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DYNAMIC ROLE OF MICROBES IN CANCER

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ABSTRACT

The microbial community is a complicated multikingdom population that connects with the host in a symbiotic manner across numerous body locations. Different cancers subtypes' formation, recurrence, spread establishment, and therapy response have all been linked to microbial populations. Exact cause of microbe effects on oncogenesis is yet unknown, This study examined the molecular mechanisms that lead to cancer's genesis and progression, as well as microbes or their secreted biologically active substances could be used as specific cancer therapies.

Keywords: Microbes; cancer; molecular pathways; diagnostics

INTRODUCTION

A total of 3 trillion bacteria live in the human body. Bacteria cells in the body have 100-fold greater genetic variability than human cells. Eukaryotic fungus, parasites, and virus make up a human microbiota, in addition to bacteria. Ultimately, the host and its microbes work together as a metabolomics studies when conditions are favorable (Pham *et al.*, 2019). The gut, skin, and oral microbiomes are known to have a highly enriched and diversified population of microbes. The vaginal microbe has been researched as well, but it is described by decreased biodiversity and very specialised and dominating microbial species (Chen, Lu, Chen, & Li, 2021).

Cancer cells effectively multiply and elude the immune system by maintaining reproduction, avoiding cellular inhibition of growth, triggering invasions and metastases routes, and generating angiogenesis (Burgos-Panadero *et al.*, 2019). The role of microorganisms on cancer genesis, recurrence, and therapy response has remained a mystery until recently (Zaman *et al*., 2019). The microbes of male and female pelvic organs have significant consequences for urological and gynaecological diseases such as prostatic, cervix, uterine, ovary, and kidney cancers. Furthermore, the "intra - tumoral microbial" may have an impact on local cancer development (Rosean, Feng, Azar, Rutkowski, & Biology, 2021) (Chandra & Mcallister, 2021).

Microbes that aid in cancer promotion

Flatworm species are closely linked to cholangiocarcinoma and hepatorenal syndrome, as well as bowel cancer in S. haematobium. Various microbes like human immunodeficiency virus-1, Clonorchis sinensis, Epstein –barr, hepatitis B and C, papillomaviruses make a contribution to tumor growth (Sammar, Farich, Rayan, Falah, & Rayan, 2019). Virus, parasite, and fungi's vital impacts to disease and suffering, especially cancer, can be found elsewhere. The virome is made up of 98 percent bacteriophages and 2% eukaryotic viruses. (Broecker & Moelling, 2021). Worldwide virome patterns may act as cancer progression biomarkers. More than 100 tumour specimens, comprising oral, breast, colon, and gastrointestinal malignancies, contain viral genome characteristics (Stern, Miller, Li, & Saxena, 2020). Bacteriophages, like eukaryotes virus, may have an effect on cancer. Certain phages may engage with cancerous cells and suppress production of integrins (Putra & Lyrawati, 2020) (Staley, Weingarden, Khoruts, & Michael, 2018). Cancer patients' guts contained more *Streptococcus*-specific phages and a Vibrio-inhabiting phage compared to the control group. These phage mutations could potentially trigger gene interchange and communal connectivity inside the host, and therefore influencing cancers (Budynek, Krystyna, Skaradzi, & Górski, 2010).

A dysbiotic mycobiome is rapidly being linked to a variety of diseases, notably transplant versus host disease and oral cancer. *Candida albicans* outgrowth has recently been linked to, and even considered to be prognostic of, stomach malignancies (Carcinogenesis & Ka, 2020) (Q. Li & Yu, 2020) (Cosola *et al*., 2021) .*Malassezia* relocates to the pancreatitis and initiates the complement cascade by adhering to cell walls with host mannose-biding lectins (Chifiriuc, 2018).

Parasitic microbial individuals may have an indirect impact on other microbial domains by creating melanoma dysbiosis. Most Gram-negative bacteria, are more prevalent in persons who have colon cancer caused by S.

haematobium (Id, Id, Id, & Fichorova, 2019). Furthermore, parasites have the potential to directly influence cancer progression by causing immune regulation (Gouveia, Brindley, Rinaldi, Gärtner, & Costa, 2019). More molecular research into the effects of these and other parasite factors on cancer is needed (Correia, Gouveia, Rinaldi, & Santos, 2021).

