

REVIEW ARTICLE

The role of fungi in colorectal cancer: Pathogenesis and therapeutic approaches

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Abstract

Colorectal cancer (CRC) remains one of the leading contributors to global cancer-associated deaths, with its development and progression closely influenced by the complex and evolving interplay between host and gut microbial communities. The gut fungal community has emerged as a crucial factor in the oncogenesis, progression, and treatment of CRC. Through multi-cohort fecal metagenomic analysis, it has been found that the gut fungal community structure of CRC patients undergoes significant changes, with pathogenic fungi becoming enriched and overall fungal diversity decreasing. In addition, fungal metabolites and other components are also associated with cancer development, including effects on cell proliferation, apoptosis, and immune responses. In terms of mechanisms, fungi may influence CRC progression by affecting intestinal immune responses, modulating inflammatory pathways, and interacting with bacteria. However, current research is mainly focused on correlation analysis, with causality remaining unclear. Moreover, the diversity of fungi across different populations limits their clinical application. This article examines the role of fungi in CRC onset and progression, summarizes current therapies, and outlines future research to support early diagnosis, precision treatment, and improved prognosis.

Keywords: Fungi; Colorectal cancer; Gut microbiota; Immunity

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1. Introduction

Humans are a superorganism composed of the human body and its associated microorganisms. A vast number of microorganisms colonize the human epithelial and mucosal surfaces.¹ Microbiota refers to the ecological community of microorganisms that live in symbiosis with animals and plants, including bacteria, fungi, archaea, viruses, and other microorganisms. Among them, approximately 1.5 million species of fungi exist in nature, and more than 300 million people worldwide have suffered from fungal-

related diseases, such as pulmonary aspergillosis.² Beyond established factors such as genetic alterations, epigenetic modifications, and the stromal microenvironment, the host microbiota plays a crucial regulatory role in cancer susceptibility and tumor development. As an integral part of the human body, these microbes influence both local and distant tumor sites primarily through indirect mechanisms, including metabolite production and modulation of the immune response.^{3,4}

Fungi, as eukaryotic microorganisms, are widely distributed in nature. They inhabit different anatomical sites of the human body.⁵ To date, over 400 fungal species have been identified in association with the human body, predominantly classified into three major phyla: Ascomycota, Basidiomycota, and Chytridiomycota.^{5,6} These fungi constitute a minor proportion of the human microbiome compared to more abundant members, such as bacteria.⁷ Gut fungi are an indispensable part of the gut microbiota. In the human gut, there are nearly 70 genera and more than 184 species of fungi, among which *Candida*, *Saccharomyces*, and *Malassezia* are the predominant

genera.² Accumulating evidence indicates that fungi play a significant role in shaping host health and disease states. They are involved in the occurrence and development of tumors.^{7,8}

Tumors represent intricate ecosystems enriched with diverse microbiota, including viruses, bacteria, and fungi, all of which contribute to oncogenesis and tumor progression.^{9,10} A landmark study by Narunsky-Haziza *et al.*¹¹ revealed the widespread presence of fungi across 35 cancer types, establishing that each tumor harbors distinct fungal communities associated with metastasis and decreased patient survival. These intratumoral fungi can be classified into six anatomical groups based on their tissue origin, including the oral cavity, gastrointestinal tract, adjacent tissues, lungs, skin, and bloodstream.¹² Similarly, Dohlman *et al.*,¹³ through cancer genomic profiling, identified tumor-associated fungal signatures in gastrointestinal, breast, lung, and head-and-neck cancers (Table 1). Notably, *Candida albicans* has been implicated in the pathogenesis of colorectal cancer (CRC), reflecting cancer-type-specific fungal patterns.¹⁴

Table 1. Fungal species associated with humans in the gastrointestinal tract

Phylum	Species	Reference
Ascomycota	<i>Candida albicans</i> , <i>Candida tropicalis</i> , <i>Candida glabrata</i> , <i>Candida parapsilosis</i>	15-17
Basidiomycota	<i>Aspergillus versicolor</i> , <i>Aspergillus clavatus</i>	18
Chytridiomycota	-	19,20
Others	<i>Penicillium</i> spp., <i>Cryptococcus</i> spp., <i>Cladosporium</i> spp., <i>Saccharomyces</i> spp., <i>Malassezia</i> spp., <i>Mucor</i> spp., <i>Galactomyces</i> spp., <i>Debaryomyces</i> spp., <i>Trichosporon</i> spp.	19,21

Colorectal cancer is currently recognized as the fourth most prevalent malignancy worldwide and the second leading cause of cancer-related mortality, resulting in over 500,000 deaths annually.^{22,23} The gastrointestinal tract of mammals is colonized by diverse microbiota comprising fungi, bacteria, and viruses. These microbial communities play essential roles in modulating both innate and adaptive immunity, thereby influencing the pathogenesis of various gastrointestinal and systemic disorders. While bacterial symbionts have been the primary focus of most microbiome research, increasing attention has been directed toward commensal fungi, which have been linked to several gastrointestinal diseases.²⁴ Fungi can be beneficial to mammalian immunity under certain conditions but may become pathogenic in specific environments, such as when the immune system is compromised or bacterial populations are reduced. Alterations in the colonic fungal community have been observed in patients with CRC.^{25,26}

Similar to the gut bacterial microbiota, a healthy gut mycobiome plays an essential role in maintaining host immune homeostasis, intestinal barrier integrity, and metabolic balance. When fungal diversity is disrupted or immune recognition and regulatory mechanisms between fungi and the host become dysregulated, certain opportunistic pathogenic fungi, such as *Candida albicans*, can undergo abnormal overgrowth. This may trigger persistent inflammatory responses and contribute to the initiation and progression of CRC to a certain extent.²⁷ Conversely, under physiological conditions, beneficial commensal fungi can exert tumor-suppressive effects by promoting the production of immune mediators, such as interleukin (IL)-18, through recognition pathways mediated by C-type lectin receptors, such as dectin-1. These pathways facilitate epithelial repair and anti-inflammatory responses.⁸

In addition to host–fungus interactions, interkingdom

crosstalk between fungi and bacteria is a key determinant of gut microbial homeostasis.²⁸ Emerging evidence suggests that fungi and bacteria rarely act in isolation; instead, they often cooperate or synergize to disrupt the microbial ecosystem associated with CRC development.²⁹ For instance, pathogenic fungi, including *C. albicans* and *Candida tropicalis*, have been shown to form complex polymicrobial biofilms with CRC-associated bacterial species such as *Escherichia coli* and *Serratia marcescens*, thereby enhancing their colonization capacity and virulence potential.³⁰ Furthermore, Lin *et al.*²⁵ reported that *Aspergillus rambellii* and other fungal species commonly coexist with pro-inflammatory, tumor-promoting bacteria, amplifying bacteria-mediated inflammatory signaling and tumorigenic effects. These fungal–bacterial interactions may intensify dysbiosis by enhancing inflammatory pathways and facilitating immune evasion, thereby accelerating CRC progression. Growing evidence has highlighted the role of fungi in human malignancies, particularly the notable enrichment of certain fungal species in tumor tissues in recent years.⁷

2. Fungi

Fungi exist in diverse forms, including unicellular yeasts, dimorphic fungi, and multicellular fungi. Dimorphic fungi can take on different forms, such as filamentous or yeast-like, under varying culture conditions and metabolic modes, indicating that fungi exist in distinct states, function in distinct environments, and engage in different interactions.³¹ A study has found that *Candida*, *Saccharomyces*, and other common fungi are present in healthy intestines.³² The Human Microbiome Project, through internal transcribed spacer 2 sequencing, has revealed that fungal diversity in the human gut microbiota is significantly lower than that of bacteria.³³ There are substantial differences in gut fungal community structures both within the same individual over time and between different individuals. Additionally, age and sex can lead to variations in gastrointestinal fungal populations.

Globally, at least 300 million people are affected by fungal diseases each year, with over 1.6 million deaths attributed to fungal-related illnesses.³⁴ Common pathogenic fungi include *Candida* spp., *Aspergillus* spp., *Pneumocystis* spp., and *Cryptococcus* spp. These fungi are ubiquitous in healthy individuals with normal immune function and exist in a dynamic equilibrium. When the immune system is compromised or antibiotics are used, potentially pathogenic fungi can proliferate, leading to local infections or even systemic disease. Common fungal diseases such as cryptococcal meningitis, candidal septicemia, and disseminated aspergillosis are focal points in clinical and basic research. Due to the widespread and

sometimes inappropriate use of antibiotics, multidrug-resistant pathogenic fungi have emerged in clinical settings, leading to high mortality rates among infected patients. In addition to strengthening new drug development, drug regulation, and vaccine research to control fungal infections,³⁵ modulating gut fungal community structure through microbiota regulation is also a promising research direction. Previous microbiota studies have primarily focused on bacteria, but the disruption of gut fungal microbiota is increasingly recognized as a cause of pathological phenomena. The stability and disruption of fungal microbiota are dynamic processes, during which the immune system is continually disturbed and reshaped. Therefore, interventions targeting gut fungal communities have the potential to regulate host immune homeostasis and treat inflammatory diseases.

3. Fungal toxins

Fungal toxins are a class of secondary metabolites produced by specific fungi. Over 400 types of fungal toxins have been identified, of which 30 are pathogenic to humans. These toxins exhibit hepatotoxicity, nephrotoxicity, dermatotoxicity, and genotoxicity. The pathogenicity of fungal toxins in humans is primarily due to ingestion of contaminated food. Toxins enter the body through contaminated food or colonization of the gut by toxin-producing fungi, leading to alterations in the gut microbiota and subsequent adverse effects on host health. Foodborne fungal toxins mainly originate from *Aspergillus* spp., *Penicillium* spp., and *Fusarium* spp.¹⁴ Common fungal toxins include deoxynivalenol (DON), zearalenone (ZEN), aflatoxin, sterigmatocystin (ST), fumonisin B (FB), ochratoxin A (OTA), and patulin. These toxins are closely associated with various human diseases, yet the majority remain under-investigated.⁶ The toxic effects of these mycotoxins are particularly pronounced in the digestive system, mainly manifesting as carcinogenicity and gastrointestinal dysfunction.

