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# The Role of LIGHT in T Cell-Mediated Immunity

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## Abstract

This review focuses on the role of homologous to lymphotoxin, exhibits inducible expression, competes with herpesvirus glycoprotein D for HVEM on T cells (LIGHT) in T-cell immunity and T cell-mediated diseases. LIGHT binds to lymphotoxin-β receptor (LTβR), and cooperates with LTβ in lymphoid organogenesis and development of lymphoid structure. Previous findings establish a crucial biological role for LIGHT, a T cell-derived costimulatory ligand, in T-cell activation and expansion via a T-T cell-dependent manner. Transgenic studies demonstrated that the dysregulation of LIGHT activity results in the disturbance of T-cell homeostasis and ultimately the breakdown of peripheral tolerance. Furthermore, the blockade of LIGHT activity ameliorates the severity of T cell-mediated diseases indicating the essential involvement of LIGHT in various pathological conditions. Here, we review the recent studies about LIGHT mainly in the context of autoimmunity and conclude with a discussion of the potential mechanisms by which LIGHT promotes autoimmunity.

## Key Words

LIGHT
LTβR
HVEM
T-cell activation
Costimulation
Autoimmunity
Lymphoid Structure
Chemokine
T cell-mediated diseases

## Receptor and Ligand Interaction

Members of the tumor necrosis factor/tumor necrosis factor receptor (TNF/TNFR) superfamily play multiple roles in the cellular differentiation, survival, and death pathways that orchestrate lymphoid organogenesis, activation and homeostasis of immune cells *(1)*. TNF and LTα, along with homologous to lymphotoxin, exhibits inducible expression, competes with herpesvirus glycoprotein D for HVEM on T cells (LIGHT) and LTβ, define a core group of ligands that bind four cognate cell-surface receptors TNFRI, TNFRII, LTβR, and herpes viral entry mediator (HVEM) with significant complexities of receptor cross-utilization (Fig. 1). Membrane-bound form of lymphotoxin (LTα/β) and its receptor LTβR have been studied extensively and their essential roles in

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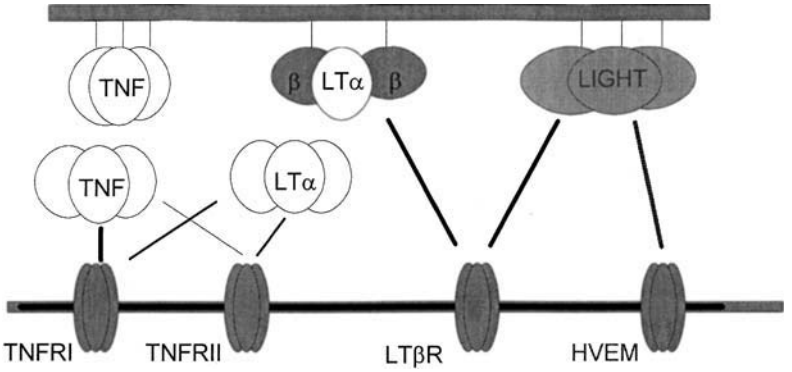


**Fig. 1.** A current model for the LT/LIGHT family. LTβR binds to both membrane LTα/β and LIGHT while HVEM binds to LIGHT and soluble $LT\alpha_3$. Therefore, LIGHT binds to both LTβR and HVEM. Soluble $TNF\alpha_3$ and $LT\alpha_3$ bind to TNFRI and TNFRII.

the development and organization of secondary lymphoid tissues and ectopic lymphoid neogenesis were well-established *(2–8).* LIGHT, a TNF superfamily member (TNFSF14), is a type II transmembrane protein expressed on activated T cells and immature dendritic cells (DCs) *(9,10).* The primary structure of human LIGHT protein predicted from the cDNA sequence contains 240 amino acids. Human LIGHT exhibits significant sequence homology with the C-terminal receptor-binding domains of LTβ (34%), Fas ligand (31%), 4-1BBL (29%), TRAIL (28%), LTα (27%), TNF (27%), and CD40L (26%) *(9).* A protein of 239 amino acids can be deduced from the mouse LIGHT cDNA, with characteristics of a type II transmembrane protein and 77% amino-acid homology with human LIGHT *(11).* The expected receptor-binding region of mouse LIGHT has substantial sequence homology with those of Fas ligand (33%), LTβ (30%), LTα (28%), TNF (27%), receptor activator of nuclear factor-κB (NF-κB) ligand (26%), and TNF-related apoptosis-inducing ligand (23%) *(11).* LIGHT can bind three receptors *(9):* LTβR expressed on stromal cells and nonlymphoid hematopoietic cells *(12–14);* HVEM expressed on T, B, and other hematopoietic cells *(15–17);* and DcR3, a decoy receptor that also binds to Fas ligand (FasL) *(18).*

