In combination with BCR signalling, this facilitates survival and maturation of autoreactive B cells that otherwise will be deleted. Identification of the molecular mechanism leading to INFb autocrine stimulation in transitional B cells should unveil new pathways for development of autoreactive B cells.

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1-05 DUAL FUNCTIONS OF TREX1 IN AUTOIMMUNE DISEASES

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Background TREX1 is an endoplasmic reticulum (ER)-associated exonuclease and a critical negative regulator of innate immunity. TREX1 mutations are associated with several autoimmune and autoinflammatory diseases, including Aicardi–Goutières syndrome (AGS), familial chilblain lupus, systemic lupus erythematosus (SLE), and retinal vasculopathy with cerebral leukodystrophy (RVCL). Both DNase-dependent and –independent functions have been described for TREX1 N-terminal DNase domain and C-terminal ER localization domain, respectively. Biallelic mutations abrogating DNase activity cause autoimmunity by allowing immunogenic self-DNA to activate the cGAS-STING-TBK1 signalling pathway leading to type I interferon (IFN) response and autoimmunity.

Methods and results We recently showed that inhibiting TBK1 by a potent small molecule inhibitor, Compound II, was able to ameliorate autoimmune disease phenotypes of Trex1^{-/-} mice, increase mouse survival, and dampen the IFN gene signature in TREX1 mutant patient lymphoblasts. We are also interested in a group of dominant frame-shift (fs) mutations that encode DNaseactive but mislocalized proteins. We found that TREX1 C-terminus suppressed immune activation by interacting with the ER oligosaccharyltransferase (OST) complex and stabilising its catalytic integrity. C-terminal truncation of TREX1 by fs mutations dysregulated the OST complex, leading to free glycan release, immune activation and autoantibody production. Proper glycosylation of proteins in immunity is critical for their function, and protein glycosylation is also important for preventing self-immune recognition and production of autoantibodies. We recently established the TREX1-V235fs knock-in mouse to better understand the disease associated with TREX1-fs mutations.

Conclusion Together, our past and ongoing studies reveal dual functions of TREX1 in regulating self-DNA and self-glycan metabolism, and suggest potential therapeutic targets and options for *TREX1* mutant-associated autoimmune diseases.

1-06 LONG INTERSPERSED NUCLEAR ELEMENT-1 RETROELEMENTS ARE EXPRESSED IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND PRIMARY SJOGREN'S SYNDROME AND INDUCE TYPE I INTERFERON

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Background Recent studies have documented numerous common and several rare genetic variants that are associated with SLE, but the endogenous and exogenous triggers that initiate and perpetuate disease have not yet been defined. The presence of elevated serum type I interferon (IFN-I) activity and a broad signature of IFN-I-induced gene transcripts and proteins in blood and tissue of patients with lupus and other systemic autoimmune diseases, including primary Sjogren's syndrome (SS), are consistent with a viral trigger, but available data have not identified an exogenous virus as an etiologic agent in these diseases. To identify diseaserelevant triggers of the IFN-I pathway we investigated whether endogenous virus-like genomic repeat elements, normally silent, might be expressed in patients with systemic autoimmune disease, activate an innate immune response and induce IFN-I.

Materials and methods Expression of IFN-I and long interspersed nuclear element-1 (LINE-1; L1) was studied in kidney tissue from lupus patients and minor salivary gland (MSG) tissue from patients with primary SS by PCR, western blot and immunohistochemistry. Induction of IFN-I by L1 was investigated by transfection of plasmacytoid dendritic cells (pDCs) or monocytes with an L1-encoding plasmid or L1 RNA. Involvement of innate immune pathways and altered L1 methylation were assessed.

Results L1 mRNA transcripts were increased in lupus nephritis kidneys and in MSG from SS patients and correlated with IFN-I expression. Using bisulfite-PCR pyrosequencing, a negative correlation of L1 expression with% L1 methylation was documented for the majority of L1 promoter CpG sites tested, suggesting that augmented demethylation processes, or alternatively impaired remethylation, might account for the observed L1 overexpression in SS MSG tissues. L1 open reading frame 1/p40 protein and IFN-beta were expressed in MSG ductal epithelial cells and in lupus kidneys, and IFN-alpha was detected in infiltrating pDCs. Transfection of pDCs or monocytes with L1-encoding DNA or RNA or U1 RNA, but not hY3 RNA, induced IFN-I. Inhibition of TLR7/8 reduced L1 induction of IFN-alpha in pDCs, and an inhibitor of IKK-epsilon/TBK1 abrogated induction of IFN-I by L1 RNA in monocytes.

Conclusions L1 genomic repeat elements represent endogenous nucleic acid triggers of the IFN-I pathway in SLE and SS and may contribute to initiation or amplification of autoimmune disease. Investigation of the genetic and environmental factors that alter regulation of L1 elements and increase availability of these endogenous immunostimulatory factors should suggest novel therapeutic interventions in SLE and related diseases.

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