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Review Article **Open Access**

Microbiomes and immune checkpoint mechanisms in cancer progression: A structured narrative review

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Abstract:

The role of the microbiome in modulating immune responses has garnered significant attention in cancer research, particularly in the context of immune checkpoint mechanisms. The microbiome influences the tumor micro-environment (TME) and the efficacy of immune checkpoint inhibitors (ICIs) by shaping immune cell function and responses. Immune checkpoints, such as PD-1, PD-L1, LAG-3, and CTLA-4, are critical in regulating immune tolerance and preventing excessive immune activation. However, in cancer, these checkpoints often suppress anti-tumor immunity, contributing to tumor immune evasion and therapeutic resistance. Emerging evidence suggests that the microbiome plays a pivotal role in regulating these checkpoints, enhancing or inhibiting the effectiveness of ICIs. Studies have shown that a balanced microbiome can promote a more favorable immune response, while dysbiosis may lead to increased inflammation and tumor progression. Additionally, the combination of microbiome modulation through probiotics, prebiotics, or dietary interventions, with immune checkpoint blockade has shown potential in overcoming resistance mechanisms and improving treatment outcomes. This comprehensive review explores the complex relationship between the microbiome and immune checkpoint mechanisms, highlighting how microbiome composition impacts immune checkpoint expression and function in cancer. It also discusses the therapeutic potential of microbiome-based interventions in conjunction with ICI therapies, emphasizing the need for further research to fully understand these interactions. Integrating microbiome science with cancer immunotherapy holds the promise of more effective, personalized treatment strategies that could improve patient outcomes and survival rates across various cancer types.

Keywords: Microbiome, immune checkpoint inhibitors, cancer progression, tumor microenvironment.

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Microbiomes et mécanismes des points de contrôle immunitaires dans la progression du cancer: une revue narrative structurée

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Résumé:

Le rôle du microbiome dans la modulation des réponses immunitaires a suscité une attention particulière dans la recherche sur le cancer, notamment dans le contexte des mécanismes des points de contrôle immunitaires. Le microbiome influence le microenvironnement tumoral (TME) et l'efficacité des inhibiteurs des points de contrôle immunitaires (ICI) en modulant la fonction et les réponses des cellules immunitaires. Les points de contrôle immunitaires, tels que PD-1, PD-L1, LAG-3 et CTLA-4, sont essentiels à la régulation de la tolérance immunitaire et à la prévention d'une activation immunitaire excessive. Cependant, dans le cancer, ces points de contrôle inhibent souvent l'immunité antitumorale, contribuant ainsi à l'évasion immunitaire tumorale et à la résistance thérapeutique. De nouvelles données suggèrent que le microbiome joue un rôle essentiel dans la régulation de ces points de contrôle, renforçant ou inhibant l'efficacité des ICI. Des études ont montré qu'un microbiome équilibré peut favoriser une réponse immunitaire plus favorable, tandis qu'une dysbiose peut entraîner une inflammation accrue et une progression tumorale. De plus, l'association de la modulation du microbiome par des probiotiques, des prébiotiques ou des interventions alimentaires, avec le blocage des points de contrôle immunitaire, a montré un potentiel pour surmonter les mécanismes de résistance et améliorer les résultats

thérapeutiques. Cette revue exhaustive explore la relation complexe entre le microbiome et les mécanismes des points de contrôle immunitaires, soulignant l'impact de la composition du microbiome sur l'expression et la fonction des points de contrôle immunitaires dans le cancer. Elle aborde également le potentiel thérapeutique des interventions basées sur le microbiome en association avec les thérapies par ICI, soulignant la nécessité de poursuivre les recherches pour comprendre pleinement ces interactions. L'intégration de la science du microbiome à l'immunothérapie anticancéreuse est prometteuse pour des stratégies thérapeutiques plus efficaces et personnalisées, susceptibles d'améliorer les résultats des patients et les taux de survie pour différents types de cancer.

Mots clés: Microbiome, inhibiteurs de points de contrôle immunitaires, progression du cancer, micro-environnement tumoral.

Introduction:

The concept of microbial communities and their influence on human health dates back to the 19th and 20th centuries. However, the word microbiome was first used by Joshua Lederberg in the early 2000s to describe a vast, complex community of commensal, symbiotic, and microorganisms that comprised of bacteria, viruses, fungi, archaea, and protozoa found in various ecosystems including living and non-living environments. Using their genetic materials, they interact with the essential component of life, influencing human health, environmental stability, and disease processes (1).

