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REVIEW ARTICLE

Title: Polymicrobial interactions of *Candida albicans* and its role in oral carcinogenesis

Running title: *Candida albicans* and carcinogenesis

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ABSTRACT

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1 The oral microbiome is composed of microorganisms residing in the oral cavity, which are
2 critical components of health and disease. Disruption of the oral microbiome has been proven to
3 influence the course of oral diseases, especially amongst immunocompromised patients. Oral
4 microbiome is comprised of inter-kingdom microorganisms, including yeasts such as *Candida*
5 *albicans*, bacteria, archaea, and viruses. These microorganisms can interact synergistically,
6 mutualistically, and antagonistically, wherein the sum of these interactions dictates the composition
7 of the oral microbiome. For instance, polymicrobial interactions can improve the ability of *C.*
8 *albicans* to form biofilm, which subsequently increases the colonisation of oral mucosa by the yeast.
9 Polymicrobial interactions of *C. albicans* with other members of the oral microbiome have been
10 reported to enhance the malignant phenotype of oral cancer cells, such as the attachment to
11 extracellular matrix molecules (ECM) and epithelial-mesenchymal transition (EMT). Polymicrobial
12 interactions may also exacerbate an inflammatory response in oral epithelial cells, which may play a
13 role in carcinogenesis. This review focuses on the role of polymicrobial interactions between *C.*
14 *albicans* and other oral microorganisms, including its role in promoting oral carcinogenesis.

16 Introduction

17 Oral cancer is one of the ten most prevalent cancers reported across the globe with more than
18 90% of mouth neoplasms identified as squamous cell carcinoma (1). With estimation of oral cancer
19 incidences at approximately 275,000 cases, two-thirds of these are reported in developing countries
20 (2). The risk factors that lead to oral squamous cell carcinoma (OSCC) include tobacco smoking,
21 heavy alcohol consumption, poor oral hygiene, unhealthy diets, and microbial infection (3).

22 Microbial infections by yeast, bacteria, and viruses appear to have a causal role in oral cancer
23 (1, 3). *Candida* spp. has been reported to be the most frequent fungal microbiome (mycobiome)
24 isolated from the oral cavity, followed by *Cladosporium*, *Aureobasidium*, *Saccharomycetales*,
25 *Aspergillus*, *Fusarium*, and *Cryptococcus* (4). *Candida* spp. may reflect a secondary infection of a
26 pre-existing altered epithelium when linked with dysplasia. Oral yeast carriage has also been found to
27 correlate with the presence of oral epithelial dysplasia (OED), which supports the function of
28 microbial infection in oral carcinogenesis (5). Despite the numerous clinical and experimental
29 conclusions describing the correlation between *C. albicans* and malignant transformation, the exact
30 role of polymicrobial interactions in *C. albicans* for the development noted in dysplastic changes
31 remains unclear.

Intra-kingdom and inter-kingdom interactions of *Candida albicans*

C. albicans has been reported to be involved in both intra- and inter-kingdom interactions (6). Intra-kingdom interaction refers to the communication of the same kingdom, such as the interaction between *Candida albicans* (yeast) and *Candida parapsilosis* (yeast), whereas inter-kingdom interaction reflects microbial communication between two or more kingdoms, such as the interaction between *C. albicans* (yeast) and *Streptococcus* spp. (bacteria). Interaction of *Candida* spp. with other oral microorganisms has been reported to occur via co-aggregation and co-adhesion (7). Co-aggregation is the association of genetically distinct microorganisms, such as the interaction between *C. albicans* and *S. mutans* in planktonic phase. On the other hand, co-adhesion is the interaction between microorganisms in planktonic phase with those on the oral surface (8). The interactions in oral cavity occur in oral biofilm (plaque), hence signifying a potential role in pathogenesis (9).

