Chapter 10

Targeting the LIGHT-HVEM Pathway

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Abstract

Tumor necrosis factor (TNF)-related cytokines function as key communication systems between cells of the immune system and mediate inflammation and tissue destruction. LIGHT (TNFSF14) is a key component of the communication system that controls the responses of T-Cells. LIGHT activates two cell surface receptors, the Herpesvirus Entry Mediator (HVEM) and the Lymphotoxin-β Receptor and is inhibited by soluble decoy receptor-3. The LIGHT-HVEM pathway is an important cosignaling pathway for T-Cells, whereas LIGHT-LTβR modifies the functions of dendritic cells and stromal cells by creating tissue microenvironments, which promote immune responses. HVEM also binds an Ig superfamily member, B and T lymphocyte attenuator (BTLA) that inhibits T-Cell activation. Thus, HVEM serves as a molecular switch between stimulatory and inhibitory signaling. Studies in humans and experimental animal models reveal that LIGHT contributes to inflammation and pathogenesis in mucosal, hepatic, joint and vascular tissues. LIGHT is accessible to biologic-based therapeutics, which can be used to target this molecule during inflammation-driven diseases.

Introduction

Signals mediated through tumor necrosis factor (TNF)-related cytokines and their receptors modulate immune and inflammatory responses,[1] thus blockade of signaling may suppress symptoms associated with inflammatory and immune mediated diseases. This concept was validated by the clinical impact of TNF inhibitors (Remicade™, an anti-TNF antibody and Enbrel™, a decoy receptor-Ig fusion protein) in patients with autoimmune diseases, such as rheumatoid arthritis, psoriasis and inflammatory bowel syndrome.[2] However, successful responses were limited to a subset of the patients and in other autoimmune diseases TNF inhibitors failed to alleviate symptoms. These clinical results and support from experimental animal models, indicate that other members of the TNF superfamily may be operative in immune mechanisms underlying pathogenic processes.

Several members of the TNF superfamily are involved in regulating T-Cell homeostasis by orchestrating the balance of proliferation and elimination of antigen-activated T lymphocytes. The genes encoding TNF-related cytokines modulating T-Cell homeostasis are clustered in four regions of the genome paralogous with the major histocompatibility complex (MHC)(Fig. 1).[3] The TNF gene is located on chromosome 6p21 within the MHC in a closely linked tripartite locus with genes for Lymphotoxin (LT)α and LTβ sandwiched between class I and II antigen presenting molecules. The conservation of the TNF related MHC paralogs is reflected in their exon-intron organization, transcriptional orientation and functional activity. The cellular receptors that bind these ligands belong to a corresponding superfamily (TNFR superfamily) defined by an extracellular ligand binding region comprised of several cysteine-rich domains (CRD). The receptors that bind these TNF related ligands are genetically linked in two clusters: *TNFR-1*,

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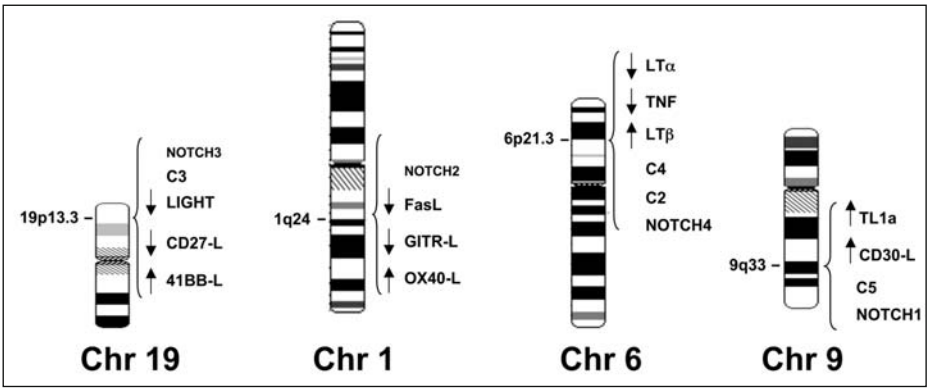

Figure 1. Organization of the TNF superfamily genes within the MHC paralogous regions present on chromosomes 1, 9, 6 and 19. Arrows indicate gene transcriptional orientation and solid blocks represent exons. *LIGHT* is 7.78kb from *C3* and ~79kb from *CD27L*. CD27L is ~235 kb from *4-1BBL*. *FasL* is separated from *GITRL* by 374kb, while *GITRL* and *OX40L* are 134k apart. *TNF* is 2.9 kb from *LTβ* and 1.3kb from *LTα*.