Microbiomes significantly influence the immune checkpoint pathways, thereby modulating immune regulation, disease progression, and responses to immunotherapy (2). The immune system itself is a complex natural defense network of cells, tissues, and organs whose mechanical synergy is useful in identifying and neutralizing infectious pathogens and harmful substances, including cancerous cells (3). Program cell death one (PCD-1), cytotoxic T-lymphocyte associated protein-4 (CTLA-4), lymphocyte activation gene-3 (LAG-3), and T-cell immunoglobulin and mucin domain containing-3 (TIM-3) are examples of immune-checkpoint pathways that function as on-and-off switches**,** inhibiting and switching off excessive immune activation and, in another way, switching on the activity of T-cells by promoting strong and sustainable activation against infections and development of cancer (4).

The inhibition of excessive immune responses is a preventive measure against autoimmunity, hypersensitivities, and graft rejection. While activation of T-cells is to eradicate infectious disease agents and cancer cells, dysregulation of immune checkpoint pathways whether through overactivation (allowing immune evasion in cancer) or suppression (leading to autoimmunity) plays a critical role in the development and progression of various chronic and life-threatening diseases (5). Factors contributing to immune checkpoint failure include; checkpoint ligand upregulation, where tumor cell overexpresses PD-L1 and inhibits T-cell activity. In another way, tumor cell can activate TIM-3, LAG-3, and V-domain Ig suppressor of T cell activation (VISTA), causing immune suppression and evasion. Furthermore, loss of major histocompatibility class I (MHC I) expression by tumor cell due to defective antigen presentation can prevent T-cell recognition and dampens immune activation. Mutation in immune-related genes can also lead to immune activation.

Microbiome dysbiosis is the hallmark of immune alteration. Certain microorganisms and their metabolites have the ability to inhibit or activate the immune checkpoint (6). Bacteria such as *Akkermansia muciniphila, Bifidobacterium,* and *Faecalibacterium* are implicated in T-cell activation and anti-tumor promotion. They also produce short-chain fatty acid (SCFAs) like butyrate and propionate that regulate effector T-cells balancing and immune tolerance activation. Some bacteria are also specifically involved in immune suppression of myeloid-derived suppression cells (MDSCs) and tumor-associated macrophages (TAMs) mounting immune surveillance response against cancer cells (7).

The exact molecular signaling pathway used by microbes to enhance anti-cancer immune checkpoint remains unclear. Microbial metabolites that influence T-cell activation and immune checkpoint specific impact on tumor microenvironments are understudied. Most research focuses on the gut microbiome, but the role of lung, skin and tumor microbiome in modulating immune checkpoint is underexplored and requires further research. Host factors such as sex, diet, genetic and pre-existing immune conditions influences microbiome-driven immune checkpoint and a standardized model to study immune interaction in different patient population is a major concern in clinical practice. This review therefore seeks to address the anti-tumoral roles of microbiomes and immune checkpoint, with the aim of providing the innovative prospects of immune checkpoint for anti-cancer immunity.

Methodology:

This review adopts a structured narrative review/evidence-based approach aimed at synthesizing current insights into the intricate relationship between microbiomes, immune checkpoint mechanisms, and cancer progression. An extensive literature search was cond-

ucted using peer-reviewed journal articles, expert reports, book chapters, and conference proceedings published over the last 30 (1995-2025) years.

The selection of literature was guided by keyword combinations including 'microbiome', 'immune checkpoint', 'cancer progression', 'immunotherapy', 'tumour microenvironment', and 'immune regulation'. Both theoretical discussions and experimental studies were reviewed, focusing on the molecular interactions, immune regulation pathways, and therapeutic implications of microbiome-immune system dynamics in cancer development. Information obtained was systematically evaluated and arranged to address the main research questions of the study (Fig 1).

For systematic approach to our main topic of review, we sectioned the article in four major parts addressing the following sections. Section 1 on human microbiome and cancer development outlines the composition, diversity, and functional roles of microbiomes, emphasizing their influence on cancer initiation and progression. Section 2 on immune checkpoint mechanisms and cancer progression highlights the molecular pathways of immune checkpoints, exploring their tumour inhibitory and tumour-promoting roles in cancer immunity. Section 3 on challenges of microbiome and immune checkpoint inhibitions in anti-tumoral efficacy discusses the factors limiting the effectiveness of microbiome manipulation and immune checkpoint blockade in cancer therapy, including inter-individual variation and tumour microenvironment complexity. Section 4 on innovative immune modulation checkpoints for future anti-cancer strategies presents emerging therapeutic concepts aimed at improving cancer treatment by synergistically targeting both the microbiome and immune checkpoint pathways.

