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REVIEW

The role of fungi in the diagnosis of colorectal cancer

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ABSTRACT

Colorectal cancer (CRC) is a prevalent tumour with high morbidity rates worldwide, and its incidence among younger populations is rising. Early diagnosis of CRC can help control the associated mortality. Fungi are common microorganisms in nature. Recent studies have shown that fungi may have a similar association with tumours as bacteria do. As an increasing number of tumour-associated fungi are discovered, this provides new ideas for the diagnosis and prognosis of tumours. The relationship between fungi and colorectal tumours has also been recently identified by scientists. Therefore, this paper describes the limitations and prospects of the application of fungi in diagnosing CRC and predicting CRC prognosis.

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1. Introduction

Colorectal cancer (CRC) is a heterogeneous disease characterised by genetic and epigenetic abnormalities (Ashktorab and Brim 2022; Joanito et al. 2022). It can occur in any part of the colon or rectum and spread to other tissues and organs through lymphatic circulation, blood circulation, and direct transmission (Galindo-Pumarino et al. 2021). Currently, CRC is the second leading cause of cancer-related mortality worldwide (Sung et al. 2021). Furthermore, the burden of CRC in many countries, including China, which has a large population (Collaborators GBDCC 2022; Qu et al. 2022), has increased each year and is influenced by lifestyle (Abu-Ghazaleh et al. 2021; Qin et al. 2022) and other factors. There is evidence that the incidence rate and mortality of early-onset colorectal neoplasms (i.e. colorectal neoplasms diagnosed in patients under 50 years old) are increasing worldwide (O'Sullivan et al. 2022; Patel et al. 2022). Fortunately, the development of CRC is not rapid (Yelorda et al. 2021). A population-based global multicenter study suggests that when the proportion of early-stage CRC among cases identified by screening is large, patient prognosis is better (Cardoso et al. 2022). Therefore, more attention should be given to the early screening of colorectal tumours.

Endoscopy (including colonoscopy and sigmoidoscopy), stool tests [including faecal occult blood test (FOBT), faecal immunochemical test (FIT), and FIT-DNA tests], and plasma SEPT9 gene methylation are widely used in clinical practice as prevention strategies and screening programmes for CRC, as supported by scholars (Kanth and Inadomi 2021; Li et al. 2021). However, it is worth noting that despite the high false positive rate of non-invasive tests currently used in clinical practice, patient compliance with undergoing non-invasive tests is better than that for invasive tests in the population (Ballester et al. 2022). A study on the correlation between risk factors and intervention strategies for CRC demonstrated that non-invasive testing is more cost-efficient for the general public and more accessible in primary care settings, reducing the risk of death due to CRC (Carethers and Doubeni 2020). Recently, a joint European multi-association guideline recommended the use of FIT to prioritise the treatment of patients with clinical characteristics of CRC in primary care facilities (Monahan et al. 2022). However, retrospective studies have also confirmed the role of endoscopy. A nationwide cohort study in South Korea suggests that colonoscopy can lower the risk of CRC more than FIT (Sung et al. 2022). These studies not only prompt us to improve visual research strategies but also urge us to identify other non-

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invasive inspection strategies with higher sensitivity and specificity (Chung et al. 2022).

Fungi and bacteria are widely distributed in nature and are also commonly present in the human oral cavity (Mukherjee and Leys 2021; Cheung et al. 2022), stomach (Liu et al. 2022), and intestines (Fassarella et al. 2021; Nel Van Zyl et al. 2022). The intestinal flora, which is an important component of the human intestinal microbiota, has been shown to have a profound impact on CRC, as evidenced by numerous studies (Kvaerner et al. 2021; Rebersek 2021; Clay et al. 2022; Shi et al. 2023). In recent years, an increasing number of tumour-associated fungi have been discovered, which provides new ideas for the diagnosis and prognosis of tumours.

The purpose of this review is to discuss recent advances in the diagnosis of CRC by fungi.

