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Review Article

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LIGHT/TNFSF14 in Tissue Homeostasis and Disease

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ABSTRACT

LIGHT is a proinflammatory cytokine expressed by immune cells. Its action is linked to the binding with the receptor HVEM, LTβR and DcR3 (The last expressed only in human cells). It has a wide range of functions and different organs and tissues can be affected according to the levels of inflammation. In this review the involvement of LIGHT in homeostasis and disease in human and animal models has been evaluated in intestine, adipose tissue, liver, bone and heart, highlighting its role as potential therapeutic target in pathologies characterized by the dysregulated LIGHT levels. All these studies are important because monoclonal antibodies against LIGHT have been realized, leading to a precise target, the studies evaluating the efficacy will be published soon and will be usefull in precision medicine.

Keywords: LIGHT/TNFSF14, Homeostasis, Disease, In Intestine, Adipose Tissue, Liver, Bone, Heart

Introduction

The tumour necrosis factor superfamily member 14 (TNFSF14), commonly known as LIGHT, is a cytokine encoded by the gene *TNFSF14* located on chromosome 19p13.3 [1,2]. LIGHT is a type II transmembrane protein that can be proteolytically cleaved to release a soluble, active form [3]. Additionally, *TNFSF14* alternative splicing can produce a distinct isoform lacking the transmembrane domain, known to remain as intracellular cytokine with unique regulatory functions [2]. LIGHT exerts its effects by interacting with the Herpes Virus Entry Mediator (HVEM), mostly expressed on T cells and other immune cells, the Lymphotoxin-β Receptor (LTβR), expressed predominantly on stromal and epithelial cells as well as on innate immune cells, and the soluble receptor Decoy Receptor 3 (DcR3), also binding TL1A and Fas ligand [4,5]. The interaction with HVEM and LTβR pathways can modulate different immunological functions, thus from driving pro-inflammatory activities to sustaining tissue repair, immune regulation, or fibrosis, depending on ligand availability, cellular context, and the local inflammatory microenvironment. In fact, membrane−bound LIGHT - HVEM interaction on effector T cells activates strong co-stimulatory signals together with T−cell activation and mucosal inflammation [1,6]. Similarly, LIGHT–LTβR signaling supports epithelial regeneration and barrier repair, and guides the pathological tissue remodeling in chronic inflammation [7-9]. In this review, it is revised the role of LIGHT/TNFSF14 in the homeostasis and disease of intestine, adipose tissue, liver, heart and bone.

Intestine

The intestinal immune system is a complex and substantially controlled environment that must provide a precise balance between tolerance to helpful commensal microbiota and strong immune responses against invasive pathogens [10]. In intestinal bowel disease (IBD), this essential equilibrium is disrupted, leading to chronic and frequently debilitating inflammation. Interestingly, the gene encoding LIGHT, *TNFSF14*, is located within a known IBD susceptibility locus, thus supporting a direct genetic link to the disease [2]. Furthermore, it is evident the involvement of LIGHT signaling in the activation of distinct downstream cascades, greatly relevant in the IBD pathogenesis. Consistently, on T cells, LIGHT-HVEM co-stimulation activated a strong Th1 inflammatory response typical of Crohn's disease by increasing the secretion of cytokines as TNF-α and IFN-γ [11]. Within the intestinal epithelium, the binding of epithelial HVEM with CD160 on Intra-epithelial lymphocytes (IEL) triggers the NIK-STAT3 axis for antimicrobial defense, whereas in intestinal progenitor cells it can sustain tissue repair by the activation of canonical NFκB signaling [12,13].

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LIGHT-LTβR interaction primarily activates non−canonical RelB/p52 NF−κB signaling with protective roles, in fact after injury in intestinal epithelial cells it promotes mucosal repair and proliferation; it guides an IL−23/IL−22 circuit that increases barrier regeneration and antimicrobial defense; and it stimulates neutrophil−attracting chemokines (CXCL1 and CXCL2) to sustain bacterial clearance and inflammation outcome [14-16]. In macrophages LTβR signaling also stimulates the NF−κB inhibitor TRIM30α, dampening acute dextran sodium sulfate (DSS)−induced colitis [17].

