NOVEL MECHANISM OF MSC MEDIATED IMMUNESUPPRESSION

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Introduction: The major function of dendritic cells (DCs) acting as regulators of immune responses is to maintain peripheral tolerance and in case it fails to respond to inflammatory challenges. Advances in our understanding of the phenotypic and functional plasticity of DCs opened up new avenues for developing strategies appropriate for modulating inflammation. We recently have characterized a stem cell line (MSCl), which could provide a theoretical basis for the therapeutic utility of these cells for increasing inherent tolerogenicity. In this study we tested the direct and indirect immune modulatory effects of MSCI on monocyte-derived DCs (moDCs).

Methods: To approach this goal we co-cultured moDCs with MSCI cells for three days at a ratio of 5:1, and then activated the cells with bacterial lipopolysaccharide (LPS). After 24 hrs the moDCs were separated from the MSCl cells by the lectin receptor CD209 and mRNA was extracted from the moDCs. To identify the genes >2.0 fold change global gene expression profiling was performed by using the Illumina HiScanSQ platform. The separated moDCs were characterized by phenotypic and activation markers by flow cytometry and by their cytokine production measured by ELISA.

Results: In the presence of MSCI cells moDCs differentiated to a cell type with a unique regulatory phenotype characterized by up-regulated expression of the inhibitory molecules PD-L1 and CTLA-4, while the expression of CD86 and MHC-II was increased. Co-culturing moDCs with MSCI cells the secretion of TNF-α, IL-12 and IFNγ was down regulated despite LPS activation, but under these conditions the secretion of IL-10 was increased. Our results also demonstrated that the expression of CXCR4 together with CCR5 is up-regulated on the surface of moDCs opposing the down regulation of CCR7 receptor. The expression of a wide variety of CXC chemokine genes were also modulated by MSCl cells resulting in the increased expression of GRO family chemokine genes. Simultaneously, the expression of CXCL9, CXCL10 and CXCL12 chemokine genes were upregulated in moDCs.

Conclusions: The changes induced by MSCl cells affected important moDC functional activities such as increased expression of the PD-L1 inhibitory molecule and the contribution of the CXCR4-CXCL12 axis, which in concert may favour the establishment of a tolerogenic environment. Thus the data outline a novel mechanism mediated by MSCI cells to promote moDC differentiation to a regulatory phenotype.

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Poster presentation
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