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Chronic lymphocytic leukemia and Chronic Lymphoproliferative Disorders

FOCAL ADHESION KINASE AS A NOVEL THERAPEUTIC TARGET IN HAIRY CELL LEUKEMIA

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Introduction: Hairy cell leukemia (HCL) is a rare B-cell neoplasm characterized by cells with hair-like projections and a unique dissemination profile. Despite knowledge of HCL's reliance on microenvironmental interactions for survival, migration, and drug resistance, these interactions remain incompletely understood. In this context, Focal Adhesion Kinase (FAK) emerges as a molecule of interest. FAK plays a crucial role in transducing signals from the extracellular environment to the cell interior and interacts with various cytoskeletal molecules. While FAK has been identified as a potential therapeutic target in another B-cell neoplasia, i.e., chronic lymphocytic leukemia, its role in HCL remains unexplored, thus further investigation of FAK in HCL could provide valuable insights into the disease's pathogenesis and potentially reveal new therapeutic vulnerabilities.

Methods: CD19+/CD11c+/CD25+/CD123+ cells from therapy-naïve HCL patients were isolated either by using the RosetteSep kit for human B cells or CD19+ microbeads for positive selection and cell purity was assessed by flow cytometry. FAK expression, activation, and localization were analyzed by western blotting (WB) and confocal microscopy. Hairy cells were treated with 5μM of the FAK inhibitor defactinib for 24h, and apoptosis was evaluated using Annexin V/PI staining. Alternatively, PBMCs from HCL patients were treated with defactinib, and apoptosis was assessed in the gated hairy cell population by flow cytometry. Defactinib treatment was performed on cells from a total of 10 HCL patients.

Results: Western blot analysis revealed significant expression of FAK protein and its activated form, p-FAK-Y397, in HCL cells. Confocal microscopy confirmed a robust expression of FAK in hairy cells, demonstrating that its localization was predominantly cytoplasmic, with a certain percentage of the protein also present in the nucleus. FAK inhibition by defactinib induced significant apoptosis of hairy cells as assessed by the Annexin V/PI flow cytometry test that demonstrated a reduced number of viable cells after the treatment with the inhibitor, confirming that defactinib is effective in hairy cells (44 ± 27% vs 66 ± 21% of the untreated condition; $p<0.001$, paired Student's t-test).

Conclusions: This study demonstrates the significance of the FAK protein in HCL, highlighting its potential as a therapeutic target. Further research is needed to fully understand FAK's role in HCL progression and to explore the clinical potential of FAK inhibitors in this rare leukemia, potentially leading to improve patient outcome.