Bacteria linked to cancer

Despite latest events in microbiology, the International Agency for Research on Cancer (IARC)-recognized top player microorganism lists has not been revised in over a decade. *H. pylori* is a known human carcinogen with a time of life annual occurrence of 8.7 cases per million people and is found in more than 50% of the world's people (Onder *et al*., 2021) . *H. pylori* interferes with the Wnt/b-catenin pathway, which regulates cellular cycle and fatality (Berg *et al*., 2020). It can indirectly influence cancer formation via an inflammatory process. The MAPK and AKT channels must be activated during Salmonella poisoning in mice models and cells in order to maintain genomic transition in gallbladder cancer. A type 3 secretion system (T3SS) transports signaling molecules into target cells, such as Typhus toxin, a cyclomodulin-like protein, and AvrA, a multifaceted activator, both of which are implicated in oncogenesis via genotoxin-mediated mutation (Silbergleit *et al*., 2021).

F. nucleatum was found at 400 times higher levels in CRC cancerous tissue than in comparable normal tissue during an experimental study to identify microbes in colorectal cancers, demonstrating that an oral disease linked with OSCC may also impact cancer at a distal area of the body (Weken, Garcia, Sanders, Cox, & Devriendt, 2021). *F. nucleatum* has been linked to liver metastases, extending its cancer-fighting potential. It produces outer membrane vesicles (OMVs), promotes inflammatory response in colon epithelial cells in vitro by secreting IL-8 and TNFa (McIlvanna, Linden, Craig, Lundy, & James, 2021) (Shang & Liu, 2018) (Martin-Gallausiaux, Malabirade, Habier, & Wilmes, 2020).

E. coli may cause aging by producing growth factors that increase cell growth and tumour formation. *E. coli*-induced Mitochondrial dysfunction, as well as the indirect influence it has on Wnt signaling resulted in colorectal cancer(Y. Wang *et al*., 2021) (Schmitt & Greten, 2021) (Doughty *et al*., 2019) (Zhong *et al*., 2021) .

Enterotoxin *B. fragilis* strains have been linked to the production of diarrhoea and colorectal carcinogenesis in patients' faeces and mucous.(Chan *et al*., 2019; Trejo-Solis *et al*., 2021). Bacteroides Fragilis Toxin ETBF genes (BFT) cause severe inflammatory responses and tissue injury in the colon (Avril & DePaolo, 2021). ETBF infection promotes colorectal tumorigenesis both in vitro and in vitro. BFT genes upregulate genomic and transcriptome regulatory values in a toll-like receptor (TLR4)-dependent pathway (Valguarnera & Wardenburg, 2020).

Intracumoral microbes

Intracumoral microbes (also known as the "cancer community") have been suggested to form unique reduced habitats. Alteration to the gut epithelial layer may have an impact on the tumoral microbial community. Following oncogenic microorganisms ascending from the cervical may enter the uterus and ovaries (Rodriguez-garcia, Palazon, Noguera-ortega, Jr, & Martin, 2020) (Guentzel, N.D.) (Smith, Affram, Bulumko, & Agyare, 2018). The Gammaproteobacteria-produced enzyme cytidine deaminase inhibited the anticancer gemcitabine in PDAC (Hatano, Sano, & Takahashi, 2021; Hughes-parry, Cross, & Jenkins, 2019). Exhaustion of the microbes led to increased CD4+ T cell polarisation and initiation of cytotoxic CD8+ T cells, which greatly reduced tumorigenesis (Borella *et al*., 2021).

Microorganisms Impacts on cancer Pathways

Knowing which microorganisms and host-microbe interactions lead to microbe tumor regulation is essential for developing putative cancer therapies. Particular microorganisms can exhibit pleiotropic relationships that affect cancer (Chifiriuc, 2018).

