

SCLC

57P INHIBITION OF THE FOCAL ADHESION KINASE HAS ANTI-TUMORAL EFFECT IN SMALL-CELL LUNG CANCER CELL LINES

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Aim: Lung cancer is the most common cancer and also the leading cause of cancer-related death worldwide among both men and women. Small cell lung cancer (SCLC) accounts for 15% of all cases. It is the most aggressive one in its clinical behavior with a 5-year overall survival as low as 5%. Focal Adhesion Kinase (FAK) is a non-receptor tyrosine kinase which regulates integrin and growth factor signaling pathways involved in cell proliferation, survival, migration, and invasion. FAK is

overexpressed and/or activated in many cancers including SCLC. We hypothesized that FAK may represent a good target for therapeutic interventions in SCLC and tested the changes of cell phenotype induced by a FAK inhibitor (PF-228).

Methods: Two suspension SCLC cell lines (NCI-H82 and NCI-H146), an adherent SCLC cell line (NCI-H196), and a mixed-morphology SCLC cell line (NCI-H446) were treated with increasing concentrations of PF-228. Cell proliferation was evaluated in these cell lines by WST-1 assay, cell cycle by flow cytometry of cells stained with propidium iodide (PI) and BrdU, apoptosis by flow cytometry of cells stained with intracellular caspase 3, and motility by wound healing assay associated to time-lapse microscopy. FAK expression/activity and signaling events downstream of FAK were evaluated by Western blotting.

Results: While PF-228 did not modify total FAK expression, it decreased the phosphorylation of FAK (Y397) in all the tested SCLC cell lines, clearly in a dose-dependent manner. Inhibition of FAK activity by PF-228 significantly decreased cell proliferation, induced cell cycle arrest in G2/M phases, and increased apoptosis in all the tested cell lines proportionally to the drug dose. PF-228 also decreased motility. In the analysis of signaling events, we observed that inhibition of FAK activity induced inhibition of phospho-ERK1/2 and phospho-Histone 3 (S10), while AKT expression/activity remained unchanged.

Conclusions: These results show that FAK activity is required for proliferation, cell cycle progression, survival, and motility in SCLC cell lines, suggesting that FAK inhibition may be an effective therapy in SCLC. The antitumoral effect of PF-228 may occur through Histone-3 phosphorylation at Ser 10, possibly mediated by ERK pathway.

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