Sialylation of anti-histone IgG from patients with systemic lupus erythematosus determines their functional capabilities

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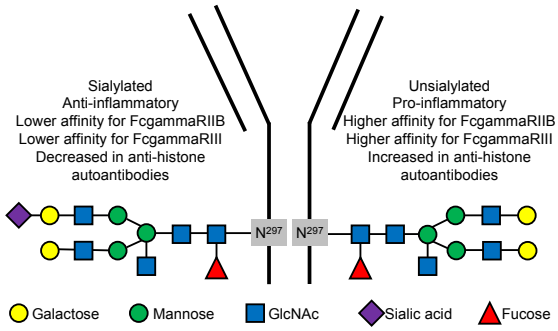
Abstract

The Fc tail of IgG molecules carries a single glycosylation site (Asp-297) as basis for a pleomorphic bi-antennary N-glycan which carries terminal sialic residues. Sialylation of the Fc fragment is critical for the structure and for certain functions of IgG molecules. Various anti-nuclear AAb (e.g. anti-histones) of patients with systemic lupus erythemathosus are reportedly responsible for the recruitment of polymorphonuclear neutrophils (PMN) in the clearance of apoptotic cells process. AAb decorating Secondary NECrotic cells (SNEC) induce pro-inflammatory responses after activation of blood-borne phagocytes. We analyzed the sialylation status of affinity purified anti-histones AAb in patients with SLE and we noticed that anti-histones AAb are preferentially contained in the desialylated fractions. In functional ex vivo phagocytosis studies, desialylated anti-SNEC AAb directed SNEC preferentially into polymorphonuclear cells but did not change the cytokine profile. In contrast, the sialylated IgG fraction reduced the phagocytosis by monocytes of SNEC. Surprisingly, the sialylated anti-SNEC-IgG significantly switched the cytokine profile from IL6/IL8 to TNFα/IL1ß.

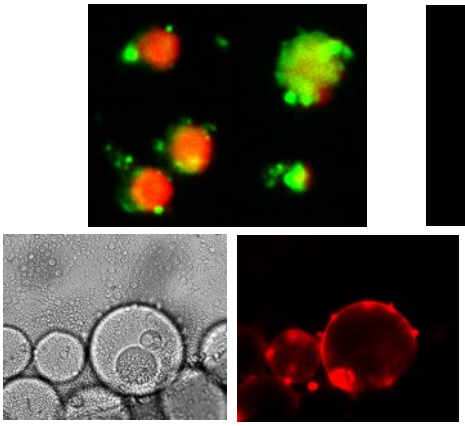
Structure of IgG with a S1-S0 sialylation state



Autoantigens are exposed on SNEC to be recognized by lupus AAb

SNEC-PI
Anti-dsDNA FITC

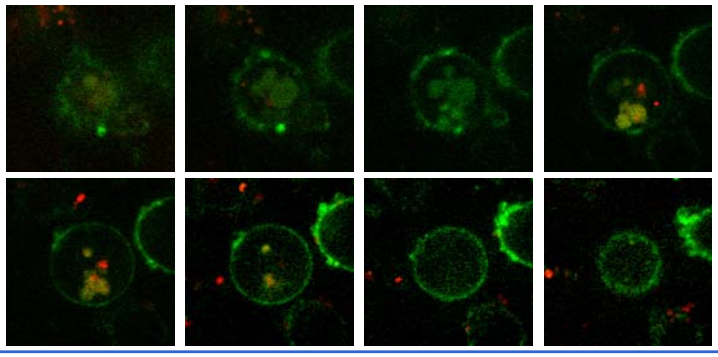
SNEC-PI
Anti- meHistone 3 FITC



SNEC-PI

Anti-dsDNA 33.C9 bound on Sepharose protein G beads

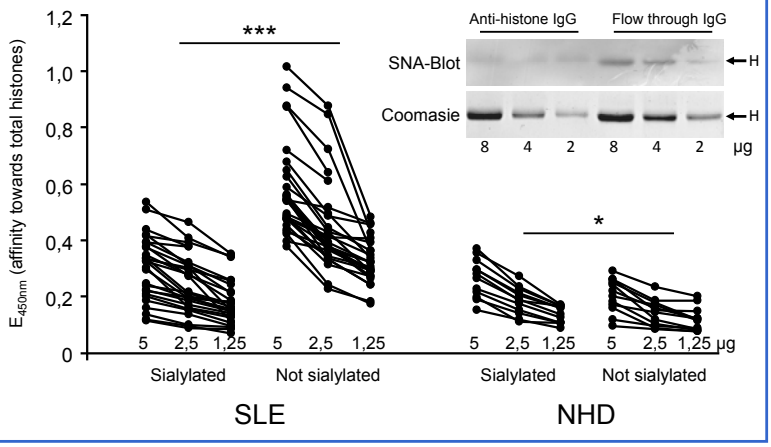
Phagocytosis by patients with SLE **of opsonized-SNEC** in whole blood cultures. Confocal pictures of a Granulocyte (CD16-FITC) which has taken up SNEC (PI)



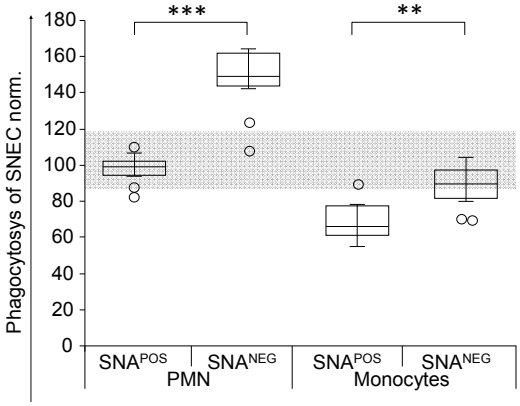
Isolation of anti-histone-IgG and of sialylated/non-sialylated IgG

1: removal of IgM and other serum proteins
2: removal of unspecific IgG

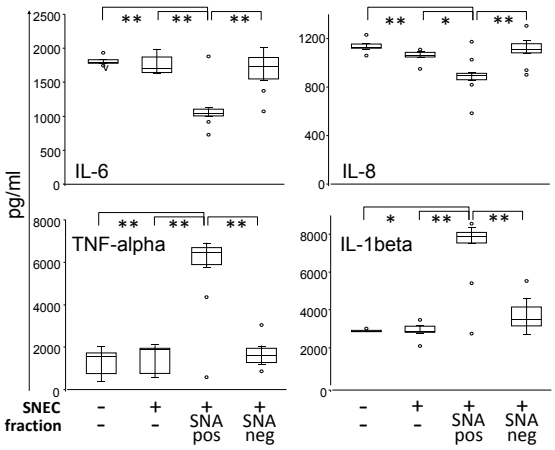
Anti-histone binding of IgG in dependence of its sialylation



Desialylated anti-SNEC-IgG sensitises SNEC for phagocytosis by polymorphonuclear cells (PMN; **p<0.0001), whereas sialylated anti-SNEC-IgG interferes with their uptake by monocytes (p<0.001).**



Sensitization of SNEC by sialylated anti-SNEC-IgG switches the cytokine secretion pattern from IL-6/IL-8 (p<0,01/p<0.05) to IL-1ß/TNF (p<0,01 for both)



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