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Is *Candida albicans* a contributor to cancer? A critical review based on the current evidence

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ABSTRACT

The association between *Candida albicans* (*C. albicans*) and cancer has been noticed for decades. Whether *C. albicans* infection is a complication of cancer status or as a contributor to cancer development remains to be discussed. This review systematically summarized the up-to-date knowledge about associations between *C. albicans* and various types of cancer, and discussed the role of *C. albicans* in cancer development. Most of the current clinical and animal evidence support the relationship between *C. albicans* and oral cancer development. However, there is insufficient evidence to demonstrate the role of *C. albicans* in other types of cancer. Moreover, this review explored the underlying mechanisms for *C. albicans* promoting cancer. It was hypothesized that *C. albicans* may promote cancer progression by producing carcinogenic metabolites, inducing chronic inflammation, remodeling immune microenvironment, activating pro-cancer signals, and synergizing with bacteria.

1. Introduction

The crosslink between human microbiota and cancer is rapidly expanding (Gilbert et al., 2018). It was estimated that about 2.2 million infection-attributable cancer cases were diagnosed worldwide in 2018, which accounted for 13% of the global cancer incidence (de Martel et al., 2020). In the past decade, lots of studies have reported the roles of microbiomes in the diagnosis, development, progression, metastasis formation, and treatment response of multiple cancer types (Cullin et al., 2021; Sepich-Poore et al., 2021). As evidence about microbiomes' roles in cancer phenotypes being increasingly compelling, polymorphic microbiomes was suggested by Douglas Hanahan to be one of the hallmarks of cancer (Hanahan, 2022).

The bacterial and viral influence on cancer has been noticed in 1868 and 1911, respectively (Sepich-Poore et al., 2021). Apart from the recognized 11 carcinogenic bacteria and virus, an increasing number of bacteria and virus were being demonstrated to promote cancer progression and metastasis (Sepich-Poore et al., 2021). Nevertheless, relatively few studies have explored the role of fungi in cancer development (Kazmierczak-Siedlecka et al., 2020).

Undeniably, there are close and complex relationships between fungi and cancer. The role of various mycotoxins (aflatoxins, fumonisins, ochratoxin, T2, zearalenone, et al.) of plant-pathogenic fungi has been reported in carcinogenesis (Ekwomadu et al., 2022). Besides, fungal communities can be found in multiple sites of human body, though they only take up a smaller part of human microbiome in comparison to bacteria (Vallianou et al., 2021). Recently, Dohlman AB et al. (Dohlman et al., 2022) and Narunsky-Haziza et al. (2022) revealed the associations between fungi detected in tumors and pan-cancer, which provide some evidence supporting the important role of mycobiome in human cancers. It is worth mentioning that *Candida* was associated with the expression of pro-inflammatory immune pathways and metastasis of gastrointestinal cancers. Among the *Candida* genus, *Candida albicans* (*C. albicans*) was the most abundant representative and was highly abundant in multiple cancers, while *Candida tropicalis* (*C. tropicalis*), *Candida dubliniensis* (*C. dubliniensis*), *Candida glabrata* (*C. glabrata*), *Candida lusitaniae* (*C. lusitaniae*), *Candida guilliermondii* (*C. guilliermondii*), and *Candida parapsilosis* (*C. parapsilosis*) were at lower abundance and prevalence across tumor samples (Dohlman et al., 2022).

Among the limited studies focusing on fungi-cancer links, *C. albicans* may be the most studied fungal species in cancer microbiome (Vallianou et al., 2021). Compared with some non-*albicans Candida* including

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Candida auris (*C. auris*), *C. tropicalis* and *C. glabrata*, higher virulence such as adhesion, biofilm formation, hydrolytic enzymes and filamentous growth could be found in *C. albicans*, both in vitro and in animal experiments (Silva et al., 2012; Fakhim et al., 2018). As a result, *C. albicans* is usually the most common *Candida* species among patients with neoplastic diseases (Wingard, 1995; Makinen et al., 2018; Talukdar et al., 2020). Thus, this study mainly focused on the role of *C. albicans* in multiple cancers. It is well recognized that the immunosuppressed status during cancer and chemoradiotherapy will cause the overgrowth of *C. albicans*. In turn, whether *C. albicans* play roles in cancer development remains to be elucidated.

Considering the close associations between *C. albicans* and cancers, and the unclarified role of *C. albicans* in cancer development, this review aims to discuss whether *C. albicans* serves as a contributor in various types of cancer. Based on the *C. albicans*' s biological characteristics and its interactions with host immunity and microbes, this review systematically and critically discussed the potential roles and underlying mechanisms of *C. albicans* in cancer progression and development, which contributes to the better understand of *C. albicans*-cancer links.

2. Interplays between *C. albicans* and host

2.1. Features of C. albicans

C. albicans shows the dimorphism to switch between separated yeast cells (blastospores) or filamentous forms (hyphae and pseudohyphae) (Mitchell, 1998). Both the yeast and hyphae are regularly found at infection sites and are important for pathogenicity, which yeast form is involved in dissemination, and hyphal form is more invasive (Mayer et al., 2013). The cell wall of *C. albicans* is a dynamic and fluid structure mainly composed of polysaccharides (80–90%), proteins (6–25%), and lipid (1–7%) (Chaffin et al., 1998). In addition, *C. albicans* can secrete extracellular vesicles (EVs) carrying a complex mixture of different molecules, such as proteins, lipids, carbohydrates, pigments, and RNA (Joffe et al., 2016; de Toledo et al., 2019).

There are many virulence factors in *C. albicans*, which contain membrane-bound and secreted proteins/enzymes (Mayer et al., 2013; Lim et al., 2021). Agglutinin-like sequence (Als) protein can help *C. albicans* binding to cadherins, and is essential for adhesion and epithelial destruction (Sheppard et al., 2004; Phan et al., 2007; Zhu et al., 2012). Membrane-bound enzyme like enolase and phytase are involved in hyphal growth, binding to host fibronectin and laminin, damaging epithelium tissues, as well as facilitating nutrient acquisition (Ko et al., 2013; Tsang et al., 2017; Reyna-Beltran et al., 2018). Besides, secreted virulence factors such as candidalysin, phospholipases and lipases are essential for tissue damage, immune cell recruitment and host invasion during *C. albicans* infection (Lim et al., 2021). In particular, candidalysin, a recently discovered toxin peptide encoded by *ECE1* gene, has been demonstrated to play important roles in inflammasome activation, cell damage and neutrophil recruitment for *C. albicans* invasion (Moyes et al., 2016; Ho et al., 2019).

2.2. C. albicans-epithelial barriers interplay

Epithelial barriers are the primary sites of interaction between *C. albicans* and the host. Various epithelial cells form a monolayer physical and biochemical barrier, and keep their secretory and immunomodulatory functions to limit the invasion of microbes (Gerbe et al., 2012; Basmaciyan et al., 2019). Apart from the tight junctions and adherent junctions sealing paracellular spaces and mucus layer, the antimicrobial peptides (AMPs) such as LL37 and β-defensins, exert anti-*Candida* abilities by induction of cell death or immune modulation (Guttman and Finlay, 2009; Allert et al., 2018; Basmaciyan et al., 2019).

However, *C. albicans* can evade the AMPs and mucus layer, and damage the epithelial barrier. Adhesins such as Ala1p, Als1p and Hwp1p can promote the adherence of *C. albicans* to host cells (Lim et al., 2012). Degradative enzymes such as secreted aspartyl proteinases and phospholipases can help *C. albicans* to damage the epithelial barrier (Monod et al., 1998; Ghannoum, 2000). Additionally, candidalysin can damage epithelial cell by inducing calcium influx, oxidative stress, mitochondrial dysfunction, ATP depletion and epithelial necrosis (Blagojevic et al., 2021).

