

REVIEW ARTICLE

***Candida albicans* and cancer: Can this yeast induce cancer development or progression?**Andoni Ramirez-Garcia¹, Aitor Rementeria¹, Jose Manuel Aguirre-Urizar², Maria Dolores Moragues³, Aitziber Antoran¹, Aize Pellon¹, Ana Abad-Diaz-de-Cerio¹, and Fernando Luis Hernando¹¹Department of Immunology, Microbiology, and Parasitology, ²Department of Stomatology II, and ³Department of Nursing, University of the Basque Country (UPV/EHU), Leioa, Spain**Abstract**

There is currently increasing concern about the relation between microbial infections and cancer. More and more studies support the view that there is an association, above all, when the causal agents are bacteria or viruses. This review adds to this, summarizing evidence that the opportunistic fungus *Candida albicans* increases the risk of carcinogenesis and metastasis. Until recent years, *Candida* spp. had fundamentally been linked to cancerous processes as it is an opportunist pathogen that takes advantage of the immunosuppressed state of patients particularly due to chemotherapy. In contrast, the most recent findings demonstrate that *C. albicans* is capable of promoting cancer by several mechanisms, as described in the review: production of carcinogenic byproducts, triggering of inflammation, induction of Th17 response and molecular mimicry. We underline the need not only to control this type of infection during cancer treatment, especially given the major role of this yeast species in nosocomial infections, but also to find new therapeutic approaches to avoid the pro-tumor effect of this fungal species.

Keywords

Carcinogen, carcinogenesis, inflammation, metastasis, tumor

History

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Introduction

Cancer is one of the most serious health problems faced by many individuals in the course of their life. As the disease progresses, there is uncontrolled cell growth, tissue invasion, and in the worst cases, metastasis. This disease progression requires the shedding of malignant cells from the primary tumor and their intravascular migration to another organ where they adhere and proliferate, in a similar way to the primary tumor. With the biotechnology revolution and the development of biomedicine, there have been important advances in the detection, control and even cure of the disease, depending on the type of cancer and stage at diagnosis. However, this dreaded disease continues to be associated with death, suffering and often a high economic burden. Specifically, cancer figures among the leading causes of death worldwide and accounted approximately 8.2 million deaths in 2012, being metastases the main cause of death from cancer (Ferlay et al., 2012).

Cancer has been linked to microbial infections because they are a likely consequence of transient immunodeficiency, this being commonly seen in cancer patients mainly due to chemotherapy. Our immune system is normally prepared to

maintain a balance with the microbiota of our bodies and to combat most microbial invasions. In contrast, in immunosuppressed states, created by cancer treatments, these functions are impaired and patients are at an increased risk of infection.

Interestingly, it seems that the inverse process is also possible, and there is a steady increase in the publication of studies that link the presence of microorganisms with a higher risk of developing cancer. Many of these publications also describe how microorganisms are, in various ways, involved in the initiation, establishment or spread of cancer.

Several mechanisms are implicated in this relation between infection and cancer development. One of them is the direct alteration in the DNA damage response, resulting in the appearance of genetic mutations that accumulate inside the cell and/or the expression of oncogenes that modify cell survival and proliferation. The pathogenic agents most widely studied as inducers of cancer by this mechanism are a range of viruses. In particular, the following viruses have been classified by the International Agency for Research on Cancer (IARC) as “carcinogenic to humans”: Epstein–Barr virus (EBV), hepatitis B virus (HBV), several types of human papillomavirus (HPV), human T-cell lymphotropic virus type 1 (HTLV-1), hepatitis C virus (HCV), Kaposi’s sarcoma-associated herpes virus (KSHV), also known as human herpes virus 8 (HHV-8) and human immunodeficiency virus type-1 (HIV-1). Conservative estimates suggest that 12% of the global cancer burden may be attributed to viruses, the

Address for correspondence: Andoni Ramirez-Garcia, Department of Immunology, Microbiology, and Parasitology, University of the Basque Country (UPV/EHU), Leioa 48940 Spain. E-mail: andoni.ramirez@ehu.es

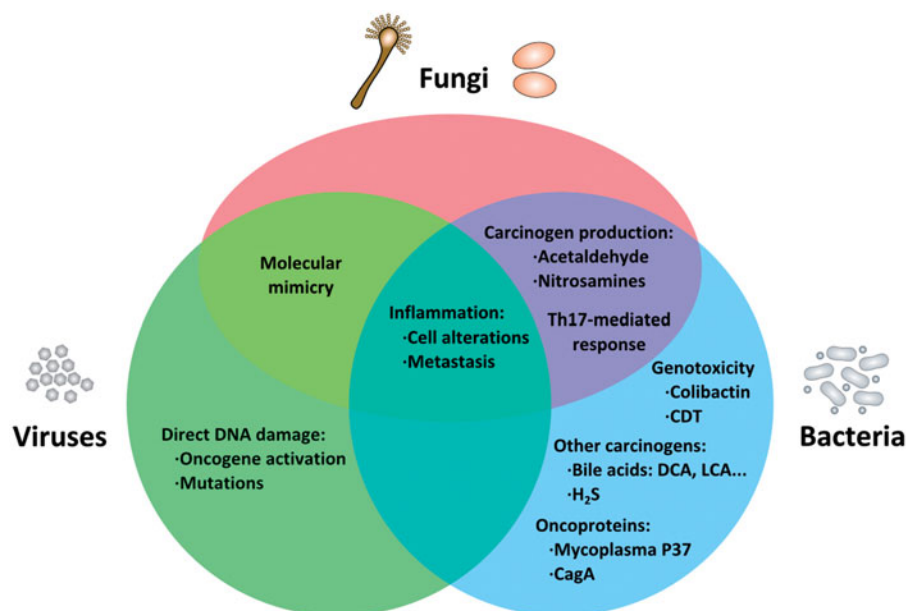
percentage being even higher in developing countries (Parkin, 2006).

