genetic integration and protein hijacking. Rather than damaging the cell from the outside, viral oncoproteins seize control of core cellular machinery (51,52).

HPV E6/E7 and HTLV-1 tax. The E6 and E7 proteins of high-risk HPV tear down the p53 and Retinoblastoma (Rb) tumor suppressors, respectively. This removes cell cycle

checkpoints and prevents apoptosis, driving the uncontrolled proliferation observed in cervical and head-and-neck cancers (53,54). The HTLV-1 Tax protein functions as a transcriptional activator, driving the expression of IL-2 and its receptor to create a malignant autocrine loop in T-cell leukemias (55).

EBV and hepatitis virus oncoproteins. EBV's latent membrane protein 1 (LMP1) mimics a constitutively active CD40 receptor, driving survival signaling via NF-κB and MAPK pathways (56), while EBV Nuclear Antigen 1 ensures viral persistence and immune evasion (57). In liver cancer, HBV X protein and HCV Core protein act as promiscuous regulators, interacting with Wnt/β-catenin and generating reactive oxygen species to promote both proliferation and genomic instability (58-61).

Unlike bacteria that manipulate cells from the exterior, oncoviruses bypass the 'Evade' phase and jump directly to hijacking the cell's central command. By dismantling tumor suppressors (p53 and Rb) and mimicking growth signals (vGPCR and LMP1), these viral proteins directly enable the Hallmarks of 'Enabling Replicative Immortality' and 'Sustaining Proliferative Signaling'. This allows the infected cell to bypass natural checkpoints, ensuring the survival and expansion required for the 'Endure' phase of malignancy.

6. Structural components and metabolites: Environmental modulators

Beyond proteins, the microbiome influences cancer through structural components and metabolic byproducts. These factors modulate the 'soil' of the TME (62).

Structural components and extracellular vesicles

Lipopolysaccharide (LPS) and inflammation. LPS from Gram-negative bacteria activates TLR4, driving NF-κB-mediated inflammation. Previous evidence highlights the role of LPS in determining organotropism; circulating LPS can 'prime' the lungs for metastasis by upregulating inflammatory adhesion molecules, creating a receptive 'pre-metastatic niche' for breast cancer cells (63,64).

Fungal β-glucans: The microbiome is not limited to bacteria; the fungal 'mycobiome' is also a key resident of tumors. β-glucans, major structural components of the fungal cell wall, are potent immunomodulators recognized by host receptors such as Dectin-1 (65). In pancreatic cancer, fungi such as *Malassezia* migrate to the pancreas, where their cell wall β-glucans activate the complement cascade. This activation promotes inflammation and has been shown to accelerate tumor progression (66).

Microbial extracellular vesicles (MEVs): An increasing area of research focuses on MEVs - nanosized lipid bilayers released by bacteria. These vesicles act as long-distance delivery vehicles for virulence factors. In lung cancer, MEVs have been shown to enter host cells and modulate signaling pathways that suppress immune surveillance and promote EMT (67). Recent findings indicate that MEVs can alter the lung microenvironment to favor tumor colonization, representing a novel mechanism of host-microbe communication (68).

Metabolites: Chemical language of cancer

Secondary bile acids: Gut bacteria metabolize primary bile acids into secondary forms such as deoxycholic acid. In the liver, high levels of hydrophobic bile acids can induce DNA damage and senescence in stellate cells, creating a pro-inflammatory environment that facilitates hepatocellular carcinoma and liver metastasis from CRC (69).

Short-chain fatty acids (SCFAs) and hydrogen sulfide (H_2S): While often protective, SCFAs such as butyrate can be co-opted by cancer cells as an energy source (Warburg effect) (70). Similarly, H_2S produced by *F. nucleatum* promotes angiogenesis and fuels tumor cell mitochondrial metabolism (71).

While proteins act as targeted weapons, these structural and metabolic factors function as the 'fertilizer' for the TME. By maintaining chronic inflammation (LPS and β-glucans) and providing alternative fuel sources (SCFAs and H_2S), they enable the 'Tumor-Promoting Inflammation' and 'Deregulating Cellular Energetics' hallmarks. Crucially, factors including circulating LPS and MEVs act as long-range signals that prepare distant organs for the 'Colonize' phase, establishing the pre-metastatic niche before tumor cells arrive.