LTβR, *CD27* reside on Chr12p13 and the others, *41BB, GITR, Ox40, TNFR-2, DR3* and herpesvirus entry mediator (*HVEM*) on Chr 1p36 (*Fas* is an exception and resides on Chr10q24). The paralogous TNFR superfamily members such CD27, 41BB and OX40 (see for example[4,5]), either function as costimulatory molecules enhancing T-lymphocyte activation and survival, or else they induce elimination of activated T-Cells, e.g., TNFR1 and Fas. Receptor signaling is mediated through two distinct types of cytoplasmic modules: the death domain module (TNFR1, Fas and DR3), which activate caspases and the TRAF binding motif, which activates cell survival

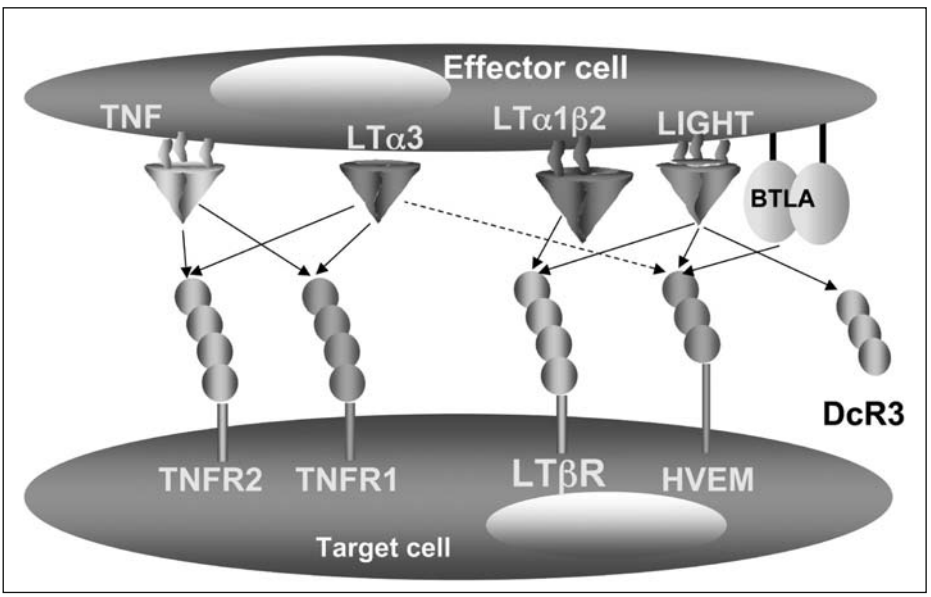

Figure 2. The Members of the immediate TNF/LT family. Arrows indicate binding interactions. Each ligand receptor interaction defines a system and these shared systems create a signaling circuit.

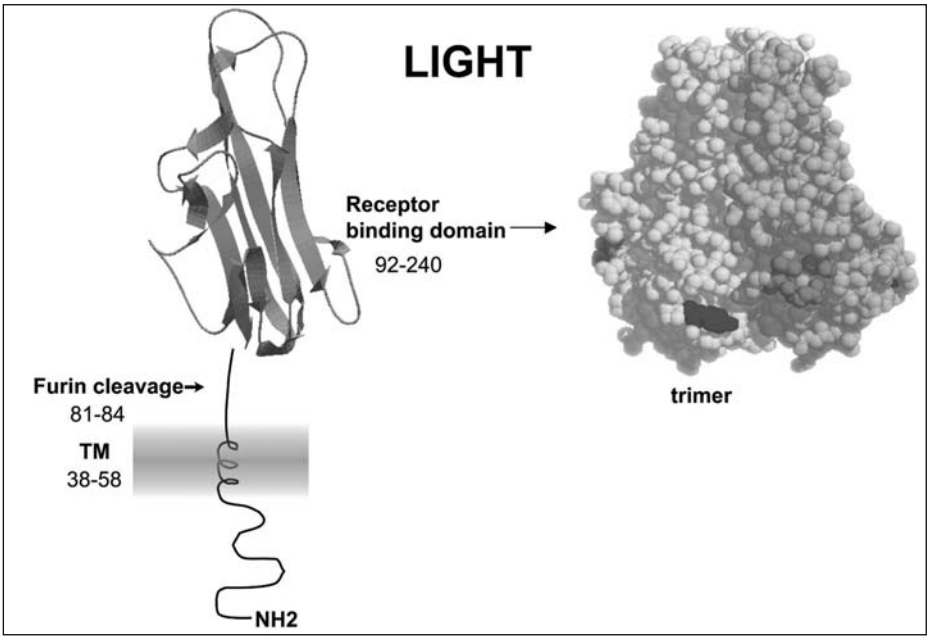

Figure 3. Molecular model of LIGHT. The theoretical LIGHT model was generated by SwissModel and encompasses amino acids Ser103 to Val240 and based on the templates for LTα and TNF (2TUN.pdb and 1TNR.pdb).[11] The domain structure of LIGHT is depicted on the left and the assembled trimeric form of the TNF homology domain is shown in space filling mode. Each subunit is shown in a different color with atoms colored red and blue have been identified as contact residues for LTβR and HVEM binding.

genes controlled by NFκB. The evolutionary conservation of the TNF-related ligands dedicated to T-Cell homeostasis and linkage to antigen recognition molecules mirrors their importance in fine-tuning antigen recognition and immune tolerance.

A broader functional link between several members of the TNF superfamily is revealed in shared ligand-receptor binding interactions. TNF, LTαβ and LIGHT overlap in binding to several cognate receptors (Fig. 2). This group, often referred to as the immediate TNF family, is viewed as an integrated signaling circuit that controls T-Cell homeostasis and a variety of other immune processes.[6] The TNF-TNFR-1 system is an important sentinel signaling system that orchestrates inflammation induced by innate recognition systems as well as by T-Cells. The LTαβ-LTβR system controls lymphoid tissue development and structure, but is also involved in regulating cellular immune processes by differentiation of stromal cells, which create microenvironments that promote cellular interactions.[7-9]

LIGHT (TNFSF14, homologous to *L*ymphotoxins exhibits inducible expression and competes with HSV glycoprotein D for *H*VEM, a receptor expressed by T-lymphocytes) displays a unique receptor binding profile that imparts its physiological functions. LIGHT has emerged as a key factor controlling T-Cell immune responses and thus is a candidate to target in different immune-mediated diseases.