Maladaptive consequences develop when this signaling is persistent or excessive. The interplay between the canonical and non-canonical NF−κB pathways can stimulate epithelial and stromal cells for a hyper-inflammatory response. In chronic inflammation, high LIGHT levels activate LTβR on fibroblasts, macrophages, and other cells, triggering JNK/TGF−β1 axis thus driving a fibrotic response [18], with extreme collagen deposition and extracellular matrix accumulation. Consistently, in experimental models LIGHT or LTβR blockade decreases fibrosis and improves disease severity [27,28]. In human IBD and experimental colitis models immunohistochemical and histological studies have shown that tissue localization and levels of LIGHT, HVEM and LTβR are altered in intestinal inflammation. In colon biopsies from active Crohn's disease and ulcerative colitis patients, elevated LIGHT expression was evident on myeloid cells, infiltrating T cells and, less commonly, epithelial cells within inflamed mucosa [7,19-21]. This positive staining is most concentrated in areas of active disease respect to adjacent non−inflamed areas [20,22]. Consistently, other methodological approaches sustain enhanced LIGHT expression in IBD lesions, specifically in lamina propria leukocytes [22-26]. Using mouse models, these results are strongly recapitulated: in TNBS- and DSS-induced colitis LIGHT is significantly increased in the inflamed colon among $CD45^+$ hematopoietic cells, including T cells and neutrophils [27]. Likewise, in the $CD4+CD45RB^{high}$ T cell transfer model, LIGHT staining is higher in inflammatory foci [7,28]. Transgenic murine or human LIGHT overexpression in mouse T cells determines spontaneous intestinal inflammation with crypt injury and dense mononuclear infiltration [29,30]. Remarkably, in these models the distribution and intensity of LIGHT and HVEM staining reflects the severity of leukocyte infiltration and mucosal injury [7,22,31], with HVEM detected on fibroblasts, epithelial cells, and immune infiltrates in both murine and human samples [25,32].

The serious consequences of dysregulated LIGHT signaling are evident in transgenic mouse models. Consistently, in transgenic mice expressing the murine *Tnfsf14* gene under the control of a T−cell−specific *Lck* promoter, systemic autoimmune disease and intestinal inflammation spontaneously occur, showing a Th1−skewed cytokine profile and extensive immune−cell infiltration, as demonstrated by in vivo histological evaluation and phenotype analysis [30]. In detail, a severalfold augment of intestine wall thickness was significantly observed in transgenic mice respect to controls together with inflammatory cell infiltration. Interestingly, by transferring bone marrow from LIGHT-transgenic donor mice (expressing constitutively LIGHT on T cells) into irradiated immunodeficient recipient mice led to the development of inflammation, tissue destruction, and severe intestinal inflammation. These discoveries prove that LIGHT expression by T-cell is enough to develop the disease phenotype, suggesting that LIGHT-expressing T- cells is the mucosal inflammation pathogenesis trigger [29]. In mouse models these strong inflammatory effects can be magnified by the natural lack DcR3 in mice [1], but expressed in human sample. Interestingly, DSS induced colitis in $LIGHT^{-/-}$ mice determines lost weight and survival with significant shortening of the colon and cecum and enhanced histologic scores with greater histologic differences in cecum than in distal colon. In detail, $LIGHT^{-/-}$ mice showed great inflammatory infiltrates, epithelial disruption, and substantial widening of the submucosal layer in the distal colon and cecum respect to wild-type mice [7]. The demonstration that T lymphocytes did not worsen the disease in LIGHT absence, chronic DSS colitis was realized in LIGHT-deficient $Rag1^{-/-}$ ($Tnfsf14^{-/-}Rag1^{-/-}$) mice. Compared with $Rag1^{-/-}$ mice, $Tnfsf14^{-/-}Rag1^{-/-}$ mice displayed reduced survival together with unresolved inflammation in distal colon and cecum, even after DSS deprivation for 7 weeks [7].

Recently, high levels of LIGHT/TNFSF14 in children with celiac disease have been reported [33]. In colorectal cancer using an engineered *Salmonella typhimurium strain*, $SLC_{VNP20009}$, to express LIGHT/TNFSF14, tumors was colonized and LIGHT released and following the interaction with HVEM to stimulate a robust cellular immune response against the tumor [34]. Overexpression of LIGHT/TNFSF14 has been reported in colorectal cancer with increased survival and enhanced tumor-infiltrating lymphocytes in patients [35].

