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Canonical WNT signaling pathway in oral squamous cell carcinoma prognosis

Via de sinalização WNT canônica no prognóstico de carcinoma de células escamosas oral

Vía de señalización canónica de WNT en pronóstico de carcinoma de células escamosas oral

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Abstract
The aim of the study was to demonstrate the immunohistochemical expression of the wnt/b-catenin pathway in oral carcinoma cells (OSCC), through a literature review. For this, a search was performed in the PubMed and SciELO databases with the keywords "β-catenin", "oral squamous cell carcinoma", "OSCC" and "Wnt signaling" with the Boolean AND operator. The inclusion criteria adopted were articles published in English, in vitro, in situ articles or clinical trials from 2010 to 2021 that relate the canonical WNT signaling pathway with oral squamous cell carcinoma and the exclusion criteria considered were duplicate articles, literature review and that did not address the issue. After reading the title, abstract, and full content of each of the studies, 110 articles were selected. IncRNA compounds, enzymes, hexachlorophene derivatives and lignin isolated from Taiwania were able to suppress growth and metastasis by inhibiting the WNT/β-catenin pathway. Cancer stem cells, PON2 type enzymes, nicotine intake, cytokine TNF-α and FAD1 gene are able to increase growth and metastasis by inhibiting the same pathway. Therefore, the expression of these biomarkers can influence the prognosis of cancer cells and help practitioners to explore new possible therapeutic effects in OSSC by modulating the Wnt/β-catenin pathway.
Keywords: β-catenin; Oral squamous cell carcinoma; OSCC; Wnt signaling.

Resumo
O objetivo do estudo foi evidenciar a expressão imuno-histoquímica da via wnt/b-catenina em células de carcinomas orais (OSCC), por meio de uma revisão da literatura. Para isso, foi realizado uma busca nos bancos de dados PubMed

e SciELO com as paravras chaves “β-catenin”, “oral squamous cell carcinoma”, “OSCC” e “Wnt signaling” com operador booleano AND. Como critérios de inclusão adotaram-se artigos publicados na língua inglesa, artigos in vitro, in situ ou ensaios clínicos dos anos de 2010 a 2021 que relacionam a via de sinalização WNT canônica com oral squamous cell carcinoma e os critérios de exclusão considerados foram artigos duplicados, revisão de literatura e que não abordavam a temática. Após a leitura do título, do resumo, e do conteúdo integral de cada um dos estudos, foram selecionados 110 artigos. Compostos de IncRNA, enzimas, derivados de hexaclorofeno e a lignina isolada de Taiwania foram capazes de suprimir o crescimento e metástases pela inibição da via WNT/ β-catenina. Células-tronco cancerosas, enzimas tipo PON2, ingestão de nicotina, citocina TNF-α e gene FAD1 são capazes de aumentar o crescimento e metástase pela inibição da mesma via. Portanto, a expressão desses biomarcadores pode influenciar o prognóstico das células cancerígenas e ajudar os profissionais a explorar novos possíveis efeitos terapêuticos em OSSC modulando a via Wnt / β-catenina.
Palavras-chave: β-catenina; Carcinoma de células escamosas oral; OSCC; Sinalização wnt.

Resumen
El objetivo del estudio fue demostrar la expresión inmunohistoquímica de la vía wnt / b-catenina en células de carcinoma oral (COCE), a través de una revisión de la literatura. Para ello, se realizó una búsqueda en las bases de datos PubMed y SciELO con las palabras clave “β-catenina”, “carcinoma oral de células escamosas”, “OSCC” y “Señalización Wnt” con el operador booleano AND. Como criterios de inclusión se adoptaron artículos publicados en inglés, in vitro, in situ o ensayos clínicos de los años 2010 a 2021 que relacionan la vía de señalización canónica del WNT con el carcinoma oral de células escamosas y los criterios de exclusión considerados fueron artículos duplicados, revisión de la literatura y que no abordó el problema. Después de leer el título, el resumen y el contenido completo de cada uno de los estudios, se seleccionaron 110 artículos. Los compuestos de ARNc, las enzimas, los derivados de hexaclorofeno y la lignina aislados de Taiwania pudieron suprimir el crecimiento y la metástasis al inhibir la vía WNT / β-catenina. Las células madre cancerosas, las enzimas de tipo PON2, la ingesta de nicotina, la citocina TNF-α y el gen FAD1 pueden aumentar el crecimiento y la metástasis al inhibir la misma vía. Por lo tanto, la expresión de estos biomarcadores puede influir en el pronóstico de las células cancerosas y ayudar a los médicos a explorar nuevos posibles efectos terapéuticos en OSSC modulando la vía Wnt / β-catenina.
Palabras clave: β-catenina; Carcinoma oral de células escamosas; OSCC; Señalización wnt.

