# Akt in Oral Squamous

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Protein kinase B (Akt) plays a very significant role in various cancers including oral cancer. However, it has three isoforms (Akt1, Akt2, and Akt3) and they perform distinct functions and even play contrasting roles in different cancers. Therefore, it becomes essential to evaluate the isoform-specific role of Akt in oral cancer. In the present study, an attempt has been made to elucidate theisoform-specific role of Akt in oral cancer. The immunohistochemical analysis of oral cancer tissues showed an overexpression ofAkt1 and 2 isoforms but not Akt3. Moreover, the dataset of “The Cancer Genome Atlas” for head and neck cancer has suggested thegenetic alterations of Akt1 and 2 tend to be associated with the utmost poor clinical outcome in oral cancer. Further, treatment of oralcancer cells with tobacco and its components such as benzo(a)pyrene and nicotine caused increased mRNA levels of Akt1 and 2isoforms and also enhanced the aggressiveness of oral cancer cells in terms of proliferation, and clonogenic and migration potential.Finally, silencing of Akt1 and 2 isoforms caused decreased cell survival and induced cell cycle arrest at the G2/M phase. Akt1/2 silencing also reduced tobacco-induced aggressiveness by decreasing the clonogenic and migration potential of oral cancer cells.Moreover, silencing of Akt1 and 2 isoforms was found to decrease the expression of proteins regulating cancer cell survival andproliferation such as cyclooxygenase-2, B-cell lymphoma 2 (Bcl-2), cyclin D1, and survivin. Thus, the important role of Akt1 and 2isoforms have been elucidated in oral cancer with in-depth mechanistic analysis.

Keywords: Akt isoforms ; oral cancer ; tissue microarray ; immunohistochemistry ; tobacco ; knockdown

## 1. Introduction

Oral cancer is one of the most challenging diseases faced by mankind, and regardless of several advances made in the field of oral cancerdiagnostics and therapeutics, it remains a global health concern.

It was responsible for approximately 145,400 deaths worldwide in the year 2012 [1]. Oral cancers are mostly carcinomas (96%), of which 91% aresquamous cell carcinomas. Variations in the incidence of this cancer are the result of several endogenous and exogenous factors such as tobacco use, alcohol intake, and human papilloma virus (HPV) infection. These factors result in numerous genetic and epigenetic changes that cause genomic instability and tumor development and progression [2][3][4][5][6][7]. The overall and disease-free survival rates of oral squamous cell carcinoma (OSCC) patients remain unchanged due to high mortality and low cure rate. This is mainly due to the lack of proper diagnostic and therapeutic biomarkers forbetter diagnosis and prognosis and the lack of effective therapies [8][9][10]. Therefore, it becomes imperative to focus on those molecular mediators that play a key role in oral cancer development and progression.

Several decades of research have established that the protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway is highly upregulated in oral cancer and leads to its development. The aforementioned risk factors for oral cancer such as tobacco, alcohol, and HPV werealso found to induce activation of the Akt/mTOR pathway [11][12][13]. This pathway is a network of many proteins that interact and induce different cellular processes such as cancer cell survival, proliferation, invasion, angiogenesis, and tumor metastasis. Akt kinase is the key protein of thispathway and its activation is responsible for inducing tumorigenesis by affecting different hallmarks of cancer [14][15][16][17][18][19][20][21][22][23][24][25][26].

Multiple lines of evidence suggest that Akt isoforms are involved in the development of different cancers such as ovarian, colorectal, pancreatic, breast, and lung cancer [27][28][29][30][31]. However, it is well-known that Akt kinase exists in three different isoforms as Akt1, Akt2, and Akt3, and these display distinct functions in various cancers [32]. Additionally, the precise role of Akt isoforms in the development of oral cancer has not been studied thoroughly. Therefore, the present study intended to evaluate the role of different Akt isoforms in the pathogenesis of oral cancer.Moreover, an attempt was made to analyze their association with tobacco, the main risk factor for oral cancer. Deciphering the molecular network ofAkt isoforms in the development of OSCC can provide a specific target against which appropriate therapeutic modalities can be developed for effective prevention and treatment of this disease.

## 2. The Role of Different Akt Isoforms in the Development of Oral Cancer

Analysis of the differential expression of Akt isoforms in oralcancer tissues showed overexpression of Akt1 and 2 isoforms. Additionally, the expression of Akt1 and 2 isoforms varied with the different stages of cancer and it gradually increased with advanced stages of oral cancer. A previous report by Iamaroon and Krisanaprakornkit has also shown theoverexpression of Akt1 and 2 in OSCC [33]. Moreover, the overexpression of Akt1 and 2 isoforms have been reported in many other cancers such as breast, liver, lung, glioma, and neuroblastoma [32].Differential expression of Akt isoforms was also observed in several tumor tissue types, and previous studies have suggested the important role ofAkt isoforms in inflammatory conditions, especially in vascular diseases [34][35]. However, no such study of Akt isoform-specific involvement in other tissue types has been reported. In line with our observations, the expression of Akt1 and 2 were found to be different in early and late stages ofbreast cancer [36].

