Background Failure to properly dispose of self-DNA can inappropriate trigger anti-viral defense systems, leading to autoimmunity. Indeed, mutations in the DNA exonuclease TREX1 are causative for a spectrum of rare lupus-like autoimmune diseases in humans. These disorders involve triggering of the cytosolic dsDNA sensor cyclic GMP-AMP Synthase (cGAS) and the Stimulator of Interferon Genes (STING), leading to chronic production of the anti-viral cytokine type I interferon (IFN-I) and the development of autoimmunity. Importantly, the exact cells in which the sensing of undegraded DNA and subsequent production of IFN-I occur remain unknown.

Methods We generated a mouse expressing the catalytically inactive TREX1 D18N allele, which causes familial chilblain lupus in humans. We examined anti-viral gene expression and the phenotype of these mice to study the immunological effects of losing TREX1 activity. We performed bone marrow transplants to determine if autoimmune pathogenesis in this model was dependent on hematopoietic or non-hematopoietic cells. Finally, we measured expression of type I interferon in various purified cell populations to identify specific cellular producers contributing to autoimmune pathogenesis.

Results In this study, we demonstrate that TREX1 catalytic inactivity induces IFN-I signaling and lupus-like autoimmunity in a mouse. Moreover, we show that TREX1 deficiency within bone marrow-derived cells causes IFN-I activation and the development of autoimmunity. We provide evidence of spontaneous IFN- production within both innate immune and T cells. T cell IFN-a expression was observed in all T cell populations, but was most enriched within naive T cells. We also demonstrate that D18N T cells express all components of the cGAS-STING pathways and generate IFN-I protein, both spontaneously and in response to small-molecule activation of STING.

Conclusions Our findings demonstrate that TREX1 enzymatic activity is crucial to prevent inappropriate DNA-sensing and IFN-I production. TREX1 inactivity within hematopoietic cells was both necessary and sufficient to induce lupus-like autoimmunity, indicating that TREX1 normally acts within immune cells to suppress inappropriate activation of anti-viral signaling. Both innate immune and T cells respond to TREX1 dysfunction by spontaneously synthesizing IFN-, a surprising result given that T cells are not canonically thought to be major IFN-producing cells. These results expand our understanding of the pathogenesis of lupus-like disease, and indicate that small molecule inhibition of TREX1 could represent an appealing strategy for anti-viral and cancer immune-therapies.

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foetus. As the prevalence of cryptorchidism in male offspring is higher when their mothers are suffering from preeclampsia or gestational diabetes, we aimed to investigate if a similar association exists between maternal SLE and cryptorchidism in the offspring.

**Methods**

Methods: We conducted a nationwide study including all male singleton live births in Denmark from 1995 to 2016. Using the Danish nationwide population based registers, we assessed the occurrence of cryptorchidism according to prenatal disease-state of the mothers (SLE/no SLE). Cryptorchidism was assessed as both any diagnosis of cryptorchidism and diagnosis of cryptorchidism and corrective surgery. Using Cox proportional hazards models we calculated hazard ratios (HRs), accounting for varying age at time of diagnosis, and adjusting for maternal age, smoking during pregnancy, pre-gestational BMI, parity, educational level and ethnicity.

**Results**

Among 6 902 400 boys, 352 boys were born of mothers with pre-existing SLE. Of those, 15 (4.3%) boys were diagnosed with cryptorchidism, and seven boys (1.9%) underwent corrective surgery. We found an adjusted HR of 1.68 (95% CI: 1.01, 2.78) for cryptorchidism and 1.46 (95% CI: 0.69, 3.06) for cryptorchidism with corrective surgery, among boys born by mothers with SLE, compared with unexposed boys. This is consistent with an increased risk of cryptorchidism among the exposed boys, even though the relatively few exposed cases limits the precision of the estimates.

**Conclusions**

Conclusions: Boys exposed to maternal SLE appears to have higher risk of cryptorchidism, compared with unexposed boys.

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### Abstract 287

**AFRICAN AMERICAN SLE PATIENTS WITH VARIABLE DISEASE ACTIVITY REVEAL ALTERATIONS IN SIGNALING PATHWAYS AND SOLUBLE MEDIATORS THAT ARE MORE PRONOUNCED THAN EUROPEAN AMERICAN PATIENTS**

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**Background**

Systemic lupus erythematosus (SLE) is an autoimmune disorder with a variable clinical presentation and periods of waxing and waning disease. Heterogeneity in SLE is influenced by genetic and non-genetic susceptibility found in different ethnicities that drive disease expression and severity. The immune pathways that contribute to heightened disease activity in lupus and immune variation by race are critical to understanding SLE disease mechanisms and outcomes.

**Methods**

Peripheral whole blood samples of European or African American healthy controls (n=18) and SLE patients with either high (SLEDAI4) (n=20) or low (SLEDAI <4) (n=20) disease activity were stimulated for 4 min with either interferon-(IFN), PMA and ionomycin, or Toll-like receptor (TLR) ligands for either TLR4, TLR7/8 or TLR9 for phospho-protein analysis, or 24 hours for cytokine analysis of cell culture supernatants. Phenotype and phospho-protein analysis was assessed by CyTOF and cell heterogeneity was analyzed using t-SNE and manual gating. Soluble mediators were assessed using 37-plex xMAP assays and ELISA. All SLE patients met ACR classification criteria.

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African Americans SLE patients with high disease activity exhibit greater dysregulation in phospho-signaling following stimulation. Peripheral whole blood from either European or African American healthy controls, SLE patients with low disease activity (SLEDAI<4) and SLE patients with high disease activity (SLEDAI≥4) were stimulated for 4 min with either no stimuli, IFNa, PMA and ionomycin, or TLR4, TLR7/8 or TLR9 agonists. Data was collected via mass cytometry, and analyzed using Cytobank. The median 95th percentile was used to calculate the fold change of high disease activity patients compared to controls and/or low disease activity patients in 8 cell population (B cells, CD4+ T cells, CD8+ T cells, dendritic cells (DC), plasmacytoid DCs (pDCs), natural killer (NK) cells, monocytes (mono) and granulocytes (gran). Significant increases or decreases in phosphorylation following stimulation in a particular signaling molecule are noted by a green box (decrease) or a red box (increase). The location of the dot coincides with significant differences found in a cell population (refer to legend). p<0.05