MOLECULAR CANCER

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Glycogen synthase kinase 3 beta: can it be a target for oral cancer

Rajakishore Mishra

Abstract

Despite progress in treatment approaches for oral cancer, there has been only modest improvement in patient outcomes in the past three decades. The frequent treatment failure is due to the failure to control tumor recurrence and metastasis. These failures suggest that new targets should be identified to reverse oral epithelial dysplastic lesions. Recent developments suggest an active role of glycogen synthase kinase 3 beta (GSK3 β) in various human cancers either as a tumor suppressor or as a tumor promoter. GSK3β is a Ser/Thr protein kinase, and there is emerging evidence that it is a tumor suppressor in oral cancer. The evidence suggests a link between key players in oral cancer that control transcription, accelerated cell cycle progression, activation of invasion/metastasis and anti-apoptosis, and regulation of these factors by GSK3β. Moreover, the major upstream kinases of GSK3β and their oncogenic activation by several etiological agents of oral cancer support this hypothesis. In spite of all this evidence, a detailed analysis of the role of GSK3β in oral cancer and of its therapeutic potential has yet to be conducted by the scientific community. The focus of this review is to discuss the multitude of roles of GSK3β, its possible role in controlling different oncogenic events and how it can be targeted in oral cancer.

Introduction

Oral cancer is the sixth most common cancer in the world, and its incidence varies in different ecogeographic regions [1,2]. Its occurrence is associated with exposure to smoking and alcohol consumption in the Western population. The majority of cases occur in Asia, where it is mainly associated with betel quid chewing [3]. Poor oral hygiene and human papillomavirus (HPV) infection of oral epithelial cells are other etiological factors [4]. In addition to genetic differences, other etiological factors promote the occurrence of this disease to different extents in different populations. Although there are several differences in disease occurrence and etiology between populations, there is one aspect of these tumors that is highly similar worldwide. Oral tumors are mainly asymptomatic initially, are aggressive, and frequently invade and migrate to distant organs, making them difficult to treat. This suggests that, although different predisposing factors activate various molecular pathways [5], eventually all of them may follow a common path thereafter to result in oral cancer.

Advances in recent decades in the surgical, radiotherapeutic and chemotherapeutic treatment of oral cancer have only modestly improved patient survival. Various approaches have been used for the clinical treatment of oral cancer patients in the last three decades, from non-targeted chemotherapy to highly targeted pharmacological inhibitors and specific monoclonal antibodies [3,6]. Although targeted therapies yield better outcomes than non-targeted therapies, frequent treatment failure suggests the need for new treatments or targets for this disease. In oral cancer, active transcription of various genes leads to rapid cell division, faster invasion and reduction of cell death. Although it has been largely overlooked, there is a potential link between key players in oral cancer, including transcription factors, cell cycle regulators, invasion/metastasis-promoting factors, and cell survival regulators, and their regulation under the control of glycogen synthase kinase 3β (GSK3β).

GSK3β plays a major role in epithelial cell homeostasis [7]. Its activity is regulated by site-specific phosphorylation of Tyr216/Ser9 residues [8]. The regulated phosphorylation of Ser9GSK3β is the main cause of various pathological conditions, and it is upregulated in epithelial cancers. Many upstream kinases protein kinase A (PKA) [9], Akt/PKB [10], PKC [11], p90 ribosomal S6 kinase/

* Correspondence: mishrark1@yahoo.co.in
[1] Dept. of Molecular Pharmacology and Therapeutics, Loyola University Medical Center, 2160 South First Avenue, Bldg 102, Maywood, IL-60153, USA
Full list of author information is available at the end of the article

MAPK-activating protein (p90RSK/MAPKAP) [12] and p70 ribosomal S6 kinase (p70S6K) [13] are known to phosphorylate Ser9 of GSK3β, depending on the cellular context and various upstream regulators. The oncogenic activation of these upstream signaling molecules is frequently reported in oral squamous cell carcinoma (OSCC) [14-16]. Many of these oncogenic pathways are activated by common etiological factors of this cancer. Overall, this evidence suggests the possible active involvement of GSK3β-mediated signaling in this neoplastic disease. This review attempts to correlate the established pathways of oral cancer with GSK3β signaling and discusses the potential of this kinase as a therapeutic target.

The GSK3 family and its regulation

GSK3 was discovered nearly three decades ago in rabbit skeletal muscle as a protein kinase that phosphorylates and inactivates glycogen synthase, the final enzyme of glycogen biosynthesis [17,18]. GSK3 is a multifunctional Ser/Thr kinase with diverse roles in various human diseases, including diabetes, inflammation, neurological disorders and various neoplastic diseases [19,20]. To date, two members of the mammalian GSK3 family (α and β) are known [18]. They are ubiquitously expressed and highly conserved and are members of the CMGC family of protein kinases [21]. Many of the substrates of GSK3 need a "priming phosphate" (which is a Ser/Thr residue) located four amino acids (aa) C-terminally from the site of phosphorylation [8]. GSK3 is constitutively active in resting cells and undergoes a rapid and transient inhibition in response to a number of external signals. Physiological regulation of GSK3 activity by various upstream kinases [9-13] in different physiological and pathological condition is established [8].

GSK3β and its role in tumorigenesis

GSK3β drives oncogenic progression either by its inhibition or its activation, depending on the cell type. In recent years, its role in cancer has become firmly established. The differences in the roles of GSK3β depending on the type of cancer are quite interesting. Whereas it has a growth-promoting role in some cancers, it suppresses growth in others. Based on the literature, it is clear that GSK3β can act either as a tumor promoter or as a tumor suppressor, as shown in Table 1.

