INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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SHORT ABSTRACT

Oral cancer is the sixth most common cancer in the world and the topmost cancer in India with worldwide mortality of mortality of approximately 145328. In India, it constitutes 30% of all cancer cases. North East region of India is regarded as the hub of oral cancer. The main risk factors associated with oral cancer are tobacco, alcohol, human papillomaviruses (HPV) etc. The major treatment modalities available for oral cancer are surgery, radiation therapy, and chemotherapy. However, chemotherapy is effective in increasing patient survival by only 8-22% due to the emergence of chemoresistance and tumor recurrence. This necessitates the need for the development of novel biomarkers for prognosis and can become a novel target for drug discovery. Recently, the store operated calcium (SOC) and the associated channels (SOCC) have been found to be regulating various cancer hallmarks in different cancers. The present study is focused on the role of SOCC in human oral squamous cell carcinoma. First, we analyzed the SOC entry (SOCE) and SOCC at in vitro level to understand the dysregulation in oral cancer cells compared non-cancerous epithelial cells. We found higher SOCE and overexpression of Orai genes (Orai1 & Orai2) in oral cancer cells. The results were verified with patients' tissue samples for Orai1 and Orai2 proteins. Next, we analyzed the effect of crude tobacco extract (TE), tobacco components (B[a]P, NNN and NNK) and 4NQO (a synthetic carcinogen) on SOCE and expression of SOCC genes. These carcinogens showed upregulated SOCE as well as overexpressed SOCC genes (Orai1 and Orai2) with very low concentrations. Next, we studied the effect of potent SOCE inhibitors (2-APB, La3+, and SKF96365) on oral cell migration. The significant inhibition of cell migration was observed with SKF96365 and also found a correlation with inhibition SOCE. Finally, we analyzed the role of Orai1 and Orai2 proteins on oral cancer cells through gene silencing using Orai1 and Orai2 siRNAs. The knockdown of Orai1 was able to significantly downregulate the SOCE which was negligible in Orai2. However, silencing of both Orai genes was able to inhibit cell migration and decreased oral cancer cell survival in the clonogenic assay. Furthermore, the changes at the molecular level were analyzed and found that silencing of Orai1 and Orai2 can downregulate the Akt/mTOR pathway key molecular mediators (mainly phospho-Akt, phospho-mTOR, REDD1, and MMP-9), decreased expression of CXCR4 and phospho-NF-κB were also observed. Additionally, the

Orai knockdown decreased the E-cadherin to N-cadherin which is a key phenomenon for epithelial to mesenchymal transition (EMT), enhanced the tumor suppressor gene (AMPK1) expression and downregulated the fatty acid synthase (FAS) genes. The overall study suggested that targeting Orai1 and Orai2 can help in regulating oral cancer cell migration, invasion, and metastasis through the modulation of Ca2+ entry which may be store dependent or independent.