Our study has shown the overexpression of Akt1 and 2 isoforms in different regions of the oral cavity such as the tongue, cheek, and gingiva.A couple of studies have shown the activation of Akt in tongue cancer is associated with adverse outcomes [37][38]. Thus, it might be possible that out of all three isoforms, only Akt1 and 2 play a key role in tongue cancer development. On exploring the TCGA dataset, it was observed that all three Akt kinase isoforms have a considerable percentage of genetic alterations in HNSCC, but in our study, the IHC analysis of oral cancer tissues showedhigh expression of Akt1 and 2 isoforms but not Akt3 compared to the normal tissues. The HNSCC includes different types of cancer including OSCC. OSCC is more confined to the oral cavity region, which is different from the other section of the head and neck region such as oropharynx andlarynx. The other regions of the head and neck are different from the oral cavity region both physiologically and histologically and this differencemight be responsible for a discrepancy in the association of Akt isoforms. The disparity in the association of Akt isoforms is not only limited to HNSCC and OSCC but prevalent in other cancers as well. Regardless of the discrepancy in the association of the Akt isoforms in HNSCC and OSCC, only the genetic alteration associated with Akt1 and 2 isoforms were associated with poor OS and genetic alteration of Akt2 isoform was linked with poor DFS of HNSCC patients. Consistent with our observations, previous reports have also implied the profound significance of Akt1 and 2 gene expression in the prognosis of different cancers such as esophageal squamous cell carcinoma and non-small cell lung carcinoma [32][39][40][41][42][43]. Therefore, it becomes evident that both Akt1 and 2 might play a significant role in clinical outcomes of oral cancer patients. Therefore, a detailed mechanistic interpretation can help in deciphering the distinct role of Akt isoforms in oral cancer development, thereby allowing effective therapeutics to be developed.

It is well recognized that tobacco is a prime risk factor for oral cancer, and our results have shown increased cell proliferation of oral cancer cells following treatment with tobacco and its components. In line with our results, previous studies have also suggested the increased proliferation of cancer cells on exposure to tobacco [44][45]. Moreover, many studies have suggested that treatment with the tobacco component BAP canincrease the proliferation of normal cells and cancer cells such as ovarian, breast, lung, and gastric cancer cells [46][47][48][49]. Nicotine is an importantcomponent of tobacco and it has long been associated with several cancers such as cancers of lung, head and neck, gastric, pancreatic, gallbladder,liver, colon, breast, cervical, urinary bladder, and kidney [50].

In our analysis, we found that the silencing of Akt1 and 2 isoforms caused an increase in the percentage of cell death in oral cancer cells. Likewise, previous studies have also suggested the importance of Akt1 and 2 in cell survival and indicated that these isoforms mediate the process ofcell survival through different routes [51][52][53]. Similar to our results, in other cancers such as breast, lung, and colorectal cancers, the important role of Akt1 and 2 isoforms have been shown in the process of cell survival through induction of apoptosis [36][51][54]. Finally, we observed that silencingof Akt2 led to the decreased expression of proteins such as Cox-2, Cyclin D1, Bcl-2, and survivin, while silencing of Akt1 only led to a reduction in Cox-2 levels. Cox-2 and serine threonine kinase Akt signaling pathway possess a strong correlation [55]. For instance, in the case of endometrial cancer,Akt was found to regulate the expression of Cox-2 at both gene and protein level in phospho-Akt expressing cells [56]. Further, in epithelial ovariancancer, overexpression of COX-2 was reported to be strongly associated with Akt activation, suggesting the correlation between Cox-2 and Akt [57].

## 3. Conclusions

The current study aimed at evaluating the expression and delineating the role of different Akt isoforms in the development of oral cancer. Ourresults suggest the overexpression of Akt1 and 2 with respect to migration and expression of Bcl-2, cyclin D1, and survivin proteins, which areimportant for cancer cell survival and proliferation. However, our study has not elucidated the detailed role of the Akt3 isoform, which might playan important role in HNSCC and hence should be studied in the near future. Therefore, general targeting of the total Akt kinases would not be effective in the prevention and treatment of oral cancer. Specific targeting of the Akt1 and 2 isoforms would result in a better prognosis for oralcancer

patients. Moreover, our results also indicated a strong association of Akt1/2 isoforms with tobacco (one of the major risk factors of oral cancer) induced cancer cell viability and migration, which can be further studied to explore the other molecular mediators linked with Akt isoforms and tobacco mediated oral carcinogenesis, and to establish a signaling axis that regulates this process. In addition, future studies should also be concentrated on selective inhibition of Akt1 and 2 isoforms, with experimental validation for the development of effective therapy against oralcancer.

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