GSK3β and its control over transcription

Alteration of the transcriptional machinery is common in neoplastic diseases, including oral cancer [22,23]. Oncogenic transcription factors (OTFs) alter the transcriptional machinery to regulate mRNA synthesis. GSK3β regulates the stability of various oncogenic TFs like the activator protein 1 (AP-1) [24], nuclear factor kappa B (NFκB) [25], c-Myc [26], β-catenin [27], Snail [28], Forkhead (FH) [29], CAAT-enhancer binding protein (C/EBPs) [30], and cAMP response element-binding (CREB) [31] by phosphorylation [8]. Most of these TFs are physiological targets of GSK3β that undergo proteasomal degradation upon phosphorylation [8,24-28]. AP-1 transcriptional activity is high in oral cancer tissue samples [2]. Active GSK3β directly phosphorylates c-Jun at Thr239 which promotes its degradation [24]. It is also known that in normal oral mucosa c-Jun is localized in the cytoplasm while it enters to the nucleus at the onset of oral carcinogenesis [32]. Both Fos and Jun are phosphorylated and activated by mitogen activated protein kinase (MAPK) and c-Jun n-terminal kinase (JNK) kinase system [33,34] may be due to inactive GSK3β. Moreover the expressions of p65 (one of the NFκB family member) have been observed in oral cancer tissue samples [35,36] and metastatic OSCC [36]. GSK3β phosphorylates p65 at Ser468 and negatively regulate its activity by promoting its degradation [25]. p65 might escape from its turnover because of inactivated GSK3β in OSCC. Recent report suggests active GSK3β physically interact with IκBα in normal epithelial cells [37]. Moreover study in different system suggests that active GSK3β blocks NFκB dependent transcription, by preventing IκBα degradation [38]. In normal epithelial cells NFκB activity is known to be inhibited by GSK3 [39]. From all these evidences, it seems like NFκB activation in OSCC may be modulated, because of inactive GSK3β like that in other epithelial cancers [40]. On the other hand, degradation of c-Myc and β-catenin is initiated by phosphorylation of GSK3β [26]. The overexpression of c-Myc and β-catenin protein in OSCC is established [41-46]. The gene mutation on hot spots i.e. Thr58 of c-Myc and Ser33, Ser37, Thr41 and Ser45 of β-catenin abolishes phosphorylation by GSK3β results in preventing ubiquitination and proteasome mediated degradation of c-Myc [47-50]/β-catenin [46,51-53] has been reported in various cancers but not so far in OSCC. In OSCC, c-Myc/β-catenin protein might get stability not because of missense mutation at these hot spot codons but because of inactivation of its phosphorylating kinase i.e. GSK3β it self. The activated Snail has been reported in OSCC [54]. GSK3β is well known regulator of Snail which phosphorylates and that leads to Snail nuclear export and deregulation [28,39,55,56]. Moreover, p53 is highly involved in OSCC [57]. Though it is inactivated by mutation in nearly half of oral cancer population [57] the cause of its inactivation is still doubtful in the other half. p53 activity is regulated by active GSK3β, due to either physical association or phosphorylation and post-translational modification [58,59]. It is possible that in OSCC cases without p53 mutations [57], p53 can be inactivated due to inactive GSK3β. These OTFs those are

Table 1: Paradoxical role of GSK3β in various human cancers

Cancer Types	**Explanation for Tumour Suppressor Role of GSK3β**
Skin cancer (Cutaneous SCC)	Inactivation of GSK3β (higher pSer9GSK3β expression) [72] Inactivation of GSK3β (lower pTyr216GSK3β expression) [60,168] Pharmacological inhibition of GSK3β in normal epithelial causes epithelial mesenchymal transition (EMT) and invasion [39]
Oral cancer (OSCC)	Inactivation of GSK3β (higher pSer9GSK3β expression) [88] The basal inactivated GSK3β (pSer9GSK3β) level in OSCC cell line is high [61-63] Activation of GSK3β, can reverse EMT [64]
Larynx cancer	Inactivation of GSK3β (higher pSer9GSK3β expression) [88]
Esophageal cancer	Inactivation of GSK3β (higher pSer9GSK3β expression) [88]
Breast cancer	Overexpression of inactive GSK3β promotes [169], and active GSK3β suppress mammary tumours [168] Active GSK3 increases chemosensitivity, cell cycle arrest and reduces mammary tumorigenecity [170-172] Pharmacological inhibition of GSK3 in breast epithelial causes EMT and invasion [39]
Salivary gland cancer	Inactivation of GSK3β (pSer9GSK3β) observed in this tumor [88]
Nasopharyngeal cancer (SCC)	Inactivation of GSK3β observed and positively correlated with its upstream inactivating kinase Akt [173]
Lung cancer (SCC)	Inactivation of GSK3β reported [40]
Adenocarcinoma of Lung	Higher level of inactivated of GSK3β (pSer9GSK3β) observed [174]
Melanoma cancer	Inactivation of GSK3β reported [60]
Skin cancer (Basal cell carcinoma)	Inactivation of GSK3β reported [60]
Cancer Types	**Explanation for Tumour Promoter Role of GSK3β**
Pancreatic cancer	Pharmacological inhibition of GSK3 attenuates survival, proliferation and induce apoptosis [162,163,175] Active GSK3β promotes growth [176] Absence of inactive GSK3β (lower pSer9GSK3β expression) in tumors [88] High level expression and nuclear accumulation association with kinase activity and tumor dedifferentiation [161,177,178]
Colorectal cancer	Pharmacological inhibition activates cell cycle arrest and induce apoptosis [158,159,175] Absence of inactive GSK3β (lower pSer9GSK3β) in majority of tumors [88] Increased expression/active GSK3β in these tumors [88,159]
Myeloma cancer	GSK3β promotes growth and use of pharmacological inhibitor promotes apoptosis [83]
Hepatic cancer	Absence of inactive form of GSK3β (pSer9GSK3β) in these tumors [88] Increase and active GSK3β expression [175]
Leukemia cancer	GSK3 activation enhances proliferation and survival [160,179-181] Missplicing at the kinase domain causing active GSK3β [179]

Table 1: Paradoxical role of GSK3β in various human cancers (Continued)

Stomach cancer	Absence of inactive GSK3β (pSer9GSK3β) in these tumours [88] Active GSK3β observed frequently and its pharmacological inhibition attenuates survival, proliferation and induce apoptosis [175]
Ovarian cancer	GSK3β expression increases and it promotes cell division [156]
Prostate cancer	GSK3 activity favors replication of DNA and S-phase progression [157]
Thyroid cancer	Inhibition of GSK3 activity leads to growth suppression [182]
Gastro-Intestinal cancer	Higher and active GSK3β expression observed [166] Absence of inactive GSK3β (pSer9GSK3β) in these tumors [88]
Renal cell carcinoma	Activation of GSK3β observed in this tumor [175] Nuclear accumulation of GSK3β and its pharmacological inhibition suppress growth [178]
Glioma cancer	Pharmacological inhibition of GSK3 induces cell death [183]

important in OSCC and are directly regulated possibly by GSK3β. Alteration of these TFs plays a vital role in various diseases, including OSCC.

