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LIGHT Expression by Mucosal T Cells May Regulate IFN-γ Expression in the Intestine

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The TNF superfamily of cytokines play an important role in T cell activation and inflammation. Sustained expression of lymphotixin-like inducible protein that competes with glycoprotein D for binding herpesvirus entry mediator on T cells (LIGHT) (TNFSF14) causes a pathological intestinal inflammation when constitutively expressed by mouse T cells. In this study, we characterized LIGHT expression on activated human T cell subsets in vitro and demonstrated a direct proinflammatory effect on regulation of IFN-γ. LIGHT was induced in memory CD45RO CD4+ T cells and by IFN-γ-producing CD4+ T cells. Kinetic analysis indicated rapid induction of LIGHT by human lamina propria T cells, reaching maximal levels by 2–6 h, whereas peripheral blood or lymph node-derived T cells required 24 h. Further analysis of intestinal specimens from a 41 patient cohort by flow cytometry indicated membrane LIGHT induction to higher peak levels in lamina propria T cells from the small bowel or rectum but not colon, when compared with lymph node or peripheral blood. Independent stimulation of the LIGHT receptor, herpesvirus entry mediator, induced IFN-γ production in lamina propria T cells, while blocking LIGHT inhibited CD2-dependent induction of IFN-γ synthesis, indicating a role for LIGHT in the regulation of IFN-γ and as a putative mediator of proinflammatory T-T interactions in the intestinal mucosa. Taken together, these findings suggest LIGHT-herpesvirus entry mediator mediated signaling as an important immune regulatory mechanism in mucosal inflammatory responses. The Journal of Immunology, 2004, 173: 251–258.

The TNFR ligand family has a critical signaling role in mammalian biology, especially in the development and regulation of the immune system (1), by controlling cell death and survival decisions (2). Significant evidence indicates that altered regulation of some TNF-related cytokines is linked to autoimmune diseases (3). For instance, deficiency of the proapoptotic Fas-Fas ligand pathway leads to autoimmune proliferative disease in humans and mice (4), whereas overexpression of the mature B cell survival factor, B cell-activating factor belonging to the TNF family, is associated with lupus nephritis in humans and mice (5). In mice, transgenic expression of lymphotixin-like inducible protein that competes with glycoprotein D for binding herpesvirus entry mediator on T cells (LIGHT) (3) (TNFSF14) by T cells induced severe intestinal inflammation with autoimmune-like pathology, suggesting a specific linkage of LIGHT-mediated signaling to the intestinal compartment (6, 7).

Like other TNF-related ligands, LIGHT is a type II membrane protein that forms a biologically active homotrimer (8), which can be cleaved into a soluble form (9) or exist in an intracellular form encoded by an alternate spliced mRNA, which deletes the transmembrane region and is thus not displayed on the cell surface (10). LIGHT signals via two members of the TNFR family, herpesvirus entry mediator (HVEM, TNFRSF14) (8), and lymphotoxin (LT) βR (TNFRSF3) which binds the LTαβ heterotrimer involved in the development and organization of peripheral lymphoid tissue (11). In addition, LIGHT binds DcR3 (TNFRSF6B), a soluble receptor (12). The LTβR is found on myeloid and stromal cells, whereas HVEM is expressed prominently on lymphocytes, which do not express the LTβR (13). LIGHT is expressed in the lymphoid compartment by activated T cells, but also by monocytes (8), and is likely to play an important immunomodulatory role mediating stimulatory T-T interactions via HVEM, since HVEM engagement constitutes a costimulatory signal augmenting proinflammatory cytokine production and T cell proliferation (14). Genetic deficiency of mouse LIGHT gene further demonstrated the significance of LIGHT to immune regulation (15–17). LIGHT–− mice have normal lymphoid cell development, but demonstrate a defect in CD8+ T cell response to Ag and compromised CD8+ T cell differentiation (16). In addition, inhibition of the LTβR signaling pathway with a LTβR-Fc chimera decoy receptor alleviated inflammatory symptoms in the CD4+CD45RBhigh T cell transfer model of colitis, suggesting a contribution from LIGHT in this CD4+ T cell-mediated pathology (6, 18). Moreover, the human LIGHT locus is closely linked to the TNF family members, CD27 ligand (CD70, TNFSF7) and 4-1BB ligand (TNFSF9), within the MHC paralogous region on chromosome 19p13.3 (10). This region on chromosome 19 has been identified as a candidate susceptibility locus for Crohn’s disease (CD) (19), providing additional circumstantial evidence of a role for LIGHT in intestinal inflammatory diseases.