Aflatoxins are a group of toxic compounds produced by fungi from the genus *Aspergillus*. Among them, aflatoxin B1 (AFB1) is the most common form and is also a potent carcinogen. Although aflatoxins are primarily associated with liver cancer, studies have shown that certain aflatoxin-producing fungi are significantly enriched in CRC patients. The metabolically active products formed from aflatoxins in the human body can bind to DNA, leading to gene mutations, disrupting normal cell growth, and promoting the carcinogenesis of CRC cells^{36,37} (Table 2). ST is a late-stage metabolite in the aflatoxin biosynthesis pathway and also exhibits significant carcinogenic and mutagenic properties. *In vitro* cell culture experiments and animal studies have demonstrated that ST can promote the

metaplasia of intestinal epithelial cells.³⁸ Moreover, in the presence of *Helicobacter pylori*, ST may participate in and drive the progression of gastric cancer.³⁸ FB are a class of mycotoxins primarily produced by the genus *Fusarium*. They can affect the metabolism of sphingolipids within cells, disrupting normal cellular physiological functions. A study has found an association between fumonisin exposure and the development of CRC.³⁹ By interfering with cellular signaling pathways, fumonisins can promote the abnormal proliferation of CRC epithelial cells, increasing the likelihood of malignancy. Among fumonisins, FB1 is the most common form. In animal models, FB1 has been demonstrated to cause hepatocellular carcinoma.⁴⁰ OTA, a mycotoxin produced by specific *Aspergillus* spp. and *Penicillium* spp., primarily targets the kidneys and is well known for its potent nephrotoxic effects. Animal models have also demonstrated hepatotoxicity, carcinogenicity, and genotoxicity.^{41,42} Studies have also found that OTA may be associated with CRC. It can inhibit the activity of enzymes involved in phenylalanine metabolism within cells, induce cellular oxidative stress, damage DNA, and disrupt normal cellular physiological functions, thereby making cells more susceptible to malignant transformation.³⁷ DON, nivalenol, and T-2 toxin, which are representative of the trichothecenes, are mainly produced by the genus *Fusarium*.⁴³ DON can cause gastrointestinal inflammation, disrupt intestinal barrier function, and induce dysbiosis of the gut microbiota. In animal models, exposure to DON has been shown to exacerbate the occurrence and development of CRC associated with inflammatory bowel disease (IBD).⁴⁴ Furthermore, low doses of DON exposure can significantly accelerate the progression of colitis-associated CRC.⁴⁴

Fungal toxins impact host health through various mechanisms, with DON, ZEN, OTA, FB1, AFB1, and patulin being identified as significantly affecting the integrity and function of epithelial cells. These fungal

toxins induce cell death, increase monolayer permeability, reduce transepithelial electrical resistance, impair the expression, intracellular localization, and function of tight junction proteins, and facilitate the translocation of harmful stressors, thereby damaging the intestinal mucosal epithelium and influencing the gut microbiota.⁴⁵ DON, a trichothecene mycotoxin, is one of the few fungal toxins that have been systematically studied. It primarily affects the gut, liver, and brain and further impacts neuroendocrine function, immune responses, the growth hormone axis, and central neural circuits related to energy homeostasis.⁴⁶ Nonetheless, numerous fungal toxins remain to be investigated.

4. Characteristics of fungal species in colorectal cancer

Colorectal cancer is the fourth most common cancer globally, causing over 500,000 deaths annually.²² It is associated with changes in the colonic fungal community of patients.^{25,26,47} A recent study found significant differences in fungal composition between tissue biopsies of colorectal adenomas and adjacent tissues in 27 cases, indicating that host-associated fungal populations are altered during CRC development.⁴⁸

Research has shown that, compared with controls, CRC patients exhibit a relative decrease in Firmicutes and an increase in Fusobacteria.²⁶ According to reported human gut mycobiota profiles, both CRC patients and control subjects are predominantly composed of Ascomycota and Basidiomycota.⁴⁹ In patients with CRC, an elevated Basidiomycota-to-Ascomycota ratio has been observed, reflecting a state of fungal dysbiosis commonly observed in disrupted microbial ecosystems.²⁶ At lower taxonomic levels, CRC patients also exhibit additional differences, including a significant reduction in yeasts and *Pneumocystis*,

Table 2. Fungal toxins and tumors

Fungal toxins	Category	Tumor	Reference
Aflatoxin (AF)	AFB1	Hepatocellular carcinoma, colorectal cancer	36
	AFG1	Gastric cancer, esophageal cancer	37
Sterigmatocystin	-	Gastric cancer	38
Fumonisin B (FB)	FB1	Hepatocellular carcinoma, colorectal cancer Esophageal cancer	40,41
Ochratoxin A	-	Renal carcinoma, liver cancer, colorectal cancer	42,43
Deoxynivalenol, nivalenol	-	Gastric cancer, esophageal cancer, colorectal cancer	44

and an increase in *Malassezia*. At the family level, CRC patients show a significant decrease in Lipomycetaceae, while Pisolithaceae, Marasmiaceae, Malasseziaceae, Erysiphaceae, Pseudorotiaceae, and Chaetomiaceae are increased. Moreover, at the genus level, CRC patients are enriched with six fungal taxa, including *Malassezia*, *Candida*, *Rhodotorula*, *Cladosporium*, *Thielaviopsis*, and *Pisolithus*. However, it is important to note that the control group used in the previous study consisted of adjacent non-tumor tissues rather than colonic tissues from healthy individuals. As such, although the findings suggest that alterations in fungal community structure may accompany the progression of colorectal adenomas, the current evidence remains insufficient to accurately characterize the differences in gut mycobiota between CRC and truly healthy colonic tissues. This limitation underscores the need for future studies to include healthy controls to clarify alterations in the fungal community during CRC development and elucidate the underlying mechanisms.

Several other studies have also shown that CRC tissues contain *Candida*, *Cyberlindnera jadinii*, and *Saccharomyces cerevisiae*.⁵⁰⁻⁵² Among these, *Candida* spp. exhibit a strong capacity for epithelial invasion by expressing specific adhesins, such as agglutinin-like protein 3p, along with tissue-degrading enzymes. These factors enable the formation of invasive hyphal structures capable of penetrating intercellular junctions and infiltrating host tissues, thereby facilitating colonization and internalization within the tumor microenvironment.⁵³ For instance, Luan *et al.*⁴⁸ detected *Candida* spp. in biopsy specimens from patients with colonic adenomas. In contrast, *C. jadinii* and *S. cerevisiae* are primarily confined to the intestinal lumen or mucosal surfaces, lacking evidence of tissue invasion. This suggests that these fungi are more likely to represent opportunistic colonizers rather than active invasive pathogens.⁵⁴ Additionally, other specific changes in the fungal composition of CRC have been identified, including *Rhodotorula* (Basidiomycota) and *Panomyces* (Ascomycota).²⁶ *Rhodotorula* is an emerging pathogen that can colonize, infect, and disrupt the fundamental microbiota of the human digestive system.⁵⁵ A study identified a marked reduction in the fungal class Saccharomycetes, along with decreased abundance of *Lipomyces* and *S. cerevisiae*, in CRC samples.²⁶ *S. cerevisiae*, a prominent member of the human gut microbiota, has also been shown to modulate host immune responses by promoting IL-10 production, thereby exerting anti-inflammatory effects.^{56,57} The observed reduction in *S. cerevisiae* in CRC underscores its potential protective role in the gut environment and suggests that restoring its abundance may offer a novel avenue for CRC prevention or therapy.²⁶

Using metagenomic profiling of whole-genome sequencing data from diverse tumor specimens across various cancer types in The Cancer Genome Atlas, researchers have characterized the microbial composition associated with different malignancies.¹³ *Candida dublinensis*, *Candida glabrata*, *Pichia membranifaciens*, *Candida guilliermondii*, *C. tropicalis*, *Candida parapsilosis*, and *Candida lusitanae* were found to have low distribution and prevalence in CRC. Nonetheless, a previous study based on fecal metagenomic sequencing revealed a significant enrichment of *Aspergillus* spp. in CRC tissues from patients in both Asia and Europe.²⁶ Other fungi, such as *Ophiocordyceps* RAO-2017, have also been detected in CRC tissues.²⁵ There are differences in the abundance of Orbiliomycetes between the CRC and polyp groups.⁵⁸

5. Gut fungi-mediated inflammation in colorectal cancer

Fungi have recently emerged as critical regulators of intestinal homeostasis and tumorigenesis. In advanced adenomas, *Fusarium* abundance is higher, indicating that fungal colonization may promote adenoma progression.⁵⁹ The antagonistic interaction between gut fungi and bacteria contributes to the development of colorectal tumors. Coker *et al.*²⁶ found that the fungal profile of CRC is characterized by an increased Basidiomycota/Ascomycota ratio and changes in the abundance of *Yeasts*, *Pneumocystis*, and *Malassezia*.

The incidence of fungal infections has increased dramatically over the past two decades, primarily in immunosuppressed populations, such as acquired immunodeficiency syndrome patients or those undergoing organ transplantation or cancer chemotherapy.⁶⁰ In addition, growing evidence suggests that certain conditions once considered unrelated to fungi, such as cystic fibrosis, hepatitis B, and IBD, are associated with distinct fungal community patterns.^{61,62}

Studies have shown that specialized mechanisms of the human immune system play a crucial role in clearing fungi from mucosal surfaces.^{63,64} Inflammation is a manifestation of the host immune response triggered by either exogenous or endogenous signals. The gut provides a distinct environment for host defense, where inflammation plays a central role in clearing pathogenic infections, preserving normal intestinal function, and potentially promoting tumorigenesis.⁶⁵⁻⁶⁷ Patients with ulcerative colitis and Crohn's disease, two major forms of IBD characterized by chronic inflammation, are widely recognized as high-risk populations for CRC.^{68,69} Previous meta-analyses demonstrated that the cumulative incidence of CRC in patients with ulcerative colitis increased by 18.4%, while

the risk in patients with Crohn's disease rose by 8.3%.^{70,71} Under physiological conditions, the intestinal mucosal barrier is composed of a single layer of epithelial cells connected by tight junctions, effectively separating the gut microbiota from the host immune system.⁷² However, in CRC patients and CRC mouse models, increased barrier permeability has been observed, facilitating microbial translocation and triggering inflammatory responses.⁷³ In dextran sulfate sodium-induced colitis models, disruption of the epithelial barrier has been shown to increase susceptibility to CRC.⁷⁴ For example, the loss of certain stromal serine proteases can impair tight junction formation, thereby promoting tumor development.⁷⁵ Additionally, the host recognizes microbial components through pattern recognition receptors, such as toll-like receptors, which initiate innate immune responses.⁷⁶ Dysregulation of these mechanisms is a significant contributing factor to CRC pathogenesis. Following the induction of myeloid differentiation, primary response 88-dependent pro-inflammatory cytokines, particularly IL-23, interact with toll-like receptors expressed on tumor-infiltrating myeloid cells, along with commensal bacteria and their components. This interaction leads to IL-23-driven upregulation of IL-17A, IL-6, and IL-22.^{73,77,78} These cytokines, in turn, promote tumor cell proliferation through the activation of the nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3) signaling pathways.^{79,80}

At the molecular level, NF-κB is considered a central transcription factor that mediates inflammatory responses. In CRC mouse models, sustained NF-κB activation promotes tumorigenesis by accelerating *Apc* gene loss.⁸¹ This pathway also contributes to carcinogenesis by inducing the production of reactive oxygen species,

enhancing IL-6 expression, and activating tumor necrosis factor signaling, all of which can lead to DNA damage accumulation and increase the risk of malignant transformation.⁸²⁻⁸⁴ Aberrant NF-κB activation has been observed in more than half of sporadic and inflammation-associated CRC cases.^{85,86} Activation of NF-κB can be triggered by pathogen-associated molecular patterns or inflammatory cytokines such as IL-1β, tumor necrosis factor, and IL-17 (Figure 1). The alternative NF-κB pathway, involving p52 and RelB, is primarily regulated by receptor activator of NF-κB ligand and lymphotoxin-beta. This pathway also plays an important role in shaping intestinal immune homeostasis and regulating microbial composition.^{83,87,88} (Table 3). Moreover, the loss of p53 increases intestinal barrier permeability, thereby activating NF-κB-dependent inflammatory cascades, promoting epithelial-mesenchymal transition, and increasing the risk of tumor development.⁸⁹ In IL-10-deficient mouse models, a significantly higher mutation rate in the colon compared to wild-type controls further supports the role of inflammation in inducing DNA damage and microsatellite instability.⁹⁰ Understanding how cancer mutations influence cytokine-driven inflammation may reveal strategies to target the tumor microenvironment, with gut fungi as potential biomarkers and therapeutic targets.