2. Fungi and tumours

2.1. Is fungi related to the occurrence and development of gastrointestinal tumors?

Fungi, bacteria, and viruses are ubiquitous microorganisms. Investigating the relationship between microorganisms and gastrointestinal tumours has been the subject of numerous studies. Many studies have demonstrated that bacterial infections, such as *Helicobacter pylori* infections, are linked to the development of gastrointestinal tumours such as gastric cancer (Smyth et al. 2020), while other studies have found that *Fusobacterium nucleatum* infection is associated with CRC (Clay et al. 2022; Wang and Fang 2023). Some researchers have linked Epstein-Barr virus (EBV) to stomach cancer (Zheng et al. 2022; Noh et al. 2023). Moreover, several viruses have been described in the context of CRC, such as EBV, human tumour virus (HPV), John Cunningham virus (JCV), and bacteriophages (Marongiu and Allgayer 2022; Sarantis et al. 2022).

In the field of fungi research, earlier investigators speculated that the fungal flora may be associated with or even promote pancreatic cancer (Dambuza and Brown 2019; Hindson 2019). Building on this, additional researchers have further found that fungi can promote IL-33 secretion and type 2 immune responses that lead to the development and progression of pancreatic cancer (Alam et al. 2022). A recent analysis of the cancerous and adjacent noncancerous tissues of 45 patients with gastric cancer in Shenyang, China, revealed that *Candida* species, especially *Candida albicans* (*C. albicans*), are enriched in gastric cancer tissue (Zhong et al. 2021). However, some scholars have summarised previous studies on the correlation between the gastric microbiota and gastric cancer and believe that it is still uncertain whether there is a correlation between the diversity of the gastric microbiota and the transformation of healthy gastric mucosa into gastric cancer (Stewart et al. 2020).

A population study has shown that patients with confirmed CRC who receive the antifungal agent terbinafine have a lower risk of death (hazard ratio = 0.50) and metastasis (hazard ratio = 0.44) than patients who do not take terbinafine (Hu et al. 2022). The mouse experiments conducted during the same project also demonstrated that terbinafine can inhibit CRC by influencing fungi (Hu et al. 2022). The researchers found significant changes in the proportion of species in the fungal community composition of the mice treated with terbinafine (Hu et al. 2022). Another mouse trial also demonstrated that terbinafine can be used synergistically with other anticancer drugs to treat CRC (Li et al. 2022). Researchers have proposed that disorders of the intestinal flora, particularly the fungal flora, promote CRC by affecting intestinal barrier function (Li et al. 2022). In addition, the two animal experiments described above indicated that terbinafine can directly inhibit the proliferation of CRC cells by targeting squalene epoxidase, a rate-limiting enzyme in cholesterol biosynthesis (Hu et al. 2022; Li et al. 2022). Mouse experiments further indicated the relationship between fungi and gastrointestinal tumours. Other researchers have found that treating Dectin-3 deficient mice with fluconazole prevented colitis-associated colon cancer (CAC) progression. They also observed an increase in *C. albicans* abundance in Dectin-3-deficient mice, which subsequently promoted CAC development (Zhu et al. 2021). These findings provide a foundation for further exploring the relationship between *C. albicans* and CRC.

2.2. Candida and gastrointestinal tumours

Candida is the most prevalent and abundant fungus in the gastrointestinal tract and on other mucosal surfaces in humans and several other animals (Perez 2021). *C. albicans* is the main cause of candidiasis

worldwide (Bilal et al. 2022). Other common disease-related *Candida* species, such as *Candida parapsilosis* (Branco et al. 2023), *Candida tropicalis* (Xu 2021), and *Candida auris* (Bing et al. 2022; Du et al. 2022), are also concerning. Recent research has revealed that digestive tract tumours (including gastric and intestinal cancers) contain high levels of *C. albicans*, which differs from other nondigestive tract tumours (Dohlman et al. 2022). In CRC, tumour metastasis and poor prognosis are more likely to occur as the *C. albicans* content increases. We need to further explore the relationship between *Candida* and CRC in greater detail.