LIGHT and HVEM

LIGHT follows the canonical paradigm of a TNF superfamily member configured as a type II transmembrane protein containing a C-terminal TNF homology domain that folds into a β-sheet sandwich, which assembles into a functional homotrimer[10,11] (Fig. 3). LIGHT engages two specific cellular receptors, the LTβR and HVEM. These TNFR are type I membrane glycoproteins that

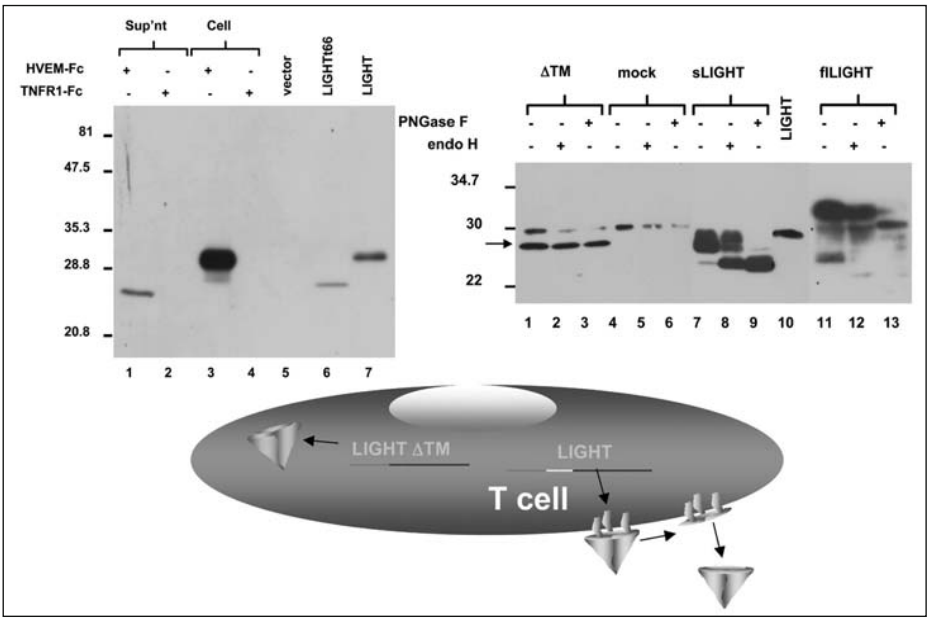

Figure 4. Processing pathway and isoforms of LIGHT Left panel, 293T-Cells were transiently transfected with plasmids encoding either membrane LIGHT or empty pCDNA3.1(+). HVEM-Fc was used to precipitate LIGHT from the tissue culture supernatant (lane 1) or cell lysate (lane 3) of full length LIGHT transfected 293T-Cells. The precipitates were resolved by SDS-PAGE and Western blot analysis using a rat anti-LIGHT polyclonal serum as a probe. TNFR1-Fc was used to control for nonspecific binding to membrane LIGHT (lane 2) or supernatants (lane 4). An equivalent amount ($5x10^4$ cell equivalents) from each transfected cell lysate was loaded in lanes 5 and 7. Purified recombinant soluble LIGHTt66 (10 ng)(lane 6) used as a molecular mass marker. Right panel, LIGHTΔTM is not glycosylated. Immunoprecipitates from the NP40 cell lysates of 293T-Cells transfected with soluble LIGHTΔTM (lanes 1-3), pCDNA3.1(+) alone (lane 4-6), LIGHTt66 (lanes 7-9) or full length LIGHT (lanes 11-13) encoding plasmids are shown. Detergent lysates were precleared with an isotype control and then immunoprecipitated with mouse anti-human LIGHT antibody and protein G. The immunoprecipitates were digested with either endoglycosidase H (lanes 2, 5, 8,12), PNGaseF (lanes 3, 6, 9,13) or left untreated (lanes 1,4, 7,11); purified soluble LIGHT (lane 10). The cartoon depicts the alternate spliced forms of LIGHT and LIGHT shedding from the membrane. Reproduced with permission from: Granger SW, Butrovich KD, Houshmand P et al. J Immunol. 2001;167:5122-5128.

have an extracellular domain comprised of four CRD. LIGHT is also bound by a soluble decoy receptor (DcR3) providing a posttranslational control mechanism to turn off signaling[12](DcR3) also binds TL1A and FasL reemphasizing the common functional links of these ligands. LIGHT can also be proteolytically cleaved (shed) into a soluble form that retains receptor-binding activity. Interestingly, an alternate transcript of LIGHT encodes a deletion of the transmembrane region, which is directed into the cytosol in a nonglycosylated form of unknown function (Fig. 4).

