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REVIEW ARTICLE

Wnt pathway in oral cancer: A review update

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KEYWORD

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Abstract The Wnt signalling pathway involves in the pathogenesis of human diseases and one of the pathways that contribute to embryogenic development. Studies about the Wnt pathway have unfolded its regulation in many cancer cell mechanisms such as cell survival, migration, polarity, and cell multiplication. Moreover, the Wnt pathway has a significant role in cell fate determination and self-renewal in stem cells. Oral cancer shares significant concern among clinicians and researchers. However, there are only a few studies done on oral cancer and its correlation with the Wnt pathway. The expression of Wnt gene members in many malignancy diseases which included oral cancer has proven a high inverse correlation with malignancy diseases and malignancy progression. Metastasis which predominantly occurred through the lymphatic system has been the principal cause of mortality in oral cancer and affected to cancer stage, main tumour site, cancer cell differentiation and cancer cell adhesion potency. With intention of contributing to oral pathology and oral medicine research and knowledge advancement, particularly in the oral cancer area, this article presents current findings regarding the Wnt pathway and its multiple mechanisms associated with the treatment of oral carcinogenesis through Wnt pathway signalling.

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Contents

1. Introduction

The name of Wnt or Wingless integrated/ NT came from a combination between the name of the Drosophila segment polarity gene wingless together with the vertebrate homolog name, integrated or int-1 which encodes a group of 19 secreted cysteine-rich glycoproteins as seen in Table 1 (Wiese et al., 2018). In mammary carcinogenesis, Wnt1 is initiated by proviral insertions and had been known in its potential role in many cancers such as breast cancer, colorectal cancer, hepatocellular carcinoma, lung adenocarcinoma, gastric cancer, as well as oral cancer (Kerdidani et al., 2019; Mao et al., 2014; Wang et al., 2018; Yan et al., 2012).

2. Literature review

2.1. Wnt pathway and its genes

There are two major types of Wnt pathway which are canonical (β-catenin dependent) and non-canonical type (β-catenin independent) signalling (Zhan et al., 2017). The crucial step in Wnt signalling is secreting cells produced by Wnt ligands (Buechling et al., 2011). The Wnt relocation from the endoplasmic reticulum towards the Golgi apparatus is induced by p24 protein and then binds tightly with afamin to prevent aggregation (Mihara et al., 2016; Port et al., 2011). Wnt proteins may release towards the plasma membrane and secrete from the cell through several paths such as immediate release from the plasma membrane by solubilisation, exosomes growth and through lipid-protein particles (Gross et al., 2012; Mulligan et al., 2011).

Aberrant regulation of the Wnt pathway has been associated with various types of cancers (Duchartre et al., 2016). Wnt pathway mechanisms interrupt the growth and/or invasion of cancer through loss of heterozygosity, polymorphisms or genetic alteration, cellular senescence, chromosome segregation, and over or low expression of Wnt protein (Ali et al., 2017). For instance, the high prevalence of Wnt1 is correlated with late-stage carcinoma of lung patients and contributes to colorectal cancer cell migration and invasion (Stanczak et al., 2011).

Table 1 Wnt pathway genes.

Wnt ligands	Receptors/Co-receptors	Transcription factors	Wnt inhibitors	Transcriptional co-activators	Transcriptional co-repressors	Transducer
β-catenin-dependent pathway activators (Wnt1-16 except Wnt4-5a and Wnt11)	Frizzled 1–10 (Fzd1-10)	T-cell factors 1,3,4 (Tcf1,3,4)	Dickkopf 1–4 (DKK1-4)	β-catenin	Transducin-like enhancer of split (TLE)/ Groucho 1–4	Adenomatous polyposis coli (APC1/2)
β-catenin-independent pathways activators (Wnt4, Wnt5a, Wnt11)	LDL receptor related protein 5/6 (LPRP5/6) co-receptor	Lymphoid enhancer factor 1 (Lef1)	Secreted frizzled-related proteins 1–5 (SFRP1-5)			AXIN 1/2
	Receptor tyrosine kinase-like orphan receptor 2 (ROR2)		Soggy			Glycogen synthase kinase 3 beta (GSK3β)
	Dishevelled 1–3 (Dvl1-3)		Wnt inhibiting factor 1 (WIF1)			Casein kinase 1 (CKN1)
	YAP		Wise (Sostdc1)			
			Gpr177			

