M.-L. del Rio [a,b], P. Schneider [c], C. Fernandez-Renedo [b], J.-A. Perez-Simon [d] and J.-I. Rodriguez-Barbosa [a,•]

[a] Transplantation Immunobiology Section, Institute of Biomedicine, University of Leon, Leon, Spain.
[b] Castilla and Leon Regional Transplantation Coordination, Leon University Hospital, Leon, Spain
[c] Department of Biochemistry, University of Lausanne, Boveresses 155 CH-1066, Epalinges, Switzerland
[d] Department of Hematology, Virgen del Rocio University Hospital and Institute of Biomedicine (IBIS), Sevilla, Spain.

in Transplantation

**M.-L. del Rio[a], P. Schneider[b],
C. Fernandez-Renedo[c], J.-A. Perez-Simon[d]
and J.-I. Rodriguez-Barbosa[a,*]**

[a] *Transplantation Immunobiology Section, Institute of
Biomedicine, University of Leon, Leon, Spain*
[b] *Department of Biochemistry, University of Lausanne,
Boveresses 155 CH-1066, Epalinges, Switzerland*
[c] *Castilla and Leon Regional Transplantation Coordination,
Leon University Hospital, Leon, Spain*
[d] *Department of Hematology, Virgen del Rocio University
Hospital, Sevilla, Spain*
*Corresponding author:
Dr. Jose-Ignacio Rodriguez-Barbosa,
ignacio.barbosa@unileon.es*

**The exchange of information during interactions of
T cells with dendritic cells, B cells or other T cells
regulates the course of T-, B- and DC-cell activation
and their differentiation into effector cells. The tumor
necrosis factor superfamily member LIGHT (*homol-
ogous to lymphotoxin, exhibits inducible expression
and competes with HSV glycoprotein D for binding
to herpesvirus entry mediator, a receptor expressed
on T lymphocytes*) is transiently expressed upon T-
cell activation and modulates CD8 T-cell-mediated al-
loreactive responses upon herpes virus entry mediator
(HVEM) and lymphotoxin β receptor (LTβR) engage-
ment. LIGHT-deficient mice, or WT mice treated with
LIGHT-targeting decoy receptors HVEM-Ig, LTβR-Ig or
sDcR3-Ig, exhibit prolonged graft survival compared
to untreated controls, suggesting that LIGHT modu-
lates the course and severity of graft rejection. There-
fore, targeting the interaction of LIGHT with HVEM
and/or LTβR using recombinant soluble decoy recep-
tors or monoclonal antibodies represent an innovative
therapeutic strategy for the prevention and treatment
of allograft rejection and for the promotion of donor-
specific tolerance.**

**Key words: coinhibition, costimulation, HVEM, LIGHT,
LTbR, transplantation**

**Abbreviations: LIGHT, homologous to lymphotoxin,
exhibits inducible expression and competes with
HSV glycoprotein D for binding to herpesvirus en-
try mediator, a receptor expressed on T lymphocytes
(also known as HVEM-L, TNFSF14, CD258); HVEM,
Herpesvirus entry mediator (TR2, HveA, TNFRSF14,
CD270); LTβR, Lymphotoxin beta receptor (TNFRSF3);**
**sDcR3, soluble decoy receptor 3 (TNFRSF6B); TL1A,
TNF-like molecule 1A (TNFSF15, VEGI).**

Introduction

The innate immune system senses potential danger stim-
uli from the environment and functions as an early bar-
rier against pathogen colonization and invasion. This type
of immunity does not require previous exposure to anti-
gen and provides rapid and effective protection against
pathogen-induced damages. Innate cells quickly transfer
this information to the adaptive immune system, which
can respond more specifically and efficiently to fight for-
eign invaders (1,2).

According to the current widely accepted paradigm, the
first signal of T-cell activation and differentiation is medi-
ated by TCR recognition of foreign peptides in the con-
text of self-MHC. This initial signal is either reinforced or
dampened by the second signal that comes from a set of
costimulatory or coinhibitory receptor–ligand pairs, whose
balance modulates dendritic cell (DC), T-, B- and NK-cell
activation, cell division, survival and the acquisition of ef-
fector functions. Surface molecules involved in this pro-
cess of exchange of information belong to either the Im-
munoglobulin Superfamily (IgSF), whose common feature
is the presence of Ig variable-like extracellular domains, or
the Tumor Necrosis Factor Receptor Superfamily (TNFRSF)
that exhibits cysteine rich domains (CRD) in the extracel-
lular region of these molecules (3–6). TNF family ligands,
such as LIGHT or CD40L, are structurally homologous to
TNF in their extracellular domains. The blockade of TNFR–
TNF family ligand interactions impacts on CD4 and CD8
T-cell activation, survival and differentiation toward effec-
tor T cells (7–13). TNFRSF members regulate the normal
physiology of the immune system, and a number of DNA
and RNA viruses have evolved a convergent mechanism to
invade cells: they target the CRD1 of various TNFRSF and
take advantage of receptor-mediated endocytosis. In addi-
tion, viruses exploit and manipulate the signaling pathways
transduced by TNFRSF members to regulate cell death and
survival of the infected cells, acting as a strong selective
pressure in the evolution of host defenses (14–16).

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The future advancement in the field of clinical transplantation will depend on the increased recruitment of donors to face donor shortage and availability, as well as the development of innovative and more specific immunosuppressive therapies to overcome the humoral and cell-mediated arms of the allogeneic immune response involved in acute and chronic rejection. Approaches aiming at inducing central and peripheral donor-specific tolerance are highly desirable in transplantation to prevent early and late episodes of rejection, the long-term side effects of continued immunosuppression (organ toxicity and morbidity due to opportunistic infections), and the subsequent chronic deterioration of graft function. The use of biologics such as recombinant soluble decoy receptors and antagonist monoclonal antibodies capable to prevent receptor–ligand interactions, as well as depleting antibodies targeting precise lymphoid subpopulations represent promising novel paradigms for the development of alternative compounds more specific and efficacious than current immunosuppressive drugs. Blockade of the costimulatory CD28/CD80/CD86 pathway with CTLA4-Ig (Belatacept) has reached the clinical arena with great expectations, particularly for the control of CD4 T-cell-mediated allogeneic immune responses (17), although CD8 T-cell-mediated rejection is still in part refractory to this approach and requires further developments, particularly to allow transplantation in high-risk patients (presensitized to donor antigens) (18,19).

