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LIGHT/TNFSF14 in Cancer

Giacomina Brunetti

University of Bari Aldo Moro, Bari, Italy

ABSTRACT

LIGHT/TNFSF14 is a member of the TNF superfamily and works as transmembrane and soluble forms. Different authors evaluated its role in cancer reaching different results. In detail, LIGHT has been described as having a dualistic role (anti-tumor or pro-tumor) in different tumors. In detail, inducing LIGHT expression in prostate and breast cancer in murine model a benefit is evident. It has been reported that higher LIGHT levels are related with a better prognosis in colorectal cancer liver metastases. In patients with glioma or glioblastoma high LIGHT levels are linked to a worsened prognosis. While for patients with osteolytic non-small cell lung cancer, multiple myeloma, an increased pattern of LIGHT expression predicted the active bone disease. In this review, the key role of LIGHT in glioma, glioblastoma, gastric, pancreatic, breast and prostate tumor, non-small cell lung cancer, chronic myeloid leukemia and multiple myeloma was described.

***Corresponding author**

Giacomina Brunetti, University of Bari Aldo Moro, Bari, Italy. E-mail: giacomina.brunetti@uniba.it

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Introduction

LIGHT/TNFSF14 is a member of the TNF superfamily and works as transmembrane and soluble forms [1]. It binds Herpesvirus entry mediator (HVEM), TNF receptor superfamily member lymphotoxin-β receptor (LTβR) and Decoy Receptor 3 (DcR3), and it is mainly expressed by immune cells, thus regulating immunity. LIGHT/TNFSF14 role has also been demonstrated in cancer, as described in this review [2].

LIGHT in Glioma and Glioblastoma

Adult-type diffuse high-grade gliomas (HGGs) are an aggressive group of infiltrative brain tumors, that originate from glial cells, including oligodendrocytes, astrocytes, and ependymal cells [3]. Classified as World Health Organization Classification of Tumors of the Central Nervous System (WHO CNS) grade 1-4 (4), these tumors exhibit significant malignancy, high recurrence rates, and poor survival outcomes despite aggressive treatment. Survival in HGGs is determined by an interplay of molecular, histological, anatomical, as well as systemic variables [3-5]. The HGG biological behavior was traditionally primarily described by tumor grade, determined by studies on histopathological samples.HGGs, remarkably grade 4 tumors, presented aggressive histological characteristics, including marked nuclear atypia, increased mitotic activity, neo-angiogenesis, and necrosis. These morphological hallmarks are linked to HGG aggressiveness, thus showing fast growth, extensive invasiveness, with consequent poor clinical outcomes. Histopathological assessment now represents just one element within the more comprehensive tumor classification framework. Earlier editions of the WHO CNS stratified gliomas into types and grades according to tumor architecture and cellular features [4]. The substantial molecular and clinical heterogeneity characterizing the same type and grade tumor determined the molecular diagnostic integration reported into the 2016 WHO CNS [5]. This update introduced key biomarkers, including1p/19q codeletion for diagnosing oligodendroglioma, and IDH mutation status, along with several other molecular markers and histologic features, to differentiate astrocytoma subtypes. The use of advanced technologies, including RNA expression profiling, next-generation sequencing, and DNA methylation profiling led to the classification of subtypes together to a more precise stratification of known tumors, led to the most recent 2021 WHO CNS fifth edition (2021 WHO CNS5) [4-6]. This updated version integrated classical histopathological evaluation with key molecular markers, as 1p/19q codeletion, IDH mutation status, histone mutations, and CDKN2A/B deletions. It also describes the category of adult-type diffuse gliomas, existing as distinct molecularly defined subtypes: IDH-mutant Astrocytoma, IDH-wildtype Glioblastoma, IDH-mutant and 1p/19q-codeleted Oligodendroglioma. Among the molecules studied in glioma development some authors evaluated the role of LIGHT/TNFSF14. The results of both CGGA (n = 693) and TCGA (n = 667) cohorts demonstrated a statistically significant positive correlation between LIGHT levels and glioma WHO grade, implying that higher LIGHT level correlated with higher glioma malignancy [6]. Furthermore, by further classification of patients according to IDH mutation status, LIGHT expression is increased in IDH wildtype glioma in both datasets compared 3 to IDH-mutant. This further indicated that LIGHT was particularly associated with a more aggressive biological behavior in glioma. The same authors demonstrated that LIGHT expression was significantly increased in mesenchymal molecular subtype with respect to other subtypes, thus LIGHT levels represent a specific biomarker for glioma mesenchymal subtype. Furthermore, the authors showed that LIGHT positively correlated with gene expression levels mainly associated with immune and inflammatory response, specifically involved in