However, although infection may be important, it does not seem to be by itself able to cause cancer (Sarid & Gao, 2011). In relation to this, current evidence indicates that some pro-cancerous infections are closely related to inflammation. This is another mechanism that could favor the development of primary tumors and metastases. Infections may alter the tumor microenvironment by inducing the expression of cytokines involved in cell proliferation, and migration. This occurs, for example, in colorectal cancer due to *Fusobacterium* spp. (Keku et al., 2013; Kostic et al., 2013; McCoy et al., 2013; Rubinstein et al., 2013), and in hepatocellular carcinoma due to HBV (Na et al., 2011) and EBV (Baumforth et al., 2008; Chetaille et al., 2009; Heller et al., 2008) infections. Moreover, the carcinogenesis induced by *Helicobacter pylori*, which is responsible for a high percentage of gastric cancers (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1994; Kato et al., 2007; Parkin, 2006), is related to the inflammation it causes, as well as many other factors (Tepes, 2009). It has even recently been suggested that commensal microbiota play a role in inflammation-induced cancer (Elinav et al., 2013; Schwabe & Jobin, 2013). In addition to inflammation, there are other mechanisms by which viruses and bacteria are able to promote cancer development or progression, such as genotoxicity, molecular mimicry and production of metabolic carcinogens.

On the other hand, relatively few studies have analyzed the influence that fungal diseases might have on tumor establishment and progression. Among the few that have been reported, one study found that tumor size in mice increased significantly after infection with *Aspergillus* conidia (Sohrabi et al., 2010) and, above all, several studies concerning *Candida albicans* and its relationship with cancer, make clear that fungi, like viruses and bacteria, should be taken into account in investigating cancer. Figure 1 shows a schematic comparison of the processes that promote carcinogenesis described in viruses, bacteria and fungi.

Figure 1. Carcinogenic mechanisms involving viruses, bacteria and fungi. CDT, cytolethal distending toxin; DCA, deoxycholic acid; LCA, lithocholic acid.

In this review, we focus on the dimorphic fungus *C. albicans* and its relationship with cancer. This yeast is a normal commensal of the human body and, as such, induces no damage. However, it is capable of becoming pathogenic when the host defenses are weakened. In such situations, *C. albicans* is able to disseminate hematogenously, and spread to multiple organs potentially causing serious problems. The relation between cancer and *C. albicans* infections has been widely studied because candidiasis is favored by the immunosuppressed state resulting from intensive chemotherapy for cancer (Almirante et al., 2005; Anttila et al., 1994; Boehme et al., 2009; Lalla et al., 2010; Lamaris et al., 2008; Matsuda et al., 2009; Pemán et al., 2002; Rafailidis et al., 2008; Ruhnke & Maschmeyer, 2002). However, it has recently been proposed that invasive candidiasis may be not only a presenting symptom of cancer, but also a predictor of cancer risk in later years (Norgaard et al., 2013). A potential explanation for this is that candidiasis and cancer share some common risk factors, such as various comorbidities, related medication, lifestyle and suppression of the immune system (Norgaard et al., 2013). What is more, studies published in recent years (Gainza-Cirauqui et al., 2013; Ramirez-Garcia et al., 2011, 2013; Rodriguez-Cuesta et al., 2010) provide cumulative evidence that *C. albicans* is even able to stimulate the onset and development of cancerous processes. These studies describe several mechanisms by which this yeast species can promote cancer: one is based on *C. albicans* producing carcinogens such as acetaldehyde which can favor the development of the disease; another pathway is via the induction of an inflammatory process that may favor metastatic progression; and there are other possible processes related to molecular mimicry, and the Th17 response of our immune system. In this review, we not only describe candidiasis as a likely consequence of the weakness of cancer patients, but also outline evidence that the opposite effect is also possible, namely, that candidiasis, subclinical infection with this yeast species and possibly even some byproducts of its metabolism favor the development of cancer or metastatic processes. To achieve this goal, we discuss a series of key questions to improve our understanding of the



different potential mechanisms of action of this fungus in cancer.

Are *Candida* infections a consequence of cancer?

The idea that there is a relation between candidiasis and cancer is not new. Ten years ago, Girmenia et al. (2004) noted that focal lesions in the liver or spleen (where *Candida* is cleared from the blood) after recovery from chemotherapy-induced neutropenia are a diagnostic sign of *Candida* infection. The penetration of this fungal species into the bloodstream and its dissemination hematogenously, causing candidemia, can be life threatening, especially in immunocompromised patients and those hospitalized with serious underlying diseases such as hemato-oncological malignancies (Nucci & Marr, 2005; Tortorano et al., 2004, 2006).

In recent decades, the prevalence of candidiasis in hospitals has increased and this has been attributed to the use of catheters and immunosuppressive treatments, above all chemotherapy, which promotes these infections (Almirante et al., 2005; Lalla et al., 2010). In consequence, diseases involving *Candida* species are also increasingly common in cancer patients (Anttila et al., 1994).

For example, it is notable that as many as 35% of candidemias were found in patients with hematological malignancies or solid tumors as the underlying disease (Zirkel et al., 2012), solid tumors being the most common underlying condition in patients with candidiasis (Pemán et al., 2002). As a complication of cancer and its treatment, these infections are associated with a higher mortality rate, prolonged hospitalization and rising healthcare costs (Leleu et al., 2002; Morgan et al., 2005; Pfaller & Diekema, 2007; Rentz et al., 1998; Sipsas et al., 2009; Wey et al., 1988; Zaoutis et al., 2005). For example, a European survey detected a mortality rate of 45% in hemato-oncological patients (Tortorano et al., 2004), and other analyses from Finland and Spain confirmed this trend with mortality rates of 35 and 44%, respectively (Almirante et al., 2005; Cisterna et al., 2010; Poikonen et al., 2010). More recently, a retrospective study indicated that mortality was even higher after the diagnosis of *Candida* bloodstream infections, with 30- and 100-day mortality rates of 56 and 67%, respectively (Zirkel et al., 2012).

Consequently, it seems clear that *Candida* species do take advantage of the situation experienced by patients with a malignancy, worsening their condition, decreasing their chances of overcoming the disease and shortening their life expectancy. The impact of *Candida* seems to vary, however, with the severity of underlying disease, and even more importantly, on patients' degree of cellular immunosuppression.

Can *C. albicans* induce cancer by producing carcinogenic substances?

There has been particular interest in the putative relation between *Candida* and cancer in the case of mucosal carcinomas, above all, in sites where the presence of the fungus is most common, namely, genital and oral mucosa. Among them, oral carcinogenesis has been the most widely

studied to explore the role of the fungus in the development of this cancer.