The LIGHT-HVEM-BTLA Switch

A new paradigm emerged with the discovery that HVEM is an activating signal for an inhibitory coreceptor known as B and T-lymphocyte attenuator (BTLA)[13](Fig. 5). BTLA has an intermediate type Ig fold[14] making it structurally diverse from other cosignaling molecules such as CD28, CTLA4, ICOS, or PD1[15,16] and providing the basis for specific interaction with HVEM. The cytoplasmic domain of BTLA contains an inhibitory tyrosine-based motif (ITIM) that counteracts

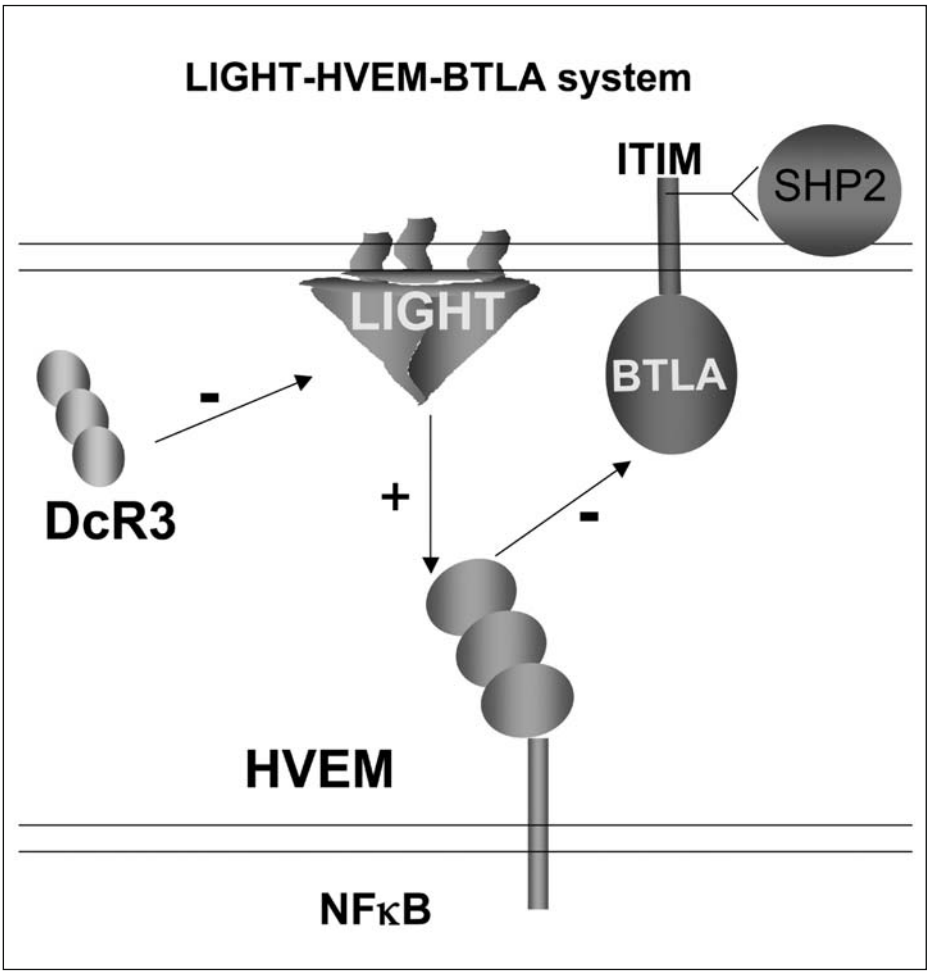

Figure 5. The LIGHT-HVEM-BTLA system. The arrows indicate the ligand-receptor binding interactions. LIGHT-HVEM activates NFκB as part of its positive signaling activity, where as HVEM activates BTLA to recruit tyrosine phosphatase SHP2, which attenuates signaling in T- and B-cells. Decoy receptor-3 binds LIGHT and can inhibit signaling.

kinases via recruitment of tyrosine phosphatases (SHP-1 and SHP-2) attenuating proliferation signals in antigen activated lymphocytes.[17-19] BTLA engages the N-terminal, first CRD of HVEM in the same topographical site occupied by Herpes Simplex virus glycoprotein D.[14,20] In contrast, LIGHT occupies a topographically distinct site in CRD2 and 3 on the opposite face of HVEM from where BTLA binds. Thus, HVEM can mediate both positive and negative signaling though different mechanisms. BTLA has a strong inhibitory effect on T- and B- cells, which is thought to function as a control for tolerance to self tissues and homeostasis.

LIGHT-Mechanism of Action

LIGHT is a key factor in the HVEM-BTLA switch between positive and inhibitory signaling.[20-22] Studies indicate that LIGHT in its membrane-anchored position disrupts the binding interaction between HVEM and BTLA.[20] This feature provides LIGHT with three functional attributes: (1) activation of LTβR, (2) activation of HVEM and (3) disruption of the HVEM-BTLA

Table 1. LIGHT in experimental pathogenesis models

Model	Result	References
Transgenic LIGHT		
LIGHT Tg in T-Cells	Acute onset, autoimmune like disease. Inflamed intestines, reproductive organs, skin and liver; abnormal lymphoid tissues	48,49
LIGHT-Tg T-Cell transfer	Atherosclerosis	46
LIGHT-Tg T-Cell transfer	Inflammatory bowel disease	50
LIGHT tumor transgene	LIGHT induced tumor rejection by CD8 T-Cells	51
Decoy Receptor		
MHC II disparte GVHD	HVEM-Fc or LTβR-Fc decreased inflammation	52,53
EAE experimental autoimmune encephalitis	LTβR-Fc suppressed paralysis	54
Cuperizone-induced demyelination	LTβR-Fc decreased demyelination and enhanced remyelination	55
CIA collagen-induced arthritis	LTβR-Fc suppressed	56
LIGHT-/- mice		
Cardiac allograft rejection	Rejection was minimized	57
Graft vs host disease	Reduced inflammation	58
Superantigen	CD8 T-Cell proliferation defect	25
Mitogen induced hepatitis	increased survival and decreased hepatic inflammation mediated by CD4 T or NK cells	30

