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Review

The Role of the Microbiome in Inflammation and Carcinogenesis

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Abstract

Inflammation has been confirmed to exist in the tumor microenvironment, while the risk of cancer occurrence increases in cases of chronic inflammation. It is estimated that approximately 10% to 20% of cancers are associated with chronic infections and attendant inflammation. Bacteria, both pathogenic and commensal, viruses, and fungi actively participate in the development and maintenance of inflammation and tumor growth in humans. The exposome, which is a sum of human environmental exposures, such as industrial diet, consumed drugs, and toxins, affects the composition and function of the human microbiome, which could lead to dysbiosis and disorders in tissue homeostasis through different mechanisms, including the intensification of the immune response, activation and abnormal proliferation, and disruption to epithelial barrier integrity. Presently, science remains at the stage of revealing the complexity associated with the mechanisms involved in building relationships that cover the microbiome–inflammation–tumor, yet it is already known how important it is to care for microbial homeostasis of the organism.

Keywords: cancer; microbiome; virus; bacteria; probiotic; inflammation; exposome; dysbiosis; yeasts/fungi; prebiotic

1. Introduction

The microbiome is now defined as an organ whose role is to supplement and complement the proper functioning of the host organism. Considering this line of reasoning, it should be assumed that multicellular organisms are no longer independent, separate units but constitute the so-called holobionts—an organism with its accompanying microbiota, which consists of viruses, bacteria, fungi, and archaea. The components of the holobiont live in a state of dynamic equilibrium and are subject to changes forced on them by the environment [1,2]. The classic definition of the human microbiome includes the microorganisms that inhabit it and their structural elements, such as nucleic acids and metabolites. The vast majority of the estimated 3.8×10^{13} bacteria live in the digestive tract, mainly in the intestines, and especially in the large intestine. However, one of the most important discoveries in recent years was of the cancer-specific microbiome, which differs significantly from the microbiome of healthy tissues and organs [3–5].

The intestinal microbiome in healthy people changes throughout life, meaning that the species composition of the microorganisms that colonize people differs between individuals. This also applies to the variability and diversity in the composition of the commensal microflora, which is a potential source of phenotypic variability in the development of the disease and therapeutic effectiveness. Thus, this variability has a huge impact on the carcinogenesis process. It also determines the therapeutic response, the characteristics of antitumor immunity, and the clinical response to immunotherapy [6].

The relationship between inflammation and carcinogenesis and the participation of microorganisms inhabiting the human body in these processes have been of interest to many scientists for over a century, with Virchow first showing the link between inflammation and cancer more than 150 years ago by observing leukocytes in neoplastic tissue [7]. Currently, data in the literature confirm the existence of inflammation in the tumor microenvironment, which is consistent with the Virchow hypothesis, and the increased risk of cancer in cases of chronic inflammation. About 10% to 20% of cancers are related to chronic infections and the accompanying inflammation [8,9]. Previous data indicate that the inflammatory microenvironment is an important element in all types of cancer, including those where a direct causal relationship with inflammation has not yet been confirmed [8,10].

Thus, this work aimed to summarize the latest information on the relationship between the microbiome, inflammation, and carcinogenesis. For this purpose, a literature review was conducted, focusing on new achievements in research on the human microbiome, with particular emphasis on selected viruses, bacterial strains, and fungal species, and their impact on inflammation and carcinogenesis. More than 100 peer-reviewed scientific articles, conference materials, and short communications that had been published between 1881 and 2023 were analyzed, although the main focus was on articles from the last 10 years, primarily regarding viruses, bacteria, and fungi as proven carcinogens, the role of inflammation in carcinogenesis, and the possibilities of therapeutic use of pro- and prebiotics.

2. Association of Microorganisms with Inflammation and Carcinogenesis

One of the groups of risk factors that may cause the development of cancer, apart from physical and chemical factors, are microbiological factors that usually precede the development of cancer, and acute and chronic inflammation [11–13]. Such factors include, among others, *Helicobacter pylori* predisposing to the development of gastric cancer, *Human papillomavirus* causing cervical cancer or hepatitis virus being conducive to the development of cancer of this organ [14,15].