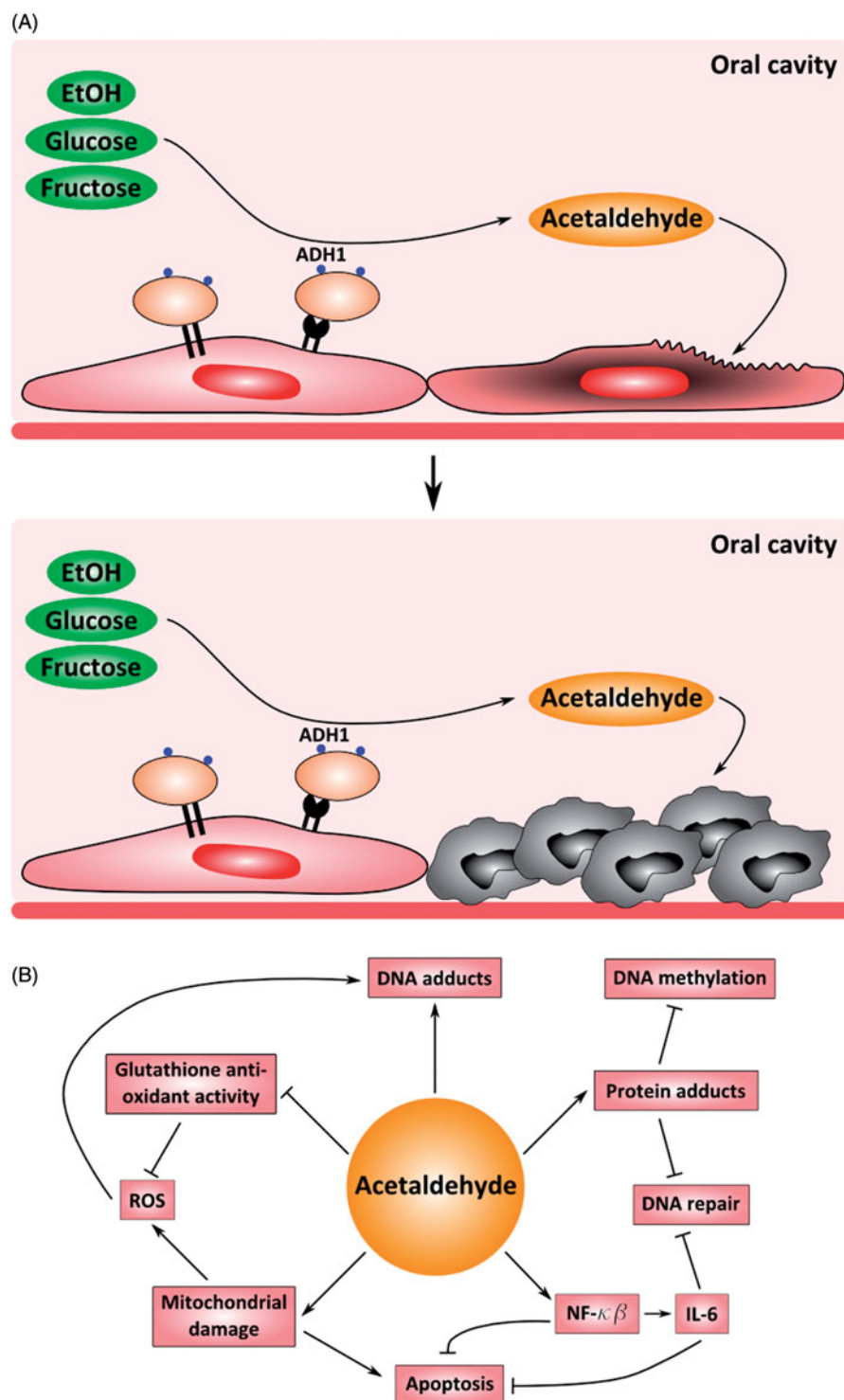
Cawson (1969) and Williamson (1969) were the pioneers in reporting the association of *Candida* with the progression of the epithelial dysplasia in oral mucosa; i.e. oral carcinogenesis. Since then, several studies have demonstrated that oral cancer and pre-cancer lesions are frequently infected by *Candida* species. However, currently there is insufficient evidence to conclude that this pathogenic relation is true or, in contrast, that it is simply a circumstance concurrent with the opportunistic infection caused by this yeast (Hooper et al., 2009; Meurman & Uittamo, 2008; van der Waal, 2010).

The most widely accepted hypothesis about the carcinogenic effect of *Candida* species, *C. albicans* being the dominant species, on the mucosal epithelium is related to the production of carcinogens and/or the metabolism of pro-carcinogens. A series of classic studies published years ago (Krogh, 1990; Krogh et al., 1987a,b) suggested that *C. albicans* might play an important role in oral carcinogenesis because it was able to produce nitrosamines, which are carcinogens that could act alone or in combination with other chemical compounds. The consequence of this is the activation of specific proto-oncogenes that could trigger the development of a cancerous lesion. The findings of these studies were supported by other research such as a study demonstrating that *C. albicans* could act as a promoter of carcinogenesis in the rat tongue after repeated applications of a nitroquinolone (4-nitroquinoline 1-oxide) (Ogrady & Reade, 1992).

Unfortunately, after these initially promising results, there has been a lack of continuity in the research in this field, and these interesting findings have not been adequately confirmed (Hooper et al., 2009). One of the few contributions is the recent study by Sanjaya et al. (2011), who re-examined the hypothesis that *C. albicans* can produce carcinogenic nitrosamines, which are capable of triggering dysplastic changes in the oral epithelium or carcinoma.