## The Role of LIGHT in T-Cell Activation

### T Cell-Derived LIGHT Functions as a Costimulatory Molecule for Expansion of T Cells

Co-stimulatory molecules on antigen-presenting cells (APCs) play an important role in T-cell activation and expansion. The well-characterized costimulatory pathway for optimal T-cell activation involves the T-cell surface molecule CD28, which responds to the costimulatory molecules B7-1 (CD80) and B7-2 (CD86) expressed on activated APCs *(19).* Previous studies have shown that murine B7 molecules could costimulate with anti-CD3 monoclonal antibody (MAb) or concanavalin A (ConA) to induce T-cell activation *(20–22).* Anti-CD3 MAb can directly crosslink the T-cell receptor (TCR) complex and stimulate T-cell proliferation in an APC-independent way, whereas ConA induces T-cell activation via an APC-dependent mechanism *(23,24).* $CD28^{-/-}$ mice have impaired responsiveness to ConA, suggesting

that the interaction of B7 and CD28 is critical for the APC-dependent T-cell activation *(25).* CTLA4-Ig, a soluble receptor for B7, could block ConA and anti-CD3 MAb induced proliferation in splenocytes or lymph node cells *(25–27).* However, cultures of T cells that had been rigorously depleted of accessory cells were found to proliferate in a B7-independent manner *(27).* These experiments, therefore, raise two possibilities that an APC-derived costimulatory signal may not be necessary under all circumstances such as direct cross-linking of the TCR, or that T cells may be able to provide costimulation to each other via the ligand(s) and receptor(s) expressed on T cells themselves. However, it is unclear whether such additional costimulatory molecules are present and whether the ligation of these molecules by T cell-derived costimulatory ligand(s) is required for further activation and/or expansion of T cells.

Our recent studies demonstrated that the blockade of LIGHT by its soluble receptor HVEM-Ig dramatically reduced the anti-CD3 mediated T-cell proliferation in the absence of APCs indicating that LIGHT can function as a costimulatory molecule for the full expansion of peripheral T cells in a T-T cell-dependent manner *(28).* In contrast to reagents that block LIGHT activity, CTLA4-Ig did not show any impact on the proliferation of T cells in our antigen-presenting cell (APC)-free system *(28).* These results are consistent with the notion that CD28 interactions with the B7 family of costimulatory ligands are essential for inducing T-cell activation via an APC-dependent mechanism *(19,29,30),* whereas LIGHT might be important for T-T cell interaction. Taken together, these results support our hypothesis that LIGHT from T cells is required for T-cell expansion via T-T cell interaction.

Other studies have also shown that LIGHT has potent, CD28-independent costimulatory activity and results in enhanced T-cell proliferation and secretion of gamma interferon (IFN-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF) in vitro *(10,11).* Although we emphasize the role of T cell-derived LIGHT in activation of T cells, Tamada et al. *(10)* reported that blockade of LIGHT by its soluble receptors, LTβR-Ig or HVEM-Ig, inhibits the induction of dendritic cell (DC)-mediated primary allogeneic T-cell response suggesting that LIGHT may function as a costimulatory molecule in DC-mediated cellular immune responses. However, whether the costimulatory activity of LIGHT is derived from T cells or DCs is unclear in that model. A recent study also suggests that LIGHT can synergize with CD40L to stimulate the maturation of DCs and LIGHT costimulation allows DCs to prime in vitro-enhanced specific cytotoxic T lymphocytes (CTL) responses *(31).* Therefore, LIGHT may be involved in the T-T cell and T-DC interactions and LIGHT-mediated signal may have crucial impacts on the functions of both T cells and DCs.

## Impaired T-Cell Activation in LIGHT Knockout Mice Indicated an Essential Role of LIGHT in T-Cell Response

Gene-targeting approaches have largely confirmed in vitro data regarding the costimulatory activity of LIGHT. LIGHT$^{-/-}$ mice showed a reduced CTL activity and cytokine production in allogeneic mixed lymphocytes reaction (MLR) studies *(32).* Detailed analysis revealed that proliferative responses of CD8$^{+}$ T cells are impaired and interleukin 2 (IL-2) production of CD4$^{+}$ T cells is defective in the absence of LIGHT *(32).* Furthermore, a reduced $^{3}$[H]-thymidine incorporation after TCR stimulation was observed for LIGHT$^{-/-}$ T cells *(32).* Collectively, these results indicate LIGHT has important costimulatory functions for T-cell activation. An independent study

also showed that Vβ8$^+$CD8$^+$ T-cell proliferation in response to staphylococcal enterotoxin B (SEB) was significantly reduced in LIGHT$^{-/-}$ mice. Consistently, induction and cytokine secretion of CD8$^+$ CTL to major histocompatibility complex (MHC) class I-restricted peptide was impaired in LIGHT$^{-/-}$ mice. However, the proliferative response of Vβ8$^+$CD4$^+$ T cells to SEB was comparable in LIGHT$^{-/-}$ and LIGHT$^{+/+}$ mice in this report. Thus, the authors proposed that LIGHT is required for proliferation of normal CD8$^+$ T cells but not CD4$^+$ T cells *(33).*