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and the third leading cause of cancer-related death worldwide. Among the chemical factors predisposing to the development of HCC, alcohol is the most important, and the risk of HCC increases at a level of consumption of 10 g of alcohol per day [16]. Another factor is smoking tobacco, which contains aromatic hydrocarbons, diethylnitrosamine, and 4-aminobiphenyl [17]. Environmental factors contributing to the occurrence of HCC include aflatoxins, vinyl chloride, arsenic compounds, polychlorinated biphenyls, and radioactive compounds [18]. Previous data indicate an extremely important role for the liver microenvironment in cancer development and metastasis. The organ's microenvironment plays a key role in the proliferation and migration of cancer cells [19]. Various components of the macroenvironment should be considered in the development of cancer and its progression in the liver, whereby both proteins included in the extracellular matrix (ECM), such as collagen, and other various cell types: bone-marrow-derived macrophages, such as tumor-associated macrophages (TAMs), Kupffer cells (KCs), liver sinusoidal endothelial cells (LSECs), immune cells like tumor-associated neutrophils (TANs), myeloid-derived suppressor cells (MDSCs), fibroblasts, hepatocytes, and hepatic stellate cells (HSCs) [20,21]. The ECM forms a framework and contains domains enabling proteins with various functions to bind, although it also contains proteins that interact with growth factors (including HGF: hepatocyte growth factor; VEGF: vascular endothelial growth factor). These factors promote cell migration and angiogenesis, which in turn enables metastatic progression. In the initial stages of tumor development, the microenvironment inhibits this process, yet at some point during tumor growth, the microenvironment eventually supports this growth [22]. Although obesity and alcohol abuse are the factors that predominantly contribute to the development of this type of cancer, hepatitis B virus (HBV) or hepatitis C virus (HCV) infection increases the chance of developing liver cancer by 15–17 times [23]. HCV and HBV prevention programs, vaccinations, and modern forms of treatment are currently changing the epidemiology of HCC, as the etiologies of non-viral diseases are evidently increasing [24,25]. Recent studies have shown that the translocation of intestinal microorganisms that contribute to the development of inflammation in the liver and its fibrosis, together with the activation of Toll-like receptors (TLRs), stimulates the development of HCC [26]. Activation of TLRs, in particular TLR-4, triggers the NF-κB pathway, which is responsible for the constitutive initiation of the mitogenic signal associated with the inhibition of apoptosis. Chronic injury exposes the liver to prolonged exposure to TLR ligands and other bacterial substances, which are mediators of inflammation and favor the development of chronic liver disease, while also creating conditions for the subsequent development of HCC [27]. The pathology of chronic liver infection is related to the immune response to viral infection, which in some patients causes the development of fibrosis and cirrhosis, and ultimately HCC. The two virus types use different molecular evasion mechanisms to avoid the immune system: HBV infection elicits a very limited immune response initially, whereas HCV causes inhibition of type I interferon (IFN-I) synthesis as well as a specific response to type I IFN [28,29].

Many infectious agents in the liver microenvironment can destabilize the normal functioning of liver cells, inter alia, by modulating components of the Wnt/β-catenin pathway. The Wingless/It (Wnt)/β-catenin signaling pathway is involved in regulating cell differentiation processes during embryonic development and tissue homeostasis in the adult organism [30]. Alterations in this pathway are frequently observed in cancer, especially in those tissues whose functioning depends on their ability to self-renew [31]. The pathway is initiated by a family of Wnt ligands, consisting of 19 glycoproteins with both autocrine and paracrine functions, thereby binding to receptors on the cell membrane to transduce intracellular signals. At the cytoplasmic level, the signaling network is defined depending on whether it is β-catenin dependent or β-catenin independent [32,33]. The dysregulation of Wnt/β-catenin signaling involves hepatotropic viruses B, C, and D and other microbial agents, including oncogenic viruses, such as Epstein–Barr virus (EBV) and human papillomavirus (HPV), and bacteria such as *Clonorchissinensis*, or parasites, e.g., *Opisthorchis viverrini* [34].

In addition to avoiding recognition by the immune system, cancer cells induce inflammation and create a favorable tumor microenvironment in order to progress to full malignancy [35]. For this purpose, they use various mechanisms through which oncogenic mutations provide cancer cells with the ability to dysregulate mitogenesis, resistance to apoptosis, and the ability to invade and infiltrate healthy tissues [36]. Signaling pathways that are disturbed during cancer transformation include receptor tyrosine kinases (RTKs). In cancer, dysregulation of RTK activation caused by oncogenic mutations is common [37]. Moreover, cancer cells are insensitive to control mechanisms related to cadherin-mediated contact inhibition, and dysregulated integrin signaling is important in the process of tumorigenesis [38]. Other metabolic reprogramming path-

ways that are associated with carcinogenesis include mutations in metabolic enzymes. Previous data indicate the presence of heterozygous mutations in one of the two genes encoding isocitrate dehydrogenase in glioma and leukemia cells [39]. Cell division is regulated by the activation of cyclin-dependent kinases (CDKs), the catalytic subunits of cyclins [40]. In various types of cancer, oncogenic mutations change various elements in the signaling network of cyclins and CDKs, whereby, among others, cyclin D1 is significantly overexpressed in breast cancer cells [41]. Research results published by Shi Y *et al*. [42] and Massague J *et al*. [43] indicate an important role of transforming growth factor beta (TGF-β) in the appearance and development of cancer. Cancer cells appear to avoid the antimitogenic signals provided by TGF-β. Suppression of apoptosis in tumors, in turn, is associated with the activation pathway of the proto-oncogenes Bcl2 and inhibitor of apoptosis protein (IAP), the inactivation of Bim and Bad, the loss of p53, and the reduction in the expressions of Puma, Noxa, and Bax [44]. A full understanding of the processes of carcinogenesis requires the elucidation of many signaling pathways that regulate the tumor microenvironment and promote its progression.

The T-cell response to viruses in patients with chronic infection and cirrhosis is delayed and transient compared to the strong response in those who are able to fight off the infection. Thus, although HCC can be induced by direct transformation of cells by HBV, tumor progression for both viruses is mainly dependent on the development of inflammation in the organ. Hepatitis caused by HBV has often been associated with intestinal dysbiosis, which is manifested by an increase in the number of fungal species and a simultaneous decrease in the number and diversity of strains belonging to the *Bifidobacterium* species. Studies on experimental animals have shown the influence of the intestinal microbiota on the progression of liver diseases and cancer in this organ [45–47]. When analyzing the impact of HBV and HCV on the possibility of HCC, the hepatitis delta virus (HDV) should also be considered. It is a small, defective virus that needs HBV to replicate and multiply effectively. Literature on the role of HDV infection in HBV-related liver disease or liver cancer is very limited; however, it suggests that HBV/HDV coinfection is associated with an increased risk of developing HCC [48].