Although *C. albicans* is the most significant *Candida* spp. in pathogenesis, the discovery of non-*albicans Candida* (NAC) species, such as *C. dubliniensis*, *C. glabrata*, and *C. tropicalis*, has increased awareness among medical practitioners (10). Surprisingly, the carriage of NAC can outnumber that of *C. albicans* in certain conditions, such as the location of isolation. Additionally, the interaction between *C. albicans* and *C. krusei* varied depending on the nutrients supplied during the experiments (6).

The inter-kingdom interaction between *C. albicans* and *Streptococcus* spp. has been reported. *C. albicans* has been reported to co-aggregate *S. mutans* in planktonic phase potentially due to the presence of cell surface proteins on the bacterium that interact with cell surface carbohydrate of the yeast (8) (Figure 1). Antigen I/II is an example of antigenic protein of *S. mutans* that is involved in adherence to bacterium (11). *S. mutans* produces polysaccharides that have a role in the development and maturation of oral polymicrobial biofilms (12). Such mutualistic interaction between *C. albicans* and *S. mutans* is significant for *C. albicans* to colonise the oral surfaces, especially the soft tissues that may lead to inflammation. Despite being proven in *in vitro* studies that mutualistic interaction between *C. albicans* and *S. mutans* occurs through adhesions (non-specific) and lectin-saccharide cell surface receptors (specific) binding (13), antagonistic correlation between the two species has been reported as well. The adhesion of *C. albicans* on acrylic sheets appears to decrease when co-cultured with *S. mutans* in Gibbons and Nygaard culture medium (14). As for the quorum-sensing molecule, Farnesol synthesised by *C. albicans* during biofilm formation disrupts the cell membrane of *S. mutans* (15). Hence, it is suggested that the inter-kingdom interaction between *C. albicans* and *S. mutans* is dependent on *C. albicans* strains.

Candida spp. and *Actinomyces* spp. have been found to co-aggregate in varying degrees. Prior research has shown that the co-aggregation of *C. albicans* with *A. naeslundii* is *C. albicans* strain-

dependent (8) (Figure 1). *A. naeslundii* has been shown to form fimbriae that assist in the attachment of bacteria to oral surfaces via cell-to-cell and cell-to-surface adhesion mechanisms (7). This characteristic aids in the formation of polymicrobial biofilms that enhance the colonisation in the oral cavity (7). Although co-aggregation of *C. albicans* and *Actinomyces* spp. has been reported (8), the adhesion of *C. albicans* to polymethylmethacrylate (PMMA) in a flow cell system when grown in TNMC buffer decreased when pre-cultured with *A. naeslundii* T14V-J1 (16). In addition, the interaction of *A. naeslundii* appeared to decrease the auto-aggregation in planktonic and the metabolic rate in static biofilm of *C. albicans* in the presence of *S. mutans* (6, 8) (Figure 1). *C. albicans* with low metabolic activity is more invasive and linked with disease; on the contrary, those with high activity are non-invasive (17). Furthermore, low metabolic activity can reduce antifungal susceptibility of *C. albicans* towards amphotericin B, potentially due to minimal absorption of antifungal agents, thus affecting inactivation kinetics (18).

A study also showed that *C. albicans* antagonistically interacted with *Pseudomonas* spp., wherein the virulence factors include secretion of alkaline protease, exotoxins, endotoxins, and biofilm forming ability (19). *P. aeruginosa* can form dense biofilm on *C. albicans* and receive nutrients from candidal hyphae, which later kills the yeast (20). *P. aeruginosa* has been reported to inhibit the formation of *C. albicans* biofilm by synthesising anti-candidal agents, such as extracellular bacterial glycocalyx, pyrrolnitrin, and 3-oxo-C12 homoserine lactone (20).

The antagonistic interaction between *C. albicans* and *Porphyromonas* spp. has also been reported. *Porphyromonas* spp. is an anaerobic and black-pigmented Gram-negative bacterium, in which *P. gingivalis* has been among the major periodontal pathogens. *P. gingivalis* produces proteases that destroy haemolysin, haeme-sequestering proteins, collagens, immunoglobulins, and complements (21). *P. gingivalis* was reported to suppress adhesion of *C. albicans* to acrylic surfaces by inhibiting germ-tube formation of *C. albicans*. Despite the inhibition of germ-tube formation of *C. albicans*, this interaction enhances invasion of *P. gingivalis* on gingival epithelial tissue potentially due to the increased expression of FimA component of *P. gingivalis* that is responsible for the adhesion of bacteria to the oral surfaces (22).