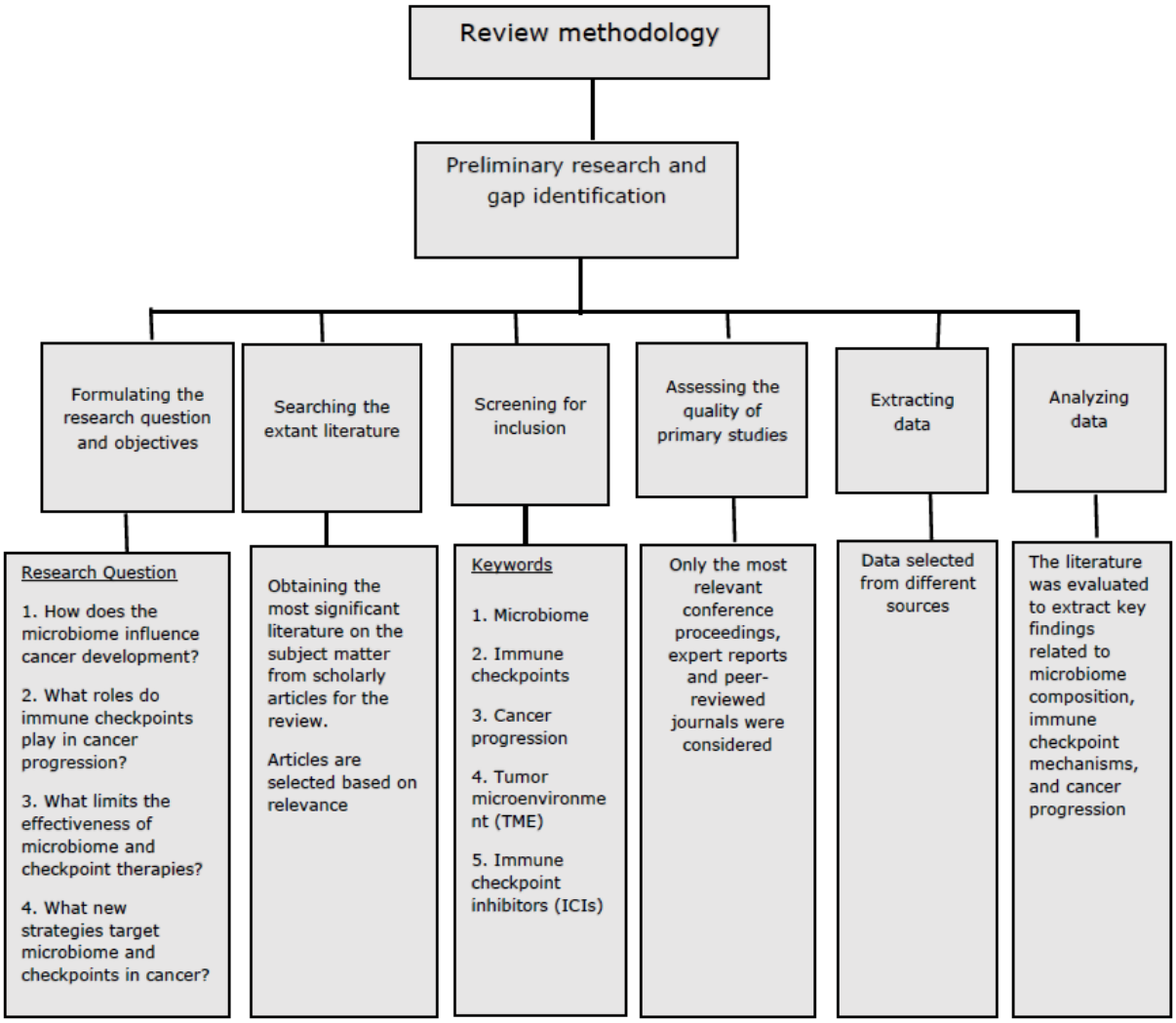


Fig 1: Schematic layout of the research review method

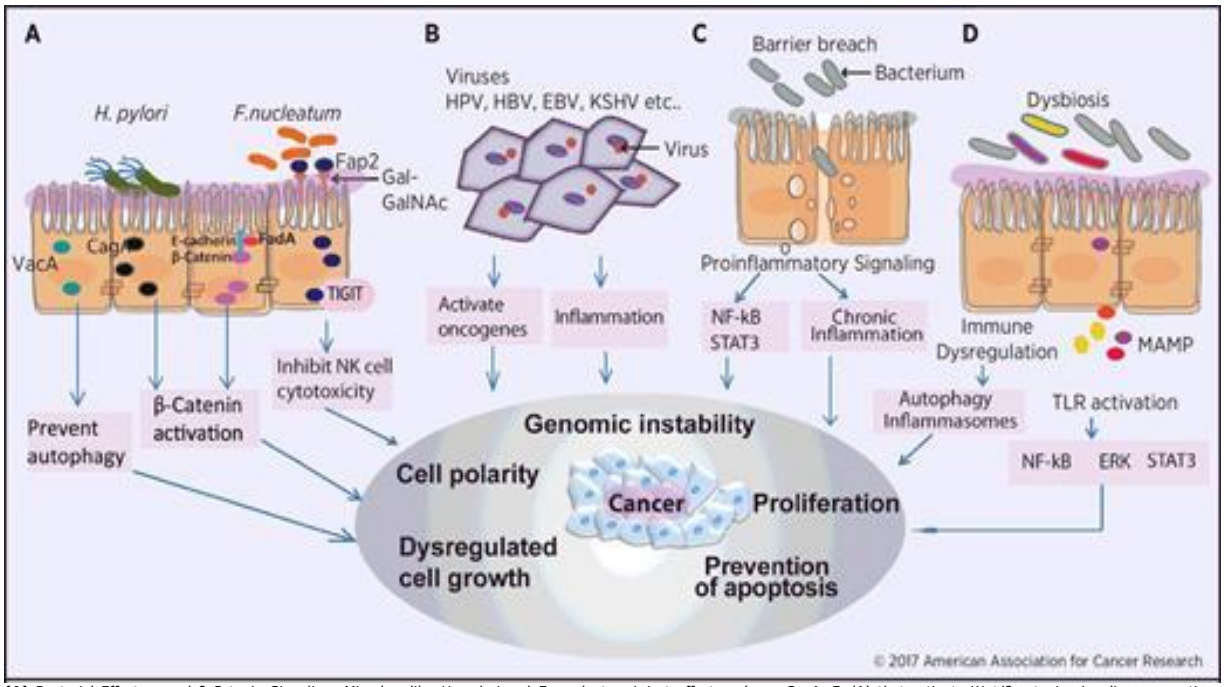
Human microbiome and cancer:

According to Rajagopala et al., (7), the human microbiome, especially the gut microbiota, influences cancer development by modulating immune responses, inflammation, and DNA repair. Specific microbial communities can either promote or inhibit cancer progression depending on their composition. Their findings revealed that pathogens promote cancer development through well-described genetic mechanisms.

There are 10 specific biological agents that have been designated by the International Agency for Cancer Research (IACR) as carcinogenic to humans. One of them, *Helicobacter pylori*, infect the stomach mucosa of half of the world population and cause chronic gastric inflammation, that can lead to gastric cancer (8) (Fig 2). The IACR noted that there are viruses that are known to cause various malignancies, some of which are sufficiently ubiquitous in the community to be considered part of the human virome. Recognized associations include human papillomaviruses (HPV) causing cervical carcinoma, hepatitis B (HBV) and C viruses (HCV) being the causative agents of hepatocellular carcinomas and human T-cell leukemia virus-1 (HTLV) being involved in T-cell leukaemia.

The composition of the gut microbiota can affect cancer onset and progression. Dysbiosis (imbalances in the microbiota) has been linked to the development of various cancers, such as colorectal cancer, breast cancer, and liver cancer. Certain microbial species, such as *Fusobacterium nucleatum*, have been associated with promoting cancer development by influencing inflammation and immune responses in the tumor microenvironment. The microbiome plays a significant role in modulating the effectiveness of cancer therapies, particularly immunotherapy, chemotherapy, and targeted therapies.

A diverse and balanced microbiome is crucial for enhancing the immune system's ability to respond to treatments like anti–PD-1 immunotherapy, as it can stimulate the immune system and reduce resistance to treatment. Some bacterial species, such as *Bifidobacterium* and *Faecalibacterium*, have been shown to enhance the effectiveness of immunotherapy by influencing immune cells like T-cells (9). The study of Gao et al., (10) emphasized the potential of microbiome modulation (through probiotics, antibiotics, diet, or fecal microbiota transplantation) to enhance cancer treatment outcomes. This can be particularly important in overcoming treatment resistance and improving overall survival rates of cancer patients.