This review highlights and updates significant experimental contributions supporting the implication of LIGHT and its receptors in the course and outcome of the alloreactive immune response. LIGHT binds two membrane-bound receptors, HVEM and LTβR, and a third, soluble decoy receptor named DcR3 present in human but with unknown counterpart in the mouse. Each of LIGHT binding partners additionally interacts with one or more TNF family ligands. Moreover, HVEM can engage BTLA, a membrane-bound protein with an Ig-like fold, and CD160, a glycosylphosphatidylinositol-anchored protein, both belonging to the immunoglobulin superfamily and unrelated to the TNF family (Figure 1). This complex network of interactions therefore offers a number of therapeutic targets, but at the same time makes it extremely challenging to disrupt one interaction, without affecting the others. However, this is theoretically possible, because even if different ligands bind a common receptor at the same site, these interactions are not absolutely identical or incompatible, as characterized for BAFF, another TNF family ligand, and its three receptors (20). More realistically, it might be beneficial to simultaneously inhibit several of these interactions, for example with a LIGHT-blocking antibody that would inhibit binding to all of its receptors. In any case, therapeutic targeting of LIGHT – HVEM and/or LIGHT – LTβR are promising strategies for the control of undesirable immune responses that needs to be revisited with more specific reagents in transplantation.

The lack of blocking antibodies against mouse LIGHT, along with the difficulty to engineer bioactive recombinant mouse LIGHT, has precluded the evaluation of the consequences of interrupting the specific interactions between LIGHT – HVEM and LIGHT – LTβR in preclinical rodent models of transplantation. Besides, the likely lysosomal localization of LIGHT (21) and its rapid and transient expression on the cell surface as described for other members of TNFSF ligands, such as FasL or CD40L (22), has slowed down the characterization of LIGHT expression pattern on different hematopoietic cell populations.

LIGHT (TNFSF14) Genomic Organization, Isoforms and Receptor Signaling

The human LIGHT gene is located on chromosome 19, in the proximity of C3 complement protein within an MHC-like region. Human LIGHT (also known as HVEM-L or TNFSF14), a ligand for both HVEM and LTβR, was discovered almost simultaneously by two different groups (23,24) followed by the identification of its mouse homologue (7). Human LIGHT mRNA was found in activated lymphocytes, granulocytes, monocytes and immature DC, but is absent in the thymus and nonhematopoietic tumor cell lines (7,21). LIGHT is a 240 amino acids (aa)-long type II transmembrane protein of 29 kDa, with a 150 aa-long extracellular C-terminal domain coined the TNF homology domain (THD). The THD is the structurally conserved portion of all TNFSF ligands, with amino acid identities typically ranging from 20 to 30%. The THD assembles as homotrimers or, in rare occasions such as in LTαβ, as heterotrimers. It contains three receptor-binding sites located at the interface between two monomeric ligand subunits (Figure 1) (3,25,26). Human and mouse LIGHT share 77% sequence identity (7). In fact, human LIGHT shows specificity for mouse HVEM (27). Two splice variants of LIGHT have been described that result from the use of different splice donor sites in exon 1, yielding a membrane-bound form and a nonglycosylated, transmembrane-deleted form with cytosolic localization in activated T cells (28). In addition, membrane-bound LIGHT can be released in a soluble form after processing by a metalloprotease at aa position 81–84, in the sequence encoded by exon 2 (28).

TNFRSF members usually signal via their intracellular death domains, or by recruiting and activating TRAF (TNF receptor associated factor) signaling molecules. LTβR and HVEM, two membrane-bound receptors for LIGHT, signal via TRAF molecules to connect the extracellular milieu to an intracellular signaling cascade through the canonical NF-κB pathway, leading to nuclear translocation of p50/RelA and subsequent transcription of proinflammatory genes, although to a lesser extent than the type of signal transduced through TNFR1 (29). In addition, LTβR can also activate the noncanonical NF-κB pathway that leads to p52/RelB translocation to the nucleus and the transcription

Figure 1: The LIGHT–HVEM–LTβ R–DcR3–BTLA molecular network. Panel A. Interactions between LIGHT and its receptors, and between receptors for LIGHT and their ligands. Numbers in brackets under the name of ligands or receptors refer to the TN-FSF or TNFRSF number. LTαβ2, LTα, LIGHT, TL1A and FasL are trimeric, membrane-bound or soluble TNF family members. For LIGHT, portions of the protein coded by exons 1 to 4 are indicated. The metalloprotease cleavage site in the region coded by exon 2 is shown as a pair of scissors. The transmembrane domain of LIGHT (dotted red line) can be spliced out in a variant, resulting in a soluble, intracellular LIGHT of unknown function. BTLA is an Ig s[...] a dimeric, GPI-anchored protein w[...] and DcR3 are TNFR family members, the latter being a soluble decoy receptor. They are schematized in their module representation with each horizontal bar representing a cysteine residue (3). Two modules usually form a cysteine-rich domain (CRD). The region of the receptors that form the TNF ligand binding sites (usually CRD2 and the beginning of CRD3) are shown by the thick vertical lines close to the receptors. BTLA engages CRD1 of HVEM in *trans*, as shown here, but the interaction can also take place in *cis*, with both partners on the same cell. BTLA, CD160, LTα, TL1A and FasL engage additional partners not depicted in this figure. Portions of ligands and receptors highlighted in yellow are those for which a crystal structure is available. Panel B. Structure of a TL1A trimer (monomers are in shades of red) bound to three monomeric DcR3 (in shades of cyan). Drawn from PDB atomic coordinate file 3K51. Panel C. Model of a LIGHT trimer (monomers are in shades of dark pink) bound to three HVEM monomers (in shades of light green and

of genes implicated in secondary lymphoid organ development (29,30).