2.3. C. albicans-Immune system interplay

The recognition of pathogen-associated molecular patterns (PAMPs) on *C. albicans* by pathogen recognition receptors (PRRs) is fundamental for initiation of the host immune system (Qin et al., 2016). Various receptors participate in the recognition of *C. albicans*, such as Toll-like receptors (TLRs) recognizing phospholipomannan, O-bound mannan and α-linked mannose, C-type lectin receptors (CLRs) recognizing β-glucans, α-mannan and high-mannose, as well as galectin 3 recognizing β-(1−2) oligomannan (Pathakumari et al., 2020). When *C. albicans* are recognized, pathways such as MAPK, NF-κB, NLRP3, IRF3 are triggered, and mediators such as interleukins (IL-1, IL-6, IL-12, and IL-23), tumor necrosis factor-α (TNF-α), and interferon gamma (IFN-γ) are produced, which result in the innate and adaptive immune responses (Netea et al., 2015; Pathakumari et al., 2020).

Both innate and acquired immune cells play roles in anti-*Candida* response. Macrophages can engulf *C. albicans*, and produce cytokines and chemokines to recruit and activate other immune cells. Dendritic cells play important roles in antigen processing and presentation to the naïve T cells. Polymorphonuclear neutrophils are essential for triggering the inflammatory response to fungal infections. Th1 cells can produce pro-inflammatory cytokines such as IFN-γ, which is important for the fungicidal activities of neutrophils and macrophages (Nathan et al., 1983; Shalaby et al., 1985; Netea et al., 2015). Th17 cells are the producers of IL-17 and IL-22, which can induce neutrophil recruitment and activation, and antifungal β-defensins release (Netea et al., 2015). In addition, other immune cells, such as Th2 cells, Tregs, $CD8^+$ T cells, and B cells also participate in the host response to *C. albicans* invasion.

Nevertheless, *C. albicans* is foxy and can escape from the immune surveillance. By downregulating or shielding the PAMPs, *C. albicans* can preclude its recognition from the PRRs (Hernandez-Chavez et al., 2017). By secreting AMP efflux pumps, *C. albicans* can inhibit AMP levels (Swidergall and Ernst, 2014). By inducing early inflammasome-dependent cell death, *C. albicans* can damage the macrophages (Uwamahoro et al., 2014). Additionally, *C. albicans* can also escape from the immune surveillance by degrading the complement factors (C3, C4b, C5), modulating Th1/Th2 cells balance and M1/M2 macrophages balance, as well as downregulating IL-17 pathway (Cheng et al., 2010; Luo et al., 2013; Reales-Calderon et al., 2014; Pathakumari et al., 2020).

2.4. C. albicans-Microbiota interplay in host

The most common synergistic relationships between *C. albicans* and bacteria may be the one between *C. albicans* and various *Streptococcal* species in oral cavity. By direct cell-to-cell interaction, the adhesion and biofilm formation abilities of both *C. albicans* and *Streptococcal* species are enhanced (Chevalier et al., 2018; Wan et al., 2021). Synergistic relationships between *Staphylococcus* species and *C. albicans* can also be noticed. *Staphylococcus aureus* (*S. aureus*) and *Staphylococcus epidermidis* (*S. epidermidis*) can bind to *C. albicans* hyphae and induce the formation of polymicrobial biofilms, while both bacteria can enhance the adhesion and biofilm formation of *C. albicans* (Carolus et al., 2019). Additionally, many other bacteria such as *Porphyromonas gingivalis* (*P. gingivalis*) (Sztukowska et al., 2018), *Fusobacterium nucleatum* (*F. nucleatum*) (Wu et al., 2015), *Escherichia coli* (*E. coli*) (Klaerner et al., 1997), and *Helicobacter pylori* (*H. pylori*) (Chen et al., 2021) have been reported to show synergic relationships with *C. albicans*.

Perhaps the relationship between *Pseudomonas aeruginosa*

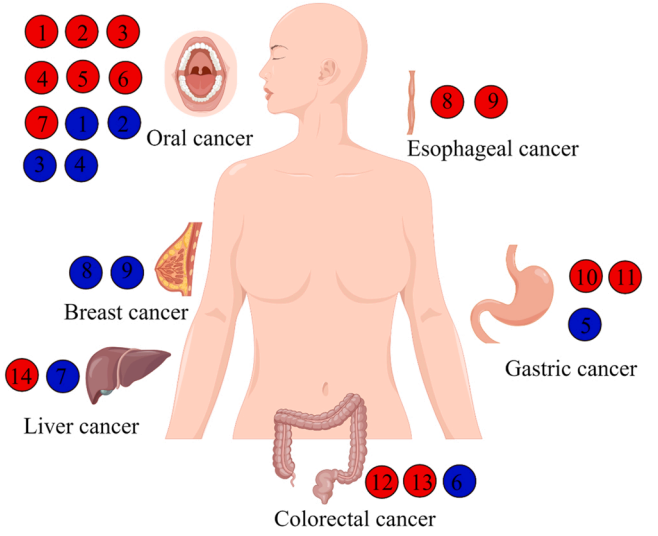

Fig. 1. *C. albicans* is associated with various types of cancer. The numbers in the red circle represent the clinical studies in Table 1. The numbers in the blue circle represent the animal studies in Table 2. (This figure was created using Figdraw: https://www.figdraw.com/, certificate number is REG8220726010300055947).

(*P. aeruginosa*) and *C. albicans* may be the best characterized example of antagonistic *C. albicans*–bacterial interactions (Shirtliff et al., 2009). *P. aeruginosa* can form a dense biofilm on *C. albicans* filaments and kill the hyphal form by several virulence factors such as type IV pili (Hogan and Kolter, 2002). In turn, *C. albicans* molecule farnesol can inhibit the pyocyanin production and swarming motility in *P. aeruginosa* (Cugini et al., 2007; McAlester et al., 2008). *Lactobacillus* spp. in vagina can inhibit the growth of *C. albicans* by producing hydrogen peroxide (Strus et al., 2005) and lactic acid (Kohler et al., 2012). Indirectly, the host microbiota can also prevent the *C. albicans* growth and invasion by regulating immune defenses. *P. aeruginosa* reduced the macrophage escape of *C. albicans* by inhibiting the survival and filamentation of *C. albicans* within macrophage phagosomes (Salvatori et al., 2020). Microbiota-AhR (aryl hydrocarbon receptor) axis was reported to induce the transcription of IL-22, which provided colonization resistance to the *C. albicans* (Zelante et al., 2013).

The interactions between *C. albicans* and various bacteria are complex and essential for the homeostasis of host environment. When the balance among *C. albicans*, microbiota and host is broken, a pathogenic switching of *C. albicans* will occur (Nobile and Johnson, 2015; D'Enfert et al., 2021).

3. Is *C. albicans* a contributor to cancer development?

3.1. Oral cancer

Among the various types of cancer, oral cancer (OC) shows the most significant association with *C. albicans* (Fig. 1 and Table 1). The prevalence of *C. albicans* is variable in OC patients according to the methods of sampling and detection, with a positive rate of 10–68.2% in different studies (Table S1). Some case-control studies demonstrated that oral *Candida* presence was a risk factor for OC (OR= 3.2 and 6.5) (Talamini et al., 2000; Alnuaimi et al., 2015). A cohort study also reported that *Candida* infection was associated with cancer incidence, including OC (Norgaard et al., 2013). In addition, oral candidiasis was associated with poor performance status in advanced cancer patients (Davies et al., 2006) and poor overall survival in OC patients (Mohamed et al., 2021).