Recently, some studies have shown that inflammatory genes are novel predictive markers of CRC, highlighting the role of inflammation in CRC (Schmitt and Greten 2021). Researchers have found that in gastrointestinal tumours with a high concentration of *Candida*, inflammatory responses can promote colonisation by *Candida*, while *Candida* itself can maintain an inflammatory environment, which is associated with the activation of inflammatory signalling pathways mediated by the proinflammatory factor IL-1 and neutropenia (Dohlman et al. 2022). In another study, it was discovered that *C. albicans* could activate glycolysis and IL-7 production in macrophages, suggesting that the fungus is associated with the inflammatory response of macrophages (Zhu et al. 2021). Some experiments in mice have shown that strains of the fungi that produce candidalysin induce an increase in the number of interleukin-17A-producing T helper cell (Th 17 cell) cells and other immune cells involved in inflammation, such as neutrophils (Li et al. 2022). Other studies have reported that *C. tropicalis* induces CRC by activating NLRP3 inflammatory bodies through glycogen metabolism-dependent glycolysis and JAK-STAT1 signalling pathways (Xu et al. 2022). Additionally, there is growing evidence that patients undergoing cholecystectomy may be at higher risk of postoperative gastrointestinal complications (such as CRC), which may be related to *Candida glabrata* (Xu et al. 2022). It can be suspected that *Candida* in the cells of CRC tumours participates in the occurrence and development of CRC by causing inflammation.

Several studies have confirmed the potential link between *Candida* infection and oral squamous cell carcinoma (OSCC), although the specific mechanism has not yet been fully defined (Stasiewicz and Karpinski 2022). After a comprehensive analysis of the spatial distribution of microorganisms in tissue samples of OSCC and CRC (Galeano Nino et al. 2022), it was speculated that the distribution of microbial populations within tumours was not random. In contrast, the microbial community exhibits a highly organised structure with immune and epithelial functions that promote cancer progression.

There is not much evidence to prove that *Candida* directly causes gastrointestinal tumours, but it appears to work through the host's immune system and intestinal epithelial function.

2.3. Fungi and inflammatory bowel disease (IBD)

IBD is a high-risk factor for CRC (Shah and Itzkowitz 2022). Recent studies have proposed the role of fungi in IBD (Iliev and Cadwell 2021). Several studies using ITS2 sequencing to analyse the fungal composition of the faecal microbiota have identified *Candida* species as the main genus responsible for IBD (Wang et al. 2021, 2023). In addition, some studies have revealed that intestinal fungi promote the occurrence of IBD (Krawczyk et al. 2023), which may be related to the Dectin-1- SYK-CARD9 /NF-κB signalling pathway (Zajta et al. 2021; Yu et al. 2023). More interestingly, recent observations indicate the involvement of the Dectin-1-PGE2-IL-22BP axis in regulating intestinal tumorigenesis. Dectin-1, encoded by the Clec7a gene, is known to play important roles in host defence against fungi and immune homoeostasis in the intestine and will likely be a therapeutic target in the future (Tang et al. 2023). Therefore, the assessment of fungal-related biomarkers may also help identify risk factors for CRC in combination with other non-invasive examination methods (Pratt et al. 2022).

3. Fungal signatures of CRC identified using different samples

3.1. Fungal signatures in tumours

In previous work, Nejman and other scientists discovered the presence of metabolically active, immunologically active, intracellular, and cancer type-specific bacteria in tumour tissue. Most of these bacteria impact cancer treatment and are therefore included in the new cancer signature (Greathouse et al. 2020; Nejman et al. 2020). Due to the low abundance of fungi in tumours and the difficulty of sample purification, there is a lack of comprehensive reporting on the

fungal community in various tumours. More recently, Narunsky-Haziza et al. (2022) drew on the work of Nejman et al. to compare and analyse fungal communities with matched bacterial groups and immune groups, further suggesting the presence of not only bacteria but also fungi in tumours and highlighting fungi as potential biomarkers for tumour diagnosis. The study revealed that fungi and bacteria have similarities, with most hiding within cancer cells or immune cells inside tumours. Therefore, fungi and their metabolism may affect not only cancer cells but also immune cells and their activity, which may provide us with new ideas for targeted treatment. The discovery of specific fungi in tumours can therefore complement biopsy tests, not only for disease diagnosis but also to determine the origin of tumours, identify tumour subtypes and guide subsequent treatment. In addition, it is important to be aware of interference from common laboratory fungal contamination in the results of oncological pathology (the diseases that may require differential diagnosis are shown in Figure 1).

