# Fungi and tumors: The role of fungi in tumorigenesis (Review)

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**Abstract.** Fungi inhabit different anatomic sites in the human body. Advances in omics analyses of host-microbiome interactions have tremendously improved our understanding of the effects of fungi on human health and diseases such as tumors. Due to the significant enrichment of specific fungi in patients with malignant tumors, the associations between fungi and human cancer have attracted an increasing attention in recent years. Indeed, cancer type-specific fungal profiles have been found in different tumor tissues. Importantly, fungi also influence tumorigenesis through multiple factors, such as host immunity and bioactive metabolites. Microbiome interactions, host factors and fungal genetic and epigenetic factors could be involved in fungal enrichment in tumor tissues and/or in the conversion from a commensal fungus to a pathogenic fungus. Exploration of the interactions of fungi with the bacterial microbiome and the host may enable them to be a target for cancer diagnosis and treatment. In the present review, the associations between fungi and human cancer, cancer type-specific fungal profiles and the mechanisms by which fungi cause tumorigenesis were discussed. In addition, possible factors that can lead to the enrichment of fungi in tumor tissues and/or the conversion of commensal fungi to pathogenic fungi, as well as potential therapeutic and preventive strategies for tumors based on intratumoral fungi were summarized.

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## 1. Introduction

Fungi are microeukaryotes that inhabit different anatomic sites in the human body. More than 400 fungal species, mainly including three phyla, *Ascomycota*, *Basidiomycota* and *Chytridiomycota,* are associated with the human body (1). Over 100 fungal species, including 50 genera, are also found in mice (2). These fungi are less abundant in the human microbiome than other organisms, such as bacteria (3). However, emerging evidence has shown that fungi significantly influence host health and disease (3); for example, fungi are involved in the occurrence and development of tumors (4-7).

Tumors have complex ecosystems. They have their own unique microbiome, which includes bacteria, viruses and fungi. These intratumoral organisms participate in tumorigenesis and tumor development (8,9). Most studies of microbial dysbiosis in tumors, especially colorectal cancer (CRC), have focused on bacteria (10). However, sequencing technologies have also detected viruses, fungi and archaea in tumor tissues and revealed cancer type-specific microbial signatures (11). In 2022, Narunsky-Haziza *et al* (12) uncovered the fungal microbiome atlas of 35 types of cancer and demonstrated that fungi were also detected in all studied tumor types. Dohlman *et al* (13) also found tumor-related fungi in cancers of the gastrointestinal (GI) tract, lung, breast and head and neck by analyzing cancer genome data. Interestingly, different cancers exhibit cancer type-specific fungal profiles, such as *Candida* species, which are involved in the pathogenesis of CRC (3,13). Notably, multi-kingdom microbiota analyses have also provided biomarkers of CRC and bacterial-fungal interactions (14). These intratumoral fungi can be classified into six categories based on different anatomic sites, including the oral cavity, gut, adjacent tissue, lung, skin and blood circulation (15). Due to the significant enrichment of specific fungi in malignant tumors, the associations between fungi and human cancer have attracted increasing attention in recent years (3).

Multiple factors, such as interactions between bacteria and fungi, interactions between different fungi, and interactions between fungi and host factors, fungal genetic factors, and epigenetic factors, might be involved in the enrichment of fungi

in tumor tissues and/or the conversion of commensal fungi to pathogenic fungi. Intratumoral fungi are potential therapeutic target(s) and/or diagnostic and prognostic indicators for tumors. These fungi are regulated by factors such as diet, fecal microbiota transplantation (FMT), probiotics, prebiotics and genetically engineered probiotics. In the present review, the associations between fungi and human cancer, cancer type-specific fungal profiles and the mechanisms by which fungi induce tumorigenesis were discussed. Furthermore, the factors that cause fungal enrichment in tumor tissues and/or the conversion of commensal fungi to pathogenic fungi, as well as potential therapeutic and preventive strategies based on intratumoral fungi were summarized.

## 2. Signatures of fungal species in tumors

Tumors are complicated ecosystems that are composed of cancer cells, immune cells, fibroblasts, endothelial cells and microbiota. The intratumoral microbiota is a novel and integral tumor component, which includes bacteria, that was recently identified in various cancer types. Poore *et al* (11) revealed cancer type-specific microbial signatures in tumor tissue. Indeed, each type of tumor has a distinct microbiota composition; for example, there is a particularly rich and diverse microbiome in breast cancer (16). Recent findings have further revealed the spatial and population heterogeneity of the intratumoral microbiome (17). These intratumoral microbiota can be used for multiple purposes, such as distinguishing normal tissue from cancer tissue, distinguishing metastatic cancers from non-metastatic cancers, distinguishing patients with cancer that respond to drugs from those that do not respond to drugs and distinguishing patients with a favorable prognosis from those with a bad prognosis (18).

Interestingly, human tumor tissues also harbor tumor-associated fungi (12,13). For example, Narunsky-Haziza *et al* (12) reported that 31 fungi, such as *Saccharomyces cerevisiae* (99.7% coverage), were present in analyzed tumor tissues. In support of this finding, another study also revealed a high abundance and prevalence of *Saccharomycetales* in different tumors (13). Other fungi, including *Candida albicans*, *Malassezia globosa*, *Malassezia restricta* and *Blastomyces gilchristii,* could also be present in different types of human cancer (12,13,19). Indeed, fungi have been found in multiple types of tumors (12), such as those associated with CRC (13,20-22), pancreatic (23), breast (24), prostate (25), ovarian (26) and esophageal cancer (27). The signatures of the main specific fungi in different tumors are illustrated in Fig. 1.