Polymicrobial biofilms of *Candida albicans* and oral microbiome

Polymicrobial biofilm is defined as the community of microorganisms attached to oral surfaces and encapsulated within extracellular polysaccharides (EPS) of microbial and salivary origin (23). Cell-cell signalling mechanisms between the members of polymicrobial biofilm contribute to the successful colonisation of bacteria.

Biofilms have been reported to increase the resistance of *C. albicans* to fluconazole, up to 1000-fold, thus increasing its pathogenicity towards the host (17). EPS encapsulates the work of biofilms, making it a barrier that limits the penetration of antimicrobial agents, subsequently reducing the susceptibility of the targeted microorganisms. Constriction of nutrients that occurs within biofilms at the basal region reduces microbial growth and metabolic rate, apart from altering the microbial cell surface composition (18). The metabolic activity of *C. albicans* is reported to increase in the presence of *A. naeslundii* in dual-cultured biofilms. Nevertheless, a decrease in metabolic activity was observed in tri-cultured biofilms, when compared to dual-cultured biofilms of *C. albicans* and *A. naeslundii*, suggesting that these microorganisms may interact in a metabolic manner (24). *C. albicans* with low metabolic activity is more invasive, which may be linked with oral carcinogenesis, while conversely, those with high activity are non-invasive (17). Slower growing microorganisms can represent 'persister cells'. Persister cells possess a resistant phenotype that minimises the susceptibility of polymicrobial community within biofilm to antimicrobial agents (25).

In addition, the biomass and the percentage surface colonisation of *C. albicans* is significantly reduced in polymicrobial biofilms of *C. albicans*, *A. naeslundii*, and *S. mutans*, in comparison to the biomass of *C. albicans* in mono-cultured biofilms when grown in flow cell environment (24) (Figure 2). This condition is due to the metabolic products of *A. naeslundii* that have been reported to both inhibit and stimulate the biofilm formation of *C. albicans*, depending on the experimental methods employed and the strains of *C. albicans* used (6).

Effect of polymicrobial biofilms of *Candida albicans* and oral microbiome on normal and cancerous oral epithelial cells phenotypes

Carcinoma refers to the ability of malignant cell to invade the underlying connective tissues, and is followed by metastases to distant sites (26). These processes demand the alteration of cell-to-cell and cell-to-extracellular matrix (ECM) interactions that involve adhesion molecules, such as collagen, laminin, fibronectin, and fibrinogen (27). Several studies have also revealed the distinct variation in the ability of normal oral epithelial cells and OSCC isolated cells to adhere to ECM components upon incubation with polymicrobial biofilm effluent, with cancerous cells increasing their adhesion to collagen IV and laminin I in a significant manner, when compared to mono-species biofilm effluent (24). The variability of adhesion for normal and cancerous cells to ECM components is due to the alteration of cell integrins following interaction with biofilm effluent (27). Integrins have been recognised as the largest family of cell adhesion molecules that consist of multiple combinations of α - and β -subunits (28). Proteins synthesised by microorganisms, such as proteases from *C. albicans* and Bcl-2 family proteins from bacteria, have been shown to induce alteration of integrins in

1 epithelial cells (3). The $\alpha 1$ -subunit of integrins that preferentially binds to collagen IV, and $\alpha 3$ -
2 subunit that functions as a receptor for laminins, have been reported to change during interaction with
3 the proteins of microorganisms (27). Subsequent trigger of a spectrum of signals involved in the
4 process of growth and proliferation may also promote oral carcinogenesis in a paracrine fashion (29).