complex, all of which act to promote immune and inflammatory processes.[20] Thus, targeting LIGHT may block signaling via its two receptors, HVEM and LTβR and leave intact the inhibitory HVEM-BTLA pathway. Interestingly, supportive evidence for this mechanism is found in a viral pathogen. A BTLA binding protein encoded by human cytomegalovirus (UL144 orf) competes with HVEM for binding BTLA and effectively inhibits human T-Cell proliferation.[20]

Expression patterns of the ligand and receptor determine the physiological cellular response. LIGHT is expressed transiently in activated T- and B-cells, but constitutively in lymphoid tissue resident dendritic cells. HVEM is expressed on T- and B-lymphocytes and other hematopoietic cells and on mucosal epithelium, whereas LTβR is broadly distributed on stroma and parenchyma cells of most organs, dendritic cells and tissue macrophages, but is conspicuously absent on T and B-lymphocytes. BTLA is also broadly expressed in all hematopoietic cells. This complex expression pattern suggests that intercellular interactions between multiple cell types will be involved in determining whether the response is ultimately stimulatory and/or inhibitory.

As a cosignaling system, LIGHT expression on antigen presenting dendritic cells is thought to engage HVEM on the surface of naïve T-Cells, enhancing proliferation and differentiation into effector cells following antigen recognition. Both HVEM and BTLA are constitutively expressed on naïve DC, B and T-Cells, thus the action of HVEM-BTLA pathway may keep naïve cells in a resting state by controlling the extent of kinase activity emanating spontaneously from antigen receptor complex on T- and B-cells. As part of the cosignaling process, the LTβR controls the proliferation of dendritic cells within lymphoid organs after binding LTαβ or LIGHT expressed on activated cells.[23] Thus, blockade of LTαβ or LIGHT may decrease the numbers of DC involved in activating T-Cells, thus dampening inflammation.

Immunobiology of LIGHT

In vivo analyses of transgenic, knockout and pharmacological models in mice indicate that LIGHT and LTαβ play a crucial role in immune regulation and targeting these molecules may impact disease processes (Table 1). An inflammatory role for LIGHT has emerged from studies of transgenic mice with constitutive LIGHT expression in the T-Cell lineage. T-Cells that express human or mouse LIGHT displayed a profound multi-organ inflammatory phenotype. LIGHT is normally transiently expressed and highly regulated at multiple steps during transcriptional and posttranslational (shedding and DcR3) stages of its expression. Although enforced expression might not replicate the physiological action of LIGHT, the model clearly demonstrates the potential of LIGHT as a potent inducer of tissue damaging inflammation. The proinflammatory action of LIGHT to induce an immune response is further underscored by the rejection of tumors engineered to express LIGHT. Additionally, some of the phenotypes within these LIGHT transgenic mice may mimic the action normally provided by LTαβ-LTβR system, or the nonphysiological disruption of inhibitory signals mediated by the HVEM-BTLA pathway needed to maintain immune homeostasis.

The use of purified receptor-Fc fusion proteins (LTβR-Fc or HVEM-Fc) as decoys to pharmacologically block the interactions of LIGHT or LTαβ with cellular receptors has provided complementary results to the genetic models (Table 1). Delineating the role of LIGHT by pharmacologic methods alone is complicated by the multiple ligand specificities of these decoy receptors.

Alternately, mice deficient in *LIGHT* provide a genetic model for understanding more directly the physiological role of this cytokine.[24-26] LIGHT deficient mice are developmentally normal, with wild type lymphoid subsets and tissues, unlike animals deficient in components of the LTαβ-LTβR pathway or the offspring of pregnant mice treated in utero with LTβR-Fc, which lack most of their secondary lymphoid tissues (intestinal Peyer's patches and lymph nodes).[27] Although both LTαβ and LIGHT can signal via the LTβR, the difference in phenotype is due in part to preferential expression of LTαβ during embryogenesis by lymphoid tissue inducer cells.[28] Deficiency in LIGHT enhanced cardiac allograft survival and decreased tissue damage in graft vs host disease, both CD8 T-Cell effector models (Table 1). CD4 T-Cells may also use LIGHT as a mediator of inflammation. LTβR-Fc blocked intestinal inflammation in the CD4 T-Cell transfer model[29] and in a hepatitis model mediated by CD4 T and NK cells, LIGHT-/- mice had significantly increased survival and decreased hepatic inflammation.[30]

Evolutionary pressures have guided multiple viral families (pox, herpes, adeno) to target the immediate TNF family as part of the pathogen's strategy to modulate host defenses.[31] For instance, poxviruses utilize soluble TNF receptors as virulence factors in controlling host defenses,[32] providing a prototype of TNFR2-Fc (etanercept). Two distinct human herpesviruses, Herpes Simplex and Cytomegalovirus, target the LIGHT-HVEM-BTLA switch, which strengthens the notion that this pathway is an important control point for regulating immunity.[20,33] Thus, viruses provide additional hints at potential pathways for controlling unwanted immune responses. Interestingly, LIGHT is dispensable for host defense to some viral pathogens indicating that genetic inactivation of LIGHT was not overwhelmingly immunosuppressive.[34,35]