*CRC*. CRC is the fourth most common cancer worldwide and is responsible for the deaths of >500,000 individuals every year (28). Interestingly, CRC is associated with changes in the fungal community of the colon in patients (14,21,22). Fungal dysbiosis was detected in patients with colorectal polyps (29) and adenomas (20), suggesting the involvement of fungi in early-stage CRC. Indeed, there was a co-abundance group associated with *Candida albicans* that included *Candida dubliniensis, Candida guilliermondii* and *Candida tropicalis,* and a group associated with *Saccharomyces cerevisiae*, which included *Saccharomyces eubayanus, Cyberlindnera jadinii* and *Candida glabrata* (13). These findings also indicated that GI tract cancers may be separated into *Candida*- and *Saccharomyces*-associated tumors (13). Notably, the abundance and prevalence of the species *Candida dubliniensis, Candida glabrata, Candida guilliermondii, Candida lusitaniae, Candida parapsilosis, Candida tropicalis* and *Pichia membranifaciens* were also lower in CRC according to a metagenomic analysis of whole-genome sequencing (WGS) data from multiple tumor samples from patients with different cancers in The Cancer Genome Atlas (13). Several other studies also indicated the existence of *Candida* species, *Cyberlindnera jadinii* and *Saccharomyces cerevisiae* in CRC tissues (30-32). However, a previous study also revealed that *Aspergillus* species were highly enriched in the CRC tissues of patients from both Asia and Europe through fecal shotgun metagenomic sequencing (22). In addition, other fungi, such as *Cordyceps* sp. *RAO-2017,* were also detected in CRC tissues (21). The abundance of *Orbiliomycetes* was different in the CRC and polyp groups (29).

*Gastric cancer (GC)*. GC, which is one of the most common malignancies and one of the main causes of tumor-associated deaths worldwide, is also related to fungi (33,34). A metagenomic analysis of WGS data revealed that several fungi, such as *Candida* species, *Saccharomyces cerevisiae* and *Cyberlindnera jadinii,* were highly abundant in the mycobiome communities of patients with GI tract cancer (13). A different study by internal transcribed spacer 2 (ITS2) analysis of GC tissues revealed significant increases in the abundance of *Candida albicans*, *Fusicolla acetilerea, Arcopilus aureus* and *Fusicolla aqueductuum* in cancer lesions and adjacent non-cancerous tissues of 45 patients with GC from Shenyang, China (35). Notably, the abundances of other fungi, such as *Aspergillus montevidensis* and *Candida glabrata,* were markedly reduced (35,36). Increased Candida abundance was also linked to the expression of proinflammatory factors, which could lead to the occurrence and development of tumors (13). Notably, *Candida albicans* might also cause GC by decreasing the diversity and richness of fungi in the stomach, which contributes to the pathogenesis of GC (35).

*Hepatocellular carcinoma (HCC)*. Using ITS2 rDNA sequencing, alpha diversity analyses revealed that patients with HCC had reduced fungal diversity when compared with controls (37). Aberrant colonization of the gut by *Candida albicans* and *Malassezia furfur* promoted the occurrence and development of HCC (37). HCC tumor weight and volume significantly increased in the *Candida albicans* and *Malassezia furfur* groups compared with the control group (37).

*Pancreatic cancer*. Pancreatic cancer, which is one of the leading causes of cancer-related deaths, is also associated with fungi. A recent preclinical and clinical study demonstrated that pancreatic ductal adenocarcinomas (PDACs) harbored significant enrichment of a specific fungus in mouse models and human specimens. Indeed, enriched fungi were observed in the pancreas of patients with PDAC and in mouse models of pancreatic cancer by principal coordinate analysis (23). *Malassezia* species were more prevalent in PDAC tissues in both mice and humans (23). Another analysis also demonstrated that *Malassezia* and *Alternaria* were the most abundant fungi

