MxA is a clinically applicable biomarker for type I interferon activation in systemic lupus erythematosus and systemic sclerosis

Rheumatology key message

- Myxovirus resistance protein 1 enzyme immunoassay robustly identifies systemic type I IFN activation in SLE and SSc.

SLE, aberrant activation of the type I IFN system has been implicated in the pathogenesis of systemic autoimmune diseases and is a potential treatment target that is currently under clinical investigation [1]. Laborious and expensive tests for type I IFN activity limit the implementation in routine diagnostics and clinical decision making. Previously we identified whole blood levels of intracellular myxovirus resistance protein 1 (MxA), measured by an enzyme immunoassay, as a clinically relevant biomarker for type I IFN activity in patients with SS [2]. Here we assessed the applicability of this assay to detect systemic type I IFN activation in patients with SLE and SSc.

Whole blood intracellular MxA protein levels were measured in SLE patients (discovery cohort, n = 25; replication cohort retrieved from the CHILL-NL cohort [3], n = 102), SSc patients (n = 28) and healthy controls (HCs) (Supplementary Table S1, available at Rheumatology online) using the MxA-EIA [2, 4]. IFN scores were determined from whole blood gene expression of IFN-inducible genes IFI44, IFI44L, IFIT1, IFIT3 and MxA as previously described [5]. The Medical Ethics Review Committee of the Erasmus University Medical Center Rotterdam approved this study and written informed consent was obtained from all participants, in compliance with the Helsinki Declaration. Further details are provided in the supplementary material, Methods section, available at Rheumatology online.

MxA levels were significantly elevated in both cohorts of patients with SLE, as well as SSc, compared with HCs and were highly correlated to IFN scores ($r_s = 0.735–0.854$, $P < 0.003$; Fig. 1A, B and Supplementary Fig. S1A, B, available at Rheumatology online). MxA-EIA robustly discriminated (area under the curve $= 0.938–0.991$, $P < 0.007$) between low and high type I IFN activity in patients with SLE, as well as SSc, with a specificity of 100% and a sensitivity of 87.5–94.7% at a cut-off level of 150 U/mL.

(A) MxA-EIA levels of SLE (replication cohort) and HCs. (B) Correlation between IFN score and MxA-EIA levels in SLE. Dashed line: IFN score threshold value. (C) MxA-EIA levels in HCs and SLE, stratified based on IFN score. (D) Receiver operating characteristic curve of MxA-EIA levels to discriminate between IFN-low and IFN-high in SLE. AUC, area under the curve. Symbols represent individual samples, horizontal lines indicate medians. Statistics: (A) Mann–Whitney U test, (B) Spearman’s correlation test, (C) Kruskal–Wallis test. ***$P < 0.001$. 

Letters to the Editor

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of 22 μg/L (Fig. 1C, D and Supplementary Fig. S1C, available at Rheumatology online). MxA is an important mediator in IFN-induced antiviral immunity that is exclusively regulated by type I and III IFNs [6]. This is reflected in the excellent positive predictive value of the MxA-EIA.

As expected, SLE patients with autoantibodies against Smith (Sm), RNP, Ro/SSA or La/SSB antigens showed higher MxA levels and IFN scores compared with patients without these antibodies (Supplementary Fig. S2A and Supplementary Table S2, available at Rheumatology online). A positive trend was observed between MxA levels and the number of autoantibodies present in each patient (Supplementary Fig. S2B, available at Rheumatology online). Patients in both the discovery and the replication SLE cohorts had relatively low disease activity, with a SLEDAI ≥ 8 in only 13% of all SLE patients. Therefore this cross-sectional study lacks statistical power to determine any association between type I IFN activity and disease activity.

In conclusion, MxA-EIA is a cheap, easy-to-measure and highly specific biomarker that accurately reflects type I IFN activity in patients with SLE and SSc. This assay enables selection of patients for IFN-targeting treatments and monitoring of the efficacy of these treatments in downregulating type I IFN activity in routine diagnostics and in the context of clinical trials. Future studies should evaluate the potential applicability of MxA-EIA for prediction of disease manifestations and monitoring of treatment responses in patient cohorts followed over time.

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Supplementary data

Supplementary data are available at Rheumatology online.

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Hydroxychloroquine significantly reduces serum markers of endothelial injury and NEMO videocapillaroscopy score in systemic sclerosis

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Hydroxychloroquine significantly reduces serum markers of endothelial injury and NEMO videocapillaroscopy score in systemic sclerosis

Rheumatology key message

- HCQ significantly reduced serum levels of Vascular cell adhesion molecule-1, E-selectin, Endothelin-1 and NEMO videocapillaroscopy score in SSc.

Sir, Based on the lack of current evidence of a possible beneficial role of HCQ in microvascular involvement in SSc, we assessed the effects of 3-month HCQ administration on serum markers of endothelial injury and neoangiogenesis, NEMO videocapillaroscopy score and giant capillaries score [1]. This was an observational prospective study (Prot: 3.18 TS ComEt CBM) on stable SSc patients admitted from outpatient clinic in different periods of the year from September 2016 to March 2018 to