Role of LIGHT on T-cell Activation, Thymic Selection and Lymph Node Hypertrophy

The functional role of LIGHT has been studied in knock-out and transgenic mice. Constitutive expression of a human LIGHT transgene under a T-cell-specific promoter led to permanent and exacerbated T-cell activation accompanied by persistent inflammatory responses at mucosal sites and tissue destruction of the reproductive organs (31). These LIGHT-mediated inflammatory alterations also affected primary and secondary lymphoid organs with an increased size of lymph nodes and splenomegaly, although spleens were lymphopenic and their architecture was disturbed. Thymocyte cell numbers and thymopoietic activity was also reduced, likely due to the critical role of LIGHT in negative selection and in the induction of apoptosis in immature thymocytes (31,32).

Several independent research groups have developed LIGHT-deficient mouse models almost simultaneously (33–35). LIGHT-deficient mice display reduced CD8 T-cell proliferation in response to plate-bound anti-CD3 or anti-CD3/CD28, or to *Staphylococcal* enterotoxin B polyclonal stimulation or to allogeneic DC stimulation, whereas CD4 T-cell proliferation is not affected (10,33,35). However, these defects in CD8 T-cell proliferation do not affect their cytotoxic effector activity and are not reversible in the presence of IL-2 or IL-12 (33).

LIGHT-ko mice exhibit normal lymph node (LN) development (35), although these lymph nodes fail to increase in size after immunization (36). Lymphocyte trafficking and migration of radio-resistant Langerhans DC into draining lymph nodes after immunization is also at least partially compromised (36). This phenotype is most probably due to the LIGHT–LTβR interaction, as draining LN of similarly immunized HVEM-deficient or HVEM-Ig-treated WT mice do undergo normal hypertrophy (36).

[...] o BTLA (in dark blue). The model was [...] cture of LIGHT trimer (PDB file 4EN0) on TL1A (PDB file 3K51) and by fitting HVEM in the structure of the HVEM–BTLA complex (PDB file 2AW2) onto DcR3 (PDB file 3K51). Note that the binding sites of HVEM to LIGHT (CRD2 and CRD3) and to BTLA (mainly CRD1) are clearly distinct. Panel D. Same as panel C, except that the structure of the HVEM–BTLA complex was replaced by that of the HVEM in complex with a portion of herpes simplex virus glycoprotein D (HSV-gD, in orange) (PDB file 1JMA). Panel E. Models of LIGHT in complex with HVEM, DcR3 or LTβR, based on PDB files 2AW2, 3K51 and 4ENO. LTβR was modeled on the structure of its close homologue HVEM using the SwissModel option of the Swiss-PdbViewer. These models indicate that HVEM, DcR3 and LTβR use similar binding sites on LIGHT.
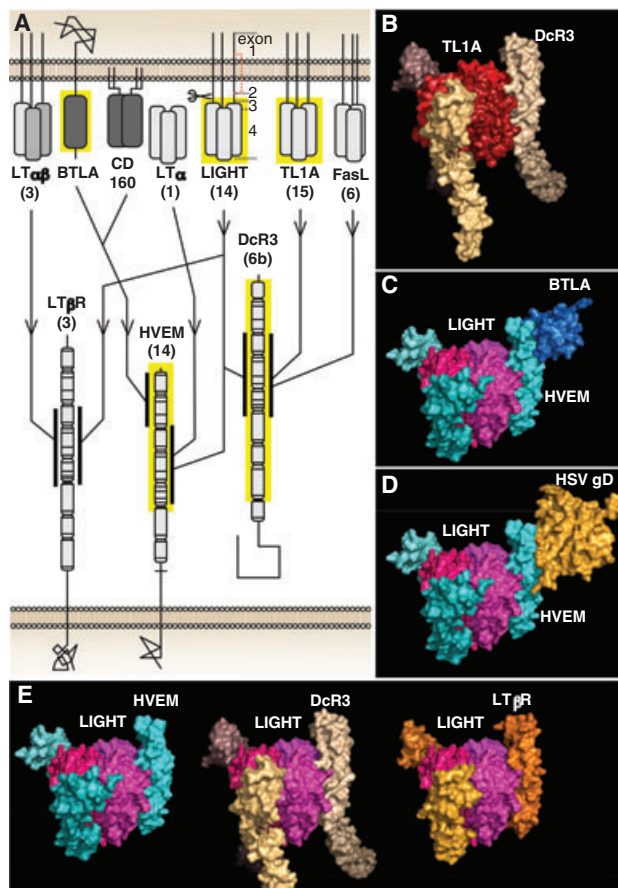
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Therefore, LIGHT plays a central role in regulating CD8 T-cell proliferation, thymocyte differentiation and lymph node hypertrophy after immunization.

Platelets-derived LIGHT in Vascular Endothelial Cell Activation and Atherogenesis

The main physiological role of platelets is to participate in hemostasis and wound healing. However, the action of platelets-derived LIGHT on endothelial cells, T cells, monocytes, macrophages and vascular smooth muscle cells has also been implicated in the development of atherogenic lesions and plaque destabilization in acute coronary syndromes (37). Despite the fact that activated T cells are the major source of soluble LIGHT (38), platelets can also release significant amounts of soluble LIGHT, which exerts pro-proinflammatory, prothrombotic and atherogenic activity through activation of vascular endothelial cells (37,39–41). The interactions of LIGHT and LTα1β2 with LTβR activate the canonical NF-κB pathway in endothelial cells to promote T-cell adhesion through E-selectin, ICAM-1 and VCAM-1 upregulation. The effect of LTβR stimulation by LIGHT is however weaker than that obtained with TNF on TNF receptors. LTβR ligation by LIGHT also activates noncanonical NF-κB and expression of the chemokine CXCL12, which is not under the regulation of TNF (42). This inducible expression of chemokines and integrins in endothelial cells facilitates the migration of leukocytes to areas of inflammation. Besides, the presence of soluble LIGHT in serum samples of individuals suffering from chronic inflammatory diseases correlates with increased levels of proinflammatory mediators (38,40,41,43). The release of soluble LIGHT by platelets appears to be a mediator of atherosclerosis by inducing proatherogenic cytokines, and of plaque rupture by promoting the release of matrix metalloproteases (MMP-1, 9 and 13) that destabilize the atherosclerotic plaque. Besides, LIGHT expression on pathological atherogenic vessels is usually associated with higher expression of MMPs and lower expression of TIMPs, their inhibitors. This is an indication that LIGHT may indirectly contribute to plaque disruption (39).