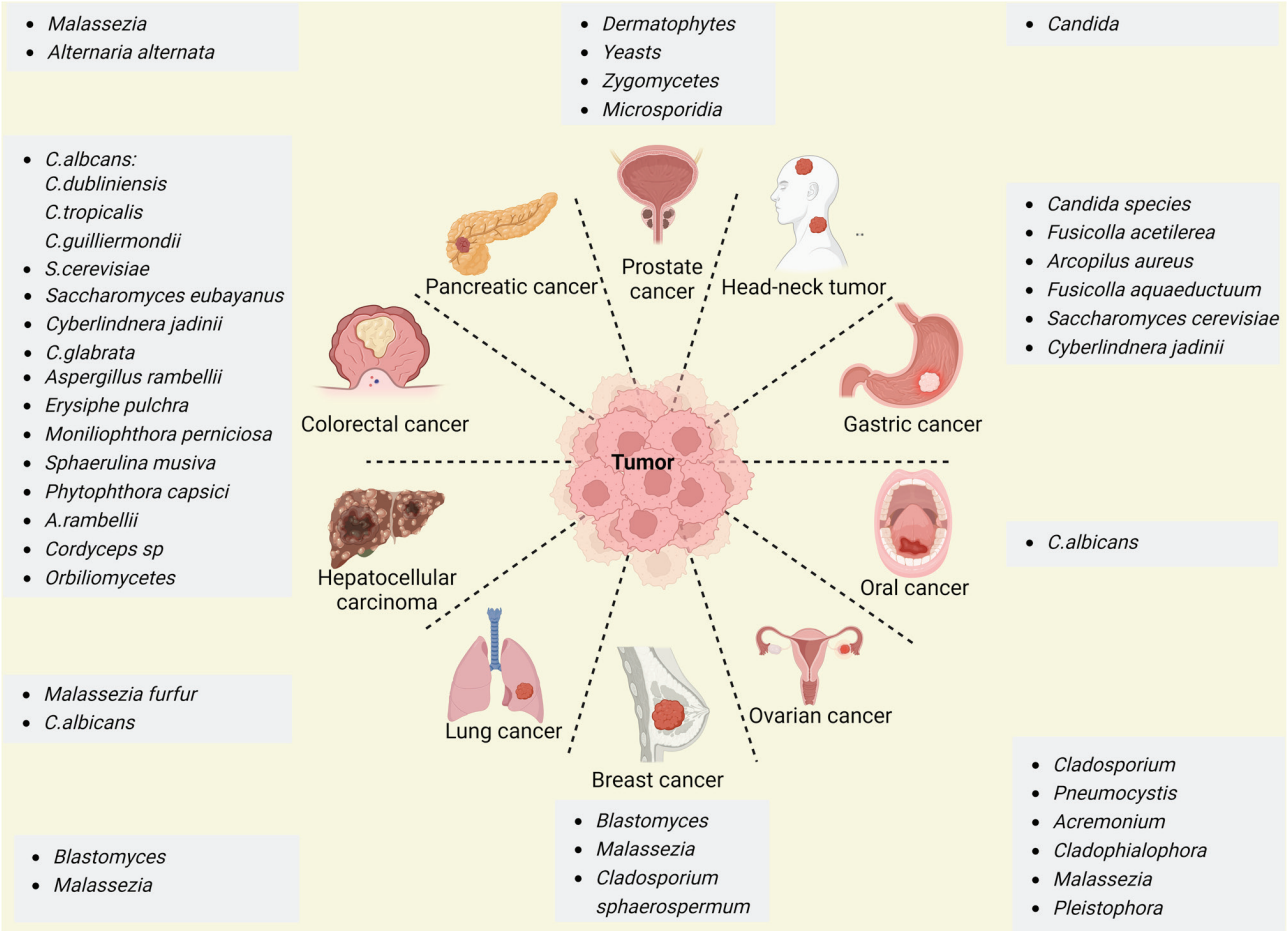


Figure 1. Signatures of specific fungi in different tumors. Fungi can be detected in different tumor tissues, including colorectal, hepatocellular, pancreatic, prostate, head and neck, gastric, lung, oral, breast, lung and ovarian cancer tissues. The figure was created with BioRender (https://servicecenter.oit.ucdenver.edu/CherwellPortal/IT).

in PDAC tumors using 18S rRNA sequencing (5). Significantly high levels of fungal and bacterial alpha diversity in the gut were also observed in patients with PDAC by 16S rRNA gene sequencing (38). Bacteria and fungi can be translocated to the pancreas and induce local and systemic changes to promote the development of PDAC (39). GFP-labeled *Saccharomyces cerevisiae* was detected in the pancreas of mice within 30 min of consumption (23).

*Ovarian cancer.* Significant differences in the abundances of *Cladosporium*, *Pneumocystis*, *Acremonium*, *Cladophialophora*, *Malassezia* and *Pleistophora* were detected in all the ovarian cancer samples. *Rhizomucor*, *Rhodotorula*, *Alternaria* and *Geotrichum* were also associated with >95% of the ovarian cancer samples according to a pan-pathogen array (PathoChip) combined with capture-next generation sequencing (26).

*Prostate cancer.* A fungal signature was observed in prostate cancer samples when compared with benign prostate hyperplasia samples (25). *Dermatophytes* (31%), yeasts (15%), *Zygomycetes* (15%) and *Microsporidia* (12%) were detected in the analyzed samples (25). The majority of fungal signatures were from the *Ascomycota* phylum (61%), but 50% of the fungi belonged to the class *Eurotiomycetes* according to hierarchical clustering analysis (25).

*Breast cancer.* A study revealed that *Blastomyces* and *Malassezia* species were abundant in breast tumors (13). ITS2 amplicon sequencing revealed that *Cladosporium* was enriched in patients with breast cancer who were ≥50 years old (12). *Cladosporium* was also enriched in human epidermal growth factor receptor 2-negative tumors (12). *Malassezia restricta*, another skin fungus, was also present in breast cancer samples (12). In addition, 7, 8 and 14% of the total hybridization signals for *Ajellomyces* were endocrine receptor-positive, endocrine receptor triple-positive and endocrine receptor 2-positive breast cancer, respectively, whereas *Rhizomucor* accounted for 19% of the hybridization signals for endocrine receptor triple-negative breast cancer (24).

*Lung cancer. B*lastomyces and *Malassezia* are associated with lung cancer (13); for instance, *Blastomyces* DNA was detected in 6 out of 50 patients with squamous cell lung carcinomas via metagenomic analysis of WGS data (13). Greater fungal diversity and a more complex network was also found in patients with non-small cell lung cancer (12,40).

*Other tumors.* A metagenomic analysis of WGS data revealed that *Candida* is related to head and neck tumors (13). Using Illumina™ 2x300 bp chemistry, *Candida albicans* was revealed to play a role in the occurrence and development of oral cancer (OC) based on the fungal ITS2 region (41).

### 3. Fungal-associated factors that lead to cancer

Numerous studies have shown that some specific fungi play important roles in the promotion, progression and recurrence of cancers. These fungi modulate the immune system (42), stimulate the production of specific metabolites (43,44) and potentially reconstruct different microenvironments such as biofilms. All of these factors affect not only immunity against tumors but also the genome, transcriptome, epigenome, epi-transcriptome, proteome and metabolome of tumor cells.

*Immune factors*. Cancers are related to fungus-mediated immune responses. Different intratumoral microbiome interactions may cause different immune responses in host tumor tissues. One study revealed three distinct clusters in tumors, termed mycotypes F1 (*Malassezia-Ramularia-Trichosporon*), F2 (*Aspergillus-Candida*) and F3 (multiple genera, including *Yarrowia*), which could discriminate the types of immune response, suggesting that these intratumoral mycobiomes could elicit different host responses (12). Tumors enriched with the F1 and F2 mycotypes were enriched in tumor suppressing inflammatory responses across 20 types of cancer (12). A previous study has also shown that the cell wall components of *Candida guilliermondii*, *Candida krusei*, *Candida tropicalis*, *Candida auris* and *Candida albicans* can trigger different types of recognition by innate immune cells in humans (42). A different study revealed the multiple mechanisms by which fungal-mediated immune factors can lead to the occurrence and development of cancers (Fig. 2). However, the aforementioned study did not examine inflammatory markers, such as C-reactive protein and albumin levels; neutrophil, lymphocyte and white blood cell counts; or the neutrophil/lymphocyte ratio, which are associated with tumor size and tissue grade in fungi-mediated tumors (45).