Oral potentially malignant disorders (OPMDs) are a type of disorders with an increased risk for malignant transformation, such as oral leukoplakia (OLK), erythroplakia, oral lichen planus (OLP), and oral

Table 1
Clinical evidence supporting the association between *C. albicans* and cancer.

No.	Cancer type	Methods	Findings	Reference
1	Oral cancer	Salivary mycobiome of oral squamous cell carcinoma and controls was assessed using an NGS-based methodology.	*Candida* genus showed higher abundance in oral squamous cell carcinoma patients.	(Mohamed et al., 2021)
2		Single-cell RNA sequencing was performed in the normal tissue, oral potentially malignant disorders lesion with *C. albicans* infection, oral squamous cell carcinoma tissue with or without *C. albicans* infection.	Certain cluster fibroblasts and macrophages were related to the oral squamous cell carcinoma development with *C. albicans* infection.	(Hsieh et al., 2022)
3		Clinicopathological data of 84 patients with oral leukoplakia were reviewed retrospectively.	*Candida* infection was a risk factor associated with malignant transformation of oral leukoplakia.	(Yang et al., 2022)
4		A case-control study enrolling 132 oral cancer and 148 controls.	Oral candidiasis showed an OR of 6.5 for oral cancer.	(Talamini et al., 2000)
5		A case-control study enrolling 52 oral cancer and 104 controls.	Multiple regression analyses showed significant association between oral squamous cell carcinoma and *Candida* (OR=3.242).	(Alnuaimi et al., 2015)
6		A retrospective analysis including 82 oral lichen planus patients who developed into oral cancer.	The time between oral lichen planus and oral squamous cell carcinoma diagnoses decreased in the patients with *Candida* overgrowth.	(Bindakhil et al., 2022)
7		A retrospective cohort study including 48 chronic hyperplastic candidiasis patients.	4.17% of the chronic hyperplastic candidiasis patients suffered malignant transformation with 6.5 ± 6.36 months.	(Zhang et al., 2021)
8	Esophageal cancer		*C. albicans* infections were associated with dysplasia of the esophageal epithelium in patients with early carcinoma.	(Hsia et al., 1981)
9		A prospective study of 131 patients with esophageal disease and 40 healthy volunteers,	*Candida* prevalence was higher in carcinoma (51.8%) than in benign disease (24%).	(Bonavina et al., 2003)
10	Gastric cancer	ITS rDNA analysis in cancer lesions and adjacent noncancerous tissues of 45 Gastric cancer cases.	Gastric cancer patients showed a lower OTU abundance than the control, but an elevated abundance of *C. albicans*.	(Zhong et al., 2021)
11		121 gastric mucosal biopsies with histologically demonstrated candidiasis.	Candidiasis was twice as common in carcinoma as in non-carcinomatous gastric ulcer.	(Oehlert and Preuss, 1980)

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Table 1 (*continued*)

No.	Cancer type	Methods	Findings	Reference
12	Colorectal cancer	Microbiome in rectal swabs from adenoma/ colorectal cancer and controls was identified using MALDI-ToF MS.	A strong and significant overrepresentation of the *C. albicans* was observed in cases.	(Stary et al., 2020)
13		Mycobiome in fecal samples from colorectal cancer patients was identified by ITS1 sequence.	Significant increase of *C. albicans* levels in the guts of colorectal cancer patients.	(Wang et al., 2021)
14	Liver cancer	Stool samples from 11 patients with liver cirrhosis and 17 patients with hepatocellular carcinoma were collected for ITS sequencing.	The composition of gut fungi in patients with hepatocellular carcinoma is significantly altered, while the abundance of *C. albicans* was significantly elevated.	(Liu et al., 2022)

submucous fibrosis (OSF) (Warnakulasuriya et al., 2021). Many studies have indicated that *C. albicans* may be associated with the development and malignant transformation of OPMDs. It was reviewed that 0.6–5% of the homogenous OLK, 20–25% of the non-homogeneous OLK, and 61% of the proliferative verrucous OLK could develop into OC (Villa and Sonis, 2018). The frequency of *C. albicans* in OLK has been pointed out before 1950 s (JEPSEN and WINTHER, 1965; Cawson, 1969). *C. albicans* can be detected in 35–67.24% of OLK patients, which is higher than healthy individuals (Table S2). Interestingly, *C. albicans* infection is more likely present in the OLK patients with increased malignant transformation risk factors: a) *Candida* infection in non-homogenous OLK (55.3%) was higher than homogenous OLK (23.3%) (Gupta et al., 2021). b) *Candida* infection showed a higher prevalence in elderly OLK patients with epithelial dysplasia (Wu et al., 2013). c) *C. albicans* infection in OLK was associated with alcohol consumption, smoking and betel-quid chewing (Dilhari et al., 2016; Weerasekera et al., 2021). Yang et al. (Yang et al., 2022) reviewed 84 OLK patients with previous OC (before OLK occurrence) and found that *Candida* infection was not only a risk factor for malignant transformant of OLK, but also an independent prognostic factor of OC development from the treated OLK. Besides, some studies also explored the associations between *C. albicans* and other OPMDs. The detection of *C. albicans* was 15–40.91% in the oral cavity of OLP patients, with a more detection in erosive OLP than non-erosive OLP (Table S2). A retrospective analysis including 82 OLP patients who developed into OC found that the time between OLP and OC diagnoses decreased in the patients with *Candida* overgrowth, which indicated that *Candida* might play a role in the field cancerization of OLP patients (Bindakhil et al., 2022). In addition, cancer-transformation rate in OSF was 1.5–15% (Shih et al., 2019), while *C. albicans* could be isolated from 10% to 50% of the OSF patients in their oral cavities (Table S2).

Chronic hyperplastic candidiasis (CHC) is probably the most direct evidence to support the link between *C. albicans* infection and oral carcinogenesis. The association between CHC and OC has been noticed before 1960 s (Williamson, 1969). Several studies have reported the malignant transformation of CHC (Williams et al., 2001). The overall malignant transformation for CHC was 4.1–19.8% (Lorenzo-Pouso et al., 2022). Our previous study also showed that 4.17% (2/48) of the CHC patients suffered malignant transformation with a mean transformation time of 6.5 ± 6.36 months (Zhang et al., 2021). Considering the malignant transformation risk, CHC was classified into OPMDs in the 4th edition of WHO classification on head and neck tumors (Reibel, Gale N, 2017). However, in 2020, due to insufficient epidemiological evidence, CHC was not recommended for inclusion within the OPMDs from a

Table 2
Animal studies supporting the association between *C. albicans* and cancer.