Adipose Tissue

The role of LIGHT/TNFSF14 has been also reported in adipose tissue homeostasis and disease. Consistently, it has been reported an augment of circulating LIGHT levels in obese children and adults and mice fed a high Fat Diet (HFD composition: 19 MJ kg^{-1}, 35% of energy from carbohydrate, 42% from fat, 23% from protein) [36-38]. Differently, an anti-inflammatory diet decreased systemic inflammation and consequently LIGHT amounts [39]. Consistently, numerous studies evaluated LIGHT effect on adipogenesis. In detail, *in vitro*, human adipocytes stimulation with LIGHT determined the production of cytokines that are linked with the inflammation, as Monocyte Chemoattractant Protein-1 (MCP-1), interleukin (IL)-6, and IL-8 [40]. LIGHT also enhanced the expression of HVEM, it led to the reduction of the expression of transcription factors mediating adipogenesis, as the peroxisome proliferator-activated receptorgamma (PPARγ) [40]. Interestingly, Tiller et al. reported [11] that in different models of adipocytes LIGHT antagonized lipid accumulation *in vitro*, possibly for LIGHT interference with the adipogenesis early stages with the reduced expression of PPARγ and CCAAT/enhancer-binding protein-α (C/EBPα) without modifying the levels of proinflammatory mediators. Additionally, Kim et al. showed that LIGHT/HVEM interaction partecipates to adipose tissue inflammation by increasing immune cell activation, that is related with the infiltration of peritoneal macrophages, $CD4^+$ and $CD8^+$ T cells [41]. Furthermore, Liu et al. found that mesenchymal stem cells stimulated with LIGHT *in vitro* differentiate in adipocytes [42]. Further studies demonstrated LIGHT/LTβR signaling pathway directly involved in adipogenesis, determining an NF-κB mediated inhibitory action on precursors of adipocytes, thus differentiating in lymphoid organ stromal cells [43], with sequentially adipogenesis inhibition in both

white and brown fat [42,43], through the inhibition of the PPARγ and C/EBPα expression. Otherwise, Kou et al., using the 3T3-L1 cell line, showed that LIGHT works as an anti-beigeing factor thus antagonizing beige adipocyte development together with white adipogenesis [44,45]. In HFD-fed Tnfsf14$^{-/-}$ mice, subcutaneous WAT from these mice was expanded compared to WT mice, suggesting that LIGHT, as cytokine secreted by activated immune cells, affects immune cell activation at adiposity expense. In a HFD model, Tnfrsf14$^{-/-}$ mice showed enhanced obesity, hepatosteatosis and glucose intolerance [38]. Interestingly, in ovariectomy, considered a model of adipose tissue inflammation, Tnfsf14$^{-/-}$ mice showed decreased inflammation, fat mass and improved glucose homeostasis [46]. Considering steroid hormone effect on adipose tissue inflammation, it has been detected a difference based on gender, thus developing a different accumulation pattern linked to sex hormones [47]. Other authors reported that female mice are safe against HFD-induced metabolic changes as preserving an anti-inflammatory milieu in the intra-abdominal WAT due to the T regulatory (Treg) cell augment, while HFD-fed male mice show adipose tissue inflammation, glucose intolerance and hyperinsulinemia [48]. In general, ovariectomy models showed estrogen involvement in WAT inflammation, specifically by modulating the growth of senescence-related T cells [49]. However, ovariectomized mice fed HFD displayed a pro-inflammatory microenvironment in the adipose tissue with enhanced M1 macrophages, T-, B-, and NK cells compared to mice with sham mice [49]. As update on the role of LIGHT in adipose tissue homeostasis and disease, a study was performed using male TNFSF14$^{-/-}$ mice as well as Rag$^{-/-}$ and TNFSF14-/Rag- (double knock-out - DKO) mice fed a HFD [50]. In detail, although there is no significant weight gain among the mice with different genotypes, it is significant within each of them. Enhanced visceral White Adipose Tissue (vWAT) weight in all mice fed HFD, even if the lowest levels of vWAT weight was demonstrated in Tnfsf14$^{-/-}$ and DKO mice fed normal diet compared to the other strain. Inguinal WAT (iWAT) weight is importantly altered by genotype and HFD. In detail, the least iWAT amount was detected in DKO mice fed normal diet. vWAT histological analysis displayed that both the diet and the genotype are determinant for the adipocyte area, while the number is influenced only by the genotype. In iWAT, the diet and the genotype meaningfully modulate mean adipocyte number and area; interestingly, the area with the least adipocyte was detected in DKO mice fed ND, signifying a potential browning effect for to the simultaneous lack of mature LIGHT and lymphocytes. Consistently, the iWAT staining with brown adipocyte marker Uncoupling Protein 1 (UCP1) showed that few positive brown adipocytes are present in DKO mice. Additionally, LIGHT deficiency is characterized by the greater levels of UCP1, lacking in Rag$^{-/-}$ mice.

