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Survivin Gene as a Potential Marker in Premalignant and Malignant Lesions of Oral Cavity

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Abstract

In a developing country where most of the people live in rural areas, Oral cancer management is a challenge with most of the cases presenting late. Carcinogenesis is a multistage process involving the activation of oncogenes and the inactivation of tumour suppressor genes. Biomarkers are important in establishing an accurate diagnosis and also can provide prognostic data. Survivin, a member of the inhibitor of apoptosis (IAP) protein family that inhibits caspases and blocks cell death, is highly expressed in most cancers and is associated with a poor clinical outcome. Survivin has consistently been identified by molecular profiling analysis to be associated with high tumour grade cancers, disease survival and recurrence. Polymorphisms in the survivin gene are emerging as powerful tools to study the biology of the disease and have the potential to be used in disease prognosis and diagnosis. The survivin gene polymorphisms have also been reported to influence tumour aggressiveness as well as survival of cancer patients. The differential expression of survivin in cancer cells compared to normal tissues and its role as a nodal protein in a number of cellular pathways make it a high target for different therapeutics. This review focuses on the literature on survivin, its role in cancerous and pre-cancerous lesions of oral cavity. It also gives a snapshot of its use in diagnosis, management and therapeutic management.

Keywords: Oral squamous cell carcinoma; Premalignant lesions; Biomarkers; Survivin; Prognostic and diagnostic indicators

Introduction

Cancer remains the second leading cause of death after cardiovascular diseases globally and third leading cause of mortality following heart and diarrheal diseases in developing countries [1,2]. Oral SCCs account for approximately 500,000 new cases worldwide, making them the 6th most common cancer type in the world and they are the third most common cancer in developing countries with high incidence in south East Asia and India [3-6]. Despite advances in treatment, the overall 5 year survival rate for oral SCCs is merely 50% [7,8] with most patients at high risk for loco regional recurrence [9-13] and distant metastasis [14,15].

Carcinogenesis is a multistage process involving the activation of oncogenes and the inactivation of tumour suppressor genes. Biomarkers are currently being used in diagnosis and prognosis of several diseases. Apoptosis has become a basic tool in developing cancer research and establishing new strategies in managing cancer.

Survivin has been found as a good prognostic marker in Oral squamous cell carcinoma. Survivin is a recently characterised IAP protein, which is expressed in most solid and haematological malignancies and the gene encoding human survivin was cloned by Ambrosini et al. [16] in 1997. Survivin is not produced in adult tissues except for the thymus, placenta, basal colonic epithelium, endothelial cells and neural stem cells [17,18].

In OSCC conventional prognostic factors such as clinical stage, tumor size, lymphnode metastasis are not always accurate. In addition due to heterogenecity of tumor biology between affected individuals, prognostic factors are currently lacking. Thus there is a need for additional factors including molecular markers for early detection and to explain the mechanism of development and recurrence in OSCC.

Premalignant lesions

OSCC occur in the presence of common premalignant conditions as epithelial dysplasia, hyperkeratosis or epithelial hyperplasia, oral Leukoplakia, erythroplakia, Lichen Planus, Submucous fibrosis [19-21]. The transformation to OSCC of epithelial dysplasia, verrucous hyperplasia and hyperkeratosis or epithelial hyperplasia are 7.62, 5.21 and 3.26 per 100 person year, respectively [22]. The annual rate of transformation of oral leukoplakia (2%), erythroplakia, 10-30%, lichen planus is <0. 5%, Oral sub mucous fibrosis 7-13% [23].

In a study by Lo Muzio et al. [24] in 2003. The presence of survivin was noted in 33% of precancerous lesions and in 94% of pre-cancerous lesions which became malignant. Survivin positivity was 100% in all malignancies which progressed from precancerous lesions [25].

In a study to observe the expression of survivin in buccal mucosa of oral submucous fibrosis in betel nut and tobacco users by Immunoreactive (IRS) score changes. It was found that increasing duration of betel nut use increases the IRS levels, i.e., both the percentage and intensity of survivin is increased [26].

In the study done by Poomsawat et al. [27] to understand the role of cytoplasmic surviving and nuclear survivin, it was found the cytoplasmic survivin was more frequently expressed in OL without dysplasia and OL with dysplasia compared with normal mucosa. It was found that positive rate of nuclear survivin expression in OSCC was

significantly higher than those of normal mucosa and only occasionally detected in premalignant lesions [28]. They suggested that cytoplasmic survivin is involved in the early and late events of carcinogenesis while nuclear survivin plays a crucial role at the late stage. These were replicated in hamster oral carcinogenesis model.