T-cell activation, whereas LIGHT levels are negatively related with genes linked to normal biological function, as intracellular signaling cascade and synaptic transmission. Thus, LIGHT works as an immune suppressor in glioma. Consistently, LIGHT expression was significantly related to immune checkpoint members, especially HVEM, TIM-3, PD1/PD-L1 pathway, and B7-H3. LIGHT was positively related with MHC-I, MHC-II, HCK, LCK, STAT1, and interferon, especially HCK, LCK, and MHC-II specifically reflecting the activities of macrophages, T-cells, and antigen-presenting cells, respectively. Thus, in glioma LIGHT appears as an immunosuppressive cytokine in the activities of macrophages, APCs and T-cells.

Similarly, Han et al [7]. reported the enhanced LIGHT expression in glioblastoma (WHO grade IV) compared with low-grade gliomas using large-scale cohorts, including TCGA (n = 667), CGGA (n = 693) and Rembrandt (n = 510). Furthermore, ROC curve analysis suggested that normal brain tissue and gliomas could be differentiated by LIGHT expression. Moreover, using the 2016 WHO classifications in TCGA, repressed LIGHT expression in the LGG-Oligo subtype (IDHmut, 1p/19q codeletion) and LGGAstro (IDHmut, 1p/19q non-codeletion) was evident compared with the LGG-IDHwt group, whereas LIGHT expression in GBM-IDHwt was elevated compared with the GBM-IDHmut group. The authors found similar results on the CGGA database. On the same patients, immunohistochemical staining was perform to confirm LIGHT protein expression in gliomas, glioblastoma and normal brain tissue, reporting that LIGHT expression was higher according to the increased glioma grade with highest levels in glioblastoma. Interestingly, the staining in one specific glioblastoma sample showed a different expression of LIGHT levels between glioblastoma and its adjacent health tissue, with marked elevated 4 LIGHT expression in the tumor tissue and lower level in the heathy tissue, suggesting that elevated LIGHT expression predicted malignant glioma and correlated with its aggressive phenotype.

In detail, a higher LIGHT expression was also found in the mesenchymal subtype than the neural, proneural glioma CpG island methylator phenotype (G-CIMP) or non-G-CIMP subtypes and the ROC curve further indicated a clear distinction of mesenchymal from non-mesenchymal tumor. Moreover, considering the different anatomical areas, higher LIGHT levels were measured within the Pseudopalisading Cells Around Necrosis (PAN) and Perinecrotic Zone (PNZ) areas than in other subareas. Glioblastoma and immune cells were the major cells expressing LIGHT, and its expression was concentrated in the tumor core instead of the peripheral area. Among all glioma patients, high LIGHT expression predicted a smaller overall survival than low LIGHT expression. Higher LIGHT expression was linked to a more unfavorable prognosis in low-grade glioma and glioblastoma patients. In parallel, high LIGHT expression indicated a shorter progression-free survival in glioma, indicating that high LIGHT levels might determine a more rapid progression. Differently higher or lower LIGHT expression in glioblastoma did not affect the progression-free survival. However, in glioblastoma patients with a molecular subtype of IDHwt, LIGHT levels were prognostic, and elevated LIGHT expression predicted a shorter overall survival.

In 2025, Zottel et al [8]. reported using the same datasets of the previously cited papers, that CD44 and LIGHT were demonstrated to be significantly overexpressed in glioblastoma respect to lower-grade glioma and heathy brain tissue. Their high levels were linked to worse overall survival and demonstrated the strong capability to differentiate glioblastoma and reference brain tissue. Remarkably, CD44 and TNFSF14were related to the mesenchymal subtype of glioblastoma and positively revealed the presence of resting natural killer cells, regulatory T cells, and PD-L1 expression. CD44 and TNFSF14 overexpression in glioblastoma is related with the potential involvement in the creation of an immunosuppressive microenvironment. CD44 and TNFSF14 levels are related with PD-L1 expression, indicating a potential involvement in immune checkpoint pathway regulation.