Regarding the metabolism of pro-carcinogens, there are studies supporting the view that while ethanol itself is not carcinogen when studied *in vitro* with human tissue culture cells or with animal models, acetaldehyde is toxic, mutagenic and indisputably carcinogenic, and therefore, it is a risk factor for carcinoma (Poschl & Seitz, 2004). Acetaldehyde is produced as the first metabolite of ethanol catabolism by the enzyme alcohol dehydrogenase (ADH), which is active both in epithelial cells and in oral microbiota, such as *C. albicans* (Figure 2A). In the oral cavity, acetaldehyde produces DNA and protein adducts, aberrant molecules with structural and functional alterations [reviewed in Seitz & Stickel, (2007); Figure 2B]. Acetaldehyde-induced DNA adducts interfere with normal DNA replication causing point mutations and chromosomal aberrations. Enzymes involved in cytosine methylation and DNA repair are also affected by this compound, promoting proto-oncogene activation and cell cycle disturbances, which may result in tumor development (IARC, 1999). Moreover, acetaldehyde binds to glutathione, an essential anti-oxidative peptide, indirectly increasing the presence of reactive oxygen species (ROS), which are related to an increase in DNA damage. Mitochondrial damage is also induced by acetaldehyde, increasing cell apoptosis, but also

Figure 2. Role of *Candida albicans* in tumor genesis by production of carcinogenic substances. (A) *C. albicans*, using the enzyme alcohol dehydrogenase (ADH1), is capable of metabolizing alcohol and other substances, such as carbohydrates, to acetaldehyde, which is carcinogenic. (B) Acetaldehyde is able to induce tumor development through various different pathways. This carcinogen binds to proteins and DNA modifying their structure and functionality, and reduces antioxidant activity of glutathione increasing the levels of reactive oxygen species (ROS) in the cell. These alterations may produce genome instability, which linked with an inhibition of the apoptotic machinery, may result in tumor development.



ROS and survival factors, such as NF- κ B, which favor tumor cell progression (Manzo-Avalos & Saavedra-Molina, 2010; Seitz & Homann, 2007).

In line with this, several studies have reported that *Candida* species promote carcinogenesis by producing acetaldehyde from ethanol (Mohd Bakri et al., 2010; Nieminen et al., 2009; Uittamo et al., 2009). Notably, *C. albicans*, *C. tropicalis* and *C. parapsilosis* produce more acetaldehyde than other species of this genus, in most cases exceeding carcinogenic levels (>100 μ M; Nieminen et al., 2009). Interestingly, *C. albicans* isolates from high acetaldehyde-producing saliva samples

showed the greatest capacity to generate acetaldehyde (>100 nmol/10⁶ CFU; Tillonen et al., 1999). Moreover, a recent study has shown that *C. albicans* strains isolated from patients with oral leukoplakia produce more carcinogenic acetaldehyde from ethanol than those from other potentially malignant oral mucosal disorders (Gainza-Cirauqui et al., 2013). Oral leukoplakia has been associated with a higher risk of malignant transformation than oral lichenoid lesions (van der Waal, 2010), and if untreated 5–10% of the patients will develop carcinoma (Krogh et al., 1987b). This observation supports the idea that this ability of *C. albicans* may

contribute, along with other factors like tobacco or alcohol consumption, to this carcinogenic effect.

In addition, another recent study (Marttila et al., 2013) has shown that *C. albicans* can also produce high levels of acetaldehyde under low oxygen concentrations. This finding underlines the relation between poor oral hygiene and squamous cell carcinoma of the oral cavity, because substrates that could be metabolized to produce acetaldehyde would be available for the microbiota for longer periods (Meurman & Uittamo, 2008). In relation to this, it should also be noted that other microbes of the human microbiota, apart from *C. albicans*, may also be involved in this carcinogen production (Schwabe & Jobin, 2013). In fact, the concentration of acetaldehyde can be up to 100 times higher in saliva than in blood due to the limited metabolism of acetaldehyde to acetate by oral bacteria (Seitz & Stickel, 2007, 2010).

However, since after the ingestion of ethanol, it is absorbed from the gastrointestinal tract and circulated in the bloodstream, acetaldehyde can also be produced in other organs such as the intestine, liver or blood, where *C. albicans* may be present. Hence, it cannot be ruled out that this acetaldehyde-mediated carcinogenesis mechanism plays a role in locations other than the oral cavity.

Can *C. albicans* promote metastasis by inducing an inflammatory response?

For some years, it has been recognized that there is a relationship between inflammation and cancer (Coussens & Werb, 2002). The existence of this relation is supported by epidemiological studies that have attributed as many as 25% of cancer deaths worldwide to chronic inflammation (Balkwill & Mantovani, 2001). This may be associated with autoimmune diseases (inflammatory bowel disease), inflammatory conditions of unknown origin (e.g. prostatitis) and smoking, among other factors. It is well-documented that all of these factors increase the risk of certain cancers, but more importantly for this review, it is also clear that chronic inflammation can also be related to microbial infections (Slattery et al., 2009).

The classic role of these inflammatory pathways in the functioning of our immune system is to avoid or remove infections. However, the inflammatory state is also necessary to maintain and promote cancer progression and accomplish the full malignant phenotype, such as tumor tissue remodeling, angiogenesis, metastasis and the suppression of the anticancer innate immune response (Wang et al., 2009). The connection between inflammation and cancer can be thought of as consisting of two pathways: an extrinsic mechanism, in which a prolonged inflammatory microenvironment contributes to increasing the risk of cancer and promotes its progression; and an intrinsic mechanism, in which acquired genetic alterations such as activation of oncogenes trigger tumor development. Several infectious agents are considered to be causes of cancer in humans, and it was estimated that infection-attributable cancer accounted for 17.8% of the global cancer burden in the year 2002 (Parkin, 2006). The effect of *C. albicans* on promoting metastasis seems to be based on an inflammatory process,

which is accomplished in various successive steps that are explained below.

Inflammatory response against *C. albicans* and the cancer cascade

Initially, endothelial cells are responsible for the first contact with the microorganisms when they disseminate. That is the reason why research with endothelial cells is of special relevance for studying the initial adhesion of *C. albicans* during the spreading by the bloodstream to different organs (Citiulo et al., 2012; Cleary et al., 2011; Falkensammer et al., 2007; Filler et al., 1995, 1996; Glee et al., 2001; Grubb et al., 2009; Jong et al., 2003; Kurihara et al., 2003; Lim et al., 2011; Mayer et al., 2012; Orozco et al., 2000; Park et al., 2009; Phan et al., 2000; Ramirez-Garcia et al., 2011, 2013; Sanchez et al., 2004; Seidl et al., 2012; Zhao et al., 2007). Once there, the recognition of the microorganisms is accomplished by pattern recognition receptors (PRRs), which recognize conserved structures called pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs; Gauglitz et al., 2012; Janeway, 1989; Medzhitov & Janeway, 1997; Mogensen, 2009). So far, of all PRRs, researchers have explored the involvement in the recognition of *C. albicans* of three main groups, Toll-like receptors (TLR), C-type lectin receptors (CLR) and Nod-like receptors (NLR), and also Mac-1 integrin (Cheng et al., 2012; Filler, 2006; Gauglitz et al., 2012; Netea & Marodi, 2010). However, we are still in the early stages of understanding the complexity of fungal recognition by endothelial cells, and almost everything we know has been obtained from models with other cell lines (Table 1).