Through direct contacts with specific host cells, a plethora of methods adopted by native microbes and invading microorganisms may alter melanoma processes. Infusion of *H. pylori* CagA into desired epithelia in the gastric mucosa can significantly interfere with E-cadherin. (Alzahrani *et al*., 2014). Infusions of *S. enterica* AvrA activate b-catenin systems, stimulating STAT3 signalling and inflammatory responses in the body. (Madani *et al*., 2021). Overexpression of downstream E-cadherin/ b-Catenin–modulated transcriptional can result to Strand breaks, epithelial proliferation and cell differentiation (Arévalo, Trespalacios, & Otero, 2009).

Tumourigenesis is caused by the direct generation and degradation of bioactive molecules, which can travel through the bloodstream to tumour and metastases locations. Microscopic organisms can also impact tumorigenesis indirect by the distant generation and destruction of bioactivities, such as fatty acids and lipopolysaccharides, researchers have shown (M. Wang *et al*., 2017). Tumor environments are dynamic with released mediators, fermented products, and catabolites. Lipopolysaccharide toxin and acetate, for example, can cause cancer. Diamine cadaverine reversed EMT and limited cellular mobility and incursions (Baghban, Roshangar, Jahanban-esfahlan, Seidi, & Ebrahimi-kalan, 2020) (Staley *et al*., 2018).

Bacteria can also metabolise hormones produced by the host, which can influence cancer. Bacterial external OMVs are a major bacterial delivery method implicated in cancerous events (Collins & Brown, 2021). Mucosal immune fortifications, regulation of mucosal wide range of factors immune responses, and altering of environmental parameters such as ph, aeration, and metal supply are important in the development of cancer (Celardo, Melino, & Amelio, 2020). Gallic acid microbes was found to play a role in the link between p53 mutations in distinct intestinal environments (Leung, Graham, & Knowles, 2018).

In cancer, innate immunity interactions occur on mucus, globally via microbes and inside lymphoid tissues or the TME directly. Both adaptive and innate immune responses may be driven by specific and distant microbe stimuli. Bacterial MAMPs can improve anti - tumor immunity by enhancing TLR signalling and acting as additives in cancer immunotherapy (Marshall, Warrington, Watson, & Kim, 2018) (Besedovsky *et al*., 2021) (Villena, Kitazawa, Wees, & Pieterse, 2018). Regulation of the tumour immune environment by the microbes shown in **Figure 1**.

In the TME, mutualistic organisms can cause a vast set of immunostimulatory actions. The attachment of FadA to colorectal cells causes the proinflammatory cytokines and the infiltration of inflammatory cells. This leads to an influx of lymphocytes for antineoplastic inflammatory processes (Besedovsky *et al*., 2021).