(A) Bacterial Effectors and β-Catenin Signaling: Microbes like *H. pylori* and *F. nucleatum* inject effectors (e.g., CagA, FadA) that activate Wnt/β-catenin signaling, promoting tumorigenesis. *H. pylori* VacA protein inhibits autophagy. *F. nucleatum* also evades immune response by interacting with T cell immunoglobulin (TIG) and immunoreceptor tyrosine-based inhibitory motif (ITIM) (TIGIT) via its Fap2 protein. **(B)** Oncogenic Viruses: Viruses such as human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-lymphotropic virus (HTLV), Epstein-Barr Virus (EBV), and Kaposi's sarcoma-associated herpesvirus (KSHV) encode oncoproteins that disrupt DNA repair, alter epigenetics, and cause genomic instability, a hallmark of cancer. **(C)** Inflammation and Genomic Instability: Barrier failure triggers chronic inflammation and DNA damage, contributing to carcinogenesis. **(D)** Dysbiosis and Immune Dysregulation: Microbial imbalance leads to bacterial translocation and immune dysregulation. Microbial associated molecular patterns (MAMPs) activate Toll-like receptors (TLRs) (e. g., TLR4), triggering nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and signal transducer and activator of transcription 3 (STAT3) pathways and promoting cancer. Inflammasome activation and autophagy also play roles.

Fig 2: Mechanisms by which microbes promote carcinogenesis [Source: Sun et al., (8)]

Immune checkpoint mechanisms and cancer progression

Immune cells express chemicals called immune system checkpoints, which alter the degree of activity of the immune system. To stop excessive or unchecked immune activity, these checkpoints serve as essential regulators of the host body immunological response. During the last few years, a variety of control molecules of the immune system have been identified, including programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), lymphocyte activating gene 3 (LAG-3), T cell immunoglobulin and mucin domain-containing gene 3 (TIM-3) among others.

Immune checkpoint inhibitors (ICIs) increase immune activation against cancer cells by blocking negative immune regulation. The review by Rui et al., (11) underlined that the importance of the immune system as an active part of carcinogenetic process and its clinical significance provides the fundamental scientific basis for therapeutic and immunotherapeutic cancer remedies leveraging on the inhibitory checkpoint blockade with friendly characteristics.

Inhibitory mechanisms of PD-1 and cancer development:

Programmed death-1 (PD-1) is a transmembrane receptor belonging to the CD28 family and is characterized by two functional domains, an extracellular Ig V-like domain that binds to its ligands, Programmed death-ligand 1 (PD-L1, also known as B7-H1) and Programmed death-ligand 2 (PD-L2, also known as B7-DC), and an intracellular domain containing immunoreceptor tyrosine-based inhibitory motifs (ITIM and ITSM) responsible for mediating inhibitory signaling (12). Under physiological conditions, PD-1 plays a crucial role in suppressing excessive immune activation and inflammation, thereby preventing immune-mediated tissue damage and maintaining immune homeostasis, especially during infections. However, tumor cells can exploit this pathway to evade immune surveillance, leading to immune escape and cancer progression (13).

During inflammatory responses, PD-1 binds to its ligands PD-L1 and PD-L2, which are typically expressed on antigen-presenting cells (APCs) such as dendritic cells and macrophages, as well as on epithelial and endothelial cells. This interaction inhibits T-cell receptor signaling and activation, resulting in immunosuppression. The Src homology region 2-containing phosphatase-2 (SHP-2) is recruited by PD-1 interaction and aids in the dephosphorylation of important T-cell signaling molecules such as CD28 (needed for co-stimulation), zeta-chain-associated protein kinase 70 (ZAP-70, essential for signal transduction), and the phosphoinositide 3-kinase (PI3K)-AKT mammalian target of rapamycin (mTOR) pathway, which is vital for T-cell metabolism and proliferation. This inhibitory cascade leads to reduced interleukin-2 (IL-2) production, impaired release of pro-inflammatory cytokines such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and IL-2, ultimately dampening T-cell immune activity. The suppersion of T-cell function not only weakens the immune response but also creates a microenvironment favorable for tumor survival and progression (14).