Upon PAMP recognition, PRRs signal shows the presence of infection to the host, at the cell surface or intracellularly, by activating multiple intracellular signaling pathways, including adaptor molecules, kinases and transcription factors (Akira & Takeda, 2004). These PRR-induced signals ultimately result in the activation of gene expression and synthesis of a broad range of molecules including cytokines, cell adhesion molecules and immunoreceptors (Akira et al., 2006; Mogensen, 2009), responsible for pro-inflammatory and antimicrobial responses.

The inflammatory response after recognition of *C. albicans* has been less studied in endothelial cells than in other cell types, but with the evidence accumulated over recent years, it seems clear that numerous cytokines are involved (Table 2). Some of these, such as CXCL1, CXCL2 and CXCL3, are very closely related to tumorigenesis and angiogenesis in cancer (Belperio et al., 2000; Haghnegahdar et al., 2000; Moore et al., 1998; Strieter et al., 2004, 2005). It should be noted, however, that this is to be expected since due to their association with inflammation, most pro-inflammatory cytokines are in one way or another related to cancer. Specifically, to date, the role of *C. albicans* in tumor adhesion and metastasis has been linked to TNF- α and IL-18 (Ramirez-Garcia et al., 2011, 2013; Rodriguez-Cuesta et al., 2010).

Increase in tumor cell adhesion by *C. albicans*

In recent years, evidence has been growing that *C. albicans* might promote cancer and metastasis through a

Table 1. Pattern Recognition Receptors involved in the innate immune response against *Candida albicans*.

Receptor	Ligand	Studied model	Effect studied	References
TLR				
TLR-1	Unknown	Human PBMCs	TLR1 polymorphisms carriers are more susceptible to candidemia and produce lower levels of pro-inflammatory cytokines than non-carriers.	Plantinga et al. (2012)
TLR-2	Phospholipomannan	TLR2 $-/-$ mice, macrophages	Lack of TLR2 reduces susceptibility to <i>C. albicans</i> . TLR2 recognizes both blastoconidia and hyphae leading mainly anti-inflammatory cytokine release.	Blasi et al. (2005), Jouault et al. (2003), Netea et al. (2002, 2004), van der Graaf et al. (2005), Villamon et al. (2004)
TLR-3	Unknown	Human PBMCs, endothelial cells, and fibroblasts	TLR3 is involved in pro-inflammatory responses. Mutated TLR3 leads to increased susceptibility to chronic candidiasis.	Mueller et al. (2007), Nahum et al. (2012)
TLR-4	O-linked mannans	TLR4 $-/-$ mice, mouse macrophage/monocytes	Lack of TLR4 increases susceptibility to <i>C. albicans</i> . TLR4 mediates pro-inflammatory responses, being lost during <i>C. albicans</i> germination.	Blasi et al. (2005), Jouault et al. (2003), Netea et al. (2002, 2006), van der Graaf et al. (2005)
TLR-6	Phospholipomannan (probably)	Macrophages	Deviation of immune system towards Th2 response.	Netea et al. (2008)
TLR-7	Candida RNA (probably)	Dendritic cells	IFN- β production.	Bourgeois et al. (2011)
TLR-9	DNA	TLR9 $-/-$ mice, dendritic cells	Involvement in dendritic cell activation.	Miyazato et al. (2009)
CLR				
Mannose receptor	N-linked mannans	Mouse endothelial cells and macrophages	Increase of pro-inflammatory cytokine release and <i>Candida</i> -induced cancer cell adhesion.	Netea et al. (2006), Ramirez-Garcia et al. (2013)
DC-SING	N-linked mannans	Human dendritic cells	Involvement in phagocytosis and IL-6 production.	Cambi et al. (2008)
Dectin-1	β -glucans (TLR2 + dectin 1)	Dectin-1 $-/-$ mice, Mouse macrophages/monocytes	Lack of Dectin-1 increases susceptibility to <i>C. albicans</i> .	Brown et al. (2002), Netea et al. (2006), Taylor et al. (2007)
Dectin-2	High-mannosa (hypha) α -mannans (both)	Dectin-2 $-/-$ mice, dendritic cells and macrophages	Increase of pro-inflammatory cytokine production. Involved in pro-inflammatory cytokine production and Th17 response.	McGreal et al. (2006), Robinson et al. (2009), Saijo et al. (2010)
Langerin	β -glucans, Mannan	Human Langerhans cells	Recognition of <i>C. albicans</i> .	de Jong et al. (2010)
Galectin-3	β -1,2-oligomannans	Galectin-3 $-/-$ mice, Mouse and human macrophages	Soluble Galectin-3 molecule induces <i>C. albicans</i> death. Involvement in pro-inflammatory cytokine production.	Jouault et al. (2006), Kohatsu et al. (2006)
Mincle	Unknown	Mincle $-/-$ mice, Mouse and human macrophages	Lack of Mincle increases susceptibility to <i>C. albicans</i> and reduces pro-inflammatory cytokines.	Bugaric et al. (2008), Wells et al. (2008)
Scavenger receptors NLRs	β -Glucans	CD36 $-/-$ mice macrophages CHO cells	SCARF1 and CD36 are involved in fungal binding to receptor and production of cytokines.	Means et al. (2009)
NLRP3	β -Glucans (curdian)	NLRP3 $-/-$ mice, dendritic cells, macrophages	Lack of NLRP3 increases susceptibility to <i>C. albicans</i> and decreases IL-1 β production.	Gross et al. (2009), Hise et al. (2009), Joly et al. (2009), Kumar et al. (2009)
NLRP10		NLRP10 $-/-$ mice, dendritic cells, and macrophages.	Lack of NLRP10 increases susceptibility to <i>C. albicans</i> but do not affect pro-inflammatory cytokine production.	Joly et al. (2012)
NLR4		NLR4 $-/-$ mice	Lack of NLR4 increases susceptibility to <i>C. albicans</i> and reduces production of pro-inflammatory cytokines and antimicrobial peptides.	Tomalka et al. (2011)

Table 2. Molecules involved in endothelial cell response to *Candida albicans*.

