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The Role Microbiome and Oncolytic Viruses Play in Controlling Cancer

Emmanuel Atiatorme [a*], Richard Osafo [b] and Simon Nyarko [c]

[a] Department of Biotechnology, College of Advance Sciences & Technology, Andhra University, Visakhapatnam-530003, India.
[b] School of Health and Life Sciences, University of the West of Scotland, Paisley Campus, Scotland, UK.
c Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.

Authors' contributions

This work was carried out in collaboration among all authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

There has been a lot of short backs from the use of the usual conventional anti-cancer therapy for treating cancer cells. Conventional anti-cancer therapy involves the use of chemical chemotherapeutics and radiation to treat cancer whereas sometimes it may include the use of surgery, hormones, and targeted therapy. These drawbacks and ineffectiveness of such therapies sometimes can aggravate other types of illness and cause tumor cells to become resistant to them. In an attempt to resolve these shortcomings, a new era of an alternative anti-tumor therapy has emerged which exhibits much greater specificity and efficacy in treating cancer. This new knowledge explores the use of microbes and oncolytic viruses as potential anti-cancer therapies. Most of these microbes and viruses are engineered or their metabolites are used as potential weapons for treating cancer cells. This review therefore discuss the role of microbiome and oncolytic viruses in controlling cancer. It also outline four ways through which microbiome control cancer treatment. We reviewed the microbiome metagenomic assessment, explained some evidence of microbiome oncogenesis, then again investigated the response and toxicity of microbiome on immunotherapy, and finally discuss the impact of microbiome activities on chemotherapy. We reported that, the metagenomic study of the 16s rRNA gene sequence plays a

**Corresponding author: Email: emmanuelmawuliatiatorme@gmail.com;*

significant role in detecting bacterial species in natural specimens and establishing phylogenetic relationships in controlling cancer. The review again established that, some metabolites and vitamins produced by bacteria may be vital tools for interactions with epithelial and cancer cells for tumor growth suppression. We also found that, the efficacy of some chemotherapies especially the use of Cyclophosphamide (CTX) were microbiota-dependent. Moving forward, there should be an establishment of methods that will not undermine ethical issues when trying this therapy on humans. Moreover, safety measures should be taken to manipulate the composition of the microbiota with the aid of a strict screening system to eliminate harmful microbes before applying them.

Keywords: Chemotherapy; hyperproliferation; immunotherapy; metagenomic; microbiome.

1. INTRODUCTION

Cancer is not a static illness; it appears to be an organised progression in cells and tissues from benign tissue through a premalignant lesion to free malignancy. The excessive multiplication of host cells is a major cause of death in human societies all over the world. The interaction of cancer cells with their surrounding tissues also promotes cancer initiation, progression, and metastasis. Changes in the extracellular environment of tumours, such as insufficient oxygenation, can lead to changes in gene expression, which can help tumours develop more aggressive characteristics [1]. These investigations have led to a better understanding of how and why cancer cells can spread from the primary tumor to metastasis, which is a property of cancer that makes it particularly difficult to treat successfully.

Different combinations of traditional treatments, such as surgery, chemotherapy, and radiotherapy, are increasingly being utilised in concert with additional medications that target specific biological networks for the treatment of cancer. These treatments have been shown to be highly effective in the treatment of cancer. However, the vast majority of them have significant adverse effects that exacerbate other illnesses. Another flaw with these treatments is that tumour cells can become resistant to them, despite the fact that patients' outcomes are generally positive. For example, resistance to imatinib developed as a result of an outgrowth of tumor cells bearing a drug-resistant mutation within Bcr-Abl, and resistance of the metastatic disease to other targeted agents develops invariably after a few months of therapy [2]. Studies have employed the service of bioremediation techniques which involves microbiome remediation and genetic engineering to augment the existing techniques.

Since the late 19th century, the association between cancer and microbiota has intrigued the biomedical community, following William Coley's partially successful attempts to cure sarcomas by local injection of bacteria, popularly referred to as ‘‘Coley's toxin.’’ After Coley's success, many experimental and clinical oncologists have tried to isolate microbial agents or products to treat malignant diseases. A few examples of such are attenuated form of *Mycobacterium bovis* treatment of superficial bladder cancer [3], treatment of melanoma with the oncolytic herpes virus [4] and the treatment of pancreatic cancer with *Listeria monocytogenes* [5].

They've discovered a link between human microbial community compositions, health, and disease, which is significant. It's vital to remember that bacteria control global nutrient cycles while studying the composition of microbial communities. Microbial life accounts for a significant amount of the world's biomass. The gastrointestinal tract, mouth cavity, epidermis, airway passages, and urogenital system are all known to be inhabited by bacteria. Although the terms microbiota and microbiome are frequently interchanged, the term microbiome has a broader definition, encompassing the genes and genomes of the microbiota, as well as the microbiota's products and the host environment, and thus includes plasmid DNA, viruses, archaea, bacteria, protozoa, and fungi.

The human microbial ecosystem plays a very important role in human health and disease. They normally reside on the surface of our body's epithelial barrier [6]. With the development of new scientific tools, there has been increasing interest in the composition, function, stability, and host specificity of the microbiome, its aggregate genes, metagenome, and this can be significantly be employed in the treatment of cancer. Therefore we present this review to discuss the role of the microbiome and

oncolytic viruses in controlling cancer. Here, we first looked at the general principles behind the microbiome metagenomic assessment and then proceeded to explain some evidence of microbiome oncogenesis, we then again investigated the response and toxicity of microbiome on immunotherapy, and finally discuss some impact of microbiome activities on chemotherapy.

2. MICROBIOME METAGENOMIC ASSESSMENT

To apply microbiome research to therapeutic usage, the relationship between the functional functions of microorganisms, particularly the gut microbiota, and the human host must be completely understood. Metatranscriptomics and metabolomics methods can be used in conjunction with metagenomics. Metatranscriptomics is a sequencing-based study of expressed transcripts in a sample that reveals which genes are active during the experiment. It may aid in the understanding of biological activities underlying microbial dysbiosis linked to a variety of illnesses. Some metatranscriptomic investigations, for example, identified the human gut microbiota and its association with inflammatory bowel disease (IBD) [7, 8]. Similarly, several studies have revealed that, specific alterations in the gut microbiome have a relationship with colorectal cancer (CRC) and can be relevant for CRC screening [9]. This effect may be useful for early diagnosis of CRC tumor (in stages 0, I, or II) and that may stand 80% chance of survival rate over five years, which is reduced to only 10% in later diagnosis (stage IV). This implies that, one promising strategy for diagnostics of CRC could be the detection of specific microbiome alterations [9] and this can be traced from the genomic level.

