Abstract: P1211

Title: TUMOR-ACTIVATED LYMPH NODE FIBROBLASTS SUPPRESS T CELL FUNCTION IN DIFFUSE LARGE B CELL LYMPHOMA

Abstract Type: Poster Presentation

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Background:

Recent transcriptomic-based analysis of diffuse large B cell lymphoma (DLBCL) has highlighted the clinical relevance of lymph node (LN) fibroblast and tumor-infiltrating lymphocyte (TIL) signatures within the tumor microenvironment (TME). However, the immunomodulatory role of fibroblasts in lymphoma remains unclear.

Aims:

LN fibroblasts (or fibroblastic reticular cells, FRCs) are specialized immune-interacting fibroblasts, that provide the highways for immune cells to migrate along and crucially regulate innate and adaptive immune responses. The aim of this study was to unmask the phenotypical, transcriptional and functional changes in FRCs following chronic exposure to DLBCL.

Methods:

We employed imaging mass cytometry, confocal microscopy, co-culture and organotypic functional assays to study DLBCL patient samples and a mouse model of disease.

Results:

Here, by studying human and mouse DLBCL-LNs, we identify the presence of an aberrantly remodeled fibroblastic reticular cell (FRC) network, expressing elevated fibroblast activated protein (FAP). RNA-sequencing analyses reveal that exposure to DLBCL reprograms key immunoregulatory pathways in FRCs, including a switch from homeostatic to inflammatory chemokine expression and elevated antigen presentation molecules. Functional assays show that DLBCL-activated FRCs (DLBCL-FRCs) hinder optimal TIL and chimeric antigen receptor T cell (CAR-T) migration. Moreover, DLBCL-FRCs inhibited $CD8^+$ TIL cytotoxicity in an antigen-specific manner. Notably, the interrogation of patient LNs with imaging mass cytometry identified distinct environments differing in their $CD8^+$ TIL-FRC composition and spatial organization that associated with survival outcomes. We further demonstrate the potential to target inhibitory FRCs to rejuvenate interacting TILs. Co-treating organotypic cultures with FAP-targeted immunostimulatory drugs and a bispecific antibody (glofitamab) augmented anti-lymphoma TIL cytotoxicity.

Summary/Conclusion:

Together, our study reveals an immunosuppressive role of FRCs in DLBCL, with implications for immune evasion, disease pathogenesis and optimizing immunotherapy for patients.

Keywords: Immunotherapy, Microenvironment, Tumor immunology, Diffuse large B cell lymphoma