## The Role of LIGHT in Systemic Autoimmunity

Results from in vitro culture models appear to support a role for LIGHT in T-cell activation *(11,15).* The phenotype of mice overexpressing LIGHT provides evidence that upregulation of LIGHT can play a critical role in T-cell mediated inflammation and autoimmune diseases. The studies from our group *(28)* and Shaikh et al. *(34)* demonstrate that constitutive expression of LIGHT results in multi-organ inflammation caused by activated T cells. Normally, LIGHT is transiently expressed on the surface of T cells following activation *(9)* and downregulated upon the termination of immune responses, but in the studies discussed here, two different lineage-specific promoters were used to drive the constitutive expression of LIGHT in T cells, which eventually leads to breakdown of peripheral tolerance and development of autoimmune syndromes. It implies that upregulation or dysregulation of LIGHT can be involved in T cell-mediated autoimmunity.

To investigate the role of T cell-derived LIGHT in the expansion of T cells in vivo, our group generated a transgenic line that constitutively expresses the LIGHT protein under the control of the proximal *lck* promoter and CD2 enhancer, which gives rise to a T-cell lineage-specific expression of LIGHT *(35,36).* Lck-LIGHT Tg mice spontaneously develop severe autoimmune disease manifested by splenomegaly, lymphadenopathy, glomerulonephritis, elevated autoantibodies, and infiltration of various peripheral tissues *(28).* In contrast to mice transgenic for BAFF, another TNF family member, which had enlarged secondary lymphoid tissues owing to the expanded B-cell compartment *(37–39),* most expansion occurred in the T-cell compartment of LIGHT Tg mice *(28,34).* These data strongly support the hypothesis that T cell-derived LIGHT is sufficient to cause the expansion of peripheral T cells in vivo.

Apart from the significantly enlarged and hyperactivated T-cell compartment, augmented cytokine production and expansion of granulocyte-macrophage lineage in the spleen were also observed in lck-LIGHT Tg mice *(28).* IFN-γ producing T cells were significantly increased in Tg mice, further demonstrating the sufficiency of T cell-derived LIGHT to induce activation of T cells in vivo *(28).* GM-CSF promotes hematopoiesis and leads to the enlargement of the spleen with the preferential increase of GM lineages *(28).* Although higher GM-CSF production was detected in LIGHT Tg mice, the source of increased GM-CSF remains to be determined. We speculate that constitutive expression of T cell-derived LIGHT may enhance the production of GM-CSF from activated T cells, leading to systemic hematopoiesis in the Tg mice. Macrophage is one of the major cellular components involved in chronic inflammation and autoimmunity, largely owing to its proinflammatory cytokine network *(40,41),* thus it would be of great interest to dissect the mechanism by which LIGHT elicits the activation and expansion of macrophage. We predict it could be mediated either by activated T

cell-derived IFN-γ or direct ligand/receptor interaction on T cells and macrophages.

Lck-LIGHT Tg mice developed severe autoimmune manifestations *(28)*. Microscopic examination of lck-LIGHT Tg mice revealed the dramatic inflammatory cell infiltrate in the lamina propria and submucosa of intestine with prominent lymphoid aggregates or lymphoid-like structure *(28)*. In addition, severe cutaneous lesions along with ulceration and scar formation were observed in some of the aged transgenic mice *(28)*. More intriguing phenotypes were revealed by renal pathological analysis in lck-LIGHT Tg mice that spontaneously developed diffuse global proliferative glomerulonephritis. Consistent with this observation, immunofluorescence staining revealed strong diffuse Ig deposition in Tg mice *(28)*. Elevation of autoantibodies serves as criteria for the clinical diagnosis of autoimmune disease and has been shown to be characteristic for MRL-*lpr/lpr* mice *(42)*. LIGHT Tg mice demonstrated elevated anti-DNA autoantibodies and rheumatoid factors (RF), another commonly detected autoantibody in chronic inflammation and autoimmune diseases. It appears that the phenotypes observed in lck-LIGHT Tg mice share certain similarity with those in MRL-*lpr/lpr* mice, an established murine model for systemic lupus erythematosus (SLE), which may be attributed to the critical roles of both TNF-related ligands in the regulation of T-cell homeostasis. However, there are some distinctions between these two models, which are discussed in a later section of this review. The findings of glomerulonephritis, increased inflammatory cell infiltrate in multiple organs, along with elevations of serum autoantibodies indicated the development of autoimmunity in lck-LIGHT Tg mice *(28)*. Therefore, the overproliferation and hyperactivation of T cells mediated by T-cell-derived LIGHT resulted in the breakdown of T-/B-cell tolerance, supporting the notion that the dysregulation of LIGHT expression may be a critical element in the pathogenesis of autoimmune diseases.