1. Introduction

Oral squamous cell carcinoma (OSCC) is the most prevalent tumor in the head and neck area (Saba et al., 2011), belonging to the ten most common tumors in the world, with approximately 300,000 cases per year (Gupta et al., 2016). Despite advances in surgical techniques, targeted radiation therapy, OSCC remains a treatment challenge (Subapriya et al., 2007) with a mortality rate in the first five years still of 50% after metastasis. One of the reasons for this is the lack of diagnostic tools to detect high-risk lesions in the early stages, in addition to differentiating between harmless and high-risk precursor lesions (Gallenkamp et al., 2017).

Early detection of potentially malignant disorders may decrease mortality associated with oral cancer (Hadzic et al., 2017). Mortality associated to oral cancer may decrease with early detection of potentially malignant disorders. To determine the risk of malignant transformation of oral leukoplakia, histological evaluation of epithelial dysplasia is the gold standard and the accuracy of the histopathological evaluation of epithelial dysplasia depends on the quality of the tissue and the site at which a biopsy is performed (Patel et al., 2011).

The loss of cell adhesion is one of the characteristics that lead to lesions with potential malignant transformation to malignize (Petridis et al., 2014). Cell-cell adhesion and extracellular cell-matrix regulate important cellular functions like growth, differentiation, migration, proliferation and cell death. B-catenin is a cell adhesion and communication protein involved in these processes, mainly related to Wnt proteins (Eberhart, C. G., & Argani, P. 2001, Gottardi, C. J., & Gumbiner, B. M., 2004).

The Wnt signaling pathway consist of two different signaling pathways: the the β-catenin-independent pathway (noncanonical Wnt pathway) and the β-catenin-dependent pathway (canonical Wntpathway). The canonical Wnt/β-catenin pathway involves β-catenin. Without Wnt ligands, cytoplasmic β-catenin goes to a destruction complex is phosphorylated by casein kinase (CK) 1α and glycogen synthase kinase 3β (GSK3β). The phosphorylated β-catenin is directly ubiquitin atedand

degraded to maintain a low level of this protein. But, when the Wnt ligand binds to the frizzled receptor sand coreceptor lipoprotein-related protein (LRP), the β-catenina cumulates in the cytoplasm and translocatesto the nucleus, where it binds to the T-cell factor/lymphocyte enhancer factor (TCF/LEF) to activate the transcription of downstream genes, such as c-Myc, cyclin D1 and metallo proteinases (Pannone et al., 2010).

Recent evidence has supported that Wnt/β-catenin signaling is associated resistance to chemotherapy in various types of cancer (Liang et al., 2017). In contrast, decreased expression of β-catenin is found in esophageal, colon, gastric, and oral cancers (Xu et al., 2015, Nayak et al., 2017).

In this way, studies of biomarkers involved in the progression of cancer and the processes regulated by them help in the better direction of the prognosis, since they are often used as a basis for the development of tools for the molecular blocking of these processes (Han et al., 2018). Some biomarkers are poorly understood by professionals, and a literature review about this theme is important to inform the role of WNT/ β-catenin pathway biomarkers, facilitating the understanding, and directing the treatment of this malignant oral lesion.

Therefore, this work aims to demonstrate the immunohistochemical expression of wnt and b-catenin in oral carcinoma cells, through a literature review.

2. Methodology

The review of articles was performed by consulting the Pubmed and SciELO databases, looking for studies published in the last 10 years. For the search, the following keywords were used: “β-catenin”, “oral squamous cell carcinoma”, “OSCC” and “Wnt signaling”. Thus, the research was prepared as follows:

2.1 Eligibility Criteria

- Articles relating the canonical WNT signaling pathway with oral squamous cell carcinoma.
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2.2 Exclusion Criteria:

- Articles that are not from 2010 to 2021.

2.3 Search

Table 1. PubMed search summary.

DESCRIPTORS	NUMBERS OF ARTICLES FOUND
“β-catenin” + “oral squamous cell carcinoma”	337
“β-catenin” + “oral squamous cell carcinoma” + “OSCC”	129
“β-catenin” + “oral squamous cell carcinoma” + “OSCC” + “Wnt signaling”	61

Source: Author himself (2021)

Table 2. Summary found in SciELO.

DESCRIPTORS	NUMBERS OF ARTICLES FOUND
"β-catenin" + "oral squamous cell carcinoma"	**1**
"β-catenin" + "oral squamous cell carcinoma" + "OSCC"	1
"β-catenin" + "oral squamous cell carcinoma" + "OSCC" + "Wnt signaling"	0

Source: Authors (2021).