*CRC*. Myeloid-derived suppressor cells (MDSCs) are immunosuppressive cells that promote the occurrence and development of tumors. Fungal dysbiosis can increase the abundance of MDSCs, which contribute to the development of CRC. Fungal overgrowth led to the accumulation of MDSCs in the colon and worsened CRC in *caspase recruitment domain 9* (*CARD9*)$^{-/-}$ mice. Treatment with the antifungal drug fluconazole suppressed CRC in *CARD9*$^{-/-}$ mice, which was associated with reduced MDSC accumulation (4). CARD9 expressed in immune cells participates in innate and adaptive immune responses via interactions between CARD9 and other molecules (46). A previous study has reported that CARD9 promotes colitis-associated cancer (47). Mutations in CARD9 are strongly associated with increased susceptibility to both fungal infections and inflammatory bowel disease in humans (48). Interestingly, when bone marrow cells were cocultured with *Candida tropicalis*, *Candida tropicalis* promoted the differentiation and function of MDSCs. In germ-free mice mono-colonized with *Candida tropicalis*, there was also an abundance of MDSCs in the colon (4). Further studies demonstrated that gut fungi promoted the immunosuppressive function of MDSCs by pyruvate kinase M1/2-dependent glycolysis, which promoted colorectal tumorigenesis (32). Multiple studies have reported that aerobic glycolysis is essential for MDSCs in tumors (49,50). To maintain immunosuppressive activities, MDSCs in tumors increase the level of glycolysis. Notably, MDSCs are able to absorb intratumoral glucose in the tumor microenvironment (TME) (51). However, Malik *et al* (6) reported that the fungal-mediated signaling axis, which is mediated by CARD9 and its upstream activator spleen tyrosine kinase (SYK), could also hinder CRC development by inducing inflammasome activation. Deletion of CARD9 or SYK in MDSCs inhibited inflammasome activation and interleukin (IL)-18 maturation and enhanced susceptibility to CRC after fungal exposure (6). Supplementation with MDSCs or IL-18 decreased the tumor burden in azoxymethane/dextran sulfate sodium (AOM/DSS)-treated *CARD9*$^{-/-}$ and *SYK*$^{fl/fl}$*LysM*$^{Cre/+}$ mice, whereas antifungal agents promoted colitis and CRC development (6).

In addition, *Candida albicans* can trigger glycolysis in macrophages and induce the production of IL-7, which causes the secretion of IL-22 in RAR-related orphan receptor gamma t innate lymphoid cells (ILCs) via the aryl hydrocarbon receptor and signal transducer and activator of transcription 3 to promote the progression of CRC (52). A previous study also demonstrated that the development of *Candida tropicalis*-mediated CRC involved reducing tumor cell-intrinsic programmed cell death protein 1 (PD-1) levels through autophagy (7). Autophagy inhibitors and *Candida tropicalis* treatment can limit CRC tumor growth and reverse downregulation of PD-1 expression. This finding suggested that *Candida tropicalis* can promote CRC progression by controlling the expression of PD-1 on tumor cells (7).

*Pancreatic cancer*. Analysis of PDAC revealed that *Alternaria alternata*, but not *Candida* or *Aspergillus*, led to the secretion of IL-33 in tumors, thereby promoting the recruitment of type 2 immune cells to promote tumor development (5). Indeed, single-cell analyses of CD45$^{+}$ cells from a mouse model of pancreatic cancer revealed the presence of T helper 2 cells (TH2) and ILC2 cells, which were hallmarks of type II immune responses (5). Genetic deletion of IL-33 or antifungal treatment decreased TH2 and ILC2 infiltration and increased survival in mice. IL-33 knockdown in tumor cells in an orthotopic model demonstrated that reduced IL-33 levels decreased the infiltration of type 2 immune cells and tumor growth. Treatment with the antifungal drug amphotericin B or IL-33 depletion caused a significant decrease in tumor burden, increased survival and reduced the number of tumor-infiltrating ILC2 and TH2 cells. TH2 cells, which infiltrate the pancreas in the early stages of tumorigenesis, can produce type 2 cytokines such as IL-4 and IL-13, which promote the metabolic reprogramming of cancer cells in murine *Kras*$^{G12D}$-driven PDAC. Consistent with type 2 immune responses that induce PDAC progression in mouse models, patients with PDAC with predominant TH2-polarized cell infiltration also exhibited reduced survival compared with patients with more TH1 cells (53). Notably, ILC2s are also present in tumors from patients with pancreatic cancer (5), and high IL-33 expression is observed in ~20% of human patients with PDAC (5).

However, the fungal community in PDAC was markedly enriched in *Malassezia* species in both mice and humans (23). The ligated product of mannose-binding lectin (MBL) can bind to glycans in the fungal wall to activate the complement cascade, thus causing an increase in C3a. Subsequently, C3a can bind to C3a receptor (C3aR) on the surface of tumor cells