Clinical Indications for LIGHT

The concept that LIGHT provides a critical proinflammatory signal during cellular immune responses is reinforced by the studies of patients with inflammatory bowel disease (IBD).[36,37] Cell surface LIGHT is expressed on human mucosal T-Cells and NK cells and a subpopulation of gut-homing $CD4^+$ T-Cells in the periphery, but not by naïve T-Cells in blood. Quantitative analysis of LIGHT mRNA in a cohort of inflammatory bowel disease patients indicated elevated expression in biopsies from small bowel and from inflamed sites, implicating LIGHT as a mediator of mucosal inflammation. In addition, CD2-mediated stimulation induced LIGHT expression on intestinal $CD4^+$ T-Cells, but not on peripheral blood T-Cells, suggesting a gut-specific, Ag-independent mechanism can regulate LIGHT expression. A susceptibility locus for IBD (*IBD6*) is found on

Chr19p13,[38-40] although this region is gene dense, the status of *LIGHT* as disease candidate is significant and is consistent with observations in experimental animal models.

LIGHT has been implicated as a key mediator in atherosclerosis and rheumatoid arthritis. In atherosclerosis, oxidized HDL induced LIGHT in vitro and LIGHT expression was detected in atherosclerotic plaques with elevated serum levels in patients with angina.[41] In a mouse model of allograft arterial disease (class II mismatch), blockade of the LIGHT pathway with HVEM-Fc attenuated luminal occlusion, decreased intragraft cytokine expression and reduced smooth muscle cell proliferation.[42] In a potentially related observation, an allelic variant of LTα (252 A—>G) is linked to dislipidemia[43] and risk for myocardial infarction[44] although the latter observation was not replicated in all populations.[45] The shared binding of LIGHT and LTα to HVEM provides a potential mechanistic link, however LTα is a low affinity ligand for HVEM[10] (high affinity for TNFR1 and TNFR2) and LTα is also part of the LTαβ-LTβR signaling pathway. Recent studies in mice support a role for LIGHT and LTαβ in regulating lipid metabolism during inflammation.[46] Moreover, LTβR-Fc reduced the dyslipidemia in mice deficient in low-density lipoprotein receptor, which lack the ability to control lipid levels in the blood, an important risk factor for coronary heart disease. Additionally, LIGHT is expressed in inflamed joints and patients with rheumatoid arthritis accumulated elevated serum levels, consistent with a role of LIGHT in bone resorption.[47]

Together, the genetic evidence, animal models, pathogen targeting and expression patterns in human disease provides evidence that therapy directed at antagonizing LIGHT or LTαβ may be effective in inflammation driven mucosal and arterial diseases and similar autoimmune disorders. Early clinical trials of LTβR-Fc in rheumatoid arthritis revealed promising results at low doses, reinforcing the idea that LIGHT and LTαβ may play a role in joint disease.

Directed Therapeutics

The discovery of the LIGHT-HVEM-BTLA switch provides three novel targets for modulating immunity that may be useful in treatment of autoimmune diseases, cancer and infections. The extracellular position of the ligands and receptors in the TNF family provides a direct route to biologic-based therapeutics. Antibodies or decoy receptors antagonize the ligand-receptor interaction, thus interfering in cellular communication. However, antibodies may have secondary effects, such as activating effector systems like complement and cellular cytotoxicity, which may eliminate disease causing cells that express LIGHT or LTαβ on their surface. By contrast, antibody based agonists to individual receptors may be useful in activating specific receptors, in contrast to polygamous ligands, thus selectively enhancing cellular responses required to help resolve persistent infections or eliminate tumors. Blockade of LIGHT and LTαβ may be useful in limiting inflammation in autoimmune diseases. Agonists directed at BTLA may be useful in preventing activation of initial immune responses for instance in allograft rejection or graft vs host disease. By contrast, agonists directed at LTβR or HVEM may be useful in promoting immune responses against tumors and pathogens causing persistent infections.

Historically, no single criterion stood out as a predictor of the relevant clinical indication to apply TNF modulators. Presently, integration of the all available data including experimental animal models and human studies coupled with a mechanistic understanding is required to identify the relevant clinical situation to apply a given inhibitor.

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References

1. Locksley RM, Killeen N, Lenardo MJ. The TNF and TNF receptor superfamilies: Integrating mammalian biology. Cell 2001; 104:487-501.
2. Feldmann M, Brennan FM, Paleolog E et al. Anti-TNFalpha therapy of rheumatoid arthritis: what can we learn about chronic disease? Novartis Found Symp 2004; 256:53-69; discussion 69-73, 106-111, 266-109.

