THE ACTIN-BUNDLING PROTEIN FASCIN CONTRIBUTES TO HTLV-1-INDUCED LYMPHOMAGENESIS IN AN ATLL XENOGRAFT MOUSE MODEL

Calabrò ML[1], Pollinger L[2], Donhauser N[2], Heym S[2], Millen S[2], Mohr C F[2], Rigotto G[1], Lazzari N[1], Hartmann A[3], Peloponese JM[4], Chieco-Bianchi L[5], Thoma-Kress AK[2]

[1] Immunology and Molecular Oncology, Veneto Institute of Oncology IOV-IRCSS, Padua, Italy.
[2] Institute of Clinical and Molecular Virology, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany.
[3] Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany.
[4] Infectious Diseases Research Institute, CNRS, University of Montpellier, Montpellier, France.
[5] Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy.

Background:
Adult T-cell leukemia/lymphoma (ATLL) is a severe malignancy with poor prognosis caused by persistent infection with the oncogenic retrovirus Human T-cell leukemia virus type 1 (HTLV-1). We previously found that the actin-bundling protein Fascin, a tumor marker crucial for metastatic dissemination in many types of cancer, is upregulated in HTLV-1-infected T cells, induced by the viral Tax oncoprotein, and important for invasion of ATLL cells. Here we asked whether Fascin also contributes to lymphomagenesis *in vivo* in a murine model of acute ATLL.

Methods:
Small hairpin RNA (shRNA)-mediated gene repression; a preclinical model of acute ATLL in non-obese diabetic/severe combined immunodeficient/ interleukin-2 receptor common gamma chain knock-out (NSG) mice; immunohistochemistry; quantitative PCR (qPCR); migration assays.

Results:
Upon knockdown of Fascin in human chronically HTLV-1-infected C91/PL cells (C91/PL/shFascin cells), injection of these cells into NSG mice led to tumor development independently of Fascin repression. However, compared to mice injected with control cells (C91/PL/shNonsense), lymphoma growth was significantly delayed in mice xenografted with C91/PL/shFascin cells, suggesting that Fascin suppression impaired tumor progression *in vivo*. Immunohistochemistry revealed that Fascin was present in tumors and metastases in control mice. qPCR confirmed repression of Fascin in the xenografted C91/PL/shFascin cells and in tumors *ex vivo,* while expression of HTLV-1 Tax was unaffected by Fascin knockdown. Mechanistically, migration assays in Jurkat control cells, compared to Fascin knock-out cells, revealed that T-cell migration is enhanced in the presence of Fascin. Finally, analysis of Fascin expression in ATLL patients showed that Fascin is significantly upregulated in patients with skin lesions.

Conclusion:
Together, our data highlight an important role of Fascin in lymphomagenesis in a murine model of aggressive ATLL, and suggest that Fascin also contributes to lymphoma dissemination in ATLL patients.

Disclosure of Interest Statement:
Nothing to declare.