Discovery and Subsequent Diagnostic Verification of Autoantibodies Against the Major Vault Protein (MVP) in Systemic Lupus Erythematosus

P. Budde[1], Johannes Schulte-Pelkum[1], Daniel Wirtz[1], Hans-Dieter Zucht[1], Heike Göhler[1], Stefan Vordenbäumen[2], Peter Schulz-Knappe[1] and Matthias Schneider[2],
[1]Protagen AG, Dortmund, Germany, [2]Rheumatology, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

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Introduction

- SLE is a clinically and genetically heterogeneous disease with a high demand for biomarkers to discriminate subgroups of patients with different risk profiles, disease activity, organ-specific involvements, and drug response profile.
- The broad spectrum of autoantibody specificities in SLE may mirror several pathogenic mechanisms and pathways promoting loss of B cell tolerance.
- Here we describe the identification of autoantibodies against the major vault protein (MVP) in SLE and its subsequent development into an ELISA based assay.
- MVP is an interesting autantibody target, because it plays a pivotal role in virus-induced host response and induces upregulation of IFN type I expression (1).

Methods

Anti-MVP antibodies were discovered by high-content autoantibody profiling using the bead-based Luminex xMAP platform SeroTag® and validated in >700 SLE samples. To assess the added benefit of this novel SLE marker, we combined MVP with classical SLE autoantigens into a multi-marker assay. The NavigAID SLE array contains 86 antigens and expands the clinician's armamentarium to stratify SLE into five serological distinct subgroups (2). To enable the development of smaller ELISA-based multi-marker panels, we have developed anti-MVP into a prototypic bead-based ELISA format.
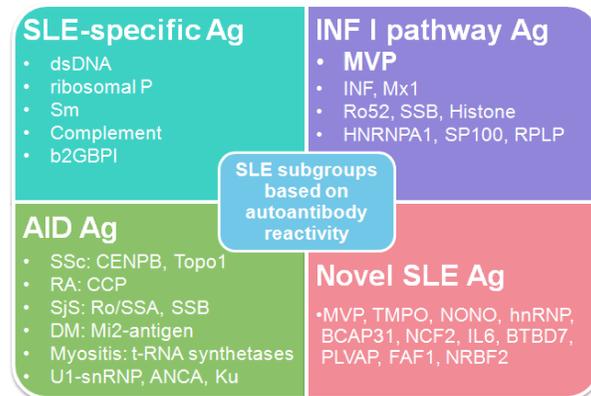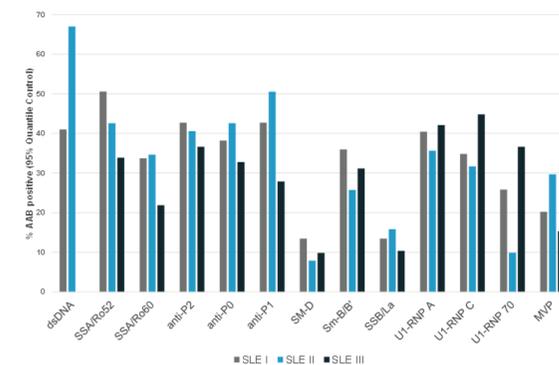

Fig. 1: Multiplex NavigAID SLE 86 Antigen Array

Results

Prevalence of anti-MVP antibodies in SLE

Anti-MVP antibodies occured with frequencies of 15-30% in three different SLE cohorts.

Specificity of anti-MVP antibodies

Anti-MVP antibodies and anti-ribosomal P have comparable sensitivity (23% vs 25%) and specificity (97%) for SLE (Fig. 3).
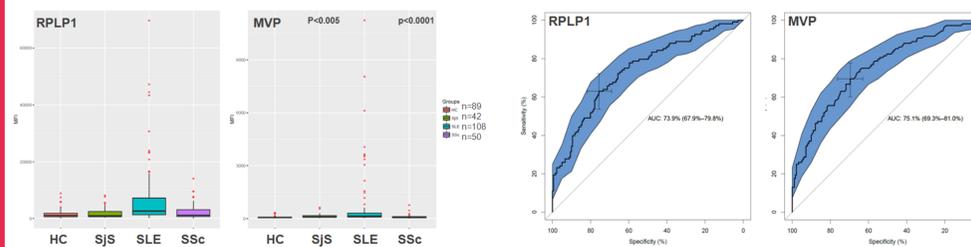

Fig. 3: Specificity of anti-MVP antibodies

Exploratory testing of multi-marker panels including anti-MVP in combination with anti-dsDNA, anti-ribosomal P and anti-SmD yielded a 6% increase in sensitivity at 98% without loss of specificity.