5 Epithelial-mesenchymal transition (EMT) is a mechanism that alters cell-to-cell and cell-to-
6 ECM interactions so as to allow the movement of cancerous cells to the surrounding environment.
7 Nonetheless, inappropriate utilisation of EMT may occur in the formation of OSCC and metastasis of
8 malignant cells (30). EMT can also be involved in increasing resistance of malignant cells to
9 apoptosis regulator molecules (31). Vimentin and E-cadherin have been widely used as markers for
10 EMT. The expression of vimentin induces changes in cell shape, motility, and adhesion of epithelial
11 cells to mesenchyme; while cadherins mediate cell-to-cell binding that is critical in maintaining tissue
12 structure and morphology (32). Functional loss of E-cadherin in epithelial cells has been considered
13 as a marker for EMT during tumour progression (33). A previous study has reported that the
14 expression of E-cadherin from normal epithelial cells increased after 24-h of incubation with mono-
15 cultured biofilm effluent, which is likely to indicate adhesion, colonisation, internalisation, and
16 potentially, invasion (24). Increment in E-cadherin expression appears to be a strategy of colonisation
17 among *C. albicans*, *A. naeslundii*, and *S. mutans* to oral epithelial cells (34). Additionally, cadherins
18 have been reported to form a route for the internalisation of *C. albicans* into epithelial cells during
19 oral thrush (34, 35). Als3 protein synthesised by *C. albicans* has also been thought to mimic
20 cadherin-cadherin binding, thus initiating the invasion of yeast to oral epithelial cells that may
21 promote oral carcinogenesis (35).

22 Inflammation induced by pathogens has been shown to be involved in carcinogenesis (36).
23 One factor that leads to inflammation is increase of pro-inflammatory cytokines due to microbial
24 infection of oral mucosa (37). Cytokines are signalling molecules that regulate the differentiation,
25 proliferation, and many other crucial functions in human inflammatory cells. Cytokine signals are
26 received at the cell surface, not only as a single message, but also in complex, subtle, synergistic, and
27 antagonistic combinations that coordinate processes, including stimulation of haematopoiesis,
28 orchestration of directed leukocyte migration (chemokinesis), activation of various inflammatory
29 cells, stimulation of lymphocyte development and maturation, as well as processes associated with
30 immune response (38). Nonetheless, in certain circumstances, such as failure to resolve an injury, this
31 condition may provoke excessive immune cell infiltration that may persistently generate cytokine. As
32 a result, the host may respond to persistent cytokine expression by enhancing cancer formation and

1 progression (39). Cytokines that have been shown to be involved in inflammation include interleukin
2 (IL)-1 α , IL-1 β , IL-6, IL-8, IL-18, TNF- α , IFN- γ , and GM-CSF (40).

3 Previous studies have reported increase in cancerous inflammatory cytokines; IL-6 and IL-8,
4 from normal and cancerous oral cell lines upon incubation in mono-species and polymicrobial
5 biofilms of *C. albicans*, *A. naeslundii*, and *S. mutans* effluents (24). The increased expression of pro-
6 inflammatory cytokines, particularly IL-6 and IL-8, are significant in both inflammation and
7 tumorigenesis of malignant cells. The increased expression of IL-6 and IL-8 by oral cancer cells may
8 be due to proteins glycosylated with N- or O-linked mannosyl residues, β -glucans, and chitins on *C.*
9 *albicans* cell wall, as well as the expression of secreted aspartyl proteinases (SAPs) from yeast (41).

10 IL-6 has been proven to exert anti-apoptotic effect on malignant cells (42). The direct autocrine
11 tumour-promoting effects of IL-6 have been demonstrated in multiple myeloma by both increasing
12 proliferation and preventing apoptosis (43). It has also been shown to promote head and neck tumour
13 metastases by inducing EMT via the JAK-STAT3-SNAIL signalling pathway (33). This cytokine is
14 one of the main chemokines present in serum samples of head and neck cancer patients, wherein
15 elevated IL-6 levels can independently predict tumour recurrence, poor survival, and tumour
16 metastasis (44). IL-6 in serum has been found to be higher in patients with OSCC, when compared to
17 controls, thus its proposal as an additional marker in early detection of oral cancer (45). This cytokine
18 is a major mediator that links inflammation to cancers, along with TNF- α (46).