Molecules	Technique	References
Cytokines		
IL-6	Northern blot	Filler et al. (1996)
CXCL8/IL-8	Microarray, northern blot and ELISA	Filler et al. (1996) Mueller et al. (2007)
CCL2/MCP-1	Northern blot	Filler et al. (1996)
TNF- α	ELISA and RT-PCR	Orozco et al. (2000), Ramirez-Garcia et al. (2011)
IL-1 α	RT-PCR	Orozco et al. (2000)
IL-1 β	RT-PCR	Orozco et al. (2000)
IL-18	ELISA and RT-PCR	Orozco et al. (2000), Ramirez-Garcia et al. (2013)
CXCL1/Gro α ,	Microarray	Barker et al. (2008), Mueller et al. (2007)
CXCL2/MIP-2 α /Gro β ,	Microarray	Barker et al. (2008), Mueller et al. (2007)
CXCL3/MIP-2 β /Gro γ	Microarray and RT-PCR	Barker et al. (2008), Mueller et al. (2007)
CXCL5/ENA78	Microarray and RT-PCR	Barker et al. (2008), Mueller et al. (2007)
CXCL6/GCP-2	Microarray and RT-PCR	Barker et al. (2008), Mueller et al. (2007)
CCL20/MIP-3 α	Microarray and ELISA	Barker et al. (2008), Mueller et al. (2007)
CCL3/MIP-1 α	Microarray	Barker et al. (2008)
CCL4/MIP-1 β ,	Microarray	Barker et al. (2008)
CXCL10	Microarray	Barker et al. (2008)
Adhesion molecules		
E-selectin	Northern blot	Filler et al. (1996)
ICAM-1	Northern blot, Microarray and RT-PCR	Filler et al. (1996), Mueller et al. (2007)
VCAM-1	Northern blot, microarray and RT-PCR	Filler et al. (1996), Mueller et al. (2007)
VEGF	Microarray and RT-PCR	Barker et al. (2008)
Others		
cyclooxygenase-2 (cox2)	Northern blot	Filler et al. (1996)

pro-inflammatory response, mediated by an increase in cytokine production and in adhesion-molecule expression.

In healthy individuals, the pro-inflammatory response is crucial to orchestrate an early host response to infection and, at the same time, to activate and recruit multiple different immune cells (Villar et al., 2005). However, patients with cancer are commonly treated with chemotherapy and, consequently, are immunosuppressed, which means that the population of leukocytes is reduced or even eliminated. Given this, circulating tumor cells, which may have evolved from a primary tumor, could be attracted and adhere to the endothelium instead of leukocytes, and this could be the first step in establishing secondary tumors and metastasis (Figure 3).

This phenomenon has mainly been studied in the liver because this organ plays a crucial role in the clearance of *C. albicans* and its antigens from the blood (Ramirez-Garcia et al., 2013; Sawyer et al., 1976). Specifically, it was first reported that a pro-inflammatory immune response of endothelial cells after stimulation with microbial molecules (LPS), tumor cells and other non-fungal microorganisms could contribute to melanoma cell adhesion and metastasis in the liver through a cytokine-dependent mechanism, as this mechanism increases the expression of the VCAM-1 used by certain melanoma cells to adhere to the endothelium (Mendoza et al., 1998; Rodriguez-Cuesta et al., 2005; Vidal-Vanaclocha et al., 2000). Nevertheless, despite the importance of bacterial nosocomial infections in cancer patients, which may favor metastasis through an inflammation-mediated process, no further studies with these types of models have been conducted so far.

More recently, this effect has been explored with *C. albicans* both *in vivo* and *in vitro*, it being demonstrated that this fungus can stimulate metastasis even when there is only sub-clinical infection (Ramirez-Garcia et al., 2011, 2013; Rodriguez-Cuesta et al., 2010). This pro-metastatic effect of

C. albicans in the liver might even be favored by hepatic endothelial cells, which have been described as a type of antigen-presenting cell. After stimulation by these hepatic cells, T cells differentiate into a regulatory T phenotype instead of a cytotoxic phenotype, inducing an immune tolerant state, which favors tumor cell survival (Berg et al., 2006; Boettcher et al., 2011; Knolle & Limmer, 2001; Limmer & Knolle, 2001; Onoe et al., 2005).

Are there other mechanisms by which *C. albicans* can promote tumor progression?

Besides the two mechanisms explained previously, some other hypotheses have been put forward to explain how *C. albicans* might promote cancer progression.

The first that we are going to consider here is related to the subset of CD4 T-cells that is dominant in the response against *C. albicans*, namely, the Th17 cells (Figure 4A). It is known that Th17 cells produce IL-17, which is required for resistance against *C. albicans* (Acosta-Rodriguez et al., 2007; Huang et al., 2004; LeibundGut-Landmann et al., 2007). However, other cytokines of the Th17 family such as IL-23 promote angiogenesis, and tumor incidence and growth (Langowski et al., 2006, 2007). Moreover, this cytokine antagonizes IL-12 and IFN- γ , both of which are crucial in Th1-type antitumor immune responses (Langowski et al., 2006, 2007). In addition to the direct effect of IL-17 on tumors, this cytokine can also favor cancer processes indirectly by recruiting neutrophils. These leukocytes are main effector cells against *C. albicans*, but their presence in tumor tissues also correlates with poor prognosis in some types of cancer (Donskov & von der Maase, 2006).

