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Session D109 - MODULATING THE FIBROTIC RESPONSE

513 - IPF Macrophage Crosstalk with IPF Mesenchymal Progenitor Cells Drives Fibrotic Progression

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Participant

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Abstract

RATIONALE: We have previously found numerous macrophages co-distributing with fibrogenic mesenchymal progenitor cells (MPCs) on the periphery of fibroblastic foci in the IPF lung. We hypothesize that IPF macrophage/IPF MPC crosstalk drives IPF fibrotic progression. We further hypothesize that the IPF macrophages have a distinct phenotype which promote fibrogenesis by stimulating self-renewal of IPF MPCs.

METHODS: Immunohistochemical analysis was performed to assess the distribution of IPF MPCs and macrophages in developing fibroblastic foci lesions. Human lung macrophages were isolated from IPF and control lung tissue. IPF MPCs were isolated from primary mesenchymal cell lines established from IPF and control patients by flow cytometry using a SSEA4 antibody. Transwell co-culture experiments were performed to analyze the effect of macrophage secretory products by using colony forming assay. Mass spectroscopy and a cytokine array assay were used to define the IPF macrophage secretome. Gain and loss of function experiments were performed to analyze the role of the CXCL5/CXCR2 axis in regulating IPF MPC self-renewal. The murine xenograft model was used to analyze the role of IPF macrophage/IPF MPC crosstalk in driving fibrotic progression *in vivo*.

RESULTS: In IPF lung tissue specimens, IPF MPCs co-distributed with numerous CD163/CD206+ macrophages on the periphery of the fibroblastic focus. In co-culture experiments, IPF macrophages stimulated IPF MPC self-renewal. Compared to control macrophages, the IPF macrophage secretome contained higher levels of CXCL1, CXCL3, and CXCL5, with CXCL5 being the most elevated. Antagonism of the CXCR2 receptor inhibited IPF MPC self-renewal in response to IPF macrophage conditioned medium. *In vivo*, the combination of human IPF MPCs and IPF macrophages acted synergistically to increase interstitial lung fibrosis in the mouse xenograft model of non-resolving lung fibrosis.

CONCLUSION: Our immunohistochemical analysis of IPF fibroblastic foci demonstrate IPF macrophages co-distributing with IPF MPCs on the periphery of the fibroblastic focus in a highly cellular, mitotically active region. Our data indicates that macrophages play an important role in self-renewal of IPF MPCs in vitro. They do so partly by secreting CXCL1, CXCL3 & CXCL5 in their microenvironment. *In vivo*, the combination of human IPF MPCs and IPF macrophages act synergistically to increase the degree of interstitial lung fibrosis. These findings support the concept that IPF macrophage/IPF MPC crosstalk drives IPF fibrotic progression.

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Participant

P. Ford;

Mechelen, BELGIUM.

Abstract

There is no abstract associated with this presentation.