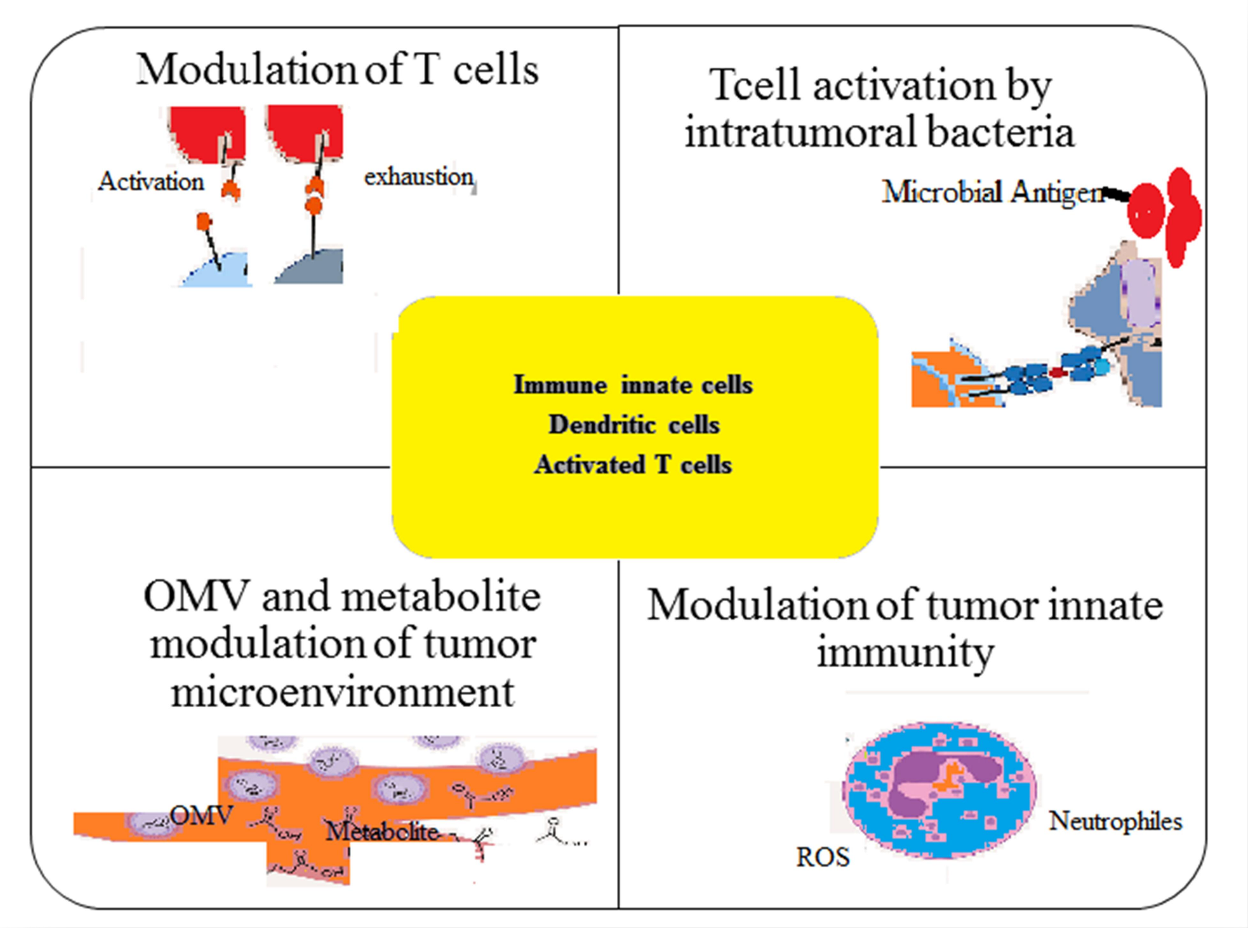

Figure 1: Microbes influence the tumor immunological environment. Microbes influence TME T cell activation and fatigue by regulating T cell stimulation, which has a direct effect on ICI efficacy. By activating innate immune cells to attack tumour cells, microbes released components can influence the TME innate immune reaction. The modalities through which microbe metabolite, OMVs, or intra - tumoral microbes can elicit a range of stimulating effect that alter cancer and immunosuppressive conditions within and outside the tumour are shown.

Cancer diagnosis with the aid of microbes

With the growing recognition that the microbes plays a role in cancer development, using microbe tailored data to integrate microbial readings into cancer detection is an attractive avenue of research depicted in **Figure 2**. Distinctive microbe DNA and RNA profiles can be discovered in samples taken, according to recent research (Whisner & Aktipis, 2019). Microbes analysis could also be used to make a predictive prognosis. The assessment of short - range and long mortality in PDAC individuals was aided by a different intra - tumoral microbes diversity and distribution. Microbes data mining could also be used to predict unfavourable effects from cancer immunotherapy and radiotherapy (Riquelme *et al.*, 2020).

Mucositis of the gastrointestinal system and mucous membranes can be linked to dysbiotic patterns in the gut microbiota, a study has shown. These patterns were used to predict oral mucositis in patients (Hong *et al.*, 2019).