2.1 The Role of Viruses in Carcinogenesis

The relationship between the direct transformation of cells by viruses and inflammation-induced carcinogenesis is also possible for many other oncogenic viruses. In addition to HBV and HCV, there are five other viruses with confirmed oncogenic effects on the human body: HPV, Merkel cell polyomavirus (MCPyV, MCV), human herpesvirus type 8 (HHV-8), which is the cause of sarcoma Kaposi and other conditions, especially in immunocompromised people due to various dysfunctions in their immune systems, the EBV, which causes Burkitt lymphoma and human T-cell lymphotropic virus type 1 (HTLV-1) (Fig. 1) [49].

EBV is associated with the uncontrolled proliferation of B lymphocytes, T lymphocytes, and natural killer (NK) cells. Malignant transformation can occur in cells as a result of latent infection, and four types of EBV latency are known that are associated with the expression of different proteins [50,51]. Type I latency is associated with Burkitt's lymphoma, while type II latency is associated with nasopharyngeal cancer, gastric cancer, Hodgkin's lymphoma, and T-cell and natural killer cell lymphoma. In turn, type III was found in people with post-transplant lymphoproliferative disease and AIDS (Acquired Immune Deficiency Syndrome) patients with diagnosed lymphoma [52, 53]. The KSHV (Kaposi's sarcoma-associated herpesvirus) virus infects B lymphocytes, macrophages, monocytes, keratinocytes, and endothelial cells of blood vessels, and causes Kaposi's sarcoma alongside exudative lymphoma and multifocal Castleman's disease [54,55]. The main oncoprotein in KSHV is the Lana protein (viral latency-associated nuclear antigen), which causes the inhibition of cell signaling pathways: the TGF-β signaling pathway, mitogen-activated protein kinase (MAPK) signaling pathways, the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway, the extracellular-signal-regulated kinase (ERK) pathway, the phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT) signaling pathway, Notch and Wnt, and the p53 protein, which consequently leads to disorders associated with the process of apoptosis and intensification of proliferation [56]. The MCPyV virus is responsible for the development of highly aggressive Merkel MCC neuroendocrine skin cancer (Merkel cell carcinoma) [57]. The virus is found on the skin, in the respiratory tract, saliva, lymph, urine, and the digestive tract, and infects Merkel cells and skin fibroblasts [58,59]. The main oncoproteins involved in the tumorigenesis process caused by the MCV virus are the LT and sT proteins, the activity of which leads to excessive cell proliferation [60]. Large T (LT) and sT are two major oncoproteins of MCV. Polyomaviruses contain the T ("tumor") antigen gene locus. MCV expresses unique gene products from early coding regions: the LT and small T (sT) [61,62].

The HPV virus infects epithelial cells causing skin, common, and flat warts, however, some HPV strains can cause cervical, anal, vaginal, penile, and vulvar cancers [63]. HPV viruses can be divided into five groups: α, β, γ, μ, and ν, of which those from the γ, μ, and ν groups do not cause neoplastic transformation. HPV16 and HPV18 viruses belong to the HR-HPV (high-risk HPV) group and are the most common viruses associated with cancer. Two oncogenic proteins E6 and E7 are responsible for the induction of the HPV-mediated carcinogenesis process, the excessive activity of which leads to neoplastic transformation of the infected cell [64,65]. Another oncogenic virus