2.4 Article screening process

Initially, articles were selected by title and abstract according to the research strategy described, articles that appeared in more than one database were considered only once. The titles were analyzed by two reviewers (L.V.V and L.M.S), independently, those who were interesting for this research had the abstracts read, or if the abstract was insufficient, the full article was read. In case of disagreement, a third author was contacted.

Table 3. Results of the search for articles.

	Number of articles
Found on PUBMED	527
Found in SciELO	1
Total articles found	528
Excluding duplicity	1
Deleted after reading the title	286
Excluded after reading the abstracts	132
Selected articles	110

Source: Authors (2021).

3. Results and Discussion

For analysis of the results of this review, Table 4 was made up containing: the author of the selected article, year of the published article, the evaluation methods, objectives and level of bias.

Table 4. Summary of selected articles:

Author	Year	Method	Purpose	Results	Levelofbias
LIU et al.	2017	Experimental Study	Investigate for how long MEG3 inhibits OSCC growth and metastasis by regulating the WNT / β-catenin signaling pathway.	MEG3 can inhibit the growth and metastasis of OSCC by negatively regulating the WNT / β-catenin signaling pathway.	Low
YANG et al.	2016	Experimental Study	Observe the expression, function and molecular mechanism of LncRNA UCA1 in the OSCC.	the positive regulation of UCA1 could increase the level of activation of the WNT / β-catenin signaling pathway. Itcanact as anoncogene.	Low

MA et al.	2017	Experimental Study	To evaluate the expression and clinical significance of the CCAT2 gene, malignant biological behaviors, and explore possible mechanisms in squamous cell carcinoma of the mouth.	The Wnt / β-catenin signaling pathway may partially restore CCCC2-mediated malignant biological behaviors of OSCC by β-catenin suppression.	Low
YU et al.	2013	Experimental Study	Provide new evidence for miR-9 as a promising genetic therapeutic target for OSCC.	There is a possible relationship between miR-9 and genes downstream of the Wnt / β-catenin pathway in the development and progression of OSCC.	Low
CUI et al.	2017	Experimental Study	To investigate the effect of KLK4 silencing on the growth of OSCC cells.	KLK4 silencing inhibited the growth of OSCC cells via the Wnt / β-catenin signaling pathway.	Low
YOKOGI et al.	2016	Experimental Study	Analyze whether the Wnt / Beta-Catenin HC-1 signal inhibitor sensitizes the OSCC along with 5-fluorouracil by reducing the positive Population CD44.	Combination treatment of HC-1 and 5-fluorouracil can stimulate the tumor suppressor effect in OSCC cells	Low
HSIEH et al.	2016	Experimental Study	Determine the effect of Taiwanin C of Taiwania CryptomerioidesHayata against the carcinogenesis associated with arecolina.	Taiwanin C blocked the cell migration effects of T28 cells mediated by GSK-3β activation to increase protein degradation and reduce nuclear β-catenin accumulation.	Low
WANG et al.	2017	Experimental Study	Nicotine stimulation mechanisms in the progression of squamous cell carcinoma of the tongue (TSCC)	Nicotine may promote the progression of SCLC cells by activating the Wnt / β-catenin signaling pathways and may play a significant role in the progression and metastasis of related SCLC to smoking.	Low
NISHIKAWA et al.	2011	Experimental Study	Investigate the mechanisms by which FAT1 is involved in the biological behavior of OSCCs.	FAT1 may be involved in OSCC migration and invasion mechanisms.	Low
LI et al.	2016	Experimental Study	Investigating the effect of β-catenin on cisplatin resistance in OSCC	theWnt / β-catenin signaling pathway may play important roles in cisplatin resistance in OSCC.	Low
KRÜGER et al.	2015	Experimental Study	Observe the enlightened regulation of anti-apoptotic PON2 through Wnt / β-catenin in OSCC.	PON2 was observed as a potential new biomarker for resistance to therapy.	Medium
ZAID	2014	Experimental Study	Establish the expression and localization of β-catenin in OSCC.	E-cadherin was closely linked to β-catenin expression in OSCC and to tumor differentiation.	Low
LEE et al.	2012	Experimental Study	Compare b-catenin expression in human oral epithelium, OSCC, and explore the potential mechanisms that may induce expression of b-catenin.	Expression of b-catenin is significantly upregulated associated with OSCC chewing. The localization of b-catenin expression is correlated with tumor size and stage.	Low
PANNONE et al.	2010	Experimental Study	Analyze why the aberrant expression of ß-catenin may be associated with the epigenetic inactivation of WNT inhibitors.	A catenin delocalization in oral cancer may be due to activation of the WNT pathway by epigenetic changes of the SFRP, WIF-1 and DKK-3 genes.	Low
CHAW et al	2012	Experimental Study	Investigate b-catenin immunohistochemical analysis for prediction of oral malignant transformation.	Aberrant expression of β-catenin are potential malignant transformation markers.	Low

YAN et al.	2017	Experimental Study	Proving that TNF-α inflammatory factor may increase fusion between oral squamous cell carcinoma (SCC-9) cells and human umbilical vein endothelial cells (HUVEC).	The positive regulation of the activation of the Wnt / β-catenin pathway of syncycine-1 is involved in the proinflammatory factor cellular fusion promoted by TNF-α between oral cancer and endothelial cells.	Low

Source: Authors (2021).

