Background Genetic and epigenetic mechanisms that may contribute to lupus susceptibility in humans and mouse models are of interest especially if they provide enzymes that could function as potential therapeutic targets. We have discovered an enzymatically mediated O-acetylation event found prominently in B cells in humans with lupus and in MRL/+ mice. Detailed studies in MRL/+ mice indicate that this modification may allow for a break in B cell tolerance and may be a major component of lupus susceptibility in these mice as well as possibly in humans as well.

Materials and methods We have used a catalytically dead influenza C hemagglutinin esterase Ig fusion protein and a bovine coronavirus hemagglutinin esterase – Ig fusion protein as tools to respectively identify and remove O-acylated sialic acid on B cells in humans and in MRL/+ mice. Enzymatic approaches were used to identify the type of glycoconjugate that exhibits enhanced O-acetylation of sialic acid moieties. We created a CasD1 knockout mouse to examine the role of this enzyme in O-acetylating sialic acid moieties in vivo. Genetics, whole genome sequencing and RNA-seq approaches are being used to identify the mechanism underlying the lateration and its link to lupus susceptibility.

Results Increased O-acetylation of sialic acid on naive B cells is observed on approximately two-thirds of subjects with active SLE. Markedly increased levels of 9-O-acytlated sialic acid are also observed in the earliest B lineage cells in lupus prone MRL/+ mice and this high level is maintained throughout B cell development and well before these mice exhibit any features of disease. This increased 9-O-acetylation of sialic acid was not observed on glycoproteins or mucins on MRL/+ B cells but was restricted to gangliosides. Acetylated gangliosides protected these B cells from BCR-dependent apoptosis. Deacetylation of sialic acid on MRL/+ B cells restored anti-IgM mediated apoptosis to wild type levels. We used a CasD1 knockout mouse to establish that this enzyme is required for the 9-O-acetylation of sialic acid in vivo. Increased 9-O-acetylation of sialic acid in MRL/+ mice is dominantly inherited and the molecular basis of this striking change is being investigated using genetics and whole genome sequencing.

Conclusions Enhanced 9-O-acetylation of sialic acid on B cells in lupus prone mice and in humans may represent a potential mechanism by which B cell tolerance is abrogated in lupus subjects and in lupus-prone mice. The CasD1 acetyltransferase may be a therapeutic target of relevance in lupus.

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