6. The mechanisms of action of fungi in colorectal cancer

Alterations in the colonic fungal microbiota have been reported in CRC patients.^{25,26} Notably, fungal dysbiosis was also observed in individuals with colorectal polyps (29 cases) and adenomas (20 cases), suggesting that fungi are involved in the early stages of CRC.¹³ An increasing

Table 3. The predominant fungal species and associated cytokines in colorectal cancer (CRC)

Fungal species	Cytokine	Function	Reference
<i>Candida albicans</i>	IL-6	<i>C. albicans</i> infection can induce the secretion of IL-6 by host cells. IL-6 promotes the proliferation and survival of tumor cells while inhibiting the anti-tumor response of the immune system.	91
	IL-8	<i>C. albicans</i> can induce IL-8 secretion by host cells. IL-8 attracts neutrophils and monocytes to the site of infection, enhancing the inflammatory response. In CRC, IL-8 upregulation may promote tumor growth and metastasis.	
	TNF-α	<i>C. albicans</i> infection can induce TNF-α production, which regulates the activity of immune cells and promotes the inflammatory response. In CRC, TNF-α may promote tumor cell survival and proliferation by activating the NF-κB signaling pathway.	
	MCP-1	<i>C. albicans</i> can induce MCP-1 secretion by host cells. MCP-1 attracts monocytes and macrophages to the site of infection. In CRC, MCP-1 upregulation may promote the infiltration of tumor-associated macrophages, thereby affecting tumor progression.	

(cont'd...)

Table 3. (continued)

Fungal species	Cytokine	Function	Reference
<i>Aspergillus</i> spp.	IL-22	<i>Aspergillus</i> infection or its metabolites may activate innate lymphoid cells, thereby promoting IL-22 secretion. IL-22 enhances the proliferation and survival of epithelial cells, thus playing an important role in CRC progression.	92
	IL-33	<i>Aspergillus</i> can induce IL-33 secretion by host cells. IL-33 may activate type 2 immune responses in CRC. These immune responses may affect tumor growth and metastasis by modulating the inflammatory microenvironment.	
	TNF-α, IL-6	<i>Aspergillus</i> infection may activate host immune cells (such as macrophages and dendritic cells), inducing the secretion of pro-inflammatory cytokines TNF-α and IL-6. These cytokines can promote inflammatory responses, creating a favorable microenvironment for tumor growth.	
<i>Saccharomyces</i> spp.	IL-18	<i>Saccharomyces cerevisiae</i> can regulate IL-18 levels, thereby enhancing the tumor cell clearance by activating immune cells.	93
	TNF-α, IL-6	<i>S. cerevisiae</i> can reduce the levels of pro-inflammatory cytokines IL-6 and TNF-α. Since these cytokines are typically associated with chronic inflammation and tumorigenesis, <i>S. cerevisiae</i> may help prevent CRC.	

Abbreviations: IL: Interleukin; MCP-1: Monocyte chemoattractant protein-1; NF-κB: Nuclear factor-kappa B; TNF-α: Tumor necrosis factor-alpha.

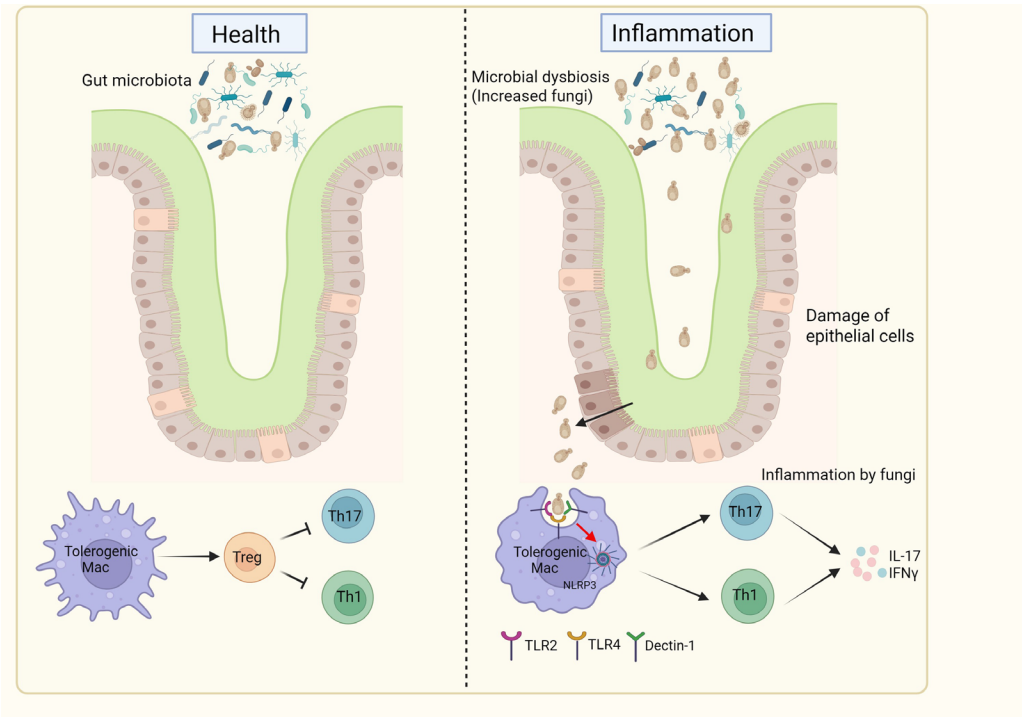


Figure 1. The mechanism of fungal-induced inflammation occurrence and development. The interaction among microbial communities leads to fungal dysbiosis, which directly damages intestinal epithelial cells and stimulates innate immune cells, such as macrophages (Mac) and dendritic cells, through dectin-1, toll-like receptor (TLR)2, and TLR4, thereby causing inflammation and subsequently increasing T-helper (Th)17 and Th1 cells. Created with BioRender.com. Ji, T. (2026) <https://BioRender.com/lfez4cg>.

Abbreviations: IFNγ: Interferon gamma; IL: Interleukin; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; Treg: Regulatory T cell.

body of evidence indicates a bidirectional relationship between fungal dysbiosis and CRC progression. On the one hand, fungal imbalance may act as a direct driver of CRC development. For example, Zhang *et al.*⁵² demonstrated that excessive overgrowth of *C. tropicalis* activates the spleen tyrosine kinase (SYK)–pyruvate kinase M2–hypoxia-inducible factor 1 alpha (HIF1 α)–glycolysis signaling axis, which enhances the immunosuppressive activity of myeloid-derived suppressor cells (MDSCs) and facilitates the initiation of CRC. In addition, homogenates of polymicrobial biofilms containing both bacterial and fungal components derived from CRC patients have been shown to induce colorectal tumorigenesis in genetically susceptible mouse models.⁹⁴ Moreover, dysregulated fungi and their metabolites may further increase disease risk or exacerbate tumor progression by amplifying inflammatory cascades, interacting with bacterial communities, and reshaping the tumor microenvironment in the context of other genetic and environmental factors, thereby acting as promoters or aggravators of CRC progression.^{29,95,96} On the other hand, tumor development can profoundly alter the intestinal ecosystem and metabolic landscape. Tumor-associated changes, including disruption of mucus integrity, local hypoxia, and immune modulation, can, in turn, remodel the composition and structure of the gut mycobiome.^{13,97,98}

Caspase recruitment domain protein 9 (CARD9) functions as a key adaptor molecule downstream of several immunoreceptor tyrosine-based activation motif-associated receptors, including dectin-1 and dectin-2.⁹⁹ CARD9 forms a complex with B-cell lymphoma 10 and the paracaspase mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1), facilitating NF- κ B activation to trigger acute inflammatory responses and initiate adaptive immune signaling.⁹⁹ CARD9 is essential for antifungal immune responses, serving as a key adaptor that links fungal recognition by surface receptors to NF- κ B pathway activation¹⁰⁰ (Figure 2). Several pattern recognition receptors within the C-type lectin receptor family require CARD9 to activate innate immunity.^{101,102} A study has found that CARD9-dependent innate immunity plays a critical role in maintaining intestinal immune homeostasis, as CARD9-deficient mice show increased intestinal colonization by *C. tropicalis*, accompanied by elevated MDSC accumulation and impaired effector T-cell function.²⁷ The absence of CARD9 in macrophages compromises their functional activity and diminishes antifungal defense, leading to alterations in the gut microbiota and increased fungal burden, particularly of *C. tropicalis*. Myeloid cells display characteristics of MDSCs and acquire immunosuppressive functions.¹⁰⁰ MDSCs constitute a diverse group of immature myeloid cells that

contribute to immunosuppression and facilitate tumor progression.¹⁰³ Pathological conditions such as chronic inflammation and malignancy can drive the expansion of MDSCs. *In vitro* studies have also shown that *C. tropicalis* can promote MDSC differentiation and enhance their immunosuppressive activity. In CRC patients, MDSC frequency in tumor tissues is positively correlated with fungal burden. Antifungal treatment with fluconazole can inhibit CRC in CARD9-deficient mice, which is associated with reduced MDSC accumulation.¹⁰⁰

Malik *et al.*⁸ found that the SYK–CARD9 signaling axis can induce inflammasome activation in response to fungal infection, thereby limiting colitis and CRC. Loss of CARD9 or SYK in myeloid cells impairs inflammasome activation, reduces IL-18 maturation, and increases susceptibility to colitis and CRC by increasing the fungal burden. IL-18 promotes the restitution of the intestinal epithelial barrier and the production of interferon-gamma by intestinal cluster of differentiation (CD)8⁺ T cells. In azoxymethane–dextran sulfate sodium-induced models, both bone marrow transplantation and exogenous IL-18 administration effectively reduced tumor burden in *Card9*^{−/−} and *Syk*^{fl/fl} *LysM*^{Cre/+} mice. In contrast, antifungal treatment worsened the severity of colitis and CRC in these animals. These findings suggest that the SYK–CARD9 signaling pathway can limit the development of colitis and colorectal tumorigenesis by preserving microbial homeostasis and facilitating inflammasome activation¹⁰⁴ (Figure 2). Moreover, under pathogen-free housing conditions lacking pathogenic organisms such as fungi, Bergmann *et al.*¹⁰⁵ demonstrated that CARD9 promotes CRC progression by inducing IL-1 β expression. Similarly, Wang *et al.*¹⁰⁰ confirmed that intestinal fungal dysbiosis can drive CRC development. These studies highlight the critical role of fungi in CRC. Commensal fungi contribute to the suppression of inflammation and tumorigenesis by modulating immune responses, preserving barrier integrity, and maintaining microbial homeostasis. In contrast, pathogenic fungi may undergo abnormal expansion under conditions of dysbiosis or immune dysfunction, triggering chronic inflammation and facilitating CRC progression. The individual variability of the fungal community further underscores the importance and complexity of interactions between microbes and their hosts.¹⁰⁶

The mammalian C-type lectin receptors, including dectin-1, dectin-2, and dectin-3, are pattern recognition receptors expressed on the surface of innate immune cells. They detect fungal pathogens and initiate downstream signaling cascades involved in innate immune responses^{107,108} (Figure 3). Dectin-3 is expressed by polymorphonuclear cells, such as neutrophils, monocytes,

and dendritic cells.¹⁰⁹ A study has shown that dectin-3 can recognize a variety of fungi, including *C. albicans*, *Paracoccidioides brasiliensis*, and *Cryptococcus*, by binding to the mannans on their surfaces.¹¹⁰ Previous research has shown that dectin-3 can form heterodimers with dectin-2 to recognize *C. Albicans*.¹¹¹ The absence of dectin-3 impairs the phagocytosis and antifungal activity of *C. tropicalis* in macrophages and promotes colitis.¹¹² (Figure 2).

Innate lymphoid cells (ILCs) have been identified as a new family of lymphoid effector cells.¹¹³ The interaction among ILC3, T cells, and macrophages is crucial for maintaining intestinal bacterial homeostasis and preventing inflammation-related diseases.^{114, 115} Experiments have found that *Dectin3*^{-/-} mice exhibit heightened susceptibility to dextran sulfate sodium-induced colitis, characterized by increased colonic mucosal erosion, inflammatory cell infiltration, crypt destruction, and goblet cell loss compared with wild-type mice.²⁷ The study also confirmed that the absence of the *Dectin3* gene impairs macrophage clearance of fungi and increases the fungal burden.