CD and ulcerative colitis (UC) are inflammatory bowel diseases (IBD), consequential to a dysregulated mucosal inflammatory response (20). The intestinal immune compartment is differentially regulated and its antigenic repertoire is independently shaped to accommodate the heavy antigenic load characteristic of the gut.

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3 Abbreviations used in this paper: LIGHT, lymphotoxin-like inducible protein that competes with glycoprotein D for binding herpesvirus entry mediator on T cells; IBD, inflammatory bowel disease; CD, Crohn’s disease; UC, ulcerative colitis; LP, lamina propria; LPL, LP lymphocyte; P/I, PMA and ionomycin, L/T, lymphotoxin, HVEM, herpesvirus entry mediator; LPMC LP mononuclear cell; PB, peripheral blood.
LIGHT EXPRESSION ON MUCOSAL T CELLS

LIGHT is a member of the TNF superfamily that can mediate T-T interactions, augmenting CD2-mediated IFN-γ synthesis by intestinal T cells. Anti-LIGHT Ab was used at 20 μg/ml in blocking experiments and IFN-γ production in vitro was assessed. Real-time RT-PCR was performed to quantify LIGHT expression in various tissues and cell lines. The results demonstrated that LIGHT expression is consistently mediated by intestinal T cells. Additionally, LIGHT may be expressed by specific T cell subsets in peripheral blood (PB) and in the mucosal compartment, as evidenced by flow cytometry and real-time RT-PCR.
activated II-23 T cells (4 h; right panel) were incubated with 5 μg/ml Gem1A.1 (solid line) or isotype control (dashed line), and binding was detected with goat anti-mouse κ chain-PE and analyzed by flow cytometry.

Flow cytometric analysis of LIGHT on activated T cells indicated a wide range of expression levels for individual CD4⁺ T cells (Fig. 2). We, therefore, tested whether LIGHT expression was associated with known CD4⁺ subsets. The expression of CD45RO is an indicator of previous Ag exposure and mature effector CD4⁺ T cell phenotype, whereas CD45RA defines a naive population (36). LIGHT expression was significantly higher (and almost exclusive) in the CD4⁺/CD45RO subset when compared with the CD4⁺/CD45RA cell subset (Fig. 3A). Moreover, LIGHT expression on CD4⁺/CD45RO T cells was as high as CD8⁺ T cells (Figs. 2 and 4). These observations indicate that a subset of CD4⁺ T cells is able to attain a high level of LIGHT expression previously believed exclusive to CD8⁺ T cells (37). Another study (38) indicated that non-naive T cells expressed intracellular LIGHT but did not distinguish which isoform of LIGHT was detected (10).

Up-regulation of the transmembrane isoform of LIGHT was validated at the mRNA level by quantitative real-time RT-PCR analysis using a specific primer probe set in highly purified (flow sorted to >99% purity) CD45RO or CD45RA preparations of CD4⁺ T cells. Marginal levels of LIGHT mRNA were detected in activated CD4⁺ CD45RA T cells, while significantly higher levels were detected in the activated CD45RO subset (~8- to 10-fold more LIGHT mRNA per cell), directly correlating with membrane LIGHT protein expression in these cell subsets (Fig. 3B). Interestingly, LIGHT mRNA encoding the transmembrane domain was never detected in resting T cells (Figs. 2C and 3B), suggesting that intracellular LIGHT protein reported in those cells (37, 38) could be an isotype lacking that domain, although variant LIGHT mRNA was not consistently detected in our system (10).