GSK3β is a key player in OSCC

GSK3β can promote or suppress growth in different types of cancer (Table 1). The inactivation of GSK3β has been reported in most cancers of epithelial origin, such as skin, breast, and in cancers of the oral cavity, salivary glands, larynx, and esophagus [60]. The basal level of inactivated GSK3β (pSer9GSK3β) in OSCC cell lines is very high [61-63] but can be decreased by inhibiting the GSK3β upstream inactivating pathway [61,62]. A recent report suggests that activating GSK3β can reverse the epithelial-mesenchymal process in oral cancer [64]. GSK3β-mediated signaling could explain numerous molecular disorders specific to oral cancer.

A) Cell cycle regulation

Cell division is a precisely regulated process that occurs obligatorily in all organisms. The ability of cells to divide is mainly attributed to the presence of three classes of molecules: CDKs (Cyclin Dependent Kinases, a family of Ser/Thr kinases), their binding partners cyclins and CDK inhibitors (CDKI) [65]. The transcriptional and post-translational regulation of cyclin D1 [66,67] and of cyclin E [68,69] in OSCC are well documented. Cyclin D1/E transcriptional upregulation is achieved by regulating TFs (e.g., AP-1, NFκB, β-catenin), and protein stability/nuclear accumulation are also increased [70,71] in OSCC [66,68,69]. Inactive GSK3β prevents the phosphorylation of Thr286 cyclin D1 and Ser380 cyclin E, which blocks their nuclear export and degradation [70-72]. An inverse correlation between cyclin D1 and GSK3β expression has been reported in oral cancer [73]. Cyclin A and cyclin B are also overexpressed in OSCC [69,74,75]. These cyclins are primarily regulated by c-Myc and p53 and thus qualify as GSK3β targets. Because these are S phase- and G2-M phase-specific cyclins, their expression is affected by the G1 phase-specific cell cycle events of cyclin D1/CDK4 and cyclin E/CDK2 activation [57,76]. Overexpression of CDK4 mRNA has been reported in different malignancies, including oral and epithelial cancer [77,78]. c-Myc controls the expression of CDK4 by binding to E-box elements present in its promoter that are not only overexpressed in OSCC [42] but also are regulated by GSK3β [26]. p21 (WAF1/CIP1) competes with cyclins for binding to CDKs, and its expression is usually decreased in various cancers. However, in OSCC, the overexpression of p21 (WAF1/CIP1) is quite evident [79], and its overexpression significantly correlates with tumor size, lymph node involvement and clinical stage [79,80]. Active GSK3β directly regulates p21 expression by phosphorylation at Thr57 [81], leading to proteasome-mediated degradation. Another explanation could be that the TFs C/EBPα and -β (which may also be stabilized because of inactive GSK3β in OSCC) interact with p21 and protect it from degradation. The possible explanations for why p21 does not halt OSCC progression are numerous. One possible explanation is that p21 is inactivated by binding to the E7 protein of human papillomavirus 16 (HPV16), which is highly prevalent in OSCC. This association of p21 and E7 blocks the ability of p21 to inhibit cyclin/CDK activity as well as PCNA-dependent DNA synthesis. In contrast, another CDKI, p27, is reportedly down-regulated in OSCC [82] in a process that might be mediated by forkhead (FH) TF [29,83]. In breast cancer (where active GSK3β acts like a tumor suppressor as in OSCC;

Table 1) knock down of PI3K promotes degradation of FH and p27 possibly via GSK3β activation [84]. GADD45 and GADD153 are checkpoint inhibitors and tumor suppressors that have roles in multiple tumor types, including OSCC [85,86]. GADD45 is also controlled by p53, and upon DNA damage, it is activated to arrest the cell cycle. Both GADD45 and GADD153 are downstream targets of c-Myc [87] and thus qualify as possible GSK3β targets in OSCC. Cell division cycle 25A (CDC25A) is also controlled by c-Myc [69,76]. Direct evidence suggests a positive correlation between pSer9GSK3β and CDC25A expression in tumors of the oral cavity, salivary glands and larynx (Ref. [88] and Fig 1).

B) Nodal invasion by epithelial-mesenchymal transition

OSCC is a cancer of epithelial cells that invades surrounding tissues and frequently migrates to distant organs (metastasizes) [89]. The extra cellular matrix (ECM) interaction is important for the survival of normal epithelial cells but this interaction is gradually lost in squamous cell carcinoma [90]. The major ECM molecules implicated in OSCC development include collagen, fibronectin [91], tenascin [92] and laminin [54,91,93]. Many ECM molecules are indirect targets of GSK3β via Snail- or AP-1 [28,94]. The degradation of basement membrane (collagen) by MMPs and its regulation by inactive GSK3β have been reported [95,96]. Focal adhesion kinase (FAK) is overexpressed in preinvasive and invasive OSCC [97]. Upregulation of FAK leads to migration, and its regulation by active NFκB is known in tongue squamous cell carcinoma cells (SCC25) [98,99] possibly via inactive GSK3β. Another group of molecules, the integrins, are transmembrane, heterodimeric, cell-surface proteins (consisting of one α and one β subunit) that primarily function as cell adhesion molecules but also participate in signal transduction leading to cell migration, growth and oncogenesis. Human integrins are upregulated in OSCC [100,101], and they are primarily controlled by those transcription factors regulated by GSK3β [102-104]. Recent evidence suggests a role for Snail in controlling multiple α/β-integrins and EMT in OSCC [54,94,105].