The function of macrophages is considered key to gastrointestinal innate immune homeostasis against IBD and colorectal tumorigenesis.^{116,117} Previous studies have

shown that intestinal bacteria, particularly *Salmonella enterica*-mediated regulation of glycolysis, can affect macrophage function and are involved in various gastrointestinal diseases.^{118,119} Recent reports have indicated that both bacterial and fungal infections can upregulate glycolysis in macrophages, leading to rapid macrophage death.¹¹¹ It has now been found that macrophages infected with *C. albicans* also increase glycolysis through an HIF-1-dependent pathway. Additionally, the importance of glycolysis in IL-7 production has been confirmed, with 2-deoxyglucose inhibition of glycolysis reducing IL-7 expression.¹¹³

Interleukin-22 is an important effector molecule produced by both innate and adaptive immune cells. It is involved in the development of gastrointestinal inflammation and cancer.¹²⁰ Previous studies have shown that the production of IL-22 and IL-23 can drive tumor progression in CRC mouse models.^{121,122} IL-22 produced by CD4⁺ T cells can stimulate tumor growth in CRC by activating the STAT3 transcription factor and the H3K79 methyltransferase in cancer cells.¹²³ Additionally, in various mouse models, IL-22 secreted by ILCs has been shown to promote CRC progression by phosphorylating and activating STAT3 in tumor cells.^{105,121}

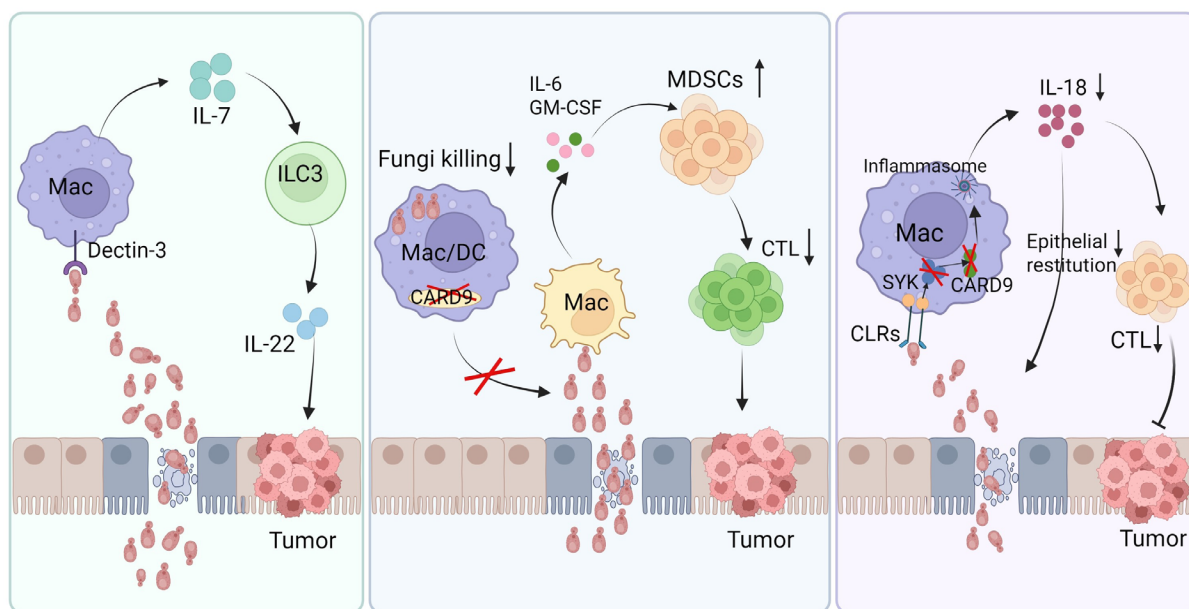


Figure 2. Fungi are involved in the occurrence and development of colorectal cancer. In colorectal cancer, macrophages (Mac) release interleukin (IL)-7, which promotes IL-22 production by innate lymphoid cells 3 (ILC3). It also disrupts caspase recruitment domain protein 9 (CARD9), leading to increased production of IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) by fungi, which in turn induces the generation of myeloid-derived suppressor cells (MDSCs) and suppresses cytotoxic lymphocytes (CTLs). Additionally, disruption of the CARD9/spleen tyrosine kinase (SYK) pathway reduces IL-18 release from macrophages, thereby decreasing inflammation and affecting the occurrence and development of colitis and colorectal cancer. Created with Biorender.com. Ji, T. (2026) <https://BioRender.com/w6w8ar7>.

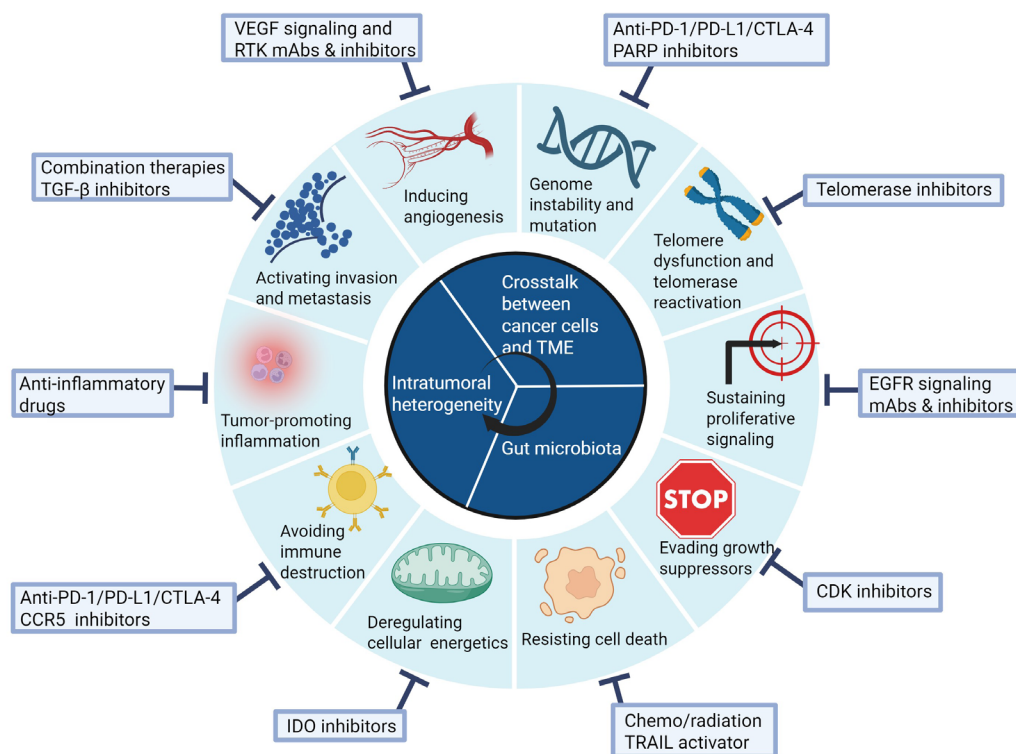


Figure 3. Characteristics of colorectal cancer and related inhibitory strategies. The current treatment strategies have been proven or tested in clinical trials, but the characteristics of colorectal cancer and knowledge gaps remain barriers to improving treatment efficacy. Created with Biorender.com. Ji, T. (2026) <https://BioRender.com/0fsvio5>.

Abbreviations: CCR5: C–C chemokine receptor type 5; CDK: Cyclin-dependent kinase; CTLA-4: Cytotoxic T-lymphocyte antigen 4; EGFR: Epidermal growth factor receptor; IDO: Indoleamine 2,3-dioxygenase; mAB: Monoclonal antibody; PARP: Poly(ADP-ribose) polymerase; PD-1: Programmed death 1; PD-L1: Programmed death-ligand 1; RTK: Receptor Tyrosine Kinase; TGF- β : Transforming growth factor-beta; TME: Tumor microenvironment; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand; VEGF: Vascular endothelial growth factor.

7. Treatment methods for colorectal cancer

Mature CRC genomic maps at the single-cell level, sophisticated genetic model systems, and targeted therapies have laid the foundation for a deeper understanding of CRC biological characteristics (Figure 3). Anti-angiogenic therapies targeting vascular endothelial growth factor (VEGF), including monoclonal antibodies such as bevacizumab,¹²⁴ aflibercept,¹²⁵ and ramucirumab, have been approved by the United States Food and Drug Administration and shown efficacy in CRC. Several clinical trials have confirmed that the combination of anti-VEGF and chemotherapy regimens is beneficial for CRC patients.^{126,127} Anti-angiogenic inhibitors may modulate immunosuppressive pathways, supporting their use in combination with immunotherapy. In addition to tumor-associated macrophages, regulatory T cells derived from CRC-bearing mice express VEGFR2 and proliferate in response to VEGF signaling. Therefore, treatment with anti-VEGF antibodies (bevacizumab) has been shown to reduce circulating regulatory T cell levels in the peripheral

blood of patients with metastatic CRC.¹²⁸

Therapeutic strategies that induce apoptosis in cancer cells have also shown promising efficacy in early-phase clinical trials for CRC. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) selectively induces apoptosis in cancer cells by binding to the pro-apoptotic death receptors (DR)4/5, subsequently recruiting fas-associated protein with death domain and procaspase-8 to initiate the apoptotic cascade.¹²⁹ ONC201, a TRAIL inducer, antagonizes DRD2 selectively, leading to the attenuation of AKT–extracellular signal-regulated kinase signaling and subsequent upregulation of TRAIL.¹³⁰ Preclinical data have shown that ONC201 exerts anti-metastatic effects in CRC by activating cell death signaling and enhancing anti-tumor immunity, as evidenced by increased intratumoral immune cell infiltration and activation of natural killer cells.¹³¹

For early CRC detection, in addition to colonoscopy, fecal tests can detect occult blood from damaged blood vessels or mutated DNA in polyps and tumors.¹³² A positive

fecal test result requires follow-up and confirmation through colonoscopy. For individuals who are unable or unwilling to undergo fecal testing or colonoscopy, the detection of circulating tumor cells¹³³ and circulating tumor DNA (ctDNA)¹³⁴ has become a less invasive and more acceptable alternative, with high sensitivity and accuracy. Moreover, ctDNA serves as a useful marker for monitoring patients' responses to treatment and for tracking clonal dynamics during therapy.¹³⁴

Recently, three-dimensional organoid model systems have been developed for the diagnostic genetics of normal intestinal epithelium. CRC tumor organoids derived from human and murine tissues are increasingly used to investigate treatment response, identify genomic alterations,¹³⁵ characterize intratumoral heterogeneity,¹³⁶ and create organoid xenografts for realistic disease modeling.¹³⁷

In addition, patient-derived tumor organoids can serve as a model system for *ex vivo* drug testing to guide personalized clinical therapy.¹³⁸ An important addition to organoid modeling is the tumor organoid–T cell co-culture system, which uses tumor tissues and immune cells from CRC patients, particularly T cells isolated from autologous peripheral blood lymphocytes.¹³⁹ In these models, autologous T cells selectively recognize and respond to tumor-derived organoids, while exhibiting minimal reactivity toward healthy organoids or tissues.¹⁴⁰ Therefore, these models may help study immunotherapy in specific genetic contexts and identify mechanisms of adaptation and resistance to immunotherapy and targeted therapies. Moreover, tumor-reactive T cells from these co-culture models may provide clues for potential selective T cell transfer therapies.¹⁴¹

8. Fungal-derived therapeutic applications in colorectal cancer treatment

Recent years have witnessed growing interest in microbiota-targeted strategies for cancer therapy, particularly in CRC. Bacteria-based interventions, including probiotics, prebiotics, and synbiotics, have shown promising preventive and therapeutic effects in CRC management.¹⁴² Similarly, certain yeast species have emerged as candidates for fungal probiotics, with *Saccharomyces boulardii* standing out due to its widespread use in fermented foods and well-documented safety profile.¹⁴³ This yeast has been reported to improve CRC-related gut dysbiosis and to exert anti-tumor effects by inhibiting NF- κ B and the mammalian target of rapamycin signaling pathways, downregulating oncogene expression, and promoting apoptosis.⁵¹ Nevertheless, the clinical efficacy and safety of fungal probiotics in cancer therapy remain controversial,

as robust, large-scale clinical trials are still lacking.

