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AB0171

THE REGULATION AND PHARMACOLOGICAL MODULATION OF IMMUNE COMPLEX INDUCED PRODUCTION OF TYPE III IFN BY PLASMACYTOID DENDRITIC CELLS

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Background: The type I Interferons (IFNs) are the most important drivers of the IFN gene signature in Systemic Lupus Erythematosus (SLE). However, both type II and type III IFNs (IFN- λ 1-3) can be measured in a proportion of patients with SLE and contribute to the IFN signature. The exact role of type III IFNs in SLE is not completely clear, but serum levels of type III IFN correlate with disease activity and specific organ manifestations, such as arthritis, nephritis and anti-dsDNA antibodies. Type III IFN can be induced in pDCs by TLR9 agonist Oligodinucleotide (ODN) 2216 and many viruses. Whether type III IFN can also be induced in pDCs by nucleic acid containing immune complexes (IC), has, to our knowledge, not been investigated before.

Objectives: We asked if RNA containing immune complexes (RNA-IC), which trigger the synthesis of large amounts of IFN- α by plasmacytoid dendritic cells (pDCs), can act as stimuli for type III IFN production, and how this production is regulated by Natural Killer (NK) cells and different cytokines. We also investigated if the type III IFN production could be blocked by hydroxychloroquine (HCQ) and an interleukin receptor 1 associated kinase 4 inhibitor (IRAK4i).

Methods: Peripheral blood mononuclear cells (PBMCs) from SLE patients or healthy individuals were used to isolate pDCs and natural killer (NK) cells, or were depleted of monocytes. Cells were stimulated with RNA-IC, and cytokines were measured by immunoassays. mRNA expression in RNA-IC stimulated pDCs and NK cells was analyzed with a microarray. The effect of HCQ and IRAK4i on the IFN- λ 1/3 production was investigated in pDCs and NK cells from healthy individuals.

Results: Type III IFN mRNA expression was strongly upregulated in co-cultures of pDC-NK cells stimulated with RNA-IC. High levels of IFN- λ 1/3 and IFN- λ 2 (medians 2000 pg/ml and 100 pg/ml) were detected in supernatants from RNA-IC stimulated pDC-NK cell co-cultures. IFN- λ 2 enhanced IFN- λ 1/3 and IFN- α production by purified pDCs. Interleukin (IL) -3, IL-6, and GM-CSF significantly enhanced IFN- λ 1/3 production (4-5 fold) by RNA-IC stimulated pDCs. Monocyte depleted PBMCs and pDC-NK cell co-cultures from 15% and 9% of SLE patients produced IFN- λ 1/3 in response to RNA-IC stimulation. Exogenous IFN- α 2b and GM-CSF in pDC-NK cell co-cultures increased the proportion of patients responding to RNA-IC stimulation from 9 to 36%. IFN- λ 1/3 production by RNA-IC-stimulated pDCs and pDC-NK cells was significantly inhibited by HCQ (by 99% and 93% respectively) and an IRAK4i (by 98% and 96% respectively).

Conclusion: pDCs produce both type I and type III IFN in response to RNA containing immune complexes. This is promoted by activated NK cells as well as a number of pro-inflammatory cytokines, including IFN type I and type III, considered important in SLE. Consequently, in order to achieve a proper control the IFN driven autoimmune process in SLE, both type I and type III IFN need to be targeted. In this system of stimulated, co-cultivated pDCs and NK cells, HCQ and an IRAK4 inhibitor blocked the type III IFN production.

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AB0172

EXPRESSION OF SLAMF6 AND ITS FUNCTIONAL SIGNIFICANCE IN PODOCYTES OF LUPUS NEPHRITIS

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Background: Systemic lupus erythematosus (SLE) is multisystem disorder that is caused by tissue damage resulting from antibody and complement-fixing immune complex deposition. Lupus nephritis (LN) is frequent complication and one of the most serious manifestations of SLE. The expression of nephrin, as podocyte marker, is reduced in various renal diseases that develop into nephrotic syndrome¹. The alteration of the structural protein in podocytes is known as a mechanism of proteinuria in LN.

Objectives: The signaling lymphocyte activation molecule family (the SLAM family) of type I transmembrane receptors consists of nine related members of the immunoglobulin superfamily and has been reported to mediate important regulatory signals between immune cells through their homophilic and heterophilic interactions². The 1q23 region (*Sle1b* region in mouse) on human chromosome 1 including the SLAMF cluster of genes, containing SLAMF6 has been identified as a lupus susceptibility locus³. It has been shown that the expression of signaling lymphocyte activation molecule family 6 (SLAMF6) is enhanced in CD4+T cells of SLE patients and is involved in IL-17 production⁴. We sought to examine the functional role of SLAMF6 in lupus podocytes.

Methods: We evaluated the co-expression of nephrin, a podocyte marker and SLAMF6 in kidney of normal controls and LN patients, also in B6 and MRL/lpr mice at the age of 8wk and 16wk by immunofluorescence analysis. We also examined nephrin positive SLAMF6 expression in isolated podocytes from B6 and MRL/lpr kidneys. Then, we analyzed the expression of SLAMF6 in CD4+T cells of isolated kidney and spleen in B6 and MRL/lpr mice. We treated human podocytes with IgG from healthy individuals and LN patients for 24 h and 48h and analyzed the expression of SLAMF6 by real-time PCR.

Results: In the histopathology, the expression of SLAMF6 was increased in nephrin positive area in LN patients and MRL/lpr mice compared to each control groups. Although the expression of nephrin in MRL/lpr mice kidney at 16 wk old decreased compared to B6 mice at same age, the expression of SLAMF6 in podocytes increased in diseased MRL/lpr mice compared to B6 mice. Similarly, the expression of SLAMF6 in CD4+ T cells increased in diseased MRL/lpr mice kidney and spleen compared to B6 mice. The level of SLAMF6 mRNA elevated in human podocytes exposed to LN-derived IgG compared to healthy individuals-derived IgG.

Conclusion: The expression of SLAMF6 is enhanced in LN podocytes, suggesting that the possibility of cooperating with CD4+T cells contributing to its dysfunction. Further examination is needed to investigate in detail how SLAMF6 is involved in the development of LN in the future.

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