3.2. Fungi in blood

3.2.1. Other CRC markers in bodily fluids

Liquid biopsy analysis of circulating biomarkers, such as circulating tumour DNA (ctDNA) (Nassar et al. 2021) and exosomes (Elmallah et al. 2022; Zheng et al. 2022), for CRC have also received increasing attention (Mauri et al. 2022; Zhou et al. 2022). These biomarkers have the advantage of better-predicting disease progression in addition to being useful for screening. Previous studies have proposed that the microbial cell-free DNA (mcfDNA) can be used to distinguish individuals with some tumours from healthy populations, and this biomarker may enable CRC screening and early diagnosis (Ajami and Wargo 2020; Poore et al. 2020; Xiao et al. 2021). The SEPT9 gene methylation test has also been approved by the United States Food and Drug Administration (US FDA) for screening for CRC in the US (Kamel et al. 2022).

3.2.2. Fungal signatures in blood

In a pan-cancer analysis, fungi from 17,401 samples from patients with 35 types of cancer were investigated, and the first pan-cancer mycology atlas was generated (Narunsky-Haziza et al. 2022). By testing blood samples from cancer patients, researchers have found that specific fungal and bacterial DNA exists in human blood. These detected fungal DNA components are only related to specific types of tumours and have no clear relationship with the tumour stage. This means that we may be able to detect CRC in individuals who do not exhibit clinical symptoms or even adenoma before detecting the cancer stage. Aberrant ctDNA methylation and exosomal microRNA markers also have promising

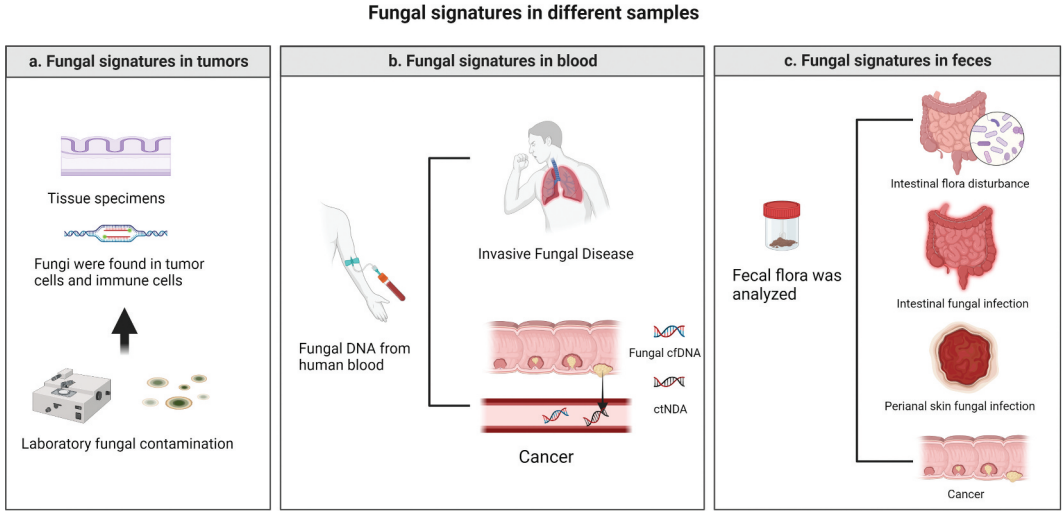

Figure 1. Diseases that require differential diagnosis. (a) Laboratory fungal infections should be considered during biopsy of tumour tissue. (b) Tumor patients are often immunosuppressed after chemotherapy and radiotherapy and are prone to invasive mycosis. Therefore, fungi and fungal antibodies can also be found in the blood. (c) If a change in faecal fungal flora abundance is found, in addition to considering CRC, intestinal flora disorders, fungal intestinal infections, and perianal skin infections should also be considered.

applications in the early detection of colorectal cancer, and mcfDNA can be combined with these liquid biopsy methods for colorectal cancer screening (Poore et al. 2020; Zhao et al. 2020). Another advantage of assessing microbial DNA-based cancer detection is that there is a considerable diversity of microbial DNA throughout different parts of the body (Narunsky-Haziza et al. 2022). Previous work suggests that it may be possible to accurately detect the presence and type of cancer at an early stage by using fungal signature information in the blood.

3.2.3. Fungi and invasive fungal disease (IFD)

Fungi are a ubiquitous class of organisms, and some can cause infections in humans. IFD, also known as invasive fungal infection (IFI), refers to disease-causing fungal invasion of human tissues and blood (Bassetti et al. 2021; Lass-Florl et al. 2021). The presence of new anticancer therapies has led to an increase in the number of immunosuppressed individuals, resulting in a higher diversity of fungal infections and an increase in the number of patients with IFD associated with cancer (Vehreschild et al. 2021; Rayens et al. 2022). *Candida* (McCarty et al. 2021) and *Aspergillus* (Foppiano Palacios and Spichler Moffarah 2021) are commonly identified causative pathogens in IFD.