No.	Cancer type	Methods	Findings	Reference
1	Oral cancer	SD rats were applied with 4NQO and *C. albicans* on the palate and tongue.	*C. albicans* participated in causing neoplastic transformation of oral cancer.	(O'Grady and Reade, 1992)
2		Immunocompetent C57BL/6 mice received daily 4NQO for 8 weeks, followed by *C. albicans* infection for 10 weeks.	*C. albicans* played a role in the promotion of oral dysplasia in mice when 4NQO was used as initiator of oral neoplasia.	(Dwivedi et al., 2009)
3		Mice were treated with 4NQO and arecoline, followed by *C. albicans* infection at the site of lesions on their tongue.	*C. albicans* infection promoted the development of oral squamous cell carcinoma in the 4NQO and arecoline-cotreated mice	(Lee et al., 2020)
4		BALB/c mice was treated with cortisone acetateto, and followed with tumor cell injection and *C. albicans* oral infection.	Oral candidiasis enhanced the progression of oral squamous cell carcinoma, induced an EMT phenotype, and enhanced the expression of genes involved in tumor progression.	(Vadovics et al., 2022)
		BALB/c mice were given 4NQO, 0.1% TCN and then infected with *C. albicans*.	Persistent infection with *C. albicans* promoted stepwise oncogenesis in oral epithelial cells in the presence of predisposing environmental conditions.	
5	Gastric cancer	Diabetic rats were orally treated with *C. albicans*.	Prolonged diabetic condition enhanced *C. albicans*-related mucosal hyperplasia in forestomach.	(Sano et al., 2014)
6	Colitis-associated colon cancer	Wild type or Dectin-3 − /− mice were treated with *C. albicans* for 9 weeks after AOM injection.	*C. albicans*-driven crosstalk between macrophages and innate lymphoid cells promoted CAC development.	(Zhu et al., 2021)
7	Liver cancer	After *C. albicans* colonization, Hepa1–6 cells were inoculated subcutaneously on the flank of the mice	*C. albicans* promoted the progression of hepatocellular carcinoma in tumor bearing mice by upregulating NLRP6 and influencing plasm metabolome.	(Liu et al., 2022)
8	Breast cancer	BALB/c mice bearing breast tumor were infected with *C. albicans* by intravenous injection.	*C. albicans* infection might have a positive effect on tumor progression and metastasis.	(Hajari et al., 2013)
9		Mice bearing breast tumor were infected with *C. albicans* by intravenous injection.	Systemic infection with *C. albicans* could induce Treg cells accumulation and dysregulation	(Ahmadi et al., 2019)

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Table 2 (*continued*)

No.	Cancer type	Methods	Findings	Reference
			of cytokine network, and thereby facilitate tumor growth.	

workshop convened by WHO Collaborating Centre for Oral Cancer (Warnakulasuriya et al., 2021). Thus, whether CHC can be classified into OPMDs remains controversial and needs more evidence.

Some studies also explored the role of *C. albicans* in OC from the perspective of oral epithelial dysplasia (OED), which means the histopathological changes in oral epithelium and indicates a risk of malignant transformation (Odell et al., 2021). It has been reported that the degree of OED was correlated with the oral carriage of fungi (McCullough et al., 2002). A large-scale study containing 597 OED biopsies reported a positive association of the PAS positive fungal infection with moderate and severe OED (Barrett et al., 1998). The incidence of *C. albicans* and *Candida* spp. in tissue also increased with mild, moderate, and severe OED (Tamgadge et al., 2017; Erira et al., 2021). Moreover, the OED infected with fungi worsened in histological severity compared with OED without fungi infection in the follow-up (Barrett et al., 1998). Thus, infection of *C. albicans* may accelerate the OED progression.

The *C. albicans* isolated from OPMDs and OC possesses some specific features, which indicate a higher pathogenicity. Serotype A was the predominant *C. albicans* biotype isolated from the oral cavity of OLK, OLP, and OC (Lipperheide et al., 1996; Alnuaimi et al., 2015). *Candida* isolated from OC patients exhibited significantly higher biofilm formation, biofilm metabolic activity, lipolytic, phospholipase and proteinase activities, cellular surface hydrophobicity, and ethanol-derived acetaldehyde-producing activity than isolated from non-OC or OPMDs patients (Alnuaimi et al., 2016; Castillo et al., 2018). Thus, it is speculated that the virulence of *Candida* in different individuals might contribute to the malignant susceptibility.

Moreover, the role of *C. albicans* in OC has been explored in some animal studies (Table 2). As early as in 1986, Franklin and Martin found that *C. albicans* caused severer hyperplastic epithelium in hamster cheek pouches painted with 50% turpentine and liquid paraffin for 10 weeks (Franklin and Martin, 1986). Later in 1992, Grady and Reade (O'Grady and Reade, 1992) demonstrated that *C. albicans* participated in the neoplastic transformation of OC in a 4-nitroquinoline-1-oxide (4NQO, a chemical carcinogen) rat model. By applying the palate and tongue of SD rats with 4NQO, they found that 4NQO plus *C. albicans* infection induced approximately 3 times carcinogenesis than 4NQO alone in both sites. Then in 2009, Dwivedi et al. (2009) showed that *C. albicans* promoted the oral dysplasia as well as P16 and Ki67 expression in a mouse model with 4NQO used as initiator of oral neoplasia. In the decade that followed, however, few studies explored this matter. Recently, some researchers have continued to pay attention to this matter. In 2020, Lee et al. (2020) supported that *C. albicans* increased the OC incidence in 4NQO and arecoline-cotreated mice by the induction of IL-1β. More recently, Vadovics et al. (2022) systematically explored the role of *C. albicans* in OC in vivo and in vitro. They found that *C. albicans* could induce the expression of oncogenes in nonmalignant cells and the occurrence of tumor in 4NQO mice (Vadovics et al., 2022). Further, they also demonstrated that *C. albicans* promoted the OC progression in a xenograft mouse model by inducing the overexpression of metastatic genes and the epithelial-mesenchymal transition (Vadovics et al., 2022). Most animal studies support the role of *C. albicans* in promoting OC, but only few studies have explored the underlying mechanisms.

Few cytological experiments explored the potential mechanisms. *C. albicans* could enhance the metastasis of oral squamous cell carcinoma (OSCC) cells, which might involve in the induction of matrix metalloproteinases (MMPs), oncometabolites, protumor signaling pathways, and metastatic genes (Vadovics et al., 2022). Zymosan, a cell wall component of *Candida*, was demonstrated to promote the adhesion of *C. albicans* to OSCC cells, induce the IL-1β expression in OSCC cells, as well as promote the proliferation of OSCC cells by TLR2/MyD88 pathway (Chen et al., 2020). In addition, metabolites from *C. albicans* biofilm upregulated oncogenes (*PI3KCA*, *hRAS*, *BRAF* and *mTOR*) and cell cycle genes (*Bcl-2* and *CDKN1A*) in OSCC cells (Amaya et al., 2021).

Additionally, the mucosal bacterial dysbiosis induced by *C. albicans* infection may participate in OC development. An endogenous bacterial overgrowth and diversity loss could be found on the oral mucosa of mice receiving 5-fluorouracil and *C. albicans*, with *Enterococcus* species dominating, increased the permeability of oral epithelial barrier (Bertolini et al., 2019). *C. albicans* has also been reported to co-aggregate with *Streptococcus* spp. (Arzmi et al., 2019), *P. gingivalis* (Sztukowska et al., 2018) and *F. nucleatum* (Wu et al., 2015), which are associated with OC (Stasiewicz and Karpinski, 2022).

Though chronic *C. albicans* infection has not been listed as a risk factor for OC, the current evidence supports the relationship between *C. albicans* infection and OC development. However, more evidence is needed to further confirm this causal relationship, not only from prospective cohort studies with large-scale sample, but also from mechanism experiments in vivo and in vitro.

3.2. Esophageal cancer

Esophageal cancer (EC) ranks the ninth most frequently diagnosed malignancy and the sixth leading cause of cancer death (Sung et al., 2021). Poor oral health, alcohol consumption and smoking are significant risk factors for EC (Song et al., 2021). The association between *C. albicans* and EC has been noticed before 1980 s (Hsia et al., 1981). In a place (Linxian) with a high incidence of EC, it was found that *C. albicans* infections were increased and associated with hyperplasia/dysplasia of the esophageal epithelium in patients with premalignant changes/early carcinoma (Hsia et al., 1981).

