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Chronic lymphocytic leukemia and Chronic Lymphoproliferative Disorders

CHARACTERIZATION OF FAK-P53 FUNCTIONAL RELATIONSHIP IN CHRONIC LYMPHOCYTIC LEUKEMIA CELLS

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Introduction: Despite the progress in treatments for chronic lymphocytic leukemia (CLL) in recent years, disease relapse or refractoriness to therapy still occur, thus highlighting the unmet clinical need to find new therapeutic targets for developing alternative drugs. In this context, focal adhesion kinase (FAK) revealed to play a key role in cancer biology, especially in solid tumors. Although knowledge about FAK in hematological malignancies is still limited, some works have begun to show a possible involvement of FAK in the pathogenesis and evolution of CLL. Therefore, carrying on investigation into FAK in CLL may pave the way for the development of new alternative therapies. In this scenario, considering the great prognostic value of *TP53* genetic aberrations in CLL and previous evidence of a reciprocal regulation between FAK and p53 in solid tumors, we aimed to determine whether a functional relationship between these two proteins exists also in CLL.
Methods: CD19+/CD5+ cells from treatment-naïve CLL patients and normal B cells from healthy donors were purified through density gradient centrifugation. Basal protein expression of FAK and p53 was quantified by western blotting (WB) in 45 CLL patients and 11 controls. Cytoplasm-nucleus protein extraction was performed in 11 CLL patients and then FAK and p53 subcellular distributions were analyzed by WB. This last aspect was also investigated through immunofluorescence (IF) in cells from 2 CLL patients. Eventually, p53 expression in CLL cells after 3 hours of treatment with 5µM of the FAK inhibitor defactinib was assessed by WB in 12 CLL samples.
Results: Our WB analysis revealed a significant overexpression of wild type p53 protein ($p<0.01$) and a higher activation of FAK (in terms of phosphorylation at Y397 residue – pFAK-Y397, $p<0.001$) in CLL than in normal B cells. Moreover, we found a significant correlation between p53 and FAK protein expression levels in CLL cells ($p<0.05$, $r=0.41$). Additionally, by WB and IF, we demonstrated that both FAK and p53 can be present in both cytoplasm and nucleus of CLL cells, with a significant higher presence of p53 ($p<0.0001$) and pFAK-Y397 ($p<0.001$) within the nucleus. Accordingly, preliminary results from immunofluorescence revealed that FAK and p53 co-localize in both cytoplasm and nucleus of CLL cells. Adopting a loss-of-function approach, we further demonstrated that FAK inhibition could reduce by 20% the protein expression of p53 in CLL cells ($p<0.05$).
Conclusions: Overall, this study reported some important insights supporting the possible existence of a reciprocal regulation between FAK and p53 also in CLL. At the same time, our results opened the way to consider the role of p53 in CLL biology under a new perspective, suggesting that p53 might have a more complex function in the CLL context than its classical tumor-suppressive activity. In this regard, continuation of this research line could potentially unveil a novel druggable molecular axis in CLL biology.