Volume 59, Issue 10
October 2020

Article Contents

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

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Rheumatology, Volume 59, Issue 10, October 2020, Pages 2992–3002,
https://doi.org/10.1093/rheumatology/keaa060
Published: 11 March 2020 **Article history** ▾

Abstract

Objective

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

Methods

IFNα 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 IFNα on IFNα production and STING expression, and *in vitro* rapamycin treatment on IFNα production and STING, pTBK1 and IRF3 expression were examined.

Results

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

Conclusion

Enhanced IFNα 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 IFNα production by monocytes.

Keywords: systemic lupus erythematosus, cGAS-STING pathway, interferon α, monocytes
Topic: rapamycin, systemic lupus erythematosus, monocytes, mtor serine-threonine kinases
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Online ISSN 1462-0332 Print ISSN 1462-0324