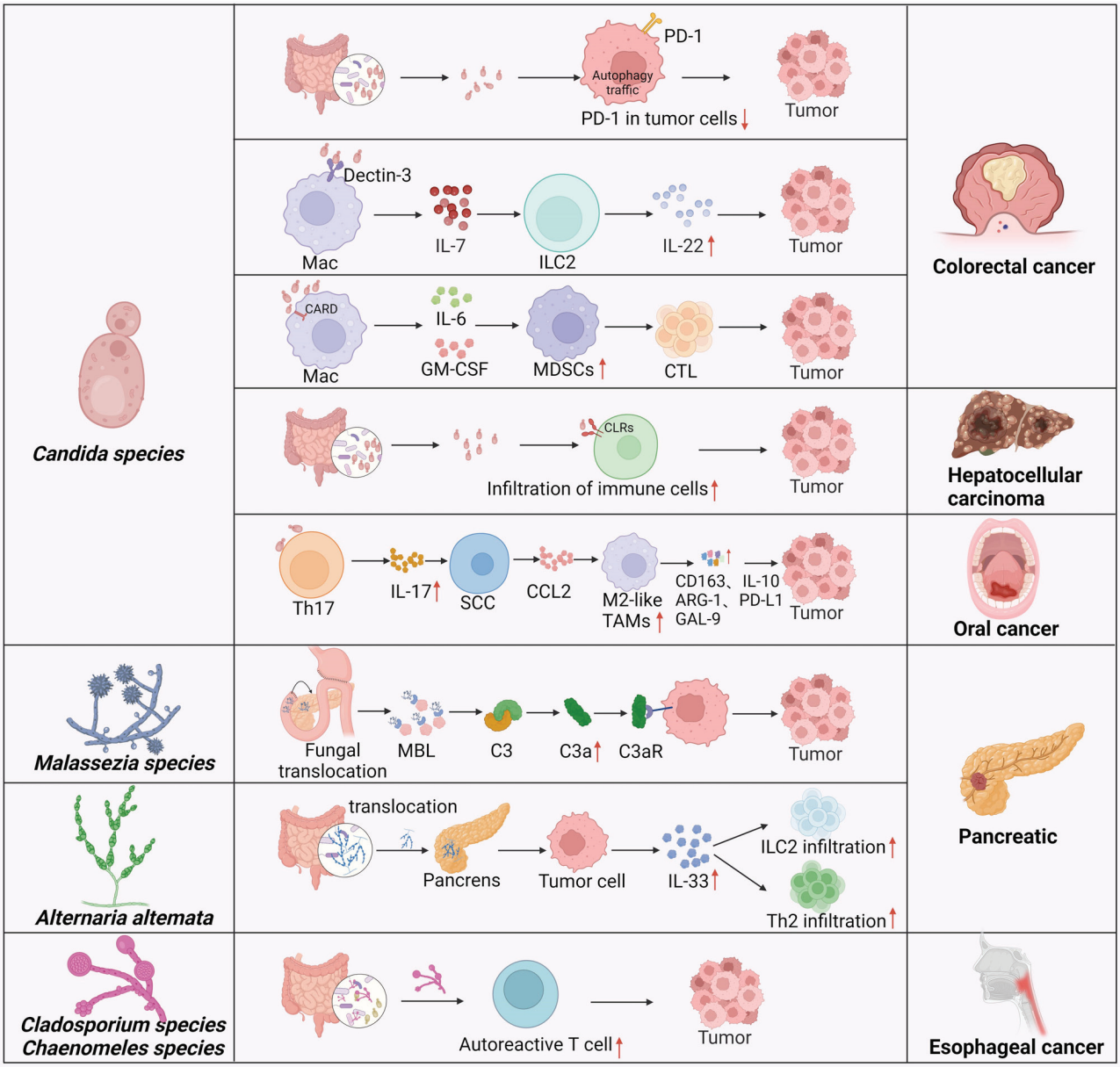


Figure 2. Fungal-associated immune factors that lead to carcinogenesis. The interactions of fungi with immune cells or tumor cells can increase or reduce the number of different immune cell populations and the level of immune cytokines, which can directly and indirectly affect carcinogenesis. MDSCs, myeloid-derived suppressor cells; PD-1, programmed cell death protein 1; Mac, macrophage; IL, interleukin; ILC2, innate lymphocyte 2; CARD, caspase recruitment domain; GM-CSF, granulocyte-macrophage colony-stimulating factor; CTL, cytotoxic T lymphocyte; CLRs, C-type lectins; Th, T helper; SCC, squamous cell carcinoma; CCL2, C-C motif chemokine ligand 2; TAM, tumor-associated macrophage; ARG-1, arginase-1; GAL-9, galentin-9; MBL, mannose-binding lectin; C3aR, C3a receptor. The figure was created with BioRender.

to promote tumor proliferation, motility and invasion (23). Indeed, MBL or C3 deletion in the extratumoral compartment or knockdown of the C3aR in tumor cells protected against tumor growth (23). Notably, *Malassezia*-mediated oncogenic progression was delayed in mice lacking MBL (23). Mice that were treated with antifungal drugs and colonized with *Malassezia globosa* had larger tumors. Increased levels of *Malassezia* were observed in human pancreatic cancer samples (23).

*Esophageal cancer.* Autoreactive T cells and chronic fungal infection cause esophageal carcinogenesis (27). *Ikkα* knock-in ($Ikk\alpha^{KA/KA}$) mice develop impaired central tolerance, autoinflammation, chronic fungal infection and esophageal squamous cell carcinoma (ESCC) (27). Interestingly, during this process, autoreactive $CD4^+$ T cells are generated, which permit fungal infection and cause tissue injury and inflammation. Antifungal treatment or the depletion of autoreactive $CD4^+$ T cells could rescue ESCC development, whereas oral fungal administration promoted ESCC development. Thus, autoreactive T cells and chronic fungal infection promote ESCC development (27). *Cladosporium cladosporioides* and *Chaenomeles lagenaria*, which are two major fungal species that colonize the oral cavities and esophagi of $Ikk\alpha^{KA/KA}$ mice, might spread from the oral cavity to the esophagus. Notably, fungal infection is highly related to ESCC in non-autoimmune patients (27).

*OC. Candida albicans* promoted OC via IL-17A/IL-17RA and macrophages (54). IL-17A neutralization and macrophage

depletion reduced the number of tumor-associated macrophages and tumor size in mice with *Candida albicans* infection (54). Mechanistically, *Candida albicans* infection promoted IL-17A production by Th17 cells. Following activation of the IL-17RA signal, tumor cells can release C-C motif chemokine ligand 2 to attract macrophages to the TME, and these macrophages exhibit an immunosuppressive phenotype with upregulated expression of IL-10, arginase-1, PD-L1 and galectin-9.

*HCC*. The expression of fungal recognition receptors C-type lectins (CLRs), such as dectin-1, dectin-2 and dectin-3, is downregulated in HCC. The expression of these genes is related to the clinical prognosis of patients with HCC (55). CLR-triggered immune responses might enhance the effects of immunotherapy against HCC (55). The expression of CLRs was significantly related to immune infiltration and immunotherapy efficacy in HCC.

Notably, there is still absence of evidence on the role of fungi in renal cell carcinoma (RCC). Since RCC is heavily infiltrated by T cells and myeloid cells (56), future studies should first solve whether fungi infection is related to the infiltration of T cells and myeloid cells in the occurrence and development of RCC.

*Metabolites and toxins*. Toxins and bioactivated amines from fungi have been linked to carcinogenesis (43,44). These factors may cause genetic, epigenetic and metabolic changes. For example, *Candida albicans* generates nitrosamine and metabolizes ethanol to acetaldehyde (57), which is an electrophilic and genotoxic substance that affects DNA repair, oxidative stress, DNA damage and gene mutations (58). The fungus-associated metabolite aflatoxin B1 that is produced by the *Aspergillus* species can induce the development of HCC via highly mutagenic DNA (59). Additionally, interactions between bacteria and fungi can also induce colorectal carcinogenesis by activating butanoate metabolism (14). Two marker genes, *oraS* and *oraE,* in the D-arginine metabolism pathway were significantly enhanced in CRC samples (14). Differential abundance analyses of the mycobiome also suggested that increased *Candida* abundance could promote metastasis, cellar adhesion, extracellular matrix-receptor interactions and focal adhesion (19).