Mature CD4⁺/CD45RO T cells are more responsive to activating stimuli, and LIGHT expression in this subset could reflect enhanced responsiveness rather than the state of differentiation. In accord, we tested for LIGHT correlation with T cell activation as marked by up-regulation of surface markers OX40 (CD134) and CD40L (CD154) (39, 40). PBL were surface stained for CD4/8, LIGHT, and OX40 or CD40L following P/I activation, indicating higher LIGHT expression levels in CD4⁺ T cells expressing OX40 (Fig. 4A) or CD40L (Fig. 4B). However, LIGHT up-regulation only partially tracked with cells expressing OX40 or CD40L, and significant LIGHT expression was detected in cells lacking the OX40 and CD40L, thus suggesting that LIGHT expression is governed by factors independent of individual cell responsiveness.

LIGHT-HVEM signals can enhance IFN-γ production by T cells (41) and could be a key mediator of T-T interaction driving...
a proinflammatory Th1 response (36). We, therefore, examined whether LIGHT is preferentially expressed by Th1 CD4+ T cells defined by IFN-γ expression. IFN-γ production was analyzed by intracellular staining following activation by P/I in the presence of brefeldin A. Multiparameter analysis of LIGHT expression in the CD3, CD4, or CD8 T cell subsets indicated LIGHT was primarily coexpressed by IFN-γ+ T cells, with an almost exclusive expression of LIGHT in the IFN-γ-producing subset of CD4+ T cells (Fig. 5A). Consistent LIGHT-IFN-γ coexpression in pure T cell preparations (>99%) precluded a contribution from a secondary cell type as an underlying mechanism (Fig. 5B).

**LIGHT exhibits a unique expression profile in the mucosal compartment**

The human intestinal mucosa may be a primary site for LIGHT-mediated proinflammatory activity. The expression profile of LIGHT was examined on T cells derived from the human intestinal immune compartment including the mesenteric lymph nodes or the LP of the rectum, colon, and the small bowel. The time course of LIGHT induction following P/I activation of CD4+ or CD8+ T cells from these tissues revealed a rapid induction of LIGHT on LP T cells, reaching maximal cell surface levels by 6 h on cells from the colon or 1–2 h in the rectum or small bowel (Fig. 6, C and D). By contrast, LIGHT induction on donor-matched T cells from PB or mesenteric lymph nodes was slower and linear for up to 24 h (Fig. 6, A and B) (37). LIGHT induction was confirmed at the mRNA level, although the time course of induction did not differ significantly between intestinal LP lymphocytes (LPL) and lymph nodes or PBL preparations, all peaking by 1 h (data not shown), suggesting that posttranscriptional mechanisms can control LIGHT expression.

Interestingly, although rapid induction of LIGHT was shared by LP T cells from all intestinal sites tested, protein levels were only induced to significantly higher peak levels in LP CD4+ and CD8+ T cells from the small bowel or the rectum, but not the colon when compared with lymph node or PB T cells (Fig. 7A). Most striking was the high peak levels of LIGHT in the CD4+ subset from the small bowel or rectum, reaching levels as high as typically seen in PB CD8+ or CD4+/CD45RO T cells (Figs. 2, 3, and 7).

The relatively rapid time course of LIGHT induction by mucosal T cells suggested that increased expression may lead to enhanced signaling activity in the gut and thus serve as a correlate for disease activity. Accordingly, we examined whether LIGHT expression levels correlated with differences in T cell activation characteristics between gut location and disease state. LIGHT expression on in vitro-activated T cells was analyzed by surface staining of activation markers OX40 and CD40L on CD4+ but not CD8+ T cells. PBMC were activated in vitro with P/I for 16 h and surface stained with anti-LIGHT Ab (shaded) or isotype control Ab (unshaded), anti-CD4/8 and anti-OX40, or anti-CD40L. Lymphocyte-gated CD4+ or CD8+ histograms are shown for A (OX40) and B (CD40L).
LIGHT regulation by intestinal T cells is placitated given their distinctively rapid induction profile and higher peak levels, although the in vitro-induced LIGHT peak levels may not reflect disease state or tissue involvement.

