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Elevated Levels of the Cytokine LIGHT in Pediatric Crohn's Disease

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LIGHT (homologous to lymphotoxins, exhibits inducible expression, and competes with HSV glycoprotein D for herpes virus entry mediator, a receptor expressed by T lymphocytes), encoded by the TNFSF14 gene, is a cytokine belonging to the TNF superfamily. On binding to its receptors, herpes virus entry mediator and lymphotoxin β receptor, it activates inflammatory responses. We conducted this study to determine whether plasma LIGHT levels are elevated in Crohn's disease (CD) in a pediatric population with the aim of nominating this cytokine as a therapeutic target. We used a single-molecule immunoassay to determine the circulating levels of free LIGHT in plasma from pediatric patients with CD in our biobank (n = 183), a panel of healthy pediatric (n = 9) or adult (n = 22) reference samples, and pediatric biobank controls (n = 19). We performed correlational analyses between LIGHT levels and the clinical characteristics of the CD cohort, including age, Montreal classification, family history, medical/surgical therapy, and routine blood test parameters. LIGHT levels were greatly elevated in CD, with an average of 305 versus 32.4 pg/ml for controls from the biobank ($p < 0.0001$). The outside reference samples showed levels of 57 pg/ml in pediatric controls and 55 pg/ml in adults ($p < 0.0001$). We found a statistically significant correlation between white blood cell count and free LIGHT ($p < 0.046$). We conclude that free, soluble LIGHT is increased 5- to 10-fold in pediatric CD across an array of disease subtypes and characteristics. ***The Journal of Immunology*****, 2023, 210: 590–594.**

Crohn's disease (CD) is a condition of the gastrointestinal (GI) tract in which the immune system undergoes an inappropriate, destructive inflammatory reaction with incompletely understood genetic and environmental causes (1). In contrast with the other major type of inflammatory bowel disease (IBD), ulcerative colitis (UC), CD lesions can occur at any point in the digestive system from mouth to anus, although the terminal ileum of the small bowel and the colon are most frequently affected. Worrisome complications of CD include a deep, full-thickness inflammation of the bowel, with possible stricturing or fistulization, as well as lesions around the anus that can be painful and infected. In addition to frequent diarrhea and abdominal pain, malabsorption can result in delayed growth and development in the pediatric population (2).

An ongoing challenge in this disease is that CD tends to progress over the lifespan despite the use of the best currently available treatments. The mainstay of therapy for CD is immunosuppression, frequently with neutralizing mAbs to TNF. Other biologics in use include ustekinumab, a blocker of IL-12 and IL-23, and vedolizumab, an Ab to integrin $\alpha_4\beta_7$. Nonbiologic drugs include salicylates, thiopurines, and corticosteroids, all of which act to reduce inflammation. Frequently, surgery is required to resect ileum or other lesions in the GI tract. However, due to their partial efficacy, new treatments are seriously needed.

In our efforts to develop new therapies, our attention was drawn to a TNF superfamily cytokine known as LIGHT (homologous to *l*ymphotoxins, exhibits *i*nducible expression, and competes with HSV *g*lycoprotein D for *h*erpes virus entry mediator [HVEM], a receptor expressed by *T* lymphocytes), or HVEM-L (*TNFSF14*). LIGHT activates TNFR superfamily members, namely, HVEM (*TNFRSF14*) (3) and lymphotoxin β receptor (*LTBR*) (4). LIGHT is inactivated by Decoy Receptor 3 (*TNFRSF6B*), a secreted, nonsignaling TNF superfamily receptor (5). LIGHT is highly expressed on T cells and dendritic cells, and to a lesser extent on macrophages and granulocytes. There are also specialized populations of epithelial cells or fibroblasts in liver and lung that express LIGHT (6). The receptor HVEM is widely expressed, with enrichment in all hematopoietic cells and in the digestive system (6). LTBR is highly expressed in macrophages, dendritic cells, fibroblasts, and epithelial cells, but it is absent from lymphocytes (6).