Some studies have reported the increased colonization of *Candida* species, especially *C. albicans* in EC patients. It was estimated that fungal culture was positive in the endoscopy brushing samples of 56.81% EC patients, and *C. albicans* accounted for 53.55% of the fungal profile (Talukdar et al., 2020). Moreover, *Candida* colonization appears to increase with the severity of the esophageal disease. In a study that included 131 patients with esophageal disease and 40 healthy volunteers, the *Candida* colonization was increased in esophageal disease (38.8%) than in healthy volunteers (7.5%), and its prevalence was higher in carcinoma (51.8%) than in benign disease (24%) (Bonavina et al., 2003).

Esophageal candidiasis is a condition usually caused by *C. albicans* infection. Candidiasis was more frequent in patients with esophageal carcinoma (27%) than in patients with esophagitis (15%) (Scott and Jenkins, 1982), which may further support the role of *Candida* infection in EC development. It was reported that most of the esophageal verrucous squamous cell cancer exhibited a white, warty, plaque-like appearance with superimposed *Candida* at endoscopy, which resulted in a frequent misdiagnosis of *Candida* esophagitis on initial presentation (Sweetser et al., 2014; Li et al., 2021). In addition, many reports revealed that patients with chronic esophageal candidiasis showed an increased risk of developing esophageal squamous cell carcinoma, especially in those with signal transducer and activator of transcription 1 (*STAT1*) or autoimmune regulator (*AIRE*) gene mutation (Rautemaa et al., 2007; Rosa et al., 2008; Domingues-Ferreira et al., 2009; Delsing et al., 2012; Koo et al., 2017).

However, very little research has addressed the potential mechanisms of *C. albicans* in esophageal carcinogenesis. Considering the coexistence of high *C. albicans* in esophageal epithelium and high nitrate/nitrite concentrations in drinking water (Hsia et al., 1981), it was speculated that the nitrosamine generated by *C. albicans* may contribute to esophageal carcinogenesis. In addition, individuals with poor oral health (provides an environment for *C. albicans* overgrowth) and ethanol

drinking have the increased risk of EC. The local acetaldehyde (ACH, a group 1 carcinogen) production of *C. albicans* may be another possible mechanism (Ohashi et al., 2015; Nieminen and Salaspuro, 2018).

Although a link between *C. albicans* and EC can be noticed, epidemiological evidence of large-scale samples is still lacking. Additionally, further animal experiments are needed to replicate the EC caused by *C. albicans* infection. Thus, more research is necessary for demonstrating the causal relationship between *C. albicans* and EC.

3.3. Gastric cancer

Gastric cancer (GC) ranks the fifth most common cancer and the third most common cause of cancer death worldwide (Smyth et al., 2020). Apart from the bad habits, *H. pylori* infection may be the most accepted risk factor for GC (Smyth et al., 2020). However, whether other microorganism including *C. albicans* can influence the development of GC has not been studied in detail (Papon et al., 2021).

As early as in 1980, Oehlert and Preuss (Oehlert and Preuss, 1980) had found that candidiasis was twice as common in carcinoma as in non-carcinomatous gastric ulcer, and gastric ulcer with *C. albicans* tended to show atrophic or dysplastic gastric mucosa at the edge of the ulcer. Since then, fewer studies have explored the relationship between *C. albicans* and GC. Recently, Zhong et al. (2021) implicated this association by performing ITS metagenome sequences in cancer lesions and adjacent noncancerous tissues. They found a significant fungal imbalance in GC tissues with an enrichment of *C. albicans*. Their further analysis demonstrated that *C. albicans* could serve as a biomarker for GC (Zhong et al., 2021). Additionally, a woman with a homozygous missense variant in *MYD88* was reported to suffer from recurrent candidiasis and develop into GC at the age of 23 years, which might imply the role of *C. albicans* in promoting GC (Vogelaar et al., 2016). Prior to this, an animal study demonstrated that *C. albicans* induced mucosal hyperplastic changes and even the occurrence of squamous cell carcinoma in forestomach of diabetic rats (Sano et al., 2014).

On the contrary, a prospective cohort study revealed that no increased risk of GC was found in individuals with *Candida*-related lesions, though individuals with denture-associated lesions (including denture stomatitis, a disease mainly caused by *Candida* infection) at baseline was demonstrated to have an increased risk of GC (Ndegwa et al., 2018). Thus, the evidence supporting the role of *C. albicans* in the development of GC remains limited.

No studies have been found to directly explore the mechanisms underlying the carcinogenesis of *C. albicans* in GC. It was hypothesized that the ACH produced by *C. albicans* may contribute to the alcohol related upper gastrointestinal tract carcinogenesis (Nieminen and Salaspuro, 2018). In addition, the reduced diversity and richness of fungi caused by *C. albicans* may contribute to the pathogenesis of GC (Zhong et al., 2021). Interestingly, *H. pylori* inside *C. albicans* vacuoles were protected from the antibiotic and stresses (especially the lower PH level), and resulted in gastritis in mice (Hiengrach et al., 2022), which may contribute to the development of *H. pylori*-associated GC.

Whether *C. albicans* contributes to the development of GC remains unrevealed. More clinical and animal studies are required to better explore this relationship.

3.4. Colorectal cancer

Colorectal cancer (CRC) ranks the fourth most common cancer and the second most common cause of cancer death worldwide (Siegel et al., 2020). Over the past 10 years, several species of bacteria such as *F. nucleatum*, *Bacteroides fragilis*, and *E. coli* have been revealed to play potential roles in colorectal carcinogenesis (Garrett, 2019). However, as another key part of gut microbiota, mycobiota' s role in colorectal carcinogenesis remains unclearly and needs to be considered.

A small number of studies have explored the association between *C. albicans* and CRC. The abundance of *C. albicans* in CRC patients were controversy between the studies. By culturing and identifying, Stary et al. (2020) revealed a significant overrepresentation of *C. albicans* in the rectal swabs of newly diagnosed CRC (OR=5.444). Similarly, Wang et al. (2021) found a significant increase of *C. albicans* in the guts of CRC by second-generation sequencing. On the contrary, Gao et al. (2022) and Luan et al. (2015) did not identify the enrichment of *C. albicans* in the fecal samples of CRC and biopsy samples of colorectal adenomas, respectively. Gao et al. (2022) even reported the considerable decrease of *Candida* species in CRC, which was similar with another study reporting the reduction of *C. albicans* in CRC and precancerous lesions (Xu et al., 2022). However, the enrichment of non-*albicans Candida* like *C. glabrata* (Xu et al., 2022) and *C. tropicalis* (Luan et al., 2015) may be associated with CRC development.

The opposite view also exists in animal studies exploring the effects of *C. albicans* on CRC. Zhu et al. (2021) revealed that *C. albicans* promoted colitis-associated colon cancer (CAC) development by triggering IL-7 secretion in macrophages, which induced IL-22 production in RORγt+ (group 3) innate lymphoid cells (ILC3s) via aryl hydrocarbon receptor and STAT3. Apart from immune induction, *C. albicans* could induce the proliferation of intestinal epithelial cells by activating Wnt signaling pathway, which pathway is involved in CRC development (Wang et al., 2021). Indirectly, it was reported that *C. albicans* co-aggregated with *Actinomyces* spp. (Arzmi et al., 2019), and was associated with the loss of intestinal mucosal bacterial diversity in mice, with *Enterococcus* spp. dominating (Bertolini et al., 2019). Both *Enterococcus* and *Actinomyces* spp. were found to be consistently associated with colorectal neoplasia (Yu et al., 2022). On the contrary, like *Lactobacillus plantarum*, *C. albicans* isolated from the healthy individuals showed positive immunomodulatory effects and efficiently improved the CRC in rats (Shams et al., 2021). In addition, though high-fat diet could change the gut microbial community and increase the susceptibility of intestine to carcinogenic factors in rats, the abundance of *Candida* was reduced (Jin and Zhang, 2020).