Dietary modulation represents another promising approach for shaping the gut mycobiome. Studies have shown a positive correlation between carbohydrate intake and *Candida* abundance, while protein and fatty acid intake may suppress its growth.¹⁴⁴ Thus, developing personalized nutritional interventions based on host characteristics and microbiome profiles has the potential to rebalance the gut mycobiota and interfere with tumor progression.¹⁴⁵

Importantly, fungi are increasingly recognized as a source of novel natural compounds with anticancer activity. For instance, ethyl acetate extracts of *Aspergillus* sp. have demonstrated strong antiproliferative effects against HT-29 CRC cells.¹⁴⁶ The fatty acid cis-10-nonadecenoic acid, isolated from the endolichenic fungal strain EL001668 (KACC 83020BP) derived from *Cetraria laevigata* Rasm., has been demonstrated to significantly suppress the stemness properties and tumorigenic potential of CRC stem cells.¹⁴⁷ Moreover, asperphenamate, a metabolite produced by the co-culture of *Penicillium soppii* and *Penicillium solitum*, can induce DNA damage response pathways, leading to apoptosis and cell cycle arrest, indicating broad-spectrum anti-CRC efficacy.¹⁴⁸ Additionally, the triterpenoid compound trichodermin from *Trichoderma viride* has been shown to significantly inhibit the migration and invasion of DLD1 and HT-29 cells via the protein kinase C α (PKC α)/PKC δ /ERK/specificity protein 1/cathepsin V signaling axis, offering a novel target for CRC therapy.¹⁴⁹ Among fungal-derived components, β -glucans from yeast cell walls are notable for their immunomodulatory properties. These polysaccharides have been shown to activate cytotoxic immune cells, stimulate the release of pro-inflammatory cytokines and chemokines, and enhance the expression of immune regulators, such as interferon regulatory factor 1 and programmed death-ligand 1, thereby demonstrating potential immunostimulatory and anti-tumor effects in melanoma, breast cancer, and CRC.¹⁵⁰

It is also noteworthy that some antifungal agents are being repurposed for cancer treatment, showing promising anticancer activity. These effects may arise from shared molecular targets or signaling pathways between fungi and tumors. For example, miconazole and terbinafine have been shown to induce cell cycle arrest and inhibit proliferation in COLO 205 cells.^{151,152} Itraconazole, a broad-spectrum antifungal drug, inhibits the growth of SW480 and HCT116 cells *in vitro* and induces apoptosis via autophagy-related mechanisms; it has also demonstrated significant tumor-suppressive effects in xenograft mouse models.¹⁵³ Ketoconazole suppresses the proliferation of various CRC cell lines by inhibiting lipoygenase and

cytochrome P450-related enzymatic activities,^{154,155} while griseofulvin enhances the efficacy of the chemotherapeutic agent nocodazole by inducing G2/M phase arrest and apoptosis, providing a potential combinatorial strategy for CRC treatment.¹⁵⁶

In summary, fungi hold dual potential in CRC prevention and therapy—as immunomodulatory targets and as sources of anticancer natural products. Future studies should focus on elucidating precise regulatory mechanisms and advancing clinical translation to broaden therapeutic options for comprehensive CRC management.

9. Conclusion

The relationship between fungi and CRC has become a research hotspot in recent years. With the rapid development of sequencing technologies, an increasing number of studies have revealed the potential roles of fungi in the occurrence, development, and treatment of CRC. Research indicates that the gut fungal communities of CRC patients exhibit significant geographical heterogeneity, with a general reduction in diversity and enrichment of certain specific fungal taxa. Moreover, fungi, through their rich chemical components (such as polysaccharides, terpenes, and flavonoids), have demonstrated significant anticancer activities *in vitro* and *in vivo*, including inhibiting cell proliferation, inducing apoptosis, and regulating immune responses.¹⁵⁷

In mechanistic studies, fungi may influence CRC progression through multiple pathways. For example, certain fungal metabolites can modulate the functions of immune cells in the tumor microenvironment, thereby affecting tumor immune evasion and chemoresistance.⁴⁵ In addition, intratumoral microbiota (including fungi) have been shown to affect the occurrence and development of CRC by influencing colonic epithelial cells, tumor cells, and immune cells.¹⁰⁵

Despite the progress made in research, many challenges remain. First, the causal relationship between fungi and CRC has not been fully established, with most studies remaining at the correlational stage. Second, the diversity of fungi varies greatly across populations, and methods for conducting precise research across geographical and dietary contexts remain to be established. Moreover, most existing studies focus on cell and animal models, while clinical translation and application face many limitations.¹⁵⁷

Future research could focus on several directions: first, using multi-omics technologies, such as metagenomics and metabolomics, to deeply explore the interaction mechanisms between fungi and hosts; second, conducting clinical studies to verify the potential of fungi as

biomarkers or therapeutic targets; and third, developing novel anticancer drugs based on fungal metabolites and exploring their application prospects in combination therapies.¹⁵⁷ In summary, the research prospects for fungi in CRC are broad, and they hold promise for developing new ideas and strategies for early diagnosis, treatment, and prognosis.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

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Consent for publication

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Further disclosure

Grammarly was used to improve the language of the paper.

References

1. Qin J, Li R, Raes J, *et al.* A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. 2010;464(7285):59–65.
doi: 10.1038/nature08821
2. Zhang D, Wang Y, Shen S, Hou Y, Chen Y, Wang T. The mycobiota of the human body: a spark can start a prairie fire. *Gut Microbes*. 2020;11(4):655–679.

- doi: 10.1080/19490976.2020.1731287
3. Garrett WS. Cancer and the microbiota. *Science*. 2015;348(6230):80-86.
doi: 10.1126/science.aaa4972
 4. Xavier JB, Young VB, Skufca J, *et al.* The Cancer Microbiome: Distinguishing Direct and Indirect Effects Requires a Systemic View. *Trends Cancer*. 2020;6(3):192-204.
doi: 10.1016/j.trecan.2020.01.004
 5. Wheeler ML, Limon JJ, Underhill DM. Immunity to Commensal Fungi: Detente and Disease. *Annu Rev Pathol*. 2017;12:359-385.
doi: 10.1146/annurev-pathol-052016-100342
 6. Wang ZK, Yang YS, Stefka AT, Sun G, Peng LH. Review article: fungal microbiota and digestive diseases. *Aliment Pharmacol Ther*. 2014;39(8):751-766.
doi: 10.1111/apt.12665
 7. Okuno K, Tokunaga M, Von Hoff D, Kinugasa Y, Goel A. Intratumoral *Malassezia globosa* Levels Predict Survival and Therapeutic Response to Adjuvant Chemotherapy in Patients With Pancreatic Ductal Adenocarcinoma. *Gastroenterology*. 2023;165(2):502-504.e2.
doi: 10.1053/j.gastro.2023.04.017
 8. Malik A, Sharma D, Malireddi RKS, *et al.* SYK-CARD9 Signaling Axis Promotes Gut Fungi-Mediated Inflammasome Activation to Restrict Colitis and Colon Cancer. *Immunity*. 2018;49(3):515-530.e5.
doi: 10.1016/j.immuni.2018.08.024
 9. Yang L, Li A, Wang Y, Zhang Y. Intratumoral microbiota: roles in cancer initiation, development and therapeutic efficacy. *Signal Transduct Target Ther*. 2023;8(1):35.
doi: 10.1038/s41392-022-01304-4
 10. Azevedo MM, Pina-Vaz C, Baltazar F. Microbes and Cancer: Friends or Faux? *Int J Mol Sci*. 2020;21(9):3115.
doi: 10.3390/ijms21093115
 11. Narunsky-Haziza L, Sepich-Poore GD, Livyatan I, *et al.* Pan-cancer analyses reveal cancer-type-specific fungal ecologies and bacteriome interactions. *Cell*. 2022;185(20):3789-3806.e17.
doi: 10.1016/j.cell.2022.09.005
 12. Wang M, Yu F, Li P. Intratumor microbiota in cancer pathogenesis and immunity: from mechanisms of action to therapeutic opportunities. *Front Immunol*. 2023;14:1269054.
doi: 10.3389/fimmu.2023.1269054
 13. Dohlman AB, Klug J, Mesko M, *et al.* A pan-cancer mycobiome analysis reveals fungal involvement in gastrointestinal and lung tumors. *Cell*. 2022;185(20):3807-3822.e12.
doi: 10.1016/j.cell.2022.09.015
 14. Bennett JW, Klich M. Mycotoxins. *Clin Microbiol Rev*. 2003;16(3):497-516.
doi: 10.1128/CMR.16.3.497-516.2003
 15. Scanlan PD, Marchesi JR. Micro-eukaryotic diversity of the human distal gut microbiota: qualitative assessment using culture-dependent and -independent analysis of faeces. *ISME J*. 2008;2(12):1183-1193.
doi: 10.1038/ismej.2008.76
 16. Biasoli MS, Tosello ME, Magaró HM. Adherence of *Candida* strains isolated from the human gastrointestinal tract. *Mycoses*. 2002;45(11-12):465-469.
doi: 10.1046/j.1439-0507.2002.00793.x
 17. Li Q, Wang C, Zhang Q, *et al.* Use of 18S ribosomal DNA polymerase chain reaction-denaturing gradient gel electrophoresis to study composition of fungal community in 2 patients with intestinal transplants. *Hum Pathol*. 2012;43(8):1273-1281.
doi: 10.1016/j.humpath.2011.09.017
 18. Li Q, Wang C, Tang C, He Q, Li N, Li J. Dysbiosis of gut fungal microbiota is associated with mucosal inflammation in Crohn's disease. *J Clin Gastroenterol*. 2014;48(6):513-523.
doi: 10.1097/MCG.0000000000000035
 19. Li J, Chen D, Yu B, *et al.* Fungi in Gastrointestinal Tracts of Human and Mice: from Community to Functions. *Microb Ecol*. 2018;75(4):821-829.
doi: 10.1007/s00248-017-1105-9
 20. Santus W, Devlin JR, Behnsen J. Crossing Kingdoms: How the Mycobiota and Fungal-Bacterial Interactions Impact Host Health and Disease. *Infect Immun*. 2021;89(4):e00648-20.
doi: 10.1128/IAI.00648-20
 21. Hallen-Adams HE, Suhr MJ. Fungi in the healthy human gastrointestinal tract. *Virulence*. 2017;8(3):352-358.
doi: 10.1080/21505594.2016.1247140
 22. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
doi: 10.3322/caac.21492
 23. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin*. 2007;57(1):43-66.
doi: 10.3322/canjclin.57.1.43
 24. Scupham AJ, Presley LL, Wei B, *et al.* Abundant and diverse fungal microbiota in the murine intestine. *Appl Environ Microbiol*. 2006;72(1):793-801.
doi: 10.1128/AEM.72.1.793-801.2006

