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Can Candida Albicans Induce Oral Cancer Development and Progression?

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Abstract **Original Research Article**

More than 90% of malignancies being squamous cell carcinoma originates from the oral mucosa and oral cancer is one of the most prevelant cancer worldwide. Candida species are common members of the oral microflora and are generally being regarded as commensals. However, they are able to cause a range of opportunistic infections and suggest a link between the presence of candida albicans in the oral cavity and development of Oral squamous cell carcinoma (OSCC). Candida species has been fundamentally linked to Cancereous processes as that takes advantage of the iumunosuppressed state of patients, particularly after Chemotherapy. However, this review will focus on the growing strength of the evidence that the Candida albicans is capable of promoting Cancer by several mechanisms: production of carcinogenic by products, triggering of Inflammation, induction of Th17 response, molecular mimicry that may be able to favour the Cancer development and dissemination. We underline the need not only to control this type of infection during Cancer treatment but also to find new therapeutic approaches to avoid the pro-tumour effect of this fungal species.

Keywords: Candida Albicans, Oral Squamous Cell Carcinoma (OSCC).

INTRODUCTION

Oral squamous cell carcinoma (OSCC) or Oral cancer is one of the most common malignancy seen throughout the world. C. albicans is a normal commensal of the human body [1], and therefore does not induce damage. But being an opportunistic one, it is capable of becoming pathogenic when the host defenses are weakened, causing an array of infections ranging from mucosal to systemic. There are evidence of role of this oral fungus in oral and esophageal carcinoma [2, 3]. In that Candida albicans is the most common pathogenic fungus [4]. There are many studies, who support this pathogenic microorganisms on the incidence rates of cancers worldwide [5]. However, the underlying mechanisms linking Candida colonization/infection with oral squamous cell carcinoma remains contentious [6]. Candida's ability to produce direct carcinogens such as nitrosamine [3], other mechanisms such as the induction of chronic inflammatory cytokines and metabolism of ethanol to the carcinogenic acetaldehyde can be involved in Candida-related oral carcinogenesis. Chronic exposure to microorganisms and/or their products, such as endotoxins (lipopolysaccharides) and enzymes (e.g. proteases, collagenases,fibrinolysin, phospholipase), which are toxic to the host cells may indirectly induce mutations or change the signalling pathways that will influence the cell proliferation and/or survival of epithelial cells [7, 8]. Candidas ability to form the biofilm and hydrolytic enzyme production are the essential virulence factors that enable this fungus to survive many challenging oral conditions and to adhere or invade the underlying host tissues [9, 10]. Oral candidiasis, (thrush) is one of the most common infections of the oral cavity characterized by fungal overgrowth, infiltration of superficial tissues involving the tongue and other oral mucosal sites. Chronic hyperplastic candidiasis (candidal leukoplakia) has been associated with the risk of malignant transformation to oral cancer [11, 12]. Hence, the chronic mucosal/epithelial colonization by Candida with enhanced virulence properties may have a role in oral carcinogenesis of host's skin, mouth, and gastrointestinal tract. So this suggest that the decrease in the host immunity enhances the risk of Candida infection. But still the association between fungal microbiota imbalance and carcinogenesis remains largely unknown, due to relatively low abundance of fungi and the lack of well-defined reference genome [13, 14]. Hence, in this article, we aim to review that Is C. albicans can induce and promote oral cancer progression.As this will eventually help us in diagnosing at the early stages and then form a treatment plan by considering the possible microbial properties in the process of carcinogenesis. In past many mechanisms of potential interactions between this fungal pathogen and oral carcinogenesis has been

described [15]. Which support the correlation between Candida infection and development of oral epithelial dysplasia [16], showing a series of histopathological changes that will affect the epithelial lining of the oral mucosae displaying increased risk of progression to oral squamous cell carcinoma (OSCC) or oral cancer [12]. Many prior researches have been done directly or indirectly linked to Candida and Oral cancer thus we also tried to find out that the candidiasis may not just be randomly coexisting with oral cancer, but can have the pathogenetic relationship in a dominant scenario, including the possibility that C. albicans may initiate or facilitate the development of oral cancer. Further, we describe the main proposed mechanisms by which this yeast species may induce cancer and highlight the need for further future mechanistic studies in oral carcinogenesis models to establish C. albicans as an opportunistic one, as it is found in one third of mouth of healthy patients with mean carriage rate of 18% and 41% in patients.