However, the identities of pathogens that commonly cause IFD can overlap with specific fungal species found in CRC tissue. Consequently, there is a risk of false positive diagnosis when fungal biomarkers in the blood are used to differentiate and diagnose IFD and CRC patients. Therefore, to improve the accuracy of diagnosis, we may need to combine other biomarkers and auxiliary methods.

3.3. Fungal signatures in faeces

3.3.1. Fecal examination

(1) **The FOBT** uses chemical analyses to detect trace amounts of blood in faeces that are invisible to the naked eye. Its sensitivity in the detection of CRC and precancerous lesions is low and influenced by diet and drugs. In clinical practice, chemical, and immune methods are commonly used in combination (Kaur et al. 2023). (2) **The FIT** is used to detect human haemoglobin in faecal samples through specific antibodies (Randel et al. 2021). (3) **Multitarget faecal DNA** for detecting DNA mutations in faecal exfoliated cells can also be used in conjunction with FIT (Anderson et al. 2022; Xu et al. 2022).

3.3.2. Fungal signatures and CRC

Several teams from Shanghai recently collaborated on a project involving shotgun metagenomic sequencing of faecal samples from CRC patients in multiple geographical regions, identifying four kingdoms of microorganisms, including bacteria, fungi, archaea, and viruses (Liu et al. 2022). The random forest analysis they performed revealed that the model comprising only fungal markers had a higher performance in predicting CRC diagnosis than the model comprising only bacterial markers in two datasets. Notably, the combined analysis of bacterial and fungal markers showed greater accuracy than the analysis of only fungal or bacterial markers, providing solid evidence of the value of the non-invasive assessment of faecal CRC biomarkers. Simultaneously, another team of researchers analysed a faecal macrogenetic dataset obtained from 1,329 patients (454 CRC patients, 350 adenoma patients, and 525 healthy individuals) and found that the combined analysis of bacterial and fungal biomarkers more accurately distinguished between CRC patients and healthy individuals than the analysis of only bacterial biomarkers, increasing the area under the curve by 1.44% to 10.60%. Additionally, *in vivo* and *in vitro* experiments confirmed the association of *Aspergillus* with CRC occurrence (Lin et al. 2022). Previous scholars have also described multikingdom diagnostic models (Dickson 2019). These studies suggest that the combined analysis of bacterial and fungal biomarkers has considerable potential for the early screening of CRC. However, the current concept of using fungal biomarkers in stool is solely based on the understanding of the relationship between the intestinal microbiota and CRC and does not consider the relationship between tumour type-specific intracellular fungi and the occurrence of CRC.

Faecal microbiota transplantation (FMT), which is a method for treating diseases by transferring healthy faecal microbiota to the recipient, is one potential method for managing CRC. Recent studies have emphasised the role of viruses and fungi, such as bacteriophages and *Candida*, in addition to bacteria, in the efficacy of FMT (Shen et al. 2021; Lam et al. 2022). Furthermore, several studies suggest that modulating the intestinal microbiota through FMT can

prevent and treat CRC (Chang et al. 2020; Huang et al. 2022). This again highlights the relationship between the intestinal microbiota and CRC.

3.3.3. Models combining bacterial and fungal features

New research urges us to reconsider the role of interactions between bacteria and fungi in CRC, as this concept has been repeatedly proposed (Lapiere and Richard 2022). Studies have demonstrated that interactions between bacteria and fungi can induce CRC pathogenesis by activating D-arginine and D-ornithine pathways and butanoate metabolism (Liu et al. 2022). Furthermore, it has been suggested that *Lactobacillus rhamnosus* is associated with the pathogenicity of the specific fungus *C. albicans* found in CRC tumour tissue (Alonso-Roman et al. 2022). In a longitudinal study of 178 premature infants, important interactions between bacteria and fungi were found in the gut beginning at birth (Rao et al. 2021). However, some studies suggest that the interaction between bacteria and fungi elicits limited effects, such as in the oral cavity (Cheung et al. 2022). These studies suggest that relationships between bacteria and fungi do not solely involve symbiosis, competition, or coordination and that the mechanisms and targets of action require further investigation. The current state of the research suggests that we need more clinical evidence (the evaluation of some faecal microbial markers is provided in Table 1).