From this perspective, the results indicate that certain chemical and biological factors influence the modulation of the WNT / β-catenin pathway as follows:

Table 5. Summary of the factors associated to OSCC:

Inhibition of Wnt/ β -catenin pathway	
• Inhibit tumor growth, migration and / or metastasis	
IncRNA	MEG 3
	Silencingof UCA1
	Silencingof CCAT2 MicroRNA-9
Enzyme	Silencingofpeptidase 4 (KLK4)
HexachloropheneDerivative	HC-1 + Fluorouracil
Lignin isolated from Taiwania	Taiwanin C
High expression of Wnt/ β -catenin pathway	
• Promote tumor growth, migration and / or metastasis	
Chemotherapeutic	Resistance to cisplatin
Enzyme	PON2
Chemical substance	Nicotine Intake
Cytokine	TNF-α
MembraneProtein	Gene FAD1

Source: Authors (2021).

IncRNAs capable of suppressing growth and metastasis by inhibition of WNT/β-catenin pathway

Long non coding RNAs (lncRNAs), a class of nonprotein coding transcripts, can serve as master-gene regulators capable of controlling coding and non-coding genes of proteins. (Quinn et al., 2016; Derrien et al., 2012) Also, they have been implicated in the regulation of a variety of cellular functions and disease processes, such as cell growth and apoptosis, as well as progression and cancer metastasis (Calin et al., 2007). Although the precise roles of the vast majority of the 40,000 lncRNAs are still under investigation (Schlosser et al., 2016), lncRNA accumulation studies lead to recurrent somatic non-coding mutations, epigenetic changes, or changes in the number of somatic copies (Melton et al., 2015, Kundaje et al., 2015, Beroukhim et al., 2010).

Cancer associations have reported their roles in the multiple pathological stages of tumorigenesis, including cell proliferation, angiogenesis, metastasis and cell signaling as the canonical Wnt pathway (Gupta et al., 2010, Guttman et al., 2011), which may provide a strong reason for the targeting of lncRNAs as a therapeutic specific and potent approach to eliminate cancer cells. (Bernard et al., 2012, Lu et al., 2016, Michalik et al., 2014, Yuan et al., 2012). And because they play a role in carcinogenesis, it is possible that this type of gene may serve as a biomarker in cancer (Derrien et al., 2012, Calin et al., 2007).

lncRNAs MEG3

One such lncRNA gene is the maternally expressed gene 3 (MEG3), located on the 14q32.3 human chromosome having a length of about 1.6 kb (Benetatos, L., et al., 2011). In humans, MEG3 is expressed in many normal tissues. Loss of MEG3 expression has been found in several types of human tumors and tumor cell lines, such as leukemia (Yao, H., 2017), thyroid carcinoma (Wang, C., 2015), lung cancer (Xia, Y.,2015), bladder cancer (Greife, A., 2014), gastric cancer (Wei, G. H., 2017), hepatocellular carcinoma (Zhuo, H., 2016) and glioma (Wang, P.,2012). In addition, the gene with a high re-expression of MEG3 was found to inhibit tumor cell proliferation in vitro, thus being a tumor suppressor gene (Cui, X., et al., 2018, Wang, P., et al., 2012).

Therefore, a study to investigate the molecular mechanism of the MEG3-regulated WNT pathway in OSCC, used the TOP / FOP flash reporter vector method, which monitors activity of the WNT / β-catenin signaling pathway in cultured cells by means of of the multimerized TCF / LEF responsive element control by measuring the level of expression of the core protein of the canonical WNT pathway in SCC15 cells with overexpression of MEG3. Thus, MEG3 inhibited OSCC cell proliferation (Liu, Z., et al., 2017), metastases and promoted apoptosis by downregulation of the WNT pathway (Chen, D., et al., 2018, Chen, L. L., et al., 2018), by decreasing transcription of the superfamily TCF / LEF.