Studies from CD2-LIGHT Tg mice in which constitutive LIGHT expression was driven by CD2 promoter and enhancer showed lymphoid tissue abnormalities, including splenomegaly, lymphadenopathy, and pronounced inflammation in the intestine, consisting of expanded populations of conventional $CD4^+$ and $CD8^+\alpha\beta$ T cells, liver, and reproductive organs *(34)*. Thus, sustained expression of LIGHT on T cells contributes to the induction and persistence of inflammation in the peripheral tissues demonstrated by both of the transgenic lines *(28,34)*.

## The Role of LIGHT in T Cell-Mediated Disease Model

Emerging evidence indicates that LIGHT is a key player in T-cell homeostasis and peripheral tolerance. Studies by Wang et al. *(28)* and Shaikh et al. *(34)* reveal that sustained expression of LIGHT can cause profound inflammation and loss of tolerance, leading to autoimmune syndromes. These new findings validate LIGHT as an important T-cell regulatory molecule and suggest its candidacy as a pharmaceutical target for diseases involving T cells.

### Type I Diabetes

Insulin-dependent diabetes mellitus (IDDM) is a T cell-mediated autoimmune disease in which the insulin-producing beta cells are selectively destroyed by autoreactive T cells. The nondiabetic (NOD) mouse is the well-established model for studies of IDDM *(43,44)*. Previous studies suggested that the administration of LTβR-Ig (a chimera of the receptor's ligand-binding domain fused with the Fc region of IgG that neutralizes both LIGHT and LTα/β)

blocked the development of IDDM *(45)*. An independent study from LTβR-Fc Tg mice also supported the protective role of LTβR in IDDM *(46)*. Because membrane LTα/β and LIGHT both bind to LTβR, the therapeutic effects of LTβR-Ig treatment could be attributed to either or both ligands. One striking feature of spontaneous autoimmune diabetes is that the prototypic formation of lymphoid follicular structures within the pancreas and membrane LTα/β has been shown to play an important role in the formation of lymphoid tissues, therefore, it was proposed that membrane LTα/β is involved in the development of type I diabetes *(45)*. The mechanisms by which membrane LTα/β contributes to type I diabetes largely reside in its ability to promote the formation of lymphoid microenvironment required for the development and progression of IDDM *(45)*. It is possible that LIGHT can contribute to the development of lymphoid tissue for IDDM because upregulation of LIGHT can stimulate LTβR and induce the formation of lymphoid structures in the absence of LT *(47)*.

To study whether LIGHT is involved in the development of autoimmune diabetes, HVEM-Ig, a soluble receptor for LIGHT, was used to neutralize LIGHT signaling in NOD mice. At the age of 6–7 wk, many islets in NOD mice were already infiltrated with autoreactive T cells, and treatment with HVEM-Ig at this time significantly prevented the development of IDDM and reduced the incidence of diabetes (80% in control vs 25% in treated group) *(28)*. HVEM is a receptor for LIGHT and does not bind to membrane LTα/β, and only shows very weak binding to $LT\alpha_3$ *(9)*. These results suggest that the blockade of LIGHT by HVEM-Ig prevents the pathogenesis of IDDM and that LIGHT may play a critical role in the development of type I diabetes *(28)*. However, there are several unresolved issues. Earlier studies showed that LTβR-Ig treatment prevented the development of IDDM induced by diabetogenic T cells in an adoptive transfer model and similar approach should be applied to HVEM-Ig treatment to test the role of LIGHT in different phases of IDDM progression. The development of insulitis needs to be addressed in HVEM-Ig treatment to determine if LIGHT is an effector molecule in the tissue-destructive phase of IDDM. Moreover, the effect of anti-LTβ antibody, which only blocks the membrane LTα/β, should be examined to distinguish the impact of two ligands for LTβR in the IDDM. We predict that administration of LTβR-Ig, which blocks both ligands, probably has more potent therapeutic effect on the type I diabetes than the blockade of either ligand.