This network of ligands and receptors regulates innate and adaptive immune responses systemically and in the mucosa of the gut. Like other TNFRs, HVEM and LTBR signal through scaffold proteins of the TNFR-associated factor family, leading to activation of the NF-κB and MAPK pathways (7). Activation of these signaling pathways in cells of the immune system results in cell survival, differentiation, and effector functions, such as cytokine release and cytolytic activity (8). It is therefore logical that elevated levels of LIGHT might enhance inflammatory processes in CD.

Our interest in this pathway was aroused by the very strong associations observed in genome-wide association studies (GWASs) of

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C.J.C., D.J.A., F.D.M., J.A.C., X.W., C.K., and P.M.A.S. collected and analyzed data. C.J.C. wrote the paper. H.H. supervised the study and obtained funding. All authors reviewed and approved the study.

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Abbreviations used in this article: CD, Crohn's disease; GI, gastrointestinal; GWAS, genome-wide association study; HVEM, herpes virus entry mediator; IBD, inflammatory bowel disease; LIGHT, homologous to *l*ymphotoxins, exhibits *i*nducible expression, and competes with HSV *g*lycoprotein D for *h*erpes virus entry mediator, a receptor expressed by *T* lymphocytes; LTBR, lymphotoxin β receptor; UC, ulcerative colitis.

CD and IBD, in which the TNF superfamily genes played a leading role (9, 10). LIGHT itself was not among the 240 loci described in IBD GWASs, although interacting partners HVEM, LTBR, and DcR3 were associated. However, LIGHT does show GWAS association with multiple sclerosis, where it is one of the strongest signals aside from the HLA locus (11).

The numerous genetic signals for this network in IBD suggest that an mAb that inhibits LIGHT's signaling to HVEM and LTBR would have beneficial immunomodulatory effects. We therefore sought to establish whether circulating levels of free LIGHT are elevated in CD patients. The cytokine is free in the sense that its transmembrane domain has been cleaved, resulting in a soluble ligand. We expect that this free level is a proxy of LIGHT's ability to stimulate immune responses.

There is limited information from prior studies about serum levels of LIGHT in CD due to the fact that it is often absent from multiplex cytokine panels or is below the limit of detection for most of the technology in use. One study in pediatric CD used sensitive assays to show that elevated LIGHT levels were predictive of reduced progression from inflammatory disease behavior to penetrating disease behavior (12). Other studies of serum LIGHT levels have examined UC. Moraes et al. (13) found that LIGHT was increased in UC compared with healthy control serum. Mavroudis et al. (14) also found elevations of LIGHT in UC patients compared with control subjects, with early UC showing higher levels than late UC. By contrast, Andersson et al. (15) reported that LIGHT is reduced in both CD and UC patients versus healthy control subjects.

In light of these discrepant studies, we conducted our own biobank-based survey for LIGHT levels in pediatric CD. Our aim is to test the hypothesis that LIGHT levels are elevated in CD and are correlated with disease subtypes and characteristics. Elevated LIGHT levels could suggest that LIGHT-blocking therapeutics would be beneficial in CD. We found that pediatric CD patients have LIGHT levels that are 5- to 10-fold higher than reference controls, but that the increased LIGHT level is consistent across different disease activities, locations, and therapies.

Materials and Methods

Design

Reference samples of pediatric and adult plasma were obtained from BioIVT (Westbury, NY) to match the age, sex, and race composition of the CD cohort. The CD patients ($n = 183$) and pediatric control subjects ($n = 19$) were recruited through the Center for Applied Genomics as part of its pediatric biobank program. All subjects were <18 y old at the time of sample collection. The CD cases were diagnosed by pediatric gastroenterologists at the Children's Hospital of Philadelphia using standard criteria (16), including physical symptoms, radiologic studies, endoscopy, and tissue biopsies. The cohort was assembled from the biobank using queries of the deidentified electronic medical record (Epic) and research intake survey to select individuals with frozen plasma samples available. Surveys that included self-reported complaints of CD or IBD were selected for further confirmation. Subjects with International Classification of Disease-10 codes in the Epic record of "K50," the category of CD, were also selected for further confirmation.

