



ORAL PRESENTATION

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# Tracing cellular sources of pathogenic type I-interferon in the $TREX1^{-/-}$ mouse model of lupus like-disease

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## Introduction

Loss of function mutations of the intracellular enzyme 3' repair exonuclease (TREX) 1 cause Aicardi-Goutières syndrome (AGS). As AGS clinically overlaps with systemic lupus erythematosus (SLE) and, like SLE, features a spontaneous activation of the antiviral type I-interferon (IFN) system as well as production of antinuclear autoantibodies, this condition may be considered a monogenic variant of SLE.  $TREX1$ -deficient mice spontaneously develop multi-organ autoimmune disease that is fully dependent on a functional type I-IFN system. This phenotype suggested a new concept of systemic autoimmunity arising from intracellular accumulations of (so far enigmatic) nucleic acid substrates of  $TREX1$ , which trigger chronic antiviral IFN responses and thereby autoimmunity. Nonhematopoietic cells were proposed to be the cellular source of the pathogenic IFN. Uncontrolled activity of endogenous retroelements was suspected to induce the chronic antiviral response.

## Objectives

We sought to identify cell types responsible for the loss of self tolerance and to clarify whether there is a role for endogenous retroelements in the disease of  $TREX1$ -deficient mice.

## Materials and methods

In order to elucidate the role of *Trex1* in the hematopoietic system, lethally irradiated mice were reconstituted with  $TREX1^{-/-}$  fetal liver cells. Furthermore we generated a *Trex1* flox mouse line which was used to specifically delete  $TREX1$  in  $CD11c$ -expressing cells ( $CD11c$ -Cre), in

DCs ( $Clec9a$ -Cre), and in B cells ( $CD19$ -Cre). To test a potential role of retroelements,  $TREX1^{-/-}$  were crossed to transgenic retrotransposition reporter mice and were treated with reverse transcriptase inhibitors.

## Results

While Cre/loxP-mediated conditional inactivation of *Trex1* in various non-hematopoietic compartments did not result in detectable inflammatory disease, selective knock out in the hematopoietic system largely reproduced the  $TREX1^{-/-}$  phenotype. Mice with inactivation of the *Trex1* gene in DCs developed only mild autoimmunity, but featured massive upregulation of interferon stimulated genes suggesting a critical pathogenic role of DCs. Interestingly, selective loss of  $TREX1$  in  $CD19+$  B cells did not result in a detectable activation of the type I-interferon system.

Treatment of  $TREX1^{-/-}$  mice with the reverse transcriptase inhibitor Truvada<sup>®</sup> did not ameliorate the phenotype. Retrotransposition events were not increased in frequency in a  $TREX1^{-/-}$  compared to a wildtype background.

## Conclusion

We demonstrate that specific cell types differentially respond to the loss of  $TREX1$  and show that DCs are an important source of type I IFN in the  $TREX1^{-/-}$  model. Our findings that loss of  $TREX1$  had no impact on *Line1* retrotransposition and that pharmacological inhibition of retrotransposition in vivo did not rescue  $TREX1^{-/-}$  mice from lethality challenges the concept of a pathogenic role of endogenous retroelements in this model.

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