3. Granger SW, Ware CF. Commentary: Turning on LIGHT. J Clinical Investigation 2001; 108:1741-1742.
4. Watts TH. TNF/TNFR family members in costimulation of T-Cell responses. Annu Rev Immunol 2005; 23:23-68.
5. So T, Lee SW, Croft M. Tumor necrosis factor/tumor necrosis factor receptor family members that positively regulate immunity. Int J Hematol 2006; 83(1):1-11.
6. Ware CF. NETWORK COMMUNICATIONS: Lymphotoxins, LIGHT and TNF. Annu Rev Immunol 2005; 23:787-819.
7. Chaplin D, Fu YX. Cytokine regulation of secondary lymphoid organ development. Curr Opin Immunol 1998; 10:289-297.
8. Gommerman JL, Browning JL. Lymphotoxin/light, lymphoid microenvironments and autoimmune disease. Nat Rev Immunol 2003; 3(8):642-655.
9. Drayton DL, Liao S, Mounzer RH, Ruddle NH. Lymphoid organ development: from ontogeny to neogenesis. Nat Immunol 2006; 7(4):344-353.
10. Mauri DN, Ebner R, Montgomery RI et al. LIGHT, a new member of the TNF superfamily and lymphotoxin a are ligands for herpesvirus entry mediator. Immunity 1998; 8:21-30.
11. Rooney IA, Butrovich KD, Glass AA et al. The lymphotoxin-beta receptor is necessary and sufficient for LIGHT-mediated apoptosis of tumor cells. J Biol Chem 2000; 275:14307-14315.
12. Yu KY, Kwon B, Ni J et al. A newly identified member of tumor necrosis factor receptor superfamily (TR6) suppresses LIGHT-mediated apoptosis. J Biol Chem 1999; 274(20):13733-13736.
13. Sedy JR, Gavrieli M, Potter KG et al. B and T-lymphocyte attenuator regulates T-Cell activation through interaction with herpesvirus entry mediator. Nat Immunol 2005; 6(1):90-98.
14. Compaan DM, Gonzalez LC, Tom et al. Attenuating lymphocyte activity: the crystal structure of the BTLA-HVEM complex. J Biol Chem 2005; 280(47):39553-39561.
15. Garapati VP, Lefranc MP. IMGT Colliers de Perles and IgSF domain standardization for T-Cell costimulatory activatory (CD28, ICOS) and inhibitory (CTLA4, PDCD1 and BTLA) receptors. Dev Comp Immunol 2007.
16. Keir ME, Sharpe AH. The B7/CD28 costimulatory family in autoimmunity. Immunol Rev 2005; 204:128-143.
17. Riley JL, June CH. The CD28 family: a T-cell rheostat for therapeutic control of T-cell activation. Blood 2005; 105(1):13-21.
18. Chemnitz JM, Lanfranco AR, Braunstein I et al. B and T-lymphocyte attenuator-mediated signal transduction provides a potent inhibitory signal to primary human CD4 T-Cells that can be initiated by multiple phosphotyrosine motifs. J Immunol 2006; 176(11):6603-6614.
19. Wu TH, Zhen Y, Zeng C et al. B and T-lymphocyte attenuator interacts with CD3zeta and inhibits tyrosine phosphorylation of TCRzeta complex during T-cell activation. Immunol Cell Biol 2007.
20. Cheung TC, Humphreys IR, Potter KG et al. Evolutionarily divergent herpesviruses modulate T-Cell activation by targeting the herpesvirus entry mediator cosignaling pathway. Proc Natl Acad Sci USA 2005; 102(37):13218-13223.
21. Croft M. The evolving crosstalk between co-stimulatory and co-inhibitory receptors: HVEM-BTLA. Trends Immunol 2005; 26(6):292-294.
22. Watts TH, Gommerman JL. The LIGHT and DARC sides of herpesvirus entry mediator. Proc Natl Acad Sci USA 2005; 102(38):13365-13366.
23. Kabashima K, Banks TA, Ansel KM et al. Intrinsic lymphotoxin-beta receptor requirement for homeostasis of lymphoid tissue dendritic cells. Immunity 2005; 22(4):439-450.
24. Scheu S, Alferink J, Potzel T et al. Targeted Disruption of LIGHT Causes Defects in Costimulatory T-Cell activation and reveals cooperation with lymphotoxin beta in mesenteric lymph node genesis. J Exp Med 2002; 195:1613-1624.
25. Tamada K, Ni J, Zhu G et al. Cutting Edge: Selective Impairment of CD8(+) T-Cell Function in Mice Lacking the TNF Superfamily Member LIGHT. J Immunol 2002; 168(10):4832-4835.
26. Liu J, Schmidt CS, Zhao F et al. LIGHT-deficiency impairs CD8+ T-Cell expansion, but not effector function. Int Immunol 2003; 15(7):861-870.
27. Rennert P, Browning JL, Hochman PS. Normal development of lymphnodes is disrupted by soluble LT beta receptor-Ig fusion protein Europe Cytokine Network 1996; 7.
28. Nishikawa S, Honda K, Vieira P. Organogenesis of peripheral lymphoid organs. Immunol Rev 2003; 195:72-80.
29. Mackay F, Browning JL, Lawton P et al. Both the lymphotoxin and tumor necrosis factor pathways are involved in experimental murine models of colitis. Gastroenterology 1998; 115(6):1464-1475.
30. Anand S, Wang P, Yoshimura K et al. Essential role of TNF family molecule LIGHT as a cytokine in the pathogenesis of hepatitis. J Clin Invest 2006; 116(4):1045-1051.