Virulence factor (table -1)

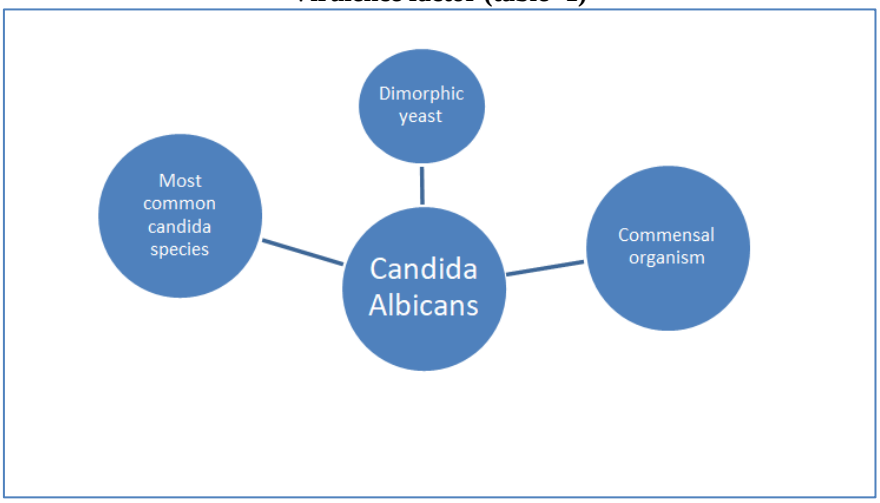

Table 1

VIRULENCE FACTOR	EFFECT
Adherence	Promote retention in the mouth.
Expression of cell surface adhesion molecule	Facilitates specific adherence mechanism
Evasion of host defenses	Promotes retention in the mouth
Hyphal development	Reduces likelihood of phagocytosis
Secreted Aspartyl proteinase production	Secretory IgA destrucion, host cell and extracellular matrix damage
Phosholipase production	Damage to host cells.

MATERIALS AND METHOD

Comprehensive reviews of the available previous literature relevant to Candida albicans and Oral cancer were undertaken. References for this review were identified through searches of PubMed with the search terms Candida albicans and Oral cancer up to august 2023. Only full length articles in English language were selected. Final references list was generated on the basis of originality and relevance while writing this review article.

DISCUSSION

The role of Candida albicans in the process of carcinogenesis tends to be complex, such as the role of virulence factors, the host genome, influence on the immune response, and oral dysbiosis, as noted in a review conducted by Di Cosola *et al.*, 2021 [17]. However, several studies have been conducted but no direct study of Candida albicans with OSCC or OPMD [18-23]. In general, there are many virulence factors of Candida albicans, mainly phenotype (Candida frequencies, hyphae, sphere, colonies, biofilm formation), genotype (Candida albicans alcohol dehydrogenase 1 (CaADH1) mRNA gene, genotypic diversity of Candida albicans strains, CSH), and metabolic production (acetaldehyde product, lipase, proteinase product, phospholipase, and esterase activity, NMBA production) [24–31]. Candida albicans damages epithelial mucosal cells and invades the host. As we know Epithelial mucosal cells are the first line of defense for the host protection against the invasion of these pathogenic microorganisms. Adhesion of this oral fungus C. albicans to epithelial cells is the first step of fungal colonization and invasion. Subsequently, it invades epithelial cells by inducing endocytosis and active infiltration, which is a main step in the pathogenesis of Candida .albicans [32- 34]. Invasive enzymes of C. Albicans will destroy the integrity of mucosal tissue structure and enhance its virulence. Hemolytic factors help them obtain nutrients for its survival and reproduction; phenotypic transformation can help C. albicans adapt to the host tissue environment; adhesin can assist in its colonization and invasion of host