MMPs are a group of extracellular matrix/basement-degrading proteases. High levels of MMP-2, -3, and -9 have been associated with poor prognosis for patients

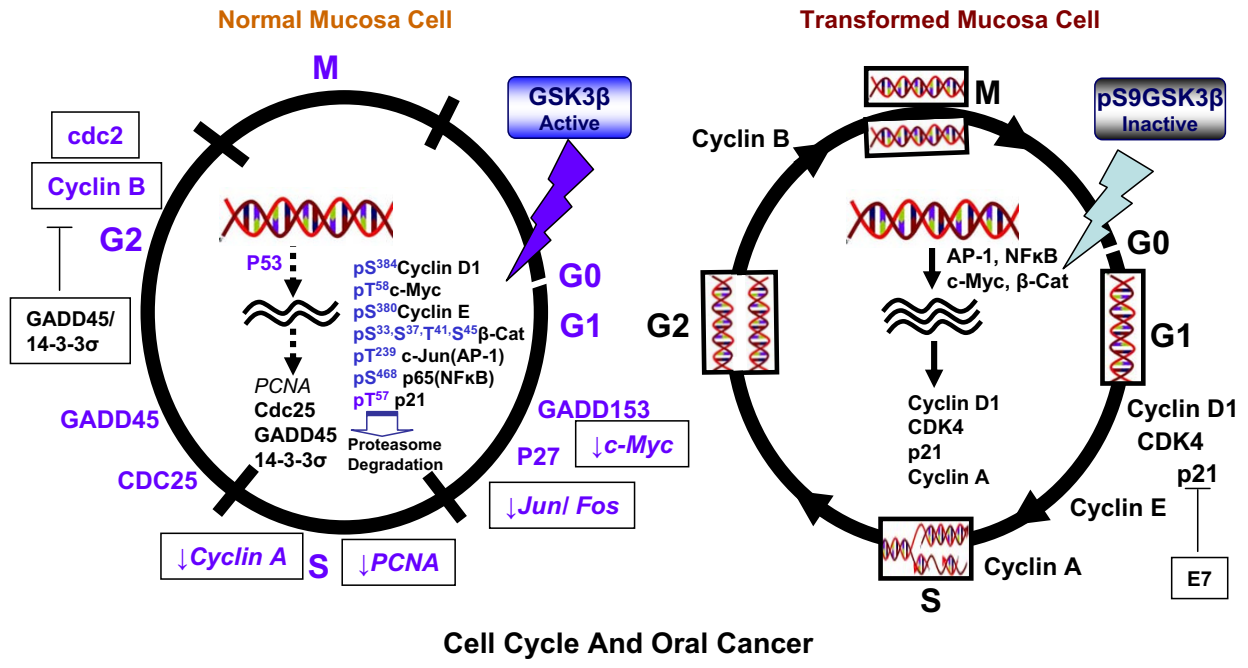

Figure 1 Progressive inactivation of GSK3β may promote accelerated cell cycle and oral cancer. As discussed in the text, most of the cell cycle regulators and their gain of function may be because of inactivation of GSK3β in oral cancer. GSK3β regulates the activity or turnover of several master cell cycle regulators like p53. Activation of p21, 14-3-3σ and GADD45 protein by p53 induces cell cycle arrest to prevent the propagation of mutations, which accumulate in cells under genotoxic stress. p53 induces the expression of the cytoplasmic scaffold protein 14-3-3σ, which prevents the nuclear import of cyclin B1 and cdc2 by sequestration in the cytoplasm. On the other hand, GADD45 destabilizes CDC2/cyclinB complexes. GSK3β-regulated c-Myc is a master regulator of the cell cycle and is essential for G0/G1-to-S progression. Myc suppresses the expression of cell cycle checkpoint genes (GADD45, GADD153) and inhibits the function of CDK inhibitors. Myc also activates cyclins D1, E1, and A2, CDK4, CDC25A, and E2F-1 and -2. Cyclin D1 is a crucial cell cycle regulator mainly regulated by the activity of TFs (NFκB, β-catenin-TCF/LEF, AP-1) and is indirectly controlled by GSK3β. Moreover, inactivation of GSK3β leads to the stabilization of cyclin D1. Oncogenic gains of function of these molecules stemming from inactive GSK3β have been established in various neoplastic diseases and might orchestrate cell cycle dysregulation in OSCC.

with oral cancer, including the development of lymph node metastasis and poor survival [100,106,107]. The transcriptional activation of MMP-1,-3, and -9 is common in OSCC [108,109], and they are all targets of AP-1, NFκB, C/EBPs or Snail, highlighting the importance of GSK3β-mediated signaling in the oral cancer invasion program [110-112].

Cadherins interact with the actin cytoskeleton to maintain tissue architecture. In some cancers, including OSCC, loss of E-cadherin favors invasion. An inverse correlation between E-cadherin and Snail expression has been reported in OSCC and epithelial cancers [113-115], which supports the regulation of E-cadherin by the inactivation of GSK3β and Snail [28,64]. Snail represses E-cadherin gene expression in epithelial tumours [116]. GSK3β is well known regulator of Snail which phosphorylates and that leads to Snail nuclear export and deregulation [28,39,55,56]. Recent findings suggest that the forced activation of GSK3β and the resultant phosphorylation and cytoplasmic translocation of Snail lead to E-cadherin up-regulation, which can potentially reverse EMT in OSCC [64]. Yang et al. have shown that EMT phenotypes can be decreased in head and neck SCC (HNSCC) by the use of siRNA-mediated repression of Snail or by the use of inhibitors of PI3K, which is a GSK3β-inactivating upstream kinase [90]. On the other hand, elevated Cox-2 levels have been reported in various human malignancies, including OSCC [117-119]. Inhibition of Cox-2 decreases integrin and MMP levels as well as the invasiveness of OSCC [118,119]. Cox-2 gene transcription is controlled by wild-type p53 protein [120] and by NFκB in betel quid-associated oral cancer [121], indirectly supporting the importance of inactive GSK3β (Ref [122] and Fig 2).

C) Anti-Apoptosis

The inhibition of apoptosis is a major cause of neoplastic disorders and an integral part of oral cancer pathogenesis. Abundant evidence suggests a possible role for active GSK3β in cell survival and apoptosis [123,124]. Apoptosis is controlled by either the intrinsic (mitochondrial) or extrinsic pathway (activation of procaspase-8) [123,125-128].

