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GUT MICROBIOME–DRIVEN PERSISTENCE AND IMMUNE ESCAPE OF HUMAN ONCOGENIC VIRUSES: MECHANISTIC INSIGHTS AND MICROBIOTA-TARGETED THERAPEUTIC STRATEGIES

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ABSTRACT

The human gut microbiome has now been identified as an essential modulator of host immunity, with a role in the susceptibility to infectious diseases, the maintenance of immune homeostasis and cancer development. Recent studies have shown that the gut Virus-Microbiota interactions are not limited to local mucosal interactions, but also have a prominent role in viral persistence, immune escape and in virus-mediated carcinogenesis. The role of the gut microbiome in the establishment of chronic viral infection and tumor-promoting immune milieu is not fully understood yet, even though significant progress has been made in understanding the molecular mechanisms of oncogenic viruses. In this review, the mechanistic connection among the gut microbial community and the major oncogenic viruses in humans such as human papillomavirus, Epstein–Barr virus, hepatitis B virus, hepatitis C virus, Kaposi's sarcoma-associated herpesvirus, and Merkel cell polyomavirus are comprehensively discussed. The importance of microbiome-mediated modulation of innate and adaptive immune responses, chronic inflammation, interferon signaling, immune checkpoint activation, expansion of regulatory T cells and production of bioactive microbial metabolites that mediate viral persistence and immune evasion is emphasized. We discuss how microbial dysbiosis is linked to disruption of antiviral defenses, promotes tolerogenic immune networks and sets the stage for viral latency, reactivation and malignant transformation. Moreover, new studies that correlate specific microbial features to virus-associated cancers are thoroughly reviewed and discussed for their possible potential as biomarkers for disease process and therapeutic response. The review further addresses novel microbiota-targeted strategies such as probiotics, prebiotics, postbiotics, fecal microbiota transplantation, dietary modulation, and microbiome engineering strategies as promising strategies to restore immune competence and promote antiviral and antitumor actions. Finally, current challenges and unanswered questions are explored as well as future research directions, with a special focus on multi-omics technologies and precision microbiome-based medicine. The body of evidence presented herein suggests that the gut microbiome is a key player in oncogenic viral persistence and immune evasion, providing new therapeutic targets in prevention, diagnosis and treatment of virus associated malignancies.

KEYWORDS: Gut microbiome; Oncogenic viruses; Viral persistence; Immune escape; Microbial dysbiosis; Cancer immunology; Microbiota-targeted therapy; Virus-associated cancers.

INTRODUCTION

Human gut microbiome is a highly complex and dynamic ecosystem of trillions of microbes co-existing, comprising bacteria, archaea, fungi and viruses and collectively contributing to host physiology and immune regulation. Recent developments in microbiome studies have revolutionized the field of microbiomes and their interactions with the host, highlighting the gut microbiota as an essential component of metabolic homeostasis, mucosal integrity, and immune competence over the past decade. In addition to its role in intestinal health, growing evidence has emerged that the gut

microbiome has distant, systemic effects on other organs and tissues via immune, metabolic, and signaling pathways, which impact susceptibility to infectious disease, chronic inflammation, and cancer.[1,2,3]

Human oncogenic viruses are a significant global health problem and cause about 10-15% of cancers worldwide. These viruses, such as human papillomavirus (HPV), Epstein–Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), Kaposi's sarcoma-associated herpesvirus (KSHV), and Merkel cell polyomavirus (MCPyV), have evolved sophisticated mechanisms that allow them to remain in the host for long periods while avoiding clearance by the immune system. Viruses are related to carcinogenesis in several ways, with persistent viral infection being regarded as an essential precondition for virus-driven cancer. While a number of molecular pathways have been identified that contribute to viral oncogenesis, the cellular components of the immune system and other host factors that allow a virus to persist and evade host immune detection are not fully understood.[4,5]

In recent years, scientists have discovered that the gut microbiome is a little-known contributor to antiviral immunity and tumor-associated immune responses. Microbial imbalance or dysbiosis has been associated with decreased interferon signaling, chronic inflammatory activation, upregulation of immune checkpoints, expansion of regulatory T cells, and generation of immunosuppressive microenvironments that support viral survival. Additionally, microbial metabolites and microbial metabolites derived signaling molecules may be able to regulate local and systemic immune pathways, which in turn may affect viral latency, reactivation and disease process.[6,7,8] The results have led to the new idea of the gut–virus–immune axis, which emphasizes the pivotal role of gut microbes in determining the fate of oncogenic viruses.

