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Inhibition of mTOR suppresses IFN α production and the STING pathway in monocytes from systemic lupus erythematosus patients

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Abstract

Objective

Increased IFN α is important in the pathogenesis of SLE. Plasmacytoid dendritic cells are considered the main producer of IFN α upon Toll-like receptor pathway activation. However, which cells produce IFN α following stimulation with cyclic GMP–AMP synthase (cGAS) and stimulator of IFN genes (STING) in SLE remains unknown. We investigated the IFN α producing capacity of myeloid cells under cGAS–STING pathway stimulation.

Methods

IFN α levels in peripheral blood mononuclear cells from SLE patients and healthy controls stimulated with 2'3'c–GAMP, a stimulator of cGAS–STING, were measured by intracellular cytokine staining and flow cytometry. STING expression and its co-localization with TBK1 were examined by flow cytometry or confocal microscopy. The effects of *in vitro* exposure to IFN α on IFN α production and STING expression, and *in vitro* rapamycin treatment on IFN α production and STING, pTBK1 and IRF3 expression were examined.

Results

IFN α was produced by monocytes, conventional dendritic cells and plasmacytoid dendritic cells upon cGAS–STING pathway activation. The frequency of IFN α -producing monocytes positively correlated with SLE disease activity. STING expression and its co-localization with TBK1 were increased in lupus monocytes. Prior exposure to IFN α enhanced the IFN α -producing capacity of monocytes. Inhibition of the mechanistic target of the rapamycin (mTOR) pathway suppressed IFN α production from monocytes and downregulated enhanced STING expression and its downstream molecules.

Conclusion

Enhanced IFN α from lupus monocytes induced by augmented STING pathway activation is associated with SLE pathogenesis. Suppression of the mTOR pathway downregulated the enhanced STING expression and the subsequent IFN α production by monocytes.

Keywords: [systemic lupus erythematosus](#), [cGAS-STING pathway](#), [interferon \$\alpha\$, monocytes](#)

Topic: [rapamycin](#), [systemic lupus erythematosus](#), [monocytes](#), [mtor serine-threonine kinases](#)

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