Liver

Another histological site affected by LIGHT levels is represented by the liver. Hepatocellular carcinoma (HCC) represents the third leading cause of cancer mortality worldwide, and its global incidence and mortality are expected to rise by more than 50% by 2040 [51]. An interesting study has been performed demonstrating LIGHT involvement using single-cell transcriptomics, cytometry by time-of-flight and two independent spatial transcriptomics platforms to study the tumor microenvironment of 22 steatotic liver disease - HCC and 31 non-steatotic liver disease HCC cases. The results were further validated using multiplex immunohistochemistry in an independent cohort including 103 patients. Increased interaction between Tregs and cancer-associated fibroblasts is driven by TNFSF14-HVEM interaction and is connected to a poorer response to immunotherapy in steatotic liver disease-HCC [52]. Furthermore, blocking HVEM in the HCC murine model realized within a fatty liver microenvironment importantly augmented the intra-tumoral immune response and enhanced anti-tumor effects with anti-PD-1 blockade. These discoveries highlight that immunotherapy effectiveness is dependent on the unique spatial interactome and architecture within the tumor microenvironment of SLD-HCCs. Studies on LIGHT showed that it can represent a biliary epithelial molecular markers for primary sclerosing cholangitis [53]. Murine models also helped to study the role of LIGHT in liver. In detail, steatosis was evaluated in livers from WT, Tnfsf14$^{-/-}$, Rag$^{-/-}$, and DKO mice fed normal diet or HFD using microscopy (Hematoxylin/Eosin staining) [50]. All mice fed HFD showed a steatotic liver, but it was remarkably evident for DKO mice, in which it seems that the vacuoles moved the nucleus to the side; thus, it is possible to distinguish macrovesicular steatosis [54]. In detail, the highest increase was observed in DKO mice, suggesting that both the genotype and the type of diet affect this system. Consistently, this strong augment was significant respect to all the conditions. Thus, these findings suggest that the simultaneous deficiency of LIGHT and lymphocytes greatly contribute in maintaining liver homeostasis. Other authors evaluated the role of LIGHT deficiency in high-fat high-cholesterol diet ameliorates hepatic glucose tolerance, and reduces hepatic inflammation and non-alcoholic fatty liver [55]. This is accompanied by reduced systemic inflammation and adipose tissue cytokine production and by modulation in the expression of key genes such as Tlr4 and Klf6 involved in non-alcoholic fatty liver disease (NAFLD). Another study reported that LIGHT serum levels were significantly increased in NAFLD patients with respect to healthy controls, without differences between simple steatosis and nonalcoholic steatohepatitis [56]. In the liver, NAFLD patients showed enhanced mRNA levels of the HVEM and LTβR, respect to the controls. LIGHT strongly enhanced the secretion of IL-8 in Huh7 hepatocytes in a time- and dose-dependent manner and the reactive oxygen species hydrogen peroxide increased the LIGHT mediated secretion of IL-8 in Huh7 hepatocytes.

Additionally, it has been shown that LIGHT - LTβR interaction on hepatocytes, but not Kupffer cells, is enough to reduce hepatic lipase expression in a manner independent by LIGHT costimulatory function [57]. Furthermore, considering the liver as fundamental to drive lipid homeostasis the role of LIGHT-mediated dyslipidemia has been evaluated. Using LIGHT Tg mice crossed with mice lacking each of HVEM and LTβR. LIGHT-mediated dyslipidemia was still present and even worsened in LIGHT Tg/HVEM$^{-/-}$ mice but was largely corrected in LIGHT Tg/LTβR$^{-/-}$ mice, suggesting that only LIGHT-LTβR interaction was fundamental for the dyslipidemia in LIGHT Tg mice [58].

In vitro, rhLIGHT promotes the differentiation of hBM-MSCs into functional hepatocyte-like cells with higher ability to uptake indocyanine green and store glycogen compared with control cells, implying functional progression [59]. Furthermore,

recombinant human rhLIGHT treatment enhanced the viability, number, and proliferation of cells by promoting the S/G2/M phase and increasing the expression of different cyclin and cyclin dependent kinase (CDK) proteins. Additionally, the hepatogenic differentiation of hBM-MSCs induced by rhLIGHT involved the activation of signal transducer and activator of transcription 3 (STAT3) and STAT5 pathways.

