through endosomal TLR inhibition effectively blocks IFN-α, is standard of care. However, few patients experience complete remission. 

Objective: We asked whether an IL-1 receptor associated kinase 4 (IRAK-4) inhibitor, for IL-12/23, (ND-2158, Nimbus Discovery), acting downstream of TLR 7/9, affects RNA-IC-induced cytokine production compared to hydroxychloroquine (HCQ). 

Methods: Plasmacytoid dendritic cells (pDCs) and natural killer (NK) cells were isolated from peripheral blood mononuclear cells (PBMCs) of healthy individuals. PBMCs from 15 SLE patients were depleted of monocytes. Cells were stimulated with RNA-IC, consisting of IgG from SLE patient sera and U1 snRNP particles, in the presence or absence of IL-12 or HCQ. Cytokines were measured by immunoassays or flow cytometry. RNA-sequencing was performed on RNA-IC stimulated pDCs from healthy individuals and the effect of IL-12 and HCQ was assessed.

Results: RNA-IC induced IFN-α, TNF-α, IL-6, IL-8, IFN-γ, MIP-1α and MIP-1β production in pDC and NK cell co-cultures. IL-12 reduced the pDC and NK cell derived cytokine production by 74.95%, HCQ interfered with cytokine production in pDCs, but not in NK cells. In monocyte-depleted SLE PBMCs IFN-α blocked TNF-α, IFN-γ, MIP-1α and MIP-1β production more efficiently than HCQ. IL-8 production was high in monocyte depleted PBMC from SLE patients, and not blocked by another drug, despite significant inhibition of IL-8 in pDC-NK co-cultures from healthy individuals. Following RNA-IC activation of pDCs, 975 differentially expressed genes were found (FDR<0.05), many connected to cytokine pathways, cell regulation and apoptosis. The IRAK4 inhibitor significantly changed more RNA-IC induced genes than HCQ (492 vs. 65 genes). Several top upregulated genes were reversed by both I92 and HCQ, including OASL, CXCL10, CD274, TNFSF10, APOL6, EAF2 and DKK4, LAD1 and EAF2 were significantly more downregulated by I92 than by HCQ.

Conclusions: Whereas both HCQ and the IRAK4 inhibitor block important pro-inflammatory cytokines, the IRAK4 I92 exhibits a broader inhibitory effect than HCQ on pathways triggered by RNA-IC, which suggests that IRAK4 inhibition could be a future therapeutic option in SLE and possibly other systemic autoimmune diseases characterized by the presence of ICs containing nucleic acid.


Background: Systemic lupus erythematosus (SLE) is a serious and intractable autoimmune disease, and lupus nephritis (LN) as one of its major complications without effective treatment. IL-37 has been identified as a natural inhibitor of innate immunity. Although increasing evidence shows that serum IL-37 correlated with SLEDAI and nephritis activity, however, it is still unclear that the therapeutic effect of IL-37 in lupus mice.

Objectives: This study aims to determine the inhibitory effect of IL-37 in lupus mice and lupus nephritis in vivo, and to expose the IL-37 related mechanisms of cell and molecules that inhibits the inflammation in lupus nephritis.

Methods: MRL-Fas-β mice with mild and advanced disease were treated with lenti-IFNα vector pLV-IL-37b. The protein levels of IL-37b in serum and tissue, IL-17, IL-6, IL-10 and TGF-β3 produced by cell culture from spleen and kidney of mice were measured by ELISA, the relative mRNA expression of these cytokines in PBMCs was detected by RT-PCR, and the frequency of Th17 and Treg cells in splenocyte were determined by FACS.

Results: Our results show that IL-37 was highly effective in prolonging survival, alleviating the pathologic characteristics of lupus nephritis (LN) in MRL-Fas-β mice by reducing the autoimmunity complex deposition such as IgM, IgG and C3, decreasing the production of inflammatory cytokines such as IL-17, IL-6 and promoting the anti-inflammatory cytokines IL-10 and TGF-β3. We also found that IL-37 protect lupus mice from LN increased with increasing the frequency of Treg cells and reducing the frequency of Th17 cells.

Conclusions: The results indicate that IL-37 is one of the protective action of IL-37 in LN, and strengthen the support for IL-37 as a new target for therapy for SLE.


Background: Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease, with different immunological alterations and clinical phenotypes. Natural killer (NK) cells participate in the regulation of several immune responses but their function in SLE is not well understood. 1 KLRG1 (killer cell lectin like receptor G1) is a trans-membrane protein expressed in humans especially on NK cells, working as an inhibitory receptor of their cytotoxic activity. Thus, KLRG1-expressing NK cells contribute to disease development, while KLRG1− NK cells are the ones that are better at eliminating tumor cells. 2 The KLRG1 gene also emerged as a disease susceptibility gene for SLE in four different ethnic groups. 3

Objectives: The aim of this study was to characterize KLRG1 expression on NK cells (both CD56dim and CD56bright) from SLE patients compared to healthy subjects (HS) and to investigate its possible correlations with clinical features, including SLE disease activity.

Methods: We enrolled 14 patients (14F, mean age±SD 37±10.7 years, mean disease duration ±SD 10.5±7.9 years) affected by SLE according to the 1997 ACR criteria, and 7 HS (7F, mean age±SD 33±5.5 years). Disease activity was measured by SLEDAI-2K. Peripheral blood mononuclear cells (PBMCs) were purified...
and phenotypic characterization was performed. All experiments were conducted by flow cytometry.

Results: KLRG1 was expressed in a statistically significant lower amount on total NK cells from SLE patients compared to HS (p<0.0007). Analysis of CD56dim and CD56bright populations showed less amount of KLRG1 in SLE patients compared to HS (p=0.0051 and p=0.0068) (figure 1). The low levels of KLRG1 on NK cells inversely correlated with the SLEDAI-2K (p=0.029) and were inversely associated with the presence of arthritis (p=0.029), arthralgias (p=0.0024) and hematological disorders (p=0.025). A direct association between KLRG1 expression on NK cells and the use of HCQ was found (p=0.001). Analysing the two main subpopulations of NK cells, we observed an inverse association between KLRG1 on CD56dim cells and arthritis (p=0.0089), arthralgias (p=0.0001), hematological disorders (p=0.0329) and SLEDAI-2K (p=0.0105). KLRG1 on CD56bright was directly associated with the use of HCQ (p=0.0010). KLRG1 on CD56dim was also directly associated with the use of HCQ and MMF (p=0.03 and p=0.014).

Conclusions: This study shows for the first time a reduced expression of KLRG1 in SLE patients. The inverse associations between the levels of this receptor on NK cells and the SLEDAI-2K and clinical features, together with the direct association with HCQ and MMF, suggest a possible role of KLRG1 in the pathogenesis of this disease. KLRG1 could be a possible therapeutic target in SLE.

REFERENCES:

Disclosure of Interest: None declared