Although many bacterial species promote the activation of other Th cell responses, it has been observed that some can also activate the Th17 immune response (McGeachy & McSorley, 2012). Such bacterial species could, therefore,

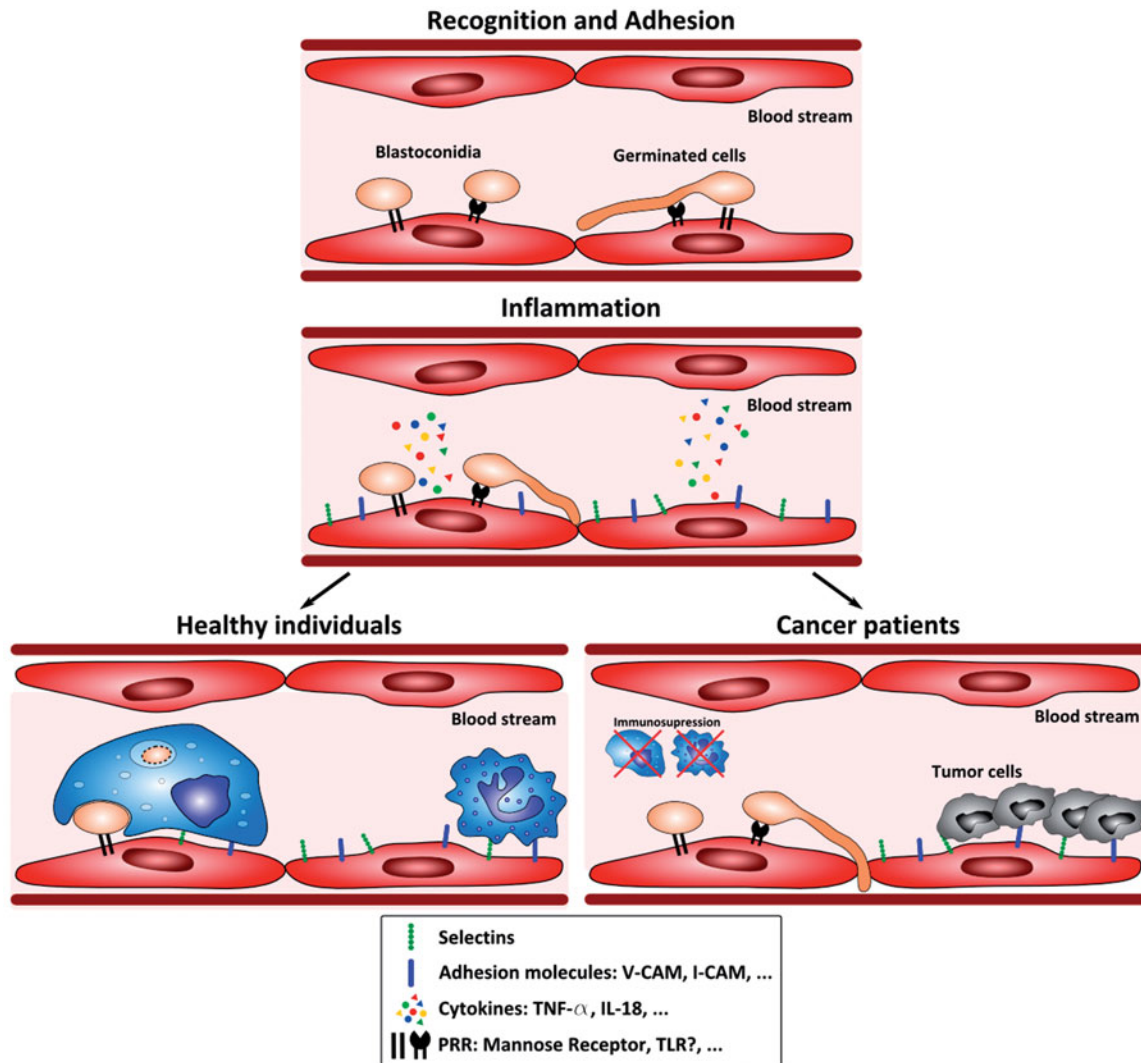


Figure 3. Increase in tumor cell adhesion and metastasis caused by an inflammatory response of endothelial cells after being stimulated by *Candida albicans*. This yeast adheres to endothelial cells and activates the production of cytokines and adhesion molecules. In healthy individuals, these molecules attract and recruit leukocytes to destroy the microorganisms. In immunosuppressed cancer patients, however, tumor cells may adhere instead of leukocytes and give rise to a secondary tumor. PRR, Pattern recognition receptors; TLR, Toll-like receptors.

be involved in carcinogenesis in a similar way to *C. albicans*. However, since the Th17 immune response is a key mechanism mainly related to anti-fungal immunity, the carcinogenic effects linked to this pathway should be further considered for fungal infections in particular.

Finally, there is another mechanism, associated with molecular mimicry of the complement receptor 3-related protein (CR3-RP) of *C. albicans*, which could favor cancer progression (Figure 4B). This protein has antigenic and structural similarities with the complement receptor 3 (CR3), also called Macrophage-1 antigen (Mac-1), which is required for the adhesion of leukocytes to the endothelium, for their subsequent extravasation. Therefore, antibodies against CR3-RP of *C. albicans* may cross-react with CR3 of leukocytes and disturb the anti-*Candida* and anti-tumor defense of the host (Gilmore et al., 1988; Gustafson et al., 1991; Hostetter, 1996). This theory might explain why serum IgG against *Candida* predicts survival in patients with metastatic renal cell carcinoma (Ramoner et al., 2010).

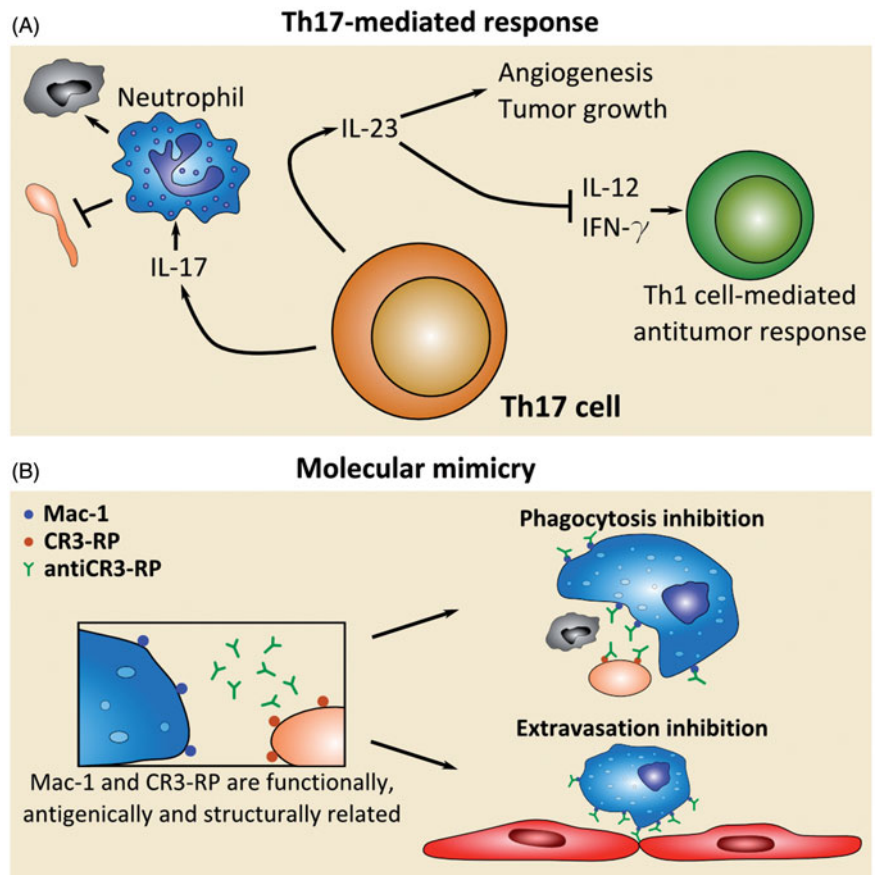
Though molecular mimicry associated with cancer promotion has not been observed for bacteria, it has been widely