IncRNAs UCA1

Other IncRNAs, the associated prostate cancer 1 (UCA1) is located on chromosome 19p13.12, which has three exons and encodes two transcripts. The long non-coding RNA UCA1 has two isoforms. One is 1.4 kb in length, (Huang, J., et al., 2014) and the other is 2.2 kb in length, which was associated with cancer where it was upregulated. (Wang, Y., et al., 2012)

Several groups reported that UCA1 is strikingly expressed in bladder cancer, breast cancer, and colorectal cancer (Fang, Z., et al., 2017, Han, Y., et al., 2014). Previous research groups have indicated that UCA1 promotes cancer progression and drug resistance through some potential target genes, for example WNT6, cytochrome P450 and CYP1A1. (Fang, Z., et al., 2017, Fan, Y., et al., 2014). Furthermore, (Fan, Y., et al., 2014, Hwang, J. T., et al., 2012) have reported that UCA1 can positively regulate the level of WNT6 expression and leads to the subsequent response of the WNT signaling pathway.

In this context, studies reveal that the positive regulation of UCA1 could increase the level of activation of the Wnt / β-catenin signaling pathway, acting as an oncogene, promoting malignant progression of human OSCC (Huang, J., et al., 2014). It suggests that UCA1 can be used as a biomarker for the diagnosis of these cancers.

Based on these observations, an analysis of UCA1 expression was performed between five different OSCC cell lines (SCC9, SCC15, SCC25, Cal27 and Tca8113). In order to identify the correlation between the level of UCA1 expression and the level of activation of the WNT / β-catenin signaling pathway, TOP / FOP flash reporters were used to assess the impacts of UCA1 (Yang, Y. T., et al., 2016). Thus, the levels of TCF-4 protein expression were detected using Western blot analysis, and thus, it was shown that UCA 1 silencing induced apoptosis of oral squamous cell carcinoma cells, while activation of the signaling pathway WNT / β-catenin was suppressed. Immunofluorescence assay results showed that the position of the β-

catenin protein moves from the nucleus to the cytoplasm in the cells, and decreased in the cytoplasm when the level of UCA1 was silenced (Yang, Y. T., et al., 2016).

IncRNA CCAT2

The colon-associated transcript-associated IncRNA gene (CCAT2), a new non-coding RNA, mapped in 8q24, was originally identified in colon cancer, inducing tumor growth, metastasis and chromosomal instability. (Ling et al., 2013)

Recently, the CCAT2 gene has been found to be highly expressed in some other tumors, including non-small cell lung cancer, esophageal carcinoma, cervical and bladder cancer (Zhao et al., 2017, Li et al., 2016). Thus, it was hypothesized that the knockdown of CCAT2 could induce apoptosis of cancer cells and suppress cell proliferation and invasion. (Wu et al., 2016, Cai et al., 2015), which revealed that CCAT2 functions as an oncogene in these tumors. (Wu et al., 2017, Zhao et al., 2017, Li et al., 2016).

In addition, Wang J, 2015 reported through the serum extracted from patients with squamous cell carcinoma of the esophagus that the detected CCAT2 can be a good prognostic marker for this type of cancer (Wang et al., 2015)

In this perspective, a drug with anticancer properties accepted by the Food and Drug Administration capable of inhibiting GSK-3β (Ma et al., 2017), an agonist that activates the Wnt / β-catenin signaling pathway, can act in conjunction with lithium chloride (LiCl) to partially restore CCAT2-mediated malignant biological reactions in squamous cell carcinoma cells. This way, to allow the quantification of WNT signaling in cells, a TOP / FOP Flash reporter luciferase assay was performed, and to confirm the induction of apoptosis by silencing the CCAT2, the Western Blot Assay test was used, noting that the drug suppressed the resources proliferation and cell invasion in OSCC cells.

In addition, Wang J, 2015 reported that CCAT2 detected in the serum of patients with squamous cell carcinoma of the esophagus could be a potential marker of serum prognosis for esophageal squamous cell carcinoma (Wang et al., 2015).

Thus, the LiCl-activated Wnt / β-catenin signaling pathway could partially restore the effects by suppressing β-catenin, CCND1 and MYC and activating GSK-3β expression. (Ma et al., 2017)

IncRNA MicroRNA-9

Among these non-coding RNAs, the miRNAs are short non-coding RNAs (approximately 22nt in length) that bind to short regions MicroRNAs play important roles in a wide variety of pathological processes related to tumor formation. Aberrant expression of miRNA has been shown to induce tumor suppression or induce oncogenic effects, resulting in the formation of tumors. (Li et al.,2021)

A growing body of evidence has suggested that aberrant expression of miRNAs may lead to the development and progression of malignancy (Li et al.,2021). Overexpressed MiR-21 exhibits oncogenic activity in various carcinomas. (Sicard et al., 2013).

One study supports a strong association of high levels of miR-21 and significantly reduced survival at five years in patients with head and neck OSCC. (Ren et al., 2014)

MicroRNA-9 (miR-9), expressed in neurogenesis, has been confirmed as downexpressed in many types of cancers, including nasopharyngeal carcinoma (Gao et al., 2013), colon cancer (Cekaite et al., 2012), breast cancer (Selcuklu et al., 2012), and melanoma (Liu et al., 2012), all of which are indicative of a tumor suppressor potential, whereas miR-9 is overexpressed in hepatocellular carcinoma, (Sun et al., 2013) in brain cancer and in Hodgkin's lymphoma (Leucci et al., 2012), suggesting miR activity -9 in these cancers.