LIGHT/TNFSF14 Role in Gastric Cancer

Gastric cancer is one of the five most common cancers and worldwide represents the third leading cause of cancer-related deaths. Gastric cancer has a complex etiology and pathogenesis involving a combination of genetic, environmental, and immunological factors [9]. Immune dysregulation has a critical role in gastric cancer development and progression, and involves LIGHT and CD160 [10]. Consistently, Keykhosravi et al. reported that among the 133 gastric endoscopic biopsies evaluated from gastric cancer patients, LIGHT showed a significant overexpression using quantitative real-time PCR compared to peptic ulcer dyspepsia, and non-ulcer dyspepsia groups. Additionally, TNFSF14 expression was higher in stages I and II gastric cancer. Moreover, gastric cancer patients with TNM stages III+IV were characterized by elevated expression of LIGHT and CD160. Interestingly, TNFSF14 higher expression has been found in older adults with gastric cancer. Furthermore, using Enrichment analysis the potential biological pathways associated with TNFSF14 effects in gastric cancer the different biological processes have been found including the negative regulation of T cell-mediated cytotoxicity and leukocyte degranulation, T-helper cell lineage commitment, positive regulation of gamma-delta T cell activation and natural killer cell chemotaxis.

Xie et al worked-on histone lysine-specific demethylase 1 (LSD1/KDM1A) playing a significant role in T cell regulation, thus combining LSD1 inhibitors with anti-PD-1 mAb has shown improved anti-tumor effects in various solid tumors [11]. In detail, in gastric cancer the knockdown of LSD1 boosts T cell-mediated anti-tumor immunity. The knockdown of LSD1 stimulated the transcription TNFSF14, and consequently T cell-mediated anti-tumor immunity was improved. LSD1 inhibition in gastric cancer increases TNFSF14 expression, leading to T cell proliferation, CD8+ T-cell activation, and chemotaxis. This increase of T cell-mediated anti-tumor immunity is additionally amplified if LSD1 inhibitors were utilized together with PDL1 blockers, thus simplifyingCD8+ T cells activation in the spleen and enhancing leukocyte infiltration in the tumor.

LIGHT/TNFSF14 in Pancreatic Adenocarcinoma

Overall survival for pancreatic adenocarcinoma (PDAC) patients remains low with 5-year survival less than 10% [12, 13]. Surgery offers the only chance of cure, adjuvant therapy has been shown to 6 significantly ameliorate outcomes and is recognized as standard care in patients with resected pancreatic cancer, however 69 to 75% of patients have a diagnosis of relapse within 2 years [14-18]. The combination of fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) has resulted in longer overall survival if administered as first-line treatment in patients with metastatic pancreatic cancer [19]. These results prompted other authors to evaluate the effect on 493 patients with resected pancreatic ductal adenocarcinoma treated with a modified FOLFIRINOX regimen (oxaliplatin, irinotecan, leucovorin and fluorouracil every 2 weeks) [20]. Chemotherapy is important as favorably modifies the tumor immune microenvironment through different mechanisms, in detail it determines DNA damage in tumors, uptake of tumor

debris and neoantigens by antigen-presenting cells, induction of adaptive immune response and T cell activity [21]. It has been reported that key differences in the PDAC microenvironment occur between primary and metastatic tumors [21]. In detail, 145 samples were included in the study (from the COMPASS trial), 83 received modified FOLFIRINOX regimen, 62 received Gemcitabine-based therapy. Compared with pancreatic tumor samples, metastatic liver biopsies showed significantly higher expression of numerous immunomodulatory genes, as ADORA2A, CSF1R, PD-L1. Differences in immunostimulatory and MHC genes based on site of biopsy were found, as CD70, CD80, CD86, CD276, IL2RA, MICB, NT5E, PVR, TNFSF14, TNFRSF14, TNFRSF18, ULBP1. However, only TNFSF14 was reduced in the liver respect to the pancreatic biopsies, whereas the others are upregulated. Multiple immunostimulatory genes were also related to worse survival in the modified FOLFIRINOX cohort, as CXCL12, C10orf54, and TNFSF14/LIGHT.