*Biofilms*. Another possible mechanism by which the microbiota affects tumorigenesis is the formation of biofilms (60). *Candida albicans* can cooperate with bacteria such as *E. faecalis* to produce biofilms. Biofilms are closely related to CRC based on the enhancement of precancerous inflammation and escaping the host immune response (61). Interestingly, biofilm homogenates from patients with CRC can cause colon tumorigenesis in mice (62).

*Fungal extracellular vesicles (EVs).* Fungal EVs can be isolated from yeast and filamentous fungi. The pathogenic role of fungal EVs has been widely reviewed (63-65). They carry pigments, carbohydrates, proteins, nucleic acids, lipids and prions, which modulate the immune responses of host cells and are tightly related to virulence (63). Furthermore, EVs play pivotal roles in orchestrating fungal communities, bolstering pathogenicity and mediating interactions with the environment (64,66). EVs from *Candida albicans* and *Saccharomyces brasiliensis* activate dendritic cells to produce cytokines such as IL-12p40, IFN-γ, TNF-α, IL-10 and TGF-β (67). EVs from pathogenic fungi also promote the production of TNF-α, TGF-β and nitric oxide by macrophages (66,68). *Exophiala dermatitidis* EVs could induce cell death. Understanding the function of fungal EVs can provide new and specific targets for antifungal drugs. However, there is lack of studies on the effects of fungal EVs on tumorigenesis.

## 4. Factors related to the enrichment and carcinogenicity of fungal species

Intratumoral fungi can come from different anatomic sites, including the oral cavity, the gut, adjacent normal tissue, the lung, skin and blood circulation (15). Multiple factors are potentially related to the enrichment and carcinogenicity of fungal species, including interactions between microbes such as fungi and bacteria, host factors including immune factors, tissue-derived factors, and fungal genetic and epigenetic factors (Fig. 3). Notably, fungi not only are the causative agents of diseases but are also isolated from mammals without diseases (69-71), suggesting that there are two fungal types, namely, commensal and pathogenic fungi (72). Indeed, the pathogenicity of some fungi depends on their ability to change from a commensal to a pathogenic fungus (73). Li *et al* (74) reported that *Candida albicans* can aggravate intestinal inflammation by inducing proinflammatory phenotypes *in vivo.*

*Interactions among the microbiome*. Multiple different kinds of microbiota exist in the organs and tissues of humans, such as the gut. These organisms live together and form complex and dynamic ecosystems to impact host health (75). Multiple kingdom analyses of fecal samples from patients with CRC revealed strong interkingdom interactions between bacteria and fungi (14,22). A different study also revealed four kingdom microbiota alterations using metagenomic datasets from 1,368 CRC samples from 8 distinct geographic cohorts. The researchers found not only significant fungal-bacterial interactions between *Aspergillus rambellii* and *Fusobacterium nucleatum* but also significant interactions between *Aspergillus rambellii* and *Parvimonas micra* in both patients with CRC and patients with adenoma (14,22). The signature of CRC-associated fungi included 6 different enriched fungi, namely, *Aspergillus rambellii, Cordyceps sp. RAO-2017, Erysiphe pulchra, Moniliophthora perniciosa, Sphaerulina musiva* and *Phytophthora capsici*. *Aspergillus rambellii* is closely related to the CRC-enriched bacterium *Fusobacterium nucleatum* (21). Notably, experimental studies have demonstrated interactions between fungi and bacteria. For example, *Lactobacillus* can produce metabolites to antagonize *Candida albicans* growth and filamentation (76,77). Reductions in short-chain fatty acid (SCFA) levels in the murine gut were associated with an increase in *Candida albicans* (78). The SCFAs butyrate and propionate also inhibited the growth of the yeast *Pichia kudriavzevii* (79). Negative correlations between *Penicillium* and *Faecalibacterium* were found in the human gut (80). In addition, bacterium-induced immunity could also limit *Candida albicans* colonization of the gut

