Title: Identification and Characterization of Senescence Phenotype in Lung Adenocarcinoma with High Drug Sensitivity

Authors List: *Seema Khadirnaikar ∗ †, Annesha Chatterjee ∗, Sudhanshu Shukla ∗*

Affiliation: *∗Department of Biosciences & Bioengineering, Indian Institute of Technology Dharwad, Dharwad, India †Department of Electrical Engineering, Indian Institute of Technology Dharwad, Dharwad, India*

Lung adenocarcinoma (LUAD) is a major health problem and has poor prognosis. Heterogeneity is a central determinant of the treatment outcome, requiring identification of new subclasses of LUAD. Senescence has emerged as a crucial regulator of metastasis and drug response. Ionizing radiation– and doxorubicin-induced senescence-associated genes in lung fibroblasts were used in K-means clustering to identify high- and low-senescence (HS and LS) classes among The Cancer Genome Atlas- LUAD (TCGA-LUAD) patients. The LS group showed significantly poorer survival ($P = 0.01$) and greater activation of proliferative signaling pathways, proliferation, wound healing, and genetic aberrations ($P < 0.05$). The TP53 mutation rate was significantly greater in the HS group ($P < 0.0001$), explaining the phenotype. Also, genome-wide hypomethylation was significantly greater in the LS group than in the HS group. Interestingly, pathway analysis identified the silencing of Wnt signaling in the HS group. The machine learning–based recursive feature elimination technique was used to identify a 20-gene senescence signature in TCGA-LUAD samples. The presence of a senescence phenotype with poor survival was validated in an independent patient cohort and a cell-line cohort using unsupervised clustering of samples based on a 20-gene signature. On further analysis, HS cells were more resistant to drugs, particularly histone deacetylase inhibitors. Taken together, this study identified a novel subtype of LUAD with reduced Wnt signaling and high drug resistance.

Keywords: Lung Adenocarcinoma, Heterogeneity, Senescence, Drug Resistance

Speaker details

Full name: Annesha Chatterjee

Email address: 193022001@iitdh.ac.in

Contact number: +91 9078024585