With the increasing appreciation of the role of microbiome-mediated mechanisms in the biology of cancer, the role of gut microbiota in viral persistence and immune evasion is an emerging research field of interest. This review will focus on understanding the mechanistic interactions between the gut microbiome and oncogenic viruses, especially their role in immune modulation, persistence, and cancer development. Further, recent advances in microbiota-targeted therapeutic approaches and future prospects for precision microbiome intervention for the prevention and treatment of virus-associated malignancies are also comprehensively discussed.[9,10]

2. The Gut Microbiome as a Regulator of Antiviral Immunity

Gut microbiome is a critical player in the development, education and regulation of the host immune system. Gut microorganisms play a role in maintaining immune homeostasis and effective antiviral defense through ongoing interactions with cells of the gut epithelium and immune cell populations. Gastrointestinal tract harbors one of the largest immune compartments in human body which is referred as gut associated lymphoid tissue (GALT) and acts as an important interface between microbial community and host immune system. In this context, microbial-derived signals alters both innate and adaptive immune responses, which impacts the host's ability to recognize and to eliminate viral pathogens.[11,12]

Multiple interdependent mechanisms are responsible for the antiviral immune functions of commensal microorganisms. The microbial associated molecular patterns (MAMPs) bind to pattern-recognition receptors (PRRs) such as Toll-like receptors and NOD-like receptors which trigger the production of type I and type III interferons which are critical for viral restriction. The gut microbiota also matures and activates dendritic cells, macrophages, natural killer (NK) cells and virus-specific T lymphocytes, thus facilitating immune surveillance and antiviral effector functions.[13,14]

Microbiota metabolites also regulate immune responses. Epithelial barrier function is regulated by short chain fatty acids (SCFAs), in particular, butyrate, acetate and propionate, which also modulate the subsets of immune cells. These metabolites are able to balance inflammatory and regulatory pathways to provide efficient control of pathogens with minimised tissue damage. On the other hand, microbial imbalance, or dysbiosis, can disrupt interferon signaling, disrupt mucosal barriers and facilitate chronic inflammatory conditions that affect antiviral immunity.[15,16]

Recent evidence indicates that interactions between the gut microbiome and the body extend beyond the gut via the gut–immune axis. Microbial products and immune mediators are systemically distributed to distant tissues and regulate immune responses to chronic viral infections. Thus, shifts in microbial diversity and function could play a role in poor viral clearance, prolonged viral infections, and immune escape and oncogenic transformation.[2,17]

Table 1: Major Gut Microbiome Components and Their Roles in Antiviral Immunity.[2,14,18]

Microbiome Component	Major Immune Function	Impact on Antiviral Defense
Short-chain fatty acids (SCFAs)	Regulation of immune homeostasis and epithelial integrity	Enhance mucosal defense and modulate antiviral responses
Commensal bacteria	Activation of innate immune signaling pathways	Promote interferon production and pathogen recognition
Dendritic cell–microbiota	Antigen presentation and T-cell priming	Strengthen adaptive antiviral immunity

interactions		
Natural killer (NK) cell activation	Early elimination of infected cells	Improves viral clearance during initial infection
Gut epithelial barrier	Prevention of microbial translocation and inflammation	Limits systemic immune dysregulation
Regulatory microbial metabolites	Immune modulation and cytokine regulation	Balance antiviral activity and immune tolerance

The compelling evidence presented here underscores the role of the gut microbiome as a hub of antiviral immunity that can affect local and systemic immune responses. The interactions between these pathways help to define an important mechanism by which microbial dysbiosis promotes the halting of immune responses and the persistence of oncogenic viruses, as described in following sections.[19,20]

Human Oncogenic Viruses: Biology, Persistence, and Cancer Development

The human oncogenic viruses are a special class of pathogens that can cause persistent infection contributing directly or indirectly to malignant transformation. Together these viruses make up a significant percentage of the cancers occurring around the world and are a significant problem in global oncology. Oncogenic viruses are able to maintain themselves for long periods of time in infected tissues through sophisticated molecular mechanisms that provide for their survival in a chronic biological environment that is conducive to the development of tumors, while acute viral infections are eliminated effectively by host immune responses.[5,17,21]