Expression of CXCR4, the CXC4 chemokine receptor gene (CXCR4), was discovered as a direct target of miR-9 and

is involved in the Wnt pathway (Jin et al., 2012, Choe et al., 2012), the wnt / β-catenin signaling pathway has been reported as enabled in OSSC (Fracalossi et al., 2010). Thus, it has been speculated that miR-9 can inhibit tumorigenesis by regulating Wnt / β-catenin signaling via chemokine receptor CXC 4 (CXCR4). To elucidate the underlying mechanism, β-catenin expression levels were detected, and the results showed that miR-9 subexpression promoted the expression of CXCR4 proteins, which activated the effect of CXCR4 on Wnt / β-catenin signaling. Activated β-catenin was then translocated to the nucleus, where, in turn, it activated its downstream effectors and functionally contributed to tumorigenesis. (Yu et al., 2014)

Enzymes capable of enhancing growth and metastasis by the inhibition of the Wnt / β-catenin pathway

Kallikreins (KLKs)

Kallikreins (KLKs) are be considered prognostic markers for the development of the disease and can exhibit abnormal expressions in various malignancies, because are a group of serine proteases encoded by 15 different genes (Scorilas et al., 2012, Mavridis, K., & Scorilas, A., 2010, Avgeris et al., 2016).

Some studies claim KLK4 is also being associated with the proliferation, metastasis and poor prognosis of cancers. Besides highly expressed in cancers like in prostate cancer and ovarian cancer (Wang et al., 2018, Tang et al., 2019, Wang et al., 2018, Riley et al., 2016, Yang et al., 2017)

In one study, KLK4 silencing inhibited the activation of the Wnt / β-catenin signaling pathway on the growth of OSCC cells by the Werken-Blot tests which further measured the levels of GSK 3β. These results demonstrate that KLK4 silencing exerts its inhibitory effect on the cell growth of OSCC via the Wnt / β-catenin signaling pathway (Cui et al., 2017).

The intracellular human enzyme Paraoxonase-2 (PON)

The intracellular human enzyme Paraoxonase-2 (PON2) is a member of the paraoxonase family (PON1, PON2 and PON3), located in the endoplasmic reticulum (ER) and nucleus (Furlong et al., 2016). Recently, a positive regulation of PON2 has been shown in several solid tumors, as well as in different leukemic diseases (Dasgupta et al., 2011, Witte et al., 2011, Schweikert et al., 2012)

Furthermore, increased expression of PON2 in various tumors has established that selected cells can undergo spontaneous apoptosis in response to PON2 knockdown, including A549 lung carcinoma cells (Dasgupta et al., 2011, Witte et al., 2011)

Overexpression of PON2 elevated the resistance of cancer cells to cytotoxic stimuli, including chemotherapeutic agents, whereas PON2 deficiency increased susceptibility (Schweikert et al., 2012)

In addition, through the regulation of β-catenin several lines of evidence support a role for PON2 in resistance to the death of malignant cells. This may be associated with the marked amount of PON2 and β-catenin levels in tumors of patients with CPB, which, in turn, may also be related to the occurrence of recurrence.

Considering this, a study systematically approached the endogenous regulation of PON2 and how this relates to tumorigenesis, demonstrating a significant role for the Wnt-β-catenin-Lef1 / TCF axis. Emphasizing the clinical impact of the newly described regulation of PON2 through Wnt / GSK3β / β-catenin

The results obtained in vitro demonstrate, for the first time, an increase in the transcription and translation of PON2 through the activation of Lymphoid enhancer-binding factor 1 (Lef-1) mediated by Wnt / β-catenin in leukemia and OSCC cells. Thus, after activation of β-catenin, Lef-1 normally regulates positively PON2 while Expression of the transcription factor T-cell factor 4 (TCF4) negatively regulates its promoter activity, Expression of the transcription factor T-cell factor 1 (TCF1) does not has effect. (Su et al., 2014)

Su et al. have recently demonstrated an overexpression of Lef-1 in OSCC samples, which was significantly associated with poor prognosis (Su et al., 2014), a finding that can be explained by PON2.