4. Techniques for detecting fungi

With advances in technology for assessing the microbiome, such as metagenomics, metabolomics, metaproteomics, and metatranscriptomics, a better understanding of intratumoral fungi has emerged (Guo et al. 2021; Lind and Pollard 2021; Dohlman et al. 2022; Ko et al. 2022; Kong and Machida 2022; Narunsky-Haziza et al. 2022; Caesar et al. 2023). In addition to identifying species, these techniques can provide insights into the metabolites of fungi. Analysing fungal metabolites can reduce the influence of dead microbes better than analysing fungal genes. However, metagenomic sequencing technology is more expensive than traditional amplicon sequencing technology. For fungi, we can use 18S rRNA gene amplicon sequencing and internal transcribed spacer (ITS) sequencing (Debeljak and Baltar 2023; Moreira et al. 2023).

Identifying fungi is generally difficult, but detecting fungi in tumours is also a challenge. There is no single way to detect all fungi. In addition, fungi in tumours are present in such small numbers that they are even more difficult to detect than bacteria in tumours, which makes identifying tumours through fungi a considerable challenge. For the detection of fungi, a microbial detection method with a low detection threshold is needed. Fluorescence in situ hybridisation (FISH) is a popular microbial detection technique (Liu et al. 2021; Sampaio et al. 2022). To detect intestinal mucosal microorganisms, CLAS-fish, BONCAT-FISH, HiPR-FISH, seq-FISH, and other techniques have been developed (Barbosa et al. 2023). However, we need to develop new probes for a wider range of fungi (Petriglieri et al. 2022). Narunsky-Haziza et al. (2022) integrated four staining methods with varying sensitivity and specificity in the above experiments to improve the accuracy and efficiency of fungal detection, mainly based on Grocott's methenamine silver (GMS) stain, cell wall antibodies, and autoantibodies, and FISH. Notably, the origin of

Table 1. Evaluation of some colorectal markers associated with microorganisms.

Biomarker panel	AUC (%)	Country
14 fungi (Coker et al. 2019)	93	Multicounty
	82	China
	74	Europe
12 bacteria plus FOBT (Yuan et al. 2021)	92	China
5 bacteriophages (Shen et al. 2021)	86	China, Austria, and Japan
	78	China and Italy
4 bacteria plus FIT (Liang et al. 2020)	90	Asia
6 bacteria and 11 metabolites (Coker et al. 2022)	94	China
11 bacteria, 4 fungi, and 1 archaea (Liu et al. 2022)	83	Multicounty
5 fungi and 9 bacteria	90	Multicounty
12 bacteria (Lin et al. 2022)	83	Multicounty