2.1 Microbiome Genomic Integration and Genotoxicity

Microbial DNA integration into a host genome is a key virulence mechanism through which multiple viruses can influence the development of cancer [10]. The human papillomavirus (HPV-16 and HPV-18), which is known to cause cervical cancer in humans, has two insertion HPV genes, E6 and E7, which are inserted into the host genome in cervical cells and provide a survival advantage by binding to and inactivating tumor-suppressor gene products (p53 and pRB) [11] (Fig.1). In this mechanism, transcription of viral proteins exerts a carcinogenic effect on the host. This mechanism may not be the same as the usual insertional mutagenesis which describes the abnormal regulation of host gene expression caused by insertion of the exogenous genetic material. However, if the host genes in question are tumor suppressor genes or oncogenes, cellular transformation to an oncogenic phenotype can take effect. Insertional mutagenesis is mostly attributed to the oncogenicity of the human T-cell lymphotropic virus which is retrovirus related [12].

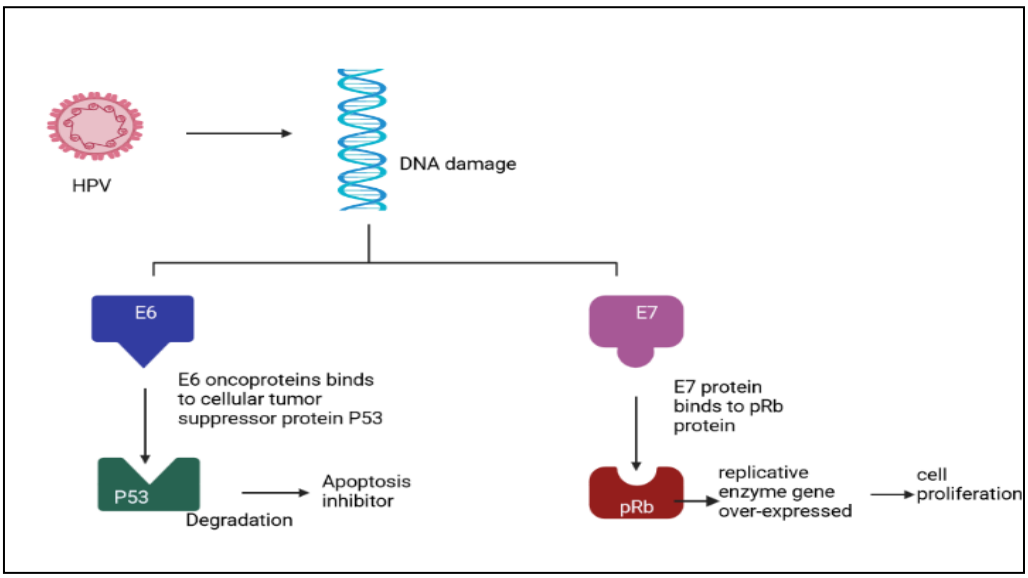

Fig. 1. Human Papilomavirus expression of oncogenes E6 and E7

The HPV DNA genome is integrated into the cellular genome in this mechanism, where it expresses high levels of two viral oncogenes, E6 and E7, which are required for cancer cell growth and viability. E6 causes the cellular tumour suppressor p53 to degrade, whereas E7 destabilizes the retinoblastoma (Rb) protein.

The bacteria Escherichia coli and Campylobacter jejuni (among others) are known to be very effective in the production of Cytolethal distending toxin (CDT) and colibactin. These two are well-known genotoxins and can induce double-strand DNA breaks via their DNAse activity [13,14]. Genotoxins damage DNA structure, break strands, adducts, delete and rearrange DNA structure. The effect of this damage may either lead to cell death or affect tumor suppressor genes or oncogenes with carcinogenic effects. CDT-deficient strains have attenuated carcinogenic potential in murine CRC models [15]. The Enterobacteriaceae family are also excellent producers of colibactin. Members of this family produce colibactin which induces and break DNA strands and has been associated with human colorectal cancer (CRC) [16]. Alternatively, some bacteria metabolites may also exert genotoxic effects. For example, oxygen reactive species normally produce by Porphyromonas sp and hydrogen sulfide reactive species produced by *Bilophila and Fusobacterium* are classical examples that are associated with colorectal neoplasia [13].

3. EVIDENCE OF MICROBIOME ONCOGENESIS

As mentioned earlier, the human body is not in pure isolation from the microbial community. The body has been detected with a vast community of microbes such as achaea, bacteria, eukaryotes, and viruses which interact with the body to form a sort of symbiotic association with it [10,17]. Primarily, these microorganisms are mostly found in the oral cavity, gastrointestinal tract, vagina, and skin of the host and help to constantly maintain the homeostasis between the local environment and immunity of the host. [18,19] .To constantly maintain this homeostasis, it depends on the commensal equilibrium of the host and its microbial community, because a shift in this equilibrium may result in inflammation. It can lastly promote tumor growth and eventually lead to cancer, albeit the onset of cancer requires a complex and multi-factorial entity [19]. Therefore it is important to note that, any change in the human microbiome could activate a chronic inflammatory response, cellular anti-apoptotic signals, release of carcinogenic factors, and modulation of anti-cancer immunity [10]. van Elsland et al. [20] indicated that, much interaction and manipulation of host cell biology and constant inducement of inflammation could contribute to carcinogenesis. From this perspective, we corroborate with the report of Chen et al. [10] that, Helicobacter pylori, a gram-negative bacterium causes gastric cancer and its both adenocarcinoma and mucosa-associated lymphoid tissue lymphoma. They again explained that, in addition to chronic inflammation which occurs due to up-regulation of cyclooxygenase-2 (COX2) expression, cytokines, reactive oxygen species and nitric oxide intermediate, Helicobacter pylori also induces oxidative DNA damage to the gastric mucosa. Moreover there is a progressive structural change, including mucous barrier degradation and increased cell turnover. This disturbance of the microenvironment may directly or indirectly be crucial to induce carcinogenesis.

