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Delineating miRNA profile induced by chewing tobacco in oral keratinocytes

Mohd Younis Bhat[1,2#], Jayshree Advani[1,3#], Pavithra Rajagopalan[1,4], Krishna Patel[1,2], Vishalakshi Nanjappa[1], Hitendra S. Solanki[1,4], Arun H. Patil[1,4,5], Firdous Bhat[1,2], P.P Mathur[4], Bipin Nair[2], T.S. Keshava Prasad[1,5], David Sidransky[6], Harsha Gowda[1*] and Aditi Chatterjee[1*]

[1]Institute of Bioinformatics, International Technology Park, Bangalore 560066, INDIA

[2]Amrita School of Biotechnology, Amrita Vishwa Vidyapeetham, Kollam, INDIA

[3]Manipal University, Madhav Nagar, Manipal 576104, INDIA

[4]School of Biotechnology, KIIT University, Bhubaneswar 751024, INDIA

[5]YU-IOB Center for Systems Biology and Molecular Medicine, Yenepoya University, Mangalore 575018, INDIA

[6]Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University; School of Medicine, Baltimore, MD 21231, USA

[#] These authors contributed equally to the manuscript

Presenting author: younis@ibioinformatics.org

Abstract

The major established etiologic risk factor for oral cancer is tobacco (chewed, smoked and snuffed forms). Chewing form of tobacco is predominantly used in India making it the leading cause of oral cancer. Despite being one of the leading causes of oral cancer, the molecular alterations induced by chewing tobacco remains largely unclear. Carcinogenic effect of chewing tobacco is through chronic and not acute exposure. To understand the molecular alterations induced by chewing tobacco, we developed a cell line model where non-neoplastic oral keratinocytes were chronically exposed to chewing tobacco for a period of 6 months. This resulted in increased cellular proliferation and invasive ability of normal oral keratinocytes. Using this cellular model we studied the differential expression of miRNAs associated with chewing tobacco and the altered signaling pathways through which the aberrantly expressed miRNAs affect tumorigenesis. miRNA sequencing was carried out using Illumina HiSeq 2500 platform which resulted in the identification of 427 annotated miRNAs of which 10 were significantly dysregulated ($\geq$ 4 fold; p-value $\leq$ 0.05) in tobacco exposed cells compared to untreated parental cells. To study the altered signaling in oral keratinocytes chronically exposed to chewing tobacco, we employed quantitative proteomics to characterize the dysregulated proteins. Integration of miRNA sequencing data with proteomic data resulted in identification of 36 proven protein targets which ($\geq$1.5 fold; p-value $\leq$ 0.05) showed expression correlation with the 10 significantly dysregulated miRNAs. Pathway analysis of the dysregulated targets revealed enrichment of interferon signaling and mRNA processing related pathways in the chewing tobacco exposed cells. In addition, we also identified 6 novel miRNA in oral keratinocytes chronically exposed to chewing tobacco extract. Our study provides a framework to understand the oncogenic transformation induced by chromic tobacco exposure in normal oral keratinocytes.

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