cells [35- 38]. Once this fungus C. albicans invades the epithelial mucosal cells, it may induce apoptosis and necrosis, destroying the host epithelial defense barrier, and finally leading to the structural changes of epithelial cells [39, 40]. These are the preconditions for the cancer promoting C. albicans infection in which Epithelial cells are damaged and the normal structure is changed, which results in abnormal proliferation and the formation of oral cancer [41]. There is a significant positive correlation between C. albicans infection and oral mucosal epithelial dysplasia, and hence the deterioration of epithelial dysplasia induced by C. albicans infection occurs [42]. Multiple studies have showed that C. albicans could induce epithelial dysplasia and further malignant tumor formation [43, 44]. Candida albicans produces carcinogenic substances such as nitrosamine [6], and acetaldehyde [45]. Which plays a critical role in promoting cancer development. A study showed that C. albicans had higher nitrosation production potential than other fungi, and could convert N-benzyl methylamine (BMA) present in vegetables, herring oil, freeze-dried coffee and nitrite produced by other microorganisms in the host's mouth into N- nitroso benzyl methylamine (NBMA), thus inducing the occurrence and development of OSCC [46]. Candida promotes 4NQO-induced oral carcinogenesis. However, the mechanism of direct carcinogenesis is still controversial. It may also be due to the fact that the integrity of oral mucosal cell barrier, smoking and other risk factors enhance the virulence of C. albicans and jointly promote oral carcinogenesis [47]. Presence of Candida hyphae correlates with severity of dysplastic epithelial changes. A study has been conducted comparing the ability of Candida isolated from oral cancer patients and matched with oral healthy subjects to produce acetaldehyde. The results showed that Candida strains producing a large amount of acetaldehyde were more in patients with oral cancer than in healthy volunteers, further indicating the possible role of Candida in enhancing the occurrence of oral cancer [30]. C. Albicans may secrete alcohol dehydrogenase, which converts ethanol into acetaldehyde and participates in the carcinogenic process [48]. Acetaldehyde can induce DNA adducts to interfere with DNA replication, resulting in point mutation and chromosome aberration. At the same time, it will affect the enzymes involved in cytosine methylation and DNA repair, leading to protooncogene activation and cell cycle disorder, which may lead to tumor progression. In addition, acetaldehyde can also leads to mitochondrial damage and promote apoptosis, which can be activated by NF-kB to offset. For example, in GC, NF-kB induced IL-6 upregulates the antiapoptotic gene MCL1 to inhibit the DNA repair and process of apoptosis [49, 50]. The combination of acetaldehyde and glutathione indirectly increases the production of reactive oxygen species (ROS), thus inducing DNA damage, which is conducive to the progress of cancer [51- 53]. But, the correlation between the acetaldehyde concentration produced by C. albicans and the severity of cancer tissue is unknown, and hence,the mechanism to promote cancer development is still unclear. Candida albicans induces tumor microenvironment. Stromal cells are composed of fibroblasts, vascular cells and inflammatory immune cells, which together constitute the TME. Both chronic disease induced inflammation and tumor induced inflammation have a great impact on the composition of TME (tumour micro environment), especially on the plasticity of tumor and stromal cells. Inflammatory substances released by immune cells in TME can directly affect the precancerous cells and cancer cells by increasing cell proliferation and their resistance to cell death and stress, so as to directly promote tumor progression [54]. Therefore, chronic inflammatory response plays an major role in the occurrence and development of cancer. Persistent Candida epithelial mucosal colonization and infection can also cause a chronic inflammatory state. C. albicans recognizes Toll like receptors (TLRs) and C-type lectin-like receptors (CLRs), and then activates the corresponding MAPK and NF-kB. This Interferon and inflammatory signaling pathway promotes the expression of a variety of related inflammatory genes and play a role in the connection between benign and malignant diseases. Virulence factor "candidalysin" activates molecular pathways that have been implicated in carcinogenesis (MAPK pathway and activation of immune responses) in an EGFR-related manner [55]. Studies have shown that the expression of inflammatory factors prostaglandin E2 (PGE2) and MMPs (mainly MMP-9) are increased after C. albicans infection in oral epithelial cells [56, 57]. Also prostaglandins, cyclooxygenase (COX) enzymes and MMPs can inhibit tumor suppressor genes through DNA methylation and post-translational modification, leading to the occurrence and development of cancer [58]. Few Studies have shown that PGE2 are overexpressed in a variety of cancer types, including breast cancer [36- 59], and CRC [60]. However, C. albicans can induce human peripheral blood mononuclear cells (PBMC) to produce PGE2 [61]. PGE2 promotes the process of tumorigenesis by producing ROS, stimulating carcinogenic transcription factors thus inhibiting antitumor immune response [62], and enhancing angiogenesis [63]. Hyperactivation of type 1 immune responses leads to epithelial destruction and subsequent Candidal superinfection which is seen in APECED syndrome, a disease which correlates with uncommon OSCC development [64]. PGE2 inhibits the cytotoxic function of NK cells and prevents them from producing IFN-g, and hence promotes the malignant growth by avoiding type I interferon and T cell-mediated cell death. PGE2 promotes the inhibitory activity of Tregs, and hence contributes to the maturation of Tregs, thereby inhibiting antitumor immunity [57]. In addition to this PGE2 also increases MDSCs, and inhibits innate and adaptive antitumor immunity by downregulating cytokines of macrophages, inhibiting cytotoxicity of NK cells, blocking the activation of cytotoxic T cells, and hence regulating the development of Tregs. PGE2 facilitates bone marrow mesenchymal stem cells migration into the tumor environment, enabling the malignant cells to