Furthermore, it has been demonstrated that LIGHT overexpression by NF-κB exerts a significant role in TLR3 involved hepatitis [60].

Bone

Homeostasis in bone is guaranteed by equilibrated bone remodeling through the bone resorbing cells, the osteoclasts, the bone forming cells, the osteoblasts, and the orchestrating cells, the osteocytes. Different molecules participate in this process, including LIGHT [61]. Different studies focus on the role of LIGHT on bone cell activity, but it is interesting to describe the bone phenotype of TNFSF14$^{-/-}$ mice [62]. *LIGHT*-deficient mice *(Tnfsf14$^{-/-}$)* show spine deformity and decreased femoral cancellous bone mass characterized by an enhancement of the osteoclast number and a delicate reduction of osteoblasts respect to WT mice. Consistently, by microCT on 1-, 3-, 6-, and 12-month-old mice a significant reduction in trabecular bone volume per tissue volume (BV/TV) in *Tnfsf14$^{-/-}$* mice, resulting from a significant decrease in trabecular thickness (Tb. Th.) and number (Tb.N.) as well as an augment in trabecular spacing (Tb.Sp.). Data supported by dynamic histomorphometry of cranial bone as well as femoral cortical and cancellous bone demonstrating a significant reduction in bone formation parameters. LIGHT effect on bone cells can be direct or indirect, involving the reduced levels of the anti-osteoclastogenic osteoprotegerin (OPG) in B and T cells and decreased levels of the pro-osteoblastogenic *Wnt10b* in CD8^{+} T cells in *Tnfsf14$^{-/-}$* mice. LIGHT treatment enhances OPG levels in B, CD8^{+} T, and osteoblastic cells, as well as Wnt10b levels in CD8^{+} T cells. The high bone mass in *TNFSF14* and T- and B-cell-deficient mice (*Rag-/Tnfsf14^{-}*, DKO mice) demonstrates the involvement of the immune system in bone homeostasis. In detail, a significant 33% enhancement in trabecular BV/TV in DKO mice resulting from a significant augment in Tb.Th (13.1%) and Tb.N (11.6%), as well as a 42% reduction in Tb.Sp. The cortical compartment was not significantly influenced despite a tendency toward the enhancement of cortical thickness (Co.Th) and the reduction of bone marrow area in DKO. Consistently, DKO showed a strong decrease of oteoclast number together with a small augment of osteoblast number per bone perimeter.

Interestingly, looking at the role of LIGHT in bone disease, its levels are increased suggesting that LIGHT is fundamental for basal bone remodeling, but they can not be high because determine bone loss. In fact, high levels of LIGHT have been found in rheumatoid arthritis, multiple myeloma, and other diseases [63,64]. Brunetti et al. reported that LIGHT was overexpressed by CD14^{+} monocytes, CD8^{+} T-cells and neutrophils of bone marrow and peripheral blood and from multiple myeloma bone disease patients. LIGHT supported osteoclastogenesis and decreased osteoblastogenesis. In cultures from healthy subjects, LIGHT promoted osteoclastogenesis directly or through RANKL. LIGHT and RANK synergically activates the phosphorylation of Akt, NFκB and JNK pathways. In osteolytic patients, LIGHT decreased the formation of CFU-F and CFU-OB together with the expression of osteoblastic markers as collagen-I, osteocalcin and bone sialoprotein-II. LIGHT indirectly decreased osteoblastogenesis partially by sclerostin produced by monocytes. LIGHT levels are also higher in patients subjected to the treatment but with active bone disease [65]. LIGHT concentration is also higher in other kind of cancer without or with bone disease [66]. In detail, human and murine models supported the involvement of this cytokine in non small cell lung cancer [67]. Furthermore, ovariectomy stimulated the T-cell co-stimulatory cytokine LIGHT, which affects both osteoblastogenesis and osteoclastogenesis by modulating osteoclastogenic cytokine expression, its involvement has been also demonstrated in the ovariectomized murine model realized using *TNFSF14$^{-/-}$* and *TNFSF14-/Rag-* [68]. Some rare diseases are characterized by increased LIGHT levels together with other pro-osteoclastogenic cytokines, as alkaptonuria. This is characterized by the deficiency of the enzyme homogentisate 1,2-dioxygenase and consequent homogentisate accumulation, which determines progressive and severe osteoarthropathy [69]. The involvement of LIGHT has been also demonstrated in the bone/immune/kidney axis in chronic kidney disease [70].

