A NOVEL MONOGENIC CAUSE OF NEONATAL INFLAMMATORY BOWEL DISEASE AND IMMUNE DYSREGULATION

nATALIA S. Chaimowitz[1], Justin Branch[2], Bo Yuan[3], Nicholas L Rider[4], Sarah K Nicholas[4], Lina B Karam[5], Kalyani Patel[6], Tiphanie P. Vogel[2]

[1] Baylor College of Medicine, Department of Pediatrics, Immunology, Allergy and Rheumatology

[2] Baylor College of Medicine, Pediatrics, Rheumatology

[3] Baylor College of Medicine, Molecular and Human Genetics, Genetics

[4] Baylor College of Medicine, Pediatrics, Immunology, Allergy and Retrovirology

[5] Baylor College of Medicine, Pediatrics, Gastroenterology

[6] Baylor College of Medicine, Pathology and Immunology, Pathology

Background: IBD is a multifactorial disorder caused by dysregulated immune responses. Children with very-early onset (VEO)-IBD, particularly those with neonatal-IBD, can have debilitating disease. Over 50 monogenic causes of VEO-IBD have been identified to date and a significant number are the result of defects in immunoregulatory genes. A now 16 month-old male born presented at 7 days of life with failure to thrive, bloody diarrhea, leukocytosis and severe thrombocytopenia. Initial intestinal biopsies were consistent with VEO-IBD. Immuno-phenotypically, the patient has decreased numbers of CD8 T cells and increased memory CD4s. He also has decreased class-switched memory B cells and absent transitional B cells. There is a marked increase in serum IgM, with normal IgG, IgA and IgE levels. Exome sequencing was obtained and it demonstrated two variants of unknown clinical significance in the TRAF2 gene, encoding TNF-receptor (TNF-R)-associated factor 2. One variant is absent in general population databases and was not identified in the mother. The other rare variant was inherited from his mother. TRAFs are signaling molecules utilized downstream of immune receptors important in both adaptive and innate immunity. Murine TRAF2-deficiency leads to incomplete embryonic lethality; viable TRAF2-deficient mice develop severe colitis and die prematurely. We hypothesized that patient's phenotype was secondary to TRAF2 deficiency.

Materials/Methods: PBMC were isolated by Ficoll density gradient centrifugation from whole-blood samples obtained from the patient, patient's mother or healthy volunteers. Primary human fibroblasts were obtained from biopsy of patient or healthy control. EBV-B cell lines were obtained from patients and normal donors as previously published. Cells were analyzed for TRAF2 mRNA by RT-PCR and TRAF2 protein by western blot.

Results: Studies of the RNA sample derived from patient's PBMCs detected TRAF2 transcripts encoding both variants. The transcript of p.G10Wfs*70 variant was detectable in PBMCs from the mother. However, Western blot of the patient's PBMCs, fibroblasts and an EBV-transformed B cell line lacked TRAF2. TRAF2 was detected normally in control cells and at reduced levels in maternal samples.

Conclusions: We report a patient with severe immune dysregulation due to a novel monogenic cause of neonatal-IBD, TRAF2-deficiency. Ongoing studies are investigating the mechanisms by which immune dysregulation develops in the absence of human TRAF2.