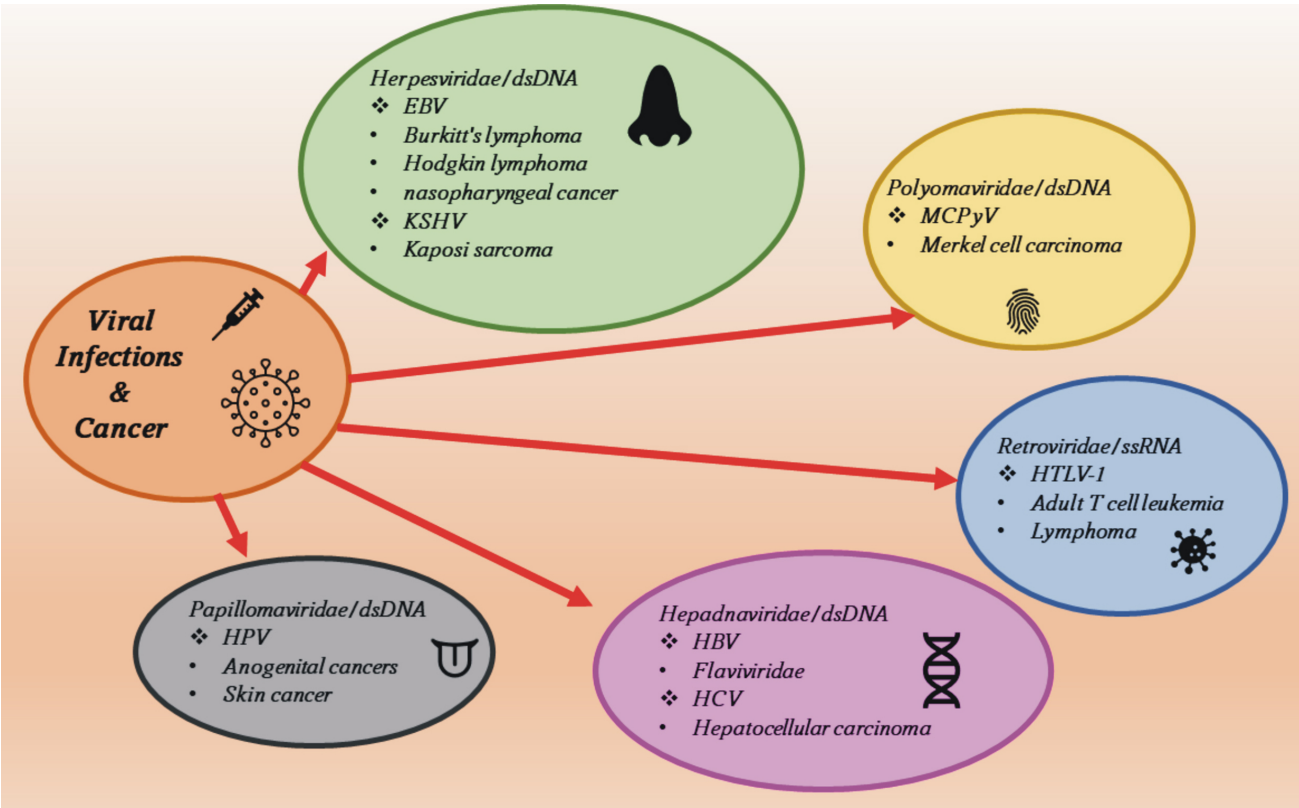

Fig. 1. Viral oncogenic agents and the diseases they cause. EBV, Epstein-Barr virus; KSHV, Kaposi's sarcoma-associated herpesvirus; HPV, Human papillomavirus; MCPyV, Merkel cell polyomavirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HTLV-1, human T-lymphotropic virus type 1.

is HTLV-1 (*human T-cell leukemia/lymphoma virus* or *human T-lymphotropic virus*), which is a retrovirus found in Japan, Iran, Peru, Brazil, Ecuador, Honduras, Papua New Guinea, West Africa, and the Caribbean. It causes adult T-cell leukemia (ATL) and has a multi-year latency period of up to 40–60 years. It infects $CD4^+$ and $CD8^+$ T cells and dendritic cells. Tax and HTLV-1 basic leucine zipper factor (HBZ) proteins are involved in malignant transformation, with HBZ also contributing to the spread of the transformed cells [66–68]. With the exception of HCV, all known oncogenic viruses encode at least one oncogene and can transform healthy cells into cells with a neoplastic phenotype. However, even infection with one of the oncogenic viruses is usually not the only factor predisposing to the development of cancer, additional factors are necessary, including hormonal, dietary, geographical, and even cultural conditions. Therefore, the neoplastic process develops after a few or even several years [69]. For example, the human papillomavirus has an evident ability to transform healthy cells into cancerous cells, yet inflammation of the genital organs combined with disturbances in the natural microbiota are also very important factors in the progression of cancer [70–72].

2.2 The Role of Bacteria in Carcinogenesis

Although many bacterial strains play an unquestionable role in the processes of carcinogenesis, *Helicobacter pylori* was classified by the International Agency for Research on Cancer as a human class I carcinogen due to its proven relationship with certain types of gastric cancer and lymphomas. *H. pylori* can be considered a commensal microorganism and an opportunistic pathogen because it is characterized by quite low virulence, while disease symptoms are observed mainly in older people. This bacterium is identified in various body fluids, and the human stomach is colonized early in life, usually in the family environment. The factors that influence the development of diseases caused by *H. pylori* are primarily diet, individual immunity, and the use of medications. All these factors affect the balance of the microbiome, which also plays an important role in *H. pylori* infections [73]. *H. pylori* has the ability to produce urease, which helps it survive in the low pH of the stomach, and long-term infection with this pathogen further raises the pH, making it easier for other microorganisms to colonize the stomach. Long-term exposure to *H. pylori* with an initial inflammatory response, including IL-1β production, epithelial damage and atrophy, and reduced secretion of hydrochloric acid and intestinal metaplasia, is required to initiate the process of carcinogenesis.

K-ras and p53 mutations are frequently found in gastric adenocarcinoma, although their slightly different pattern suggests that *H. pylori*-induced inflammation is the cause of gastric cancer [74–76]. In addition, *H. pylori* may produce virulence factors such as CagA (cytotoxin-associated gene A), CagPAI (Cag pathogenic islands), and VacA (vacuolating cytotoxin A), which may introduce disturbances in the regulation of the intracellular tyrosine phosphorylation-dependent and tyrosine phosphorylation-independent signaling pathways (in which NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; Erk1/2: extracellular signal-regulated kinase1/2, are both involved) and lower the threshold necessary for cells to enter the malignant transformation pathway. Increased vacuolytic cytotoxin (VacA) activity induces cell apoptosis. Literature data indicate that CagA may interact with host proteins by activating various signal transduction pathways, including the MEK/ERK pathway, the NF-κB pathway, and the β-catenin pathway, thereby enhancing the response of the immune system and stimulating the cell proliferation process. Infections caused by cag (+) strains producing this protein are accompanied by an increase in the level of proinflammatory cytokines (IL-8, IL-1, IL-6, and TNFα) and the formation of radical morphological changes in gastric epithelial cells [77]. The CagA protein also affects the regulation of the body's response to oxidative stress. Increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) leads to DNA damage in the host cells and accelerates their death. In addition, ROS and RNS reduce the secretion of RUNX3 (Runt-related transcription factor 3), which is a protein that protects cells from oxidative stress. RUNX3 belongs to a group of transcription factors that regulate the expression of many genes but also participates in the formation of tumors [78]. According to Li *et al*. [79], a significant reduction in RUNX3 expression correlates with the induction and development of gastric cancer and even with a poor prognosis in this type of cancer. RUNX3 inactivation, which occurs due to promoter hypermethylation or protein mis-localization, has been identified at various stages of gastric cancer development, starting from the initiation stage. The factor causing RUNX3 inactivation is still unknown and undescribed [80]. However, it should also be mentioned that although *H. pylori* infections are considered to be one of the factors that induce the formation of certain types of cancer, they also clearly reduce the risk of, for example, adenocarcinoma in the esophagus, stomach, and gastric cardia [81,82].