Higher levels of Bcl-2 and lower levels of Bax are frequently reported in oral cancer [127]. A recent report suggests that, in an OSCC cell line, Bcl-2 expression is affected even by slight changes in the status of pSer9GSK3β [63]. Active GSK3β blocks CREB-dependent expression of the anti-apoptotic protein Bcl-2 [128]. Additionally, active GSK3β regulates p53 activity, which increases Bax protein levels to initiate apoptosis [125]. Modulation of GSK3β can markedly increase p53-dependent activation of Bax, leading to cytochrome *c* release, loss of mitochondrial membrane potential and caspase-9 processing [125]. Moreover, the physiological effect of p53 is governed by inactivation of GSK3β (pSer9 GSK3β) [125] (and not by pTyr216GSK3β). Inhibition of Akt (a well-known kinase upstream of GSK3β) can only induce tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) -mediated apoptosis by regulating the levels of Bcl-2 and Bax in OSCC [125]. All of this evidence suggests that the survival advantage of OSCC cells over the normal oral epithelium might be due to progressive inactivation of GSK3β, which could be responsible for an increased Bcl-2/Bax protein ratio [63,125-127].

On the other hand, oral cancer cells are resistant to cell death mediated by TRAIL [126], which can be achieved only by inactivation of the GSK3-inactivating PI3K/Akt pathway [127]. Additionally, inhibition of caspase-8 reduces PI3K inhibitor-mediated apoptosis in OSCC [127]. In the extrinsic apoptotic pathway, active GSK3β promotes the activation of the initiator caspase-8 [122]. Therefore, active GSK3β targets both intrinsic and extrinsic pathways to maintain control over growth and proliferation in normal epithelium by promoting apoptosis [Fig. 3]. This control might be disrupted in OSCC.

Oral cancer therapy and role of GSK3β signaling

The inhibition of GSK3β is regulated by various upstream kinases (PKA, PKB/Akt, PKC, p90RSK/MAPKAP, p70RS6K) [7,9,10,12,13,129]. PKA is predominantly controlled by extracellular signals (epidermal growth factor: EGF, platelet derived growth factor: PDGF), carcinogens and second messengers, mainly c-AMP. PKA activation in an OSCC cell line has been reported [63]. PKA-anchoring protein 220 (PKAP220) binds to both PKA and GSK3, bringing GSK3 into close proximity with PKA, which phosphorylates GSK3β to block its activity [130]. Recently, PKA has been identified as a therapeutic target in HNSCC; moreover, inhibition of PKA is known to affect many molecules (e.g., NFκB, Cyclin D1, Bcl-2, Cox-2 and p21), most of which are direct/indirect targets of GSK3β [131]. On the other hand, the activation of the PI3K/Akt pathway has been well studied in OSCC [15,127,132]. Direct evidence suggests that the pSer9GSK3β level in OSCC cell line is very high and can be decreased by inhibiting Akt signaling [62]. In addition, in oral cancer cells, blocking PI3K/Akt signaling causes more cells to undergo apoptosis; this effect is reversed by the use of a GSK3β inhibitor [63]. Akt signaling is important in HNSCC and is considered as a potential therapeutic target [133]. There is also evidence of PKC signaling in OSCC [11], and inhibition of PKC by pharmacological inhibitors reduces MMP-2 and MMP-9 [134], possibly via GSK3β. Suppression of PKC activity promotes GSK3β activity in epithelial cells, which increases apoptosis [7]. Targeting of PKCε has shown promising results in decreasing the invasion and mortality of HNSCC [135]. Moreover, p90RSK is known for its role in epithelial cell