Immune mechanism of CTLA-4 and cancer development:

The immune checkpoint inhibitory role of CTLA-4 is crucial in downregulating early T-cell activation, which is essential for the prevention of autoimmune reactions and maintaining immune homeostasis (16). Tumor cells can evade this immune mechanism, impeding natural T-cell immune surveillance and promoting cancer development (17). The CTLA-4 (CD152) is a transmembrane receptor found on activated $CD4^+$ and $CD8^+$ T cells. Its binding on regulatory T cells enhances their immunosuppressive functions (18). In situations where the CTLA-4 receptor has to perform activation and inhibitory roles synergistically, CTLA-4 competes with CD28, for binding to B7-1 (CD80) and B7-2 (CD86) ligands on antigen-presenting cells (APCs) (19). Although CTLA-4 has 10 to 20 times higher binding affinity for the B7 molecules than CD28, it is important to note that the binding of CD28 to B7 ligands activates T cells, leading to cytokine production (IL-2, IFN-γ), enhancing immune responses against infections and tumor cells (20).

When CTLA-4 binds to B7 ligands, T-cell activation is suppressed because B7 is no longer available to stimulate CD28 (17). Intracellularly, there is recruitment of SHP-2 and protein phosphatase 2A (PP2A). SHP-2 dephosphorylates ZAP-70 and PI3K, inhibiting TCR signaling, while PP2A dephosphorylates the AKT-mTOR pathway, reducing T-cell metabolism and survival (18). CTLA-4 signaling inhibits IL-2 transcription, decreases T-cell proliferation and activation, and prevents progression to the G1 phase of the cell cycle (21). The overall immune signalling cascade in cancer development and progression centers on T-cell anergy (dysfunction), exhaustion, and apoptosis, contributing to the increased prevalence of cancer (21).

Stimulatory checkpoint mechanism and cancer development:

The anti-tumoral role of stimulatory checkpoint mechanisms in cancer develop-

ment relies on the complete activation of T cells and the modulation of regulatory T cells (Tregs). These checkpoints also influence interactions within the tumor microenvironment, promote synergy with inhibitory checkpoints, enhance long-term immune memory, and support the activation of dendritic cells, natural killer (NK) cells, and cytotoxic T lymphocytes (CTLs) (22). Stimulatory checkpoints are primarily responsible for providing co-stimulatory signals, such as the interaction between CD28 on T cells and B7 (CD80/CD86) on antigen-presenting cells (APCs). This interaction lowers the activation threshold of T cells and strengthens a durable immune response against tumor antigens (19).

Furthermore, co-stimulatory signaling involving OX40, CD137 (4-1BB), and inducible T-cell co-stimulator (ICOS) promotes T-cell proliferation, cytokine production, and survival, which are essential for establishing long-lasting anti-tumor immunity (23). It is also important to note that stimulatory checkpoints can exert dual immune effects on Tregs in cancer. For instance, under certain conditions, the engagement of OX40, ICOS, and glucocorticoid-induced tumor necrosis factor receptor (GITR) can enhance Treg function, promoting immune suppression and facilitating tumor immune evasion, which may increase the risk of cancer progression (24). However, the interaction of OX40 and CD137 immune signaling has been shown to strengthen T-cell differentiation, thereby preventing tumor relapse after initial clearance and ensuring sustained immune surveillance (25).

Challenges of microbiome and immune checkpoint in anti-tumoral efficacy:

The influence of inter-individual differences on the anti-tumoral efficacy of the microbiome and immune checkpoints is substantial, particularly with respect to variability of major histocompatibility complex (MHC), also known as human leukocyte antigen (HLA) in human. The MHC or HLA is a group of genes located on chromosome 6 that encode proteins responsible for distinguishing self from non-self, making them essential mediators of immune recognition in contexts such as organ transplantation, autoimmune diseases, and cancer immunotherapy. Studies have shown that individuals with high HLA heterozygosity tend to exhibit improved responses to programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors in cancer treatment. Conversely, the diversity of HLA alleles shapes antigen presentation and immune responses to tumors, directly influencing the success of immunotherapeutic strategies (24).

Additionally, germline mutations contribute to variability in the anti-tumoral efficacy of both the microbiome and immune checkpoints. Pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and the MHC/HLA are germline-encoded and play central roles in immune cells recognizing pathogen-associated molecular patterns (PAMPs) and initiating immune clearance. Mutations in TLR genes can influence the composition of the gut microbiome and impair immune surveillance mechanisms, thereby affecting the response to immune checkpoint blockade therapy. Furthermore, single nucleotide polymorphisms (SNPs) in genes encoding CTLA-4, PD-1, FoxP3, and interleukin-10 have been shown to modulate immune checkpoint signaling and microbiome composition, further influencing the effectiveness of cancer immunotherapy (26).