**LIGHT-HVEM regulates IFN-γ production as a component of CD2-mediated activation**

CD2 responsiveness has been proposed as a unique character of LP T cells (42), providing a gut-specific mechanism of IFN-γ activation (43). We investigated whether LIGHT can contribute to intestinal inflammation by augmenting LP T cell production of IFN-γ in the context of CD2-mediated activation. Isolated human LPL were activated in vitro with anti-CD2 cross-linking or P/I in the presence of a blocking anti-LIGHT or isotype control Abs, and secreted IFN-γ was measured in culture supernatants by ELISA (Fig. 8A). Activation with anti-CD2 stimulation induced modest amounts of IFN-γ; however, those levels were significantly reduced in the presence of LIGHT-blocking Abs, although variation was seen between donors (0–45% inhibition for 12 intestinal samples tested). Costimulation by anti-CD28 Abs induced maximal IFN-γ production and abrogated anti-LIGHT inhibition of CD2-mediated IFN-γ synthesis (Fig. 8A).

Interestingly, IFN-γ production was induced by cultured LPL stimulated with recombinant soluble human LIGHT (LIGHT66) or an agonistic anti-HVEM Ab in the absence of TCR/CD3 or CD2 signal (Fig. 8B). Furthermore, stimulation by LIGHT66 or anti-HVEM did not further augment CD2-mediated induction of IFN-γ and showed no synergy with CD28-mediated costimulation (Fig. 8C). Finally, since CD2 mediates Ag-independent T cell activation in the intestine, LIGHT could play a role in autoimmune pathology by inducing Ag-independent T cell activation.

**Discussion**

The intestinal immune compartment is tightly regulated to prevent excessive reactivity to the heavy antigenic load characteristic of the gut environment (20, 23, 44). Perturbation in these mucosal immunoregulatory mechanisms may lead to breakdown of tolerance to intestinal Ags and an ensuing chronic mucosal inflammation (22, 23, 45). Several studies established mucosal CD4+ T cells and, in particular, those with specificity to bacterial Ags (46), as key mediators of the aberrant inflammatory response underlying IBD. More specifically, CD4+ CD45RO+ Th1, and a deficiency in T regulatory type 1 cells have been implicated in IBD pathology (18, 24, 25, 47). However, the characteristics of these pathogenic T cells and mechanism by which breakdown of tolerance occurs remain largely unknown. Signaling via TNF family members have been a key costimulatory mechanism modulating T cell responses to a TCR and MHC peptide engagement, which is critical during T cell maturation, and several specific TNF family members have been implicated in thymic T cell selection (1, 3). Of those, LIGHT recently emerged as a significant mediator of T cell development and negative selection (15), which also plays a unique regulatory role within the mucosal immune compartment (6, 7). Consequently, since the repertoire of the mucosal immune compartment is continuously and independently reconstructed (21), LIGHT-mediated signaling could play a role in mucosal T cell selection and thus partake in the shaping of pathological immune repertoire underlying IBD (22). Our observations described here demonstrate how the CD45RO memory/effector population is selectively differentiated to express LIGHT. Moreover, the requirement of LIGHT for IFN-γ production and the direct ability of HVEM to

**FIGURE 5.** Membrane LIGHT protein is induced primarily on IFN-γ-producing T cells in the absence of accessory cells. A, PBMC were activated in vitro with P/I for 16 h and surface stained with anti-LIGHT Ab (shaded) or isotype control Ab (unshaded), anti-CD4/8, and intracellularly stained with anti-IFN-γ. Gated CD3+/CD4+ or CD3+/CD8+ histograms are shown for the IFN-γ and IFN-γ subsets. B, CD3+CD4+ or CD3+CD8+ T cells were purified by flow cytometry (>99%) before activation and stained with anti-LIGHT Ab or isotype control and intracellular anti-IFN-γ.