This study showed suppression of apoptosis by survivin occurs early and this antiapoptotic function continues until late. At the late stage, survivin increases cell proliferation whereas caspase 3 promotes apoptosis, which is insufficient. The cytoplasmic plus nuclear staining within the same cells of survivin or caspase 3 is common in OSCC, implying that this specific expression pattern may be a useful tool for treatment plan of premalignant lesion and that nuclear survivin rather than cytoplasmic survivin may serve as a therapeutic target of OSCC.

In a recent study, Negi et al. [29] observed an up regulation of survivin expression in leukoplakia and OSCC and more than 50% of the cases of leukoplakia had positive survivin expression. They postulated that survivin which is an antiapoptotic protein may accumulate in the involved tissue at an early stage and similar to other precancerous lesions and could be an important therapeutic target [30].

In a Systematic review by Smith et al. [31] it was found that survivin, along with MMP 9 and DNA content are potential markers for increased risk of progression from oral dysplasia to cancer.

Malignant lesions

In oral cavity, 90% are oral squamous cell carcinomas followed by adenocarcinoma and rarely other types [32].

Survivin is over-expressed in malignant tissues rather than benign and normal ones. Reports showed that various mechanisms including gene amplification, hypomethylation and upstream signalling factors influence the expression of surviving and its splice varients [33].

Lo Muzio et al. [34] on examination of 78 cases of OSCC found that survivin expression may identify patients at risk of more aggressive and disseminated disease. It was also associated with patient survival. Kim et al. [35] also found that surviving expression has significance, in that positive cohort had 2.5 times greater OSCC risk than negative group.

In terms of cellular localization, Marioni et al. [36] found that in survivin-positive oral and oropharyngeal primary SCCs and lymph node metastatic cells showed prominent nuclear staining. This suggests that in OSCC, survivin may act to promote cellular proliferation [37].

In a review article by Taghavi et al. [38] they found that survin can be an independent prognostic factors in survival rate of OSCC [39]. Patients with advanced stage, positive lymphnode metastasis and lower survival rate showed high expression (>25%) of survivin [40].

Survivin has been shown to play different roles depending on the location within the cell. An evaluation of 71 oral and oropharyngeal SCC by IHC staining showed nuclear expression significantly correlated with favourable relapse free survival [41].

In a study in Taiwanese population in OSCC, survivin-31 GG was significantly associated with risk for oral cancer among Taiwanese men, but CG was not. +9194 GG showed significantly greater tumor size than patients carrying ancestral genotypes, when combined with betel quid chewing. +9809 TT polymorphism is located at the 3′-UTR of the survivin gene, regulatory events such as mRNA stability and posttranscriptional modification might occur through binding of microRNAs thus increasing the risk of OSCC [42].

In a meta-analysis of clinicopathological variables [43] there was was found a significant relationship between survivin mRNA expression and lymphatic metastasis and clinical stage.

Survivin as Diagnostic Marker

In a study to detect survivin levels in saliva in patients with OSCC by using a specific ELISA test it was found that the survivin levels in patients with OSCC are significantly higher than those of healthy subjects and the difference in survivin levels between early stages of OSCC and control subjects were found to be significant [44].

Antisurvivin was associated with tumor aggressiveness, indicating that the serum autoantibody may represent cellular status. Detection of circulatin anti-survivin autoantibody could potentially serve as a useful noninvasive marker for determining head-and neck cancer status. In a study using r-survivin protein as the antigen, it was found to be may be useful for screening of healthy individuals or patients with head-and-neck cancer and to monitor the development of survivin autoantibody during oncogenesis [45].

In a study done to identify and verify panel of salivary auto-Antibodies in premalignant and malignant lesion of oral cavity. It was found the antibodies to Survivin were elevated along with other biomarkers in well differentiated OSCC compared with moderately differentiated OSCC when compared with healthy subjects. Antibodies were also elevated in high risk premalignant lesions (speckle leukoplakia, erythroplakia, verrucous hyperplasia, oral submucous fibrosis (OSF) and histologically epithelial dysplasia) compared to normal [46].