Another evidence was reported from the association between specific bacterial infection and the kind of cancer they promote. They again established that, Chlamydia pneumonia is related to lung cancer, Salmonella typhi responsible for gallbladder cancer, Streptococcus bovis contributes to colon cancer formation and Propioni bacterium acnes also promotes prostate cancer [21]. Similarly, it was again reviewed that viral infections such as hepatitis B virus (HBV), Epstein –Barr virus (EBV), and Human papillomaviruses (HPV) have been proven to cause cancer, due to their ability of initiation through DNA integration into the human genome and promoting capabilities [22].

3.1 How Viruses Promote Cancer

Viruses that are known to cause a variety of malignancies are common enough in the population to be included in the human virome. Although the human virome's makeup and significance in health are unknown, several well-known human-associated viruses include the human papillomaviruses (HPV), which cause cervical carcinoma, and the hepatitis B (HBV) and C viruses (HCV), which cause hepatocellular carcinoma. T-cell leukaemia is caused by the human T-cell leukaemia virus-1 (HTLV-1), B-cell lymphoproliferative disorders and nasopharyngeal cancer are caused by the Epstein-Barr virus (EBV), and Kaposi sarcoma and primary effusion lymphomas are caused by the Kaposi sarcoma-associated herpesvirus (KSHV) (Fig.2) [23].

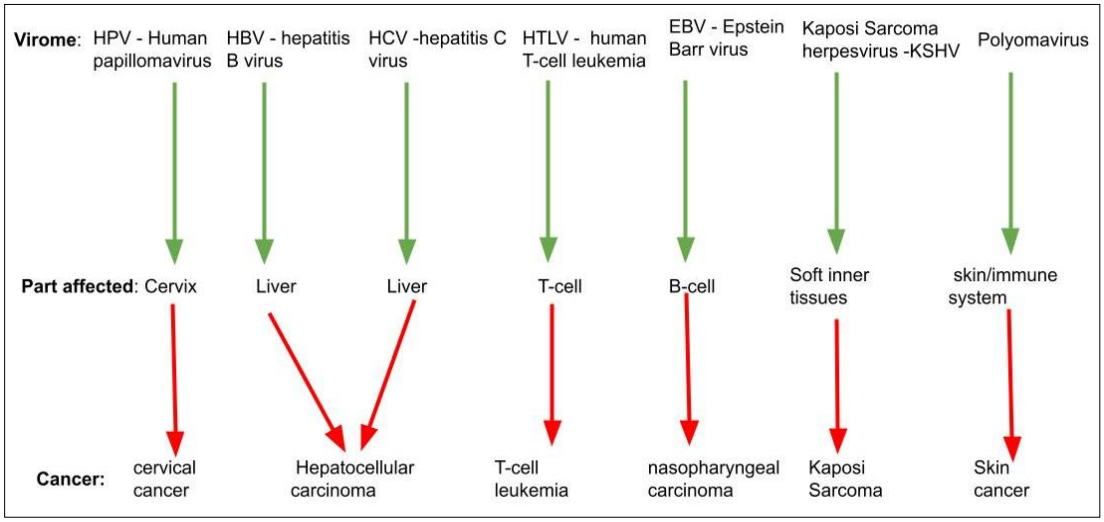

Fig. 2. Cancer promoting viruses

Merkel cell polyomavirus (MCV) and Simian Virus 40 (SV40), both human polyomavirus variants, are also involved in Merkel cell carcinoma (MCC) and mesothelioma, respectively [24]. MCV, a member of this category, is a widely spread virus that can cause an aggressive form of skin cancer in the elderly and immunocompromised people [23].

Epidemiologically, these viruses contributed to about 1.3 million new cancer cases worldwide in 2008. It is quite complex to fully understand their biology and the mechanisms by which they cause cancer [23]. The association of these viruses with cancer is complicated and has given several viruses' high prevalence in the human population. However, the malignancies that are related to this are relatively rare, and genetic or environmental cofactors are required for their development. For example in the United State of America, the seroprevalence of EBV is >80% [25]. Nasopharyngeal cancer is caused by EBV, which has a particularly high incidence in specific geographic locations and has given indication that there are additional important cofactors present for the development of the disease [23]. For example, as in Burkitt lymphoma, the EBV is present in nearly 100% of Burkitt lymphoma cancers but is not itself the causative agent. The Burkitt lymphoma is caused by chromosomal translocations that deregulate the protooncogenic c- mycgene [26].

These viruses are well-known for their unique encoding and ability to change cells in vitro and in vivo, and they appear to play a unique role in the pathogenesis of some human tumour cells [23]. These viruses, like other viruses, attack and actively infect the host cell by exploiting the host cell machinery for replication, which includes altering cellular structures, manipulating signalling pathways, modifying epigenetic programmes, and impairing DNA repair mechanisms in various ways, all of which eventually lead to genome instability and cancer onset [27]. In addition, as stated earlier, many of these viruses can either integrate into the host genome or maintained as latent episomal genomes to cause lifetime infections, as seen in (HPV, HTLV-1, and HBV among others) and (EBV and KSHV) respectively. In the case of HPV, its hallmark is the integration of its genome into the host to induce oncogenesis, because it results in the overexpression of the viral E6 and E7 genes which synergistically act to cause lethal host cells [27]. For MCV, the genome is clonally integrated into the MCC tumors to activate its small T antigen to acts as a potent oncogene capable of inducing cell transformation [28]. Latent virus on the other hands, though undergo silenced viral gene expression, other viral genes, including oncogenes, are expressed and manipulate pathways that can lead to genome instability [23].