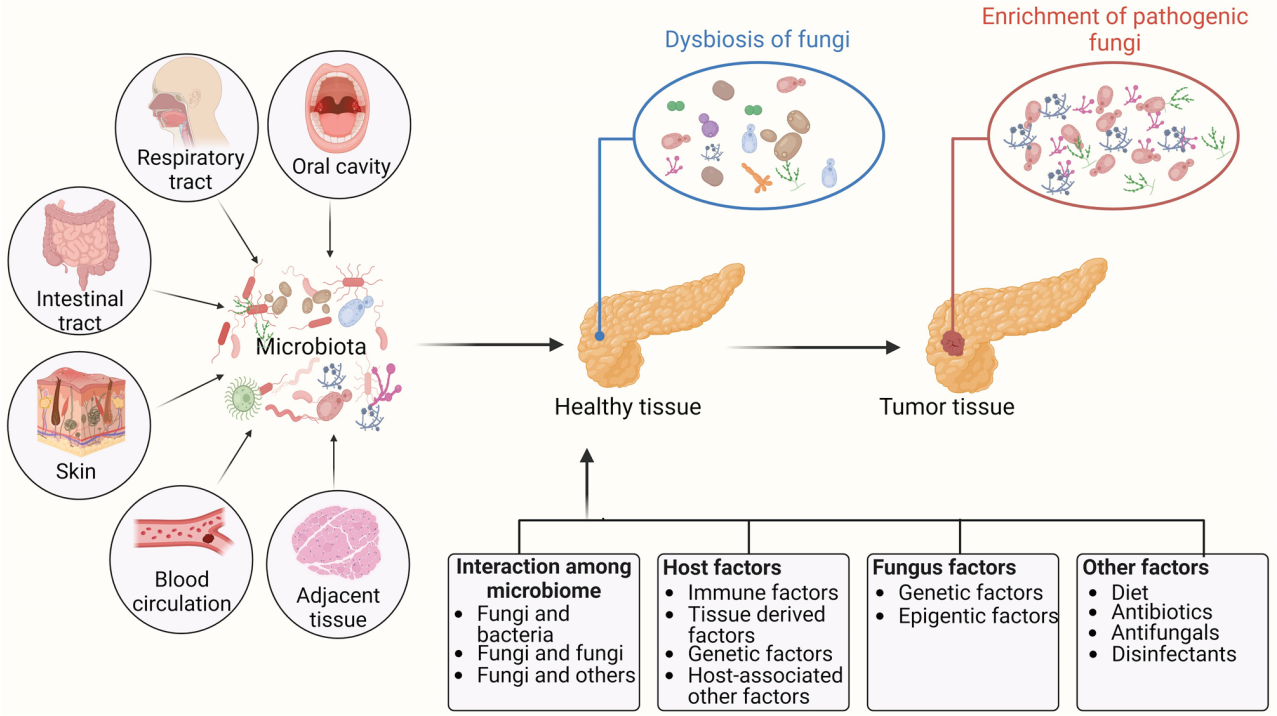


Figure 3. Factors related to enrichment of fungi and/or the conversion of commensal fungi to pathogenic fungi in tumor tissues. Fungi from the oral cavity, respiratory tract, intestinal tract, skin, blood circulation or adjacent tissues can be modulated through microbiome interactions, host factors and fungal genetic and epigenetic factors to cause fungal enrichment and/or the conversion of commensal fungi to pathogenic fungi in tumor tissues, leading to tumorigenesis. The figure was created with BioRender.

lumen. Anaerobic bacteria promoted the expression of cathelicidin-related antimicrobial peptide, which can eliminate *Candida albicans* (78). *Lactobacillus* exhibits an enhanced probiotic potential following coculture with *Kluyveromyces marxianus* (81). Notably, bacteria-fungi interactions have revealed that bacteria can shape the immune environment that controls fungi (12). *Lactobacillus kefiranofaciens* and *Saccharomyces cerevisiae* isolated from Tibetan kefir grain alleviated AOM/DSS mediated inflammation and colorectal carcinogenesis (82). Interestingly, the presence of *Candida* and *Saccharomyces* was associated with different *Fusobacterium spp*. in colon cancer (13). In stomach cancer, *Candida* was positively associated with *Dialister* abundance and negatively associated with *Akkermansia municiphila*, *Ruminococcus* and *Barnesiella intestinihominis* abundance (13).

In addition, the fungal community also affects bacteria. *Candida albicans* has been shown to antagonize colonization by *Escherichia* and *Klebsiella* species. Cocolonization experiments in mice confirmed that *Candida albicans* could limit *Klebsiella* colonization in the gut (83). *Lactobacillus spp*., especially *Lactobacillus gasseri*, are frequently found in the presence of *Candida* and *Saccharomyces* (13). This observation was consistent with studies reporting that the interaction between *Lactobacillus spp*. and *Candida* influences pathogenicity (76). *Candida* was strongly associated with *Lactobacillus* in GC (13). In head and neck tumors, *Candida* and *Saccharomyces* are related to similar bacteria, such as *Bifidobacterium*, which support intestinal barrier function in head and neck cancers (13). Fungal dysbiosis with an increased *Basidiomycota*: *Ascomycota* ratio was observed in the feces of patients with CRC (22), implying that interactions between bacteria and fungi could contribute to colorectal carcinogenesis (22,84).

*Host factors*. Host factors including tissue-derived, genetic, immune and other factors can affect the enrichment and/or conversion of fungi from a commensal state to a pathogenic state. There have been several reviews on fungal immunity (85,86) and the correlations between immune responses and genetics (86). Notably, tissue-derived factors were found to affect fungi such as *Candida auris*, which led to the observation of subpopulations of aggregative and filamentous isolates in some clinical studies (72). Host genetic factors are also related to the transition of fungi from a commensal to a pathogenic fungus. Typically, *Dectin-3*$^{-/-}$ mice exhibited an increase in pathogenic *Candida albicans* (52).

*Fungal genetic and epigenetic factors*. Multiple fungal genetic and epigenetic factors, which are related to the enrichment and carcinogenicity of fungal species, such as ume6, which is a master regulator from yeast to hyphae *Candida albicans*, can suppress gut colonization by promoting the expression of the hypha-specific proinflammatory protease secreted aspartic protease 6 and the hyphal cell surface adhesion protein glutathione peroxidase-like peroxiredoxin HYR1 (87). *Candida albicans* in the gut causes a developmental switch of the white-opaque regulator 1 transcription factor, which leads to a commensal cell type (88). Fungi can also regulate iron uptake genes via Sef1/Sfu1, which play a role in fungal virulence and colonization (89). *Candida auris* also activates a stress response program via mitogen-activated protein kinase HOG1, which is necessary for virulence (90). Notably,

*Candida* species can generate numerous more phospholipases than other fungal strains (91). In intestinal inflammation, *Candida* can produce candidalysin, which induces damage to cause hyphal invasion across mucosal barriers (92). Additionally, set1-mediated H3K4 methylation was required for *Candida albicans* virulence based on controlling reactive oxygen species levels. *Candida auris* also modulates genome integrity, stress responses, cell filamentation and virulence via the lncRNA DINOR (93).

*Other factors*. Other host factors, such as diet and age, can affect the variability of the gut mycobiota (94-96). Antibiotics, antifungals and disinfectants also affect the enrichment of fungi and/or the conversion of fungi from a commensal state to a pathogenic state. For example, antibiotics can lead to an increase in *Candida* in the gut, oral cavity and vagina (97,98), which facilitates invasive fungal infection through bloodstream translocation from the gut (99).

## 5. Application of intratumoral fungi in the diagnosis and treatment of cancers

*Potential therapeutic targets*. Fungi can be engineered to enhance their effects on the occurrence and development of tumors. Furthermore, intratumoral fungi can also induce innate and adaptive immune responses to prevent tumor progression (6,100). Fungi, such as *Capnodiales* and its genus *Cladosporium*, which are significantly enriched in non-responders, are also associated with immunotherapy response in patients with metastatic melanoma (12). Thus, fungi in tumor tissues might be a new potential therapeutic target in cancer therapy. At present, other microbiota, such as bacteria, have been approved by the Food and Drug Administration for the treatment of cancer (101,102).