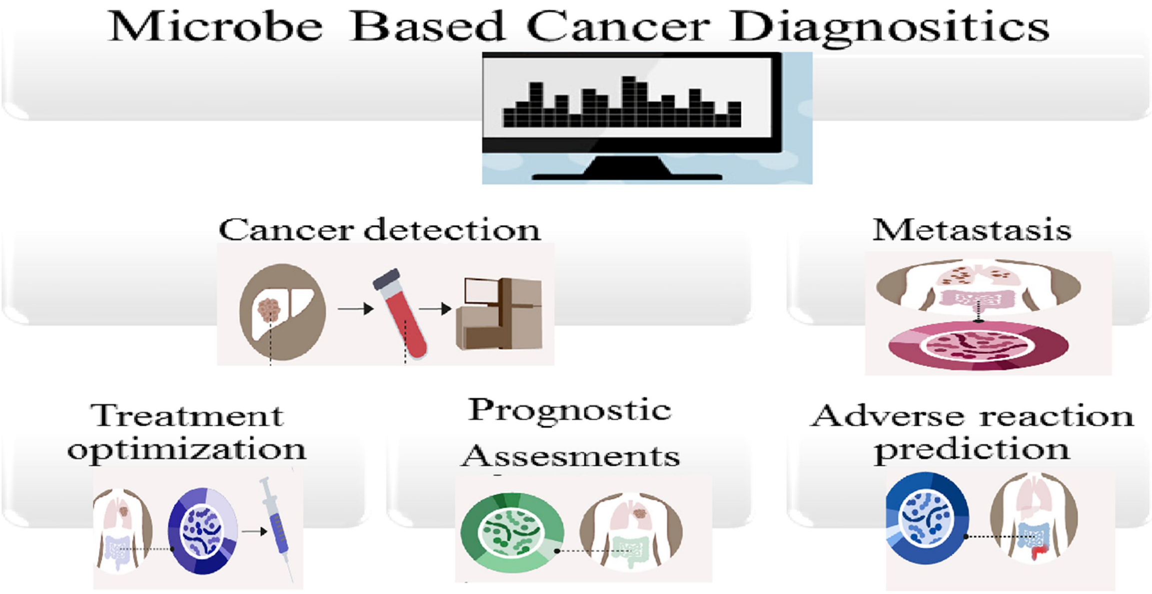

Figure 2: Information about microbes is employed in clinical testing and treatment evaluation

Microbe analysis process could help in the creation of new cancer diagnostics, such as detection of cancer using microbe's genetic material, observing for micro-metastatic development in types of cancer, determining prognostic value, customizing therapeutic strategies to the person, and using machine learning technique for treatments.

Microbes in Cancer Treatment

Aside from the diagnostic use of microbe data mentioned above, one of the most exciting and potentially directional aspects of medical research is examining microbe effects on cancer therapy attentiveness, which might result in data improvement of the diagnosis and treatment medicinal decision process.

Immunotherapy

Immune-based anticancer therapies aim to boost a patient's immune system to combat cancer. Treatments targeting inhibitory regulators of Cytokine production, known as "signalling pathways," are currently spearheading this strategy. These regulators are frequently "subverted" by the cancer in establishing a highly resistant TME (H. Li *et al.*, 2020). Monoclonal antibody against leading to apoptosis protein 1 (PD-1) and its linker PD-L1, as well as antibodies against anticancer T lymphocyte-associated protein 4

(CTLA-4), can prevent T cells from interacting with their mast cells resulting in an antineoplastic immune reaction (Ghosh, Luong, & Sun, 2021) The results of this treatment, which have been observed in a limited group of patients, vary from full remission in rare instances to major life extension even in metastatic cancers (Akinleye & Rasool, 2019; Dummer, 2018) (Cai *et al*., 2021).

Chemotherapy

Chemotherapy efficiency can be modulated by microbes. *E. coli* can affect the efficiency of two chemotherapeutic medicines, by establishing tolerance and triggering toxicity in tumours. (Sawant, Patil, Gupta, & Kunda, 2020). Gemcitabine is also digested by microorganisms found in human PDAC (Geller *et al*., 2018). Oxaliplatin and cyclophosphamide are less effective in preventing tumour growth (Luo *et al*., 2020). Chemotherapy can affect the microbial community in the body. 16S rRNA sequencing determined a reduction in *Eubacterium and Ruminococcus* spp. Further research into the involvement of these microbial modifications in carcinogenesis, treatment responses, and chemotherapy-induced side effects is needed (Mik, Kov, & Seb, 2019; Schubert, Rohrbach, Schmitt, & Stein-thoeringer, 2021).