19 Meanwhile, the expression of IL-8 by human carcinoma cells has been reported to directly
20 correlate with tumour vascularity and cancer progression. Research has shown that IL-8 can be
21 produced by various types of tumours, both constitutively and in response to cytokines (47). This
22 cytokine has been detected in surgical specimens, freshly cultured cell lines, as well as well-defined
23 cell lines of head and neck squamous cell carcinoma (48). IL-8 stimulates a substantial number of
24 physiopathological functions in various tumour cells, including prostate carcinoma, ovarian
25 carcinoma, melanoma, and gastric carcinoma cell lines (49). The high expression of IL-8 in
26 cancerous liver tissue has been associated with a higher frequency of portal vein, venous, and bile
27 duct invasion in hepatocellular carcinoma patients with surgical resection, thus may be crucial in
28 invasion and metastasis (50).

30 Conclusion

31 Polymicrobial interactions of *C. albicans* with oral microorganisms *A. naeslundii* and *S.*
32 *mutans* appears to promote oral carcinogenesis by not only enhancing invasion of oral squamous cell

carcinoma as demonstrated by increased adhesion to extra-cellular matrix proteins, but also by increasing pro-inflammatory cytokine expression. This potentially may have profound clinical implications, and further research to elucidate the exact mechanism is necessary.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Pushalkar S, Mane SP, Ji X et al. Microbial diversity in saliva of oral squamous cell carcinoma. *FEMS Immunol Med Microbiol* 2011; **61**: 269-77.
2. Ferlay J, Bray F, Pisani P, Parkin D. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. IARC Cancer Base No. 5. version 2.0. Lyon: IARC Press; 2004.
3. Khajuria N, Metgud R. Role of bacteria in oral carcinogenesis. *Indian J Dent* 2015; **6**: 37.
4. Ghannoum MA, Jurevic RJ, Mukherjee PK et al. Characterization of the oral fungal microbiome (mycobiome) in healthy individuals. *PLoS Pathog* 2010; **6**: e1000713.
5. McCullough M, Jaber M, Barrett A, Bain L, Speight P, Porter S. Oral yeast carriage correlates with presence of oral epithelial dysplasia. *Oral Oncol* 2002; **38**: 391-3.
6. Arzmi MH, Alnuaimi AD, Dashper S, Cirillo N, Reynolds EC, McCullough M. Polymicrobial biofilm formation by *Candida albicans*, *Actinomyces naeslundii* and *Streptococcus mutans* is *Candida albicans* strain and medium dependent. *Med Mycol* 2016; DOI: 10.1093/mmy/myw042.
7. Kolenbrander PE, Palmer RJ, Periasamy S, Jakubovics NS. Oral multispecies biofilm development and the key role of cell-cell distance. *Nat Rev Microbiol* 2010; **8**: 471-480.
8. Arzmi MH, Dashper S, Catmull D, Cirillo N, Reynolds E, McCullough M. Co-aggregation of *Candida albicans*, *Actinomyces naeslundii* and *Streptococcus mutans* is *Candida albicans* strain dependent. *FEMS Yeast Res* 2015; DOI: 10.1093/femsyr/fov038.