*Diagnosis and prognosis evaluation*. Several studies have also reported the role of intratumoral microorganisms in diagnosis (103,104). Due to the presence of tumor type- and subtype-specific fungal profiles, intratumoral fungi have the potential to be used as diagnostic tools. However, whether fungi can be used for diagnosis has not been determined. In addition, the tumor microbiome is related to the survival rates of different patients. The presence of some intratumoral fungi may be closely related to the poor prognosis of patients with tumors. For example, in GI tumors, the presence of *Candida* DNA is predictive of decreased survival. Narunsky-Haziza *et al* (12) also suggested that fungi have prognostic and diagnostic roles in tumor tissues by comparing intratumoral fungal communities with matched bacteriomes and immunomes. The associations of fungi with clinical parameters such as the detection of early-stage cancers, overall survival in breast cancer patients and immunotherapy response in melanoma patients supported the clinical application of fungi as potential biomarkers and therapeutic targets (12).

*Strategies to modulate the fungal community*. Multiple therapeutic strategies targeting the microbiota (105,106), such as antifungal drugs, have been used to inhibit the oncogenic progression of PDAC. As some specific fungal species are related to the occurrence and development of tumors, antifungal chemical compounds such as terbinafine, fluconazole and itraconazole could be used for tumor therapy. The combination of an antifungal drug and chemotherapy exhibited a synergistic anticancer effect against PDAC in animal models (3). Notably, broad antibiotic application also increased the risk of cancer incidence and impaired the response to immunotherapy (107).

Specific modulation of intratumoral fungi in the clinical practice is challenging. However, the factors that regulate the gut fungal community are also potential tools for therapy against tumors.

*Diet*. Diet and nutrition can affect the composition of the gut microbiota and are involved in CRC onset (108). Diet-induced changes in the gut microbiome depend on whether volunteers consume a plant- or animal-based diet (109).

*FMT*. FMT can regulate the composition of fungi to affect tumor therapy efficacy. A high abundance of *Saccharomyces* and *Aspergillus* in donor stool was associated with effective FMT, whereas reduced FMT efficacy was related to an increase in *Candida albicans* in donor stool. Further study revealed that *Candida* was negatively correlated with total saturated fatty acids and positively correlated with carbohydrates, whereas *Aspergillus* was negatively correlated with the recent ingestion of SCFAs. These metabolites could directly and indirectly affect the therapeutic effectiveness of FMT against tumors.

*Probiotics and prebiotics*. Several functions of probiotics, such as the suppression of pathogen growth by the production of certain antimicrobial mediators (110), have been reported. Prebiotics can prevent CRC development by modifying the composition of the gut microbiota (111) and exert strong preventive effects against CRC. Notably, *Saccharomyces cerevisiae* plays a probiotic role in CRC by promoting cancer cell apoptosis. *Saccharomyces cerevisiae* reduces CRC progression by modulating the microbial structure in the mucus (31). In addition, genetically engineered microbiota could also be used as a vehicle to provide metabolic support for intratumoral T cells (112), which is essential for the proper functioning of cytotoxic T cells (113).

## 6. Conclusion and perspective

Omics analyses of host-microbiome interactions in human health and diseases have revealed associations between fungi and human cancer. Several cancer type-specific fungi have been identified, such as *Candida* species in CRC, *Malassezia* species in pancreatic cancer and *Blastomyces* species in lung and breast cancer. Importantly, some specific fungal species that lead to the occurrence and development of tumors, such as *Candida* species, induce CRC through the accumulation of MDSCs, and *Malassezia* species promote pancreatic oncogenesis by activating the complement cascade. In addition, multiple factors, such as interactions among the microbiome, are related to the enrichment of type-specific fungi in tumor tissues and/or conversion from a commensal to a pathogenic fungus. A growing body of evidence has revealed the diagnostic, prognostic and therapeutic potential of intratumoral fungi in cancer. Fungal dysbiosis in the gut can be regulated by multiple factors, such as diet, FMT, probiotics and prebiotics, which potentially affect tumor development.

However, these studies are just a start for studying intratumoral fungi, and numerous questions remain to be answered: i) What determines the abundance and composition of intratumoral fungi? Studies have shown that there is abundance of fungi in tumor tissues. Furthermore, the composition of fungi in different tumor is also different. At present, it is unclear what determines the abundance and composition of intratumoral fungi. ii) What are the origins of the intratumoral fungi? Fungi can be found not only in colorectal carcinoma but also in other tumors, such as those associated with prostate, ovarian and breast cancer. But, the origins of these intratumoral fungi are incompletely clear. iii) How do intratumoral fungi bridge cancer cells and the immune system? Fungi-mediated immune factors play important roles in tumorigenesis. It is also incompletely clear how these intratumoral fungi bridge cancer and immune cells. iv) What exact mechanism(s) do specific fungi use to induce tumorigenesis? There are different mechanisms involved in fungus-mediated tumorigenesis. An exact mechanism to induce any specific tumor needs to be investigated. v) What is the difference between commensal fungi and fungi isolated from tumor tissues, such as commensal fungi in the gut and fungi in CRC and what kind of factor(s) cause the conversion of commensal fungi to pathogenic fungi? There are two kinds of fungi, commensal fungi and fungi in the tumor tissues. At present, the difference between commensal and pathogenic fungi remains unclear. In addition, it also is unclear what kinds of factor can cause the conversion of commensal fungi to pathogenic fungi. vi) What are the functional differences between intracellular tumor-resident and extracellular tumor-resident fungi? Intracellular and extracellular fungi can be found in tumor tissues. The existence and type of differences between intracellular and extracellular fungi are unclear. In addition, the functional and physiological significance of these fungi in the TME is also unclear.

The investigation of the aforementioned questions will be decisive not only for understanding the mechanism of fungi-mediated tumor development but also for new opportunities for cancer therapy and diagnosis.

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**Authors' contributions**

WC, FL and YG wrote the original draft and created the figures. RY conceptualized the study and contributed to the writing of the final version of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

**Ethics approval and consent to participate**

Not applicable.

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Not applicable.

**Competing interests**

The authors declare that they no competing interests.

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