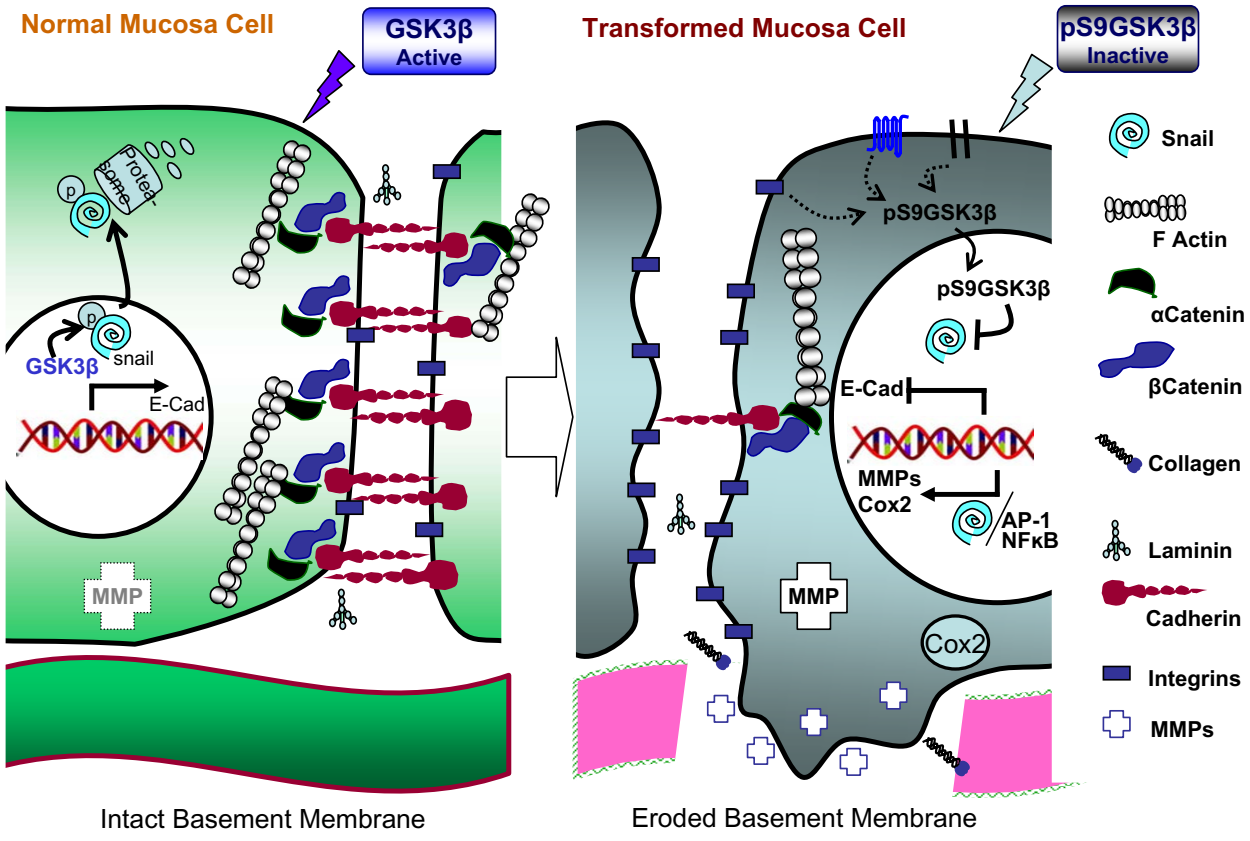

Figure 2 Progressive inactivation of GSK3β may promote enhanced EMT and oral cancer. GSK3β regulates several molecules that participate in epithelial-mesenchymal transformation, invasion and metastasis in cancer. Normal epithelial cells are connected to each other by E-cadherin, which binds to α- and β-catenin, which in turn connect E-cadherin to the actin cytoskeleton. Levels of E-cadherin are decreased in EMT. E-cadherin expression is suppressed by Snail. MMPs degrade the BM and facilitate the migration of cancer cells. Several MMPs upregulated and activated in OSCC are controlled by TFs such as Snail, AP-1, and NFκB. All of these events are directly or indirectly linked to the inactivation status of GSK3β.

motility and invasiveness [136]. Tumor-promoting phorbol esters inhibit GSK3β via a classical MAPK cascade [19] by activating p90RSK (MAPKAP-KI). Therefore, the role of the p90RSK/GSK3β pathway might be important in oral cancer. Finally, GSK3β is inactivated by the mammalian target of rapamycin (mTOR) pathway, in which p70S6K phosphorylates GSK3β. In a SCC cell line, EGF inactivates GSK3β [137], which can be reversed by rapamycin at a concentration that blocks the activation of p70S6K [138]. Epidermal growth factor receptor (EGFR) activation in OSCC [137] might activate the p70S6K pathway [138]. Moreover, in HNSCC, p70S6K is reportedly very active, and targeting it with rapamycin has a potential anti-tumor effect *in vivo* [139], possibly due to the activation of GSK3β. All of these signaling pathways may have definite oncogenic properties and are activated by a variety of carcinogens or other cancer-promoting factors to induce oral cancer or cancers of similar epithelial origin. However, one thing that these oncogenic pathways share is that they all impinge on GSK3β inactivation. This may be the reason why, beyond geographical boundaries, all oral cancers are similar in their aggressiveness and their potential for migration and metastasis. Crosstalk is abundant in signal transduction pathways. Therefore, although targeting each of these pathways has a modest impact on oral cancer and causes toxicity to the patient, targeting GSK3β directly may be highly beneficial in treating OSCC [Fig. 4].

Oral cancer etiology and intracellular signaling

The activation of established GSK3-inactivating upstream biological pathways by oral cancer-predisposing factors, such as tobacco, alcohol, and HPV, support the proposition of a causative role for GSK3β in OSCC. The role of carcinogens (from chewing and smoking tobacco) in oral cancer is firmly established [15,140]. Smokers show elevated levels of adenyle cyclase (AC) and PKA activity in oral epithelial cells [141,142]. Chewing areca nuts can lead to DNA damage and increased oxidative stress. The lime (calcium hydroxide) that coats the