LIGHT/TNFSF14 in Clear Cell Renal Cell Carcinoma

Clear cell renal cell carcinoma (ccRCC) represents the major type of kidney cancer, about 85% of the whole subtypes and a better prognosis [12, 22, 23]. The main treatment for RCC is represented by radical nephrectomy. Although the therapy is mature, about 60% of patients relapse within 5 years. In advanced or metastatic RCC patients the 5-years overall survival falls to 30% [24]. TNFSF14 was upregulated in RCC (n= 539) respect to the controls (n= 72), and it is related to advanced clinical stage, high TNM stage and poor histological grade (22). High TNFSF14 levels determined poor survival outcomes and the 5-year 7 8overall survival rate in high- and low-TNFSF14 patients' groups was 48.3 and 70.7% respectively, thus suggesting that TNFSF14 can represent a prognostic biomarker. The potential biofunction of TNFSF14 was explored by GSEA, which showed that some immune-related signaling pathways were enriched in patients with elevated TNFSF14 levels, as antigen processing and presentation, T cell receptor, primary immunodeficiency and natural killer cell-mediated signaling pathways. Consistently, other authors described the altered immune microenvironment in RCC [25]. Furthermore, overexpressed TNFSF14 was also reported to be involved in some tumor-related signaling pathways, such as toll-like receptor and JAK-STAT signaling pathways. Thus, the authors concluded that LIGHT/TNFSF14 may contribute to RCC malignant progression and immune process.

LIGHT/TNFSF14 and Leukemia Stem Cells

LTβR and LIGHT regulate quiescence and self-renewal of murine and human Hematopoietic stem cells (HSCs) and Leukemic stem cells (LSCs) [26]. LIGHT/LTβR signaling on HSCs supports symmetric cell division, decreases cell cycling, and avoids HSCs from exhaustion in genotoxic stress and serial retransplantation. Interestingly, LTβR and LIGHT deficiency decreases primitive LSC number in the bone marrow and extends the survival in a murine chronic myeloid leukemia (CML) model. It is known that the primitive LSC accumulation and the differentiation lack determine disease progression in leukemia [27]. Consistently, LSCs are the cause of leukemia beginning and propagation [28]. Similarly, LIGHT/LTβR signaling in human granulocyte colony-stimulating factor mobilized HSCs and LSCs with consequent augmented colony forming activity in vitro. Importantly, mouse and human CML cells overexpress LTBR and LIGHT when compared to normal hematopoietic stem/progenitor cells. Knockdown of LTBR in human CML hematopoietic stem/progenitor cells led to the decrease of stemness- and Wnt-related genes, as MSI2, TNIK, and CTNNB1 and a decreased LSC number. Thus, targeting the LIGHT/LTβR pathway may represent a new strategy to support differentiation and to remove LSCs, as other TNF receptors [29].