Therefore, LIGHT may be a relevant player in the development of chronic allograft dysfunction and could be behind thrombotic episodes in transplanted patients.

LIGHT–HVEM–LTβR Pathway in T-cell Proliferation and DC Maturation

LIGHT binds to LTβR (44) and HVEM (23), and in humans also interacts with DcR3/TR6 (45). Whereas LTβR is constitutively expressed in stromal cells of secondary lymphoid organs, thymus and in the myeloid cell lineage (46), HVEM exhibits a pattern of expression not only restricted to hematopoietic cells but also expands to a broad variety of nonhematopoietic cells (47). In contrast, the ligand of these receptors, LIGHT is only induced upon T-cell activation, although it is also expressed on immature DC (24) (Figure 2).

HVEM was initially identified as a receptor for herpesvirus entry into target cells during infection (48). The intracellular region of HVEM interacts with TNFR-associated factors (TRAF) family members to activate the classical NF-κB pathway (49,50). Human HVEM-Ig and mouse antihuman HVEM mAbs inhibit T-cell proliferation in mixed lymphocyte reaction (51,52) and in response to stimulation with allogeneic DC (8). On the contrary, soluble human LIGHT (shLIGHT) costimulates T-cell proliferation through HVEM at low dose, but this effect declines as shLIGHT concentration increases (51,52). Therefore, LIGHT can regulate T-cell responses via HVEM, which is constitutively expressed in all lymphocyte subsets.

Membrane-anchored or soluble Flag-tagged human LIGHT can costimulate T-cell growth when T-cell receptor is engaged with a suboptimal dose of anti-CD3 monoclonal antibody, in the presence of IL-2 (24). This costimulation is independent of CD28 signaling and preferentially induces IFN-γ and GM-CSF, but not IL-4 or IL-10. LIGHT-mediated T-cell proliferation can be reversed by a LTβR-Ig fusion protein or by neutralizing anti-LIGHT polyclonal antibodies directed against a peptide of LIGHT (aa 209–232 ML209-peptide) important for its interaction with HVEM and LTβR (7,35).

LIGHT and CD40L are TNF superfamily members transiently expressed upon T-cell activation and the interaction with their respective receptors synergize cooperatively in the differentiation of immature DC or monocytes to mature DC and augment their ability to stimulate CTL priming against tumor antigens (53,54) (Figure 2). However, when used alone, LIGHT is much less effective than CD40L at inducing DC maturation (53,54). LIGHT-induced DC maturation most likely requires HVEM, because it can be blocked to a large extent by an antagonist anti-HVEM antibody (53). Moreover, the engagement of LTβR and HVEM by LIGHT induces CCL27 expression in a dose-dependent manner on DC by a TRAF2-dependent signaling mechanism (55).