9. Tan K, Seers CA, Dashper SG et al. *Treponema denticola* and *Porphyromonas gingivalis* exhibit metabolic symbioses. *PLOS Pathog* 2014; DOI: 10.1371/journal.ppat.1003955.
10. Alnuaimi AD, Wiesenfeld D, O'Brien-Simpson NM, Reynolds EC, McCullough MJ. Oral *Candida* colonization in oral cancer patients and its relationship with traditional risk factors of oral cancer: A matched case-control study. *Oral Oncol* 2015; **51**: 139-45.
11. Chuzeville S, Dramsi S, Madec J-Y, Haenni M, Payot S. Antigen I/II encoded by integrative and conjugative elements of *Streptococcus agalactiae* and role in biofilm formation. *Microb Pathog* 2015; **88**: 1-9.
12. Koo H, Xiao J, Klein M, Jeon J. Exopolysaccharides produced by *Streptococcus mutans* glucosyltransferases modulate the establishment of microcolonies within multispecies biofilms. *J Bacteriol* 2010; **192**: 3024-32.
13. Ledger RG, Timperley AS, Friswell MK, Macfarlane S, McBain AJ. Coaggregation between and among human intestinal and oral bacteria. *FEMS Microbiol Ecol* 2008; **66**: 630-6.
14. Barbieri DSAV, Vicente VA, Fraiz FC, Lavoranti OJ, Svidzinski TIE, Pinheiro RL. Analysis of the in vitro adherence of *Streptococcus mutans* and *Candida albicans*. *Braz J Microbiol* 2007; **38**: 624-631.
15. Černáková L, Jordao L, Bujdáková H. Impact of farnesol and Corsodyl® on *Candida albicans* forming dual biofilm with *Streptococcus mutans*. *Oral Dis* 2018; **24**: 1126-31.
16. Millsap KW, Bos R, Van Der Mei HC, Busscher HJ. Dot assay for determining adhesive interactions between yeasts and bacteria under controlled hydrodynamic conditions. *J Microbiol Methods* 2000; **40**: 225-32.
17. Tobudic S, Kratzer C, Lassnigg A, Prestler E. Antifungal susceptibility of *Candida albicans* in biofilms. *Mycoses* 2012; **55**: 199-204.
18. Mah TF, O' Toole GA. Mechanisms of biofilm resistance to antimicrobial agents. *Trends Microbiol* 2001; **9**: 34-39.
19. García-Contreras R, Pérez-Eretza B, Lira-Silva E et al. Gallium induces the production of virulence factors in *Pseudomonas aeruginosa*. *Pathog Dis* 2014; **70**: 95-98.
20. Hogan DA, Kolter R. *Pseudomonas-Candida* interactions: an ecological role for virulence factors. *Science* 2002; **296**: 2229-32.
21. Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. *Nat Rev Microbiol* 2012; **10**: 717.
22. Sztukowska MN, Dutton LC, Delaney C et al. Community Development between *Porphyromonas gingivalis* and *Candida albicans* Mediated by InlJ and Als3. *mBio* 2018; **9**: e00202-00218.