In addition to queries of discrete fields in the Epic record, a genetic counselor (D.J.A.) reviewed clinical notes including gastroenterology visits, discharge summaries, and biopsy/endoscopy reports to ascertain the subgroups of the disease cohort. We excluded biobank subjects flagged by these searches who had indeterminate colitis, UC, celiac disease, eosinophilic esophagitis, or other conditions that had been evaluated for CD but were later reclassified.

LIGHT immunoassay

The plasma samples were collected between 2006 and 2018 and were kept at −80°C. Free LIGHT was determined using single-molecule array immunoassay (Simoa) technology from Quanterix. The assays were performed in an outside services laboratory (Myriad RBM, Austin, TX). In brief, LIGHT was captured by Ab immobilized on magnetic beads followed by a biotinylated detection Ab. The beads were washed and incubated with streptavidin–β-galactosidase. The beads were loaded on the Simoa disc and incubated with the fluorescent enzyme substrate, and the disc was imaged with fluorescent optics. In this method, the number of positive beads, rather than the intensity of the fluorescence, is used to determine the level of free LIGHT compared with recombinant standards, resulting in high sensitivity and wide dynamic range (0.8–4000 pg/ml).

Statistics

The clinical characteristics and LIGHT levels of the CD cohort were tabulated in a spreadsheet and in Prism 9 (GraphPad Software). The comparison between cases and control subjects (Fig. 1) was by the nonparametric Kruskal–Wallis test with Dunn's post hoc multiple comparisons tests, because the LIGHT levels are not normally distributed. In Fig. 2, for continuous variables (WBC levels, age at sample collection, age at diagnosis, and C-reactive protein), a simple linear regression was computed, followed with an F test of the null hypothesis that the slope of the regression line is zero. For categorical variables (sex, biologic therapy, surgery, disease location/behavior, and family history), the nonparametric Mann–Whitney U test (for two-class comparisons) or Kruskal–Wallis test (for multiclass comparisons) was used to compare groups.

Ethics approval and consent

Patient, parents, and family members gave written informed consent for the study. The research was performed in accordance with regulations and guidelines of the Declaration of Helsinki. Ethical approval for the study was granted by the Children's Hospital of Philadelphia's Committees for the Protection of Human Subjects Institutional Review Board 004886.

Data availability

Data are available on request of the corresponding author.

Results

We identified a group of 183 CD patients with available plasma samples from the general-purpose pediatric biobank of the Center for Applied Genomics of the Children's Hospital of Philadelphia, consisting of >80,000 enrolled subjects. All patients had been diagnosed and treated at this hospital with regular follow-up. Summary statistics on the clinical makeup of the cohort are given in Table I. This population has high rates of surgery and biologic therapy use, as would be expected for a tertiary referral hospital with a specialized program in IBD. The cases are 80% Caucasian with approximately equal male and female subjects. These samples were tested along with 19 control plasma samples from the biobank, 9 purchased pediatric reference samples, and 22 purchased adult reference samples at the Myriad RBM services laboratory using a custom Simoa single-molecule immunoassay (Quanterix). The CD patients exhibited an average free LIGHT level of 305 pg/ml, in comparison with the biobank controls, which averaged 32.4 pg/ml ($p < 0.0001$) (Fig. 1). The adult and pediatric reference samples were very similar, with average LIGHT levels of 55 and 57 pg/ml, respectively. In our sample, 83% of CD subjects had LIGHT levels two SDs more than the average of the pediatric reference samples (>128 pg/ml).

We investigated the relationship between the clinical characteristics of the patients and the level of free LIGHT. These parameters included age, sex, disease behavior/location according to the Montreal classification, family history, and history of surgery or biologic therapy. The only significantly nonzero correlation was found with the WBC count, showing a modest increase with higher LIGHT levels ($p < 0.046$) (Fig. 2). Samples were collected independently of current disease activity, duration of illness, or treatment with anti-inflammatory agents. The level of free LIGHT in our samples remained stable over the 12-y range of frozen storage (Fig. 3).