Interestingly, human LIGHT and HVEM expression are reciprocally regulated on the same cell after T-cell activation. Thus, HVEM is downregulated whereas LIGHT is transiently expressed on activated T cells (21). Furthermore, LIGHT expression is more pronounced on CD8 T cells than on CD4 T cells. This HVEM downregulation could be partially reversed by adding a neutralizing monoclonal antibody against LIGHT or soluble HVEM-Ig during T-cell activation (21). These observations suggest that T-cell activation induces the expression of membrane-bound LIGHT and also activates the proteolytic machinery that permits LIGHT processing and shedding LIGHT to the extracellular milieu. Both soluble and membrane-bound
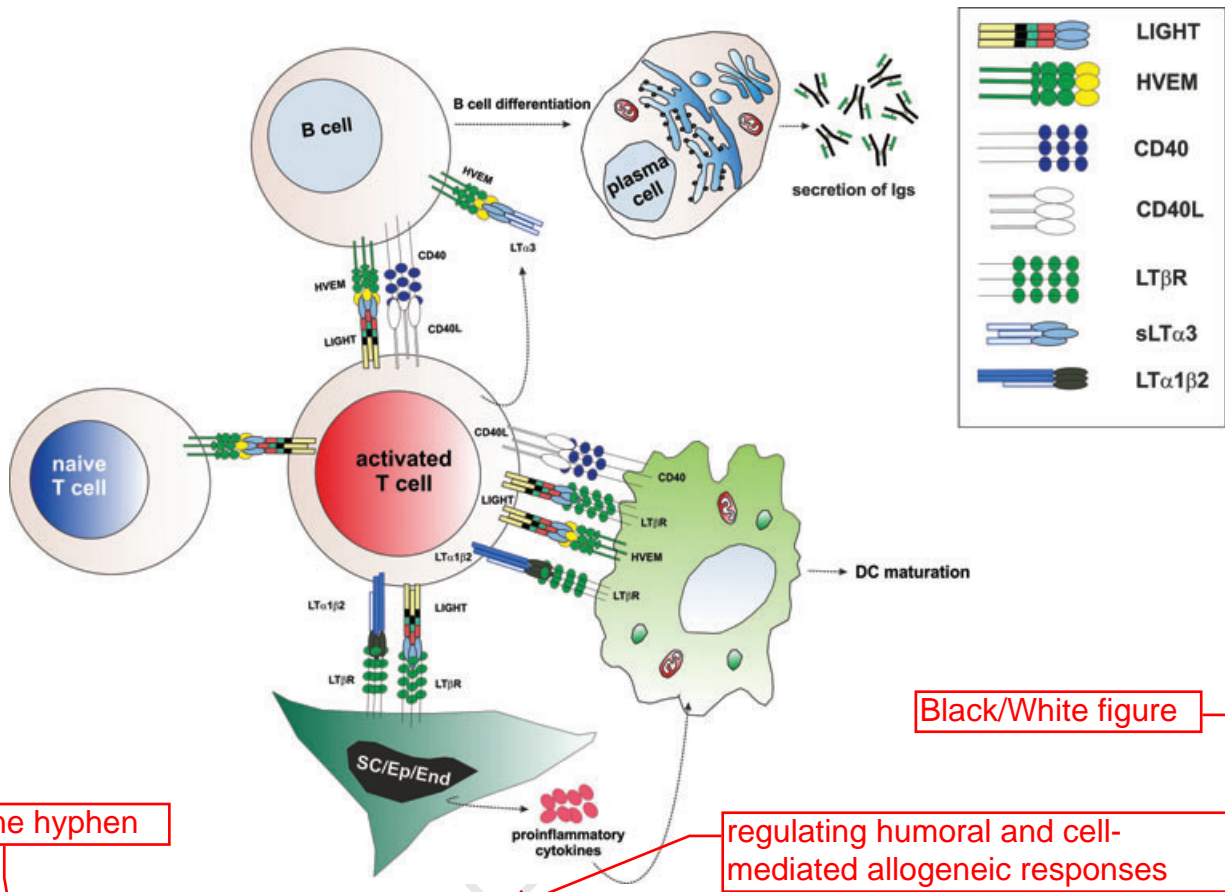
Figure 2: Pivotal role of LIGHT in regulating humoral- and cellular-mediated allogeneic responses. The transient expression of TNFSF ligands on activated T cells is a common feature of members of this family such as OX40, CD40L, LTα1β2, FasL and LIGHT. This inducible expression upon T-cell activation enables T cells to deliver costimulatory signals to surrounding naïve T cells, B cells, dendritic cells, epithelial, stromal and endothelial cells. The close proximity of an activated T cell expressing LIGHT and a naïve T cell with specificity for alloantigen will allow HVEM activation and the delivery of a costimulatory signal to the naïve cell. Alloantigen-specific activated T cells encounter B cells that in turn may be recognizing conformational epitopes on foreign allogeneic MHC. This would permit the delivery of T-cell help to B cells through the exchange of LIGHT–HVEM, LTα3–HVEM and CD40L–CD40 costimulatory interactions to drive B-cell activation, plasma cell differentiation and subsequent secretion of alloreactive host antidonor antibodies. Dendritic cells in response to an inflammatory stimulus migrate to draining lymph nodes where they encounter T cells. CD4 T cells license DC for CTL priming thanks to the exchange of costimulatory signals between CD40L and CD40, and perhaps other interactions such as LIGHT–HVEM–LTβR and LTα1β2–—LTβR, allowing DC to costimulate T-cell proliferation and subsequent differentiation toward effector T cells. Similarly, LIGHT and LTα1β2, whose expression is induced on activated T cells, would bind to HVEM and LTβR on stromal, epithelial and endothelial cells, promoting the release of proinflammatory cytokines that cooperate in the process of DC maturation and in the acquisition of a proficient machinery of antigen processing and presentation so that they can efficiently stimulate alloreactive T cells.

LIGHT can induce HVEM downregulation and subsequent degradation (21).

The transient expression of LIGHT also perturbs BTLA–HVEM *cis* and *trans* interactions. Thus, naïve T cells coexpress HVEM and BTLA that form a *cis* complex and this prevents BTLA and CD160 to act in *trans* and prevents costimulation of HVEM expressing cells (56–59). Upon T-cell activation, LIGHT expression is induced and binding to HVEM disrupts the *cis* complex of BTLA – HVEM by a noncompetitive mechanism. This permits LIGHT to engage and activate HVEM in *trans* (60). Interestingly, when soluble LIGHT embraces the HVEM–BTLA *cis* complex,

it reinforces the interaction to prevent HVEM signaling in *trans* instead of disrupting it. LIGHT–HVEM *trans* interaction can also deliver reverse signaling through LIGHT, activating MAPK costimulatory signaling (51,61). Finally, binding of the soluble form of LIGHT to the BTLA–HVEM *trans* complex stabilizes this interaction, since it can compete with BTLA for binding to HVEM.(4,50,57) (Figure 3).