There are different opinions concerning the role of *C. albicans* in CRC. More evidence is needed to support whether *C. albicans* plays a positive, negative, or neutral role in CRC development. Moreover, the role of non-*albicans Candida* in promoting CRC needs to be noticed.

3.5. Cervical cancer

The association between *C. albicans* and cervical cancer (CC) has been explored by several studies, but most of the studies did not support a relationship.

Some large population-based studies revealed that *C. albicans* was not associated with CC. A study including 310,545 females recruited for CC screening in China concluded that *C. albicans* was not associated with the detection of cervical lesions (Yang et al., 2020). Similarly, a study enrolling 445,671 asymptomatic women showed no statistically significant relationship between (pre)neoplasia and *Candida* infection (Engberts et al., 2006). Additionally, a retrospective, longitudinal, cohort study including 1439 women with vaginal *Candida* and 87,903 women with normal cervical smears also revealed that *Candida* vaginalis was not associated with an increased risk for squamous intraepithelial lesions over time (Engberts et al., 2007). Therefore, women carrying *Candida* may not be at an increased risk of developing CC.

Persistent infection with high-risk human papillomavirus (HPV) is accepted as a major causal factor in the development of CC (Burd, 2003). A cross-sectional study of 616 female sex workers found an association between vaginal *Candida* spp. and HPV 16 and 53 infections (Menon et al., 2016). Nevertheless, there is insufficient evidence to support an association between *C. albicans* and HPV infections in CC. A study including 106 CC patients showed that co-infection with *Candida* spp. did not increase the carcinogenic effect of HPV on cervix (Ghosh et al., 2017). A meta-analysis even showed that the *C. albicans* (vulvovaginal candidiasis) was associated to decreased HPV infection (5 studies included) and was not significantly associated with cervical

intraepithelial neoplasia (2 studies included) (Liang et al., 2019). In addition, in patients with HPV-negative cervical lesions (low-grade or high-grade squamous intraepithelial lesion, cervical squamous cell carcinoma), the *Candida* decreased with the lesion progressed (Zheng et al., 2020). An in vitro study also showed that recurrent *C. albicans* infection blocked proliferation and prostaglandin E_2 (PGE2) production in the vaginal epithelial cells inserted with HPV 16 viral sequence, which indicated that *C. albicans* might not contribute to the development of genital cancer induced by HPV 16 (Deva et al., 2010).

In conclusion, most of the studies suggested that cervical infection of *Candida* spp. was not a risk factor for the development of CC, regardless of the presence of HPV or not. Conversely, disturbances of vaginal microbiota, especially some species of bacteria, may be associated with cervical carcinogenesis (Engberts et al., 2007; Liang et al., 2019; Kovachev, 2020).

3.6. Liver cancer

Several studies support the role of *C. albicans* in liver cancer (LC) development, but with insufficient evidence. Firstly, the abundance of *C. albicans* was shown to increase in the gut of hepatocellular carcinoma patients when compared with liver cirrhosis patients, though the diversity of gut mycobiome was decreased (Liu et al., 2022). Further, *C. albicans* promoted the progression of hepatocellular carcinoma in tumor bearing mice by influencing the plasm metabolome, which was NLRP6 dependent (Liu et al., 2022). Interestingly, intestinal *Candida* in hepatic cancer patients could affect serum fatty acid metabolism (Usami et al., 2013), which may be a link between *C. albicans* and LC. Additionally, the association between *C. albicans* and alcoholic hepatitis might indirectly involve in the progression of LC. Alcohol-related liver disease was reported to account for 30% of hepatocellular carcinoma cases (Ganne-Carrie and Nahon, 2019). Alcohol-dependent patients displayed reduced intestinal fungal diversity but overgrowth of *Candida*, especially *C. albicans* (Yang et al., 2017). *C. albicans* was able to translocate from gut into liver during alcoholic hepatitis (Furuya et al., 2019), where its candidalysin and β-glucan could exacerbate ethanol-induced liver disease (Yang et al., 2017; Chu et al., 2020).

3.7. Breast cancer

Though there were few epidemiological evidence, several animal studies have explored the role of *C. albicans* in breast cancer (BC). Ahmadi et al. (2019) revealed that systemic infection with *C. albicans* could increase Treg cells in tumor microenvironment and dysregulate the cytokine network, which facilitated breast tumor growth in mice. Systemic infection with *C. albicans* also induced the increase of MMP-3, MMP-9, and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) in BC bearing mice, which might promote tumor progression and metastasis (Hajari et al., 2013). Additionally, the BC could aggravate the systemic candidiasis, and vice versa the presence of candidiasis seemed to promote the organ metastases of BC (Choo et al., 2010). However, these animal studies mainly focused on the systemic candidiasis and tumor metastases. The immune disorders caused by systemic candidiasis may be the main cause of tumor metastases.

3.8. Lung cancer

It was reported that *C. albicans* was colonized in the bronchus of 13.9–42.9% patients with lung cancer (Laroumagne et al., 2011; Laroumagne et al., 2013). We didn't find studies exploring the relationship between *C. albicans* and lung cancer, though *C. albicans* airway colonization was demonstrated to facilitate the development of *S. aureus* (Roux et al., 2013), *E. coli* (Roux et al., 2013), *P. aeruginosa* (Roux et al., 2009; Roux et al., 2013), and *Acinetobacter baumannii* (Tan et al., 2016) pneumonia in rat models. Some in vitro studies demonstrated that β-glucans extracted from *C. albicans* might possess anti-cancer effect by increasing lung cancer cells apoptosis (Peymaeei et al., 2020) and inhibiting the expression of genes involved in Lewis lung carcinoma cell line (LL/2) cells metastasis (Sadeghi et al., 2020).

3.9. Others

Fewer studies explored the role of *C. albicans* in other types of cancer. It was reported that *C. albicans* did not appear to contribute to the development of upper aerodigestive tract cancer (Macfarlane et al., 2012), prostate cancer (Bergh et al., 2007) or pancreatic cancer (Aykut et al., 2019), though *Malassezia* spp. showed an association with pancreatic cancer (Aykut et al., 2019).

4. Potential mechanisms for *C. albicans* promoting cancer

4.1. The involved factors from C. albicans

Some cell wall components, toxins, enzymes, and metabolites from *C. albicans* may contribute to cancer development. However, a definite carcinogen has not been found or determined from *C. albicans*.

4.1.1. Cell wall components

C. albicans glycoprotein enhanced the carcinogenesis effect of 3-methylcholanthrene in rodents (Mankowski, 1971). Zymosan promoted the adhesion of *C. albicans* to OSCC cells, as well as IL-1β production and proliferation of OSCC cells (Chen et al., 2020). β-glucan could induce liver inflammation and hepatocyte damage, and promote development of ethanol-induced liver disease (Yang et al., 2017). Additionally, recognition of PAMPs by TLRs, CLRs and galectin 3 will trigger various pathways such as MAPK, NF-κB, NLRP3, and IRF3 to induce inflammation and immune responses, which may participate in cancer progression.

4.1.2. Candidalysin

The cytolytic toxin candidalysin can damage epithelial cells and activate EGFR and MAPK pathways, both of which are involved in cancer progression (Ho et al., 2021). Activation of MAPK by candidalysin will lead to heat shock protein 27 (Hsp27) activation, IL-6 release, and EGFR phosphorylation in epithelial cells (Nikou et al., 2022). Activation of EGFR can result in c-Fos activation and release of G-CSF and GM-CSF (Nikou et al., 2022). Proto-oncogene c-Fos is a recognized gene involved in cancer progression (Tsiambas et al., 2020). Besides, IL-6 (Hirano, 2021), Hsps (Wu et al., 2017), and G-/GM-CSF (Aliper et al., 2014) can participate in cancer development via maintaining chronic inflammation, promoting cellular proliferation, inducing immunosuppressive microenvironment, and other mechanisms. Additionally, candidalysin can trigger NLRP3 inflammasome response and the following secretion of IL-1β from macrophages (Rogiers et al., 2019). Considering the newly discovered candidalysin can activate various signals associated with cancer progression, it makes sense to further explore its role in carcinogenesis.