Based on these findings, the targeting of PON2 in cancer cells, directly or indirectly through Wnt / β-catenin, may contribute to the restoration of death signaling in tumor cells. (Krüger et al., 2016)

Proteins linked to adhesion molecules capable of suppressing growth and metastasis by inhibition of the Wnt / β-catenin pathway

Cancer Stem Cells

A small subpopulation of cells similar to stem cells are developing in recent studies, they are called cancer stem cells present in several types of cancer, including OSCC (Sotgia et al., 2019, Meacham, C. E., & Morrison, S. J., 2013), they show resistance to radiotherapy and chemotherapy with characteristics of self-renewal and asymmetric division (Nik-Zainal et al., 2012). Signal control via the Wnt / beta-catenin signaling pathway is crucial for the functioning of these CSCs (Cabrera et al., 2015, Takahashi-Yanaga et al., 2010)

CD44

The expression levels of stem cell-related genes, including cell surface glycoprotein involved in cell-cell interactions, cell adhesion and migration, to CD44, are regulated by this pathway. Interestingly, HC-1, a compound derived from hexachlorophene (antiseptic), clearly and effectively reduced the CD44-positive population compared to other compounds, suggesting that HC-1 efficiently targets the CSCs of the OSCC cells.

Decreased population positive for CD44, by treatment with HC-1 raised the possibility that HC-1 increases the cytotoxicity of conventional anticancer drugs, such as 5-fluorouracil (5-FU). These results suggest that HC-1 enhances the cytotoxic effect of 5-FU by increasing apoptosis in HSC2 cells.

Of these compounds, HC-1 showed an efficient reduction of the CD44-positive population, without affecting cell viability. In addition, HC-1 sensitized HSC2 cells to 5-FU, which inhibits DNA / RNA synthesis in non-CSCs. These results suggest that HC-1 is an effective compound to increase cell cytotoxicity by shifting CSCs to non-CSCs.

Since HC-1 efficiently displaced CSCs for non-CSCs in OSCC cells, HC-1 may also be beneficial for cancer therapy (Yokogi, S.et al., 2016).

Thus, HC-1 inhibits the Wnt / beta-catenin signal promoting the degradation of ubiquitin-E3-dependent protein dependent SIAH1 beta-catenin (Yokogi, S.et al., 2016). And, therefore, beta-catenin degradation may be associated with a reduction in the CSC population.

FAT1

The gene product of the FAT1 gene [Homologoss 1 of the Homo sapiens tumor suppressor (Drosophila)] is an intrinsic membrane protein of large molecular weight (~ 500 kD) which is classified as a member of the cadherin superfamily. This gene product regulates actin dynamics, cell-cell contact and cell polarity, and β-catenin is associated (Chen et al., 2019).

On the other hand, FAT1 is involved in the structure and function of the glomerular cleft by podocytes and (Yu et al., 2017), it is important to note that FAT1 is also considered a tumor suppressor gene (Chen et al., 2019). An earlier study reported the loss heterozygosity of FAT1 may be an important factor in the development of astrocytic tumors (Nie et al., 2016).

The cytoplasmic domain of FAT1 binds to β-catenin and plays a key role in cell migration, polarization and morphogenesis (Morris et al., 2013). Therefore, the deletion of this gene could imply the characteristics and the biological

behavior of CCEs that involve cell adhesion, migration and / or invasion, and may result in poor prognosis.

One study revealed that FAT1 expression in most cases of OSCC and cell lines by RNAi assay, which either inhibits gene expression in the translation phase or hinders the transcription of specific genes, was used to clarify the role of FAT1 in cell proliferation, as well as in the morphological alteration of OSCCs.

FAT1 and β-catenin showed that HSC2 control exhibited positive staining for both FAT1 and β-catenin, whereas HSC2 transfected with siFAT1 did not show positivity for FAT1 and showed the staining of β-catenin to accumulate in the cytoplasm and in the core

Thus, silencing of FAT1 resulted in a reversed reduction in cell-to-cell adhesion, and change in cell morphology associated with disorganized β-catenin localization. On the other hand, the absence of the organized FAT1 and β-catenin complex may result in loss of both cell polarity and migration capacity. (Nishikawa et al., 2011)

TNF-α

Although the "cell fusion" theory of tumor metastasis was proposed in the early twentieth century (Gast et al., 2018), it never received extensive attention during the next 100 years. In recent years, there is a growing body of evidence demonstrating the association of cell fusion with cancer progression, including melanoma (Lazova et al., 2013) breast cancer (Noubissi et al., 2015) Recently, inflammation has also been suggested as a possible trigger for cellular fusion (Weiler et al., 2018)

There is an association between the tumor microenvironment and chronic inflammation, due to the relationship between inflammation, cell fusion and cancer. One study reported that tumor-associated macrophages could promote the progression and metastasis of breast cancer through fusion with breast cancer cells. (Ding et al., 2012)

It was then discovered that the proinflammatory cytokine TNF-α along with hypoxia were strong inducers of cellular fusion in humans and that during the fusion of embryonic stem cells with somatic cells, the periodic activation of the Wnt signal pathway / β-catenin could significantly increase cell-mediated cellular reprogramming (Weiler et al., 2018).