Dietary influence on microbiome and immune checkpoint:

High fiber, Mediterranean diet improves microbiome community such as *Bifidobacterium, Faecalibacterium prausnitizii* and *Akkermansia muciniphila,* which in turns promote better ICI efficacy, reduce inflammation and promote anti-tumor immunity. However, easy accessibility and availability of excessive processed foods also known as ultra-processed food (UPFs) containing artificial additives, preservatives and unhealthy fats are often low in fiber, high in sugar, and sodium. This group of foods contributes to metabolic and cardiovascular diseases. Wei et al., (27) reported 95% cardiovascular related deaths attributed to low fiber diets. They also reported that the benefit of high fiber intake was statistically significant ($p<0.001$) among study groups, highlighting the link between dietary fiber consumption and a lower risk of metabolic syndrome (28).

Environmental factors and their effects on microbiome and immune checkpoint:

Geographical settlement, urban or rural, developing or under developing exposes and individual to diverse microbiome, alter immune system priming, different types of toxins and pollutants. All these can contribute to chronic inflammatory shift in microbiome composition, increase the presence of pro-inflammatory species, impairing ICI efficacy (29-31).

Microbiome dysbiosis in cancer development:

Johnson et al., (29) reported that microbiome dysbiosis is associated with disease duration and increased inflammatory gene expression. Research has also indicated that this microbiome imbalance can lead to deregulation of bodily functions, contributing to cardiovascular disease condition, cancer and respiratory diseases. The microbiome im-

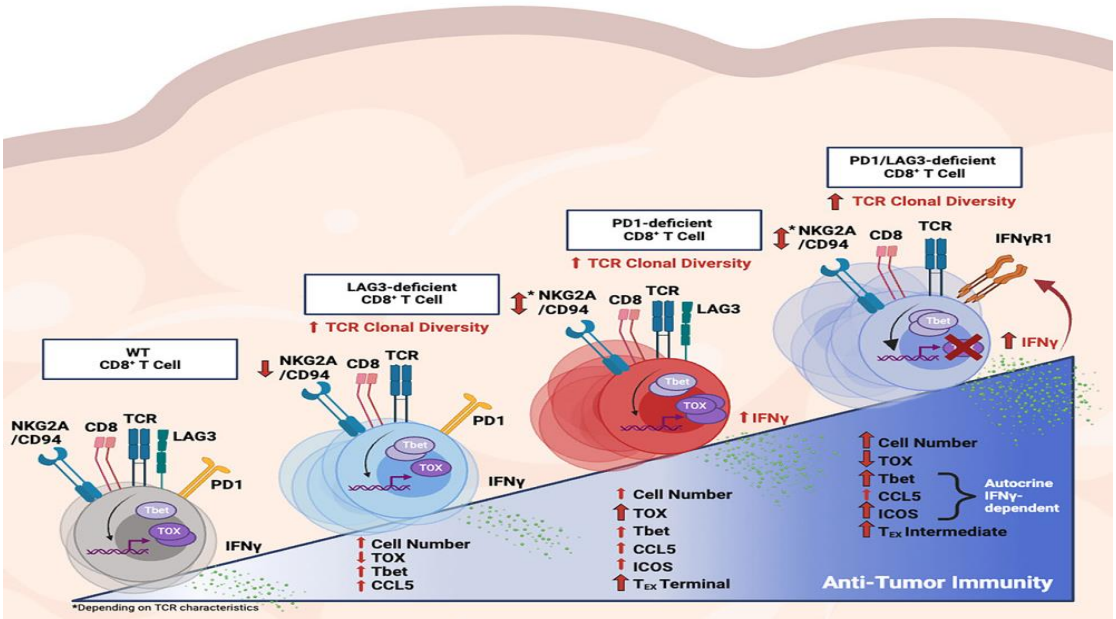
balance (dysbiosis) increases the release of pro-inflammatory (IL-6, TNF-α) cytokines leading to chronic inflammation, the hallmark of tumor progression. In dysbiosis, there is loss of beneficial microbiome which lead to promotion of myeloid-derived suppressor cell (MDSCs) and regulatory T cells (Tregs) which suppresses anti-tumor immunity. Alteration in drug metabolism leads to reduction in chemotherapy efficacy and allow tumor cell to evade immune destruction.