Role of survivin in cancer treatment

It has been opined that cancer cells return to a fetal pattern of survivin expression to enhance cell viability, resist apoptotic stimuli and thereby become capable to overcome the cytotoxic effects of chemotherapeutic agents. Furthermore, it has been seen that survivin-transfected cells demonstrate resistance to anticancer drug-induced apoptosis [47,48].

In a retrospective study of tissue microarray (TMA) sections of OSCC high survivin expression was associated with favourable patients' outcome in advanced OSCC treated with Radiotherapy [49]. This study speculated that increased proliferation activity of the tumor cells induced by high survivin expression makes the tumor cells more liable for radiation-induced cell damage.

In a study to evaluate the prognostic significance of survivin mRNA expression in OSCC and its correlation to resistance to chemotherapy [50]. Patients with high survivin mRNA expression showed lower 5 year survival rates than patients with low survivin mRNA expression. They demonstrated that survivin down-regulation could significantly enhance cytotoxicity of chemotherapeutic agents (4 mg/mL cisplatin or 2 μg/mL 5-FU) in OSCC cells even at comparably low doses and postulated that survivin might be a potential molecular target for cancer therapy.

Survivin expression in primary oral and oropharyngeal SCC'S may identify patients at risk of disseminated disease. This helps in treatment options as patients with high level of survivin expression,

elective neck dissection can be done in clinically N0 patients with primary SCC [51].

Therapeutic use of survivin

In a study on the use of survivin-2B80-88 peptide vaccination in HLA-A24-positive patients with advanced or recurrent oral cancer [52]. The Vaccination was given subcutaneously or intratumorally six times at 14 day intervals, it was found that vaccine was well tolerated and safe and had therapeutic potention in SCCs. It is possible that advanced protocols such as a more intense immunization schedule and delivery in combination with a specific adjuvant and/or an immunestimulatory cytokine might improve the efficacy of the survivin-2B peptide vaccine against oral cancer. Recent evidence suggests antisense oligonucleotides that reduce survivin expression, also induce apoptosis, polyploidy and sensitize tumor cells to chemotherapy *in vitro*.

Kojima et al. [53] has found that a replication-deficient adenovirus encoding a survivin antisense gene down regulates survivin expression and activity, causes spontaneous apoptosis in KB cells and inhibits tumor growth in a mouse model of HNSCC [54]. When combined with Cisplatin, this group discovered antisense-mediated down regulation of survivin can sensitize tumor cells (KB cells) to chemotherapy *in vitro* and *in vivo*.

Using a 206 bp survivin antisense oligonucleotide in combination with Cisplatin and Etoposide (which triggers cell death via cytochrome c release), Sharma et al. [55] also provide indirect evidence that down-regulation of Survivin expression sensitizes cells to death induction via the mitochondrial pathway. By reducing caspase-3 and -7 generation, anti-survivin has been shown to facilitate cell death with the hallmarks of mitochondrial-dependent apoptosis; release of cytochrome c and loss of mitochondrial transmembrane potential.

Expression of Survivin in endothelial cells results in a cytoprotective response counteracting apoptosis, reducing the generation of active caspases and preserves cellular survival. Survivin appears to stabilize the three-dimensional capillary networks *in vitro* providing a proangiogenic response.

Ambrosini et al. [16] work has proposed that survivin expression during angiogenesis may provide a pivotal advantage factor to maintain a good blood supply during tumor growth. Furthermore, antisense survivin targeting during angiogenesis caused endothelial cell apoptosis and promoted involution of capillary-like vessels *in vitro*.

Tran et al. [56] and his Toronto group have also suggested that targeting survivin might inhibit tumour growth by inducing involution of tumor blood vessels. Therefore it seems that greater tumor control can be accomplished with treatment of anti-angiogenically potent chemotherapy, particularly microtubule-inhibiting drugs.

These studies illustrate that survivin functions as a novel upstream regulator of mitochondrial-dependent apoptosis and molecular targeting of this pathway results in anticancer activity via a dual mechanism of induction of tumor cell apoptosis and suppression of angiogenesis [57].

Conclusion

Survivin in oral premalignant lesions can be a marker for progression to malignancy. It has a role in malignancy as a diagnostic marker, predicting progression and can be used for therapeutic purpose .A prospective study is needed to explore the various roles of survivin in pre-cancerous and cancerous lesions of oral cavity.

Compliance with Ethical Standards

This article does not contain any studies with human participants or animals performed by any of the authors.

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