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A proteomic approach to unveil the non-apoptotic functions of FADD in T-cell lymphoblastic neoplasms.

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INTRODUCTION

The role of FADD in cancer is controversial, but the apparent discrepancies between studies could be explained by the fact that FADD exhibits apoptotic and non-apoptotic roles [1]. However, the mechanism(s) whereby FADD carries out its non-canonical functions is still unknown. A decrease of FADD associated with poor clinical outcome like drug resistance, inferior survival, more recurrence or metastasis has been described in many tumour types [1-3]. Specifically, we have observed that T-cell lymphoblastic lymphomas (T-LBL) exhibit a significant reduction of FADD protein levels [4, 5], but the mechanism whereby this confers a significant advantage for the tumour cell is still unclear. In this study, we set out to get insight into the landscape of deregulated cell signalling events in FADD-deficient tumour T cells through mass spectrometric-based quantitative proteomics, using stable isotope labelling of amino acids in cell culture (SILAC). This is the first analysis of endogenous FADD interactome and proteome using SILAC-based and label-free quantitative proteomic techniques in non-apoptotic conditions.

OBJECTIVES

The purpose of this study is to identify the protein–protein interaction network of endogenous FADD (interactome analysis) and to quantitatively compare protein expression levels (proteome analysis) in FADD-expressing vs FADD-deficient tumour T cells.

METHODOLOGY

Stable Isotope Labelling of Amino acids in Cell culture (SILAC) and label-free quantification (LFQ) were used to evaluate FADD interactome. GSEA analysis was used to validate results from SILAC-based proteome of FADD-deficient tumour T cells. Functional interactions between FADD and several novel binding partners were confirmed by immunoprecipitation and western blot.

RESULTS

The results indicated that energy metabolism is deregulated in FADD-deficient T-cell lymphoblastic neoplasms. Moreover, a comparative analysis of the results from two different

quantitative proteomic strategies revealed 18 candidate proteins that interact with endogenous FADD. Interestingly, they are involved in mRNA processing and maturation.

CONCLUSIONS

FADD deficiency in T-cell lymphoblastic neoplasms would not only result in apoptotic impairment, as defined by FADD canonical function, but it would also be related to deregulation of non-apoptotic processes such as energy metabolism and mRNA processing.

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