3.2 Microbiome Effect on Host Immunity

There is a special link between the human microbiota and the immune system and this association has significant implications for a wide range of infections from atopy and autoimmunity to cancer [29]. It is usually important to note the key roles played by the host immune system in preventing carcinogenesis by inducing cell death

in abnormal host cells with neoplastic potential. During this relentless effort made by the host immune system to prevent carcinogenesis, the microbiome may interfere with this process at multiple levels. For instance, HIV tropism affects CD4+T lymphocytes as a result leads to impairing the host's ability to detect potentially neoplastic cells and increasing the rate of carcinogenesis. Another effect is the expression of the Fap2 cell by the F. nucleatum to express a surface protein that interacts with T and Natural Killer cells to suppress anti-tumor cytotoxicity [13]. This indicates that the microbiota may suppress host immunity, in the healthy state, but it has been hypothesized that microbiota-immune crosstalk facilitates the maintenance of an immune 'tone' promoting basal anticancer immunosurveillance. This leads to the proposition of various mechanisms to broadening the T cell receptor repertoire which will enhance the intensity of immune responses.

3.3 Microbiome Effect on Host Metabolism

Another important level of interaction between the host and the bacteria is metabolism. The genes produced by the human microbiome regulate the metabolism of food vitamins and nutrients, xenobiotics, and host-derived substances such bile acids [13]. In this regard, bacterial metabolism appears to be a key cofactor in the documented links between food and various malignancies [30]. Gut bacteria is believed to play an important role in suppressing oncogenesis via its anti-inflammatory and anti-proliferative effects which are induced by fermentation of dietary fiber to SCFA, such as butyrate [31]. Contrary to this, when bacterial metabolize bile acids and proteins, it leads to the formation of carcinogenic aromatic amines and sulfides [30]. Other microbiomes play a substantial xenometabolic function that can lead to the development of ultimate carcinogenic end products, such as the generation of acetaldehyde from alcohol [13]. Normally, the effects of microbial metabolites are determined by the host factor. This is seen in the generation of microbial butyrate, which causes CRC in mice lacking the MSH2 gene (which codes for a protein involved in DNA mismatch repair) by driving colonocyte hyperproliferation [32].

4. MICROBIAL CONTROL OF TUMOR CELL PROGRESSION

Bacteria and its associated products can accumulate in many tumor types, primary or metastatic. Several studies also reported that, mostly microbiota is responsible for the mediation and regulation of this tumorigenesis and tumor microenvironment. [33,34]. As discussed earlier that many bacteria and their products were responsible for tumor promotion, some bacteria exert protective functions during the process of tumorigenesis (Fig.3) or facilitate various forms of cancer therapies by several unique mechanisms discussed below [35,36].

The first mechanism here discusses the ability of some bacterial species to initiate and sustain the formation of favorable conditions for the growth of other beneficial bacteria and together form the niche which suppresses the overgrowth of pathogenic bacteria [45] (Fig. 3). These beneficial bacteria include Lactobacillus or various Clostridium species protecting against pathogenic Escherichia coli or Salmonella sp colonization in the context of intestinal inflammation [35,37].

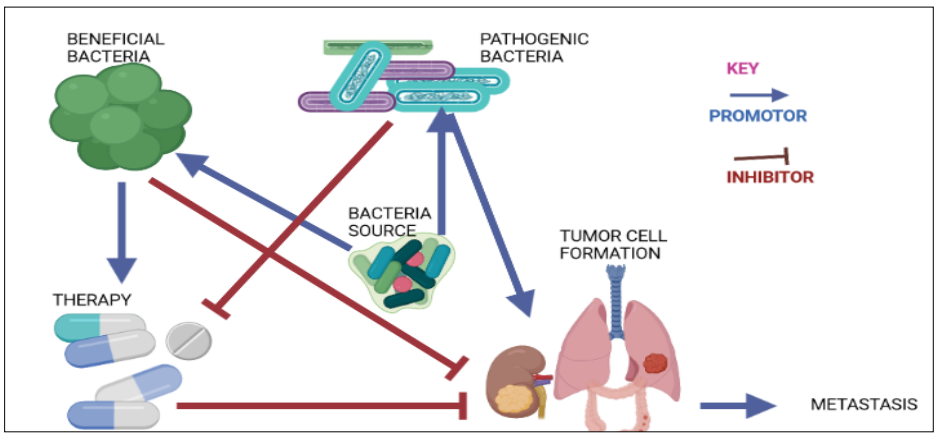

Fig. 3. Interaction of microbiome in primary tumor development and metastasis

Different microbiota species coexist with their hosts, exhibiting different metabolic activities and other properties within the tissue. These species have distinct roles in primary tumor growth, metastasis, and anti-cancer treatment. These bacteria's specificity allows them to inhibit tumor cell growth and improve anticancer therapies through a variety of mechanisms. They can also control overgrowth and outcompete 'pathogenic' bacteria, reducing the number of cancer cells produced. Pathogenic were also involved in the promotion of tumor development, metastasis, and therapy resistance. 'Arrow' denotes promoting activity, whereas 'block end' denotes inhibiting activity.

Another possibility is that some bacteria-produced compounds may be important tools for interacting with epithelial and cancer cells and suppressing tumour growth. Short-chain fatty acids (SCFA) produced by various commensals from fibre fermentation, for example, help to inhibit myeloid cell-driven protumorigenic inflammation and regulate the proliferation of epithelial and stem cell compartments by suppressing oncogenesis via the anti-inflammatory and antiproliferative effects mentioned earlier [38]. Some report also indicates that several vitamins, such as biotin, cobalamin, folate, niacin, pantothenate, pyridoxine, and others have the capacity for generation of antitumor activities [35]. The benefits of phytochemicals are also necessary. Some phytochemicals such as polyphenols, which are mostly present in fruits and vegetables, are metabolized by some gut bacterial species into the active forms, and may impact cell cycle arrest and apoptosis and also act through inhibition of inflammatory cytokines production [35]

The next mechanism could be, the immunosurveillance functions play by some distinct bacterial species, this microbiota leads to the maturation and tonic stimulation of the immune system, as a result, exhibits immunosurveillance functions at different stages of tumor development [39]. This gives reference to coley's classical experiment and antitumor effect of Coley toxins, where bacterial infections led to regression of established tumors and now serving as a foundation for studies in this direction [35].In contrast, an experimental study suggests that germ-free mice lack a fully matured immune system and have a reduced microbial load which resulted from the use of a large spectrum of antibiotics and eventually leads to the reduction of efficacy of immunosurveillance in mouse models [40]. Consequently, Cai, Shirong, et al [41] also observed that, microbes have the ability to stimulate and activate various immune cell subsets; a classical example will be members of Lactobacilla phylum activating antitumor immune responses from dendritic cell (DC) maturation. This function later leads to the acquisition of cytotoxic properties by T cells, NK cells, NK T cells, and antitumorigenic myeloid cells [42]. Many other types of bacteria are also known to activate macrophages, neutrophils, and DC and B cells.