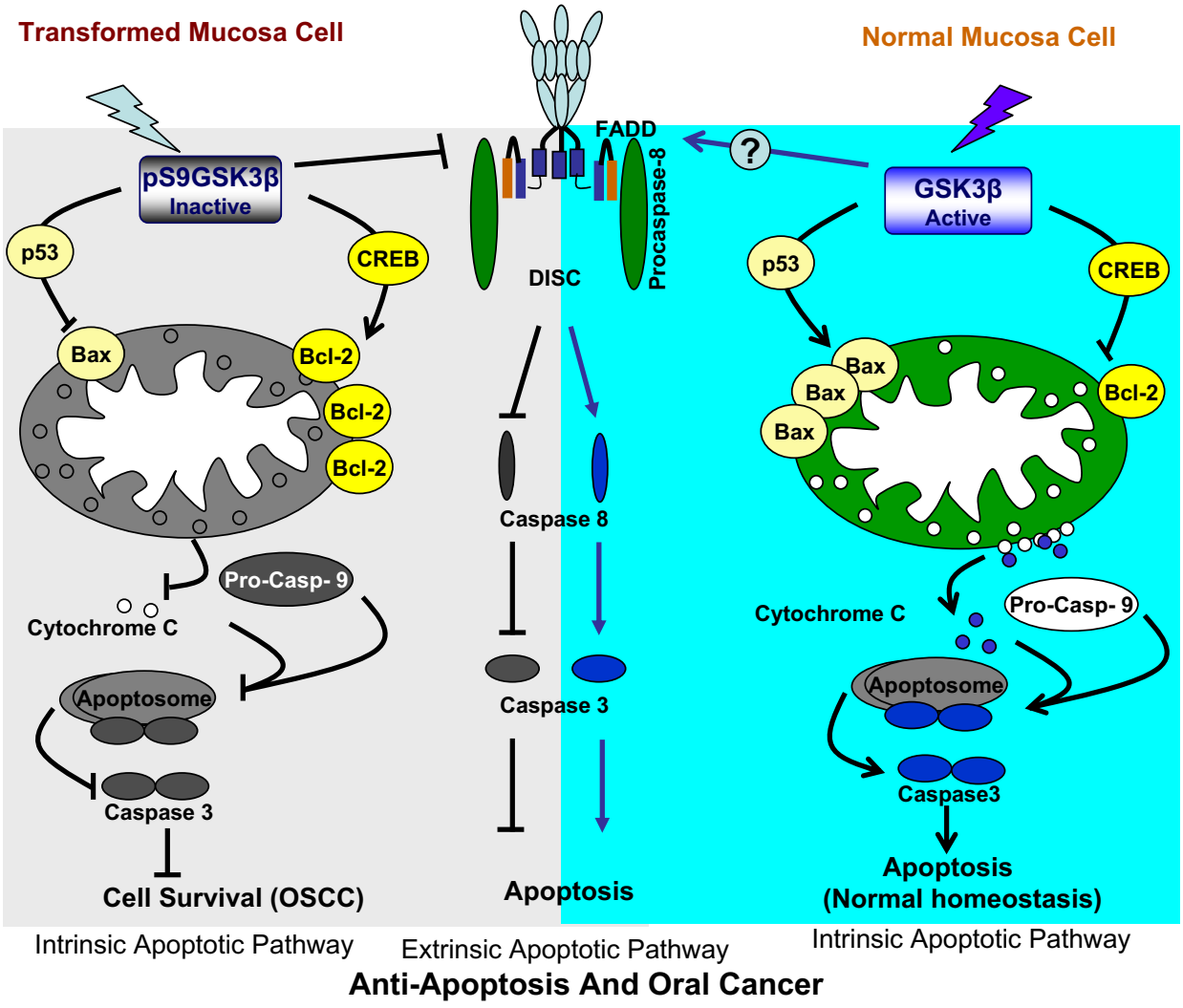

Figure 3 Progressive inactivation of GSK3β may promote increased anti-apoptosis and oral cancer. GSK3β-mediated signaling controls apoptosis in OSCC. In the intrinsic apoptotic pathway, inactive GSK3β fails to promote apoptosis by the disruption of mitochondrial membrane potential resulting from disruption of the Bcl-2/Bax ratio. Overexpression of Bcl-2 and suppression of Bax occur frequently in OSCC. This may be due to either inactive p53 (in the subgroup of cases in which p53 is not mutated or silenced) or active CREB; both are controlled by GSK3β. In the extrinsic pathway, active GSK3β promotes apoptosis by inducing procaspase-8 activation. Moreover, the inactivated GSK3β might send survival signals via the extrinsic pathway by blocking procaspase-8 activation in OSCC. By doing this, GSK3β might maintain the balance between proliferation and death and contribute to tissue homeostasis in normal oral epithelium; these might be perturbed in OSCC.

betel leaf promotes an alkaline oral environment, which activates Akt signaling [15]. There is accumulating evidence that connects nicotine-induced tumorigenesis to the activation of MAPK signaling [143], activation of PI3K/Akt signaling [144] and blocking of cytochrome *c*-mediated apoptosis [145]. Alcohol abuse increases the permeability of cells to carcinogens and activates PKA in cell culture [146]. HPV activates Akt in epithelial keratinocytes [4,147]. Moreover, a recent evaluation of epithelial tumors suggests that HPV infection can alter many biological pathways to maintain malignant processes by decreasing focal adhesion and up-regulating Wnt signaling and cell cycle genes [148]. Therefore, it is logical to hypothesize that the inactivation of GSK3β contributes to oral cancer.

Evaluation of therapeutic potential and possible methods of targeting GSK3β in OSCC

Before selecting GSK3β as a therapeutic target in OSCC, its biological functions should be explored in detail. Though GSK3β has several isoforms, the isoform(s) specifically expressed in OSCC remain to be identified. If multiple isoforms are expressed, it will be important to understand their respective functions in oral cancer