Discussion

The presence of high levels of free LIGHT in comparison with the healthy population, combined with genetic associations between

Table I. Summary statistics of the pediatric CD cohort compared with pediatric controls

Parameter	Cases (SD)	Outside Controls (SD)	*p*	Biobank Controls (SD)	*p*
n	183	9		19	
Age at sample collection, y	14.6 (4.0)	13.3 (1.9)	0.33	8.2 (5.2)	*<0.0001*
Age at diagnosis, y	11.4 (3.8)				
Sex, % male	57%	67%	0.30	58%	0.97
Family history (first degree)	20%				
Race					
White/Caucasian	80.3%	67%	0.32	53%	*0.0058*
African American	12.6%	33%	0.076	26%	0.099
Mixed or non-white/non-African	7.1%	0%	*0.041*	21%	*0.037*
Location (Montreal)					
Upper GI involvement	74%				
Ileal only	17%				
Ileocolonic	73%				
Colon only	12%				
Behavior (Montreal)					
Nonstricturing, nonpenetrating	53%				
Stricturing	33%				
Penetrating	28%				
Perianal involvement	27%				
Treatment					
Surgery	31%				
Biologic drug	67%				
LIGHT level, pg/ml	305 (210)	57.1 (35.4)	*<0.0001*	32.4 (11.4)	*<0.0001*

Italics show the statistically significant *p* value

polymorphisms in the TNF superfamily genes and disease status, supports the hypothesis that this cytokine plays a role in the pathogenesis of pediatric CD.

The results are consistent with a model that serum LIGHT levels are increased in pediatric CD, but that subtypes of disease location and behavior are not associated. These findings may be related to certain limitations of this study. The samples originate from a biobank and were collected from a heterogeneous population with different durations of illness, disease progression, and therapy at the time of sample collection. As biobank specimens, the phenotypic data are inferred from the medical record and validated through chart review, but they were not collected according to a standard format for prospective research studies. The lack of uniformity may lead to subgroups of CD not showing associations with LIGHT levels. However, if the lack of relationship with disease subgroups holds true, a hypothetical explanation is that LIGHT levels are highly dynamic, with a high degree of variation within an elevated range, as is seen with diabetic blood glucose levels. Our biobank control population skewed somewhat younger and more diverse than the CD cases (Table I), but because LIGHT levels do not seem to correlate with age or race (Fig. 2), it is unlikely to be contributory to the difference we observed.

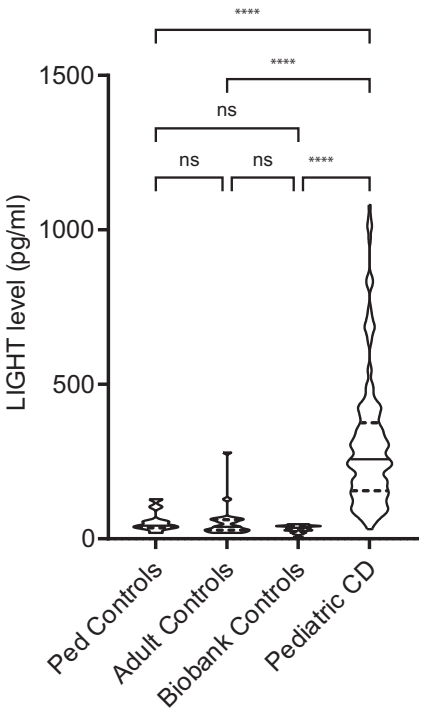

FIGURE 1. Levels of free LIGHT cytokine are elevated in pediatric CD patients ($n = 183$) compared with a panel of purchased healthy pediatric reference samples ($n = 9$), purchased healthy adult reference samples ($n = 22$), and pediatric controls from the source biobank ($n = 19$). Levels were determined by Simoa single-molecule immunoassay on preserved plasma samples from a hospital research biobank and displayed as a violin plot. Horizontal lines in the "violins" indicate the 25th, 50th, and 75th percentiles. Due to the data not being normally distributed, we performed a nonparametric Kruskal–Wallis test with Dunn's post hoc multiple comparisons tests (****$p < 0.0001$).