The fourth mechanism simply builds upon the above-mentioned ability of bacteria to aid in the activation of the host immune system, which energies some bacteria to improve anti-cancer therapies [36]. This mechanism is illustrated in germ-free or antibiotic-treated tumor-bearing mice which do not properly respond to standard chemotherapeutic treatment, oxaliplatin [35], and therefore needs a gut bacterium to effect cyclophosphamide, an anticancer immunomodulatory agent, which acts through an increase in the intestinal permeability and translocation of immunostimulatory bacteria into secondary lymphoid organs, such as lymph nodes. This again indicates that microbiota is essential for the effectiveness of various immunotherapies, like the combination of CpG-oligodeoxynucleotides (O DN), a ligand of Toll-like receptor 9 (TLR9), and inhibitory interleukin-10 (IL-10) receptor antibodies (anti-IL -10R) therapy [35]. Alistipes and Ruminococcus, commensal bacteria are directly responsible for the production of antitumorigenic TNF and regulation of reactive oxygen species essential for tumor restriction [35]. We can again appreciate the microbiota action from its ability to induce and amplify the responses to immunotherapies based on the use of immune checkpoint blockade approaches. The responses to the use of these two approaches in cancer treatment (anti-CT LA4 or anti -PD-1/ PD-L1) or the combination of the therapies positively correlated with the overall diversity of microbiota as well as with the presence of particular species, such as Bacteroides and others [39.43]. In other to understand these findings, several trials of probiotics or fecal transplants from responders to non-responders were tried to relate the mechanisms underlining these effects of microbiota. The production of cytokines with antitumorigenic and immunostimulatory properties, such as IL-1 2, TNF, and others is

a regulation of microbiota activities [35]. From this, Leng, Qibin, et al. [44] hypothesize that microbial genes provide an excellent basis for molecular mimicry of cancer neoantigens, that is when the same peptides present as cancer neoantigen in the tumor are present within one of the bacterial proteins. This enables the bacteria to produce two signals, the first signal (so-called 'signal 1') stimulate the innate immunity and the second signal ('signal 2') is the major histocompatibility complex (MHC) peptide complex, which is identical to that on cancer cells, hence providing checkpoint blocker to alleviate the exhaustion or repression of neoantigen/ tumor-specific T cells [45]. This technique usually happened in Bacteroides fragilis which encodes for the peptide found in melanoma [43]. Similarly, it's also encoded for a bacteriophage infecting Enterococcus species which triggers a response to anti -PD-1 immunotherapy [35,46].

5. IMPACT OF MICROBIOME ACTIVITIES ON CHEMOTHERAPY

In the early 1900s, Paul Ehrlich, a well-known German chemist, pioneered the development of medications to treat infectious diseases. Paul invented the word "chemotherapy," which he described as the use of chemicals to treat sickness. He used animal models to screen a series of compounds for their potential anti-disease action, a feat that had far-reaching implications for cancer therapy development. "In the 1960s, Until it was discovered that cure rates after radical local treatments had plateaued at around 33% due to the presence of unappreciated micrometastases, surgery and radiotherapy dominated the field of cancer therapy. Later, new data showed that combination chemotherapy could cure patients with various advanced cancers [47]. This was observed in applying drugs in conjunction with surgery and/radiation to treat the issue of micrometastases and was initially used in breast cancer patients, hence herein adjuvant chemotherapy. Subsequently, these combined modality treatments became a standard clinical practice for effective minimal toxicity to normal tissues [47].

5.1 Microbiome-Assisted Chemotherapy

The use of the microbiome to control tumor cells later emerge from the handworks of William Coley (1862-1936), this saw significant improvement in the treatment of cancer. The ineffective nature of the use of chemotherapy for treating cancer has led to the onset of microbiome-assisted chemotherapy. Several kinds of research have reported on how inefficient the chemotherapy has been without the microbiome interaction. For example, it was reported that cyclophosphamide and platinum salts lost their ability to reduce tumor growth in mice raised in germ-free conditions or sterilized with a combination of broad-spectrum antibiotics. When the innate and adaptive immune responses of germ-free or antibiotics-treated animals were compared to litter-mates, germ-free responses were compromised as against the responses of the litter-mates reared in specific pathogen-free (so-called "normal") conditions [48]. Cyclophosphamide (CTX), a DNA-alkylating agent has the property of immuno-modulating and anti-angiogenesis [49]. Its tumoricidal activity depended upon its ability to induce the translocation of selective Gram-positive bacteria niching in the small intestine, as in the case of Enterococcus hirae or Lactobacillus johnsonii to reside in secondary lymphoid organs [48]. There is always gut barrier integrity perturbing to disrupt intestinal homeostasis which will lead to host immunization against some bacterial strains any time Cyclophosphamide is used. Again, vancomycin, an antibiotic that kills Gram-positive bacteria and colistin which also eliminates Gram-negative bacteria were shown to compromise the polarization of pathogenic Th17 in the spleen. And the full-blown anticancer activity of CTX in vivo in mastocytoma- and sarcoma-bearing mice, supporting the notion that the efficacy of CTX was microbiota-dependent [50].