## Transplantation and Tumor Rejection

The effect of LIGHT in transplantation was first examined in a graft-versus-host disease (GVHD) model *(11)*. Blockade of LIGHT by administration of soluble receptor LTβR-Ig or neutralizing antibody against LIGHT led to ameliorated GVHD. When $LT\alpha^{-/-}$ mice were used as recipients lacking both soluble $LT\alpha_3$ and membrane LTα/β, the therapeutic effect of LTβR-Ig persisted in this GVHD model, which strongly argued the critical role of LIGHT in the development of GVHD *(11)*. Chen's group has demonstrated that infusion of an MAb against CD40 ligand (CD40L) further increases the efficacy of LTβR-Ig, leading to complete prevention of GVHD and tolerance *(48)*.

The role of LIGHT-HVEM costimulation was examined in a murine cardiac allograft rejection model *(49)*. Allografts upregulated the expression of LIGHT and HVEM on infiltrating leukocytes starting from 3 d after transplantation, although normal hearts lacked both LIGHT and HVEM mRNA expression. There was no significant difference between the mean survival of fully MHC-mismatched cardiac allografts in

LIGHT$^{-/-}$ mice, cyclosporine A (CsA)-treated LIGHT$^{+/+}$ or LIGHT$^{+/+}$ mice. In contrast, mean survival of allograft in CsA-treated LIGHT$^{-/-}$ recipients was considerably prolonged compared with either untreated LIGHT$^{-/-}$ or CsA-treated LIGHT$^{+/+}$ mice. The beneficial effects of the deletion of LIGHT in CsA-treated recipients were associated with the reduction of IFN-γ, inducible protein-10 (IFN-γ-induced chemokine), and its receptor CXCR3 in the allografts *(49).* Consistently, it has been reported earlier that DcR3/TR6, a soluble decoy receptor for LIGHT, can also delay the onset of cardiac allograft rejection *(50).* These data suggest that T-cell to T cell-mediated LIGHT/HVEM-dependent costimulation is a significant component of the host response mediating cardiac allograft rejection. In addition to its impact in the cardiac rejection model, LIGHT has been shown to act synergistically with CD28 in skin allograft rejection in vivo *(32).*

Gene transfer of LIGHT into tumor nodules induced an antigen-specific CTL response to tumor antigens and therapeutic immunity against established mouse P815 tumor *(11).* Depletion of CD8$^+$ T cells completely abrogated the antitumor effect of LIGHT, whereas the antitumor effect was partially inhibited by depletion of the CD4$^+$ T cell *(11).* These results indicate that LIGHT co-stimulation in vivo can enhance the CTL response to tumor antigen and eradicate tumors via a T cell-dependent mechanism.

Our recent studies further dissect the mechanism for LIGHT-mediated tumor rejection. In sporadic cancer, the initiating lesion affects a single cell in an otherwise normal environment and tumorigenesis is governed not only by the tumor cells *per se,* but also by the tumor microenvironment *(51).* However, the tumor microenvironment or barrier is poorly understood and infrequently considered for immunotherapy, which may be an important cause to the failure of tumor rejection. We introduce the LIGHT gene into a tumor cell line Ag104-L$^d$ and our data showed that LIGHT expression in Ag104L$^d$ led to the regression of this otherwise very progressive fibrosarcoma *(52).* Within the tumor microenvironment, LIGHT binds to both LTβR expressed on infiltrating stroma *(12,13).* and HVEM expressed on T cells *(9,53).* LIGHT-mediated LTβR signaling on stromal cells induces the production of chemokines and adhesion molecules that recruit naïve T cells *(52).* This recruitment may fundamentally facilitate the interplay between tumor and immune system to support the inflammatory response against the tumor. The ability to prime naïve T cells within the tumor itself permits several advantages: (1) owing to the high tumor antigen load *in situ,* the efficiency and specificity of T-cell priming will be enhanced; (2) a broader repertoire of tumor-specific naïve T cells can be selectively activated in the presence of potent co-stimulation (LIGHT); (3) no additional migration steps are required to reach the site of effector function; (4) ongoing T-cell responses may react more readily to the shifting tumor antigen-expression profile *in situ (52).* Another interesting possibility is that LIGHT expression may trigger the activation of autoreactive T cells against the stromal elements within the tumor environment, and the subsequent killing of stromal cells mediated by the autoreactive T cells may fundamentally eliminate the growth ground for tumor cells and lead to tumor rejection. Our study thus suggests that targeting the tumor barrier may be an effective strategy for cancer immunotherapy *(52).*