Elevated levels of LIGHT have been found in other immune-mediated diseases, including sepsis-induced multiorgan injuries and acute respiratory distress syndrome (2-fold increase over healthy control plasma) (17), pulmonary arterial hypertension (3-fold) (18), renal cell carcinoma (19), adenoviral pneumonia (16-fold) (20), aneurysmal subarachnoid hemorrhage (2.5-fold) (21), glioblastoma (22), obesity (2.7-fold) (23), infantile colic (24), adverse cardiovascular events in atherosclerosis (25), bone disease in multiple myeloma (26), pre-eclampsia of pregnancy (27), among others. This study shows a 5- to 10-fold increase, which is a stronger effect than those previously reported. The ~300 pg/ml level of LIGHT measured in our CD subjects is much higher than the absolute levels reported in the earlier studies, but differences in assay technology limit the ability to make direct comparisons.

In the TNBS and dextran sulfate models of colitis in mice, neutralization of LIGHT reduced inflammation and promoted healing (28, 29). Transgenic mice expressing LIGHT on T cells had increased intestinal inflammation (30), but conversely, mice lacking LIGHT also show greater susceptibility to colitis (31, 32). Using single-cell RNA sequencing, Kinchen et al. (33) identified a population of colon mesenchymal cells (e.g., fibroblasts) that upregulated expression of LIGHT in response to experimental colitis in mice and in samples from human IBD patients, leading to increased disease.