In view of this, the TNF-α treatment led to the activation of the Wnt / β-catenin signal pathway in SCC-9. Accordingly, inhibition of Wnt / β-catenin activation by DKK-1 (Dickkopf-related protein 1) or β-catenin specific shRNA could significantly reduce the number of OSCC cells. (Miki et al., 2011)

Thus, the proinflammatory factor TNF-α can activate the Wnt / β-catenin signal pathway and thus increase the fusion between squamous cell carcinoma cells and endothelial cells by upregulating the fusogenic protein syncicine-1. These results demonstrate the signal transduction pathway that links inflammation, the Wnt / β-catenin signal pathway and cell fusion in the tumor microenvironment (Yan et al., 2017). Being an interaction between cancer cells in the mouth and endothelial cells through a new vision.

Chemical agents capable of controlling growth and metastasis by inhibition of the Wnt / β-catenin pathway. Around the world, 25% of oral cancers are attributable to tobacco use (smoking and / or chewing), 7% to 19% to alcohol, 10% to 15% to micronutrient deficiency, more than 50% to betel in areas of high prevalence of mastication (Hydes et al., 2019).

The high incidence of tobacco abuse is linked to nicotine, the addictive component of cigarettes, has been shown to promote the proliferation and metastasis of tumor cells promoting cell cycle progression, epithelial-mesenchymal transition (EMT), migration, invasion, angiogenesis and anti- apoptosis via various signaling pathways (Kang, J. Y., He, J., & Duan, X. F., 2019).

Furthermore, nicotine stimulation has been shown to induce proliferation, angiogenesis and metastasis in non-small cell lung cancer cells and squamous cell esophageal cancer (Shi et al., 2015, Yoneyama et al., 2016). Nicotine may even

promote metastasis via Wnt / β-catenin signaling in normal human airway epithelial cells and human alveolar interstitial fibroblasts (Zou et al., 2013, Sakurai et al., 2017).

Thus, in one study (Wang et al., 2017) it was found that nicotine can promote the progression of squamous cell carcinoma cells by activating the Wnt / β-catenin signaling pathways in a Western blot analysis and TOP / FOP tests, CCK-8, wound healing and Transwell invasion that were used to assess Cal27 in response to nicotine stimulation, and it has been found that it can play a significant role in the progression and metastasis of smoking-related SCLC.

Still, a popular oral habit that should be mentioned is chewing betel, with potential links to the occurrence of oral cancer. A study has shown that areca nut extract can demonstrate mutagenic and genotoxic effects, as well as induce pre-neoplastic and neoplastic lesions in experimental animals. (Madathil et al., 2016) Arecoline, the main alkaloid of areca nut, exerts cytotoxicity and inhibits the growth of several human cells in culture, including oral epithelial cells (Tseng et al., 2012) that promoted carcinogenesis together with 4-nitroquinoline-1-oxide (4-NQO) that mimics the biological effects of ultraviolet light on various organisms. (Araújo et al., 2018) in mice. (Chang et al., 2010)

Taiwania (TaiwaniacryptomerioidesHayata) is an endemic plant in Taiwan. In one study, it was envisaged that one of its isolated lignins, Taiwanin C, could reduce the migration mechanism in T28 cells from arecoline and 4-NQO induced oral cancer cells. In short, Taiwanin C blocked the cell migration effects of T28 cells mediated through the activation of GSK-3β to increase protein degradation and reduce nuclear β-catenin accumulation. (Hsieh et al., 2017)

In view of this, β-catenin can be considered to contribute to the development, progression and metastasis of tumors in various types of cancer including OSCC. Also, β-catenin expression was found in 87% of SCC cells well differentiated, 67% moderately differentiated and 43% poorly differentiated, expression was significantly associated with histological grade, reflecting an association in tumor progression. (Pannone et al., 2010).

Another study suggests that a cause of catenin delocalization in mouth cancer may be due to the activation of the WNT pathway by epigenetic alterations of Genes SFRP, WIF-1 and DKK-3. (Freitas et al., 2010)

Furthermore, Li, et al (2016) discusses the overexpression of β-catenin which promoted resistance to cisplatin in OSCC in vitro and in vivo, and thus, GSK-3β was confirmed to be involved in β-catenin mediated drug resistance.

4. Conclusion

In summary, activation of the Wnt/β-catenin pathway has effects on oral epithelial proliferation, differentiation and transition, which regulates the invasive behavior of tumor cells. Thus, further studies are expected in future studies regarding the expression of these biomarkers in influencing the prognosis of cancer cells, which may also help professionals to explore new possible therapeutic effects on OSSC by modulating the Wnt/β-catenin pathway.

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