HPV, EBV, HBV, HCV, KSHV, and Merkel cell polyomavirus (MCPyV) are the main oncogenic viruses that infect humans. These viruses have a number of similarities as well as differences, in terms of their genomic structure, cellular tropism and transmission routes, but they share the characteristic of being able to evade immune surveillance and persist in the host. Important for viral oncogenesis is viral persistence, which means that over a long period viral proteins are continuously expressed that disrupt or interfere with the host cells' pathways controlling proliferation, apoptosis, DNA repair, and immune regulation.'[4,8,22]

Multiple viruses are oncogenic and have the ability to become latent. In latency, genomes of viruses are preserved in host cells, and the expression of immunogenic viral antigens is inhibited, reducing the recognition of viral antigens by the immune system. Viral reactivation then can lead to chronic inflammation, tissue damage and repeated cycles of cellular regeneration, which can lead to the development of oncogenic mutations. In addition, viral oncoproteins can activate critical pathways that regulate tumour suppressor genes such as the p53 and retinoblastoma (Rb) pathways, which can cause cells to multiply in an uncontrolled way and become unstable.[5,6,23]

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Persistent Virus Infections significantly remodels the tumor microenvironment in addition to their direct oncogenic activity. Chronic antigenic stimulation leads to immune exhaustion, an imbalance of cytokines and the recruitment of immunosuppressive cell subsets, such as regulatory T cells and myeloid-derived suppressor cells. These changes allow for immune evasion and also promote tumor growth. In addition, there is growing data that host-associated factors, especially the gut microbiome, affect the efficiency of these mechanisms through mechanisms that affect antiviral immunity and systemic inflammatory responses.

Thus, the biological mechanism of viral persistence and oncogenesis is key to understanding how gut microbiota regulation of host immune responses might promote the onset and development of virus-induced malignancies.'[4,8,24]

Gut Microbiome–Mediated Mechanisms Promoting Viral Persistence

However, the persistence of oncogenic viruses in the host is not only dependent on the virus, but also heavily affected by the microbial environment. Emerging evidence suggests that changes in the gut microbiota may affect immune system activity and establish a state that promotes viral persistence. This relationship is especially important in the case of oncogenic viruses, where the basis for malignant transformation and disease progression is persistent infection.[12,15,25]

Microbial dysbiosis may affect antiviral immunity in many ways. This has one of the most significant effects, blocking interferon-mediated signal transduction pathways, which are crucial in controlling viral replication and also in augmenting immune surveillance. A decrease in microbial diversity has been linked to a decrease in the activation of innate immune cells, like dendritic cells and natural killer cells, which serve as a crucial early defense mechanism against virus. At the same time, intestinal barrier dysfunction can allow microbes to leak through into the bloodstream and lead to chronic low-grade inflammation, leading to immune dysfunction.[1,18,26]

Viral persistence is also controlled by the production of bioactive metabolites by the gut microbiome. Variations in the numbers of beneficial microbial species can impact the production of metabolites which can influence cytokine production, T-cell differentiation and antigen presentation. These changes can affect the virus clearance efficiency, enhance immune tolerance and

tolerance. Moreover, an environment of chronic inflammation, due to an imbalance of the microbial communities, induces a microenvironment with a constant stimulation of the immune system and tissue remodeling, which may facilitate the latent periods and periodic reactivation of viruses.[24,27]

Recent studies indicate that microbiome-mediated immune modulation is not limited to the gastrointestinal tract and its effect is also observed in systemic antiviral functions, as well as in the susceptibility of hosts to persistent viral infections. The results underscore the significance of the gut microbiome in shaping the control of oncogenic viruses or their long-term persistence.[28]

Table 2: Mechanisms by Which Gut Microbiome Dysbiosis Promotes Viral Persistence.[24,29]