E. hire as stated earlier, induced the most potent IFNg and IL-17 CD4+T cell responses and stimulate related tumor-specific CD8+ T cells [51]. The E. hire again reduces immunosuppressive intratumoral T regulators and IL-17-producing gamma delta T cells. E. hirae mono-association antibiotics-treated mice were reported to greatly improved tumor growth reduction by CTX, and this effect was blocked by the depletion of CD8+T cells or the neutralization of IFN g [48]. It was also revealed that the cytoplasmic sensor nucleotide-binding oligomerization domain 2 (NOD2) serves as a gut immune checkpoint which regulates the efficacy of the CTX. Similarly, the mice having the genetic defect in the intestinal NOD2 expression were identified showing a great improvement of tumoricidal activity of CTX .we also saw that, the Gram-negative bacterium Barnesiella intestinihominis mostly found in the

proximal colon, was overrepresented after chemo-therapy with CTX in the gut microbiota of animals with NOD2-deficient. This demonstrated the connection between the abundance of B. Intestinihominis in the colon and the higher anticancer efficacy of CTX in NOD2-deficient mice. It was again reported that mono-associated mice with B. intestinihominis displayed more abundant polyfunctional Th1 CD4+, CD8+ and gamma delta T cells in the spleen that could also be found in tumor beds. [51]. Goubet, Anne-Gaëlle, et al [48] reported that CTX combined B. intestinihominis in mice with antibiotics-induced symbiosis, usually dulled the tumoricidal activity of CTX, and restoring the CTX tumoricidal activity was observed alongside a variety of transplantable cancers. In simpler terms, we pinpoint that, clinically these findings indicate the adjuvanticity of distinct commensals microbes to chemotherapy and have again been confirmed by the findings of Trinchieri's group that gut microbiota has higher efficacy on chemotherapies [48]. These confirmations revealed that that gut bacteria are responsible for the release of reactive oxygen species (ROS) from tumor-infiltrating hematopoietic cells during platinum-based anticancer therapies. Therefore it is relevant for this review to put forward that the gut microbiota has a great influence on the therapeutic effects of various chemicals currently used for treating cancer.

6. RESPONSE AND TOXICITY OF MICROBIOME ON IMMUNOTHERAPY

As revealed earlier, the onset of cancer is a progressive state, and that the outcomes of its therapy depends on the immune system response. It is therefore important to comprehensively explore the influence of the microbiome on the human immune response, specifically to immunotherapy. Simply, the idea of Immunotherapy relies on the specificity of the patients´ immune system to degrade cancerous tumors. One way of immunotherapy administration is the injection of antigen-specific T-cell treated ex-vivo into the patients. Vaccination is also another way, which involves the injection of both the antigen and the T-cell into the patients. The immune system mainly is made up of many immune cells, such as antigen-presenting cells (APCs) and innate lymphoid cells (ILCs). Its major acquaintance includes the CD4+ and CD8+ T cells, which are major immune system players. Moreover the gut microbiota has a significant impact on the immune system's local immunity and the systemic immunity responses.

6.1 Microbiome Regulation of Host Immunity

As earlier noted, the microbiome modulates host immunity, and play an important role in influencing the response and toxicity of different forms of cancer treatment. Usually, microbe or pathogen-associated molecular patterns (MAMPs or PA MPs) can traverse the mucosal barrier and enter circulation. For example, when bacterial LPS aberrantly enters circulation following total body irradiation, it augments the activity of adoptive T cell therapy in mouse models [52]. Similarly, bacteria-derived nucleic acids have also been found to act as a natural adjuvant in immunotherapy. It is been reported that. serum from healthy individuals contain stimuli capable of activating a range of TLR and NOD receptors [53]. In terms of impact on immune function, it was experimentally proven that bacterial translocation into the MLN and spleen generated a Th1 memory response specific to the translocated species [52, 54}. Consequently, tumor cell killing may result due to T cell cross-reactivity or activation within the tumor microenvironment (TME). One pathogen earlier reported was the EBV, during its life cycle stimulates its host innate signaling pathways, to release NFKB, TNF-a, and Notch receptor pathways. This virus has a significant way of initiating response to immunotherapy. It begins when viral envelope glycoprotein (gp350/220) binds to host B cell surface CD21 and TLR2 which leads to persistent NF kB classical pathway activation [55]. The alternative and the classical NFkB pathways activation properties of EBV enhance its ability to achieve its mortal property [56]. Another property of this virus is the ability to transform host B lymphocytes into lymphoblastoid cell lines by expressing EBV nuclear antigens (EBNAs) and latent membrane proteins (LMPs)) to regulate transcription through the Notch and TNF- a receptor pathway [57]. Another group of microbes that were reported to have contributed immensely in immunotherapy was the members of the Ruminococcaceae family, such as Faecalibacterium prausnitzii. These microbes were consistently found to be associated with the beneficial treatment of ICI therapy [58;59]. Complementary results also indicated that when a separate study of patients with late-stage melanoma and different baseline microbiota were conducted, it was reported that between the responders and non-responders, the gut microbiota of responders was found to be enriched in Bifidobacterium longum, Collinsella aerofaciens, and Enterococcus faecium [60].

Akkermansia muciniphila were also studied in animals and the result suggests that this species is sufficient to restore anti- PD-1 activity in germ-free mice mediated by an increase in the ratio of CD4þ T cells to CD4 þ FoxP3þ regulatory T cells [61].

That notwithstanding, it was also found that a favorable microbiota may increases the densities of CD8 + T cells and de-creases those of FOXP3+ Tregs in tumor beds [29]. Similarly, the review found out that microbiota promotes DCs to secrete IL-12 to recruit CCR9+CXCR3+CD4 + T cells into tumor beds [62]. This gives a clear indication that microbiota-host induced cytokines interplay and augment the efficacy of so-called immune checkpoint inhibitor (ICI) therapy. Again, Sivan et al., [63] gave account on how a favorable microbiota activates DCs and tumor-specific CD8 + T cells, to supplement the efficacy of anti-PD-1/PD-L1 therapy. Significantly, this explains immunomodulatory roles played by the microbiota from suppression to stimulatory effects, which extensively rely on the mechanisms of modulation of T-regulatory and myeloid-derived suppressive cell functions. Then also it rely on the priming of the adaptive immune responses through the interaction of toll-like receptors on antigen-presenting cells and microbial components such as MAMPs or PAMPs on the mucosal interface [61]. The induction of inflammatory signaling pathways through microbiota induced cytokine production by lymphocytes, and systemic dissemination of microbial products or metabolites is another stimulatory effect revealed so far. These findings explicitly suggest that modifying the microbiome could have an impact on the response of immunotherapy. Bacteria and viruses are significant players in this bio adjuvanticity. However, viral oncolytic therapy is among the various types of immunotherapy techniques studied ever, therefore we present a summary of how some viruses affect immunotherapy and cancer treatment in our subsequent discussion.