46% sens.
dsDNA
Ribosomal P
SmD

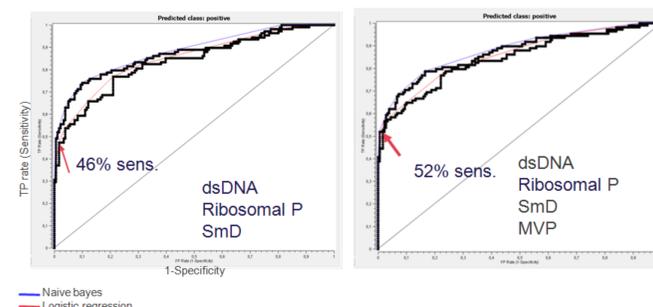52% sens.
dsDNA
Ribosomal P
SmD
MVP

Fig. 4: Exploratory testing of multi-marker panels

Anti-MVP defines a distinct subset of SLE patients

VisRank data visualization was applied to analyze whether anti-MVP in combination with established markers can separate the groups. The RadViz plot in Fig. 5 shows that anti-MVP is detected in a subset of SLE patients with little overlap to other markers.
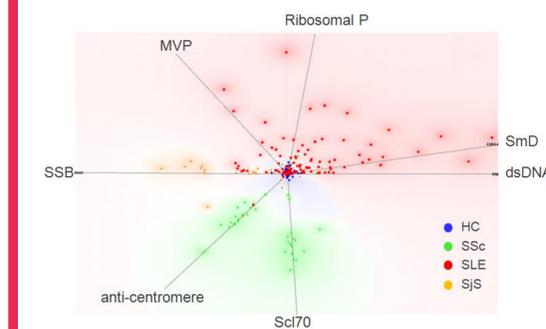

Fig. 5: RadViz projection of samples and groups shown in Fig. 4

Development of anti-MVP prototype ELISA

A bead-based ELISA was developed for measuring anti-MVP antibodies. The performance of the anti-MVP ELISA was asssessed in a small sample set. The Pearson's correlation coefficient of ELISA values with Luminex signal intensities was R=0.88 indicating successful platform transfer.
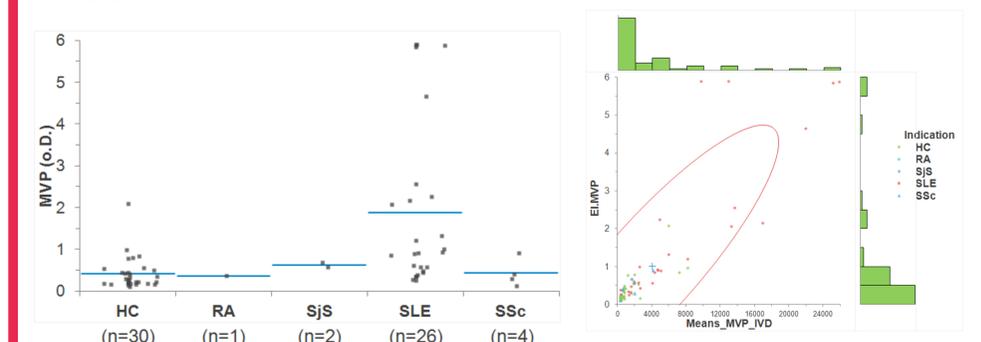

Fig. 3: Performance of anti-MVP ELISA

Conclusions

Anti-MVP autoantibodies represent a useful diagnostic marker in SLE and, in combination with anti-dsDNA, anti-Sm and anti-ribosomal P, optimizes the strategy for autoantibody testing. Furthermore, although more studies are needed, our findings suggest a previously undescribed linkage of type I INF and autoantibody targets in SLE.

(1) Liu S, Hao Q, Peng N, Yue X, Wang Y, Chen Y, et al. Major vault protein: A virus-induced host factor against viral replication through the induction of type-I interferon. Hepatology. 2012;56(1):57–66
(2) Budde P, Zucht H-D, Vordenbaeumen S, Goehler H, Fischer-Betz R, Gamer M, et al. Multiparametric detection of autoantibodies in systemic lupus erythematosus. Lupus. 2016 Jul 1;25(8):812–22