Mechanism	Biological Effect	Consequence for Oncogenic Viruses
Reduced microbial diversity	Impaired immune homeostasis	Decreased antiviral surveillance
Defective interferon signaling	Weakened innate antiviral responses	Enhanced viral replication and persistence
Intestinal barrier disruption	Increased microbial translocation	Chronic systemic inflammation
Altered microbial metabolites	Dysregulated cytokine production and T-cell function	Reduced viral clearance
Chronic inflammatory activation	Persistent immune dysfunction	Promotion of viral latency and reactivation
Impaired dendritic and NK cell activity	Reduced recognition of infected cells	Facilitation of immune evasion and long-term infection

The collective impact of these mechanisms underscores the critical role of gut microbial homeostasis in regulating antiviral immunity and determining the long-term outcome of oncogenic viral infections.[5]

Microbiome-Driven Immune Escape Mechanisms in Oncogenic Viral Infections

Immune escape is a hallmark of chronic oncogenic viral infections and a critical process in the evolution from chronic infection to malignancy. In addition to their intrinsic immunity-avoidance mechanisms, oncogenic viruses also have the potential to influence immunological pathways that support their immune evasion, and emerging evidence suggests this is a key role played by the gut microbiome. Microbial changes in flora and microbial activity can have a profound effect on innate and adaptive immune responses, establishing a environment conducive to a long term presence of viruses.[25,28]

Promoting immunosuppressive cellular networks is one of the main mechanisms by which the gut microbiome is associated with immune escape. An increasing proportion of regulatory T cells (Tregs) have been linked to microbial dysbiosis, and Tregs inhibit antiviral effector mechanisms and reduce the activity of CD8+ T cytotoxic lymphocytes. At the same time, dysbiotic conditions can promote the accumulation of myeloid-derived suppressor cells (MDSCs), which also promote immune tolerance and inhibit antigen-specific immune responses.[4,15]

Gut Microbiome also impacts the expression of Immune Checkpoint molecules that control T cell function. The continued inflammatory response caused by the changes in the microbiota can lead to upregulation of inhibitory receptors like programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Chronic activation of these pathways results in a state of T-cell exhaustion, which involves decreased proliferative ability, loss of cytokine production and decreased antiviral activity. These circumstances give oncogenic viruses a chance to escape immune mediated eradication.[22,28]

Furthermore, microbiota metabolites and microbial signaling molecules can regulate the cytokine network, promoting a tolerant immune response. Chronic infection is maintained by increased amounts of immunosuppressive mediators such as transforming growth factor-β and interleukin-10, which aid in viral persistence. Together, these microbiome-driven mechanisms create a tolerogenic immune environment that facilitates oncogenic viruses to outsmart immune surveillance, to remain in host tissues and eventually to promote the initiation and progress of tumors.[8]

Evidence Linking Gut Microbiota to Specific Oncogenic Virus-Associated Cancers

Recent studies have revealed a strong link between changes in gut bacteria and the development and progression of various virus-related cancers. While oncogenic viruses are the main causes of these cancers, gut microbiome has been shown to be a key modifier of disease susceptibility, immune responses, and tumor behavior. The gut microbiota could affect viral persistence and the oncogenic effects of chronic infection via its role in the regulation of systemic inflammation, immune surveillance, and metabolic signalling.[5,9]

In HPV related cancers such as cervical and/or oropharyngeal cancers, microbial dysbiosis has been associated with chronic infection and decreased local immune responses. Likewise, EBV-associated malignancies including nasopharyngeal carcinoma and some lymphomas demonstrate immune changes which could be potentially affected by microbiome-derived inflammatory and immunoregulatory signals. Hepatitis B

virus (HBV) and hepatitis C virus (HCV) are known to cause chronic infection, which increases the risk of developing hepatocellular carcinoma (HCC). Microbial imbalance plays a role in the gut–liver axis in chronic HBV and HCV infections, leading to hepatic inflammation and immune dysfunction.