Other oncogenic pathogenic microorganisms are some bacterial strains known to promote the development of colorectal cancer, e.g., selected strains of *Escherichia coli, Streptococcus bovis, Bacteroides fragilis, Enterococcus spp*., and some species of the *Enterobacteriaceae* family (Fig. 2). They can directly adhere to the intestinal epithelial layer and stimulate cell proliferation, leading to hyperplasia. In addition, they synthesize enzymes and toxins, such as 20 kDa heat-labile metalloproteinase, called *B. fragilis* toxin (BFT), and adhesin FadA, a virulence factor identified from *Fusobacterium nucleatum,* which violate the integrity of the epithelial layer, damage cells, and cause inflammation [83,84]. Of these species, the most thoroughly studied in terms of its association with cancer is *E. coli*. Its stimulating effect on the progression of colorectal cancers is confirmed due to its adhesion to intestinal epithelial cells, which causes hyper-proliferation and inflammation. Major virulence factors, mainly adhesins, toxins, iron-acquisition factors, lipopolysaccharides, and invasins, are carcinogenic through damage to DNA and epithelial/mucosal barriers [85]. Particularly pks+ strains that produce polyketide synthase are characterized by high toxicity and an incidence associated with colorectal cancer. Enterotoxic *Bacteroides fragilis* also generates toxins, as was mentioned above, which lead to the development of colorectal cancer. They induce a variety of responses at the molecular level, including cleavage of E-cadherins and activation of β-catenin, stimulation of the NF-κB signaling pathway, and induction of the Th17 immune response. It has also been shown that *Fusobacteria* stimulates carcinogenesis in colorectal cancer by binding to the E-cadherins on cancer cells through their FadA adhesion proteins, which then stimulate the growth of cancer cells. *Fusobacteria* also has the ability to infect neighboring tissues, where it produces a pro-cancer immune response [86–88].

2.3 The Role of Fungi in Carcinogenesis

Following the development of the research area related to analyzing the microbiome, fungi were found to be included in it and to also be important in the development of cancers [89]. Fungi that inhabit the human digestive system are characterized by high species variability and dependence on environmental factors, mainly diet [90]. They have been identified in the esophagus, stomach, pancreas, and intestines, while the most common genera are *Candida, Saccharomyces, Malassezia, Cladosporum, Cryptococcus, Trichospora*, and *Aspergillus*, among many others [91]. In cancers of the gastrointestinal tract, a disturbed ratio of Basidiomycota to Ascomycota has been reported. A particular overgrowth of *Candida albicans* was found in ESCC (esophageal squamous cell carcinoma), *Cladosporium cladosporoides* in esophageal tumors, and *Malasseziomycetes* in CRC (colorectal carcinoma) [92] (Fig. 2). In the case of fungi, as in the case of bacteria, pathogenic changes are usually caused by a disruption in the specific dynamic balance, leading to the occurrence of infections, often chronic ones. Fungi–bacteria interactions also seem to be key here, as they have been observed in cases of CRC. Disturbances in the composition and functioning of the microbiome are a way in which fungi influence the appearance and development of gastrointestinal cancers.