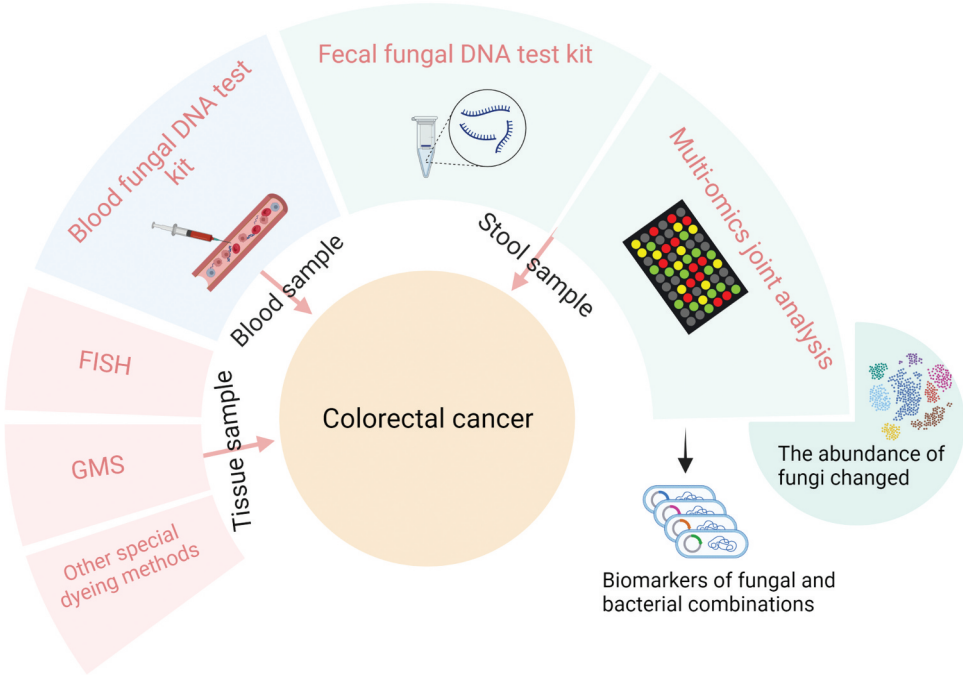

Figure 2. Different samples used for the diagnosis of colorectal cancer.

the fungus in the tumour is also unclear. Scientists have explored the possible origin of bacteria in tumours from mucosal sites, normal adjacent tissues, and the circulatory system (Xie et al. 2022). Whether fungi come from places similar to the origins of bacteria still needs to be explored. Because the mechanisms through which the fungus circulates throughout the body and within specific organs and tissues remain unclear, technical limitations and a lack of understanding have hindered the specific detection and localisation of microorganisms within tumours (Strickland and Shi 2021).

The gold standard for the diagnosis of fungal infections remains the visualisation of fungal elements in samples from usually sterile sites (Borman et al. 2022). Although metagenomics has shown great promise in the study of both fungal infection and the fungi associated with tumours, microscopic examination and direct culture are still very important methods for obtaining evidence (Kamau and Yang 2023). At present, there is no real indicator with independent diagnostic value, so we tend to use a combination of multiple methods to improve the accuracy of fungal diagnosis. Therapeutic approaches such as FMT continue to inspire us to study the aspects of tumour-associated microorganisms in pure cultures, which remains important because the results of *in vitro* and *in vivo* experiments based on microbial cultures not only provide more reliable evidence but can also be used to support further treatment (Yu et al. 2023).

Moreover, because fungi are prevalent in nature, which makes sample contamination a serious problem, researchers must be very careful to filter out any potential contamination from the results (Narunsky-Haziza et al. 2022). In the study of fungi in tumours, contamination by host DNA and environmental microbial DNA is also an obstacle. We can consider establishing and using a contaminant-controlled analysis framework (Zozaya-Valdes et al. 2021). Dohlman et al. developed a decontamination algorithm that can remove contamination from The Cancer Genome Atlas (TCGA) data (Dohlman et al. 2021, 2022).

Overall, to date, there are no experimental methods that are both reliable and cost-effective for detecting fungi (Figure 2).

5. Conclusions and outlook

Numerous studies have investigated the role of the tumour microbiota in tumour formation, development, and treatment, but comparatively limited attention has been given to studies on fungi in tumours. This review aims to address this gap and suggest the potential for fungi as a diagnostic and

prognostic tool for CRC. The latest understanding of microorganisms within tumours is largely due to the development of techniques to detect microbial species and their metabolites. However, despite advancements in our understanding of the number of fungi in tumours and the relationship between tumours and fungi, more specific and sensitive techniques are necessary.

The use of fungi as biomarkers for CRC has considerable potential. However, several considerations must be addressed. First, for tumour patients with an immunosuppressive condition and concurrent fungal infections, such as fungemia or fungal enteritis, the diagnostic value of fungal biomarkers may decrease. Thus, further investigation is necessary to distinguish between the two conditions. Additionally, a more in-depth understanding of the relationship between fungi and CRC prognosis is essential for utilising fungi to assess CRC prognosis. This method offers the advantage of dynamically monitoring patients' conditions, surpassing endoscopy and other currently used diagnostic methods. However, there is a lack of animal model experiments and clinical data to explain the relationship between fungi and CRC occurrence and development. Nonetheless, the strategy of diagnosing CRC through fungi is undoubtedly worthy of further consideration.

Disclosure statement

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Author contributions

Xu-Huan Li and Ming-Ming Luo: Conceptualisation, Formal analysis, Visualisation, Writing-Original Draft, and Review & Editing. Zu-Xiu Wang: Visualisation, Review, and Editing. Qi Wang and Bin Xu: Conceptualisation, Funding acquisition, Supervision, Writing – Review & Editing.

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