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MiR-146a induces the cancer stem cell and EMT phenotype in oral squamous cell carcinoma by regulating CD24-β-catenin axis

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Cancer stem cells emerges as one of the most vital tumor initiation and maintenance system in almost all types of malignancies. Implicit is the role of CD44 in defining CSCs but CD24 is not well-explored in Oral Squamous Cell Carcinoma. Here we show that $CD44^{high}CD24^{low}$ cells isolated from the oral cancer cell lines, not only express stem cell related genes but also exhibit Epithelial-to-Mesenchymal transition (EMT) characteristics. Typical Cancer Stem Cell (CSC) phenotypes like increased colony formation, sphere forming ability, migration and invasion were also confirmed in $CD44^{high}CD24^{low}$ cells. These cells also showed enhanced resistance to apoptosis inducing stimuli owing to their slow-cycling state and high expression of drug transporters. Dysregulation of microRNAs (miRNAs) are known to be implicated in tumor prognosis but whether it regulates stemness in OSCC remains unclear. We have shown miR-146a to be significantly up-regulated in CSCs derived from oral cancer cell lines and tumors. Enforced expression of miR-146a caused enhanced expression of CSC markers and clonogeneic potential. It was also linked with epithelial-mesenchymal transition (EMT) in addition to activated wnt signaling. Interestingly, miR-146a induces CSC traits by stabilising β-catenin that co-incide with loss of CD24. We identified and validated CD24 as a direct and functional novel target of miR-146a and found that CD24 over-expession rescued miR-146a mediated tumorigenicity. We observed a unique negative co-relation between CD24 and β-catenin under the supervision of miR-146a by positively regulating AKT activity. We show that AKT inhibition is actually conferred by CD24 that subsequently leads to β-catenin degradation. In agreement to the previous findings, we acknowledged a positive feedback loop in β-catenin mediated transactivation of miR-146a that possibly contributes to stem cell maintence. Taken together, these results provide a proof-of-principle that miR-146a plays a key role in sustaining CD44high CD24low status in OSCC.

Biography:

Sangeeta Ghuwalewala is a PhD student in Indian Institute of Chemical Biology, Kolkata, under the guidance of Dr. Susanta Roychoudhury. She did her graduation in Microbiology from St. Xavier's Collegiate School, followed by M.Sc. Biotechnology, University of Calcutta. She has first research experience during a 2-month summer research working under Dr. Gaiti Hasan, at National centre of Biological Sciences, Bangalore. She has qualified CSIR-NET December 2009 in first attempt with an all India 23rd rank and was invited for the prestigious SPM fellowship. She works in Cancer Stem Cells and its epigenetic involvement in tumorigenesis. She has explored various aspects of tumor heterogeneity and went through quite a diverse type of research endeavours including establishment of Primary Cell line from tumors, Next Generation Sequencing, Transcriptomics as well as study of miRNA and chromatin regulatory mechanisms. She has also attended a course held in NCBS "Hands on Workshop on Epithelial Stem Cell Biology" and also have a brief exposure to NGS data analysis. She owned a "Best Poster Presentation Award" for part of her work on "PRC2 mediated CSC reprogramming" in Indian Association for Cancer Research, 2014. She has one publication in "Stem Cell Research" under revision and a few more to be communicated.