In summary, the inducible expression of LIGHT on T cells costimulates T-cell proliferation by a CD28-independent mechanism that requires IL-2, and involves a conformational change of the preexisting HVEM–BTLA complex from the *cis* to the *trans* conformation, which facilitates
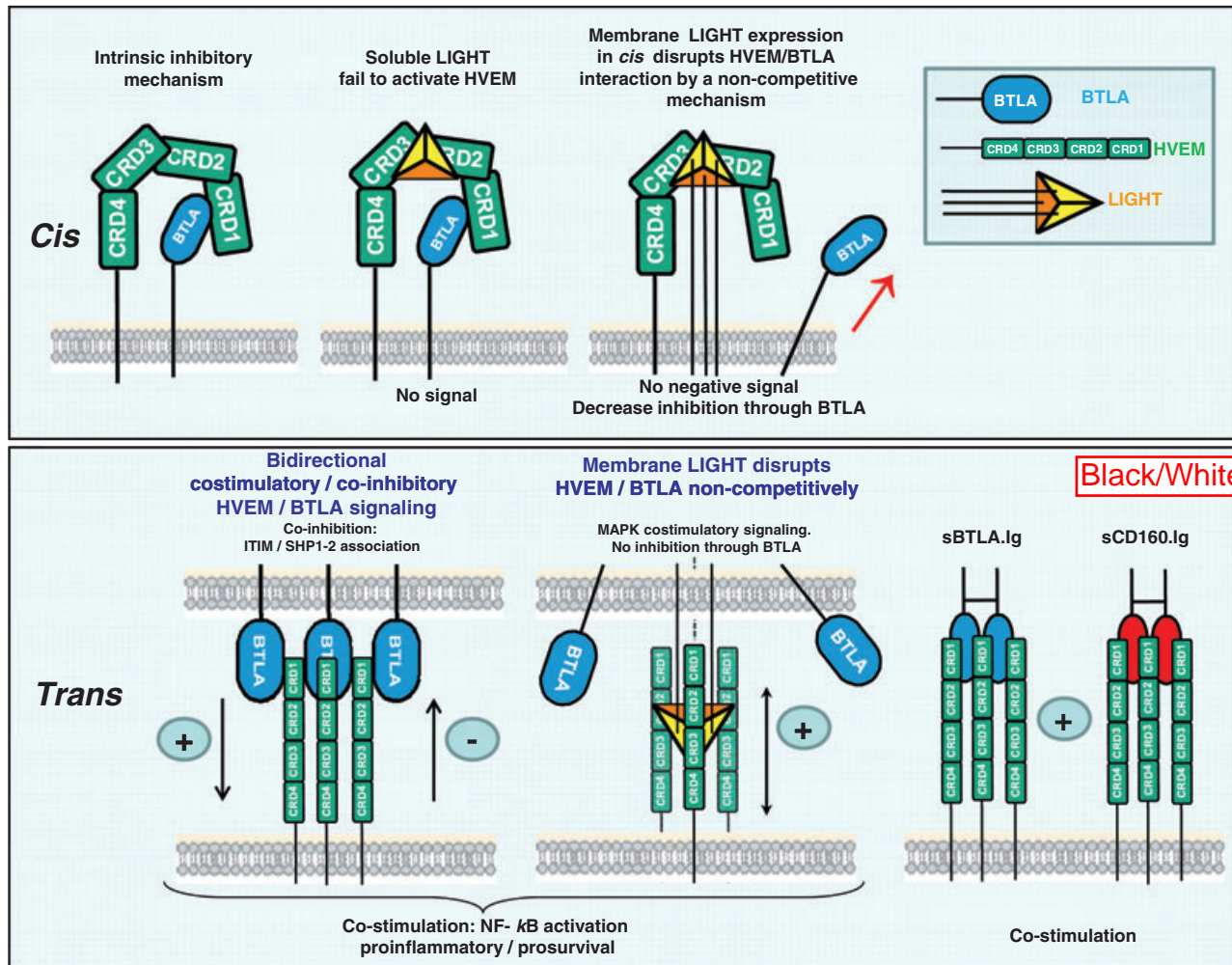
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Figure 3: LIGHT modulates HVEM–BTLA *cis* and *trans* interactions. HVEM and BTLA are constitutively expressed on T cells. Upon T-cell activation, BTLA is upregulated, HVEM is downregulated and LIGHT is only transiently expressed (27). Upper panel: *cis* interactions. Ligand and receptor are expressed on the same cell. Left-upper part: BTLA interacts with CRD1 of the extracellular domain of HVEM. The HVEM–BTLA *cis* interaction is an intrinsic coinhibitory mechanism that prevents HVEM or BTLA from interacting in *trans* with their partner molecules. Middle upper part: binding of soluble LIGHT to the *cis* HVEM–BTLA complex does not activate HVEM and signal transduction, but stabilizes the inactive complex. Right-upper part: T-cell activation leads to transient expression of membrane-anchored LIGHT, which interacts in *cis* with CRD2 and CRD3 of HVEM. This disrupts the interaction of HVEM with BTLA. Lower panel: *trans* interactions. Ligand and receptor are expressed on different cells. Left-lower part: in the absence of LIGHT, the HVEM–BTLA interaction in *trans* delivers inhibitory signals to T cells. Soluble LIGHT can bind and reinforce the *trans* HVEM–BTLA complex, without disrupting it. This complex delivers coinhibitory signals through BTLA but also provides costimulation through HVEM. Middle-lower part: the transient expression of membrane-anchored LIGHT after T-cell activation disrupts the HVEM–BTLA *trans* interactions enabling LIGHT to engage HVEM expressed in surrounding cells. In this scenario, costimulation could be bidirectional with HVEM providing costimulation to activated T cells via reverse LIGHT signaling. Right-lower part: triggering HVEM by soluble BTLA-Ig or soluble CD160-Ig costimulates T-cell activation and proliferation.

productive signaling of LIGHT through HVEM and vice versa.

Targeting LIGHT Interaction with HVEM and/or LTβ R in Cellular and Solid Organ Transplantation

Costimulatory pathways are central players in the regulation of allogeneic immune responses and their targeting with biologic compounds would help to the development of approaches to reduce allograft rejection and to improve long-term transplantation tolerance. Those CD8 T-cell-mediated rejections that are refractory to costimulation blockade with CTLA4-Ig and/or CD40-CD40L remain an unsolved problem and a subject of intense research in the field of transplantation. Since LIGHT is more actively expressed on activated CD8 T cells than on CD4 T cells, it could represent a potential target to dampen CD8 T-cell-mediated responses.

Table 1: Experimental evidence for the role of LIGHT and its receptors in the control of allogeneic immune responses in different transplantation settings