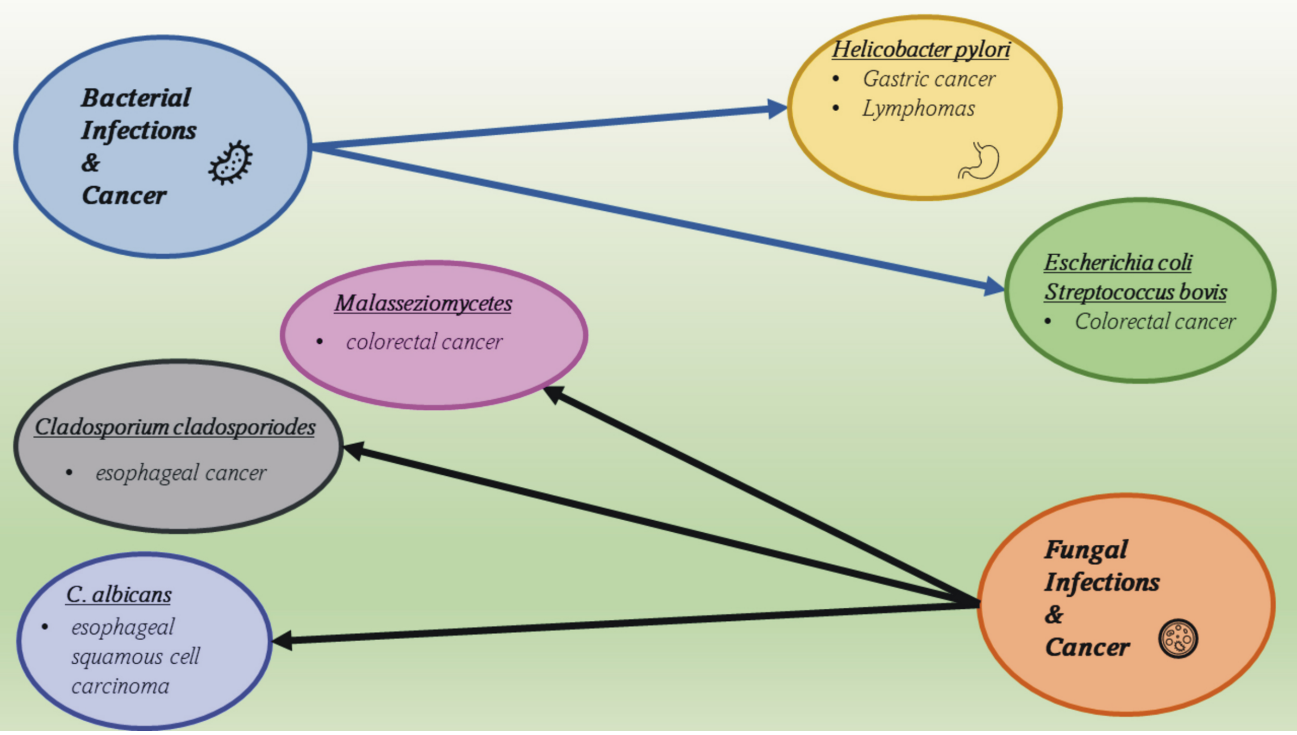

Fig. 2. Bacterial and fungal oncogenic agents and the diseases they cause.

2.4 Inflammation-Induced Carcinogenesis

Chronic inflammation significantly predisposes the initiation of cancer but also favors its development, creating the inflammatory tumor microenvironment, where cells change their phenotypic and functional characteristics. In approximately 20% of cancer cases, the appearance of the tumor is preceded by infection and long-term inflammation [93]. Disturbances in microbiome homeostasis and interactions by microorganisms with hematopoietic cells are associated with both inflammation and carcinogenesis. In animal models, it has been shown that IL-18 has a protective function in relation to mucous membranes. Mice that are deficient in synthesizing and responding to IL-18 are characterized by intestinal dysbiosis and increased sensitivity to chemically induced colorectal cancer. Short-chain fatty acids (SCFAs), such as butyric acid, which is a product of bacterial fermentation of fiber in the intestine, induce the synthesis of IL-18 by intestinal epithelial cells by activating GPR109a receptors, yet also act directly on macrophages and T cells. SCFAs induce the expansion of Treg cells to produce anti-inflammatory cytokines, including IL-10, which inhibits the development of inflammation and carcinogenesis. IL-18 stimulates the repair of tissues, mainly mucosa, by regulating the production and increasing IL-22 availability through its production by intestinal lymphoid cells and, by activating STAT3, which induces epithelial cell proliferation and synthesis of antibacterial peptides. Therefore, IL-22, by stimulating the repair of damaged epithelia, may act, depending on the degree of damage, as a pro- or anti-carcinogen [94,95].

In inflammation caused by pathogenic microorganisms that contribute toward the development of cancer, the accumulation of reactive oxygen and nitrogen species plays an important role. Both types of free radicals cause the formation of cross-links in DNA and breakage of DNA and RNA strands, which promotes genome instability and mutations in oncogenes and tumor suppressor genes. Inflammatory conditions in the body create conditions conducive to the development of the tumor microenvironment, in which the decisive role is played by hematopoietic cells, such as macrophages, which, under the influence of tumor cells secreting, among others, IL-10 and TGF-β, change their phenotype to one capable of secreting anti-inflammatory cytokines and immunosuppressants (Fig. 3) [96,97].

Tumor-associated macrophages (TAM macrophages) produce pro-angiogenic factors (VEGF-A, TNF-α, and IL-8), growth factors (PDGF: platelet-derived growth factor; EGF: epidermal growth factor) and metalloproteinases, which are involved in the processes of remodeling the extracellular matrix, facilitating tumor growth, and intensifying inflammatory processes. The release of pro-inflammatory cytokines is related to the nuclear factor NF-κB, which is a transcription factor for over 150 genes related, among others, to the development of inflammation and carcinogenesis. It is activated by detaching the inhibitor (IκB) after exposure to any appropriate factors, e.g., oncogenic viruses, and is translocated to the cell nucleus, where it allows the transcription of specific genes, including TNF-α, IFN-γ, IL-1β, IL-2, and IL-6. Cancer cells release a number of different cytokines that stimulate proliferation, an-