## Inflammatory Bowel Disease (IBD) and IgA Nephropathy (IgAN)

Human inflammatory bowel disease (IBD) is a chronic, relapsing, and remitting inflammatory condition of unknown origin. Recent

immunologic studies of the disease indicated that IBD is owing to a dysregulated mucosal immune response to one or more unknown antigens present in the normal, indigenous bacterial flora *(54).* Various animal models of IBD have been helpful in the dissection of the mechanisms involved in IBD pathogenesis. An experimental model of mucosal inflammation has been produced by creating mice that overexpress TNF (TNFΔARE mice) *(55).* Similarly, overexpression of LIGHT leads to development of intestinal inflammation *(28,34),* which implicates the critical role of LIGHT in IBD pathogenesis. Furthermore, LTβR-Ig, a soluble receptor for LIGHT/LT, prevents colitis in a CD4 T cell–dependent transfer model *(6).*

IgA nephropathy (IgAN), the most common type of human glomerulonephritis (GN) worldwide, is characterized by elevated serum IgA in 50% of patients and renal mesangial deposition of IgA and complement *(56).* The molecular mechanism of human IgAN has not been well-defined and the source of pathogenic IgA is under debate. Our previous data demonstrated that LTβR in the intestine is required for production of IgA, because LTβR$^{-/-}$ mice display profoundly low levels of baseline IgA in serum and fecal extracts *(57).* LIGHT is a ligand for LTβR and expressed on activated T cells *(9)* with a potent co-stimulatory activity for T cells *(11,28).* We hypothesize that an increase of activated lymphocyte infiltration in the gut, such as in the case of IBD, will cause the dysregulated IgA production via LTβR signaling, which might serve as a mechanism for IgAN pathogenesis.

We have found that the IBD patients with active intestinal inflammation show significantly increased IgA producing cells in the gut, elevated serum IgA and increased incidence of hematuria, a hallmark of IgAN *(58).* LIGHT Tg mice develop T cell-mediated intestinal inflammation, which causes profound dysregulation of polymeric IgA (pIgA) production, impaired transportation, and clearance leading to dominant mesangial IgA deposition *(58).* LIGHT itself was the critical component in our model and we do not believe that any intestinal inflammation causes the increase of serum IgA. To discern between a LIGHT-specific perturbation in the gut leading to increase of serum IgA and hyperserum IgA resulting simply as a consequence of an inflamed gut environment, we examined the serum IgA level in young Tg mice (7 wk old) with no histological identifiable intestinal inflammation. In these young Tg mice, serum IgA level was also significantly elevated suggesting that the increase of serum IgA occurs rather early and precedes the florid inflammation. The subsequent intestinal inflammation causes the further overproduction and impaired transport of pIgA into lumen. The compound effects of all these elements eventually lead to the dramatically increased serum pIgA and IgA deposits in the kidney of Tg mice *(58).*

Our previous study showed that LIGHT Tg mice shared certain similarity with MRL/lpr mice, a well-established model for SLE. However, after detailed analysis we found there are some distinctions between these two models: (1) LIGHT Tg mice overall have a dominant IgA response, whereas in MRL/lpr mice IgG response appears to be dominant. (2) Although LIGHT Tg mice have elevated anti-DNA IgG antibody, the increase of anti-DNA IgG in Tg mice is only about four- to fivefold *(28).* However, the level of anti-DNA IgG in MRL/lpr mice was about 50–100 fold higher than that of age-matched LIGHT Tg mice (Wang et al., unpublished data). Thus, the immunoglobulin response is very different between these two models. (3) In addition, anti-DNA IgA level was dramatically increased in LIGHT Tg mice. Owing to the severe intestinal inflammation in LIGHT Tg mice, it is likely that DNA was released from necrotic cells and exposed to immune system leading to the gen-

eration of anti-DNA antibodies. Because the intestinal environment favors the IgA class switching, the dominant class of anti-DNA antibody is IgA in LIGHT Tg mice. These mucosal-derived anti-DNA IgA may contribute to the glomerular damage in Tg mice. (4) The level of anti-DNA antibodies in young Tg mice was very low and comparable to wt ones. These results suggest that anti-DNA antibodies may be a consequence of self tissue damage in the aged LIGHT Tg mice *(58).* However, the mechanism by which LIGHT mediated the breakdown of T-cell tolerance and self tissue destruction is still unclear.

Our Tg model closely resembles human IgAN rather than SLE; furthermore, it may be more related to secondary IgAN. The distinction between primary and secondary forms of IgAN is that most patients with primary ("idiopathic") IgAN do not produce anti-DNA autoantibodies or display evidence of florid intestinal inflammation, whereas secondary IgAN is known to occur in association with IBD, celiac disease, and other inflammatory conditions *(59).* A better understanding of such mechanism(s) may allow us to make proper diagnosis and develop therapeutic approaches to human IgAN in the future.