LIGHT/TNFSF14 in Breast Cancer

Breast cancer represents worldwide the leading cause of cancer death among females [23]. It is known that the tumor microenvironment has a key role in breast cancer development and progression. It includes tumor-associated stroma, cytokines, immunosuppressive cells, and immune inhibitory checkpoints in a hypoxic environment. All these factors can develop local immune suppression, or both immune and physical barriers to the host immune system, thus it represents a target to counteract tumors [30]. Interestingly, in experimental models, LIGHT restoration in the tumor microenvironment could recruit effector T cells, stimulate tumor vessel adjustment, and decrease regulatory T cell mediated immunosuppression, that are important to induce tumor-specific immune responses to increase host tumor immune against the tumor [31-34]. In this scenario, LIGHT is an important bio-therapeutic drug for cancer immunotherapy, thus different approaches were used to optimize its role. Among other oncolytic viruses, selectively replicating in the tumor cells in order to develop oncolysis, have been used as alternative approaches also because they can lead to immune activation [35]. The development of oncolytic adenoviruses targeting the tumor microenvironment, as rAd.sT and rAd.DCN seems very promising, as they repressed tumor growth and metastasis in different tumor models through the inhibition of transforming growth factor β (TGF-β) signaling [36, 37]. Importantly, immune tolerance was activated after adenoviral infection, and consequently negatively affected anti-tumor reactions of oncolytic adenovirus. This issue can be overcome by transducing oncolytic adenovirus with LIGHT gene, thus telomerase reverse transcriptase promoter controlled oncolytic adenovirus expressing LIGHT, rAd.Light replicate, generate LIGHT protein expressed on tumor cells and *in vitro* determine cytotoxicity in human and murine breast cancer cells [38]. In mouse breast cancer injecting 4T1 tumor cells subcutaneously, histopathological analysis demonstrated that rAd.Light showed an anti-tumor effect in situ inducing tumor cell apoptosis, enhancing T cell infiltration and activating systemic anti-tumor immune reactions. Consistently, on day 15, compared to rAd.Null, in rAd.Light treatment, it can be observed the Treg decrease, the augment of Th1 cytokine interleukin (IL)-2 levels, and decreased Th2 cytokines expression, as TGF-β and IL-10 in the tumors. At sacrifice, rAd.Light mice displayed reduced tumor volume and weight, with increased positivity to caspase-3 in tumor biopsies.

LIGHT/TNFSF14 in Prostate Cancer

Prostate cancer represents a significant health challenge, with >375,000 annual deaths worldwide in men, mainly due to the development of resistance to standard-of-care [39]. Thus, different studies focus on drug development or systems to ameliorate drug delivery or activate the immune system. Consistently, chimeric antigen receptor (CAR) T cells have demonstrated therapeutic efficacy in hematological cancers [40], but limited effects in solid tumors. Accordingly, engineered CAR-T cells with cytokines enhance the infiltration, accumulation, and survival of CAR-T cells in various solid tumors with major chances of counteract the tumor [41]. Furthermore, in the tumor microenvironment reconstitution of tertiary lymphoid structures gains the clinical outcome of cancer immunotherapy. Consistently, it is known that LIGHT facilitates tertiary lymphoid structures formation in tumor tissues [42, 43]. Zhang et al. realize a system using soluble LIGHT with a vascular targeting peptide (VTP) in CAR-T cells to overcome the problems of immunotherapy in solid tumors. Thus, the secreted LIGHT binds HVEM to augment CAR-T cell cytotoxicity and through LTβR interaction rescue the

immunosuppressive tumor microenvironment on the surrounding cells. Therefore, CCL19 and CCL21, tertiary lymphoid structure markers, were increased in LIGHT co-expressing CAR-T cells both *in vitro* and *in vivo*. In murine models, the cells were injected subcutaneously, with great success, as shown by the increase of overall survival and tumor mass decrease. Parallel interesting results were also observed for the intratibial tumor injection. Moreover, CAR-T cell infiltration and cytotoxicity in the tumor were enhanced significantly, implying the critical potential of LIGHT in facilitating CAR-T therapy to solid tumors.

LIGHT/TNFSF14 in Cancer with Bone Involvement

The bone is a frequent metastatic site for solid tumor, with consequent alteration in the mineralized bone and the bone marrow microenvironment [44]. However,the bone disease is also evident in hematological cancers as multiple myeloma [45].