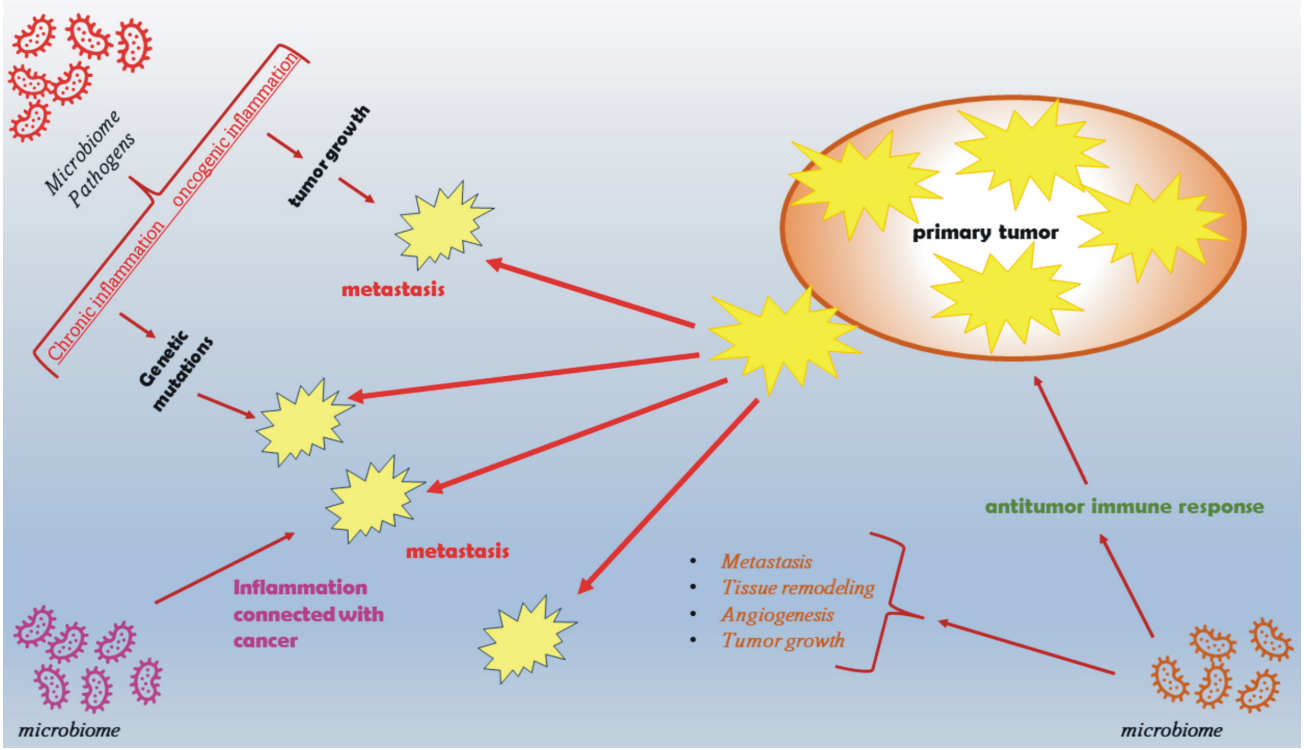

Fig. 3. The role of inflammation and the microbiome in tumor initiation, promotion, metastasis, and response to therapy. The microbiome directly and indirectly influences the development and maintenance of inflammation in the body, which in turn stimulates the development of cancers by increasing genetic instability and by creating a microenvironment conducive to tumor growth. The microbiome may also influence the emergence of cancer-promoting factors, such as obesity and metabolic syndrome, and modulate the immune response mechanisms that regulate tumor initiation and progression.

giogenesis, and the emergence of an invasive phenotype and metastasis. Especially, TNF-α that is produced over a long-time acts as an endogenous stimulator of many disease processes, including cancer [98,99]. When a tumor appears in the body, whether its origin is inflammatory or not, a tumor-related inflammation occurs that creates an environment conducive to tumor growth and enhances immunosuppression. Many mechanisms are involved in the prevention of an effective antitumor immune response. These are immunosuppressive and anti-inflammatory factors, e.g., NO, arginases, TGF-β, and IL-10, which are synthesized by macrophages, Treg cells, and various types of leukemic cells. In addition, cancer cells express ligands belonging to the B7 and PDL1/2 families, which affect the T cell receptors, CTLA-4 and PD1, by inhibiting their anti-cancer activity. Fig. 3 schematically illustrates how inflammation affects carcinogenesis, tumor progression, comorbidities, and response to therapy at various levels, and how microorganisms modulate host responses to pathogens, inflammation, and tumor-induced tissue damage. Therefore, it is believed that both commensal and pathogenic microorganisms play a huge role in the development of inflammation and any possible carcinogenesis associated with it [97].

3. Therapeutic Goals

A better understanding of the mechanisms involved in cancer development at the molecular level will allow the inclusion of therapeutic factors, such as pro- and prebiotics, the better use of antibiotics and manipulations at the level of individual bacterial proteins to enable or disable specific factors responsible for the toxicity and carcinogenicity of selected bacterial strains (Fig. 4) [100]. When considering the impact of the microbiome on carcinogenesis, we should also mention the exposome theory, the impact on the human body, which is crucial. The exposome is composed of many factors interacting (Fig. 4). The exposome can be defined as an integrated function of the exposure of the human body, which includes everything that surrounds us, the place we live in, the relationships we create, the food we consume, the drugs we use, and the activities we perform. It is worth noting that exposure is not limited to the substances or stimulants that we consume but also includes chemical compounds produced in the body in metabolic processes [101]. Therefore, the microbiome and its functioning and impact are important components of the exposome, which to some extent can reduce the unfavorable impact of selected elements of the exposome on the human body.