7. Future perspectives: Translating a virulence-centric model into clinical impact

The shift to a virulence factor-centric framework does more than reorganize the understanding of the microbiome's role in cancer; it provides a direct, mechanistic roadmap for intervention. This perspective aligns with the United Nations' Sustainable Development Goal 3, specifically Target 3.4, which calls for a one-third reduction in premature mortality from non-communicable diseases, with cancer being a primary target (72). By targeting the microbial drivers of malignancy, the 'toolkit' described in the present review, an entirely new front can be opened in this global effort.

A new frontier in diagnostics: Functional risk profiling. As understanding deepens, the future of cancer diagnostics lies in assessing the functional threat posed by the microbiome rather than just its taxonomic composition. The presence of the pks genomic island (encoding Colibactin) or specific alleles of fadA or vacA could serve as powerful prognostic biomarkers (73,74). Detecting the DNA of these virulence factors in a tumor biopsy or 'liquid biopsy' could identify patients at high risk for metastasis. For example, quantifying *F. nucleatum* load via fadA detection in blood shows promise for screening and predicting recurrence in CRC. Furthermore, the composition of the gut microbiome is now a validated predictive biomarker for patient response to immune checkpoint inhibitors (75). The future will involve developing precisely defined microbial signatures to predict treatment responses and determine if microbiome modulation is required before therapy begins.

Pioneering a new generation of therapeutic strategies. Targeting the microbial drivers of cancer represents a paradigm shift, offering therapies that complement and enhance traditional oncology. These strategies can be grouped into three main categories:

Disarming the pathogen (anti-virulence therapy): This precise approach aims to neutralize specific virulence factors without inducing broad-spectrum dysbiosis. Strategies include small molecule inhibitors designed to block the active sites of microbial enzymes, such as gingipains or bacterial collagenases, to prevent tissue invasion (76). Additionally, monoclonal antibodies could block critical adhesin-receptor interactions; for instance, blocking the Fap2 adhesin to prevent it from binding TIGIT on NK cells could restore antitumor immunity (77).

Precision microbiome editing: This strategy aims to selectively remove harmful 'oncomicrobes' or introduce beneficial ones. Bacteriophage therapy offers a highly specific method to eliminate bacteria such as *F. nucleatum* while leaving the beneficial microbiota unharmed (78). Furthermore, the development of preventative vaccines against oncogenic agents such as *H. pylori* or EBV remains a major goal for long-term cancer prevention (79).

Reshaping the ecosystem: This strategy aims to engineer the microbial community to support cancer therapy. This includes next-generation probiotics engineered to produce anti-inflammatory molecules or compete with pathogenic species (80). It also involves metabolic interventions, such as using prebiotics to favor butyrate-producing bacteria or drugs that inhibit the conversion of primary to secondary bile acids (81).

Charting the path forward: Key research frontiers. To translate these concepts into clinical reality, research must move from establishing correlations to proving causation. While animal models provide compelling evidence, a major hurdle remains in definitively proving that a specific microbial virulence factor is a driver, not just a 'passenger', in human cancer. This will necessitate sophisticated multi-omics analyses of large, longitudinal patient cohorts. Furthermore, recreating the complexity of the TME including hypoxia, immune cell infiltrate, and polymicrobial communities, through advanced co-culture systems and human tumor organoids will be essential for validating these new therapeutic targets.

8. Conclusion

The evidence presented in the present review reframes the role of the microbiome from a passive bystander to an active and versatile participant in cancer progression. By dissecting the microbial arsenal through the lens of its virulence factors, a clear picture emerges: The microbiome provides a functional 'toolkit' that cancer cells exploit to acquire and enhance the Hallmarks of Cancer. This analysis reveals a crucial pattern of functional convergence, where diverse microbes repeatedly target core host pathways including NF-κB, Wnt/β-catenin and p53 to facilitate the 'Evade, Endure and Colonize' phases of metastasis.

In essence, the tumor is not a solitary entity but a malignant ecosystem. Understanding its non-host members is a critical frontier in oncology. The intricate relationship between the microbiome and cancer is no longer a niche interest but a central theme in modern cancer biology. By continuing to unravel the functions of the microbial virulence toolkit, a powerful new pillar to our strategies for preventing and treating metastatic disease is ready to be introduced, directly contributing to the global goals of reducing cancer mortality.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

KV conceptualized the study, performed the literature search, and was a major contributor in writing the manuscript. BCP supervised the work and critically revised the manuscript for intellectual content. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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