25. Lin Y, Lau HC, Liu Y, *et al.* Altered Mycobiota Signatures and Enriched Pathogenic *Aspergillus rambellii* Are Associated With Colorectal Cancer Based on Multicohort Fecal Metagenomic Analyses. *Gastroenterology*. 2022;163(4):908-921.
doi: 10.1053/j.gastro.2022.06.038
26. Coker OO, Nakatsu G, Dai RZ, *et al.* Enteric fungal microbiota dysbiosis and ecological alterations in colorectal cancer. *Gut*. 2019;68(4):654-662.
doi: 10.1136/gutjnl-2018-317178
27. Zhu Y, Shi T, Lu X, *et al.* Fungal-induced glycolysis in macrophages promotes colon cancer by enhancing innate lymphoid cell secretion of IL-22. *EMBO J*. 2021;40(11):e105320.
doi: 10.15252/embj.2020105320
28. Li X, Feng J, Wang Z, Liu G, Wang F. Features of combined gut bacteria and fungi from a Chinese cohort of colorectal cancer, colorectal adenoma, and post-operative patients. *Front Microbiol*. 2023;14:1236583.
doi: 10.3389/fmicb.2023.1236583
29. Kang Z, Jiang S, Fang JY, Chen H. Intestinal dysbiosis and colorectal cancer. *Chin Med J*. 2025;138(11):1266-1287.
doi: 10.1097/CM9.0000000000003617
30. Hager CL, Isham N, Schrom KP, *et al.* Effects of a Novel Probiotic Combination on Pathogenic Bacterial-Fungal Polymicrobial Biofilms. *mBio*. 2019;10(2):e00338-19.
doi: 10.1128/mBio.00338-19
31. Kong HH, Segre JA. Cultivating fungal research. *Science*. 2020;368(6489):365-366.
doi: 10.1126/science.aaz8086
32. Tang J, Iliev ID, Brown J, Underhill DM, Funari VA. Mycobiome: Approaches to analysis of intestinal fungi. *J Immunol Methods*. 2015;421:112-121.
doi: 10.1016/j.jim.2015.04.004
33. Nash AK, Auchtung TA, Wong MC, *et al.* The gut mycobiome of the Human Microbiome Project healthy cohort. *Microbiome*. 2017;5(1):153.
doi: 10.1186/s40168-017-0373-4
34. Almeida F, Rodrigues ML, Coelho C. The Still Underestimated Problem of Fungal Diseases Worldwide. *Front Microbiol*. 2019;10:214.
doi: 10.3389/fmicb.2019.00214
35. Fisher MC, Hawkins NJ, Sanglard D, Gurr SJ. Worldwide emergence of resistance to antifungal drugs challenges human health and food security. *Science*. 2018;360(6390):739-742.
doi: 10.1126/science.aap7999
36. Chen CJ, Wang LY, Lu SN, *et al.* Elevated aflatoxin exposure and increased risk of hepatocellular carcinoma. *Hepatology*. 1996;24(1):38-42.
doi: 10.1002/hep.510240108
37. Ekwomadu T, Mwanza M, Musekiwa A. Mycotoxin-Linked Mutations and Cancer Risk: A Global Health Issue. *Int J Environ Res Public Health*. 2022;19(13):7754.
doi: 10.3390/ijerph19137754
38. Kusunoki M, Misumi J, Shimada T, *et al.* Long-term administration of the fungus toxin, sterigmatocystin, induces intestinal metaplasia and increases the proliferative activity of PCNA, p53, and MDM2 in the gastric mucosa of aged Mongolian gerbils. *Environ Health Prev Med*. 2011;16(4):224-231.
doi: 10.1007/s12199-010-0190-x
39. Suzuki A, Iwasaki M, Kato M, Wagai N. Sequential operation of ceramide synthesis and ICE cascade in CPT-11-initiated apoptotic death signaling. *Exp Cell Res*. 1997;233(1):41-47.
doi: 10.1006/excr.1997.3498
40. Persson EC, Sewram V, Evans AA, *et al.* Fumonisin B1 and risk of hepatocellular carcinoma in two Chinese cohorts. *Food Chem Toxicol*. 2012;50(3-4):679-683.
doi: 10.1016/j.fct.2011.11.029
41. Mondani L, Palumbo R, Tsitsigiannis D, Perdakis D, Mazzoni E, Battilani P. Pest Management and Ochratoxin A Contamination in Grapes: A Review. *Toxins*. 2020;12(5):303.
doi: 10.3390/toxins12050303
42. Pfohl-Leskowicz A, Manderville RA. An update on direct genotoxicity as a molecular mechanism of ochratoxin A carcinogenicity. *Chem Res Toxicol*. 2012;25(2):252-262.
doi: 10.1021/tx200430f
43. Hsia CC, Wu ZY, Li YS, Zhang F, Sun ZT. Nivalenol, a main Fusarium toxin in dietary foods from high-risk areas of cancer of esophagus and gastric cardia in China, induced benign and malignant tumors in mice. *Oncol Rep*. 2004;12(2):449-456.
doi: 10.3892/or.12.2.449
44. Djouina M, Waxin C, Caboche S, *et al.* Low dose dietary contamination with deoxynivalenol mycotoxin exacerbates enteritis and colorectal cancer in mice. *Sci Total Environ*. 2023;900:165722.
doi: 10.1016/j.scitotenv.2023.165722
45. Robert H, Payros D, Pinton P, Théodorou V, Mercier-Bonin M, Oswald IP. Impact of mycotoxins on the intestine: are mucus and microbiota new targets? *J Toxicol Environ Health B Crit Rev*. 2017;20(5):249-275.
doi: 10.1080/10937404.2017.1326071
46. Lebrun B, Tardivel C, Félix B, *et al.* Dysregulation of energy balance by trichothecene mycotoxins: Mechanisms and

- prospects. *Neurotoxicology*. 2015;49:15-27.
doi: 10.1016/j.neuro.2015.04.009
47. Liu NN, Jiao N, Tan JC, *et al.* Multi-kingdom microbiota analyses identify bacterial-fungal interactions and biomarkers of colorectal cancer across cohorts. *Nat Microbiol*. 2022;7(2):238-250.
doi: 10.1038/s41564-021-01030-7
 48. Luan C, Xie L, Yang X, *et al.* Dysbiosis of fungal microbiota in the intestinal mucosa of patients with colorectal adenomas. *Sci Rep*. 2015;5:7980.
doi: 10.1038/srep07980
 49. Richard ML, Lamas B, Liguori G, Hoffmann TW, Sokol H. Gut fungal microbiota: the Yin and Yang of inflammatory bowel disease. *Inflamm Bowel Dis*. 2015;21(3):656-665.
doi: 10.1097/MIB.0000000000000261
 50. Alnuaimi AD, Wiesenfeld D, O'Brien-Simpson NM, Reynolds EC, Peng B, McCullough MJ. The development and validation of a rapid genetic method for species identification and genotyping of medically important fungal pathogens using high-resolution melting curve analysis. *Mol Oral Microbiol*. 2014;29(3):117-130.
doi: 10.1111/omi.12050
 51. Li JQ, Li JL, Xie YH, *et al.* *Saccharomyces cerevisiae* may serve as a probiotic in colorectal cancer by promoting cancer cell apoptosis. *J Dig Dis*. 2020;21(10):571-582.
doi: 10.1111/1751-2980.12930
 52. Zhang Z, Zheng Y, Chen Y, *et al.* Gut fungi enhances immunosuppressive function of myeloid-derived suppressor cells by activating PKM2-dependent glycolysis to promote colorectal tumorigenesis. *Exp Hematol Oncol*. 2022;11(1):88.
doi: 10.1186/s40164-022-00334-6
 53. McBride AE. Messenger RNA transport in the opportunistic fungal pathogen *Candida albicans*. *Curr Genet*. 2017;63(6):989-995.
doi: 10.1007/s00294-017-0707-6
 54. Glinka P, Nowacka K, Kulesza K, Ejdy E, Dynowska M. Share of the *Saccharomyces* genus in the mycobiota of the gastrointestinal tract of oncology patients – potential effects of a fruit-based diet. *Ann Parasitol*. 2018;64(3):199-202.
doi: 10.17420/ap6403.152
 55. Wirth F, Goldani LZ. Epidemiology of *Rhodotorula*: an emerging pathogen. *Interdiscip Perspect Infect Dis*. 2012;2012:465717.
doi: 10.1155/2012/465717
 56. Bajaj JS, Liu EJ, Kheradman R, *et al.* Fungal dysbiosis in cirrhosis. *Gut*. 2018;67(6):1146-1154.
doi: 10.1136/gutjnl-2016-313170
 57. Jawhara S, Habib K, Maggioro F, *et al.* Modulation of intestinal inflammation by yeasts and cell wall extracts: strain dependence and unexpected anti-inflammatory role of glucan fractions. *PLoS One*. 2012;7(7):e40648.
doi: 10.1371/journal.pone.0040648
 58. Gao R, Kong C, Li H, *et al.* Dysbiosis signature of mycobiota in colon polyp and colorectal cancer. *Eur J Clin Microbiol Infect Dis*. 2017;36(12):2457-2468.
doi: 10.1007/s10096-017-3085-6
 59. Gao R, Kong C, Huang L, *et al.* Mucosa-associated microbiota signature in colorectal cancer. *Eur J Clin Microbiol Infect Dis*. 2017;36(11):2073-2083.
doi: 10.1007/s10096-017-3026-4
 60. Quéro L, Girard V, Pawtowski A, *et al.* Development and application of MALDI-TOF MS for identification of food spoilage fungi. *Food Microbiol*. 2019;81:76-88.
doi: 10.1016/j.fm.2018.05.001
 61. Dixon DM, Merz WG, Elliott HL, Macleay S. Experimental central nervous system phaeohyphomycosis following intranasal inoculation of *Xylohypha bantiana* in cortisone-treated mice. *Mycopathologia*. 1987;100(3):145-153.
doi: 10.1007/BF00437040
 62. Fothergill AW. Identification of dematiaceous fungi and their role in human disease. *Clin Infect Dis*. 1996;22(suppl 2):S179-S184.
doi: 10.1093/clinids/22.supplement_2.s179
 63. Brown GD. Innate antifungal immunity: the key role of phagocytes. *Annu Rev Immunol*. 2011;29:1-21.
doi: 10.1146/annurev-immunol-030409-101229
 64. Romani L. Immunity to fungal infections. *Nat Rev Immunol*. 2011;11(4):275-288.
doi: 10.1038/nri2939
 65. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet*. 2001;357(9255):539-545.
doi: 10.1016/S0140-6736(00)04046-0
 66. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436-444.
doi: 10.1038/nature07205
 67. Netea MG, Balkwill F, Chonchol M, *et al.* A guiding map for inflammation. *Nat Immunol*. 2017;18(8):826-831.
doi: 10.1038/ni.3790
 68. Rubin DC, Shaker A, Levin MS. Chronic intestinal inflammation: inflammatory bowel disease and colitis-associated colon cancer. *Front Immunol*. 2012;3:107.
doi: 10.3389/fimmu.2012.00107
 69. Baker AM, Cross W, Curtius K, *et al.* Evolutionary