proliferate without interference from the host immune system [57]. PGE2 binds to PGE receptor (EP1) and activates protein kinase d (protein kinase Cd, PKCd)/c-Src/AP- 1signaling pathway, upregulates intercellular adhesion molecule1 (ICAM-1), and promotes the metastasis of cancer cells [65]. However, the exact mechanism by which PGE2 produced by C. albicans in the process of chronic inflammation promoting the cancer development is not clear. Prior studies have shown that MMP-9 is highly expressed in cancer tissues such as oral cancer [66], GC [67], CRC [68], breast cancer [69], and cervical cancer [70], and has been used as a potential marker of cancers [71]. Some studies have shown that the high expression of MMP-9 leads to the enhancement of tumor invasion, which maybe because of the effect on the transforming growth factor (TGF-b1) induced epithelial mesenchymal transition (EMT) process, which promotes the invasion and metastasis of cancer [72]. At the same time, MMP-9 can degrade type IV collagen of basement membrane, destroying the integrity of basement membrane, and contribute to the invasion and metastasis of tumor cells [73]. MMP-9 degrades ECM components and activates angiogenic factor VEGF and TGF-b helping in cancer angiogenesis. Cleavage of osteopontin (OPN) also contributes to cancer metastasis [74]. These results suggest that MMP-9 has a role in cancer promoting mechanism. However, a study showed that epithelial origin MMP-9 exerts tumor inhibitory effect by activating MMP9-Notch1-ARF-p53 axis, resulting in increased apoptosis, and starts cell cycle arrest by activating p21WAF1/Cip1, and checks the damaged DNA until DNA repair. In addition to this in colitis associated CRC, MMP-9 can prevent gH2AX reduced levels of genotoxicity playing a tumor suppressive role [75]. Another study found that the expression of MMP-9 was related to the decrease of ROS level, the decrease of DNA damage and the upregulation of mismatch repair pathway. This suggests that the expression of MMP-9 is a natural biological way to inhibit CRC by limiting ROS accumulation and colonic DNA damage. Therefore, inhibition of MMP-9 may be harmful to patients with CRC [76]. Results indicate that MMP-9 has a protective host effect in CRC. Hence, MMP-9 has both cancer promoting and inhibiting cancer effects. But, it is not clear that whether MMP- 9 produced by host with C. albicans infection plays a role in promoting or inhibiting cancer formation or not and also whether it is related to the site of C. albicans infection or the type of tumor formation. These need to be further studied. Candida albicans infection induces both host innate and adaptive immune responses, and the core of protection is often from adaptive Th1 and Th17 cell immune response, which is also considered to be the primary factor in the successful immune defense against C. albicans infection [77]. However, Th17 cells are found in various types of human tumors. Th17 cells and their effector molecules (such as IL-17 and IL-22) can regulate oncogene activated cancer cells themselves and adjacent normal epithelial cells, fibroblasts, endothelial cells, and other stromal cells [78]. Recent studies have found that IL-17 could promote tumor growth through IL-6-Stat3 signaling pathway [72], and also release IFN-g and other cytokines through stimulating T cells, dendritic cells, NK cells and other immune cells, thus inhibiting tumor growth [79, 80]. In addition to its direct effect on tumor, IL-17 can also reshape the TME by recruiting neutrophils and macrophages and promoting tumor occurrence, development, and metastasis [81, 82]. IL-17 driven antitumor immunity is attributed to its ability to recruit dendritic cells [83]. That can be related to various tumor types or TME. Studies have found that C. albicans can induce the increase of glycolysis of macrophages through HIF-1 pathway and promote the secretion and release of IL-17 by macrophages. Increased IL-17 can effectively promote the expression of STAT3 and AHR transcription factors in intestinal innate lymphocyte 3 (ILC3), which in turn leads to the increase of IL-22 and hence promotes the proliferation of intestinal epithelial cells and the progress of CRC [84]. Candida induces increased migration, expression of matrixmetalloproteinases, activation of epithelial to mesenchymal transition, and expression of genes implicated in metastatic processes by OSCC cells. The tumor promoting roles of Candida in a 4NQO model were also highlighted [85]. However still the exact mechanism of the immune response induced by C. albicans infection remains unclear.

CONCLUSION

C. Albicans is a normal commensal within the oral cavity and simply presence itself does not relate to the etiology of cancers. But various adverse factors can cause compromised host immunity, leading to C. albicans infection. C. Albicans infection increases the risk of cancer development and exacerbates cancer progression. The progression of cancer further aggravates C. albicans infection. Therefore, it seems that C. albicans infection may be accompanied by cancer development, and the two promote each other, which in turn aggravates the process of malignancy. Herein we have described range of mechanism by which C. Albicans may be able to favor cancer development and dissemination. By knowing the molecule and mechanism involved, more specific drugs can be developed and designed for the novel specific treatment against these molecule. Hence could inhibit the dissemination of this fungus and its pro tumor effect.

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