Overall, these studies indicate that LIGHT is involved in T cell-mediated diseases and its dysregulation may trigger the abnormal activation of T cells, spawning severe tissue destruction and autoimmune manifestations. Thus, beneficial effects may be obtained by blockade of LIGHT upregulation in autoimmune diseases and GVHD. In contrast, the enhancement of LIGHT expression may be desired in tumor rejection.

## The Potential Mechanism for LIGHT-Mediated Autoimmunity

Is the tissue destruction observed in the LIGHT transgenic mice owing to nonspecific inflammation by activated T cells or true autoimmunity owing to loss of tolerance? The current data seem to suggest that there is a loss of self-tolerance, but the detailed mechanism remains to be determined. Interestingly, in both types of LIGHT transgenic mice, the size of the thymi is remarkably reduced and less CD4/CD8 double-positive (DP) cells are observed. Because DP thymocytes are normally subject to negative selection, these results raise the possibility that LIGHT might be involved in negative selection *(34,60).* Moreover, our study showed that blockade of LIGHT signaling in vitro and in vivo prevented negative selection induced by intrathymically expressed antigens, resulting in the rescue of thymocytes from apoptosis *(60).* Although speculation abounds, no other TNF family member has yet been confirmed as a factor in modulating negative selection *(61).* The current studies *(34,60)* suggest that LIGHT affects central differentiation processes critical for T-cell tolerance. However, LIGHT deficient mice showed no obvious defects in thymus *(32,33),* thus experiments designed to test whether central tolerance is affected by the absence of LIGHT or whether the LIGHT-mediated thymocyte deletion is dependent on the interaction between TCR and self-MHC/peptide probably will provide more insights into this issue. One of our recent studies suggests that LIGHT-mediated deletion of thymocytes may indeed depend on the specific interaction between TCR and self-MHC/peptide in a TCR transgenic system *(62).*

Our findings with LIGHT provide an example of a T cell-derived costimulatory ligand that is sufficient to induce a program of downstream events leading to T-cell activation, breakdown of peripheral tolerance, and induction of autoimmunity (summarized in Fig. 2). Although LIGHT can potentially bind three receptors *(9,18),* HVEM is probably the receptor responsible for T-T cell

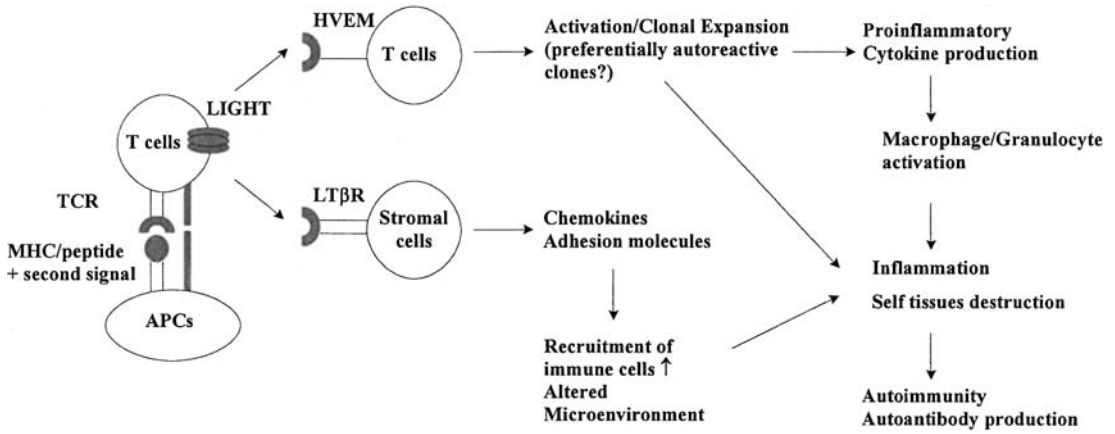


**Fig. 2.** Proposed model for the LIGHT-induced autoimmunity. Question mark means the unresolved issues.

interaction as LTβR is not found on T cells *(12–14)* and DcR3/TR6 is a decoy receptor that lacks a transmembrane domain *(18)*. Certainly, it is possible that LIGHT may have an unidentified receptor expressed on T cells. Moreover, a recent study suggests that LIGHT, although a ligand, can receive co-stimulatory signal when expressed on the T-cell surface *(63)*. Owing to the upregulation of LIGHT upon T-cell activation, the simultaneous presence of both the ligand and receptor could provide a stimulatory mechanism for the clonal expansion of peripheral T cells in an autocrine or paracrine fashion because LIGHT can be secreted. The existence of central tolerance implies that immature thymocytes respond differently to the antigen encountered than do mature T cells. Interestingly, LIGHT as a co-stimulatory molecule causes differential responses of immature vs mature T cells. Upregulation of LIGHT promotes the deletion of potentially autoreactive T cells in thymic selection but activates mature T cells in periphery, leading to autoimmune diseases *(28,34,60,62)*. However, it is still remains to be addressed whether LIGHT preferentially triggers the activation of autoreactive T cells vs foreign antigen-specific T cells.