described that there are many proteins encoded by viruses that mimic proteins involved in regulation of cell growth and survival and, in consequence, in cancer (Mesri et al., 2014).

Future perspectives: searching for molecular targets against pro-tumor and pro-metastatic effects of *C. albicans*

It is now common to use antifungal drugs, such as azoles, in patients treated for cancer to prevent invasive yeast infections, due to the increased risk and incidence of candidemia (de Pauw, 2004; Pfaller et al., 2010), in spite of most antifungals being potentially toxic and their overuse generating unnecessary direct and indirect costs (Parvez, 2003; Schlesinger et al., 2009). These problems might be avoided by more specific drugs that could potentially be designed if we knew more about the mechanisms explained in this review and the molecules involved, which could be new molecular targets. The design of novel specific treatments against these molecules could inhibit the dissemination of the fungus and, at the same time, its pro-tumor effect.

Figure 4. (A) Effect of Th17 response induced by *Candida albicans* on cancer. Th17 cells produce IL-17, which is required for resistance against *C. albicans* but favors cancer process indirectly by recruiting neutrophils. They also produce other cytokines, such as IL-23, which not only promote angiogenesis and tumor growth, but also antagonize with IL-12 and IFN- γ , both of which are crucial in Th1-type antitumor immune responses. (B) Molecular mimicry of the complement receptor 3-related protein (CR3-RP) of *C. albicans* with the Macrophage-1 antigen (Mac-1). Antibodies produced against CR3-RP of *C. albicans* may cross-react with Mac-1 of leukocytes and disturb the anti-*Candida* and anti-tumor defense of the host.



Recently published studies have opened the possibility of two main approaches to addressing the pro-metastatic inflammatory effect stimulated by *C. albicans*: the identification of the receptors involved in the recognition of the microorganism, and the characterization of the molecules of *C. albicans* recognized to initiate the process.

On the one hand, so far, only the involvement of the endothelial mannose receptor (MNR) has been studied. This receptor mediates most of the increase in tumor adhesion by this process, and its blockade reduces the effect by as much as 60% (Ramirez-Garcia et al., 2013). Although this could imply that the use of anti-MNR antibodies in therapies may help to reduce tumor invasiveness induced by *C. albicans* or its mannoproteins, the authors suggested that other receptors and pathways may also be involved in the same stimulation of the endothelium. It can be speculated that, among these other candidates, CXCR2 might have an important role in the process, since it is a receptor for the cytokines CXCL1/Gro α , CXCL2/Gro β , CXCL3/Gro γ , CXCL5/ENA78, CXCL6/GCP-2 and CXCL8/IL-8. The same could be said of IL-1R because is the receptor of the IL-1 superfamily, which include, among others, IL-1 α , IL-1 β and IL-18.

On the other hand, the mannoprotein fraction of *C. albicans* has been demonstrated to be of special relevance to the enhancement of tumor adhesion by stimulation of endothelial cells and inflammation. Proteins identified in this fraction include: alcohol dehydrogenase (ADH1), aminopeptidase Y (APE3), isocitrate dehydrogenase subunit (IDH2), enolase (ENO1), fructose-bisphosphate aldolase (FBA1), ketol-acid reductoisomerase (ILV5), disulfide isomerase (PDI1), phosphoglycerate kinase (PGK1),

ubiquinol-cytochrome-c reductase (QCR2) and translation elongation factor Tu (TUF1; Ramirez-Garcia et al., 2011). One of the proteins that increases tumor adhesion by induction of inflammation on endothelial cells, ADH1, has also been related to the first mechanism described in this review, namely, the stimulation of cancer via acetaldehyde production. The mannoproteins identified, especially ADH1, should be studied because of their potential role as therapeutic targets to avoid the effect of *C. albicans* on promoting cancer and metastasis.

Moreover, it should not be forgotten that CR3-RP of *C. albicans* is important for the last mechanism described, mimicry, and that there must be numerous other molecules, whose relation to cancer remains totally unknown. Hence, the mechanisms by which *C. albicans* favors angiogenesis, cancer progression and metastasis merit further study in the future to identify such molecules and improve our understanding of the processes involved.

Conclusion

It is well known that there is an increased risk of developing *C. albicans* and other infections during the immunosuppression caused by chemotherapy for cancer. However, this review has been focused on the growing strength of evidence that the reverse is also true. There are many studies reporting mechanisms by which bacteria and viruses stimulate cancer development or progression, but there are very few concerning the role of fungi in this context. Herein, we have described in depth a range of mechanisms by which *C. albicans* may be able to favor cancer development and dissemination.

The processes involved are related to the production of carcinogenic substances, inflammation, the Th17 response and molecular mimicry. Taking into account these mechanisms and that dead yeast and even the molecules it produces may be inducers of tumor processes, it can be concluded that the presence of *C. albicans* should be avoided in cancer patients. Moreover, consideration should be given to the possibility of including drugs, concurrently with anti-tumor therapies, to minimize the risk of *C. albicans* being present and its effects, including the creation of pro-tumor micro-environments. However, to develop appropriate treatments more research is required to deepen our understanding of the process by which *C. albicans* promotes cancer.

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