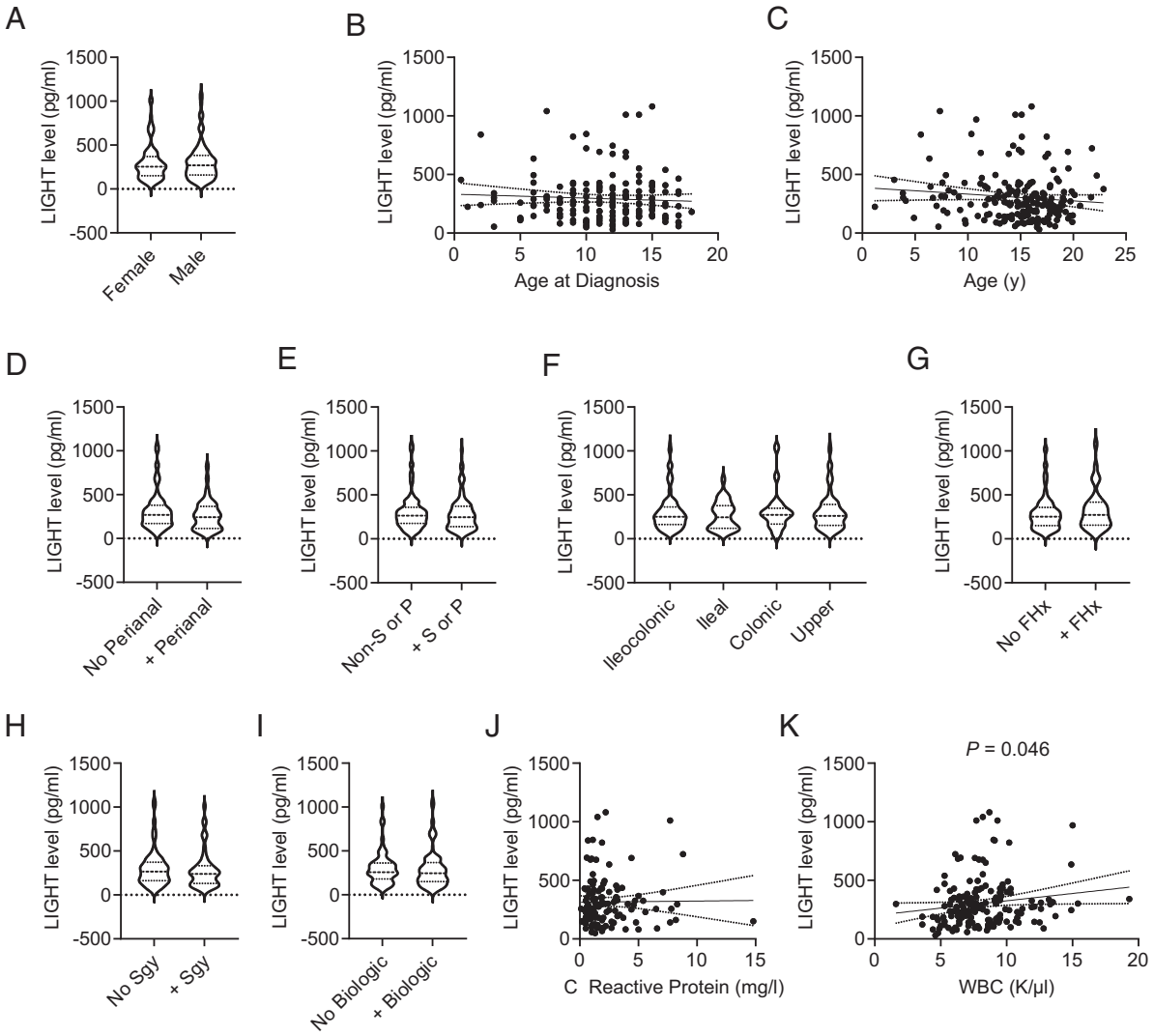

FIGURE 2. Plasma-free LIGHT levels are stable in CD patients ($n = 183$) across a wide range of phenotypes. Violin plots are displayed of the LIGHT level in different clinical parameters, including (**A**) sex, (**B**) age at diagnosis, (**C**) age of subject at sample collection, (**D**) presence of perianal involvement, (**E**) presence of structuring or penetrating disease behavior, (**F**) disease location, (**G**) presence of family history in a first-degree relative, (**H**) history of surgery for CD, (**I**) history of biologic therapy with infliximab or adalimumab, (**J**) level of C-reactive protein within 6 mo of sample collection (mg/l), and (**K**) WBC count on hemogram. Null hypothesis tests were nonsignificant, except that the slope of the regression line of WBC versus LIGHT was significantly nonzero ($p = 0.046$ by F test).

LIGHT plays a role in other cell types and organ systems. LIGHT can signal to HVEM expressed in keratinocytes to cause dermal hyperplasia, proliferation, and inflammation in a mouse model of atopic dermatitis (34). LIGHT expressed in pancreatic islets exacerbates type 2 diabetes by promoting inflammation and vascular endothelial activation leading to enhanced permeability (35). Thus, increased infiltration of leukocytes from activated vascular endothelium could contribute to inflammation in CD. That study also showed that plasma LIGHT levels are strongly impacted by release of LIGHT from activated platelets, another possible connection with CD. In a study of colon cancer, LIGHT expression by tumor cells increased T cell proliferation, activation, and infiltration, resulting in immune-mediated tumor regression (36). Collectively, these findings show that LIGHT signaling enhances inflammation in the gut, and this is corroborated by our observation of high LIGHT levels in CD patient plasma.

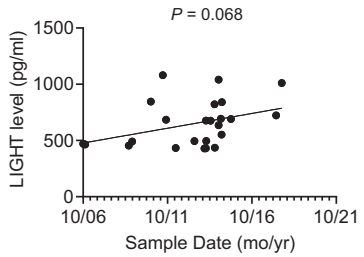

FIGURE 3. LIGHT levels show a modest decline in older samples, as shown by the collection dates of the 25 highest LIGHT levels measured in the cohort. The x-axis is the date of collection (month/year), and the p value is for the F test of the null hypothesis that the slope is zero. The degradation of samples with time was not statistically significant.

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Disclosures

C.J.C., C.K., P.M.A.S., and H.H. are inventors on a patent licensed by Cerecor Inc/Avalo Therapeutics. H.H. and the Children's Hospital of Philadelphia own stock in Avalo Therapeutics. The other authors have no financial conflicts of interest.

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