Category :**Respiratory: other**

A49 - ***Modulation of NET release by plasma derived immunoglobulins: Trimodulin (polyvalent IgM, IgA, IgG solution) vs. standard IVIg***

R Zapf [1] ; U Steffen [1] ; F Bohländer [2]

[1]Friedrich-Alexander University (FAU) Erlangen-Nürnberg and Universitätsklinikum Erlangen, Department of Internal Medicine 3 - Rheumatology and Immunology, Erlangen, Germany, [2]Biotest AG, Translational Research, Dreieich, Germany

Introduction:

The release of neutrophil extracellular traps (NETs) represents an important mechanism of pathogen defense by neutrophils. However, in case of dysregulated immune responses (as in severe lung infectious diseases), overwhelming NET formation can be detrimental [1]. Trimodulin is a polyvalent immunoglobulin preparation (~23% IgM, ~21% IgA and ~56% IgG) in development for the treatment of hospitalized patients with severe respiratory tract infections (e.g. sCAP). The immunomodulatory activity of trimodulin on neutrophils was shown *in vitro* and by analysis of clinical trial data [2]. The aim of this study is to investigate if modulation of NET release could be another relevant immunomodulatory mode of action for trimodulin.

Methods:

Neutrophils were isolated from healthy donors and NET release was induced by PMA or immune complexes (heat aggregated IgA or IgG). Trimodulin, IVIg or buffer were added and NET release was measured by cytox green fluorescence intensity. Furthermore end-point measurements of NET markers were performed.

Results:

The addition of trimodulin to PMA- or immune complex stimulated neutrophils leads to a strong dose-dependent reduction of NET release (up to 57% reduction in amount of external DNA compared to untreated control), while standard IVIg has only little effect. Mechanistically trimodulin and standard IVIg seem to condense the NETs, but there are no distinct effects on the measured NET markers.

Conclusion:

The results of this *in vitro* study demonstrate that modulation of NET release may be a viable mode of action for trimodulin, which may be relevant in the treatment of severe lung infectious diseases. The superior immunomodulatory effects of trimodulin on neutrophils could be mediated by the additional IgM and IgA antibodies within trimodulin. Further studies are needed to unravel the mechanism and clinical relevance of these findings.

References:

[1] B. N. Porto and R. T. Stein, *Front. Immunol.*, vol. 7, Aug. 2016

[2] M. Singer *et al.*, *Crit Care*, vol. 27, no. 1, p. 436, Nov. 2023