Lung cancer sheds malignant cells directly into the arterial blood flow, from where they can be seeded far and wide, in detail 30-40% of patients with non-small cell lung cancer (NSCLC) develop bone metastases during the course of their disease [46]. LIGHT is involved in bone metastatic NSCLC [47]. The 10 study involved 61 neo-diagnosed patients with NSCLC, among them 24 presented bone metastases at diagnosis and 37 no metastases. NSCLC bone metastatic patients display significantly higher levels of LIGHT expressed on monocytes compared with non-bone metastatic patients and healthy controls. Serum LIGHT levels were elevated in bone metastatic patients than in healthy subjects. Working on bone biopsies notably, LIGHT staining was intermediate or strong in bone metastases with no gland forming NSCLCs, whereas it was minimal or negative in NSCLCs associated with a gland-forming component. Additionally, in bone metastatic patients elevated RNA expression and serum RANKL levels were detected. Both LIGHT and RANKL are involved in the formation of osteoclast, the bone resorbing cells, thus in PBMC cultures by adding anti-LIGHT or RANK-fragment crystallizable region (RANK-Fc), a significant decrease of spontaneous osteoclastogenesis was demonstrated. To model this observation in mice, we injected intratibial the mouse lung cancer cell line LLC-1 in *Tnfsf14*$^{-/-}$ mice. At sacrifice, wildtype mice displayed an augmented osteoclast number together with a decreased osteoblast numbers and reduced osteoid formation. Interestingly, *Tnfsf14*$^{-/-}$ mice displayed no significant bone loss or significant other changes in bone. These data suggest LIGHT as key control mechanism for the regulation of bone homeostasis during metastasis development.

Multiple myeloma is a neoplasm of plasma cells that proliferate abnormally in the bone marrow and osteolytic bone disease is described in about 80% of patients at diagnosis [45]. Myeloma osteolytic lesions are 'punched-out' areas of bone destruction that most commonly involve the axial skeleton. These lesions expose patients to pathological fractures (about 60%), spinal cord compression and bone pain, reduced bone mineral density is also a frequent feature in multiple myeloma [48,49]. Different mechanisms have been demonstrated in the pathogenesis of multiple myeloma bone disease, including LIGHT/TNFSF14. In detail, Brunetti et al. demonstrated that LIGHT was overexpressed by CD14+ monocytes, CD8+ T-cells and neutrophils from peripheral blood and bone marrow samples of multiple myeloma-bone disease patients [50]. LIGHT was also detected in the biopsies of osteolytic patients. LIGHT supported spontaneous osteoclastogenesis and inhibited the differentiation of osteoblasts, the bone forming cells, in vitro. In cultures from healthy-subjects, LIGHT induced the formation of 11 osteoclasts without or with RANKL, consistently in the presence of a sub-optimal RANKL concentration, LIGHT and RANKL synergically promoted osteoclastogenesis, through the phosphorylation of NFκB, Akt, and JNK pathways. In BM sample cultures from bone disease patients, LIGHT reduced the formation of CFU-F and CFU-OB as well as the osteoblastic marker levels, as osteocalcin, collagen-I and bone sialoprotein-II. Further insights help to demonstrate that LIGHT indirectly antagonized osteoblastogenesis in part throughout sclerostin expressed by monocytes. In another paper, Brunetti et al. reported that the levels of LIGHT can be associated to active bone disease in multiple myeloma patients also if are experiencing therapeutic regimens [51]. LIGHT over-expression was found by circulating CD14+ monocytes from MM patients still showing active bone disease, despite the treatment together with the over-expression of receptor activator of nuclear factor kappa-B ligand (RANKL), in Tells isolated from the same patients. The percentages ofCD14+CD16+ circulating osteoclast progenitors were higher in all patients than in the controls, but spontaneous osteoclast differentiation occurred only in PBMC cultures derived from patients with unresponsive bone disease. These osteoclastogenesis was partly or fully reduced dose-dependently by the treatment with RANK-Fc or anti-LIGHT neutralizing antibody, indicating the involvement of both LIGHT and RANKL to the increased osteoclastogenesis. Additionally, high serum levels of resorption markers TRAP5b and CTX were measured in multiple myeloma patients with bone disease not responsive to treatment.

Conclusions

LIGHT has been described as having a dualistic role (anti-tumor or pro-tumor) in different tumors. In detail, inducing LIGHT expression in prostate, breast cancer and chronic myeloid leukemia in murine model a benefit is evident. It has been reported that higher LIGHT levels are related with a better prognosis in colorectal cancer liver metastases [52]. In patients with glioma, glioblastoma, gastric, RCC, PDAC, high LIGHT levels are linked to a worsened prognosis. While for patients with osteolytic NSCLC, multiple myeloma, an increased pattern of LIGHT expression predicted the active bone disease. All these findings suggest that it is important to establish the correct conditions in order to inhibit or enhance LIGHT expression in immunotherapy, possible looking at the phenotype of the involved immune cells.

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