LIGHT is a unique pro-inflammatory cytokine that not only effectively regulates T lymphocyte activation and effector function but also exerts its action on LTβR of stromal cells to mediate the formation of lymphoid structure in the absence of LT *(47)*. Highly organized lymphoid structures provide the intricate microenvironment essential for the effective immune responses. Compared with $LT\beta^{-/-}$ mice, $LT\beta R^{-/-}$ mice present with more severely disorganized splenic structures, suggesting the potential involvement of another ligand *(5,64)*. We show that the complementation of $LT\alpha^{-/-}$ mice with a LIGHT transgene (LIGHT Tg/$LT\alpha^{-/-}$) leads to the restoration of secondary lymphoid-tissue chemokine (SLC) and T-/B-cell zone segregation. LIGHT Tg/$LT\alpha^{-/-}$ mice also preserve DCs, follicular dendritic cell networks (FDC), and germinal centers (GCs), though not the marginal zone (MZ). Consequently, IgG responses to soluble (KLH) but not particulate (SRBC) antigens are restored, confirming the differential role of primary follicle and MZ in the responses to soluble

and particulate antigens. However, LIGHT transgene failed to rescue the defective splenic structures in LIGHT Tg/LTβR$^{-/-}$ mice. These findings demonstrate the sufficiency of LIGHT transgene to trigger LTβR signaling in vivo and uncover the potential interaction between LIGHT and LTβR in supporting the development and maintenance of lymphoid microenvironment *(47)*. A later study further confirmed that LIGHT cooperated with LTβ, another ligand for LTβR, in mesenteric lymph node (MLN) organogenesis *(32)*. Moreover, one of our recent studies also demonstrated that sustained expression of LIGHT led to the upregulation of MAdCAM-1 on the endothelial cells *(58)*. Taken together, it is likely that high expression of LIGHT could provide strong signal to trigger the formation of lymphoid-like structures during local immune response or inflammation.

T cells that mediate inflammation in a number of the experimental models have to migrate from sites of sensitization to sites of effector function to initiate and/or perpetuate the inflammatory response. Such migration is directed and depends on interaction between tissue-specific integrins and addressins, which in the case of traffic to mucosal tissues involves interactions between circulating cells bearing the $\alpha_4\beta_7$ integrin and the MAdCAM-1 on surface of endothelial cells *(65,66)*. Consistent with this possibility, MAdCAM-1 function has been shown to be critical to the development of colitis in the CD45RB$^{high}$ T-cell transfer model *(67)*. Thus, molecules that may be relevant to recruitment and/or retention of cells within mucosal tissues can contribute to the mucosal inflammation. The ability of LIGHT inducing the production of chemokine *(47)* and adhesion molecules *(58)* may serve as an alternative mechanism by which upregulation of LIGHT can attract more T cells migrating into the local inflammation site and promote the transformation of the gut mucosa from a normal immune structure into a pathological lymphoid site. Similarly, local expression of LIGHT in tumors leads to tumor rejection, probably owing to both enhanced T-cell activation and increased migration of naïve T cells into tumor mediated by upregulation of chemokines and adhesion molecules inside tumor *(52)*.

## Summary

The unique features of LIGHT are still a matter of intense investigation. We know that LIGHT can function as a co-stimulatory molecule for T cells and promote the activation and expansion of T cells, presumably by interacting with HVEM expressed on T cells *(11,15,28)*. LIGHT, cooperating with membrane LTα/β, plays an essential role in MLN organogenesis *(32)*. Moreover, LIGHT transgene can support the development and maintenance of lymphoid microenvironment independent from LT *(47)*. We propose that LIGHT plays a unique role in two key checkpoints for autoimmunity: (1) activating autoreactive lymphocytes and (2) promoting the tissue infiltration of autoreactive T cells. Recent studies provide compelling evidence that LIGHT plays a critical role in T cell-mediated diseases, including type I diabetes, GVHD, IBD, and tumor rejection *(11,28,45, 48,49,52,58)*. Thus, LIGHT may be an attractive candidate for therapeutic intervention, and a better understanding of the mechanism(s) of its involvement in pathogenesis will allow us to develop effective treatment in the future.

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