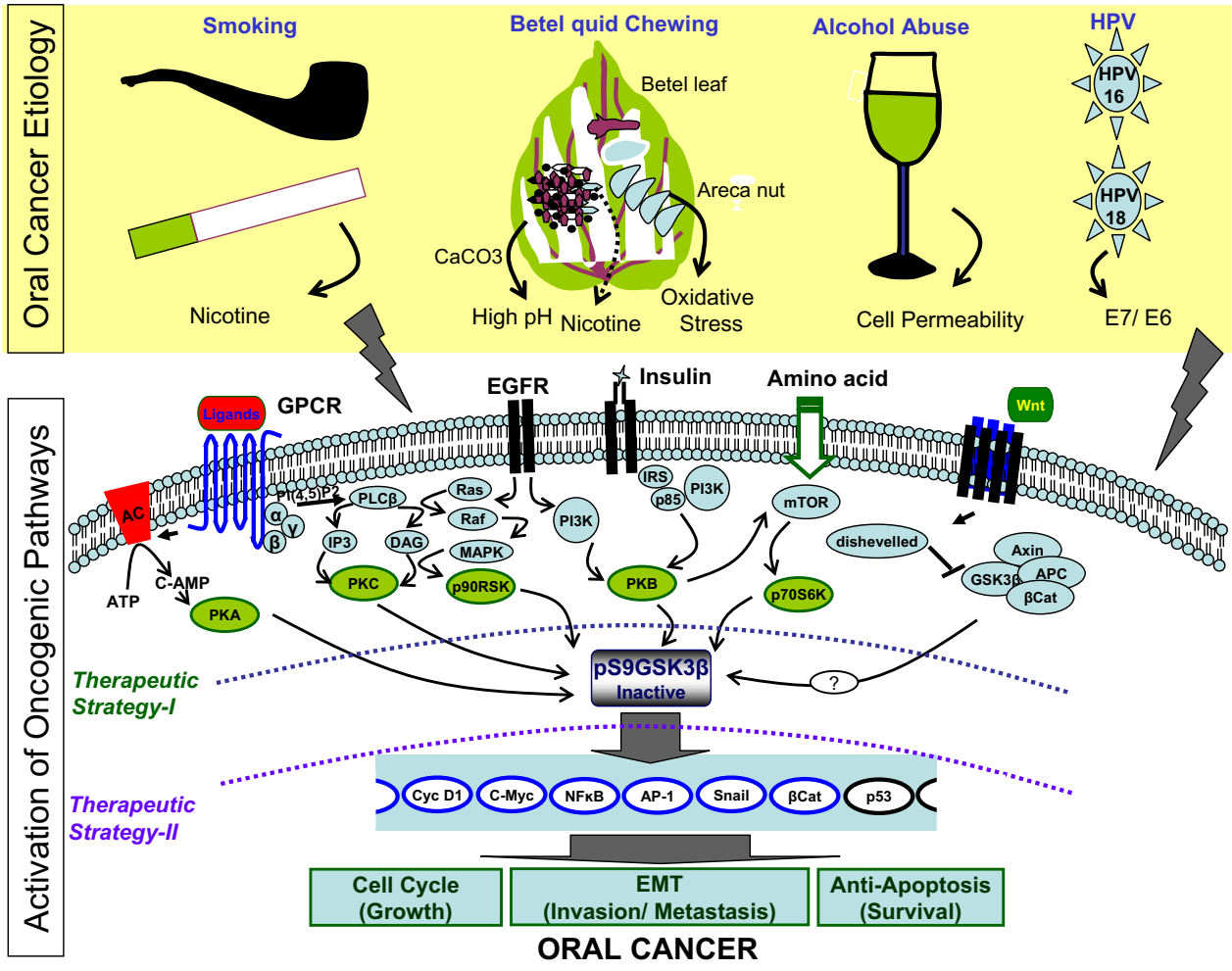

Figure 4 Targeting GSK3β pathway may be highly beneficial for curing oral cancer. Inhibition of GSK3β activity by the activation of several oncogenic pathways in cancer as discussed in the text. Activation of these pathways by several oral cancer etiological factors is interesting and fuel for inactivating GSK3β by targeting its inactivating pathways to promote oral cancer. Two major therapeutic strategies may be adopted to keep GSK3β active. First and the most important will be to (**---**) prevent the inactivation of GSK3β, by targeting its upstream inhibitory kinases, so that they will remain unassociated. Second will be to (---) reconstitute the active GSK3β (Ala9GSK3β by gene therapy) to affected oral cancer sites.

pathogenesis. The upstream cause of activation or inactivation of GSK3β as well as downstream target molecules and their status in OSCC should be thoroughly investigated at the patient level. Because it is an enzyme involved in regulating growth, cell cycle progression, apoptosis, and invasion, GSK3β may qualify as an ideal therapeutic target [123,149] for OSCC. Because of its role in both extrinsic and intrinsic apoptotic pathways, and because active GSK3β is nontoxic to non-cancerous cells (e.g., in a knock-in mouse study replacing Ser9 of GSK3β with Ala) [150], targeting the GSK3β pathway might be helpful in reducing unwanted apoptosis (in normal cells) and increasing useful apoptosis (in cancer cells).

The activation status of upstream molecules and the inactivation of GSK3β should be tested in different patients because each patient has a different lifestyle, etiological factors and genetic abnormalities. GSK3β can be inactivated by different upstream molecules in different oral tumors, even in the same patient. Inhibiting the upstream molecules pharmacologically by using peptide competitors and blocking phosphorylation at Ser9 certainly will keep GSK3β in an active state. The crystal structure of GSK3β peptide with an activated Akt ternary complex has been reported [151-154]. This may enable the design of small molecules that will disrupt the interaction of upstream kinases and GSK3β [Therapeutic strategy-I, Fig. 4] and thus prevent inhibitory kinases from associating with GSK3β. After checking the status of those patients who have inactivated GSK3β, Adenoviral vector carrying Ala9GSK3β may be tested along with other (chemo/radio) therapy, or with Ad-p53 (WT), which is known to block the progression of oral cancer to

a certain extent [155]. However, although the chances are remote, some OSCC tumors will contain active GSK3β. It will be easy to test the inhibitors of GSK3 in these cases. The use of LiCl and SB-216763 in ovarian cancer [156]; LiCl and TDZD-8 in prostate cancer [157]; TDZD-8, SB-216763 and AR-A014418 in colorectal cancer [158,159]; LiCl, SB-216763, and TDZD-8 in myeloma [83]; TDZD-8 in AML and AML progenitor and stem cell cancer [160]; and LiCl and AR-A014418 in pancreatic cancer [161-163] has been evaluated, with positive outcomes. Almost all GSK3 inhibitors are able to inhibit two isoforms of GSK3 (α & β) with similar potency. The production and clinical evaluation of small-molecule inhibitors of particular isoforms will improve the chances of successful treatment in the future. Recent advancements in molecular biology have proven the effectiveness of small RNA interference (RNAi) in reducing the level of one protein by promoting mRNA degradation. This has been tried in an animal model of OSCC and as an alternative therapeutic strategy in patients who have developed drug resistance [164,165]. Similarly, RNAi has been used to counteract the overexpression of GSK3β in pancreatic [163], gastrointestinal [166], and prostate cancer [157], and it may be tried for OSCC.

Conclusion

The goal of cancer drug discovery is to design non-toxic therapeutics that will be free of side effects. Thanks to a deepening understanding of cell biology and technological advancements, the concept of cancer therapy is being fine-tuned every day. Beginning with metabolic enzyme targeting using folate and methotrexate, to targeting of DNA polymerase and topoisomerase (tamoxifen), to selective hormonal targeting of estrogens/androgens via their nuclear hormone receptors, to the more recent advancement of targeting human growth factor receptor kinases and their effectors, the gradual improvements in our understanding of cancer biology have led to new and numerous therapeutics. Recent developments in molecular research have led to the hypothesis of "oncogene addiction," which suggest the continuous dependence of tumor cells on these oncogenes [167]. The inactivation of GSK3β in OSCC may behave like an oncogene, and its gradual/sustained inactivation may promote oral cancer. Though most of the upstream and downstream targets and their expression status correlate with the understanding of GSK3β inactivation, real, direct assessment should be attempted. If the activated form of GSK3β is non-toxic to normal oral epithelial cells, as was found in animal models [150], then the manipulation of the activated GSK3β provides hope for treating oral cancer. Unlike other molecules, GSK3β is one of the most attractive targets and is well understood because of extensive prior research on it. Therefore, it should be evaluated thoroughly as a potential target for the treatment of oral cancer.

Competing interests
The authors declare that they have no competing interest.

Authors' contributions
RM reviewed the literature, drafted and finalized the manuscript.

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Author Details
Dept. of Molecular Pharmacology and Therapeutics, Loyola University Medical Center, 2160 South First Avenue, Bldg 102, Maywood, IL-60153, USA

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