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AB0041

DO FUNCTIONAL INTERACTIONS BETWEEN MACROPHAGES AND SYNOVIAL FIBROBLASTS DRIVE SYNOVIAL PATHOLOGY OR RESOLUTION OF INFLAMMATION?

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Background: We recently uncovered heterogeneity in human synovial tissue macrophages during inflammation and resolution of inflammation (remission) in rheumatoid arthritis (RA). The transcriptomic profiles of distinct macrophage subpopulations suggest distinct functions, ranging from inflammatory to regulatory. Prior studies propose reciprocal interactions between macrophages and synovial fibroblasts (FLS) exist in the joint; however, the exact contribution of these interactions to synovial pathology or resolution of inflammation remains unknown.

Objectives: The aim of this study was to examine the functional interactions between different macrophage phenotypes and synovial fibroblasts.

Methods: To model different macrophage phenotypes, monocyte-derived macrophages (MOMs) were pre-stimulated (16h) with LPS (100ng/ml) to model inflammatory macrophages, or stimulated with Dex (1μM) to model regulatory macrophages. To model different periods of time. Prior to co-culture, FLS and MOMs were labelled with CellTraceTM-Violet and CellTraceTM-Red, respectively. After 24 & 48 hours of co-culture, both cell types were cultured separately and, FLS and MOMs were sorted based on positivity for CellTraceTM Vio- let (FLS) or Red (MOMs) using FACS ARIA III, and expression of IL-6 and MMP3 proteins in FLS and MOMs were evaluated in co-culture supernatants by ELISA. To investigate the nature of the contact (40min meandering velocity) of individual MOMs on FLS monolayers was evaluated using Delta Vision fluorescence microscopy.

Results: After 24 & 48 hours of co-culture, FLS and MOMs were sorted based on positivity for CellTraceTM Vio- let (FLS) or Red (MOMs) using FACS ARIA III, and expression of IL-6 and MMP3 proteins in FLS and MOMs were evaluated in co-culture supernatants by ELISA. To investigate the nature of the contact (40min meandering velocity) of individual MOMs on FLS monolayers was evaluated using Delta Vision fluorescence microscopy.

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REFERENCE

AB0042

PRECLINICAL EVALUATION OF JAK1 SELECTIVE INHIBITORS INCBO39110 AND INCBO54707 AS TARGETED THERAPY OF CUTANEOUS LUPUS ERYTHEMATOSUS

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Background: Cutaneous lupus erythematosus (CLE) is an autoimmune disease with heterogeneous subtypes presenting with inflammatory skin lesions, a histological pattern called “interface-dermatitis” and enhanced type-1-interferon (IFN)-regulated JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathway signaling. Despite deeper understanding of the pathogenesis still no specifically approved drugs for CLE exist.

Objectives: The aim of our study was to investigate the effect of JAK1 selective inhibition as potential therapeutic approach for CLE in established preclinical models of cutaneous autoimmunity.

Methods: The expression of IFN-regulated proteins and genes after JAK1 inhibitor treatment was analysed in cultured, stimulated immortalized and primary human epidermal keratinocytes. In addition the impact of JAK1 inhibition on CLE-like skin lesions in lupus prone mouse model were determined.

Results: In vitro investigation revealed a significantly decreased gene- and protein expression of proinflammatory cytokines, in particular CXCL10 as key driver chemokine of lesional inflammatory, and other pathophysiologic important IFN-regulated mediators in inflamed keratinocytes after treatment with JAK1 inhibitors. Moreover JAK1 inhibition generated an amelioration of skin lesions in lupus prone mice.

Conclusion: Our findings indicate that inhibition of JAK1 results in a decreased chemokine expression, subsequent less cytotoxic T cell induced keratinocytic cell death leading to an improvement of lesional skin. By breaking the vicious inflammatory cycle JAK1 inhibitors appear to be promising agents as targeted therapy of CLE. Further investigation has to be performed in clinical trials.

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