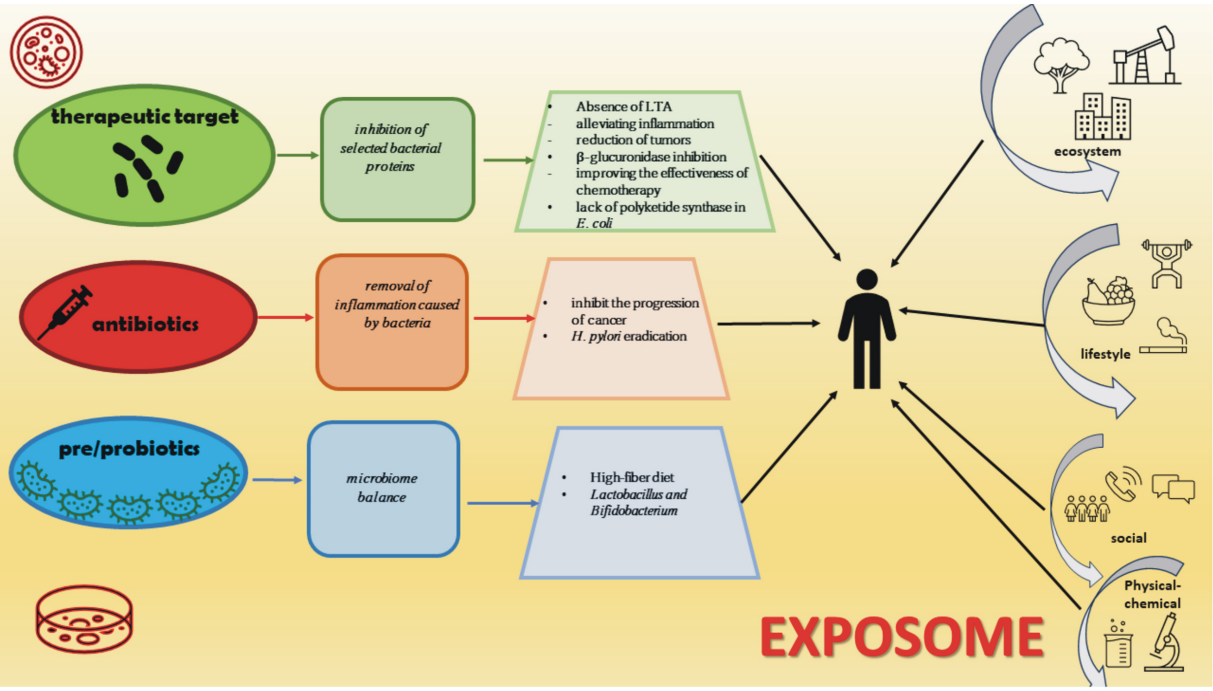

Fig. 4. The microbiome, cancer, and exposome. Three potential interventions point to improved patient responses to cancer therapy and the impact of the exposome on the human body.

In recent years, the following have become very popular:

• prebiotics (non-digestible food ingredients, which selectively stimulate the growth of certain strains of commensal bacteria that are beneficial to humans).

• probiotics (live microorganisms with a beneficial effect on the functioning of the intestinal microbiota).

Both are used in the prevention and treatment of certain diseases, mainly in the gastrointestinal tract and have even become a key element in the daily diet. There have been reports showing the positive effect of dietary fiber on the synthesis of SCFAs by intestinal bacterial strains and its possible beneficial effect on cancer cells. In addition, the consumption of large amounts of fiber increases methanogenesis, which leads to a reduction in the number of hydrogen-producing bacteria, which is extremely important because excess hydrogen in the intestine prevents the regeneration of NAD (nicotinamide adenine dinucleotide). Another beneficial aspect resulting from the consumption of large amounts of fiber is the colonization of the intestines by microorganisms that eliminate possible inflammation, e.g., *Faecalibacterium prausnitzii*. The most commonly used probiotic strains are *Lactobacillus* and *Bifidobacterium spp*., which enhance the detoxification of toxic metabolites and carcinogens in the intestines, thereby stimulating the body's anticancer response and producing anticancer and antimutagenic components that directly interact with cancer cells, inhibiting their growth, and synthesizing substances such as SFCAs that are important for maintaining the immune balance [102,103].

Although probiotics are very intensively studied, therapeutic strategies also include pathogenic microorganisms. There are animal studies that have shown the ability to inhibit specific bacterial proteins without disturbing the microbial balance of the host. For example, animals infected with a strain of *Lactobacillus acidophilus* and lacking lipoteichoic acid (LTA-) showed milder inflammation of the colon and inhibition of intestinal tumor growth. Another group of researchers showed the alleviation of intestinal inflammation associated with cancer after infection with the *E. coli* pks- strain in an animal model. Cyclomodulins, e.g., colibactin (*pks*), are virulence factors that modulate cellular differentiation, apoptosis, and proliferation. The depletion of bacteria with selected proteins, such as pks, can alleviate the symptoms of the disease. The effects of manipulating bacterial enzymes on human health were also studied. The anticancer drug irinotecan causes constant diarrhea in patients, which limits the possibilities of effective therapy. Wallace *et al*. [104] developed inhibitors for the bacterial enzyme β-glucuronidase, which reactivates the conjugated forms of irinotecan and also causes diarrhea in patients. Inhibition of β-glucuronidase reduced the toxic effects associated with chemotherapy without affecting commensal bacteria, as demonstrated in a mouse model. The next step in the future seems to be to create such inhibitors against the potential oncogenic properties of commensal bacteria without disturbing the delicate balance of the microbiome [105].

4. Conclusions

Overall, it should be said that the impact of microorganisms on the functioning of the human body is huge and indisputable. The microbiome can indeed be considered a separate "organ". Both pathogenic and commensal bacteria actively participate in the formation of inflammation and the development of cancer in humans. Moreover, external and environmental factors, such as diet, consumed drugs, and toxins have an impact on the composition and function of the human microbiome, which can lead to dysbiosis and tissue homeostasis disorders through various mechanisms, including the enhancement of the immune response, activation of epithelial proliferation, and impairment of barrier integrity. Currently, although science is at the stage of revealing the complexity of the mechanisms involved in building the microbiome-inflammation-cancer relationship, we already know that taking care of the body's microbial homeostasis is as important as any other organ in our body.

Author Contributions

AJT designed the research study, analyzed the information, and wrote and edited the manuscript. AJT contributed to editorial changes in the manuscript. AJT read and approved the final manuscript. AJT has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

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Conflict of Interest

The author declares no conflict of interest.

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