**FIGURE 6.** Intestinal LP T cell induce LIGHT earlier than T cells from the PB or mesenteric lymph nodes. Lymphocytes were isolated as described in Materials and Methods and activated with P/I for the indicated time. Cells were then surface stained with anti-LIGHT Ab or isotype control Ab and anti-CD3/8. CD4+ T cells were defined as CD3+CD4+ and mean fluorescence changes from the isotype control are plotted for CD4+ and CD8+ T cells from A, PB; B, mesenteric lymph node; C, colonic LP; and D, small bowel LP.
induce IFN-γ support the notion that LIGHT is a putative mediator of proinflammatory T-T interactions in the intestinal mucosa.

LIGHT expression levels as detected by flow cytometry in the activated CD4+ T cell population was heterogeneous, in contrast to the more uniform level on activated CD8+ T cells (Fig. 2). This heterogeneity arises because a relatively small subset of CD4+ T cells up-regulate LIGHT to levels similar to those of CD8+ cells, while the majority expresses little or no LIGHT at all. We demonstrated that LIGHT expression is restricted to the mature CD4+CD45RO subset, a population with previous antigenic exposure and thus highly pertinent to IBD pathology (Fig. 3). Partial correlation between LIGHT expression levels and expression of T cell activation markers indicated that variation in LIGHT expression levels may reflect activation state to a degree, but that additional factors contribute to the potential up-regulation of cell surface LIGHT (Fig. 4).

Intensive immune interface with intestinal Ags plays a key role in IBD pathology (23, 46, 48). However, T cell maturation and repertoire shaping via Ag exposure is not sufficient in itself for the induction of an inflammatory response, given that Ag-specific T cells can be regulatory, as well as effector cells (49). Thus, a proper balance between tolerogenic and nontolerogenic specificities is essential to immune homeostasis and protective vs pathogenic responses. In CD, this balance is lost and data suggest an unopposed Th1 response as an underlying mechanism (24, 25). Our findings here indicate almost exclusive LIGHT expression by IFN-γ-producing CD4+ T cells and suggest a role for LIGHT in mediating

![FIGURE 7.](image_url) Maximal membrane LIGHT fluorescence intensity is higher in small bowel and rectal LP T cells. Lymphocytes were isolated as described in Materials and Methods and activated with P/I for 24 h (PBL) or 6 h (LPL). Cells were then surface stained with anti-LIGHT Ab or isotype control Ab and anti-CD3/8. CD4+ T cells were defined as CD3+CD8- and mean fluorescence changes from the isotype control are plotted for CD4+ and CD8+ T cells. 

A, Comparison of membrane LIGHT expression between CD4+ and CD8+ T cells of the PB, mesenteric lymph node (LN), and the LP of the rectum (Rec), colon, and small bowel (SB). Student two-sided t test p values are tabulated when statistically significant. 

B, Analysis of membrane LIGHT expression in CD4+ and CD8+ T cells from inflamed vs uninvolved, mesenteric lymph node or the LP of the rectum, colon, and small bowel. 

![FIGURE 8.](image_url) Signal via the LIGHT receptor, HVEM independently induces IFN-γ and partakes in CD2-mediated IFN-γ production by LP T cells. LP T cells were activated for 24 h. Secreted IFN-γ in culture supernatants was measured by sandwich ELISA and quantified based on a standard curve. 

A, LPL were activated with anti-CD2 Abs, anti-CD2 and anti-CD28, or P/I in the presence of anti-LIGHT Ab (GemA.1.1; 20 μg/ml) or isotype control Abs. 