Transplantation setting	Experimental approach	Outcome	Quotes
B6 to Balb/c islet allotransplantation	sLTβR-Ig + CTLA4-Ig	Survival >100 days	(62)
	CTLA4-Ig	MST: 55 days	
	LTbR-Ig	MST: 27 days	
Fully MHC-mismatched cardiac allografts	Balb/c to B6 WT	MST: 7 days	(34)
	Balb/c to B6 LIGHT-ko	MST: 10 days	
	Balb/c to CyA-treated B6 WT	MST: 10 days	
	Balb/c to CyA-treated B6 LIGHT-ko	MST: 30 days	
	Balb/c to HVEM-Ig-treated B6 WT	MST: 7 days	
	Balb/c to HVEM-Ig + CyA-treated B6 WT	MST: 21 days	
Fully MHC-mismatched cardiac allografts	Human DcR3-Ig	Slightly enhanced survival	(63)
Fully MHC skin allografts	LIGHT/CD28 double KO	Prolonged survival	(35)
Parental into F1 bone marrow transplantation	Polyclonal antireceptor binding site of LIGHT	Partial inhibition of GvHD	(7)
	LTβR-Ig	Partial inhibition of GvHD	
Parental into lethally irradiated F1 recipients and B6 to fully MHC-mismatched lethally irradiated Balb/c bone marrow transplantation	LTα-ko (lacks LTα3 and membrane LTα1β2) parental splenocytes to F1 or Balb/c recipients.	Attenuate of skin and colon GvHD	(65)
	LTβ-ko (lacks membrane LTα1β2) parental splenocytes to F1 or Balb/c recipients	No attenuation of GvHD	
Xenogeneic bone marrow transplantation model	Depleting antihuman LTα monoclonal antibody	Attenuation of GvHD	(68)
	Adoptive transfer human T cells to SCID/Beige mutant mice		
Parental into nonlethal and lethal F1 recipients and B6 into nonlethal and lethal fully MHC-mismatched lethally irradiated Balb/c bone marrow transplantation	Anti-HVEM blocking antibody of LIGHT/HVEM and HVEM/BTLA interaction	Attenuation of GvHD	(11)
Parental B6 WT or B6 IL-12Rβ2 KO into lethally irradiated MHC class II-mismatched F1 (bm12xB6) recipients	Adv-human LTbR.Ig or Adv-mouse HVEM.Ig treated recipients	Attenuation of mixed lymphocyte reaction or intestinal GvHD	(67;68)

MST = mean survival time, GvHD = graft versus host disease.

The proof of concept for targeting the LIGHT pathway to prevent graft rejection comes from numerous experimental preclinical rodent models of transplantation that are summarized in the following section and Table 1.

Islet Allograft Transplantation

Long-term survival of allogeneic islets can be achieved through a combined therapy with sLTβR-Ig plus CTLA4-Ig. This treatment increased tolerance to the donor and prolonged graft survival. It is likely that the critical interaction blocked by sLTβR-Ig fusion protein was that of LIGHT with HVEM, because the administration of an antagonist anti-LTβR monoclonal antibody to block the LTβR–LTα1β2 interaction failed to increase graft survival compared to isotype-matched treated controls (62).

Cardiac and Skin Transplantation

Cumulative evidence supports that solid organ transplantation can also benefit from blockade of the LIGHT–HVEM–

LTβR pathway. Thus, Balb/c cardiac allografts survived for 7 days in C57BL/6 WT mice, but for 10 days in LIGHT-deficient mice or in WT mice treated with low dose cyclosporine A (CyA), and for up to 30 days in LIGHT-deficient mice treated with low dose CyA. When LIGHT-deficiency was mimicked by administration of HVEM-Ig, cardiac allografts survived for 7 days and graft survival augmented to 21 days when combined with low dose CyA (34). In more stringent models of transplantation, blockade of LIGHT pathway also delayed graft rejection significantly. Although LIGHT-deficient or CD28-deficient mice used as recipients of skin allografts showed similar rejection kinetics as WT mice, recipient mice deficient for both LIGHT and CD28 exhibited delayed skin graft rejection, suggesting that LIGHT and CD28 cooperate for costimulation (35).

The soluble decoy receptor DcR3 competes with HVEM for binding to LIGHT. DcR3 also binds to FasL, preventing FasL-mediated apoptosis and also interferes with the costimulatory pathway TL1A–DR3. *In vitro*, the addition of shDcR3-Ig to mixed lymphocyte reactions prevents the priming phase of the response, in which CD8 T cells differentiate toward effector T cells, but does not affect the

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cytotoxic phase of the *in vitro* [51]Cr release CTL assay (63). Moreover, administration of soluble human DcR3-Ig fusion protein moderately enhanced heart allograft survival across a full MHC barrier by suppressing CTL-mediated responses and preventing cytokine production (63).

Bone Marrow Transplantation and GvHD

Allogeneic bone marrow transplantation and the side effects of graft versus host disease (GvHD) can also benefit from the blockade of LIGHT. Thus, *in vivo* administration of a LIGHT-blocking polyclonal antibody partially inhibited the course of GvHD (7). Also, *in vivo* administration of soluble LTβR-Ig attenuates rejection of host hematopoietic cells by inhibiting the donor antihost CTL response. This resulted in delayed and less aggressive elimination of host splenic B lymphocytes and host double positive thymocytes, which are the hallmark features of GvHD side effects on the host hematopoietic system (7).

In contrast to LIGHT, the inducible expression of membrane LTα1β2 upon T-cell activation is more pronounced on CD4 T cells than on CD8 T cells (only activated memory CD8 T cells) (64). Lethally irradiated F1 recipients rescued with a syngeneic bone marrow transplant that receive a low dose of semiallogeneic splenocytes deficient for LTα developed a less severe form of skin and colon GvHD pathology compared to that reported after TNF blockade (65). These observations suggest that both LTα and TNF are relevant targets for clinical evaluation of efficacy on preventing skin and intestine GvHD. The blocking hamster antimouse HVEM monoclonal antibody, clone LBH1, antagonizes both HVEM–BTLA and HVEM–LIGHT interactions. When it was administered to lethally irradiated mice rescued with allogeneic, T-cell-depleted bone marrow cells plus allogeneic splenocytes, an effective protection against the rejection of host hematopoietic cells in various bone marrow transplantation settings across distinct histocompatibility barriers was observed (11). In agreement with these results, the adoptive transfer of allogeneic HVEM-ko or LIGHT-ko splenocytes to nonirradiated or irradiated F1 recipients also reduced the donor antihost response (11).

