Abstract 54 – Paper ID: 074

Hypoxia-Driven nAChR–AKT–HIF Signaling in Lung Adenocarcinoma: A Biotechnology-Based Approach to Understanding Cancer Progression in Never-Smokers

Jonita Chongtham[1], Namita Pandey[1], Tapasya Srivastava[1]

[1]Department of Biotechnology, Manipur University, Canchipur, Imphal–795003, India

Email: jonitachongtham08@gmail.com

Abstract

Lung cancer in never-smokers remains a challenging biomedical problem, with clinical outcomes nearly as poor as those of smokers. In our analysis of 1,727 lung cancer patients, we found only a 47-day difference in overall survival between smoker and never-smoker lung adenocarcinoma patients, underscoring the similarly aggressive disease course irrespective of smoking status. To investigate the molecular basis for this parity, we explored hypoxia-mediated crosstalk between the nicotinic acetylcholine receptor (nAChR) pathway and key oncogenic signaling networks using tumor cells and complementary biotechnological approaches. We discovered a previously unrecognized hypoxia-induced elevation in acetylcholine levels and nAChR-α7 expression in non-small cell lung cancer (NSCLC) cells, a pattern further validated across multiple cancer cell lines and primary tumor tissues. Mechanistic analysis revealed direct binding of HIF-1α to a hypoxia-response element located 48 base pairs upstream of the nAChR-α7 transcriptional start site, establishing nAChR-α7 as a hypoxia-inducible gene. Elevated acetylcholine reinforced this response by activating the PI3K/AKT pathway, creating a positive feedback loop that stabilized HIF-1α and strengthened hypoxia-adapted tumor behavior. Functionally, this signaling axis promoted metastasis and enhanced hypoxia-driven cellular responses. Importantly, pharmacological inhibition of nAChR-α7 with bungarotoxin significantly reduced HIF-1α accumulation and reversed hypoxia-mediated metastatic activity, highlighting its therapeutic relevance. Collectively, our findings identify a novel nAChR–AKT–HIF signaling network that operates independently of nicotine and may contribute to the equally poor prognosis observed in never-smoker lung adenocarcinoma patients. This work demonstrates how biotechnological tools can reveal mechanisms underlying cancer progression and identifies potential molecular targets for improving therapeutic outcomes.

Keywords: Lung adenocarcinoma, Never-smokers, hypoxia signaling, nAChR-α7, HIF-1α, PI3K/AKT pathway, Tumor metastasis

ISBN: 978-81-989164-2-6; DOI: 10.21467/abstracts.8.1