23. O'donnell LE, Millhouse E, Sherry L et al. Polymicrobial *Candida* biofilms: friends and foe in the oral cavity. *FEMS Yeast Res* 2015; **15**.
24. Arzmi MH, Cirillo N, Lenzo JC et al. Monospecies and polymicrobial biofilms differentially regulate the phenotype of genotype-specific oral cancer cells. *Carcin* 2018.
25. Cameron DR, Shan Y, Zalis EA, Isabella V, Lewis K. A genetic determinant of persister cell formation in bacterial pathogens. *J Bacteriol* 2018; **200**: e00303-00318.
26. Clark AG, Vignjevic DM. Modes of cancer cell invasion and the role of the microenvironment. *Curr Opin Cell Biol* 2015; **36**: 13-22.
27. Lyons A, Jones J. Cell adhesion molecules, the extracellular matrix and oral squamous carcinoma. *Int J Oral Maxillofac Surg* 2007; **36**: 671-9.
28. Streuli CH. Integrins as architects of cell behavior. *Mol Biol Cell* 2016; **27**: 2885-8.
29. Meurman JH. Infectious and dietary risk factors of oral cancer. *Oral Oncol* 2010; **46**: 411-3.
30. Heerboth S, Housman G, Leary M et al. EMT and tumor metastasis. *Clin Transl Med* 2015; **4**: 6.
31. Brabletz T, Kalluri R, Nieto MA, Weinberg RA., EMT in cancer. *Nat Rev Cancer* 2018; **18**: 128.
32. Mendez MG, Kojima SI, Goldman RD. Vimentin induces changes in cell shape, motility, and adhesion during the epithelial to mesenchymal transition. *FASEB J* 2010; **24**: 1838-51.
33. Yadav A, Kumar B, Datta J, Teknos TN, Kumar P. IL-6 promotes head and neck tumor metastasis by inducing epithelial–mesenchymal transition via the JAK-STAT3-SNAIL signaling pathway. *Mol Cancer Res* 2011; **9**: 1658-67.
34. Delva E, Kowalczyk AP. Regulation of cadherin trafficking. *Traffic* 2009; **10**: 259-67.
35. Phan QT, Fratti RA, Prasadaraao NV, Edwards JE, Filler SG. N-cadherin mediates endocytosis of *Candida albicans* by endothelial cells. *J Biol Chem* 2005; **280**: 10455-10461.
36. Dzutsev A, Goldszmid RS, Viaud S, Zitvogel L, Trinchieri G. The role of the microbiota in inflammation, carcinogenesis, and cancer therapy. *Eur J Immunol* 2015; **45**: 17-31.
37. Fantini MC, Pallone F. Cytokines: from gut inflammation to colorectal cancer. *Curr Drug Targets* 2008; **9**: 375-80.
38. Budhu A, Wang XW The role of cytokines in hepatocellular carcinoma. *J Leukoc Biol* 2006; **80**: 1197-213.
39. Roshani R, McCarthy F, Hagemann T. Inflammatory cytokines in human pancreatic cancer. *Cancer Lett* 2014; **345**: 157-63.
40. Lippitz BE. Cytokine patterns in patients with cancer: a systematic review. *Lancet Oncol* 2013; **14**: e218-e228.

41. Dongari-Bagtzoglou A, Kashleva H. *Candida albicans* triggers interleukin-8 secretion by oral epithelial cells. *Microb Pathog* 2003; **34**: 169-77.
42. Chen Y, Zhang F, Tsai Y et al. IL-6 signaling promotes DNA repair and prevents apoptosis in CD133+ stem-like cells of lung cancer after radiation. *Radiat Oncol* 2015; **10**: 227.
43. De Simone V, Franze E, Ronchetti G et al. Th17-type cytokines, IL-6 and TNF- α synergistically activate STAT3 and NF-kB to promote colorectal cancer cell growth. *Oncogene* 2015; **34**: 3493.
44. Duffy SA, Taylor JM, Terrell JE et al. Interleukin-6 predicts recurrence and survival among head and neck cancer patients. *Cancer* 2008; **113**: 750-7.
45. Rao M, Ramesh A, Adapa S, Thomas B, Shetty J. Correlation of salivary levels of interleukin-6 and albumin with oral squamous cell carcinoma. *J Health Res Rev* 2016; **3**: 11.
46. Balkwill FR, Mantovani A. Cancer-related inflammation: common themes and therapeutic opportunities. *Semin Cancer Biol* 2012; **77**: 33-40.
47. Kolář M, Szabo P, Dvořánková B et al. Upregulation of IL-6, IL-8 and CXCL-1 production in dermal fibroblasts by normal/malignant epithelial cells in vitro: Immunohistochemical and transcriptomic analyses. *Biol Cell* 2012; **104**: 738-51.
48. Polanska H, Raudenska M, Gumulec J et al. Clinical significance of head and neck squamous cell cancer biomarkers. *Oral Oncol* 2014; **50**: 168-77.
49. Yin J, Zeng F, Wu N, Kang K, Yang Z, Yang H. Interleukin-8 promotes human ovarian cancer cell migration by epithelial–mesenchymal transition induction in vitro. *Clin Transl Oncol* 2015; **17**: 365-370.
50. Bai ZF, Tai Y, Li W et al. Gankyrin activates IL-8 to promote hepatic metastasis of colorectal cancer. *Cancer Res* 2013; doi: 10.1158/0008-5472.can-12-4586.

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