INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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SHORT ABSTRACT

Oral cancer remains the global health concern and Akt kinase is found to be overexpressed. However, it has three isoforms and isoform-specific involvement is yet to be deciphered completely. Here we attempted to elucidate the isoform-specific role of Akt isoforms in oral cancer. Immunohistochemistry (IHC) was performed on oral cancer tissues. The genetic alterations data was retrieved from "The Cancer Genome Atlas" (TCGA) database of 530 patients of HNSCC. Role of Akt isoforms was analyzed through siRNA-mediated gene silencing by checking their effect on the expression of different hallmarks of cancer by western blotting. Also, FACS methods were utilized to study cell survival and cell-cycle arrest. The effect of tobacco on aggressiveness in terms of proliferation (MTT assay), clonogenic (colony formation assay), and migration (wound healing assay). The promoter sequence of the Akt isoforms was analyzed through *in silico* methods of Eukaryotic Promoter database and Genomatix program. To categorize the general Akt inhibitors and other natural inhibitors, computational docking method of Schrodinger software was used. IHC on tissue microarray slides showed the overexpression of Akt1 and Akt2 isoforms but not Akt3 in cancer tissues. The TCGA data have suggested the maximum genetic alteration in Akt1 and Akt2 protein of HNSCC patients with worst clinical outcome. The knockdowns of Akt1 and Akt2 isoforms led to decreased cell survival and cell cycle arrest. Also, knockdown caused the reduced expression of molecular mediators involved in cancer progression such as Cox-2, Bcl-2, cyclin D1, and Survivin. Furthermore, their knockdown significantly diminished tobacco-induced aggressiveness by decreasing the clonogenic and migration potential. The promoter sequences have shown significant variation. Based on the affinity towards the Akt isoforms selectively, the inhibitors were further classified and ranked. Non-redundant functions of Akt isoforms in oral cancer were observed indicating differential clinical outcome. Akt1 and Akt2 knockdown decreased the expression of protein involved in cell proliferation, inflammation, anti-apoptosis, migration and invasion of cancer cells. Further, their knockdown reduced the action of tobacco-induced carcinogenesis. The promoter sequence variation might be responsible for differential expression of Akt isoforms. The ranking of general Akt inhibitors into isoform-specific inhibitors is a significant step towards developing precise chemotherapy against oral cancer. The present study is a preliminary step to understand the distinct role of Akt isoforms in oral cancer to develop Akt isoform-specific therapy to reduce the off-target toxicity and increase the therapeutic efficacy.