6.2 Oncolytic Viral Therapy

Viruses that are considered to be oncolytic are viruses that preferentially infect and kill cancer cells. These viruses are particles that infect or enter our cells and then use the cell's genetic machinery to make copies of them and subsequently spread to surrounding uninfected cells. This behavior from the virus were investigated by the early scientists around 1912 following a case that reported a dramatic response in cancer patients recovering from viral syndromes. Build up knowledge of the observation from this finding led to the discovery of Oncolytic virotherapy. This technique is an emerging experimental treatment platform for cancer therapy where explicative-competent viruses are engineered to replicate selectively in cancer cells with specified oncogenic phenotypes [64]. The technique saw a surge in its efficient application from the onset of recombinant technology, which makes it possible to genetically engineer DNA viruses to enhance their safety by increasing their selectivity for tumor cells. This approach was first demonstrated with herpes simplex virus type one (HSV-1) in an experimental glioma model, and later, an engineered adenovirus Onyx-015 became the first engineered oncolytic virus to undergo a clinical trial in cancer patients [65]. Certain RNA viruses or their naturally occurring attenuated mutant strains were also studied to possessed intrinsic tumor selectivity without the need for genetic engineering in the laboratory [66].

Reference [66] reported that, the oncolytic viruses with which clinical experience has been reported consist of three DNA viruses engineered in the laboratory to achieve tumor selectivity (adenovirus, HSV, and vaccinia) and two wild-type or spontaneously arising attenuated RNA viruses with intrinsic tumor selectivity (Newcastle disease virus (NDV) and reovirus).In this regard, we investigated how these viruses affect immunotherapy and cancer treatment.

6.2.1 Adenoviruses

Adenoviruses are non enveloped DNA viruses that normally cause upper respiratory tract infections. The adenoviral genome has E1A, E1B, E2, E3, and E4 sub-regions which regulate a temporal cascade of gene expression. Its 36 kb double-stranded DNA genome undergone several regional deletions to make it accessible to accommodate up to 10 kb of foreign DNA [67]. The tumor selectivity properties of the adenovirus are attributed to the deletion of the E1B region of its vector ONYX-015. The deletion of the E1B would facilitate the replication of the vector in cells with a defective p53 pathway usually in cancer cells, even though this virus is not specific for p53-null cells. The genome of this virus is retained as an extra chromosomal element that is rapidly lost in dividing cells but has no major impediment during lytic infections of tumor

cells [5]. The present of coxsackievirus and adenovirus receptors (CARs) on the surface of some cells make is possible for the adenovirus to infect them. This explains that the adenovirus does not infect cells that lack the expression of the CAR on their surface. The expression of the CAR occurs in some human tumor cells, in the case of adenovirus therapy used to treat CAR-expressing tumors like prostate cancer, whose CAR expression increases with Gleason score [68]. The immunogenicity of the Oncolytic adenoviruses may express positive responses if it leads to an antitumor immune response. However it can be negative if the immune response blocks viral propagation or leads to toxicity.

Similarly, the immunogenic nature of adenovirus may be lethal after an arterial infusion of a replication-defective adenovirus vector during a gene therapy trial for ornithine transcarbamylase deficiency (report of the National Institutes of Health Recombinant DNA Advisory Committee, 2002). This could result from the massive cytokine response to the adenovirus vector, usually resulting in disseminated intravascular coagulation.

6.2.2 Herpes simplex virus (HSV)

HSV is a double-stranded DNA virus that is selective within tissues. The oncolytic virus selective activity within malignant tissue is a result of its genetic modification. One of such modifications involve the inactivation of the viral gene ICP6, which encodes the large subunit of ribonucleotide reductase, an enzyme required for viral DNA replication [69]. Normally this enzyme is expressed in abundance in rapidly dividing tumor cells but is meager in normal cells, which may result from the modification of the HSV-1 ICP6 gene to replicate selectively in the tumor cells. Another gene modification approach is the deletion of the viral gene, g -34.5 gene, which functions as the virulence factor during HSV infection81. When this gene mutate, it also limit replication in non-dividing cells [64]. It was recorded that, the replicative-sensitive HSV1 g-34.5 viral mutants are effective in the treatment of both the central nervous system and non-central nervous system tumors in animal models. We saw from the report from reference [64] & [70], that combining the HSV mutants with chemotherapy or radiotherapy had shown an enhanced antitumor activity. Another report also proved that radiation increased the anticancer activity of HSV when used in pancreatic, glioblastoma, and cervical cancer models but did not alter the antitumor effect of HSV in prostate cancer [71]. In another research when a high dose of radiation was combined with the oncolytic HSV virus, there was improved efficacy in the prostate cancer models [64]. It was again observed that, at low dose irradiation, the efficacy of the HSV viral therapy in a cervical cancer model improved [72]. As we discussed earlier on the microbial effect on chemotherapy, here again, it is proven that the HSV which is a virus enhanced antitumor effect when combined with a variety of chemotherapy agents (mitomycin-C, cisplatin, methotrexate, taxanes) [64]. Additionally, the use of the HSV to deliver other genes, such as those that convert benign pro-drugs into cytotoxic agents were evaluated and in one case we saw cytochrome p450 gene and HSV-1 thymidine kinase (TK) gene delivered using a HSV-1 replication-competent virus through intratumoral injection in a hepatocellular carcinoma model. One other development in the treatment of melanomas that cannot be removed completely by surgery is the introduction of the Talimogene laherparepvac usually known as the Imlygic into the melanoma lesions. The Imlygic is a weakened form of Herpes simplex virus type1,normally known as the cold sore viruses which is directly injected into the tumor [73].It has a selectivity ability and stimulate antitumor immune response[74].