Recent research has also suggested that microbiome-mediated immune modulation is involved in the development of Kaposi's sarcoma-associated herpesvirus (KSHV) associated malignancies and Merkel cell polyomavirus (MCPyV) associated Merkel cell carcinoma. While the mechanism of action is not fully understood, microbial metabolites, inflammatory mediators and immune checkpoint pathways could all play a role in creating tumour-promoting environments. These observations provide a strong rationale for gut microbial composition to be used as a marker of disease and as a future therapeutic target and/or diagnostic marker in virus-associated cancers.[18,19,25,30]

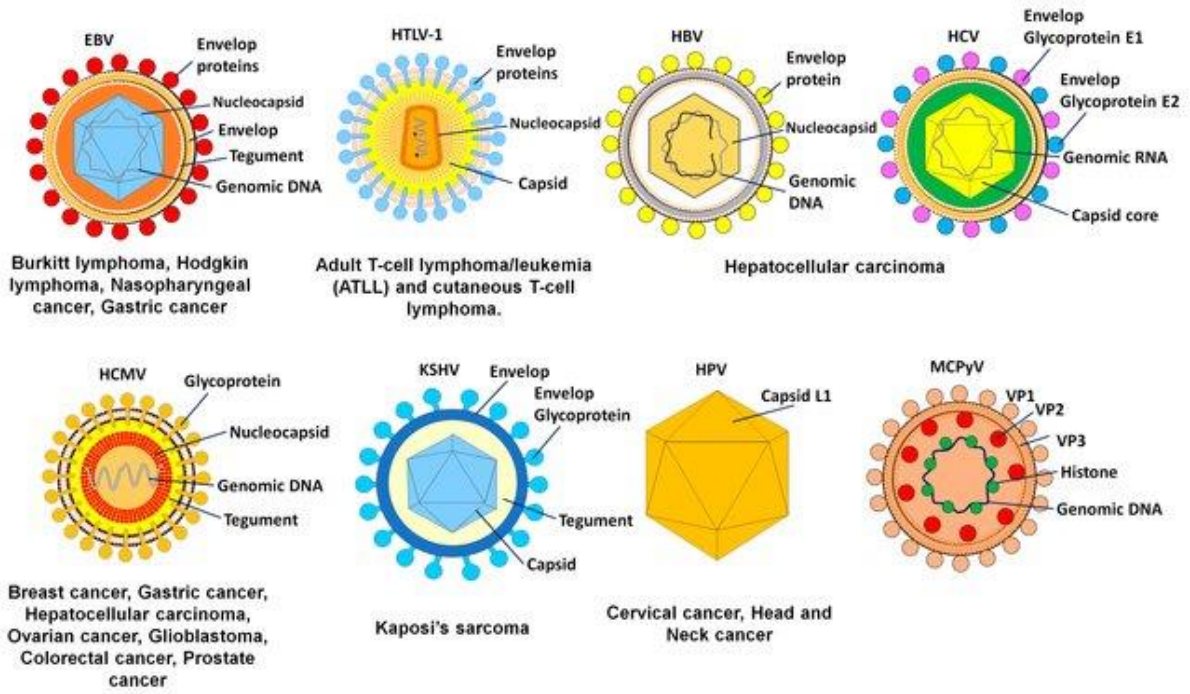

Figure 1: Major human oncogenic viruses and their associated malignancies. The diagram illustrates the principal cancer types linked to HPV, HBV, HCV, EBV, KSHV, and MCPyV, highlighting the tissue-specific tropism and oncogenic potential of these viruses. Adapted from Abyar et al.(2025).

Table 3: Associations Between Oncogenic Viruses, Related Malignancies, and Gut Microbiota Influence.[17,26]

Oncogenic Virus	Major Associated Cancer(s)	Potential Role of Gut Microbiota
Human papillomavirus (HPV)	Cervical cancer, oropharyngeal cancer	Promotes viral persistence and local immune dysregulation
Epstein–Barr virus (EBV)	Nasopharyngeal carcinoma, lymphomas	Modulates inflammatory and immunosuppressive pathways
Hepatitis B virus (HBV)	Hepatocellular carcinoma	Influences liver inflammation through the gut–liver axis
Hepatitis C virus (HCV)	Hepatocellular carcinoma	Contributes to chronic inflammation and immune dysfunction
Kaposi's sarcoma-associated herpesvirus (KSHV)	Kaposi sarcoma	May enhance immunosuppressive tumor microenvironments
Merkel cell polyomavirus (MCPyV)	Merkel cell carcinoma	Potentially affects immune surveillance and tumor progression

Collectively, these findings highlight the growing importance of the gut microbiome as a biological factor influencing the clinical outcomes of oncogenic viral infections and their associated malignancies.[26]

Microbiota-Targeted Therapeutic Strategies to Counter Viral Persistence and Immune Escape