LIGHT blockade with LTbR-Ig or HVEM-Ig also perturbs CD4 T-cell-mediated mechanism of GvHD after bone marrow transplantation. Thus, intravenous injection of parental B6 WT or B6 IL-12Rβ2 KO CD4 T cells into lethally irradiated MHC class II-mismatched F1 (bm12 × B6) recipients that were treated with a recombinant adenoviral vector expressing either human LTβR-Ig or mouse HVEM-Ig and rescued with T-cell-depleted B6 bone marrow cells, showed attenuated CD4 T-cell infiltration and reduced IFNγ production. This resulted in less intestinal GvHD than untreated controls by a mechanism that is IL-12 independent (66,67).

Soluble human DcR3 cross-reacts with mouse LIGHT and its administration to nonirradiated F1 recipient that received a large dose of B6 splenocytes delayed GvHD-induced death of the recipient mice (63).

In conclusion, mice deficient for molecules involved in the HVEM–LIGHT–LTβR pathway or treated with blocking antibodies or soluble decoy receptors that disrupt the interaction between these binding partners displayed attenuated symptoms in GvHD models, pointing to the therapeutic potential of targeting this molecular network of interactions to prevent GvHD after allogeneic bone marrow transplantation.

Therapeutical Interventions Aiming at Targeting LIGHT Interactions with Its Receptors

The LTαβ and LIGHT duet and their cognate receptors form a network of interactions essential for the normal development and homeostasis of the immune system and for the modulation of the onset and maintenance of the allogeneic immune responses. The blockade of costimulatory ligand and receptor interactions can be achieved with either soluble decoy molecules that prevent receptor–ligand interactions or with depleting or nondepleting antagonist antibodies. These biologic compounds represent promising drugs to reinforce the current immunosuppressive therapy with the potential application of improving the conditioning protocols for the induction of tolerance at the early phase posttransplant that would allow reducing immunosuppressant doses during the posttransplant maintenance phase. This innovative therapy would improve the quality of life of transplanted patients mitigating the long-term metabolic disorders and chronic organ deterioration.

Because of their inducible and transient expression, LIGHT and LTα1β2 are more suitable targets for the selective removal of recently activated allogeneic T cells than HVEM or LTβR, which are more widely expressed on hematopoietic and nonhematopoeitic cells. In this sense, LTα has been recently proposed as a clinical target for the depletion of alloreactive T cells in a humanized mouse model (68). It would be extremely interesting to be able to specifically interfere with LIGHT–HVEM, LIGHT–LTβR or LTα1β2—LTβR interactions to study the contribution of each of these individual pairs to the overall allogeneic immune response. The specific targeting of LTβR should allow specific disruption of the later pair, but for the others, the production of specific inhibitors will be a challenge as both the ligands and receptors bind several partners at the same sites. In practice, it may however be preferable to target several of these interactions, which could be achieved either with blocking antibodies against the ligands, or with receptor-Ig fusion proteins that can simultaneously target multiple ligand–receptor pairs. The theoretical possibility that a receptor.Ig fusion protein might exhibit nondecoy functions, such as initiating reverse-signaling through membrane-bound ligands, should be kept in mind. An example of a molecule inhibiting multiple interactions is DcR3. Soluble DcR3-Ig

behaves as a potent immunosuppressant compound capable to block at once the interactions of LIGHT with HVEM and LTβR, and of TL1A with DR3, and of FasL with Fas. The *in vivo* administration of soluble human DcR3-Ig attenuates IL-2 secretion by T cells, which decreases CD4 proliferation and immune deviation toward a Th2 type response, dampening cellular-mediated immunity (69). Prolonged administration of DcR3-Ig may however induce autoimmune side effects, as described in a DcR3 transgenic mice. These side effects probably arise because the inhibition of FasL interferes with activation-induced cell death by apoptosis of low affinity autoreactive T cells (70). Another example of recombinant compound with potent immunosuppressive activity is soluble LTβR-Ig that can theoretically target LIGHT – LTβR – HVEM and LTα1β2 – LTβR simultaneously. LTβR-Ig synergizes with CTLA4-Ig to prolong long-term survival of islet graft and to induce donor-specific tolerance (62).

Targeting two pathways simultaneously when several ligands and receptors interactions are interrupted in each of the pathways may lead to unwanted consequences, because too much immunosuppression could be achieved. In line with this notion, a worrying number of posttransplant lymphoproliferative disorders (PTLD) and intracellular bacterial infections has been reported after costimulation blockade with CTLA-Ig alone (17). The simultaneous blockade of two or more pathways could be indicated only in a selected group of patients who are not responding adequately to standard immunosuppressive protocols or blockade with CTLA4-Ig/belatacept, such as sensitized patients with ongoing host antidonor humoral immune responses or undergoing refractory CD8 T-cell-mediated episodes of rejection.

The therapeutic strategy that we would favor is the use of an antagonist or depleting anti-LIGHT antibody instead of LTβR-Ig. Taking into account that HVEM and LTβR bind the same region in the TNF homology domain of LIGHT (Figure 1), it seems reasonable to predict that an antagonist antibody against the TNF receptor-binding region of LIGHT would completely block LIGHT signaling through both receptors. However such an antibody against LIGHT should ideally lack signaling ability to avoid undesirable T-cell costimulation through LIGHT. The other reason for the use of an anti-LIGHT antibody would be the neutralization of LIGHT in its soluble form. Sanofi-aventis and Kyowa Hakko Kirin pharma groups have reached licensing collaborative agreements for the clinical development of a fully human anti-LIGHT antibody raised by investigators at the La Jolla Institute for Allergy and Immunology as therapeutic indication in ulcerative colitis and in Crohn's disease and with further indications in rheumatoid arthritis and in the prevention of airways remodeling in asthma (71), which could be extended to prevention or treatment of graft rejection in transplantation. This is because not all patients affected by these pathologies can benefit from therapies with anti-TNFs biologics.

In conclusion, specific targeting of the interaction between LIGHT—HVEM and/or LIGHT—LTβR using recombinant soluble decoy receptors or more selective topographically specific monoclonal antibodies against LIGHT binding site may be a novel potential therapeutic intervention for the prevention and treatment of allograft rejection and for the promotion of donor-specific tolerance that deserves to be explored in human transplantation and other diseases.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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