4.1.3. Production of nitrosamines

The link of *C. albicans*- nitrosamines- carcinoma noticed in Linxian (Hsia et al., 1981) has been discussed above. Further experiment demonstrated that *C. albicans* could cause the local formation of benzylmethylnitrosamine (NBMA; N-nitroso-N-methylbenzylamine), which is a carcinogen (Hsia et al., 1981). Notably, *C. albicans* strains with high nitrosation potential were generally isolated from more advanced precancerous lesions (Krogh et al., 1987).

4.1.4. Production of acetaldehyde

C. albicans possesses the ability to convert ethanol into ACH (a group 1 carcinogen) by its alcohol dehydrogenases (ADH) (Bakri et al., 2015). Poor oral health, alcohol consumption and smoking are risk factors for the oral and esophageal cancer. Compared with *C. albicans* isolated from

non-smokers and non-drinkers, the *C. albicans* isolated from oral mucosa of smokers and drinkers produced higher ACH (Gainza-Cirauqui et al., 2013). It was also demonstrated that *C. albicans* isolated from OPMDs can produce mutagenic amounts of ACH (Gainza-Cirauqui et al., 2013), and high ACH-producing *Candida* were more prevalent in oral cancer than non-oral cancer (Alnuaimi et al., 2016).

4.1.5. Secreted aspartyl proteinases

The secreted aspartyl proteinases (Saps) are virulence factors of *C. albicans* to persist on mucosal surfaces and penetrate into deeper tissues. Saps activity of *C. albicans* isolates from OLP, OLK and OSCC was significantly higher than that from healthy oral cavity (Kuriyama et al., 2003; Rehani et al., 2011), which indicates that Saps may play a role in disrupting mucosal barrier and inducing disease status of mucosa.

4.1.6. Metabolites

Both the fungal metabolites and host metabolites associated with *C. albicans* infection can promote cancer development. On the on hand, metabolites from *C. albicans* can upregulate oncogenes (*PI3KCA*, *hRAS*, *BRAF* and *mTOR*) as well as cell cycle genes (*Bcl-2*) in neoplastic cell lines (Amaya et al., 2021). On the other hand, *C. albicans* was demonstrated to reprogram metabolism and promote hepatocellular carcinoma in mice (Liu et al., 2022), which indicates a link of *C. albicans* infection-metabolome dysregulation-cancer progression.

4.2. The involved biological process

During *C. albicans* infection, the barrier destruction, unrestrained immune responses, and changed microbiome may facilitate the growth, metastasis and invasion of tumor.

4.2.1. Mucosal barrier destruction

C. albicans has been shown to diminish cell adhesion proteins and degrade tight junctions, such as E-cadherin, occluding, desmoglein-2, fibronectin and CLDN4 (Frank and Hostetter, 2007; Nawaz et al., 2018). In addition, Saps (Naglik et al., 2003) and candidalysin (Blagojevic et al., 2021) can also destroy host epithelial cells. The epithelial barrier dysfunction and hyperpermeability may not only lead to the infiltration of microbes and virulence factors, but also result in the persistent inflammation (Yu, 2018), which provides a microenvironment for cancer development. Additionally, the damaged epithelial barrier is beneficial for the invasion and metastasis of tumor cells (Martin and Jiang, 2009).

4.2.2. IL-17 signaling activation

IL-17, mainly produced by Th17 cells, is important for antifungal activity. However, unrestrained IL-17 signal is associated with immunopathology and cancer progression (Amatya et al., 2017; Eyerich et al., 2017). Increased IL-17 genes can be found in multiple human cancers, and the increased IL-17 can activate stromal cells to produce angiogenic and immune-suppressive molecules, as well as promote proliferation of epithelial cells (McGeachy et al., 2019). As another proinflammatory cytokine produced by Th17 cells, IL-22 can also promote epithelial cell proliferation, and tumor outgrowth and metastasis, which may be mediated by *STAT3*, an oncogene (Eyerich et al., 2017; Aggor et al., 2020).

γδ-T cells are non-conventional lymphocytes which can also produce IL-17 to resist the invasion of *C. albicans*. It was reported that γδ-T cells induced the accumulation of neutrophil and breast cancer metastasis by producing IL-17 (Coffelt et al., 2015). Similarly, a recent study demonstrated that $V\gamma4^+$ and $V\gamma6^+$ γδ-T cells, mainly the PD-1^+ and IL-17 producing tumor-infiltrating γδ-T cells showed protumorigenic roles in colorectal cancer progression (Reis et al., 2022). Even more interesting is that the use of a broad-spectrum antibiotic cocktail could reduce the frequency of IL-17 and PD-1 expressing γδ-T cells in these mice (Reis et al., 2022). Our research being published also found the significant enrichment of IL-17 signaling pathway in oral tumors with chronic *C. albicans* infection in mice model, which indicates the role of unrestrained IL-17 signaling in *C. albicans* promoting oral cancer.

4.2.3. Synergy with bacteria

Inter-kingdom interactions between *C. albicans* and bacteria may provide a pathway for *C. albicans* to promote cancer development. *C. albicans* infection could disrupt the mucosal bacterial diversity with a significant enrichment of *Streptococcal* and *Enterococcal* species (Bertolini and Dongari-Bagtzoglou, 2019a; b). The *Enterococci* isolated from mice with oropharyngeal candidiasis were involved in degrading the epithelial junction protein and increasing the permeability of the epithelial barrier (Bertolini et al., 2019). Additionally, coexistence of *C. albicans* and *Enterococci* could up-regulate inflammatory cytokines (Du et al., 2021). The metabolites from dual biofilms of *C. albicans* and *S. aureus* were reported to upregulate oncogenes (*PI3KCA* and *hRAS*) as well as cell cycle genes (*Bcl-2* and *CDKN1A*) in cancer cells (Amaya et al., 2021). The internalization of *H. pylori* into *C. albicans* protected *H. pylori* from strict conditions (Chen et al., 2021).

4.3. The formation of microenvironment facilitating cancer development

The *C. albicans* infection may finally induce an immunosuppressive microenvironment with persistent inflammatory stimuli and proliferative signals, which contributes to cancer development.

4.3.1. Chronic inflammation

C. albicans infection can upregulate multiple proinflammatory cytokines, such as IL-1β, IL-6, IL-8, IL-17, IL-18, TNF-α, and IFN-γ (Hofs et al., 2016). The overexpression of TNF-α and IL-18 caused by *C. albicans* was revealed to promote the hepatic metastasis in mice bearing murine B16 melanoma (Rodriguez-Cuesta et al., 2010). The induction of IL-1β might participate in the oral cancer development in mice with *C. albicans* infection (Lee et al., 2020). Additionally, the inflammatory cytokine dysregulation associated with *Candida* infection might be associated with oral carcinogenesis (Gupta et al., 2021) and breast tumor growth (Ahmadi et al., 2019).

4.3.2. Dysregulated proliferative signals

As discussed above, the EGFR and MAPK signals are activated during *C. albicans* invasion. Both EGFR and MAPK signals are key regulators in cell proliferation, survival, and cancer development (Guo et al., 2020; Sabbah et al., 2020). As a result, the increased cell proliferation markers Ki67, p53 and PCNA could be detected in the tissues with *C. albicans* infection (Kaplan et al., 1998; Dwivedi et al., 2009).