B, Inflamed, uninvolved, and non-IBD LPL were activated with an anti-CD2 Ab or anti-CD2 and anti-CD28 in the presence of an agonistic anti-HVEM Ab or isotype control Abs. Means and SDs for three representative experiments are plotted.
a Th1 response, thus further tying LIGHT with CD pathology (Fig. 5). LIGHT signaling via HVEM and the LTβR activates major signaling cascades and modulates transcription via NF-κB as well as NF-κB-independent mechanisms. For example, Morel et al. (37) described LIGHT-mediated down-regulation of HVEM, and Lee et al. (50) reported LIGHT-mediated induction of TNF and IL-8 in the THP1 monocytic cell line model. Morel et al. (38) recently reported a role for T cell-derived LIGHT in the production of IL-12 by activated dendritic cells. In T cells, LIGHT has been reported to provide costimulation augmenting proliferation and cytokine production (14), and our data demonstrate for the first time that HVEM signaling by itself induces IFN-γ production in LP T cells (Fig. 8B). Consequently, LIGHT expression by IFN-γ-producing T cells may initiate a self-propagating loop, escalating a Th1 response via T-T interaction. Furthermore, LIGHT can be induced on LP NK cells (mean ± SD; 10.3 ± 2.3% vs. 5.3 ± 1.3% in PB NK cells) (Fig. 8B). This enhanced expression on LP NK cells, therefore, may account for the unique expression of IFN-γ and the Th1 immune response in the intestinal compartment (RO/RA 2:1 in the LP vs 1:2 in the PB) (Fig. 6). Interestingly, IFN-γ is also differentially regulated at the transcriptional level in the intestinal T cell compartment (43). Considering the significance of LIGHT-mediated signaling to IFN-γ production (52), it is plausible that sustained or elevated LIGHT expression in the intestine could contribute to the gut-specific regulation of IFN-γ.

Rapid kinetics of LIGHT up-regulation on T cells as well as higher peak levels (Figs. 6 and 7) may account for an increased activity of LIGHT within the intestinal immune compartment. In addition, higher peak levels of cell surface LIGHT were recorded in small bowel T cells when compared with colonic or peripheral T cells. Interestingly, these observations further support a linkage between LIGHT and IFN-γ pathways since the small bowel is the primary affected organ in Th1-mediated CD, while LIGHT peak levels were lower in the colon, which is the primary target in UC for which there is less evidence of a Th1-mediated pathology (24). In addition, elevated LIGHT expression in mucosal T cells agree with our data localizing LIGHT expression to mature T cells considering the massive antigenic exposure unique to the gut immune compartment. The CD4+CD45RO subset of T cells is more prominent in the mucosal compartment (RO/RA 2:1 in the LP vs 1:2 in the periphery) (31), and since these are the LIGHT-expressing cells, their increased abundance may account for the unique expression profile of LIGHT in LP T cells.

 Constitutive T cell expression of LIGHT in the murine was observed in mucosal inflammation and provided the initial evidence for LIGHT role in mucosal immune regulation (6, 7). Elevated LIGHT expression on human intestinal T cells further supports a proinflammatory role for LIGHT in human IBD pathology (Fig. 7). In this study, LIGHT expression levels following maximal in vitro activation of T cells from IBD mucosa was similar to controls. Nonetheless, cell surface protein expression is abolised during enzymatic disruption of the intestinal mucosa and activation-induced expression in vitro may not directly reflect in vivo expression. Thus, LIGHT proinflammatory signaling or function in T cell selection may still play a significant role propagating a primary pathological event such as elevated antigenic sampling, leading to a pathological immune repertoire and an aberrant inflammatory response.

In summary, our findings demonstrate for the first time that LIGHT can be expressed at high levels on human mucosal CD4+ T cells. Furthermore, LIGHT expression was localized to the mature Th1-type CD4+ T cells, key cellular effectors of an inflammatory response and crucial to IBD pathogenesis (24–26). In addition, we identified a more rapid induction and higher peak levels of LIGHT on human mucosal T cells, which is especially interesting since data from transgenic mouse studies indicated LIGHT-dependent inflammation selectively targeted the intestine. In conclusion, the mucosal specificity of LIGHT-mediated inflammation could have significant pathological implications in human IBD, and thus merits further investigation of gut-specific immune regulatory mechanisms.

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