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Hypothesis testing: A role for inflammasome activation in pediatric autoimmune hepatitis

Introduction: An infectious trigger in a genetically susceptible host has been proposed as etiopathogenic in autoimmune hepatitis (AIH). Often formalin-fixed paraffin-embedded liver biopsies (FFPE) are the only hepatic tissues available for pathogenetic investigations but retrieval of mRNA from small biopsies is problematic. Our overall goal was to develop methods to obtain high quality mRNA from FFPE liver biopsies in order to perform unbiased high throughput sequencing of transcriptomes.

Methods: 45 FFPE liver biopsies, 25 from AIH type 1 patients' and 21 from controls were used to generate RNA libraries and analyzed using RNAseq. Total RNA was extracted from two cored tissue samples, cDNA libraries were constructed using the Illumina TruSeq Stranded Total RNA Sample Preparation Kit with Ribo-Zero to remove cytoplasmic and mitochondrial rRNA and indexed paired-end sequencing was performed on an Illumina HiSeq2000 with 90 million paired reads per sample.

Results: There was up-regulation in AIH patients; vs. controls of a number of intrahepatic genes; among these were genes related to B cell development and several consistent with activation of the NLRPEi inflammasome. The approach to further investigating a role of NLRPi inflammasome activation in AIH will be discussed including PCR and immunohistochemistry of liver biopsies and serum ELISA assays for inflammasome components as well as PBMC assays.

Conclusions: Possible therapeutic implications, including monoclonal antibodies against inflammasome components as well as anakinra (anti IL-1), beta hydroxybutyrate and the sulfonyl urea MCC950 which block NLRPEi will be discussed.

Biography

Kathleen B Schwarz was graduated from Washington University School of Medicine, USA. She is a Professor of Pediatrics at the Johns Hopkins University School of Medicine where she is the Director of the Pediatric Liver Center. She is the President of the Federation for International Societies of Pediatric Gastroenterology, Hepatology and Nutrition. She has published more than 165 papers in peer-reviewed journals.