Radiotherapy

Microbes dysbiosis is defined by a reduction in symbiotic *Bifidobacterium, Faecalibacterium and Clostridium spp*. and a rise in *Bacteroides* and *Enterococcus* after radiation. (Mori & Pasca, 2021). Patients undergoing pelvis irradiation had a 3percentage rise in intestinal *Fusobacteria taxa* which could have major consequences considering that numerous species of this family have tumor-promoting potential. (Nam, Kim, Seo, Kang, & Bae, 2013). Oral vancomycin-induced decrease of Gram-positive gut endosymbionts was linked to improved radiation efficacy in melanoma, lung, and cervical cancer models (Y. Wang *et al*., 2021).

Attenuation of the Microbes

For effective cancer treatment in contrary to the genetic code, the microbe, which is referred to as a "second genetic code," has a distinctive property: it can be modulated. Such rational microbe actions could eventually lead to cancer or cancer-related problems being treated.

Microbes are being targeted towards cancers.

Altered mutant strains were tested in a phase I trial using the migration attraction elements of *Salmonella*, however they lacked tumour selectivity. The combination of the active drug with a *Bifidobacterium strain* that expresses deaminase suppressed tumor development in mice. (Bruno, Salemme, Centonze, Cavallo, & De, 2021; Irfan, Zoraida, Delgado, & Frias-lopez, 2020). *Salmonella and a Bifidobacterium* strain that expresses deaminase suppressed tumor development in mice(Ding, Fan, Deng, Huang, & Zhou, 2020) (Redeker & Arens, 2016) . To evaluate the positive effects of transplanted microorganisms in the malignant tumors setting while assuring safety, robust trials are needed (Morelos & Fuzi, 2018)

Transplantation of microbes

Faecal microbiota transplantation could be helpful in treating Crohn's disease. ICIs have been used to introduce cancer victim faeces into antibiotic-treated mice treated with antibiotics. Early results from vaginal microbiota transplant in the treatment of persistent bovine venous disease (BV) are encouraging(Bibb *et al*., 2020) (Therapies & Hoffmann, 2019). The efficacy of transplantation of the donor material in the recipient gastrointestinal system was largely dependant on donors screening and engraftment in these studies. Regardless of these preliminary findings, significant clinical, legal, and technical concerns must be resolved before this strategy can be widely used(Ng *et al*., 2020) (Cammarota *et al*., 2017)

Probiotics

Lactobacilli and *Bifidobacteria* have been shown to diminish tumour incidence, progression, and volume in AOM/DSS CRC models in mice. Probiotic supplementation has been found to have little or no benefit on cancer patients, and even to cause severe effects (Bermúdez-humarán, 2017; Cancer *et al*., 2021; Markowiak-kope, 2021). Precise probiotic formulations with improved gut colonisation capability and reproducible cancer reactivity while maintaining safety of patients is an interesting subject of active research. Such studies combine phenotype screenings pipelines and microbial engineering, involving clarification of released specific molecular affects on tumour and immune cells (Rodriguez-arrastia, Martinez-ortigosa, Rueda-ruzafa, Ayora, & Ropero-padilla, 2021). Precise probiotic formulations could be tailored to the individual depending on their microbiota and clinical characteristics and utilised as a cancer treatment complement (Markowiak-kope, 2021).

Antibiotics

Antibiotic-induced microbial elimination in malignancy is solely recommended for the prevention of gastric carcinoma and MALT lymphoma caused by *H. pylori*. In laboratory mice subcutaneous injection injected with MC-26 carcinoma cell lines, innovative antibiotic have recently been focused against intratumoral bacteria that can metabolise gemcitabine (A H *et al*., 2019; Li and Yu, 2020; Celardo *et al*., 2020). Antibiotics facilitated the loss of *Bifidobacterium.* or *Akkermansia* spp. and were affiliated with exhaustion of microbial metabolites such as SCFA in treated patients with allograft hematopoietic cell transfer therapy for hematologic malignancies and ICIs for advanced malignant tumors (Kaźmierczak-Siedlecka *et al*., 2021; Microbiome, 2019). Antibiotics' use for elimination of melanoma pathobionts will probably be limited in the future due to their haphazard effects on the native microbes. New techniques that allow for the targeted removal of cancer-promoting symbiotic organisms with minimum microbial damage are currently being researched (Chathuranga, Dissanayake, Fernando, & Wanigatunge, 2021; Marshall *et al*., 2018).