Innovative immune modulation checkpoints for future anticancer therapy:

Emerging research is expanding beyond traditional immune checkpoint inhibitors (ICIs) of PD-1/PD-L1, LAG-3, and CTLA-4 to identify next-generation immune modulation checkpoints. These innovations aim to enhance anti-tumor immunity and overcome the resistance mechanisms observed in cancer therapies. T cells that are worn out or malfunctioning express the immunoglobulin superfamily member lymphocyte activation gene-3 (LAG-3). LAG-3 is structurally and functionally similar to CD4, with multiple binding partners. Its expression negatively regulates T cell proliferation and differentiation, particularly inhibiting $CD8^+$ T cells that express higher levels of LAG-3 than $CD4^+$ T cells. Although they can express themselves separately, LAG-3 and PD-1 frequently coexist in the tumor microenvironment. LAG-3 contributes to T cell fatigue by suppressing anti-tumor T cell activity, just like PD-1 does.

Bispecific dual blockade of PD-1 and LAG-3 in the tumor microenvironment, where they are co-expressed, offers an opportunity to utilize immune checkpoint blockade while minimizing relapse and systemic toxicity (32). Research by Andrews et al., (24) demonstrated that the synergistic blockade and deletion of PD-1 and LAG-3 lead to distinct transcriptional and functional profiles in $CD8^+$ T cells, unleashing the full potential of the anti-tumor immune response. This finding offers valuable insight into potential therapeutic strategies for cancer immunotherapy (Fig. 3).

In particular, bispecific blockade of PD-1 and LAG-3 enhances T cell anti-tumor activity. In wild-type models, $CD8^+$ T cells with functional PD-1 and LAG-3 showed a higher degree of clonal diversity. Deleting LAG-3 in $CD8^+$ T cells induces clonal diversity by removing inhibitory signals, allowing more T cell variants to participate in tumor antigen recognition (32). Furthermore, in PD-1-deficient $CD8^+$ T cells, there is an upregulation of IFN-γ, accompanied by the production of other cytokines. Blocking PD-1 restores the maximum immune activity of T cells, leading to the production of IFN-γ, which in turn enhances cytotoxicity, promotes tumor cell killing, remodels the tumor microenvironment (TME), stimulates tumor immunogenicity, increases tumor antigen presentation, and promotes type I immune polarization (32).



The increasing improvement of anti-tumor immunity in several $CD8^+$ T cell populations, such as wild-type (WT), LAG3-deficient, PD1-deficient, and PD1/LAG3 double-deficient cells, is shown in this figure. When comparing modified T cells to WT, the image demonstrates increased expression of exhaustion markers (TOX, Tbet, ICOS, and CCL5), T cell clonal diversity, and IFN-γ production. Notably, $CD8^+$ T cells with PD1/LAG3 double-deficit have the highest levels of IFN-γ production and anti-tumor potential, most likely due to an IFN-γ autocrine feedback loop. This demonstrates how PD1 and LAG3 work together as inhibitors and how dual inhibition of them may be used therapeutically in cancer immunotherapy.

Fig. 3: PD1 and LAG3 play distinct functions in CD8 T cell-mediated anti-tumor immunity
[Source: Andrews et al., (24)]

Mice lacking both PD-1 and LAG-3 exhibit prolonged anti-tumor immunity due to enhanced T-cell receptor (TCR) clonal diversity, elevated autocrine IFN-γ, and an anti-tumor impact in the TME. The clinical relevance of dual PD-1 and LAG-3 blockade has led to the development of approved monoclonal antibody drugs such as Relatlimab (FDA-approved combination with Nivolumab), which shows potential for use in melanoma, lung cancer, colorectal cancer, and other solid tumors. Additionally, investigational drugs such as MBG453 and TSR-022 are in clinical trials for advanced solid tumors and haematological cancers (23,33,34).

Conclusion:

The interaction between the microbiome and immune checkpoint mechanisms plays a significant role in cancer progression and treatment outcomes. The microbiome can modulate immune responses, influencing the effectiveness of immune checkpoint inhibitors (ICIs) by enhancing anti-tumor immunity or contributing to immune evasion. Targeting immune checkpoints such as PD-1, PD-L1, LAG-3, and CTLA-4, in combination with microbiome modulation, shows promising potential for improving efficacy of cancer therapy.

However, further research is needed to better understand the complex interactions and optimize microbiome-based strategies for personalized cancer treatments. Ultimately, integrating microbiome research with immune checkpoint therapy offers a promising approach to improving patient outcomes in cancer treatment.

Contributions of authors:

EMO conceptualized the review topic, performed the initial literature search, and drafted the first version of the manuscript; ANN contributed to organizing the structure of the review and assisted in literature synthesis and referencing; CG critically reviewed the manuscript, ensuring clarity, accuracy, and intellectual depth and EGM supervised the entire process, provided strategic direction and final approval of the manuscript for publication.

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Conflict of interest:

Authors declare that there are no conflicts of interests regarding the publication of this review.

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