Heart

LIGHT involvement has also been demonstrated in heart. It is known that this organ is subjected to numerous diseases consistently cardiovascular diseases (CVD) represent one of the most frequent causes of mortality [71]. Plaque rupture is the principal cause of most cardiovascular events, as stroke and myocardial infarction. LIGHT/TNFSF14 has been identified in foam cell-rich regions of atherosclerotic plaques [72]. LIGHT levels are linked to the incidence of preoperative cerebrovascular symptoms, including stroke. LIGHT levels are related to a histological plaque vulnerability index, inflammatory cytokine levels and necrotic core size [73]. Furthermore, expression of extracellular matrix turnover mediators, as fibromodulin, matrix metalloproteinases 1, 2, 9, and 10, correlated with plaque LIGHT levels. Thus, in atherosclerotic plaques the levels of LIGHT are also significantly increased in plaques from symptomatic respect to those from asymptomatic patients.

Myocardial ischemia-reperfusion (MIR)-induced arrhythmia is a major reason of death in CVD patients. The Cx43 decrease represents a major inducer of arrhythmias after MIR, and it is linked to LIGHT [74]. Consistently, its levels are enhanced in peripheral blood mononuclear cells and the serum of patients with MIR-induced arrhythmia. Recombinant LIGHT/TNFSF14 suppressed the cardiomyocyte viability of but also reduced Cx43 by stimulating LTβR.

LIGHT levels in peripheral blood represent a prognostic marker for atrial fibrillation and to assess its severity [75]. LIGHT determines cardiac fibrosis and atrial fibrillation inducibility by sustaining macrophage M2 polarization, wherein PI3Kγ and SGK1 activation is fundamental.

LIGHT also promotes angiogenesis in tumors and induces the formation of endothelial venules; destroys the extracellular matrix in thoracic aortic dissection, and induces the expression of cyclooxygenase-2, IL-8, and cell adhesion molecules in

endothelial cells [76]. In animal study LIGHT injection prevented angiogenesis in ischemic limbs. *In vitro* studies, LIGHT reduced the expression of E-selectin and integrins, migration and tube formation, succinate dehydrogenase activity, mitochondrial respiration, and supported senescence in endothelial progenitor cells.

In addition, enhanced LIGHT/TNFSF14 levels were independently relate to the incidence of cardiovascular events in patients with stable coronary artery disease [77]. LIGHT is also highly expressed in patients with coronary disease [78]. LIGHT significantly increased inflammation response in oxLDL-induced THP-1 macrophages. The same authors reported that LIGHT significantly reduced the expressions of lipolytic genes and enhanced the levels of lipogenic genes in oxLDL-induced THP-1 macrophages. LIGHT realised its pro-inflammatory and prolipogenesis roles by triggering nuclear factor-kappa B (NF-κB) signaling pathway.

LIGHT with HVEM and LTβR were modulated in experimental approaches with intense expression in the infarcted area together with HVEM overexpression in endothelial cells and cardiomyocytes also in the non-ischaemic side of the left ventricle [79]. Heart failure patients had significantly enhanced levels of LIGHT on CD3(+) T-cells together with enhanced HVEM expression on monocytes and within the failing myocardium. In endothelial cells LIGHT enhanced IL-6 expression. In heart failure patients, but not in healthy subjects, IL-6-inducing effect was evident in LIGHT activated peripheral blood mononuclear cells.

LIGHT pathway exerts a fundamental role in the regulation of smooth muscle cell proliferation and consequently thus its inhibition led to prevention of graft arterial disease [80].

It is known that inflammation shows a pathogenic role in chronic heart failure (CHF), using peripheral blood samples from patients and controls it has been demonstrated high levels of LIGHT together with APRIL, FasL, CD27L, TNFα and TRAIL [81]. Using *TNFSF14*$^{-/-}$ mice it has been demonstrated that T cell to T cell-mediated LIGHT/HVEM-dependent co-stimulation is a strong component of the host response determining cardiac allograft rejection [82].

Conclusions

This review highlights the critical role of LIGHT/TNFSF14 in homeostasis and disease of intestine, adipose tissue, liver, bone and heart. Thus LIGHT when dysregulated can represent an important therapeutic target, consistently monoclonal antibodies have been realized to antagonize its action and improve patients' health, and trials are ongoing or in evaluation [1].

Grant

Founding

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