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

Outcomes: We asked whether an IL-1 receptor associated kinase 4 (IRAK-4) inhibitor for IBD (ND-2158, Nimbus Discovery), acting downstream of TLR7/9, affects RNA-IC-induced cytokine production compared to hydroxychloroquine (HCQ).

Methods: Plasmacytid 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 U1snRNP particles, in the presence or absence of IBD or HCQ. Cytokines were measured by immunoassays or flow cytometry. RNA-sequencing was performed on RNA-IC stimulated pDCs from four healthy individuals and the effect of IBD 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. IBD 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 IBD 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 neither 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 observed (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 repressed by both IBD and HCQ, including IFN2A, IFIT2-3, OASL, CXCL10, CD274, TNFSF10, APOL6. Gene expressions such as HK4, LAD1 and EAF2 were significantly more downregulated by IBD than by HCQ.

Conclusions: Whereas both HCQ and the IRAK4 inhibitor block important pro-inflammatory cytokines, the IRAK4 inhibitor shows 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.

Reference:

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