2.2. Wnt pathway in oral cancer

Oral cancer has become a major concern in Southeast Asia predominantly because of the high incidence of social or personal habits such as betel quid chewing, tobacco and alcohol consumption (Karaca and Ozturk, 2019). More than 90% of oral cancers in oral squamous cell carcinoma (OSCC), and the prognosis upon diagnosis for OSCC patients remains unsatisfactory (Bagan et al., 2010; Khor et al., 2013). Therefore, the identification of novel therapeutic targets and prognostic markers for oral cancer is crucial. Several studies highlight the contribution of Wnt signalling pathway activation in oral neoplastic transformation and epithelial to mesenchymal transition (EMT) toward oral cancer progression. Oral cancer expresses some of the Wnt genes and activates the signalling pathway. A set of Wnt genes were expressed in oral cancer cells meaning that several of Wnt genes affected the structural form of cancer cells (Castilho and Gutkind, 2014; Shiah et al., 2016).

In oral cancer, several Wnt and Frizzled genes are expressed, mostly Wnt5a and Fzd5 but the role of Wnt5a has not yet been thoroughly revealed. Furthermore, not only Wnt5a stimulates the non-canonical Wnt/Ca (2^{+}) /PKC pathway, but it also contributes to oral cancer cell migration and invasion. This evidence may suggest how the increase of the Wnt5a gene in the tumour tissue induces oral carcinogenesis (Prgomet et al., 2015). In addition, Prgomet et al. detected higher expression of Wnt5a compared to oral dysplasia and normal oral mucosa (Prgomet et al., 2017). Wnt5a expression increased following the grade of dysplasia and the highest was expressed in oral cancer. These outcomes offer an opportunity for Wnt5a which could be used as a potential biological marker for oral carcinogenesis.

Some of the evidence suggests that many regulatory genes of the Wnt signalling pathway are dysregulated in the head and neck APC gene, Wnt antagonists the secreted Frizzled-related proteins (SFRPs) gene, Wnt inhibition signalling can contribute to increase growth, metastatic and resistance to chemotherapy in cancer treatment (Castilho and Gutkind, 2014; Li et al., 2016; Pannone et al., 2010). A study was done by L. Li et al. (2016) found that Wnt/ β -catenin signalling pathway may play important roles in cisplatin resistance in

Table 2 Emerging roles of Wnt pathway genes in oral cancer.

No	Gene	Function	Role	Author, year
1	Wnt1	Ligand	Wnt1 used as combination target therapy in OSCC treatment	Ma et al., 2017
2	Wnt2	Ligand	Wnt2 activation increase invasiveness of HNSCC (upregulation role)	Le et al., 2019
3	Wnt3a	Ligand	Wnt3a may be an indicator of poor prognosis in OSCC	Marimuthu et al., 2018
4	Wnt7a	Ligand	Wnt7b as a therapeutic target in oral cancer Wnt7a has an upregulation role in HNSCC	Shiah et al., 2016 Le et al., 2019
5	Wnt16	Ligand	Upregulation role in HNSCC	Le et al., 2019
6	Fzd7	Receptor	Fzd7 as a therapeutic target in OSCC cisplatin resistance treatment	Liu et al., 2019
7	AXIN1	Transducer	Upregulation role	Andrade Filho et al., 2011
8	AXIN2	Transducer	AXIN2 was expressed low in HNSCC but associated with advanced clinical stage	Le et al., 2019
9	APC	Transducer	APC as a tumour suppressor gene	Alamoud and Kukuruzinska, 2018
10	β-catenin	Transcription factor	Targeted therapy	Kartha et al., 2018
11	LEF-1	Transcription factor	LEF1 as a transcription factor	Sogutlu et al., 2018
12	TCF4	Transcription factor	Transcription factor in OSCC	Lee et al., 2014
13	DKK1	Inhibitor	Increasing migration and invasion of OSCC cells	Ogoshi et al., 2011
14	DKK2	Inhibitor	Target therapy for OSCC	Souza and Saranath, 2015
15	DKK3	Inhibitor	Play role in cellular proliferation, invasion, migration, and tumour cell survival of OSCC	Katase et al., 2020
16	SFRP1	Inhibitor	SFRP1 showed a significantly upregulated expression in low-grade OSCC and survived patients	Marimuthu et al., 2018
17	SFRP2	Inhibitor	SFRP2 showed a significantly upregulated expression in low-grade OSCC and survived patients	Marimuthu et al., 2018
18	SFRP4	Inhibitor	SFRP4 showed higher expression in a male patient with OSCC compared to female	Marimuthu et al., 2018
19	SFRP5	Inhibitor	SFRP5 showed a significantly upregulated expression in low-grade OSCC and survived patients	Marimuthu et al., 2018
20	WIF1	Inhibitor	Catenin delocalization in oral cancer	Pannone et al., 2010
21	Wnt5a	Ligand	Increasing migration and invasion of OSCC cells	Prgomet et al., 2017
22	Wnt11	Ligand	Downregulation role as a tumour suppressor gene during OSCC development	Andrade Filho et al., 2011