- history of human colitis-associated colorectal cancer. *Gut*. 2019;68(6):985-995.
doi: 10.1136/gutjnl-2018-316191
70. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut*. 2001;48(4):526-535.
doi: 10.1136/gut.48.4.526
 71. Canavan C, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2006;23(8):1097-1104.
doi: 10.1111/j.1365-2036.2006.02854.x
 72. Lee TC, Huang YC, Lu YZ, Yeh YC, Yu LC. Hypoxia-induced intestinal barrier changes in balloon-assisted enteroscopy. *J Physiol*. 2018;596(15):3411-3424.
doi: 10.1113/JP275277
 73. Grivennikov SI, Wang K, Mucida D, *et al*. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. *Nature*. 2012;491(7423):254-258.
doi: 10.1038/nature11465
 74. Tanaka T, Kohno H, Suzuki R, *et al*. Dextran sodium sulfate strongly promotes colorectal carcinogenesis in Apc(Min/+) mice: inflammatory stimuli by dextran sodium sulfate results in development of multiple colonic neoplasms. *Int J Cancer*. 2006;118(1):25-34.
doi: 10.1002/ijc.21282
 75. Kosa P, Szabo R, Molinolo AA, Bugge TH. Suppression of Tumorigenicity-14, encoding matriptase, is a critical suppressor of colitis and colitis-associated colon carcinogenesis. *Oncogene*. 2012;31(32):3679-3695.
doi: 10.1038/onc.2011.545
 76. Goodman B, Gardner H. The microbiome and cancer. *J Pathol*. 2018;244(5):667-676.
doi: 10.1002/path.5047
 77. Song X, Gao H, Lin Y, *et al*. Alterations in the microbiota drive interleukin-17C production from intestinal epithelial cells to promote tumorigenesis. *Immunity*. 2014;40(1):140-152.
doi: 10.1016/j.immuni.2013.11.018
 78. Cremonesi E, Governa V, Garzon JFG, *et al*. Gut microbiota modulate T cell trafficking into human colorectal cancer. *Gut*. 2018;67(11):1984-1994.
doi: 10.1136/gutjnl-2016-313498
 79. Kortylewski M, Xin H, Kujawski M, *et al*. Regulation of the IL-23 and IL-12 balance by Stat3 signaling in the tumor microenvironment. *Cancer Cell*. 2009;15(2):114-123.
doi: 10.1016/j.ccr.2008.12.018
 80. Wang K, Kim MK, Di Caro G, *et al*. Interleukin-17 receptor a signaling in transformed enterocytes promotes early colorectal tumorigenesis. *Immunity*. 2014;41(6):1052-1063.
doi: 10.1016/j.immuni.2014.11.009
 81. Shaked H, Hofseth LJ, Chumanovich A, *et al*. Chronic epithelial NF- κ B activation accelerates APC loss and intestinal tumor initiation through iNOS up-regulation. *Proc Natl Acad Sci USA*. 2012;109(35):14007-14012.
doi: 10.1073/pnas.1211509109
 82. Tilstra JS, Robinson AR, Wang J, *et al*. NF- κ B inhibition delays DNA damage-induced senescence and aging in mice. *J Clin Invest*. 2012;122(7):2601-2612.
doi: 10.1172/JCI45785
 83. Greten FR, Eckmann L, Greten TF, *et al*. IKK β links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. *Cell*. 2004;118(3):285-296.
doi: 10.1016/j.cell.2004.07.013
 84. Schwitalla S, Fingerle AA, Cammareri P, *et al*. Intestinal tumorigenesis initiated by dedifferentiation and acquisition of stem-cell-like properties. *Cell*. 2013;152(1-2):25-38.
doi: 10.1016/j.cell.2012.12.012
 85. Kojima M, Morisaki T, Sasaki N, *et al*. Increased nuclear factor- κ B activation in human colorectal carcinoma and its correlation with tumor progression. *Anticancer Res*. 2004;24(2B):675-681.
 86. Karin M, Greten FR. NF- κ B: linking inflammation and immunity to cancer development and progression. *Nat Rev Immunol*. 2005;5(10):749-759.
doi: 10.1038/nri1703
 87. Terzić J, Grivennikov S, Karin E, Karin M. Inflammation and colon cancer. *Gastroenterology*. 2010;138(6):2101-2114.e5.
doi: 10.1053/j.gastro.2010.01.058
 88. Ramakrishnan SK, Zhang H, Ma X, *et al*. Intestinal non-canonical NF κ B signaling shapes the local and systemic immune response. *Nat Commun*. 2019;10(1):660.
doi: 10.1038/s41467-019-08581-8
 89. Schwitalla S, Ziegler PK, Horst D, *et al*. Loss of p53 in enterocytes generates an inflammatory microenvironment enabling invasion and lymph node metastasis of carcinogen-induced colorectal tumors. *Cancer Cell*. 2013;23(1):93-106.
doi: 10.1016/j.ccr.2012.11.014
 90. Sato Y, Takahashi S, Kinouchi Y, *et al*. IL-10 deficiency leads to somatic mutations in a model of IBD. *Carcinogenesis*. 2006;27(5):1068-1073.
doi: 10.1093/carcin/bgi327
 91. Filler SG, Pfunder AS, Spellberg BJ, Spellberg JP, Edwards JE Jr. *Candida albicans* stimulates cytokine production and

- leukocyte adhesion molecule expression by endothelial cells. *Infect Immun*. 1996;64(7):2609-2617.
doi: 10.1128/iai.64.7.2609-2617.1996
92. Galloway-Peña J, Iliev ID, McAllister F. Fungi in cancer. *Nat Rev Cancer*. 2024;24(5):295-298.
doi: 10.1038/s41568-024-00665-y
 93. Kaźmierczak-Siedlecka K, Dvořák A, Folwarski M, Dąca A, Przewłócka K, Makarewicz W. Fungal Gut Microbiota Dysbiosis and Its Role in Colorectal, Oral, and Pancreatic Carcinogenesis. *Cancers*. 2020;12(5):1326.
doi: 10.3390/cancers12051326
 94. Hold GL, Allen-Vercoe E. Gut microbial biofilm composition and organisation holds the key to CRC. *Nat Rev Gastroenterol Hepatol*. 2019;16(6):329-330.
doi: 10.1038/s41575-019-0148-4
 95. Yuan K, Xu H, Li S, *et al*. Intraneoplastic fungal dysbiosis is associated with colorectal cancer progression and host gene mutation. *EBioMedicine*. 2025;113:105608.
doi: 10.1016/j.ebiom.2025.105608
 96. Zhang W, Zhang H, Gao Y, Lei J, Suo C. Fungi and cancer: unveiling the complex role of fungal infections in tumor biology and therapeutic resistance. *Front Cell Infect Microbiol*. 2025;15:1596688.
doi: 10.3389/fcimb.2025.1596688
 97. Zong Z, Zhou F, Zhang L. The fungal mycobiome: a new hallmark of cancer revealed by pan-cancer analyses. *Signal Transduct Target Ther*. 2023;8(1):50.
doi: 10.1038/s41392-023-01334-6
 98. Bilal H, Khan MN, Khan S, *et al*. Fungal Influences on Cancer Initiation, Progression, and Response to Treatment. *Cancer Res*. 2025;85(3):413-423.
doi: 10.1158/0008-5472.CAN-24-1609
 99. Underhill DM, Iliev ID. The mycobiota: interactions between commensal fungi and the host immune system. *Nat Rev Immunol*. 2014;14(6):405-416.
doi: 10.1038/nri3684
 100. Wang T, Fan C, Yao A, *et al*. The Adaptor Protein CARD9 Protects against Colon Cancer by Restricting Mycobiota-Mediated Expansion of Myeloid-Derived Suppressor Cells. *Immunity*. 2018;49(3):504-514.e4.
doi: 10.1016/j.immuni.2018.08.018
 101. Bi L, Gojestani S, Wu W, *et al*. CARD9 mediates dectin-2-induced IkappaBalpha kinase ubiquitination leading to activation of NF-kappaB in response to stimulation by the hyphal form of Candida albicans. *J Biol Chem*. 2010;285(34):25969-25977.
doi: 10.1074/jbc.M110.131300
 102. Jia XM, Tang B, Zhu LL, *et al*. CARD9 mediates Dectin-1-induced ERK activation by linking Ras-GRF1 to H-Ras for antifungal immunity. *J Exp Med*. 2014;211(11):2307-2321.
doi: 10.1084/jem.20132349
 103. Veglia F, Sanseviero E, Gabrilovich DI. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. *Nat Rev Immunol*. 2021;21(8):485-498.
doi: 10.1038/s41577-020-00490-y
 104. Li F, Gao Y, Cheng W, Su X, Yang R. Gut fungal mycobiome: A significant factor of tumor occurrence and development. *Cancer Lett*. 2023;569:216302.
doi: 10.1016/j.canlet.2023.216302
 105. Bergmann H, Roth S, Pechloff K, *et al*. Card9-dependent IL-1 β regulates IL-22 production from group 3 innate lymphoid cells and promotes colitis-associated cancer. *Eur J Immunol*. 2017;47(8):1342-1353.
doi: 10.1002/eji.201646765
 106. Conche C, Greten FR. Fungi Enter the Stage of Colon Carcinogenesis. *Immunity*. 2018;49(3):384-386.
doi: 10.1016/j.immuni.2018.09.002
 107. Saijo S, Ikeda S, Yamabe K, *et al*. Dectin-2 recognition of alpha-mannans and induction of Th17 cell differentiation is essential for host defense against Candida albicans. *Immunity*. 2010;32(5):681-691.
doi: 10.1016/j.immuni.2010.05.001
 108. Zhu LL, Zhao XQ, Jiang C, *et al*. C-type lectin receptors Dectin-3 and Dectin-2 form a heterodimeric pattern-recognition receptor for host defense against fungal infection. *Immunity*. 2013;39(2):324-334.
doi: 10.1016/j.immuni.2013.05.017
 109. Graham LM, Gupta V, Schafer G, *et al*. The C-type lectin receptor CLECSF8 (CLEC4D) is expressed by myeloid cells and triggers cellular activation through Syk kinase. *J Biol Chem*. 2012;287(31):25964-25974.
doi: 10.1074/jbc.M112.384164
 110. Huang HR, Li F, Han H, *et al*. Dectin-3 Recognizes Glucuronoxylomannan of Cryptococcus neoformans Serotype AD and Cryptococcus gattii Serotype B to Initiate Host Defense Against Cryptococcosis. *Front Immunol*. 2018;9:1781.
doi: 10.3389/fimmu.2018.01781
 111. Tucey TM, Verma J, Harrison PF, *et al*. Glucose Homeostasis Is Important for Immune Cell Viability during Candida Challenge and Host Survival of Systemic Fungal Infection. *Cell Metab*. 2018;27(5):988-1006.e7.
doi: 10.1016/j.cmet.2018.03.019
 112. Wang T, Pan D, Zhou Z, *et al*. Dectin-3 Deficiency Promotes Colitis Development due to Impaired Antifungal