Therapy with phages

Bacteriophages, or viruses that may commonly infect, are abundant in nature and can have an effect on the intestinal flora. The establishment of bacterial phage tolerance, possible immunogenicity, and rapid bacteriophage elimination are all challenges (Lin, Koskella, & Lin, 2017). Phage delivery may avoid systemic autoimmunity while target disease-related gut commensals without causing significant collateral damage to other microbiota components. Instead, therapeutic cargo-carrying phages might be directed at cancer-causing bacteria, allowing cargo to be released into the TME (Principi *et al*., 2019; Polakovicova *et al*., 2018). *F. nucleatum*–specific bacteriophage, for example, have been designed to transport irinotecan nanomaterials, released at the TME after the phages moved to CRC sites occupied by F. nucleatum (Hsieh *et al*., 2021).

Microbes and cancer research problems

Transdisciplinary study must recognise and solve important technological and conceptual challenges, such as how do we make progress in understanding our host-microbes. (Berg *et al*., 2020; Pham *et al*., 2019). Computer interpretation of gut bacteria could improve the accuracy and repeatability of cancer-microbiome analyses. (Thursby & Juge, 2017). Intra - tumoral microbial signals, while hard to collect, may be clinically useful. In patients with pancreatic cancer, the variety of tumour microbiota at the surgical site may predict mortality (Riquelme *et al*., 2020; Zhao *et al*., 2021).

The lack of uniformity and harmonisation of data processing and assessment methods and techniques like extractions of DNA limits the opportunity "(Martínez-Rodríguez *et al*., 2021; Martinez & Moon, 2019). Developments in NGS, metabolic engineering, and proteomic have made it possible to create higher data for finding unique compositions and operational microbial biomarkers (Amiri-dashatan, Koushki, Abbaszadeh, & Rostami-nejad, 2018).

Microbes data may reflect real biologic diversity that is not always due to technical flaws. This large inter - individual variance is influenced by a variety of environmental factors factors, including topography, aging, sexuality and habits. It could lead to identification of customised and clinical context–specific microbial effects to diverse disease presentations (Danielle X. Morales, Sara E. Grineski, 2016; Doña, Virrueta Herrera, Nyman, Kunnasranta, & Johnson, 2021). Machine learning predictions of tailored physiology and melanoma features and reactions may be aided by personalised microbes 'signatures,' which provide a large data fingerprints. New computational methods will almost certainly be required as part of these efforts to correctly record detailed trends of person- and illness-specific microbial dynamics deviating through time, as well as their longterm consequences on clinical disease monitoring systems(Patel *et al*., 2021).

Cancer-microbes research aims to move beyond the detection of connections and associations to the demonstration of causation and mechanisms. In vitro mouse models of cancer are useful for assessing the effects of microorganisms and their released chemicals on malignancy (Enteritis *et al*., 2021; Elinav *et al*., 2020 ; Chan *et al*., 2019). Transfer of complete microbial configuration, specific communities, or individual microorganisms into microbe mice is a frequently used method for proving microbiota causality (Pearce *et al*., 2018). Immunology and other TME cells, as well as diverse microbial ecosystems, can now be integrated into organoids thanks to new observational breakthroughs. Indeed, in summary 3D cultures, patient-derived organotypic tumour organoids including immune system may be able to respond to immune checkpoint suppression(Yuki, Cheng, Nakano, & Kuo, 2020).

CONCLUSION

Human malignancy has been related to distinct microbial modifications and worldwide variations in microbial community composition. Studying causal and molecular relationships among commensal microorganisms in mucous body areas and the TME is likely to give new light on the human diversity in tumor genesis, recurrence, and response to therapy. Microbe-based approaches to cancer biology will likely take the stage in cancer research during the next decade, with a growing presence in diagnosis of cancer, clinical classification, and therapy. Such research faces tremendous hurdles relating to sample procurement, handling, sequence, and analysis of data.

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