oral cancer treatment (Li et al., 2016). Moreover, for APC, its activity as a tumour suppressor gene appears muted on a relatively frequent basis in oral cancer (Pérez-Sayáns et al., 2012). Some regulations of Wnt genes in oral cancer mentioned above are described in Table 2.

2.3. Current treatment in oral cancer targeting Wnt pathway

2.3.1. Medical treatment in oral cancer targeting Wnt pathway

Head and neck squamous cell carcinoma (HNSCC) cell line (SNU 1076) therapy approach by using anti-Wnt1 antibodies show decreasing mechanism in Wnt/Fzd dependent transcription factor LEF/TCF and reduced cyclin D1 and β-catenin proteins expression. Likewise, delaying Wnt1 signalling offers inhibition of proliferation and induce cell apoptosis. The study by Ma et al. (2017) found potential therapy through combination therapy of polyethene glycol-polyethyleneimine-chlorin e6 (PEG-PEI-Ce6) nanoparticles in Wnt1 siRNA production together with photodynamic therapy (PDT) in oral cancer therapy. They found that the therapy would inhibit the EMT activation that may lead to tumour relapse and development. In summary, Wnt1 siRNA combined with PEG-PEI-Ce6 nanoparticle facilitated PDT constrained cell growth and increased the apoptosis effect extraordinarily (Ma et al., 2017).

2.3.2. Herbal treatment in oral cancer targeting Wnt pathway

Adjacent to the medicinal treatment, many researchers uncovered many herbal substances that perform in eradicating oral cancer through Wnt pathway signalling (Javed et al., 2019). Aminuddin and Ng stated that curcumin has been investigated widely as natural inhibitors of the Wnt signalling pathway. Curcumin shows suppression of the Wnt canonical signalling by inhibiting β-catenin and blocking Wnt and TCF4 interaction, through a dose-dependent manner (Aminuddin and Ng, 2016). Moreover, not only that curcumin restrains the Wnt/β-catenin signalling pathway, but it also can suppress proliferation and induce apoptosis of cancer cells through the Wnt signalling pathway (Choi et al., 2010; Xu et al., 2013).

Despite curcumin, green tea also verified to be effective in inhibiting the Wnt pathway in some cancers such as lung cancer, invasive breast cancer, colon cancer, cervical cancer and gastric cancer (Chen et al., 2017; Hussain, and Ashafaq, 2018; Yang et al., 2016; Zhu et al., 2017). Epigallocatechin-3-gallate (EGCG) is one of the major bioactive elements in green tea that believed could suppress cell proliferation (Singh et al., 2011). Green tea as a treatment for oral cancer also has been studied by Irimie et al., in 2015 who found EGCG in green tea has shown evidence in activating the expression of Wnt11 and other genes that could inhibit CASP8, MYC, and TP53 in cell proliferation. This result suggests that green tea is highly potential as a therapeutic alternative mixture for OSCC patients, by initiating tumour cell death through autophagy and apoptosis (Irimie et al., 2015).

3. Conclusion

The Wnt pathway remains as a part of the fundamental factor as a well-maintained intracellular signalling pathway during embryonic development as well as performs crucial regulation in regeneration, differentiation and function of many cells and tissues involving oral tissues. The involvement of the Wnt pathway in oral carcinogenesis occurs through cell proliferation upregulation; initiation of EMT activation, genetic mutation, epigenetic alteration, and local invasiveness activation mechanisms. The Wnt pathway also plays a role in oral cancer deregulation through cell proliferation inhibition and apoptosis induction. Furthermore, some Wnt genes which act as tumour suppressor genes could be used as potential biomarkers for early detection and therapeutically target agent for oral cancer treatment.

Ethical statement

This review article requires no human or animal in research.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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