- Innate Immune Responses in the Gut. *PLoS Pathog.* 2016;12(6):e1005662.
doi: 10.1371/journal.ppat.1005662
113. Serafini N, Vossenhricht CA, Di Santo JP. Transcriptional regulation of innate lymphoid cell fate. *Nat Rev Immunol.* 2015;15(7):415-428.
doi: 10.1038/nri3855
 114. Mortha A, Chudnovskiy A, Hashimoto D, *et al.* Microbiota-dependent crosstalk between macrophages and ILC3 promotes intestinal homeostasis. *Science.* 2014;343(6178):1249288.
doi: 10.1126/science.1249288
 115. Hepworth MR, Fung TC, Masur SH, *et al.* Immune tolerance. Group 3 innate lymphoid cells mediate intestinal selection of commensal bacteria-specific CD4⁺ T cells. *Science.* 2015;348(6238):1031-1035.
doi: 10.1126/science.aaa4812
 116. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. *Nat Rev Clin Oncol.* 2017;14(7):399-416.
doi: 10.1038/nrclinonc.2016.217
 117. Na YR, Stakenborg M, Seok SH, Matteoli G. Macrophages in intestinal inflammation and resolution: a potential therapeutic target in IBD. *Nat Rev Gastroenterol Hepatol.* 2019;16(9):531-543.
doi: 10.1038/s41575-019-0172-4
 118. Bowden SD, Rowley G, Hinton JC, Thompson A. Glucose and glycolysis are required for the successful infection of macrophages and mice by *Salmonella enterica* serovar typhimurium. *Infect Immun.* 2009;77(7):3117-3126.
doi: 10.1128/IAI.00093-09
 119. Li C, Wang Y, Li Y, *et al.* HIF1 α -dependent glycolysis promotes macrophage functional activities in protecting against bacterial and fungal infection. *Sci Rep.* 2018;8(1):3603.
doi: 10.1038/s41598-018-22039-9
 120. Harrison C. Cancer: IL-22: linking inflammation and cancer. *Nat Rev Drug Discov.* 2013;12(7):504.
doi: 10.1038/nrd4065
 121. Kirchberger S, Royston DJ, Boulard O, *et al.* Innate lymphoid cells sustain colon cancer through production of interleukin-22 in a mouse model. *J Exp Med.* 2013;210(5):917-931.
doi: 10.1084/jem.20122308
 122. Chan IH, Jain R, Tessmer MS, *et al.* Interleukin-23 is sufficient to induce rapid de novo gut tumorigenesis, independent of carcinogens, through activation of innate lymphoid cells. *Mucosal Immunol.* 2014;7(4):842-856.
doi: 10.1038/mi.2013.101
 123. Kryczek I, Lin Y, Nagarsheth N, *et al.* IL-22⁺CD4⁺ T cells promote colorectal cancer stemness via STAT3 transcription factor activation and induction of the methyltransferase DOT1L. *Immunity.* 2014;40(5):772-784.
doi: 10.1016/j.immuni.2014.03.010
 124. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet.* 2019;394(10207):1467-1480.
doi: 10.1016/S0140-6736(19)32319-0
 125. Holash J, Davis S, Papadopoulos N, *et al.* VEGF-Trap: a VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci USA.* 2002;99(17):11393-11398.
doi: 10.1073/pnas.172398299
 126. Cremolini C, Loupakis F, Masi G, *et al.* FOLFOXIRI or FOLFOXIRI plus bevacizumab as first-line treatment of metastatic colorectal cancer: a propensity score-adjusted analysis from two randomized clinical trials. *Ann Oncol.* 2016;27(5):843-849.
doi: 10.1093/annonc/mdw052
 127. Kuboki Y, Nishina T, Shinozaki E, *et al.* TAS-102 plus bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE): an investigator-initiated, open-label, single-arm, multicentre, phase 1/2 study. *Lancet Oncol.* 2017;18(9):1172-1181.
doi: 10.1016/S1470-2045(17)30425-4
 128. Terme M, Pernot S, Marcheteau E, *et al.* VEGFA-VEGFR pathway blockade inhibits tumor-induced regulatory T-cell proliferation in colorectal cancer. *Cancer Res.* 2013;73(2):539-549.
doi: 10.1158/0008-5472.CAN-12-2325
 129. Allen JE, El-Deiry WS. Oxaliplatin uses JNK to restore TRAIL sensitivity in cancer cells through Bcl-xL inactivation. *Gastroenterology.* 2011;141(2):430-434.
doi: 10.1053/j.gastro.2011.06.026
 130. Allen JE, Kringsfeld G, Mayes PA, *et al.* Dual inactivation of Akt and ERK by TIC10 signals Foxo3a nuclear translocation, TRAIL gene induction, and potent antitumor effects. *Sci Transl Med.* 2013;5(171):171ra17.
doi: 10.1126/scitranslmed.3004828
 131. Wagner J, Kline CL, Zhou L, *et al.* Dose intensification of TRAIL-inducing ONC201 inhibits metastasis and promotes intratumoral NK cell recruitment. *J Clin Invest.* 2018;128(6):2325-2338.
doi: 10.1172/JCI96711
 132. D'Souza N, Georgiou Delisle T, Chen M, Benton S, Abulafi M; NICE FIT Steering Group. Faecal immunochemical test is superior to symptoms in predicting pathology in patients with suspected colorectal cancer symptoms referred on a 2WW pathway: a diagnostic accuracy study. *Gut.* 2021;70(6):1130-1138.

- doi: 10.1136/gutjnl-2020-321956
133. Tsai WS, You JF, Hung HY, *et al.* Novel Circulating Tumor Cell Assay for Detection of Colorectal Adenomas and Cancer. *Clin Transl Gastroenterol.* 2019;10(10):e00088.
doi: 10.14309/ctg.0000000000000088
 134. Dasari A, Morris VK, Allegra CJ, *et al.* ctDNA applications and integration in colorectal cancer: an NCI Colon and Rectal-Anal Task Forces whitepaper. *Nat Rev Clin Oncol.* 2020;17(12):757-770.
doi: 10.1038/s41571-020-0392-0
 135. Bolhaqueiro ACF, Ponsioen B, Bakker B, *et al.* Ongoing chromosomal instability and karyotype evolution in human colorectal cancer organoids. *Nat Genet.* 2019;51(5):824-834.
doi: 10.1038/s41588-019-0399-6
 136. Bruun J, Kryeziu K, Eide PW, *et al.* Patient-Derived Organoids from Multiple Colorectal Cancer Liver Metastases Reveal Moderate Intra-patient Pharmacotranscriptomic Heterogeneity. *Clin Cancer Res.* 2020;26(15):4107-4119.
doi: 10.1158/1078-0432.CCR-19-3637
 137. Roper J, Tammela T, Cetinbas NM, *et al.* Corrigendum: In vivo genome editing and organoid transplantation models of colorectal cancer and metastasis. *Nat Biotechnol.* 2017;35(12):1211.
doi: 10.1038/nbt1217-1211a
 138. Narasimhan V, Wright JA, Churchill M, *et al.* Medium-throughput Drug Screening of Patient-derived Organoids from Colorectal Peritoneal Metastases to Direct Personalized Therapy. *Clin Cancer Res.* 2020;26(14):3662-3670.
doi: 10.1158/1078-0432.CCR-20-0073
 139. Cattaneo CM, Dijkstra KK, Fanchi LF, *et al.* Tumor organoid-T-cell coculture systems. *Nat Protoc.* 2020;15(1):15-39.
doi: 10.1038/s41596-019-0232-9
 140. Dijkstra KK, Cattaneo CM, Weeber F, *et al.* Generation of Tumor-Reactive T Cells by Co-culture of Peripheral Blood Lymphocytes and Tumor Organoids. *Cell.* 2018;174(6):1586-1598.e12.
doi: 10.1016/j.cell.2018.07.009
 141. Li J, Ma X, Chakravarti D, Shalapour S, DePinho RA. Genetic and biological hallmarks of colorectal cancer. *Genes Dev.* 2021;35(11-12):787-820.
doi: 10.1101/gad.348226.120
 142. Kaźmierczak-Siedlecka K, Daca A, Fic M, van de Wetering T, Folwarski M, Makarewicz W. Therapeutic methods of gut microbiota modification in colorectal cancer management - fecal microbiota transplantation, prebiotics, probiotics, and synbiotics. *Gut Microbes.* 2020;11(6):1518-1530.
doi: 10.1080/19490976.2020.1764309
 143. Shamekhi S, Lotfi H, Abdolalizadeh J, Bonabi E, Zarghami N. An overview of yeast probiotics as cancer biotherapeutics: possible clinical application in colorectal cancer. *Clin Transl Oncol.* 2020;22(8):1227-1239.
doi: 10.1007/s12094-019-02270-0
 144. Wu X, Xia Y, He F, Zhu C, Ren W. Intestinal mycobiota in health and diseases: from a disrupted equilibrium to clinical opportunities. *Microbiome.* 2021;9(1):60.
doi: 10.1186/s40168-021-01024-x
 145. Greathouse KL, Wyatt M, Johnson AJ, *et al.* Diet-microbiome interactions in cancer treatment: Opportunities and challenges for precision nutrition in cancer. *Neoplasia.* 2022;29:100800.
doi: 10.1016/j.neo.2022.100800
 146. Makhouloufi H, Pinon A, Champavier Y, *et al.* In Vitro Antiproliferative Activity of Echinulin Derivatives from Endolichenic Fungus *Aspergillus* sp. against Colorectal Cancer. *Molecules.* 2024;29(17):4117.
doi: 10.3390/molecules29174117
 147. Varlı M, Lee EY, Park SY, *et al.* An Endolichenic Fungi-Derived Fatty Acid, cis-10-Nonadecenoic acid, Suppresses Colorectal Cancer Stemness. *Biomol Ther.* 2025;33(5):842-851.
doi: 10.4062/biomolther.2025.062
 148. Yang X, Bao Q, Xiao S, *et al.* Anti-colorectal cancer bioactive metabolites from endophytic fungi of *Pyrola* spp. targeting p-ATM/P53 pathway driven by in vitro experiments and network pharmacology. *Fitoterapia.* 2025;187:106906.
doi: 10.1016/j.fitote.2025.106906
 149. Lai CT, Hsieh YH, Wang YH, *et al.* Trichodermin, an endophytic fungal sesquiterpene, suppresses colorectal cancer cell migration and invasion by targeting the PKC-ERK-Sp1-CTSV axis. *Phytomedicine.* 2025;145:157063.
doi: 10.1016/j.phymed.2025.157063
 150. de Graaff P, Berrevoets C, Rösch C, *et al.* Curdlan, zymosan and a yeast-derived β -glucan reshape tumor-associated macrophages into producers of inflammatory chemo-attractants. *Cancer Immunol Immunother.* 2021;70(2):547-561.
doi: 10.1007/s00262-020-02707-4
 151. Lee WS, Chen RJ, Wang YJ, *et al.* In vitro and in vivo studies of the anticancer action of terbinafine in human cancer cell lines: G0/G1 p53-associated cell cycle arrest. *Int J Cancer.* 2003;106(1):125-137.
doi: 10.1002/ijc.11194
 152. Wu CH, Jeng JH, Wang YJ, *et al.* Antitumor effects of miconazole on human colon carcinoma xenografts in nude mice through induction of apoptosis and G0/G1 cell cycle arrest. *Toxicol Appl Pharmacol.* 2002;180(1):22-35.

doi: 10.1006/taap.2002.9352

153. Deng H, Huang L, Liao Z, Liu M, Li Q, Xu R. Itraconazole inhibits the Hedgehog signaling pathway thereby inducing autophagy-mediated apoptosis of colon cancer cells. *Cell Death Dis.* 2020;11(7):539.

doi: 10.1038/s41419-020-02742-0

154. Forgue-Lafitte ME, Coudray AM, Fagot D, Mester J. Effects of ketoconazole on the proliferation and cell cycle of human cancer cell lines. *Cancer Res.* 1992;52(24):6827-6831.
155. Chen RJ, Lee WS, Liang YC, *et al.* Ketoconazole induces G0/G1 arrest in human colorectal and hepatocellular carcinoma cell lines. *Toxicol Appl Pharmacol.* 2000;169(2):132-141.

doi: 10.1006/taap.2000.9062

156. Ho YS, Duh JS, Jeng JH, *et al.* Griseofulvin potentiates antitumorigenesis effects of nocodazole through induction of apoptosis and G2/M cell cycle arrest in human colorectal cancer cells. *Int J Cancer.* 2001;91(3):393-401.

doi: 10.1002/1097-0215(200002)9999:9999<::aid-ijc1070>3.0.co;2-#

157. Liu X, Sun K, Feng L, *et al.* Review of the Bioactivities and Mechanisms of Fungus Extracts and Compounds in Colon Cancer. *Crit Rev Eukaryot Gene Expr.* 2025;35(1):37-48.

doi: 10.1615/CritRevEukaryotGeneExpr.2024054308