6.2.3 Vaccinia virus

Vaccinia virus is a linear genome double-stranded enveloped lytic DNA virus, whose life cycle entirely occurs within the cytoplasm of host cells. This virus has a large DNA size (approximately 200 kb) and easy manipulative, in addition to its exclusively cytoplasmic replication to eliminate any risk of integration, and short replication cycle [66]. Vaccinia virus was known to be a natural derivative of a cowpox strain that was serially passaged while being used as a smallpox vaccine in the 1930s. Vaccinia virus has added advantages over other oncolytic viruses, in that it can infect cells from a variety of animal models and a variety of cell types. The virus can be stored as a dry powder for prolonged periods without significant loss of infectivity [66].

Basically, the oncolytic vaccinia viruses, was developed using three techniques, firstly, the highly efficient in infection and replication in the cytoplasm without chromosomal integration, and as well as its genomic allowances of the insertion

of a large amount of recombinant DNA without loss of infectivity. Second technique is, it immune-stimulatory properties that is being harnessed to incite an immune response against cancer cells and the third technique was related to the construction of the replicative-conditioned viral mutants to target specific cancer types [66]. The practices of these techniques led to a case study, where recombinant vaccinia viruses were constructed in an effort to enhance the immunogenicity of transfected melanoma cells [75]. The result from this study indicated that, the virus expressed a mini-gene encoding a fusion product that combined an endoplasmic reticulum targeting signal and the HLA-A201 binding peptide. Infection of the melanoma cells with this recombinant virus resulted in high levels of cytotoxicity from specific cytotoxic T lymphocyte clones in vitro. In another scenario, when a recombinant vaccinia virus vector was created to contain the tumor-suppressor p53 gene, the virus demonstrated a high level of p53 expression in transfected glioma cells, resulting in high levels of apoptosis [64] several studies also identified vaccinia virus as an immunotherapeutic agent and has been studied as a vaccine in early-stage melanoma [76]. It was also investigated that, the vaccinia virus carried a prostate-specific antigen transgene for the treatment of prostate cancer in patients with both minimal disease and metastatic disease. That notwithstanding, Pexa-Vec (JX 594) treatment is widely used for the expression of transgenes encoding human granulocyte-macrophage colony-stimulating factors (GM-CSF) and B-galactosidase which promote antitumor immune response. Pexa-vec(JX 594) is a thymidine kinase gene-inactivated oncolytic and immunotherapeutic agent derived from vaccinia virus which are best for intratumoral injection and intravenous infusion [77]. Pexa-Vec (JX 594) works by infecting and selectively replicating in cancer cells and causing lysis. It is again reported to help in reducing the blood supply to tumors through infection of tumor associate vasculature and at the same time activates the body's immune system to recognize and kill tumor cells [78].

6.2.4 Reovirus

Reovirus is a non-enveloped RNA virus which belongs to the family *Reoviridae* and the genus *Orthoreoviridae*. It contains segmented double-stranded RNA genomes. Approximately 30% of human tumors possess an activating mutation of the Ras pathway. Reoviruses achieve tumor selectivity, hence can replicate in cells with an activated Ras pathway [64]. This indicates that, the virus will replicate and produce lysis in specifically transformed cells possessing an activated Ras pathway without affecting the normal cells. The activated Ras pathway presents in many of these ovarian, breast, colon, and lung cancers, prevents viral-induced PKR activation and subsequent EIF-2 a -phosphorylation, and potentiates cellular protein production and viral replication [66]. This is significant because normal cells without Ras activation will trigger early viral replication to induce EIF-2 a -phosphorylation, which inhibits cell protein synthesis. Therefore it has a significant role in oncolytic effects in Ras-activated cancer cells.

6.2.5 Newcastle disease (NDV)

Newcastle disease (NDV) is an enveloped negative-stranded RNA virus belonging to the *Rubulavirus* genus of the *Paramyxoviridae* family. It selectively replicates in human cancer cells that have developed defects in the interferon signaling pathway [64]. That is, the tumor selectivity is believed to originate from viral induction tumor necrosis factor (TNF) - a secreted by peripheral blood mononuclear cells (PBMCs) and viral enhancement of the sensitivity of neoplastic cells to the cytotoxic effects of TNF-a. NDV was first noted to replicate and destroy tumor cells in 1955. The oncolytic strain of NDV is the 73-T, which gains its name from its ability to pass through mouse ascites tumor cells 73 times in vitro [66]. The NDV is notable for oncolysis as a result of rapid growth and the ability to stimulate an antitumoral immune response. Early studies have demonstrated that the Newcastle virus could be an oncolysate for tumor vaccine.

7. CONCLUSION

Free and effective treatment of cancer has seen a major drawback since the days of the use of conventional methods such as chemotherapy, radiotherapy, surgery, hormones, and drugs that target specific biological networks for cancer treatment. Following the major side effect and ineffective treatment using such therapies which sometimes aggravate into other types of illness, then again tumor cells become resistant to some of them, irrespective of their relatively progressive outcome seen in some patients. Today, there is a new therapeutic technique that involves the use of microbes and viruses to treat or control illness. They may be used as

adjuvants to augment the usual conventional therapy to redress some of those drawbacks. Increasing knowledge in the field of microbiome research has seen major improvement on oncology. The advanced knowledge in molecular biology, genetics, and virology paved the way for the engineering of microbes to achieve tumor selectivity treatment of cancer. For instance, the engineering of DNA viruses to achieve tumor selectivity or identification of RNA viruses with intrinsic tumor selectivity. Data from this emerging field only gives the onset discoveries and opportunities that will lead to the improvement of clinical outcomes. A lot of data suggest that, commensal microbiota can significantly influence therapeutic value in patients undergoing cancer treatment. Most clinical and pre-clinical studies assessing microbiome modulation treatments suggest that these therapies have an advantage over synthetic drugs, at least in terms of their potential side-effects. Given the potential relationships between the microbiota in tumor cell progression and suppression, there is the need to explore microbiome-related therapies for aiding in the prevention and treatment of cancer. Similarly from these findings, it vividly shows that the microbiome has a role in controlling cancer treatment.

However, even though there is much advancement in this new treatment era, several clarifications are yet to be addressed. A deep understanding of the functional roles of the gut microbiota and its interactions with the human host is yet to be answered.

We recommend that incorporating the findings of microbiome-based research to the clinical used, there should be an establishment of methods that will not undermine ethical issues and safety measures to manipulate the composition of the microbiota with the aid of a strict screening system to eliminate harmful microbes.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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