Immune Escape

In recent years, the gut microbiome has emerged as a major regulator of antiviral immunity, sparking a great deal of interest in therapeutic strategies that aim to target the gut microbiota. By restoring microbial homeostasis,

it is suggested that microbial imbalances, which are linked to immune dysfunction and oncogenic viral persistence, can be reduced, tumor immunity can be improved, and perhaps even immune system disorders can be reversed. In recent years, the study of the microbiome has led to new therapeutic strategies that seek to alter the composition and function of the microbiome in order to enhance clinical results for virus associated malignancies.[11,19,25]

Some of the highest studied interventions include probiotics and prebiotics. Enhancing integrity of epithelial barrier, controlling inflammatory responses and activation of antiviral immune pathways are all properties known to be beneficial for some microbial strains. In the same way, prebiotics promote some types of microorganisms, restoring the microbial diversity and immune homeostasis. Besides these methods, postbiotics such as microbial metabolites and bioactive compounds have recently gained interest as therapeutic candidates, because they are able to communicate with the immune system via signaling without the need to be ingested in the form of viable organisms.[16,22]

Another potential approach to treating extreme microbial dysbiosis is fecal microbiota transplantation (FMT). FMT has shown potential to restore microbial diversity, boost immune function and increase responsiveness to immunotherapeutic interventions by introducing a healthy community to a recipient. Use in oncogenic viral infections is still being investigated, but there is growing evidence suggesting its possible role in the modulation of antiviral and antitumor immune responses.[26,28]

The progress of recent technologies has also enabled the creation of microbiome engineering strategies, such as genetically engineered bacterial strains and precision microbiome interventions with specific immunomodulatory effects. In addition, the potential synergistic effects of microbiota-targeted therapies when used in combination with antiviral therapy, immune checkpoint inhibitors, and cancer immunotherapies would be beneficial because they would not only inhibit the virus, but they would also disrupt immune escape mechanisms.

As a whole, these new strategies point to the therapeutic promise of manipulating the microbiome as a new approach to virus-associated cancer prevention and treatment. Future precision medicine strategies involving oncogenic viral diseases may involve microbiota based interventions as an important part of their precision medicine strategies, with the understanding of the mechanisms expanding.[30]

Challenges, Knowledge Gaps, and Future Perspectives

Although the link between the gut microbiome and oncogenic viral infections is well established, many questions remain regarding how the microbial community may affect viral persistence, immune escape, and cancer development remains. The current evidence strongly indicates a gut–virus–immune axis, but most of the evidence comes from observational studies, animal models, and small-scale clinical studies, which makes establishing direct causal relationships difficult.[31]

A significant interindividual variability in the microbiome composition is one of the major challenges in this field. Microbial diversity and functionality can be significantly affected by factors such as age, diet, genetic makeup, lifestyle, geographical location, medication and environmental exposures. It is therefore challenging to determine which are the universal microbial signatures of particular oncogenic viral infections. In addition, the microbial composition of the gut is constantly changing and it is difficult to know if changes in the microbiome are contributing factors to disease progression or if they are a result of disease progression.[32]

The molecular mechanisms that connect microbial metabolites and immune signaling pathways to viral latency, reactivation and oncogenesis is another important gap in knowledge. Although there is emerging evidence for roles of short-chain fatty acids, bile acid metabolites, and inflammatory mediators, the downstream pathways responsible for antiviral immunity regulation have yet to be fully characterized. A combination of cutting-edge multi-omics technologies, such as metagenomics, metabolomics, transcriptomics, and single cell immune profiling will be needed to answer these questions.[33,34]

Standardized methodologies for microbiome analysis and validation of microbiota-based biomarkers in a range of patient populations should be developed in the future. Complementarily, the emerging precision microbiome medicine will drive new and faster progress towards precision therapeutic approaches based on patient-specific microbial and immune characteristics. Combination of microbiota-targeting interventions and antiviral therapies, immunotherapy and cancer prevention programs could offer new avenues for enhanced clinical outcomes.[34,35]

In summary, future research into microbiome–virus interactions can deepen understanding of the mechanisms of virus-driven cancer and help to translate microbiome research into novel diagnostics and therapeutics for cancer caused by viruses.[36,37,38]

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