4.3.3. Immunosuppressive microenvironment

Immune checkpoints (ICPs) and immunosuppressive myeloid cells including myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) in the tumor microenvironment are important factors for cancer progression (Nakamura and Smyth, 2020). ICPs are important factors for tumor immunosuppressive microenvironment. A single-cell RNA-sequencing study demonstrated that the immune checkpoints CTLA-4 and PD-1 pathway were up-regulated in immunocytes stimulated with *C. albicans* (Deng et al., 2021). Additionally, *C. albicans* also induced the expression of PD-L1 in cancer cells (Wang et al., 2022). Another single-cell RNA-sequencing study found a crucial role of certain clusters of macrophages in OSCC carcinogenesis with *C. albicans* infection (Hsieh et al., 2022). From our unpublished work, there was more tumor-infiltrating macrophages in the 4NQO mice with *C. albicans* infection, while deleting the local macrophages could alleviate the oral tumor progression caused by *C. albicans* infection. The Dectin-1 signal activated by *C. albicans* infection was able to induce infiltration of Tregs and MDSCs in the tongues, which was correlated with OSCC progression (Bhaskaran et al., 2021). Similarly, our unpublished work also demonstrated that MDSCs in peripheral blood was

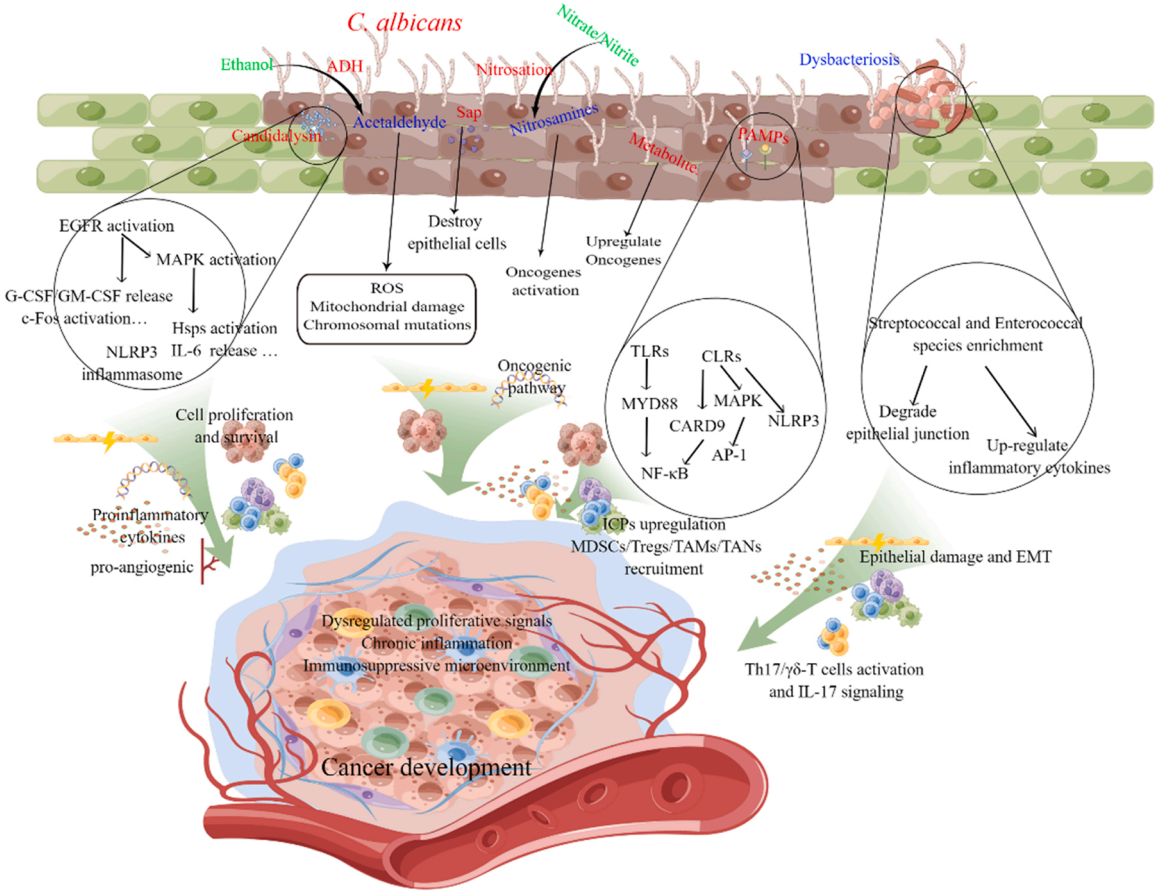

Fig. 2. Potential mechanisms of *C. albicans* in promoting cancer development and progression. (This figure was created using Figdraw: https://www.figdraw.com/, certificate number is REG8220722009900040226).

evaluated in the 4NQO mice with *C. albicans* infection.

4.4. Others

It's worth noting that genetic factors from both *C. albicans* and the host may be involved in *C. albicans* promoting cancer. From the aspect of *C. albicans*, as discussed above, most of the *C. albicans* isolated from precancer and cancer lesions belong to serotype A. *C. albicans* strains from lung cancer patients seemed to cause more incidence of carcinoma in mice, though with no significant difference (Wang et al., 2019). As for the host, patients with *STAT1* or *AIRE* gene mutations are prone to chronic *C. albicans* infection and subsequent squamous cell cancer. Squamous cell carcinomas were found in 4% of the chronic mucocutaneous candidiasis (CMC) patients with *STAT1*-GOF mutations, which patients had suffered from a long-term candidiasis (Okada et al., 2020). Similarly, the incidence of oral or esophageal squamous cell carcinoma in Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) patients with *AIRE* gene mutations was 6–10.5% in their young ages, which might be associated with CMC (Rautemaa et al., 2007; Humbert et al., 2018).

5. Conclusion and perspectives

As one of the most common fungi isolated from healthy and cancer patients, *C. albicans* is associated with the development and progression of various types of cancer. Among them, oral cancer is the most studied cancer with relatively strong evidence supporting *C. albicans*'s role in oral cancer progression. Besides, many researchers also noticed and explored the associations between *C. albicans* and gastric cancer, colorectal cancer, esophageal cancer and other types of cancer, but with relatively insufficient evidence (Fig. 1). Thus, more clinical and laboratory evidence is necessary in order to support the role of *C. albicans* in cancer development.

Though a definite carcinogen has not been found within *C. albicans*, its cell wall components, candidalysin, enzyme, and metabolites seem to participate in the cancer development (Fig. 2). Remarkably, considering that candidalysin can activate various signals associated with cancer progression, it makes sense to further explore its role in carcinogenesis. Additionally, the biotypes of *C. albicans* should not be ignored.

C. albicans may promote cancer progression by producing carcinogenic metabolites, inducing chronic inflammation, remodeling immune microenvironment, activating pro-cancer signals, and synergizing with bacteria (Fig. 2). Previous studies mainly focused on the production of nitrosamines and acetaldehyde. Now, increasing research has revealed the tumor microenvironment shaped by microbial invasion. Thus, future studies are suggested to explore the roles of *C. albicans* infection in the induction of IL-17 producing γδ-T cells and the accumulation of MDSCs, Tregs, TAMs and tumor-associated neutrophils (TANs) during cancer progression.

Conflict of interest

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

Data Availability

No data was used for the research described in the article.

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Supplementary information

Supplemental material includes Table S1 and Table S2.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.micres.2023.127370.

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