31. Rahman MM, McFadden G. Modulation of tumor necrosis factor by microbial pathogens. PLoS Pathog 2006; 2(2):e4.
32. Smith CA, Davis T, Anderson D et al. A receptor for tumor necrosis factor defines an unusual family of cellular and viral proteins Science 1990; 248:1019-1024.
33. Kinkade A, Ware CF. The DARC conspiracy—virus invasion tactics. Trends Immunol 2006; 27(8):362-367.
34. Sedgmen BJ, Dawicki W, Gommerman JL et al. LIGHT is dispensable for CD4+ and CD8+ T-Cell and antibody responses to influenza A virus in mice. Int Immunol 2006; 18(5):797-806.
35. Banks TA, Rickert S, Benedict CA et al. A-lymphotoxin-IFN-beta axis essential for lymphocyte survival revealed during cytomegalovirus infection. J Immunol 2005; 174(11):7217-7225.
36. Cohavy O, Zhou J, Granger SW et al. LIGHT expression by mucosal T-Cells may regulate IFN-gamma expression in the intestine. J Immunol 2004; 173(1):251-258.
37. Cohavy O, Zhou J, Ware CF et al. LIGHT is constitutively expressed on T and NK cells in the human gut and can be induced by CD2-Mediated signaling. J Immunol 2005; 174(2):646-653.
38. Rioux JD, Silverberg MS, Daly MJ et al. Genomewide search in Canadian families with inflammatory bowel disease reveals two novel susceptibility loci. Am J Hum Genet 2000; 66:1863-1870.
39. Low JH, Williams FA, Yang X et al. Inflammatory bowel disease is linked to 19p13 and associated with ICAM-1. Inflamm Bowel Dis 2004; 10(3):173-181.
40. Tello-Ruiz MK, Curley C, DelMonte T et al. Haplotype-based association analysis of 56 functional candidate genes in the IBD6 locus on chromosome 19. Eur J Hum Genet 2006; 14(6):780-790.
41. Scholz H, Sandberg W, Damas JK et al. Enhanced plasma levels of LIGHT in unstable angina: possible pathogenic role in foam cell formation and thrombosis. Circulation 2005; 112(14):2121-2129.
42. Kosuge H, Suzuki JI, Kakuta T et al. Attenuation of graft arterial disease by manipulation of the LIGHT Pathway. Arterioscler Thromb Vasc Biol 2004.
43. Padovani JC, Pazin-Filho A, Simoes MV. Gene polymorphisms in the TNF locus and the risk of myocardial infarction. Thromb Res 2000; 100(4):263-269.
44. Tanaka T, Ozaki K. Inflammation as a risk factor for myocardial infarction. J Hum Genet 2006; 51(7):595-604.
45. Clarke R, Xu P, Bennett D et al. Lymphotoxin-alpha gene and risk of myocardial infarction in 6,928 cases and 2,712 controls in the ISIS case-control study. PLoS Genet 2006; 2(7):e107.
46. Lo JC, Wang Y, Tumanov AV et al. Lymphotoxin beta receptor-dependent control of lipid homeostasis. Science 2007; 316(5822):285-288.
47. Edwards JR, Sun SG, Locklin R et al. LIGHT (TNFSF14), a novel mediator of bone resorption, is elevated in rheumatoid arthritis. Arthritis Rheum 2006; 54(5):1451-1462.
48. Shaikh R, Santee S, Granger SW et al. Constitutive expression of LIGHT on T-Cells leads to lymphocyte activation, inflammation and tissue destruction. J Immunol 2001; 167:6330-6337.
49. Wang J, Lo JC, Foster A et al. The regulation of T-Cell homeostasis and autoimmunity by T-Cell derived LIGHT. J Clin Invest 2001; 108:1771-1780.
50. Wang J, Anders RA, Wang Y et al. The critical role of LIGHT in promoting intestinal inflammation and Crohn's disease. J Immunol 2005; 174(12):8173-8182.
51. Fan Z, Yu P, Wang Y et al. NK-cell activation by LIGHT triggers tumor-specific CD8+ T-cell immunity to reject established tumors. Blood 2006; 107(4):1342-1351.
52. Brown GR, Lee EL, El-Hayek J et al. IL-12-independent LIGHT signaling enhances MHC class II disparate CD4+ T-Cell alloproliferation, IFN-gamma responses and intestinal graft-versus-host disease. J Immunol 2005; 174(8):4688-4695.
53. Wu Q, Fu YX, Sontheimer RD. Blockade of lymphotoxin signaling inhibits the clinical expression of murine graft-versus-host skin disease. J Immunol 2004; 172(3):1630-1636.
54. Gommerman JL, Giza K, Perper S et al. A role for surface lymphotoxin in experimental autoimmune encephalomyelitis independent of LIGHT. J Clin Invest 2003; 112(5):755-767.
55. Plant SR, Iocca HA, Wang Y et al. Lymphotoxin beta receptor (Lt betaR): dual roles in demyelination and remyelination and successful therapeutic intervention using Lt betaR-Ig protein. J Neurosci 2007; 27(28):7429-7437.
56. Fava RA, Notidis E, Hunt J et al. A role for the lymphotoxin/LIGHT axis in the pathogenesis of murine collagen-induced arthritis. J Immunol 2003; 171(1):115-126.
57. Ye Q, Fraser CC, Gao W et al. Modulation of LIGHT-HVEM costimulation prolongs cardiac allograft survival. J Exp Med 2002; 195(6):795-800.
58. Xu Y, Flies AS, Flies DB et al. Selective targeting of the LIGHT-HVEM costimulatory system for the treatment of graft-versus-host disease. Blood 2007; 109(9):4097-4104.